The International Stress and Behavior Society (ISBS)
Institute of Experimental Medicine (IEM)
Institute of Translational Biomedicine, St. Petersburg State University
The Russian Society for Biopsychiatry (RSBP)

# Program and Proceedings

## 27th Multidisciplinary International Neuroscience and Biological Psychiatry Conference

## "Stress and Behavior"

### JUBILEE SYMPOSIUM DEDICATED TO THE 130th ANNIVERSARY OF THE INSTITUTE OF EXPERIMENTAL MEDICINE

*St. Petersburg, Russia*
*September 16-18, 2020*

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# ПРИВЕТСТВЕННОЕ СЛОВО ДИРЕКТОРА ИЭМ

Дорогие друзья!

От имени ФГБНУ «Институт экспериментальной медицины», одного из организаторов 27-ой междисциплинарной международной конференции «Стресс и поведение», позвольте приветствовать и поблагодарить всех участников за то, что в период пандемии коронавирусной инфекции вы нашли возможность принять участие в конференции. Впервые в своей истории она проходит в необычном формате, и этот формат дает возможность участия еще большему числу слушателей. Сама конференция приурочена 130-летнему юбилею нашего Института экспериментальной медицины – учреждению, подарившему мировой науке выдающихся ученых и новые научные направления.

За свою историю Институт экспериментальной медицины пережил тяжелые периоды – Первую мировую, гражданскую и Великую Отечественную войны, голод, эпидемии, разрухи, репрессии, разгул псевдонауки. Несмотря на это, Институт экспериментальной медицины бережно хранил свой научный потенциал и из года в год кропотливо вносил значительный вклад в решение актуальных проблем биологии и медицины.

Славная история Института связана с именами выдающихся ученых: первого российского лауреата Нобелевской премии в области физиологии и медицины И.П. Павлова, С.Н. Виноградского, Д.К. Заболотного, В.Л. Омелянского, А.А. Заварзина, Н.Г. Хлопина, В.А. Энгельгардта, Е.М. Крепса, Е.С. Лондона, П.С. Купалова, Л.А. Орбели, К.М. Быкова, Н.Н. Аничкова, С.В. Аничкова, А.А. Смородинцева, В.И. Иоффе, Б.И. Ткаченко и многих других, внесших существенный вклад в отечественную и мировую науку. Институт стал первым в стране академическим медико-биологическим научным учреждением, удостоенным Ордена Трудового Красного Знамени.

Сегодня Институт экспериментальной медицины представляет собой современный медицинский исследовательский, образовательный и клинический центр. В научных отделах проводятся исследования в области молекулярной медицины, геномики, протеомики, метаболомики и нанотехнологий. В Клинике и Медицинском научном центре осуществляется трансляция фундаментальных разработок в медицинскую практику. На молекулярном, клеточном, организменном и популяционном уровнях изучается патогенез распространенных заболеваний человека, разрабатываются методы профилактики и диагностики, передовые технологии лечения и реабилитации.

Многие научные данные, полученные в Институте экспериментальной медицины за последние годы, будут представлены на конференции «Стресс и поведение». Обращает на себя внимание тот факт, что большинство работ выполняются на стыке научных дисциплин, что позволяет глубоко разобраться в природе явлений и процессов. Из года в год в конференции участвует все большее количество как молодых исследователей, так и их опытных наставников. Именно юношеский максимализм и научная смелость с одной стороны, а также опыт и научная мудрость с другой стороны, позволяют двигаться отечественной науке вперед, к новым победам и свершениям. Искренне желаю всем участникам 27-ой междисциплинарной международной конференции «Стресс и поведение» дальнейших научных успехов и достижений!

С уважением,
Директор ФГБНУ «ИЭМ»,
доктор биологических наук, профессор РАН А.В. Дмитриев

# CONFERENCE PROGRAM

## Day 1. Wednesday, September 16, 2020

**Venue: Oktiabrskaya Hotel,10 Ligovsky Prospect, St. Petersburg, Russia**

**11.00-11.15** **OPENING AND WELCOMING ADDRESSESS**
Prof. AV Kalueff, ISBS President and Conference Chair
Prof. AV Dmitriev, Institute of Experimental Medicine Director
Prof. VM Klimenko, Program Committee Chair

**11.15-11.35** **EVALUATING THE PROTECTIVE EFFECTS OF DIOSGENIN ON THE AGING PROCESSES IN RATS WITH ACCELERATED SENESCENCE.** TG Amstislavskaya, MA Tikhonova, Y-J Ho, Scientific Research Institute of Physiology and Basic Medicine, Novosibirsk, Russia

**11.35-11.55** **MECHANISMS OF HIPPOCAMPAL NEUROGENESIS INDUCED BY A TRAUMATIC BRAIN INJURY.** TG Amstislavskaya, YL Yang, MA Tikhonova, KT Lu, Novosibirsk State University, Novosibirsk, Russia, National Chia-Yi University, Chia-Yi, Taiwan, National Taiwan Normal University, Taipei, Taiwan

**11.55-12.15** **NEURONAL FUNCTION AND PHARMACOLOGY OF TRACE AMINE-ASSOCIATED RECEPTORS (TAARS).** RR Gainetdinov, Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia

**12.15-12.35** **METRIS PRESENTATION: LABORAS SYSTEM APPLICATION FOR MOTOR BEHAVIOR IN ASSESSMENT OF THE ZINC SUCCINATE TOXIC EFFECT.** R Bulthuis, L Bachdasarian, G Piavchenko, Metris B.V., Hoofddorp, The Netherlands, Sechenov University, R&D Pharmaceutical CJSC “Retinoids”, Moscow, Russia

***12.35-12.50*** ***BREAK 1***

**12.50-15.45** **SYMPOSIUM 1: LAPIN SYMPOSIUM ON NEUROPSYCHOPHARMACOLOGY**
Chairs: AV Kalueff (China, Russia, USA) and PD Shabanov (Russia)

**12.50-13.00** **INTRODUCTION: PROFESSOR IZYASLAV LAPIN**

**13.00-13.15** **NEURONAL ROLE OF TRACE AMINE-ASSOCIATED RECEPTOR 2 (TAAR2).** EV Efimova, SR Kuvarzin, NV Katolikova, D Smirnova, AA Kozlova, MS Mor, RR Gainetdinov**,** Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia

**13.15-13.30** **EXPERIMENTAL MODELING OF DOUBLE DIAGNOSIS: ANXIETY DISORDER AND ALCOHOLISM.** AY Egorov, IV Demyanko, AE Veraksa, EV Filatova, I.M. Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, I.I. Mechnikov North-West State Medical University, St. Petersburg State University, St. Petersburg, Russia

**13.30-13.45** **EFFECT OF HORMONAL AND NON-HORMONAL CORRECTORS ON SEXUAL MOTIVATION IN RATS AFTER CHRONIC SOCIAL ISOLATION.** IYu Tissen, LA Magarramova, AS Kraskova, AA Lebedev, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

**13.45-14.00** **LOCOMOTOR EFFECTS OF PDE10A INHIBITORS IN DOPAMINE-DEPLETED RATS: ACUTE AND REPEATED ADMINISTRATION.** A Dorotenko, A Savchenko, S Kuvarzin, RR Gainetdinov, A Bespalov, I Sukhanov, First St. Petersburg State Medical University, Valdman Institute of Pharmacology, Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia

**14.00-14.15** **THE TRACE AMINE-ASSOCIATED RECEPTORS 5 MAY INVOLVE IN LOCOMOTOR FUNCTION.** D Kalinina, A Goriainova, R Gainetdinov, P Musienko, Institute of Translational Biomedicine, St. Petersburg State University, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, Russian Research Center of Radiology

and Surgical Technologies, Ministry of Healthcare, Pavlov Institute of Physiology RAS, St. Petersburg, Russia

**14.15-14.30** **LONG-TERM EFFECTS OF BISPHENOL A ON LIPID METABOLISM OF FEMALE RATS.** NK Apraksina, NN Klyueva, IO Suchkova, TV Avaliani, NI Dergacheva, EL Patkin, SG Tsikunov, Pavlov Department of Physiology, Institute of Experimental Medicine, St. Petersburg, Russia

**14.30-14.45** **CALPAIN ACTIVITY IN THE CNS DAT-KO RATS**. DS Traktirov, NS Pestereva, TV Tyutyunnik, VS Artemova, ZS Fisenko, MN Karpenko, VM Klimenko, Pavlov Department of Physiology, Institute of Experimental Medicine, Peter the Great St. Petersburg Polytechnic University, Institute of Translation Biomedicine, St. Petersburg State University, St. Petersburg, Russia

**14.45-15.00** **EARLY LIFE LIPOLYSACCHARIDE EXPOSURE ALTERS STRESS-INDUCED CHANGES OF THE NMDA AND AMPA RECEPTOR EXPRESSION IN THE RAT BRAIN.** OE Zubareva, VA Nikitina, AN Trofimov, MV Zakharova, AA Kovalenko, GV Beznin, DU Krytskaya, AP Schwarz, SG Tsikunov, Pavlov Department of Physiology, Institute of Experimental Medicine, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia

**15.00-15.15** **GHRELIN CONCENTRATION AND KINASE ACTIVITY ARE IN THE RELATIONSHIP AFTER STRESS EXPOSURE AND DRUG ADMINISTRATION.** AA Blazhenko, PP Khokhlov, ER Bychkov, AS Devyashin, AA Lebedev, SN Proshin, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

**15.15-15.30** **DANIO RERIO AS A NEW MODEL TO STUDY HORMONAL RESPONSE TO STRESS.** PP Khokhlov, EA Sekste, AA Blazhenko, ER Bychkov, AA Lebedev, LK Khnychenko, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

***15.30-16.00*** ***BREAK 2***

**16.00-19.05** **SYMPOSIUM 2: JUBILEE SYMPOSIUM DEDICATED TO THE 130th ANNIVERSARY OF THE INSTITUTE OF EXPERIMENTAL MEDICINE (IEM)**
Chair: VM Klimenko (Russia)

**16.00-16.15** **WELCOMING ADDRESS FROM THE INSTITUTE OF EXPERIMENTAL MECICINE**

**16.15-16.35** **ABNORMAL BEHAVIOR IN THE OFFSPRING OF RATS SUBJECTED TO HYPOXIA DURING PREGNANCY IS CORRECTED BY LACTOFERRIN.** VB Vasilyev, AV Sokolov, VA Kostevich, NM Dubrovskaya, NN Nalivaeva, DS Vasilev, OL Runova, ET Zakharova, IV Semak, AI Budevich, IA Zhuravin, Institute of Experimental Medicine, St. Petersburg State University, Sechenov Institute of Evolutionary Physiology and Biochemistry, St. Petersburg State Pediatric Medical University, St. Petersburg, Russia, Belarus State University, Minsk, Scientific Practical Centre of Animal Breeding, Zhodino, Belarus

**16.35-16.50** **RESTRAINT STRESS AND BEHAVIORAL CHANGES IN MICE OF DIFFERENT GENOTYPE.** II Poletaeva, NA Ogienko, AD Suleimanova, OV Perepelkina, IV Koshlan, AV Revishchin**,** Moscow State University, Institute of Gene Biology RAS, Moscow, Joint Institute for Nuclear Research, Dubna, Moscow Region, Russia

**16.50-17.05** **DIFFERENTIAL CONTRIBUTION OF CONTEXTUAL AND DISCRETE CONDITIONAL STIMULI TO FEAR MEMORY RETRIEVAL IN RATS.** BT Varga, F Kassai, AJ Ernyey, A Gáspár, I Gyertyán, Semmelweis University, Department of Pharmacology and Pharmacotherapy, Cognitive Translational Behavioral Pharmacology Group, University of Veterinary Medicine, Institute for Biology, Budapest, Hungary

**17.05-17.20** **MANGANESE-INDUCED NEUROTRANSMISSION REMODELING.** IS Ivleva, TV Tyutyunnik, VA Maystrenko, MN Karpenko, VM Klimenko, I.P. Pavlov Department of Physiology, Institute of Experimental Medicine, St. Petersburg, Russia

**17.20-17.35** **REVERSE BEHAVIORAL PATTERN OF DAT-KO RATS UNDER PROGRESSIVE RATIO SCHEDULE OF REINFORCEMENT.** AA Savchenko, RR Gainetdinov and IM Sukhanov, Valdman Institute of Pharmacology, Pavlov First St. Petersburg State Medical University, Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia

**17.35-17.50** **BEHAVIORAL CHANGES IN THE DOPAMINE TRANSPORTER (DAT) HETEROZYGOTE RATS.** AR Gainetdinov, ZR Khismatullin, Department of Biology, Bashkir State University, Republic of Bashkortostan, Ufa, Russia

**17.50-18.05** **INVESTIGATION OF THE PHYSIOLOGICAL FUNCTIONS OF TRACE AMINE-ASSOCIATED RECEPTOR 9 (TAAR9).** RZ Murtazina, SR Kuvarzin, IS Zhukov, EV Efimova, OM Korenkova, NV Alenina, RR Gainetdinov, Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia, Max Delbrück Center for Molecular Medicine, Berlin, Germany

**18.05-18.20** **INTESTINAL MICROBIOTA AND MENTAL HEALTH. CAN PROBIOTICS HELP?** IN Abdurasulova, VM Klimenko, Pavlov Department of Physiology, Institute of Experimental Medicine, St. Petersburg, Russia

**18.20-18.35** **KINETIC ANALYSIS OF PHASIC DOPAMINE INCREASES IN THE RAT N. ACCUMBENS CORE AND SHELL CHANGING UNDER THE ACUTE INFLUENCE OF AMYLOID B 25-35.** V Mukhin, V Sizov, K Pavlov, I Borovets, VM Klimenko, Pavlov Department of Physiology, Institute of Experimental Medicine, St. Petersburg, Russia

**18.35-18.50** **THE DE RITIS RATIO AS A MARKER OF CATABOLIC AND ANABOLIC REACTIONS IN HYPERACTIVITY AND OBESITY.** SA Apryatin, MV Bolshakova, AL Manasyan, EK Turkeeva, VM Klimenko, Pavlov Department of Physiology, Institute of Experimental Medicine, St. Petersburg, Russia

**18.50-19.05** **THE INFLUENCE OF TREADMILL SPEED ON DIFFERENT LOCOMOTOR MODES OF DECEREBRATE CAT.** V Lyakhovetskii, N Merkulieva, O Gorskii, P Musienko, Pavlov Institute of Physiology RAS, Russian Scientific Center for Radiology and Surgical Technologies, St. Petersburg State University, St. Petersburg State Research Institute of Phthisiopulmonology, Ministry of Healthcare, St. Petersburg, Russia

# Day 2. Thursday, September 17, 2020

**Venue: Oktiabrskaya Hotel, 10 Ligovsky Prospect, St. Petersburg, Russia**

**10.00-11.30** **SYMPOSIUM 3: CLINICAL STRESS NEUROSCIENCE**
Chair: D Kozic (Serbia)

**10.00-10.15** **WORK STRESS INTERVENTIONS: RESILIENCE TRAINING, SYSTEM INTERVENTIONS AND LEADERSHIP BASED CHANGE.** JAK Erskine and GJ Georgiou**,** St George's, University of London and University of Hertfordshire, London, Hertfordshire, UK

**10.15-10.30** **SELF-STRESS MANAGEMENT IN THE WORKPLACE.** Ph Fauquet-Alekhine, B Guion de Meritens, SEBE-Lab, Department of Psychological and Behavioural Science, LSE, London, UK, Lab. for Research in Science of Energy, France, Nuclear Power Plant of Chinon, EDF-FARN (Nuclear Fast-Action Force), France

**10.30-10.45** **THE PSYCHOLOGICAL NATURE OF ALEXITHYMIA AND FUNCTIONAL CONNECTIVITY REORGANIZATION.** SV Tukaiev, TV Vasheka, ON Dolgova, Research Institute, National University of Physical Education and Sports of Ukraine, Kiev, Ukraine

**10.45-11.00** **GENDER DIFFERENCES IN EMOTION INDUCTION BY MANUPULATED FEEDBACK DURING DESICION MAKING TASK.** AT Kamzanova, V Pivkina, G Matthews, AM Kustubayeva**,** Center for Cognitive Neuroscience, al-Farabi Kazakh National University, Almaty, Kazakhstan, University of Central Florida, Orlando, USA

**11.00-11.15** **INITIALLY UNRECOGNIZED NEUROMYELITIS OPTICA SPECTRUM DISORDER WITH CONSEQUENT END-STAGE SPINAL CORD ATROPHY.** I Nosek, J Boban, D Vlahovic, B Radovanovic, D Tihomir, D Kozic**,** University of Novi Sad, Faculty of Medicine, Oncology Institute of Vojvodina, Novi Sad, Serbia

**11.15-11.30** **PREDICTION OF AUTONOMIC DYSFUNCTION TO MOTOR SEVERITY IN PARKINSON'S DISEASE IN SOUTHERN CHINESE.** C Cui, East Hospital, Tongji University School of Medicine, Shanghai, China

***11.30-11.45*** ***BREAK 1***

**11.45-12.05** **NOLDUS PRESENTATION: THE STANDARDIZATION PARADOX: BETTER DATA WITH NATURALISTIC BEHAVIORAL TESTS.** A Willemsen, Noldus IT, Wageningen, The Netherlands

**12.05-12.25** **BIOGEN-ANALYTICA PRESENTATION: MODERN ANIMAL CARE SYSTEMS (USA).** M Chemeris, Biogen-Analytica, LLC, Moscow, Russia

**12.25-16.20** **SYMPOSIUM 4: ZUKOWSKA STRESS NEUROSCIENCE SYMPOSIUM**
Chairs: AV Kalueff (China, Russia, USA) and VM Klimenko (Russia)

**12.25-12.35** **INTRODUCTION: PROFESSOR ZOFIA ZUKOWSKA**

**12.35-12.50** **MODERN IMAGING IN CLINICAL AND BEHAVIOURAL NEUROSCIENCE.** D Kozić, University of Novi Sad Faculty of Medicine, Novi Sad, Serbia

**12.50-13.05** **BLOOD-BASED LIPIDOMICS OF SCHIZOPHRENIA AND OTHER PSYCHIATRIC DISORDERS.** D Petrova, A Tkachev, Ph Khaitovich**,** Skolkovo Institute of Science and Technology, Moscow, Russia

**13.05-13.20** **MATERNAL HYPERHOMOCYSTEINEMIA DISRUPTS NEUROPIL FORMATION IN RAT HIPPOCAMPUS INDUCING MEMORY DEFICIT IN ADULTHOOD.** DS Vasilev, AD Shcherbitskaia, NL Tumanova, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia

**13.20-13.35** **MODULATION OF DETRUSOR MUSCLE AND EXTERNAL URETHRAL SPHINCTER ACTIVITY BY SITE-SPECIFIC ELECTRICAL STIMULATION OF RAT SPINAL CORD.** Y Sysoev, E Bazhenova, V Lyakhovetskii, G Kovalev, P Shkorbatova, N Pavlova, O Gorskii, N Merkulyeva, D Shkarupa, P Musienko, Institute of Translational Biomedicine, St. Petersburg State University, Department of Pharmacology and Clinical Pharmacology, St. Petersburg State Chemical-Pharmaceutical University, Pavlov Institute of Physiology RAS, Russian Research Center of Radiology and Surgical Technologies, Ministry of Healthcare, Clinic of High Medical Technologies, St. Petersburg State University, St. Petersburg, Russia

**13.35-13.50** **ACTIVATION OF STRESS- AND NEUROPLASTICITY-RELATED GENES IN THE HIPPOCAMPUS OF RATS FOLLOWING MORRIS WATER MAZE TRAINING.** PE Panchenko, HM Goss, KR Mifsud, EM Price, JMHM Reul, Neuro-Epigenetics Research Group, University of Bristol, Bristol Medical School, Bristol, UK

**13.50-14.05** **INTEGRATING ELEVATED PLUS MAZE AND DARK/LIGHT BOX TO DETECT ANXIETY-RELATED BEHAVIOR DUE TO SYNERGISTIC EFFECT OF PSYCHOSOCIAL STRESS IN OBESE MALE MICE.** C Baroni, C Spalletti, J Agrimi, V Casieri, M Caleo, V Lionetti, Sant'Anna School of Advanced Studies, Neuroscience Institute, National Research Council (CNR), Pisa, Italy

***14.05-14.35*** ***BREAK 2***

**14.35-14.50** **MOLECULAR ALTERATIONS IN BRAIN, BONE MARROW, TESTIS AND ADRENAL GLANDS OF STRESSED MICE.** MP Petrova, TS Glinin, VA Mamontova, V Shcherbinina, AB Volnova, PA Starshova, EV Daev, PE Khaitovich, CAS-MPG Partner Institute for Computational Biology, Shanghai Institutes for Biological Sciences CAS, Shanghai, China

**14.50-15.05** **ACUTE PAIN AS A POSSIBLE CAUSE OF A NEGATIVE STRESS REACTION THAT PROVOKES TACHYARRHYTHMIA IN ELDERLY PEOPLE.** VP Nesterov, AI Burdygin,

KB Ivanov, SA Filenko, SV Nesterov, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia

**15.05-15.20** **NOREPINEPHRINE AND SEROTONIN IN THE DIFFERENT REGIONS OF THE CENTRAL NERVOUS SYSTEM OF DAT -/- RATS.** NS Pestereva, DS Traktirov, AZ Marshak, VS Artemova, ZS Fisenko, MN Karpenko, VM Klimenko, Pavlov Department of Physiology, Institute of Experimental Medicine, Peter the Great St. Petersburg Polytechnic University, Institute of Translation Biomedicine, St. Petersburg State University, St. Petersburg, Russia

**15.20-15.35** **EMOTIONAL OVEREATING INDUCED BY BRAIN STIMULATON REWARD IN FREE-FED RATS.** NS Efimov, AA Lebedev, YuN Bessolova, ER Bychkov, VA Lebedev, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

**15.35-15.50** **ANTICONVULSANT PROPERTIES OF THE NEW GLUTAMATE NMDA-RECEPTOR COMPLEX ANTAGONISTS – 1,2-SUBSTITUTED IMIDAZOL-4,5-DICARBOXYLIC ACIDS.** EE Jakovleva, SP Foksha, MA Brusina, LG Kubarskaja, LB Piotrovskij, ER Bychkov, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

**15.50-16.05** **ROLE OF THE GRELIN SYSTEM IN ANXIETY AND STABILITY OF THE PERIPHERAL BLOOD GENOME AFTER VITAL STRESS.** GP Kosyakova, AG Pshenichnaya, KE Gramota, IV Kazurov, VA Lebedev, Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg State University of Chemical Pharmaceuticals, St. Petersburg, Russia

**16.05-16.20** **DYNAMICS OF GLUTAMATE METABOTROPIC RECEPTOR GENES EXPRESSION IN THE RAT BRAIN IN THE MODEL OF TEMPORAL LOBE EPILEPSY.** AA Kovalenko, MV Zakharova, AP Schwarz, OE Zubareva, AV Dyomina, AV Zaitsev, Sechenov Institute of Evolutionary Physiology and Biochemistry, St. Petersburg, Russia

**16.20-17.20** **SYMPOSIUM 5: ZNRC ZEBRAFISH NEUROSCIENCE SYMPOSIUM**
Chair: AV Kalueff (Russia, USA, China)

**16.20-16.35** **METHODS FOR MODELING PTSD IN ZEBRAFISH: A PILOT STUDY.** AV Zhdanov, SL Khatsko, KN Zabegalov, AV Kalueff, Ural Federal University, Yekaterinburg, Russia

**16.35-16.50** **NON-PHARMACOLOGICAL AND PHARMACOLOGICAL APPROACHES FOR PSYCHIATRIC DISORDERS FROM ZEBRAFISH MODELS.** MS de Abreu, ACVV Giacomini, R Genario, N Rech, J Carboni, AM Lakstygal, TG Amstislavskaya, KA Demin, BE Leonard, M Vlok, BH Harvey, A Piato, LJG Barcellos and AV Kalueff, Bioscience Institute, Postgraduate Program in Environmental Sciences, University of Passo Fundo, Passo Fundo, Brazil, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Center, St. Petersburg, Institute of Physiology and Basic Medicine, Novosibirsk, Russia, University College Galway, Pharmacology Department, Galway, Ireland, Center of Excellence for Pharmaceutical Sciences, School of Pharmacy, North-West University, Potchefstroom, South Africa, Postgraduate Program in Neurosciences, Federal University of Rio Grande do Sul, Porto Alegre, Postgraduate Program in Pharmacology, Federal University of Santa Maria, Santa Maria, Brazil, School of Pharmacy, Southwest University, Chongqing, China

**16.50-17.05** **MODELING ANTIDEPRESSANT DISCONTINUATION SYNDROME (ADS) VIA REPEATED WITHDRAWAL FROM PAROXETINE TREATMENT IN ZEBRAFISH.** KN Zabegalov, AV Zhdanov, SL Khatsko, and AV Kalueff, Ural Federal University, Ekaterinburg, Russia, School of Pharmacy, Southwest University, Chongqing, China

**17.05-17.20** **DEEP LEARNING-BASED APPLICATION FOR PREDICTION OF DRUG-INDUCED BEHAVIOR IN ZEBRAFISH.** DV Bozhko, GK Galumov, AI Polovjan, SM Kolchanova, VO Myrov, VA Stelmakh and AV Kalueff, ZebraML, St. Petersburg, Russia, School of Biological Sciences, University of Queensland, Queensland, Australia, Neuroscience Center, Helsinki Institute of Life Science, University of Helsinki, Helsinki, Finland, Department of Neuroscience and Biomedical Engineering, Aalto University, Helsinki, Finland, Skolkovo Institute of Science and Technology, Center of Life Sciences, Moscow, Russia, School of Pharmacy, Southwest University, Chongqing, China

# Day 3. Friday, September 18, 2020

**Venue: Oktiabrskaya Hotel, 10 Ligovsky Prospect, St. Petersburg, Russia**

**10.00-13.00 CONFERENCE POSTER SESSION**

**FIGHT, FLIGHT OR FREEZE? MECP2 INVOLVEMENT IN CHOOSING THE STRATEGY TO COPE WITH STRESS.** L Cosentino, F Zidda, S Witt, L Di Crescenzo, H Flor, B De Filippis, Center for Behavioral Sciences and Mental Health, Istituto Superiore di Sanità, PhD Program in Behavioral Neuroscience, Sapienza University of Roma, Italy, Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

**MORPHOLOGICAL ANALYSIS OF THE HUMAN STRIATAL NEURONS FOLLOWED BY A REVIEW OF THEIR ROLE IN MEDIATING BEHAVIOR.** B Krstonošić, NT Milošević, R Perić, University of Novi Sad, Faculty of Medicine, Department of Anatomy, Novi Sad, Serbia

**MODELING WITHDRAWAL FROM CHRONIC PAROXETINE TREATMENT IN ZEBRAFISH.** KN Zabegalov, SL Khatsko, MV Bytov, I Yushchenko, and AV Kalueff, Ural Federal University, Ekaterinburg, Russia, School of Pharmacy, Southwest University, Chongqing, China

**NEUROCHEMISTRY OF THE ZEBRAFISH TAIL IMMOBILIZATION EXPOSURE.** NA Krotova, KA Demin, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare, St. Petersburg, Russia

**DOSE-DEPENDENT EFFECTS OF SERTRALINE EXPOSURE IN ZTI ASSESSED USING AUTOMATED BEHAVIORAL VIDEO-TRACKING.** NA Levchenko, AS Taranov, NP Ilyin, KA Demin, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare, St. Petersburg, Russia

**BIDIRECTIONAL EFFECTS OF RESERPINE ON DESPAIR-LIKE BEHAVIOR IN THE ZEBRAFISH TAIL IMMOBILIZATION TEST.** M Seredinskaya, KA Demin, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare, St. Petersburg, Russia

**IL-1RA THERAPY PARTIALLY PREVENTED EPILEPTOGENESIS AND BEHAVIORAL DYSFUNCTION IN RATS IN THE LITHIUM-PILOCARPINE MODEL OF TEMPORAL LOBE EPILEPSY.** AV Dyomina, OE Zubareva, IV Smolensky, AA Karepanov, AM Ishchenko, AV Zaitsev, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, Research Institute of Highly Pure Biopreparations, Federal Medical-Biological Agency, St. Petersburg, Russia

**INVESTIGATION THE DOPAMINERGIC CONTROL OF POSTURAL FUNCTION.** D Kalinina, O Gorsky, V Lyakhovetskii, N Pavlova, R Gainetdinov, P Musienko, Institute of Translational Biomedicine, St. Petersburg State University, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, Russian Research Center of Radiology and Surgical Technologies, Ministry of Healthcare, Pavlov Institute of Physiology RAS, St. Petersburg, Russia

**THE INFLUENCE OF SOBER OR DRINKING RAT CAGE MATES ON ALCOHOL PREFERENCE.** EV Filatova, IV Demynko, SV Afanasyev, AA Orlov, AY Egorov, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia

**BEHAVIORAL CHANGES CAUSED BY BISPHENOL A IN RESPONSE TO AN AVERSIVE STIMULUS IN FEMALE RATS.** NK Apraksina, IO Suchkova, TV Avaliani, NI Dergacheva, EL Patkin, SG Tsikunov, Pavlov Department of Physiology, Institute of Experimental Medicine, St. Petersburg, Russia

**THE EFFECT OF VITAL STRESS ON ANXIETY AND BRAIN GENOME WIDE DNA METHYLATION OF MALE RATS.** NK Apraksina, TV Avaliani, IO Suchkova, NI Dergacheva, EL Patkin, SG Tsikunov, Pavlov Department of Physiology, Institute of Experimental Medicine, St. Petersburg, Russia

**BLOOD CATALASE CONTENT IN CHILDREN WITH VARIOUS FORMS OF AUTISM SPECTRUM DISORDERS.** EM Malsagova, IS Ivleva, VA Maistrenko, SG Belokoskova, and SG Tsikunov, Pavlov Department of Physiology, Institute of Experimental Medicine, St. Petersburg, Russia

**SERUM CYTOKINES LEVELS IN PATIENTS WITH PARKINSON'S DISEASE AND ESSENTIAL TREMOR.** ZM Muruzheva, DO Sholokhova, DS Traktirov, IS Ivleva, VA Maystrenko, MN Karpenko, VM Klimenko, Pavlov Department of Physiology, Institute of Experimental Medicine, Peter the Great St. Petersburg Polytechnic University, St. Petersburg, Russia

**THE EFFECTS OF GLIBENCLAMIDE ADMINISTRATION ON CNS CELLS IN NORMAL CONDITIONS AND UNDER ENDOTOXEMIA.** AS Zubov, AG Karaev, TV Tiutiunnik, MN Karpenko, VM Klimenko, Institute of Experimental Medicine, St. Petersburg Chemical Pharmaceutical University, Peter the Great St. Petersburg Polytechnic University, St. Petersburg, Russia

**LINGERING EFFECT OF CHRONIC SLEEP RESTRICTION ON LONG-TERM MEMORY IN RATS.** MA Guzeev, NC Kurmazov, VV Simonova, YuF Pastukhov, IV Ekimova, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia

**INVESTIGATION OF CHRONIC SLEEP RESTRICTION EFFECT ON EMOTIONAL BEHAVIOUR IN RATS.** MB Pazi, KV Lapshina, DV Belan, MV Chernishev, IV Ekimova, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia

**EFFECTS OF MELANOCORTIN MC4 RECEPTOR ANTAGONIST ML00253764 ON THE EMOTIONAL BEHAVIOR AND CONDITIONED PLACE PREFERENCE OF ETHANOL IN RATS.** ME Abrosimov, EA Vetlugin, AR Moskalev, AG Pshenichnaya, IYu Tissen, KB Abasova, PP Khokhlov, ER Bychkov, AA Lebedev, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

***11.45-12.00 BREAK***

**THE ALCOHOL WITHDRAWAL CHANGES EXPRESSION OF GENES OF TOLL-LIKE RECEPTORS IN THE STRUCTURES OF THE RAT BRAIN.** MI Airapetov, SO Eresko, ER Bychkov, AA Lebedev, PD Shabanov, Institute of Experimental Medicine, St. Petersburg State Pediatric Medical University, National Research ITMO University, St. Petersburg, Russia

**THE EXPRESSION OF POSTSYNAPTIC DENSITY PROTEIN-95 IN THE STRIATUM IN RAT MODEL OF PARKINSON'S DISEASE AND LEVODOPA-INDUCED DYSKINESIA.** ER Bychkov, EV Gurevich, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia, Vanderbildt University, Nashvile, USA

**EFFECTS OF CHRONIC TREATMENT WITH DOPAMINERGIC DRUGS ON ERK SIGNALING IN PARKINSONIAN RATS.** ER Bychkov, EV Gurevich, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

**ASSESSMENT OF DOSE-DEPENDENT EFFECTS OF ANXIOLYTIC DIAZEPAM IN DANIO RERIO.** AS Devyashin, AA Blazhenko, VA Lebedev, AA Lebedev, ER Bychkov, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

**FEATURES OF THE INVOLVEMENT OF THE DOPAMINE AND SEROTONIN BRAIN SYSTEMS IN POSITIVE AND NEGATIVE EMOTIONAL STATES IN RATS.** NS Efimov, ER Bychkov, AA Lebedev, IV Karpova, AE Kryukov, SS Pyurveev, NS Pavlov, BB Daliev, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

**EFFECTS OF NEW COUMARIN COMPOUNDS ON BEHAVIOR IN RATS.** AO Kashirin, AG Pshenichnaya, ER Bychkov, VA Lebedev, AA Lebedev, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

**ROLE OF OREXIN IN THE KARIOTYPIC STABILITY OF PERIPHERAL BLOOD MONONUCLEARS AND OBSESSIVE-COMPULSIVE BEHAVIOR IN ALCOHOLIZED RATS.** GP Kosyakova, IYu Tissen, PV Shalyapin, VA Lebedev, Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg State University of Chemical Pharmaceuticals, St. Petersburg, Russia

**ACTIVATION OF MITOCHONDRIAL KATP CHANNEL WITH URIDINE CAN LIMIT THE MYOCARDIAL STRESS CAUSED BY POSTISCHEMIC REPERFUSION.** IB Krylova, EN Selina, VV Bul'on, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

**CONSEQUENCES OF HYPOXIC-ISCHEMIC DAMAGE IN THE BRAIN OF INFANT RATS.** NN Kuznetsova, Institute of Experimental Medicine, St. Petersburg, Russia

**EFFECTS OF KRAMIZOLE ON THE EXPRESSION OF APO A-I, ApoC2, and SR-B1 GENES IN THE RAT'S HYPERCHOLESTEROL DYSLIPIDEMIA MODEL.** AV Lizunov, IV Okunevich, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of the Experimental Medicine, St. Petersburg, Russia

**THE EFFECTS OF KRAMIZOLE AND PHENOFIBRATE DRUGS ON TRYGLICERIDES IN RATS, TREATED WITH CHOLESTEROL DIET.** AV Lizunov, IV Okunevich, GP Kosyakova, LB Piotrovskiy, PD Shabanov, Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

**MECHANISMS OF NEUROADAPTATION TO ACUTE STRESS INFLUENCE: UNEXPECTED EXPERIMENTAL DATA.** AV Lyubimov, IYu Thyssen, PP Khokhlov, AA Lebedev, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

**PHARMACOLOGICAL ANALYSIS OF THE EFFECT OF THE Y1R ANTAGONIST NEUROPEPTIDE Y BMS 193885 ON THE EMOTIONAL, INTRASPECIFIC BEHAVIOR AND REINFORCING PROPERTIES OF ETHANOL IN RATS.** AR Moskalev, ME Abrosimov, EA Vetlugin, AG Pshenichnaya, IYu Tissen, AS Ivankov, ER Bychkov, NR Evdokimova, AA Lebedev, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

**PROTECTIVE ACTION OF TAUREPAR, URIDINE AND ITS NUCLEOTIDES UNDER FORCED SWIMMING AND COLD EXPOSURE.** AF Safonova, OM Rodionova, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

**LOPERAMIDE AND LACTITOL INTENSIFY THE PHYSICAL ENDURANCE OF RATS DURING EMOTIONAL-PHYSICAL STRESS.** AF Safonova, IB Krylova, KA Shemerovsky, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

**ANXIOLYTIC AND ANTIADDICTIVE EFFECTS OF MELANIN CONCENTRATING HORMONE ANTAGONIST 1R SNAP 94847 IN RATS.** EA Vetlugin, ME Abrosimov, AR Moskalev, AG Pshenichnaya, IYu Tissen, KG Konkova, PP Khokhlov, ER Bychkov, AA Lebedev, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

**DISTRIBUTION OF LAYER-SPECIFIC MARKERS IN HUMAN NEOCORTEX DURING THE SECOND HALF OF GESTATION.** EA Kozubenko, NA Sidorova, LA Tkachenko, PA Zykin, EI Krasnoshekova**,** St. Petersburg State University, Russia, St. Petersburg State Pediatric Medical University, St. Petersburg, Russia

**DETERMINATION OF THE OPTIMAL CONCENTRATION OF THE PROTEIN-ANTIGEN COMPLEX FOR THE DETECTION OF CORTISOL BY IMMUNOCHROMATOGRAPHY.** EV Panfilova, Institute of Biochemistry and Physiology of Plants and Microorganisms RAS, Saratov, Russia

**ACUTE BEHAVIORAL EFFECTS OF ASPIRIN (ACETYLSALICYLIC ACID) IN ADULT ZEBRAFISH.** DS Galstyan, KA Demin, TO Kolesnikova, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Ural Federal University, Ekaterinburg, Russia, School of Pharmacy, Southwest University, Chongqing, China

**SCHIZOPHRENIA - MINOR PHYSICAL ANOMALIES OF HANDS AND FEET.** S Zigic, B Srdic Galic, SS Babovic, S Lovrencic, DJ Siladji Mladenovic, Z Gajic**,** University of Novi Sad, Faculty of Medicine, Serbia

**DELAYED EFFECT OF ACUTE HYPOBARIC HYPOXIA ON ABSENCE EPILEPSY.** KR Abbasova, EA Volkova. Department of Human and Animal Physiology, School of Biology, Lomonosov Moscow State University, Moscow, Russia

**12.50-13.00 CONFERENCE CLOSING**

# ABSTRACTS

## Day 1. Wednesday, September 16, 2020

**Venue: Oktiabrskaya Hotel,10 Ligovsky Prospect, St. Petersburg, Russia**

**EVALUATING THE PROTECTIVE EFFECTS OF DIOSGENIN ON THE AGING PROCESSES IN RATS WITH ACCELERATED SENESCENCE.** TG Amstislavskaya, MA Tikhonova, Y-J Ho, Scientific Research Institute of Physiology and Basic Medicine, Novosibirsk, Russia. **INTRODUCTION:** Oxidative stress and reactive oxygen species (ROS) have been proposed as major causes of aging, age-related neurodegeneration and cognitive decline (Olanow, 1993; Valko et al., 2007). Such age-related disturbances can be ameliorated by antioxidants. Diosgenin is an important bioactive ingredient of dioscorea, widely used in Chinese medicine. It shows an anti-oxidant activity and improves some aging-related deficits in senescent and menopausal animals. Here, we aimed: 1) to compare alterations in behavior, biochemical parameters, and sperm motility in D-galactose-induced aging Wistar male rats with that in OXYS male rats; 2) to examine the protective effects of the natural-derived antioxidant diosgenin on these aging models. **METHODS:** We compared alterations in behavior, biochemical parameters, and sperm motility in two models of accelerated senescence: 1) D-galactose-induced (150 mg/kg/d, i.p., 57 days) aging in Wistar rats vs. 2) genetically defined in OXYS rats and examined the protective effects of diosgenin (10 or 50 mg/kg/d, p.o., 57 days). **RESULTS AND DISCUSSION:** Both models had augmented levels of ALT activity indicating hepatopathology. Compared to D-galactose-treated animals, OXYS rats are a superior aging model since they demonstrated profound biochemical alterations (hypocalcemia, hypophosphatemia, and hypocholesterolemia) and behavioral deficits (impaired object recognition, decreased sexual motivation and locomotor activity, retarded learning) typically seen in old individuals. We first showed diminished sperm motility in males of both models of accelerated senescence studied. **CONCLUSION:** Chronic diosgenin treatment at doses used failed to improve biochemical and behavioral disturbances and had some undesirable side effects on body weight and working memory in OXYS rats. However, diosgenin restored moderately decreased sperm motility in D-galactose-treated Wistar males and might be recommended for treatment of mild age-related reproductive dysfunctions. We suggest that this effect may be attributed to diosgenin effects on hormonal systems; diosgenin has a similar chemical structure to sex hormones and has long been used as a precursor in the manufacture of steroid hormones, such as estrogen, progesterone, testosterone and cortisol (Djerassi, 1992). **RESEARCH SUPPORT:** Bilateral Russian-Taiwanese grant 11-04-92009-HHC_a from the Russian Foundation for Basic Research (RFBR).

**MECHANISMS OF HIPPOCAMPAL NEUROGENESIS INDUCED BY A TRAUMATIC BRAIN INJURY.** TG Amstislavskaya, YL Yang, MA Tikhonova, KT Lu, Novosibirsk State University, Novosibirsk, Russia, National Chia-Yi University, Chia-Yi, Taiwan, National Taiwan Normal University, Taipei, Taiwan. **INTRODUCTION:** Traumatic brain injury (TBI) is one of the most prevalent causes of morbidity and mortality all over the world and apparently has consumed an enormous social cost and economic burden. It has been proven that TBI can induce the neurogenesis in the forebrain through the stimulation of neuronal progenitor cells in mammals and thus initiate neuroregeneration of damaged cells of the adult brain. Among the proteins involved in the regulation of neurogenesis, the search for those that may become potential targets for pharmacotherapy is relevant. Thus, the study of signaling pathways, which play a key role in the processes of neurogenesis in neurotrauma, becomes an urgent task. Here, we studied the detailed mechanisms related to Na-K-2Cl cotransporter (NKCC1) upregulation in hippocampus. **METHODS:** A conventional weight drop device was used to induce focal impact in the rat for inducing TBI. The TBI-associated alternations in the expression of NKCC1, HIF-1α, VEGF, MAPK cascade, and CREB phosphorylation were analyzed by Western blot. TBI-induced neurogenesis was determined by immuno-fluorescence labeling. Chromatin immunoprecipitation was used to elucidate whether HIF-1α would activate VEGF gene after TBI. **RESULTS AND DISCUSSION:** We found that the level of hippocampal NKCC1 and VEGF began to rise 8 h after TBI, and both of them reached maxima at day 7. Along with the upregulation of NKCC1 and VEGF, MAPK cascade was activated and hippocampal neurogenesis was promoted. Administration of CREB antisense oligonucleotide significantly attenuated the expression of HIF-1α, while HIF-1α antisense oligonucleotide exhibited little effect on the expression of CREB. However, HIF-1α antisense oligonucleotide administration effectively reduced the expression of VEGF. The chromosome immunoprecipitation also indicated that HIF-1α could directly act on the VEGF promoter and elevate the VEGF expression after TBI. All these results evidenced the correlation between NKCC1 upregulation and TBI-associated neurogenesis. The pathway involves the activation of Raf/MEK/ERK cascade, CREB phosphorylation, and HIF-1α upregulation, and

finally leads to the stimulation of VEGF expression and the induction of neurogenesis. **RESEARCH SUPPORT**: Partially supported by the Russian Science Foundation grant 20-65-46006.

**NEURONAL FUNCTION AND PHARMACOLOGY OF TRACE AMINE-ASSOCIATED RECEPTORS (TAARS).** RR Gainetdinov, Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia. **INTRODUCTION:** Trace amines are endogenous compounds classically regarded as composing beta-phenylethyalmine, p-tyramine, tryptamine, p-octopamine, and some of their metabolites. They are also abundant in common foodstuffs, and can be produced and degraded by the constitutive microbiota. The ability to utilize trace amines has arisen at least twice, with unrelated receptor families present in invertebrates and vertebrates. The term trace amine was coined to reflect the low tissue levels in mammals, however, in invertebrates relatively high levels are present where they serve the role of an invertebrate adrenergic system involved in “fight or flight” responses. Vertebrates express a family of receptors termed trace amine-associated receptors (TAARs). Humans possess 6 functional receptors: TAAR1, TAAR2, TAAR5, TAAR6, TAAR8 and TAAR9. With the exception of TAAR1, all other TAAR are expressed in olfactory epithelium neurons, where they detect diverse ethological signals. **METHODS:** Results from studies involving mutant animals lacking TAARs will be discussed. **RESULTS AND DISCUSSION:** Outside the olfactory system TAAR1 is the most thoroughly studied with both central and peripheral roles. TAAR1 has been already identified as a novel therapeutic target for several neuropsychiatric disorders, including schizophrenia and depression. Among other TAARs, TAAR5 represents the most interest as regard to schizophrenia and depression since it is expressed in limbic brain areas and TAAR5 knockout mice have remarkable alterations in emotional behaviors. Further investigations of TAARs by using knockout animals and identification of natural and synthetic ligands of these receptors could bring new approaches for the treatment of neuropsychiatric disorders. **RESEARCH SUPPORT:** Project ID: 51143531 of St. Petersburg State University, St. Petersburg, Russia.

**METRIS PRESENTATION: LABORAS SYSTEM APPLICATION FOR MOTOR BEHAVIOR IN ASSESSMENT OF THE ZINC SUCCINATE TOXIC EFFECT.** R Bulthuis, L Bachdasarian, G Piavchenko, Metris B.V., Hoofddorp, The Netherlands, Sechenov University, R&D Pharmaceutical CJSC “Retinoids”, Moscow, Russia. **INTRODUCTION:** The presented morpho functional approach for the toxicity evaluation included the study of behavioral responses using the automated Laboras complex, histological evaluation of animal organs and tissues: social affiliation/motivation, as well as social memory and novelty. Motor cortex in rats is the main source of activating impulses to the motor neurons of the spinal cord, being the region of the motor response initiation. The signals sent by certain parts of the motor cortex stimulate the motor activity in one or another part of the body, indicating the presence of the activating effect projection zones. Structurally it represents an agranular type of the cortex and has the predominantly expressed III and V layers, which contain large and giant pyramid neurons. These cells send the impulses downstream for the signal transduction. Morphological analysis of organs and tissues is the golden standard for the investigation of systemic toxicity. Along with the routine morphology, an effective method for evaluation of the chemical substance action on the organism is the evaluation of the behavioral reactions of animals. In this study implementing a complex morpho-functional approach, we evaluated the behavioral and structural changes in the organs and tissues of male Wistar rats 1 month after intragastric administration of zinc succinate at a single dose of 100 mg/kg. Along with a significant decrease in motor activity, histological analysis revealed the presence of toxic and dystrophic processes in the cerebral cortex, heart, lungs and liver of the exposed animals. **METHOD:** The study of motor activity in rats was performed on validated Laboras device (Metris, The Netherlands), which is an automated, non-invasive system for recognition and analysis of such behavioral responses as motion, immobility, vertical stand, grooming, water and food intake, locomotion as well as the parameters of motor activity (i.e. the distance travelled, speed of motion, etc.). The animals were euthanized by inhalation of CO2 in the gas chamber, and brain was collected to perform morphological assessment of the intragastric zinc succinate administration effects on the organism. Organ samples were fixed in Carnoys fluid and embedded in paraffin. 5 µm-thick sections were stained with 1% cresyl violet aqueous solution with acetate buffer (56°C) for 20 minutes (for brain sections). **RESULTS:** A decrease in motor activity was noted in all animals from the experimental group in comparison to the controls, which clearly indicates the inhibitory effect of intragastric administration of zinc succinate at the chosen concentration on the behavioral activity in rats. After studying the behavioral reactions and brain was performed in animals. The corresponding organs of intact animals served as control. Morphological analysis of the internal organs demonstrated pronounced structural changes in rats treated with zinc succinate in comparison to the intact animals. Thus, when the motor cortex was studied in intact animals, the neurons were predominantly of pyramidal form, their bodies in most cases look rounded, the cytoplasm was faintly stained and had the appearance of a narrow rim containing basophilic granules with poorly outlined contours. The analysis of the brain structures in animals treated with zinc succinate showed that the soft meninx could be traced in the form of small fragments, and the vessels were mostly full-blooded. In some areas, the expansion of the perivascular space was visualized. The overall brain histoarchitecture was normal. Most of the neurons were stained pale, rounded, with a swelling noted in some of them, and a small number of neurons presented in the form

of shadow cells. Small glial cells with hyperchromic, intensely stained nuclei were observed. No signs of neurophagy were observed. **CONCLUSION:** Thus, the morphological analysis of organs and tissues in rats treated with zinc succinate at a single intragastric dose of 100 mg/kg compared with animals of the control group clearly demonstrated toxic and dystrophic changes in the structures of the brain 1 month after treatment. Our study demonstrated a decrease in motor activity in rats of the experimental group.

## SYMPOSIUM 1: LAPIN SYMPOSIUM ON NEUROPSYCHOPHARMACOLOGY

Chairs: AV Kalueff (China, Russia, USA) and PD Shabanov (Russia)

**INTRODUCTION: PROFESSOR IZYASLAV LAPIN.** This regular ISBS symposium is dedicated to Professor Izyaslav 'Slava' P. Lapin (1930-2012), a true pioneer of experimental neuro-psychopharmacology and biological psychiatry. Prof. Lapin graduated from Pavlov Medical School in St. Petersburg, and shortly after receiving PhD, was invited in 1960 to establish the first psychopharmacology laboratory at the Bekhterev Psychoneurological Institute. The most important scientific contribution of Prof. Lapin was establishing the link between serotonin levels and mood-elevating (thymoleptic) action of antidepressants. He suggested that enhanced central serotonergic tone is essential for the mood-elevating effects of antidepressants. This serotonin hypothesis of antidepressant action, published (together with G Oxenkrug) in Lancet in 1969, became one the most cited papers published in this journal in the last 50 years. Lapin's studies have contributed greatly to the development of newest serotonergic antidepressants, such as SSRIs, currently representing the most prescribed group of psychotropic drugs in the world. Prof. Lapin was also the first to report the neuroactive effects of kynurenine and its derivatives – a discovery that opened another rapidly expanding area of glutamatergic psychopharmacology. A talented professional musician, prolific writer, painter, and an enthusiastic athlete, Prof. Lapin was a strong supporter of ISBS, and generously shared his knowledge with colleagues and students at our "Stress and Behavior" conferences and ISBS summer schools. His enthusiasm, friendship, generous support of junior colleagues, and the deep knowledge as both a clinical and experimental neuropharmacologist ('humanists' and 'animalists', as he called them), made a long-lasting impact on his colleagues and students. This ISBS symposium will continue Lapin's scientific legacy in the field of biological psychiatry and translational neuroscience.

**NEURONAL ROLE OF TRACE AMINE-ASSOCIATED RECEPTOR 2 (TAAR2).** EV Efimova, SR Kuvarzin, NV Katolikova, D Smirnova, AA Kozlova, MS Mor, RR Gainetdinov**,** Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia. **INTRODUCTION:** Trace amines are structurally close to classical monoamine neurotransmitters and can play an important role in the disorders like anxiety and depression. But functions of these amines and their GPCR receptors are still remain unknown. The trace amine system may represent a great interest for the study of pathology of brain diseases, as well as for the development of new approaches for their therapy. The understanding of the functional role beyond olfaction of a member of trace amine-associated receptor (TAAR) subfamily TAAR2 can be important in general for understanding the brain organization and function. The aim of our study was to identify a functional role of TAAR2 receptors and characterise their contribution to the behavior, physiology and brain neurochemistry in mice. **METHODS:** TAAR2 knockout (TAAR2-KO) mice were used in this study. Littermate mice on C57/Bl6 background were used for the experiments. Mice were provided with food and water ad libitum and were housed in a standard 12h:12h light-dark cycle. Expression pattern of TAAR2 was analysed by assessing LacZ staining in knockout animals. we performed behavioral studies, measured monoamine level in several brain structures and assessed mRNA expression levels by rtPCR. **RESULTS AND DISCUSSION:** We found, that TAAR2 is expressed in several brain regions including hippocampus, cerebellum, cortex, rahpe nuclei and habenula. TAAR2-KO mice showed no change in locomotor activity or anxiety. In forced swimming test knockout animals had significantly lower immobilization time, indicating that they have reduced depression-like symptoms. Also, open field with novel object test showed that TAAR2-KO mice have sniffed novel objects longer than wild-type mice, that can be a sign of less fear and stress or changes in their memory. Furthermore, TAAR2-knockout animals had significantly lower body temperature and higher temperature change after stress. HPLC-EC analysis of tissue monoamines levels showed some interesting changes in the levels of monoamines in the striatum. In particular, TAAR2 knockout animals had significantly higher level of dopamine in the striatum tissue. In addition, knockout animals had lower level of norepinephrine in hippocampus. No changes in monoamine levels in the cortex, hypothalamus and olfactory bulb was found. We also found that levels of monoamine metabolizing enzyme MAOB expression measured by rtPCR in midbrain and striatum was significantly lower in TAAR2 knockout mice. **CONCLUSION:** TAAR2

is expressed in several limbic brain areas involved in emotional behaviors. TAAR2-KO mice show significant alterations in the behavioral tests and brain neurochemistry, having reduced level of depression-like behaviour and changes in brain dopamine and norepinephrine systems. **RESEARCH SUPPORT:** The Russian Science Foundation (RSF) grant 19-75-30008.

**EXPERIMENTAL MODELING OF DOUBLE DIAGNOSIS: ANXIETY DISORDER AND ALCOHOLISM.** AY Egorov, IV Demyanko, AE Veraksa, EV Filatova, I.M. Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, I.I. Mechnikov North-West State Medical University, St. Petersburg State University, St. Petersburg, Russia. **INTRODUCTION:** Experimental models of anxiety disorders and alcoholism in animals can give an idea of the brain mechanisms of the formation of this pathology, which, in turn, will help optimize approaches to the treatment of this category of patients. The goal of the study was to create an experimental model of dual diagnosis: anxiety disorder using the example of OCD and the formation of alcohol preferences in rats. **METHODS:** The experiment was performed on 49 Wistar male rats, of which 29 individuals from the 9th to the 16th day after birth were injected with clomipramine at a dose of 15 mg / kg daily, and the remaining 20 were injected with saline in the same volume. At the age of 2 months, different behavioral parameters were evaluated in all rats in the tests “Marble burring”, “Sound reaction” and “Open field”, as well as the preference for alcohol in the “Two bottle test”. After the first control test, rats were randomized into 4 groups. Rats receiving clomipramine in the postnatal period were divided into a group subjected to semi-forced alcoholization - clomipramine + alcohol (CA) and a group that drank water - clomipramine + water (CW). Rats that received saline in the postnatal period were also divided into groups; alcohol drinkers were saline + alcohol (SA), and the group that drank water - saline + water (SW). The following tests were carried out on the 4th and 8th weeks of the experiment. **RESULTS AND DISCUSSION:** Rats of the experimental group, postnatally treated with clomipramine, showed an increased level of anxiety in the tests “Instillation of glass balls”, “Open field” and “Reaction to sound”. In addition, in this group of rats, a preference for alcohol was revealed even before the start of alcoholization. After 4 weeks of alcoholization, the CA group reliably prefers alcohol more than the CW and SW groups. By the 8th week, all three experimental groups significantly preferred alcohol than rats of the SW group. The data obtained indicate that after a month of forced alcoholization, the fact of alcohol consumption itself becomes an important factor in the formation of ethanol preference along with the anxiety behavior caused by postnatal administration of clomipramine.The proposed experimental model demonstrates that anxiety disorder can contribute to the further development of alcoholism. In the process of alcoholization, the preference for ethanol is associated with both the anxiety disorder factor and the semi-forced alcoholization factor itself, and their combined effect is most pronounced after a month of experiment. **RESEARCH SUPPORT:** RF State Assignment topic AAAAA-A18-118012290373-7.

**EFFECT OF HORMONAL AND NON-HORMONAL CORRECTORS ON SEXUAL MOTIVATION IN RATS AFTER CHRONIC SOCIAL ISOLATION.** IYu Tissen, LA Magarramova, AS Kraskova, AA Lebedev, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** Social isolation in early life deregulates the serotonergic system of the brain, compromising reproductive function via gonadotropin-inhibitory hormone (GnIH) neurons. It is known that kisspeptin stimulates secretion of gonadotrophin releasing hormone (GnRH).The aim of this study was to examine the effects of social isolation on sexual motivation behavior in male rats and trying to correct them with hormonal and non-hormonal regulators. **MATERIALS AND METHODS:** 60 copulation naive male Wistar rats (100 days, 250g) were used, divided into 6 groups. Control animals were intact. In the other groups, the rats were housed in conditions of full social and partial sensory isolation since the 17$^{th}$ up to the age of 100 days. Control animals were administrated with saline while the remaining groups were administrated with Buserelin acetate 2µg/µl intranasally 20 µl, Kisspeptin-10 0.15µg/µl intranasally 20 µl, Kisspeptin-10 0.15µg/µl intraperitoneally 200 µl and Yoquimbine HCl 1mg/ml intraperitoneally 200 µl. Open-field reward-proximity chamber was used for assessment of the appetitive behaviors for sexual reward. The front perforated wall allowed the subjects to approach and investigate estrous female in the chamber but prevented tactile contact or copulation. Male’s behaviour was registrated in the dark room with red light for 10 minutes. Blood samples were collected at 30 min following the substance administration from tail vein. Testosterone concentrations in serum were measured by solid-phase ELISA. **RESULTS AND DISCUSSION:** Social isolation didn't significantly act on latent time before trying to reach the female (11,2±9,6 vs 8,0±4,5 s in control). Intranasal administration of buserelin and intraperitoneal administration of kisspeptin-10 and Yoquimbine HCl did not act on latent time before trying to reach the female Intranasal administration of kisspeptin-10 reduced latent time (5,3±1,7s). Social isolation did not alter the number of attempts to reach a female (11,6±3,0 vs 13,8±3,1 in control). Buserelin acetate haven't any significant effects. Both Kisspeptin-10 forms and Yoquimbine induced trying to reach the female (17,5±3.5 Kiss-10 I/N , 19,3±3.9Kiss-10 I/P , 21,7±6,6Yoquimbine). Social isolation decrease testosterone level twice (7,5±2,9 vs 14,5±6,2 nmol/ml in control). Buserelin acetate and intraperitoneal kisspeptin-10 administration restore testosterone level about control counts (19,5±4,3 and 13,6±4,2 nmol/ml). No significant differences in testosterone level were found after kisspeptin-10 intranasal and Yoquimbine administration. These data show that the effect of social isolation affects hormonal status

more than sexual motivation per se. This provides the preconditions for finding new mechanisms underlying the regulation of reproductive behavior and the effect of stress factors on its realization.

**LOCOMOTOR EFFECTS OF PDE10A INHIBITORS IN DOPAMINE-DEPLETED RATS: ACUTE AND REPEATED ADMINISTRATION.** A Dorotenko, A Savchenko, S Kuvarzin, RR Gainetdinov, A Bespalov, I Sukhanov, First St. Petersburg State Medical University, Valdman Institute of Pharmacology, Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia. **INTRODUCTION:** Phosphodiesterases (PDEs) are a family of enzymes that hydrolyse such second messengers taking part in intracellular signaling, as cAMP and cGMP. PDE10A is expressed mainly in striatum. That unique pattern of PDE10A expression provides the opportunity to modulate the activity of the crucial locomotion pathways: striatonigral ("direct", D1-dependent) and striatopallidal ("indirect", D2-dependent). The dysregulation of these pathways was assumed to cause motor disabilities in patients with hypodopaminergic states, for example, Parkinson's disease. The present study was aimed to investigate the action of PDE10A inhibitors on locomotion in dopamine-depleted rats following acute/repeated administration. **METHODS:** Pharmacologic and pharmacogenetic approaches were used to model hypodopaminergic states in rats. In the pharmacologic paradigm locomotion was analyzed in the "Actometer" apparatus in tetrabenazine-treated (TBZ, 3 mg/kg i.p.) Wistar rats. During the experimental procedure, the animals were placed in the apparatus for 60 minutes to evaluate horizontal and vertical locomotor activity level. For the assessment of catalepsy (pharmacogenetic approach) α-methyl-p-tyrosine (αMPT, 250 mg/kg i.p.) pretreated DAT-knockout rats were subjected to "standard" rodent bar test. In the bar test rats' forepaws were placed on the bar and descent latency was recorded. The experimental session was terminated after 180 s cut-off time if descent latency could not be measured. Treatment with the PDE10A inhibitors, MP-10 (0.3-3 mg/kg i.p.) and RO5545965 (0.1-0.9 mg/kg p.o.), were performed 90 minutes before each test. Additional experiments were designed to compare the previously described effects of MP-10 following repeated (5 days) administration. **RESULTS AND DISCUSSION:** Both tested compounds reinstated locomotor activity after TBZ treatment in dose-dependent manner and reduced catalepsy in αMPT-treated DAT-knockout rats. Probable development of tolerance to action of MP-10 was observed in additional experiments with repeated administration of the drug. The obtained results allow us to conclude that PDE10A inhibitors can be the promising pharmacological class for Parkinson's disease therapy. However, the found tolerance may restrict clinical use of these agents. **RESEARCH SUPPORT:** The Russian Science Foundation (RSF) grant 17-75-20177.

**THE TRACE AMINE-ASSOCIATED RECEPTORS 5 MAY INVOLVE IN LOCOMOTOR FUNCTION.** D Kalinina, A Goriainova, R Gainetdinov, P Musienko, Institute of Translational Biomedicine, St. Petersburg State University, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, Russian Research Center of Radiology and Surgical Technologies, Ministry of Healthcare, Pavlov Institute of Physiology RAS, St. Petersburg, Russia. **INTRODUCTION:** It is known that monoamines (e.g. norepinephrine and dopamine) are important neurotransmitters in the processes of behavior and motor activity. The trace amines (TA) are biochemically similar to monoamines and can modulate their synaptic transmission. It has been determined that knockout of a gene that expresses the trace amine-associated receptors 1 (TAAR1) in mice can affect the uptake and release of serotonin, thereby increasing the firing of serotonergic neurons (Revel et al., 2011). In this study, we investigated the role of type 5 receptors to TA in locomotor function. **METHODS:** The research was performed on mice with a knockout gene (TAAR5-KO) encoding the expression of this receptor (n = 13) and wild-type mice WT (n = 13). The horizontal irregular ladder, vertical stairs and the footprint were used to analyze motor function. The horizontal irregular ladder is a 10 cm wide corridor with a rungs different distances from each other. The combination of the ladder changed each trials to prevent mice from remembering the location of the rungs and so minimize compensations through learning. The number of errors was counted (i.e. the limb completely missed a rung). This test shows the motor coordination abilities of animals. We used a vertical ladder to evaluate the muscle strength of mice. The ladder was installed on a flat surface at an angle of 90 with a distance of 1 cm between rungs. The time it takes animals to pass task was analyzed. Footprint test was performed in the glassy corridor with a width of 10 cm and then the distance between the footprint patterns was measured. **RESULTS AND DISCUSSION:** It was found that TAAR5-KO mice spent significantly more time on climbing the vertical ladder ($p<0.05$) than WT mice (17.01 ± 1.621 sec and 23.98 ± 2.756 sec, respectively). However, on a horizontal irregular ladder the TAAR5-KO showed a less number of foot total miss ($p <0.05$) relative to wild type. In the footprint test there were no significant differences between the WT and TAAR5-KO groups (0.3231 ± 0.01196 sec and 0.3069 ± 0.02259 sec). Thus, knockout mice demonstrated less muscle strength, better motor coordination without changes in gait, which may indicate that TAAR5 receptors are involved in the neuronal control of muscle tone and motor coordination during locomotor activity.

**LONG-TERM EFFECTS OF BISPHENOL A ON LIPID METABOLISM OF FEMALE RATS.** NK Apraksina, NN Klyueva, IO Suchkova, TV Avaliani, NI Dergacheva, EL Patkin, SG Tsikunov, Pavlov Department of Physiology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** Currently, many chemical and physical environmental factors lead to the development of many diseases,

both in adults and in offspring. One of the common chemicals found in soil, air, water, food, and some industrial products is the potential endocrine disruptor bisphenol A (BPA). The biological effects of ecotoxicants are associated with hepatotoxicity, cancer, pathologies of the nervous, cardiovascular, reproductive, and endocrine systems (Dergacheva et al., 2019). The purpose of this work was to assess the indicators of lipid metabolism in female rats after five times the intraperitoneally introduction of bisphenol A in different concentrations. **METHODS:** The experiments were performed on the adult female rats of Wistar weigh 300 gram (n=20). The experimental groups of animals were intraperitoneally injected with 0.3 ml of bisphenol A solution at a concentration of 0.4 mg/ml (group A) and 4 mg/ml (group B) for five days, and the control groups were injected with 0.3 ml of saline solution (C1) and a solution of dimethylsulfoxide in sesame oil (C2). The exposure of the lipid spectrum in the blood and liver of rats we evaluated a month after. Blood serum levels of total cholesterol (TC), triglycerides (TG), and cholesterol of high-density lipoproteins (HDL cholesterol) and liver samples of TC and TG were determined. The study was performed by enzymatic method using sets of Randox company (England). For statistical processing of the data, we used Mann-Whitney criteria and Student's t-test for independent samples adjusted for multiple Bonferroni comparisons. The differences were considered statistically significant at $p<0.05$. **RESULTS AND DISCUSSION:** A month after intraperitoneally administration of bisphenol A of 0.4 mg/ml and 4 mg/ml concentration we detected significant decrease in serum triglycerides in female rats compared to control groups (group A -78.4±8.1 vs. 107.0±12.7; $p=0.004$; group B-77.2±5.0 vs. 107.0±12.7; $p=0.003$). Other indicators of lipid metabolism showed no significant changes in comparison with the control (C1, C2). Thus, we show the long-term effects of the five-fold introduction of bisphenol A solution on the lipid metabolism rates of female rats. The detected hypotriglyceridemic properties of bisphenol A might be associated with epigenetic mechanisms that lead to changes in gene expression that regulates the activity of lipid peroxidation reactions and require further research.

**CALPAIN ACTIVITY IN THE CNS DAT-KO RATS**. DS Traktirov, NS Pestereva, TV Tyutyunnik, VS Artemova, ZS Fisenko, MN Karpenko, VM Klimenko, Pavlov Department of Physiology, Institute of Experimental Medicine, Peter the Great St. Petersburg Polytechnic University, Institute of Translation Biomedicine, St. Petersburg State University, St. Petersburg, Russia. **INTRODUCTION:** The calpain system is the system of intracellular cysteine proteases, presented both in the central nervous system and in the peripheral nervous system. Calpain-1 and calpain-2 are the most studied representatives of this system, whose proteolytic activity leads to limited cleavage of substrates, including protein kinase C, various signaling molecules, and transcription factors (e.g., c-fos, c-jun, nuclear factor-κB ( NFκB), cytoskeletal proteins (talin, fodrin), numerous adhesion molecules. As was shown for Parkinson's Disease, Alzheimer's disease, Multiple Sclerosis hyperactivation of the calpain system is a marker of the neurodegenerative process. One of the factors leading to disruption of work of the calpain system is an increase in the intracellular concentration of calcium. That is also the reason for the intensification of the vesicular transport of neurotransmitters into the synaptic cleft, in particular, dopamine, which plays a key role in the regulation of physiological functions. The aim of this work was the study the activity of calpains 1 and 2 under a determinately elevated level of extracellular dopamine. **METHODS:** The experimental group consisted of 5 male Wistar rats with a knockout of the dopamine active transporter gene (DAT) DAT-KO-/-. As a result of this mutation, dopamine accumulates in the extracellular medium in large quantities. The control group consisted of Wistar rats (n = 5). The level of calpain 1, 2 activities were determined in the striatum, spinal cord, and medulla oblongata. Calpain activity we measured by casein zymography. Data were expressed arbitrary units and presented as m ± SEM, and after we used the t-test was. **RESULTS AND DISCUSSION:** We have shown that in the medulla oblongata and the spinal cord, the level of calpain-2 is 1.6 times higher than the control group (5.3 ± 1.5 vs 8.4 ± 1.9, $p=0.01$; 4.8 ± 0.9 vs 7.5 ± 0.8, $p<0.05$), i.e. it is hyperactive, which talks about a possible degenerative process in these regions of the central nervous system. In the striatum, the level of both calpains is increased: calpain-1 1.8 times (1.6 ± 0.1 vs 2.9 ±0.5) and calpain-2 1.2 times (5.6 ± 0.3 vs 6.8 ± 0.7), $p<0.05$. These results we explained by the inclusion of the compensatory mechanism, for which calpain 1 is responsible. **RESEARCH SUPPORT:** RFBR grant 19-34-90030.

**EARLY LIFE LIPOLYSACCHARIDE EXPOSURE ALTERS STRESS-INDUCED CHANGES OF THE NMDA AND AMPA RECEPTOR EXPRESSION IN THE RAT BRAIN.** OE Zubareva, VA Nikitina, AN Trofimov, MV Zakharova, AA Kovalenko, GV Beznin, DU Krytskaya, AP Schwarz, SG Tsikunov, Pavlov Department of Physiology, Institute of Experimental Medicine, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia. **INTRODUCTION:** Early-life pro-inflammatory activation can affect CNS maturation and have negative effect on brain functions in adulthood including changed stress reactivity. One of possible mechanisms of such impairments may involve changes of glutamatergic transmission due to the re-modeling of NMDA and AMPA receptor subunit structure. We aimed to investigate stress-induced changes of NMDA and AMPA receptors subunit gene expression in the brain of rats treated with bacterial lipopolysaccharide (LPS) in early life. **METHODS:** Male Wistar rats 3 m.o. were subjected to life threatening stress by a 40-min contact with a predator (black-tailed python) either without neonatal manipulation or after LPS treatment (25 or 50 μg/kg, i.p.) at P15, P18, P21. The brain structures, amygdala (A), ventral hippocampus (VH), dorsal

hippocampus (DH) and medial prefrontal cortex (mPFC), were extracted 7 or 25 days after stress. We performed RT-qPCR analysis to assess the levels of mRNA expression of NMDA (GluN1, GluN2a, GluN2b) and AMPA (GluA1, GluA2) subunits. **RESULTS AND DISCUSSION:** The most notable changes 7 days after stress were revealed in animals injected with 50 μg/kg LPS. In mPFC of stressed LPS-treated rats, GluN1, GluN2a, GluN2b, GluA1, GluA2 mRNA, as well as GluN2a/GluN2b ratio were increased; in DH, GluN2a and GluA1 mRNA and GluN2a/GluN2b ratio decreased compared with vehicle-treated control groups. 25 days after stress, we observed no intergroup differences among stressed animals, whereas in non-stressed rats neonatal injected with LPS, the expression of GluA1, GluA2 and GluN2a mRNA in DH was downregulated compared with control. In VH of LPS-treated rats, GluA1 and GluA2 mRNA levels were higher than in control. Thus, early-life LPS treatment alters NMDA and AMPA receptors subunits expression in the brain under normal and stressful conditions, which may contribute to neurological and psychiatric pathology. **RESEARCH SUPPORT:** RFBR grant 17-04-02116A.

**GHRELIN CONCENTRATION AND KINASE ACTIVITY ARE IN THE RELATIONSHIP AFTER STRESS EXPOSURE AND DRUG ADMINISTRATION.** AA Blazhenko, PP Khokhlov, ER Bychkov, AS Devyashin, AA Lebedev, SN Proshin, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** Nowadays there are a lot of data to suggest about a key role of ghrelin signaling system in stress response and reinforcement mechanisms. There is a common opinion that a protein kinase system plays a role of a second intracellular messenger for ghrelin system. Zebrafish has a conservative nervous system and it is the best model for genetic and molecular analysis of mechanism which play role in emotional and motivational behavior. Ghrelin can be a biomarker of stress because its level is higher in organisms after cachexia and anorexia. The aim of our study is to compare the kinase activity with ghrelin levels in the different zebrafish brain parts after stress exposure and drug administration. **METHODS:** The all procedures have been held according to the Local Ethical Committee of Institute of Experimental Medicine. In our study it has been used 120 zebrafish 6-8 months of age. There also has been used a predator (*Hypsophrys nicaraguensis*). During the experiment a fish has been firstly placed into a tank of water with a dissolved pharmacological substance for 5 min, then it has been transferred into a tank with predator also for 5 min. The ghrelin antagonist Agrelax has been used in 0.333 mg/L dosage. Agrelaxis a recombinant peptide analogue of ghrelin with molecular weight 3500 KD, invented in our Institute but not yet patented. A benzodiazepine anxiolytic Phenazepam was used at 1 mg/L. The brain was divided into three anatomical parts: telencephalon, midbrain and cerebellum, for kinase activity assay and ELISA testing (Ghrelin FISH, MyBioSource ELISA kit; ADPsensor Universal Kinase Activity Assay kit, BioVision). **RESULTS AND DISCUSSION:** The evoked psycho-emotional stress significantly altered ghrelin concentrations in the different brain regions. Protein kinase system has taken part in the stress response. In Controls, the kinase activity was detected in all tested brain structures. After predator exposure, the kinase activity has significantly changed. In the cerebellum, the kinase activity was the highest after Agrelax administration. Pharmacological action on ghrelin receptors altered the kinase system in zebrafish brain structures. The impact of the anxiolytic has led to reduced predator stress effect on fish by lowering brain ghrelin. Agrelax and Phenazepam demonstrate the same effects on the Telencephalon and the Midbrain.

**DANIO RERIO AS A NEW MODEL TO STUDY HORMONAL RESPONSE TO STRESS.** PP Khokhlov, EA Sekste, AA Blazhenko, ER Bychkov, AA Lebedev, LK Khnychenko, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** Danio rerio (zebrafish) is well known experimental model for various behavioral studies, especially on stress response. Here, we evaluate the significance zebrafish for stress research focusing on its underlying molecular mechanisms. **METHODS:** The wild type zebrafish have been used, assayed by ELISA and RT-PSR. **RESULTS AND DISCUSSION:** During our study we have tried to determine a range of utility Danio rerio for hormonal response to stress and following pharmacological treatment. We have tried to highlight the biochemical properties which are common to all vertebrates. We have also noted certain unique peculiarities of zebrafish as an experimental animal. One of such unique features is the drug administration by incubation in micro-tanks. The combination of high-sensitive quantitative methods as ELISA and RT-PCR are efficient approach for stress studies in zebrafish. Our experimental data suggest similarity between one of the stress-related peptides (ghrelin) in rats and zebrafish under stress, calling for further stress research in fish models.

## SYMPOSIUM 2: JUBILEE SYMPOSIUM DEDICATED TO THE 130th ANNIVERSARY OF THE INSTITUTE OF EXPERIMENTAL MEDICINE (IEM)

Chair: VM Klimenko (Russia)

**WELCOMING ADDRESS FROM THE INSTITUTE OF EXPERIMENTAL MEDICINE.** Dear friends! On behalf of the Institute of Experimental Medicine, one of the organizers of the 27th Interdisciplinary

International Conference "Stress and Behavior", let me welcome and thank all the participants for finding the opportunity to take part in the conference during the coronavirus pandemic. For the first time in its history, the conferment has an unusual mixed hybrid format, and this format provides an opportunity for participation by an even larger audience. The conference is dedicated to the 130th anniversary of the Institute of Experimental Medicine - an institution that has given world science outstanding scientists and new scientific directions. Throughout its history, the Institute of Experimental Medicine has gone through multiple difficult periods - the First World War, the Civil, and the Great Patriotic War, famine, epidemics, devastation, repressions, and pseudoscience rampant. Despite this, the Institute of Experimental Medicine carefully preserved its scientific potential and, from year to year, made a significant contribution to solving urgent problems of biology and medicine. The glorious history of the Institute is associated with many prominent scientists: the first Russian Nobel Prize winner in the field of physiology and medicine I.P. Pavlov, as well as S.N. Vinogradsky, D.K. Zabolotny, V.L. Omelyanskiy, A.A. Zavarzin, N.G. Khlopin, V.A. Engelhardt, E.M. Kreps, E.S. London, P.S. Kupalov, L.A. Orbeli, K.M. Bykov, N.N. and S.V. Anichkov, A.A. Smorodintsev, V.I. Ioffe, B.I. Tkachenko and many others who have made a significant contribution to domestic and world science. Today, the Institute of Experimental Medicine is a modern medical research, educational, and clinical center. Scientific departments research the fields of molecular medicine, genomics, proteomics, metabolomics, and nanotechnology. The Clinic and the Medical Research Center are translating fundamental developments in medical practice. At the molecular, cellular, organismal, and population levels, the pathogenesis of common human diseases is studied, methods of prevention and diagnosis, advanced technologies of treatment and rehabilitation are being developed. Much of the scientific evidence from the Institute for Experimental Medicine in recent years will be presented at the Stress and Behavior Conference. Attention is drawn to the fact that most of the work is carried out at the intersection of scientific disciplines, which allows a deep understanding of the nature of phenomena and processes. From year to year, an increasing number of both young researchers and their experienced mentors participate in the conference. It is youthful maximalism and scientific courage, on the one hand, as well as experience and scientific wisdom, on the other hand, that makes it possible for Russian science to move forward to new victories and new achievements. I sincerely wish all the participants of the 27th Interdisciplinary International Conference "Stress and Behavior" further scientific success and achievements! Respectfully, Professor A.V. Dmitriev, Director of the Institute of Experimental Medicine, Doctor of Biological Sciences, Professor of RAS

**ABNORMAL BEHAVIOR IN THE OFFSPRING OF RATS SUBJECTED TO HYPOXIA DURING PREGNANCY IS CORRECTED BY LACTOFERRIN.** VB Vasilyev, AV Sokolov, VA Kostevich, NM Dubrovskaya, NN Nalivaeva, DS Vasilev, OL Runova, ET Zakharova, IV Semak, AI Budevich, IA Zhuravin, Institute of Experimental Medicine, St. Petersburg State University, Sechenov Institute of Evolutionary Physiology and Biochemistry, St. Petersburg State Pediatric Medical University, St. Petersburg, Russia, Belarus State University, Minsk, Scientific Practical Centre of Animal Breeding, Zhodino, Belarus. **INTRODUCTION:** Cationic transferrin of mammalian milk, lactoferrin (LF) is also present in other body fluids and leukocytes. In human milk LF is mostly iron-free (apo-LF) and shows extreme affinity towards Fe(III) [1]. Being an iron chelator, LF stabilizes hypoxia-inducible factor-1 alpha (HIF-1α). At normoxia HIF-1α is modified by iron-sensitive hydroxylases, becomes ubiquitinated and undergoes proteasomal degradation. Hypoxia or iron deficiency cause the ingress of HIF-1α into the nucleus and binding to HIF-1β, which stimulates expression of *ca.* 200 genes. Some of those encode regulators of iron metabolism and erythropoiesis, *e.g.* ceruloplasmin (CP) and erythropoietin (EPO), and secure the survival of cells under stress. Our recent data showed that human apo-LF is a physiological mimetic of hypoxia. It stabilizes HIF-1α and HIF-2α, stimulating expression of their target *CP* and *EPO* genes [2,3], which makes apo-LF an antagonist of oxidative stress. Hypoxia during pregnancy causes postnatal motor and cognitive dysfunctions, as shown in our previous works [4,5]. Here we present the analysis of effects provided by LF on cognitive function in the offspring of rats subjected to hypoxia at pregnancy. **MATERIALS AND METHODS:** Recombinant human LF branded “CAPRABEL” was purified from the milk of transgenic goats at the Belorussian State University and Scientific Practical Centre of Animal Breeding (Belorussian National Academy of Sciences). Ca. 90% of such LF was iron-free (apo-LF). On the 14$^{th}$ gestation day pregnant Wistar rats (200g) were subjected to hypoxia in an altitude chamber (7% $O_2$, 3h) [4]. CAPRABEL was injected *i.p.* to half the pregnant rats (10 mg per rat) on the 9, 12, 13 and 15th day of gestation or during nurturing (from P0 after delivery up to P15 every day). Western blotting or ELISA with anti-HIFs or anti-EPO was used to explore organ homogenates of some females and suckling pups. Other pups were allowed to grow and their short-term memory was tested in a two-level radial maze. Both short-term and long-term memory were assayed in the “Novel Object Recognition” (NOR) test. **RESULTS:** Western blotting revealed HIF-1α, HIF-2α and EPO in the brain, liver, heart, spleen and placenta, but not in the embryos, of hypoxia-treated pregnant rats injected with CAPRABEL and sacrificed 3 h after the last injection. Neither HIFs, nor EPO were revealed in the organs of control pregnant rats. Radial maze and NOR tests showed significant memory improvement in young (P22) or adult (P40) rats born from the apo-LF-treated mothers subjected to hypoxia, as compared with the compromised memory in the offspring of apo-LF-untreated rats. In accord with previous findings [6], CAPRABEL injections to hypoxia-treated lactating dams caused persistence of human apo-LF in their

milk for 4-24 hrs. Concomitantly HIF-1α, HIF-2α and EPO were detected in the pup brain, liver and spleen. Injections of CAPRABEL to dams during lactation were followed by significant improvement of short- and long-term memory of their offspring in NOR test on P22 and P40 in comparison with the compromised memory in the offspring of apo-LF-untreated rats. **CONCLUSION:** Apo-LF mitigates the harmful effect of prenatal hypoxia on developing brain when applied both during prenatal and postnatal ontogenesis. Beneficial effect probably is provided by its ability to induce EPO biosynthesis in brain and other tissues *via* HIF-signaling mechanism. This explains the corrective effect of CAPRABEL on the compromised behavior of rats that experienced hypoxia during intrauterine development. Beneficial effect probably is provided by its ability to prevent oxidative stress when triggering the potent anti-hypoxic (and anti-oxidative) pathway, the crucial element of which is rescuing HIFs from destruction with subsequent elevation of EPO synthesis, which alleviates or abrogates neurological impairment resulting in cognitive dysfunctions. **SUPPORT:** RUSSIAN STATE BUDGET project AAAA-A18-118012290373-7.

**RESTRAINT STRESS AND BEHAVIORAL CHANGES IN MICE OF DIFFERENT GENOTYPE.** II Poletaeva, NA Ogienko, AD Suleimanova, OV Perepelkina, IV Koshlan, AV Revishchin**,** Moscow State University, Institute of Gene Biology RAS, Moscow, Joint Institute for Nuclear Research, Dubna, Moscow Region, Russia. **INTRODUCTION:** Restraining animal for 1 or 2 h in the narrowl tube or cage induces the stress reaction, the effect of which could be evaluated in different tests, including behavioral tests. **METHODS:** Male mice of two strains, differing by relative brain weight and F1 hybrids CBA x C57DL) were submitted to the restraint stress in plastic tubes and tested in puzzle-box test (evaluating cognitive ability for elementary logic task solution, based on the rule of object permanence), and in neophagophobia test (measuring the reaction to novel food in new environment). Large brain (LB) and small brain (SB) mice were first selected for relative brain weight differences. After F23 of selection these strains are bred (for more than 10 generations) as outbred strains without supporting selection. Inter-strain brain weight differences still persist. The F1 hybrid males were subjected to head proton irradiation (4Gy). Part of these animals were subjected to restraint stress, and another part served as controls. **RESULTS AND DISCUSSION:** The results of both tests demonstrated different stress-reactivity in mice LB and SB mice, SB mice were more sensitive to activating effects of restraining. The F1 hybrid mice demonstrated minor differences between stressed and control animals. Data on behavioral indices demonstrated differences in ability to solve puzzle box test (object permanence, by J. Piajet). SB stressed mice were more active in searching the masked entrance into the safe box compartment (in several trials), while in LB groups the differences were practically absent. The response to novelty (in the neophagophobia test) also revealed increased reactivity in SB stressed vs. LB animals. The data obtained indicated: first, the importance of experiments with animals differing in genotype as the stress effect can differ in such groups and, second, the importance of investigating the effect of stress on cognitive domain of mouse behavioral repertoire. The research was performed according to Bioethical rules of EC 2010 Declaration. Authors claim no conflict of interests. **RESEARCH SUPPORT:** RFBR grant 17-29-01001.

**DIFFERENTIAL CONTRIBUTION OF CONTEXTUAL AND DISCRETE CONDITIONAL STIMULI TO FEAR MEMORY RETRIEVAL IN RATS.** BT Varga, F Kassai, AJ Ernyey, A Gáspár, I Gyertyán, Semmelweis University, Department of Pharmacology and Pharmacotherapy, Cognitive Translational Behavioral Pharmacology Group, University of Veterinary Medicine, Institute for Biology, Budapest, Hungary. **INTRODUCTION:** In this study we investigated the extent to which the discrete conditional stimuli used during the acquisition and the contextual elements of the experimental set-up contribute to the retrieval of fear memory. **METHODS:** We divided naïve Hannover Wistar rats into three groups differing in their conditioning parameters. During the five-day-long acquisition period, five mild electric shocks were presented in daily sessions, paired with light and sound stimuli, while during the retention Sessions, memory retrieval was examined in familiar and new contexts, with or without the originally conditioned discrete stimuli. Five of these sessions were conducted next week to the acquisition period and two additional sessions were performed after additional 3 weeks. **RESULTS AND DISCUSSION:** Analyzing the occurrence of freezing reaction within sessions unveiled that in the acquisition period the freezing response time increased in the pre-shock period and decreased immediately thereafter, while in the retention sessions, the freezing reaction showed a bell-shaped curve as the stimuli were repeatedly exposed. In the retrieval period, fear memory was evoked by the discrete stimuli in other contexts too, though to a lesser extent than in the original environment. Familiar context without the conditioned discrete stimuli did not cause a significant rise in freezing, however, after 3 weeks of intersession break, the familiar context elicited partial but significant freezing, both with and without conditional stimuli. The results suggest that freezing is an anticipatory reaction, and animals anticipate the aversive experience based on the previously conditioned stimuli rather than the familiar context in the short-term, but in the long-term, the environment of the negative experience is also tagged. **RESEARCH SUPPORT:** The National Brain Research Program (NAP) contract 2017-1.2.1-NKP-2017-00002, the Ministry of Innovation and Technology's "New National Excellence Program" (code: ÚNKP-19-2-I).

**MANGANESE-INDUCED NEUROTRANSMISSION REMODELING.** IS Ivleva, TV Tyutyunnik, VA Maystrenko, MN Karpenko, VM Klimenko, I.P. Pavlov Department of Physiology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** Manganese (Mn) is an essential trace element. However, chronic exposure to Mn causes a wide variety of neurotoxic effects, termed manganism, which resembles symptoms of Parkinson's disease (PD). As well known, in PD, affective, and cognitive impairment develop, including due to neurotransmission remodeling. Our study aims to determine two main biogenic monoamines: dopamine (DA) and norepinephrine (NE), and the enzymes involved in their metabolism in the CNS of rats treated with $MnCl_2$. **METHODS:** Adult male Wistar rats, 220–250 g, were used in this study. The experimental group of Mn-exposed rats received intranasal injections 20 µl/rat in total 1mg $MnCl_2$ once per day for one month, and rats of control group received the same volume of sterile saline. HPLC-ED measured the level of DA and NE and its metabolites, and the data presented as ng/mg protein. The levels of mRNA and protein concentrations of tyrosine hydroxylase (TH) and dopamine β-hydroxylase (DBH) were measured. The presented data as mean ± SD, statistical analysis was applied with ANOVA, Post-hoc Tukey criterion, the differences were considered significant when p is less than 0.05. **RESULTS AND DISCUSSION:** Here, we showed that in rats, treated with $MnCl_2$, level of Mn increases in striatum and hippocampus (2.5-fold, p=0.000, and 2.2-fold, p=0.011 respectively) compared with control rats. mRNA and protein levels of TH in the striatum of experimental rats decreases (1.6-fold for mRNA, p=0.031 и 2-fold for protein, p=0.002), however mRNA and protein levels of TH (3-fold for mRNA, p=0.011 и 1.5-fold for protein, p=0.049) in hippocampus increases, compared to control rats. In the hippocampus of rats received $MnCl_2$, we observed reduced content of DBH protein (1.8 times lower than control, p=0.048), although the mRNA level of DBH increases (2.7 times higher than control, p=0.037). It turned out, that DA level of experimental rats decreases (40.5 ± 6.3 vs 70.7 ± 1.6, p=0.001), that related with increase in DA level (4.3 ± 0.6 vs 1.4 ± 0.4, p=0.004) and decrease in NE level (10.1 ± 1.7 vs 14.9 ± 2.4, p = 0.027) in hippocampus, which can explain mechanisms of affective and cognitive impairment development. **RESEARCH SUPPORT:** RFBR grant 19-315-90009.

**REVERSE BEHAVIORAL PATTERN OF DAT-KO RATS UNDER PROGRESSIVE RATIO SCHEDULE OF REINFORCEMENT.** AA Savchenko, RR Gainetdinov and IM Sukhanov, Valdman Institute of Pharmacology, Pavlov First St. Petersburg State Medical University, Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia. **INTRODUCTION:** The dopaminergic mesolimbic pathway is thought to be strongly implicated in reward-related processes, which are often affected in humans with psychiatric disorders (e.g. addictions). The rat strain with the lack of the dopamine transporter (DAT) is a new promising model of hyperdopaminergia. These rodents are characterized by dramatically increased levels of synaptic dopamine. The present study was aimed to evaluate the impact of increased synaptic dopamine on the reward-related processes in rats. **METHODS:** The adult male rats (DAT-knockouts (KOs), heterozygotes (HTs), wild-types (WTs)) were housed in individual cages with limited access to food (15 g per 24 h) so that their body weights were reduced to approximately 85% of the initial levels. To estimate the reward-related processes the classic operant schedules of food reinforcement, fixed (FR) and progressive (PR) ratios, were performed in the rats. The experiments were carried out in standard Skinner's operant chambers equipped by a houselight, a lever, a food dispenser, and a food tray. The rats were first habituated to the operant chambers and to food pellet feeding. Following training of the lever press responses, FR1 schedule was started. FR was gradually increased to 5. Each FR schedule session carried on until either 60 minutes expired or an animal got 50 pellets. The schedule was changed to PR when a rat reached a criterion (50 earned pellets) for two consequent days under FR5 schedule. We used PR3 schedule that means the ratio of reinforcement increased by 3 after each got reinforcement. PR3 session lasted for 120 minutes. The number of the earned reinforcements, the latency of the reinforcements getting, and the response rate were recorded or calculated for each experimental session. **RESULTS AND DISCUSSION:** (1) Lever press training of KOs was found to take more sessions than control animals' training. (2) Under FR5 schedule KOs were indicated to exhibit much lower response rate than WTs and HTs. (3) Under PR3 schedule, KOs showed distinct pattern of lever pressing in compare to the control animals. KOs' response rate gradually increasing as required number of responses to obtain a reward grew. On the contrary, the local response rate of the control animals decreased. Our results demonstrate that the chronically elevated synaptic dopamine is able to dramatically affect the behavioural patterns of the rats under operant schedules of reinforcement. The findings of the present study are in strict concordance with the previous works suggesting that elevated synaptic dopamine is accompanied by increased "wanting" a particular reward. Thus, the rats with the lack of the dopamine transporter can be used for search and development of new treatment approaches for addiction. **RESEARCH SUPPORT:** The Russian Science Foundation grant 17-75-20177.

**BEHAVIORAL CHANGES IN THE DOPAMINE TRANSPORTER (DAT) HETEROZYGOTE RATS.** AR Gainetdinov, ZR Khismatullin, Department of Biology, Bashkir State University, Republic of Bashkortostan, Ufa, Russia. **INTRODUCTION:** In 2018, transgenic rats with a fully or partially reduced level of dopamine transporter (DAT) protein have been developed. The model with partical DAT gene

deletion was called "DAT-HET" or "DAT-heterozygotes." The concentration of striatal extracellular dopamine in these animals increased almost 3 times in comparison with wild type rats. At the same time, no decrease in the concentration of intracellular dopamine was observed. The aim of the study was to study the behavioral characteristics of DAT-HET rats in comparison with the control group of wild-type rats of the Wistar strain. **METHODS:** The following behavioral test system were used: "Open field", "Elevated plus maze", "Extrapolation escape task". **RESULTS AND DISCUSSION:** In the Open Field test, we found that DAT-HET rats have a higher number of crossed squares (77.00 ± 7.13) and rearings (16.83 ± 5.27), which may indicate increased motor and explorative activities compared to wild-type rats, in which the number of crossed squares was 42.50 ± 6.95 and number of rearings was (8.17 ± 3.43). In the “Elevated plus maze” test, DAT-HET showed a greater number of crossed squares (71.33 ± 6.02) and handing down (11.50 ± 2.43), a longer time spent in open arms - (34.67 ± 9.42) and a shorter time spent in closed arms - (177.66 ± 22.40) than in control Wistar rats, in which the number of crossed squares was 36.17 ± 7.41, hanging down (3.83 ± 2.23), time spent in open arms (20.17 ± 7.11), time spent in closed arms (230.33 ± 21.16), which may indicate increased motor and explorative activities, but also reduced anxiety in DAT-HET rats. In the test “Extrapolation escape task” in DAT-HET rats a cognitive impairment was detected, which was manifested as an increase in the latent diving period (17.67 ± 6.98) and the number of unsuccessful attempts to avoid (11.50 ± 2.17) compared with the control group of Wistar rats, the diving latent period of which was 5.83 ± 1.47, and the number of unsuccessful avoidance attempts was 3.67 ± 2.16. Also, a cognitive impairment was indicated by a decrease in the latency period of the motor activity in, DAT-HET rats (0.50 ± 0.84) compared with the control wild-type group (4.67 ± 1.37). It can be concluded that the genetically determined partical hypofunction of the dopamine transporter in these animals alters the functioning of the central nervous system leading to a behavioral phenotype similar to symptoms of neuropsychiatric diseases such as attention deficit hyperactivity disorder, schizophrenia and bipolar disorder.

**INVESTIGATION OF THE PHYSIOLOGICAL FUNCTIONS OF TRACE AMINE-ASSOCIATED RECEPTOR 9 (TAAR9).** RZ Murtazina, SR Kuvarzin, IS Zhukov, EV Efimova, OM Korenkova, NV Alenina, RR Gainetdinov, Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia, Max Delbrück Center for Molecular Medicine, Berlin, Germany. **INTRODUCTION:** Trace Amine-Associated Receptors (TAARs), discovered twenty years ago, are now considered as promising new targets for treatment neuropsychiatric disorders. Trace amines are structurally close to classical amine neurotransmitters but their level in brain tissue is much lower. There are 6 functional members of this family in human with the most studied TAAR1 that is already validated as a novel target for the treatment of schizophrenia. Other 5 TAARs are originally considered just as olfactory receptors sensing socially-relevant innate odors. Currently, there is a lack of information on TAAR9 receptor function and expression beyond olfactory system. **METHODS:** In our laboratory, two different TAAR9 knockout rat strains were generated via CRISPR/Cas9 method. Knockout animals from both strains were evaluated in behavioral tests (Open Field, Elevated Plus Maze, T maze, Porsolt Swimming Test, Stress-Induced Hyperthermia). The concentrations of monoamines and mRNA levels of neuronal markers (DAT, TH, COMT, etc.) were measured in various brain structures using HPLC-ED and RT-qPCR, respectively. Blood biochemistry and hematological tests were performed using automated analyzers. **RESULTS AND DISCUSSION:** There was no significant difference in the most behavioral tests. mRNA levels of various neuronal markers (TH, COMT, DAT, MAOA, MAOB, DRD1, DRD2, TPH2, GAT1, NMDAR1, BDNF, CDNF, GDNF) in brain structures were similar to wild type levels. Dopamine, serotonin and noradrenaline levels in the hypothalamus, striatum, and cortex were also not altered in knockout rats. However, the level of dopamine metabolite DOPAC in the hypothalamus was significantly higher in knockout than in wild type rats. Interestingly, thermometry showed an increased baseline temperature of knockout rats and altered response in Stress-Induced Hyperthermia test. It is worth noticing that in other TAAR knockouts we have also observed an altered SIH, that might indicate a general role of TAARs in stress response. Unexpectedly, blood biochemistry comparative analysis revealed decreased total cholesterol and LDL-cholesterol levels (so-called “bad” cholesterol) in TAAR9 knockout rats. These data show that the TAAR9 deficiency causes certain physiological effects beyond the olfactory system and more studies are necessary to further elucidate the functional role of TAAR9 in the brain and periphery. **RESEARCH SUPPORT:** The RSF grant 19-75-30008.

**INTESTINAL MICROBIOTA AND MENTAL HEALTH. CAN PROBIOTICS HELP?** IN Abdurasulova, VM Klimenko, Pavlov Department of Physiology, Institute of Experimental Medicine, St. Petersburg, Russia. Human microbiome research has made a significant contribution to psychoneuroimmunology. 70% of the whole microbiota is contained in the intestines, dominated by the *Bacteroidetes* and *Firmicutes* phyla. Various phyla that exist in the intestinal microbiota in smaller quantities include *Proteobacteria, Verrucomicrobia, Actinobacteria, Fusobacteria*, and *Cyanobacteria*. The intestinal microbiota helps digestion, promotes colonization resistance, maintains the integrity of the gut and blood-brain barriers, and participates in the development and functioning of the immune and nervous systems. Intestinal bacteria produce a wide range of biologically active substances, including antimicrobial peptides, short-chain fatty acids, vitamins, peptides, and neurotransmitters. The intestinal microbiota has significant systemic effects. Disorders of the gastrointestinal tract accompanied by

neurodegenerative and mental diseases, but the digestive tract disorders accompanied by the psycho-emotional impairment, and violation of the composition of the intestinal microbiome (dysbiosis) contributes to both of these disorders. Research on experimental models of various diseases or GF (germ-free) animals using infectious agents, probiotics, or fecal transplantation helps us understand how the intestinal microbiota affects the functions of the CNS. So, administration of subclinical doses of pathogenic bacteria (*Citrobacter rodentium or Campylobacter jejuni*), which do not cause an immune response and "sickness behavior", animals showed anxiety-like behavior and decreased cognitive abilities. On the contrary, oral administration to animals antibiotics that alter the composition of the intestinal microbiota, decreased anxiety. Similar effects observed with the oral administration of lactobacilli. When using probiotic bifidobacteria in animals, anxiety-depressive as well as depressive-like behavior also levels, and besides, stress hormones reduced. Moreover, *Lactobacillus helveticus* r0052 and *Bifidobacterium longum* R0175 in rats improved memory dysfunction caused by infection and cognitive defects induced by diabetes. Interestingly, the behavioral phenotype can be transferred by fecal transplantation from a donor to a recipient. Collins et al. (2013) showed that transplant of intestinal microbiota from mice with an alarming phenotype caused an increase in anxiety in the low anxiety line of mice and vice versa. Earlier, we showed that different probiotic strains differently affect the behavior of animals (Abdurasulova et al., 2015). Oral administration of *Enterococcus faecium* L-3 for 5 days stimulated research activity in rats, and *Lactobacillus plantarum* and *Escherichia coli* M-17 reduced b, while animals treated with *E. col*i M-17 showed anxious-like behavior — and increase in grooming time. Some studies on the effects of the probiotics discover in the clinic. A meta-analysis of 5 clinical studies showed that patients with depression cured with probiotics were associated with a significant reduction in depression. Using probiotics that included three strains of *Lactobacillus acidophilus, Lactobacillus rhamnosus, and Bifidobacteria longum*, for 3 months have beneficial effects on ASD. In patients with MS, oral *E. faecium* L-3 within three weeks improved the psycho-emotional state. Thus, further investigations are needed to study the composition of the intestinal microbiota in various diseases of the central nervous system and the search for the most effective probiotic strains for specific patients.

**KINETIC ANALYSIS OF PHASIC DOPAMINE INCREASES IN THE RAT N. ACCUMBENS CORE AND SHELL CHANGING UNDER THE ACUTE INFLUENCE OF AMYLOID B 25-35.** V Mukhin, V Sizov, K Pavlov, I Borovets, VM Klimenko, Pavlov Department of Physiology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION**: Dysfunction of the dopaminergic pathways of the brain may underlie some clinical syndromes of Alzheimer's disease, such as cognitive impairments, apathy, and parkinsonism. Such dysfunction can be caused by impairment of normal metabolism of amyloid β in the brain. Earlier, we reported that acute elevation of amyloid-beta in the rat brain upregulates evoked dopamine increase in the n. accumbens shell and downregulates one in the n. accumbens core. But it remains unclear that these impairments are due to changes in release or uptake of this neurotransmitter. To answer this question, we perform the kinetic analysis of the dopamine increases. **METHODS**: To increase the level of amyloid β in the brain solution of aggregated amyloid β fragment 25-35 was intracerebroventricularly administered in urethane-anesthetized rats. Changes of the extracellular dopamine level were determined with the fast-scan cyclic voltammetry before and 15 to 30 min after amyloid β administration. We apply two techniques of kinetic analysis of the dopamine increases. One of them is the estimation of dopamine wave parameters. The other one is the mathematical model based on the Michaelis-Menten equation. **RESULTS AND DISCUSSION**: In both the core and the shell of nucleus accumbens, dopamine wave disturbances are due to change in its release, not reuptake. These changes are the opposite. Dopamine release increases in the shell and decreases in the core. In accordance with this, the parameters of the dopamine wave change, such as dopamine per pulse of stimulation release, slope and duration of the segments of the dopamine curve from maximum to 80%, and from 80% to 20% and the area under the curve (AUC). **CONCLUSION**: Amyloid β 25-35 increases dopamine release in the n. accumbens shell and decreases one in the n. accumbens core. No effect on dopamine reuptake was found.

**THE DE RITIS RATIO AS A MARKER OF CATABOLIC AND ANABOLIC REACTIONS IN HYPERACTIVITY AND OBESITY.** SA Apryatin, MV Bolshakova, AL Manasyan, EK Turkeeva, VM Klimenko, Pavlov Department of Physiology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** Dopamine and leptin play a key role in shaping the reward system and a sense of fullness that underlie food intake and eating behavior. The consumption of diets high in fats and carbohydrates, predisposing to the development of obesity, metabolic syndrome, and other nutritional disorders, causes persistent changes in metabolic reactions, leading to nutritional pathology and disruption of monoamine systems. Another important indicator is the biochemical parameters of blood, including the De Ritis ratio (the ratio of the activity of the alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT)) enzymes, which is not only an indicator of cardiac and hepatic dysfunction but can also be a marker of catabolic and anabolic reactions that affect metabolism not only with nutritional pathology but also with various disorders of the dopamine system, for example, hyperactivity. Thus, biochemical markers of dopaminergic and leptin-ghrelin systems disorders can be considered as promising targets for the comprehensive diagnosis of nutrition-dependent diseases (obesity, metabolic syndrome, etc.) and also various behavioral disorders (hyperactivity, etc.). The aim of the research work

was a comparative analysis of the influence of a high-fat/high-carbohydrate and high fructose diets of integral and biochemical (including the De Ritis ratio) indicators of the dopamine transporter DAT-KO knockout line (hyperactivity model), Zucker-*Lepr*$^{FA}$ line (model of obesity) and Wistar outbred rats. **METHODS:** Studies involved rats of different genotypes: groups 1, 2, 13 and 14 (homozygous *DAT-/-*), groups 3 and 4 (heterozygous *DAT+/-*), groups 5, 6, 11 and 12 ("wild type" +/+); Zucker-*Lepr*$^{FA}$ rat line: groups 7 and 8 (homozygous *Lepr*$^{FA}$/*Lepr*$^{FA}$) and Wistar outbred rat: groups 9 and 10. For 8 weeks, animals of groups 1, 2, 3, 7, 9, 11, and 13 received a balanced semi-synthetic diet, groups 4, 5, 6, 8, and 10 - a high-fat, high-carbohydrate diet (HFHCD) - 30% fat by weight of solids and 20% fructose solution instead of water, groups 12 and 14 - 20% fructose solution instead of water. At the end of the experiment, integral (body weight, relative organ weight) and biochemical (De Ritis ratio (AsAt/AlAt ratio), AsAt and AlAt activity) indicators were evaluated. **RESULTS AND DISCUSSION:** The study showed that rats with ablated *DAT* were characterized by lower body mass, relative liver mass, and high De Ritis ratio regardless of the type of dietary effects (groups 1-6, 13, and 14). In contrast, Zucker-*Lepr*$^{FA}$ rats (groups 7 and 8), homozygous for mutations in the leptin receptor, was showed higher body weight and the lowest ratio among all the studied lines. Moreover, the activity of the enzymes AST and ALT in the blood did not change in all the studied lines, depending on the type of diet. The value of the AST/ALT ratio was reduced in the HFHCD and fructose groups in Zucker-*Lepr*$^{FA}$ and Wistar rats, respectively, but not *DAT-/-* vs. control group. The homozygous *DAT-/-* and heterozygous *DAT+/-* genotypes correlated with higher AsAt/AlAt ratio and reduced body weight, which may result from higher rate of catabolic processes in these animals, and the homozygous *Lepr*$^{FA}$/*Lepr*$^{FA}$ genotype, on the contrary, correlates with an increase in body weight and can indicate the activation of anabolism. Thus, the De Ritis ratio can be used as a marker of catabolic and anabolic reactions affecting the metabolism not only in nutritional pathology but also in various disorders of the dopamine system, for example, hyperactivity.

**THE INFLUENCE OF TREADMILL SPEED ON DIFFERENT LOCOMOTOR MODES OF DECEREBRATE CAT.** V Lyakhovetskii, N Merkulieva, O Gorskii, P Musienko, Pavlov Institute of Physiology RAS, Russian Scientific Center for Radiology and Surgical Technologies, St. Petersburg State University, St. Petersburg State Research Institute of Phthisiopulmonology, Ministry of Healthcare, St. Petersburg, Russia. **INTRODUCTION:** An influence of locomotor speed on the kinematic parameters of stepping and the patterns of muscle activity is well studied during backward (BW) and forward (FW) walking as in human (Neptune et al., 2008) as in intact quadrupedal animals (Buford et al., 1990). The decerebrate animal is the common neurophysiological model for studying spinal and brainstem neuronal circuitries in the absence of cortical control. It is able to the FW locomotion and to the BW one (Musienko et al., 2012; Merkulieva et al., 2018), as well as to simultaneous bidirectional (BIDI) locomotion at chosen treadmill speed (Lyakhovetskii et al., 2018). An ability of these animals to adapt to the different speed of the treadmill was shown only for FW stepping (Barbeau, Rossignol, 1987). In the present work, the influence of treadmill speed onto other locomotor modes of the decerebrate cat was studied. **METHODS:** Four adult cats were decerebrated at precollicular-postmammilar level. The hindlimb locomotion was elicited by epidural stimulation of the dorsal surface of the spinal cord. For every animal, the same point of dorsal surface (L6-L7 segments) was used to elicit FW, BW, and BIDI stepping. The direction of the hindlimb movements was determined solely by the direction of movement of the treadmill belts. The “base” speed of belts was 0,45 m/s. The low (0,2 m/s) and high (0,7 m/s) speeds were also used. The kinematics of movements was recorded with the help of reflecting markers. **RESULTS AND DISCUSSION:** One animal could not perform BIDI locomotion in high speed. Other one could not perform stable continuous BW locomotion in low speed. The “angle ranges” in the hip, knee and ankle in low and high speed were similar to the “angle ranges” at the “base” speed for each locomotor mode. In the low speed, the step periods for all walking modes were significantly increased, while the high speed could lead to either increase or decrease of the step duration. The step length during BIDI walking increased with increasing speed of the treadmill. The asymmetry of the stepping period increased for BW walking with any changes in speed. The stability of the FW step length increased in high speed. The preliminary results suggest studying the characteristics of different locomotor modes more appropriate to use low relative to “base” speed. **RESEARCH SUPPORT:** The RFBR grant 19-015-00409A.

## Day 2. Thursday, September 17, 2020

**Venue: Oktiabrskaya Hotel, 10 Ligovsky Prospect, St. Petersburg, Russia**

### SYMPOSIUM 3: CLINICAL STRESS NEUROSCIENCE

Chair: D Kozic (Serbia)

**WORK STRESS INTERVENTIONS: RESILIENCE TRAINING, SYSTEM INTERVENTIONS AND LEADERSHIP BASED CHANGE.** JAK Erskine and GJ Georgiou**,** St George's, University of London and University of Hertfordshire, London, Hertfordshire, UK. **INTRODUCTION:** Occupational stress results in significant costs to industry worldwide. Furthermore, it is involved in the etiology of numerous health

conditions worldwide - both physical, chiefly cardiovascular disease and psychological, anxiety, depression and stress associated disorders. As a result, most nations and organizations have an interest in reducing stress in the workforce. In order to accomplish this they have recently mandated workplace resilience and well-being interventions. In addition, legal changes have been made to working practices to attempt to reduce stress, such as reducing working hours. **METHODS:** I have been involved with designing evidence-based workplace interventions and implementing resilience and management training within St George's, University of London Medical School. These interventions have focused on a 6 week (2 hours per week) resilience training course delivered to postgraduate and undergraduate students, and seminars on leadership based interventions delivered to 20 senior managers including the chief operating officer and University Chancellor and Vice Chancellor. **RESULTS AND DISCUSSION:** Design of the interventions will be discussed and outcomes will be investigated. One result that will be discussed will be the darker side of resilience training, in that a successful outcome is a more resilient worker that poorer functioning organizations can then further exploit to extract more work. It is our contention that individually based resilience interventions need to train the individual to be sensitive to these possible outcomes and resist abusive practices by moving away from exploitative organizations. A dark side of managerial based interventions is their tendency to show a confirmation bias towards believing they already practice in optimal ways in spite of evidence from staff surveys to the contrary. Managerial interventions need to be mindful of these biases and take managers back to the evidence by working through staff feedback and implementing changes that are evidence based and likely to result in successful stress reduction and natural productivity increments as staff become healthier, take less days off and show greater organizational engagement. **RESEARCH SUPPORT:** St George's, University of London Medical School.

**SELF-STRESS MANAGEMENT IN THE WORKPLACE.** Ph Fauquet-Alekhine, B Guion de Meritens, SEBE-Lab, Department of Psychological and Behavioural Science, LSE, London, UK, Lab. for Research in Science of Energy, France, Nuclear Power Plant of Chinon, EDF-FARN (Nuclear Fast-Action Force), France. **INTRODUCTION:** A way to categorize stress is to consider the context: for example, pregnancy may induce specific stress for the mother (see for example Cole-Lewis et al., 2014) or for the fetus (Abbott et al., 2018); stress may relates to social interactions (Lehman and Conley (2010); the workplace may induce stress, referred to as occupational stress since long (see Frideman et al., 1958), as work environment may provide stressful contexts. Stress at work is an actual issue: in West Europe, the cost of work-related depression was estimated to be 617 billion€ per year (Hassard et al., 2014: 7). This combination of health and economical concerns make stress at work an issue that is worth to deal with. Reactions to stress are immediately consecutive to the subject's perception of factors of stress (or stressors) and are universal: this touches everyone but not with the same intensity depending on the psychological experience and state of each and also on the social context. But it is adaptive and adaptable according to the degree of intensity and is also cumulative because the stressors add up. In the case of crisis situations occurring at work, the distinction should be made between the "usual" stressors, related to the peculiarities of the work (e.g. disturbance of sleep-wake cycles for shift teams, presence of hazards for chemical industries, isolation or "additional" stressors that are added when nuclear power plant operators encounter unexpected situations) and "additional" stressors that are added when operators encounter situations outside the ordinary (operating in a medical theatre, piloting a nuclear reactor in accidental phase, interacting with the enemy for militaries). For individuals concerned by chronic stress, these stressors generate acute stress that cumulates with chronic stress, increasing the difficulty to cope with the situation: chronic stress reduces the ability to cope with acute stress situations. When increasing stressors intensity, acute stress may lead to posttraumatic stress disorder (PTSD), a psychological state characterized by the development of specific symptoms following exposure to a traumatic events such as serious accidents, physical or sexual assault, war or torture (www.nhs.uk). Managing stress at work might help individuals to reduce the impact of acute stress, to lessen the perceived intensity of stressors (thus reducing the risk of PTSD) and also to reduce the impact of repeated exposure (thus reducing the risk of chronic stress). This article presents methods and tools that are currently taught to teams operating the French nuclear fleet for stress management. **METHODS:** Following the Fukushima accident, several analyses among which this of EDF pointed out organizational and psycho-social weaknesses in case of an accident with the same intensity as in Japan (whatever its nature). Within a few months, corrective actions were identified and implemented (Fauquet-Alekhine, 2012). For example, the FARN (*Force d'Action Rapide du Nucléaire*, Fast Task Force of the Nuclear) was created: the FARN teams are able to go beyond the conventional means in a short time and give immediate assistance to a nuclear power plant that might need a fast logistic rescue. Other solutions came later. An example is that of self-stress management: a working group carried out a reflection on the impact of stress on nuclear reactor operation; the need of specific training for the call-on and operating teams was identified with the aim to help them to self-manage stress in extreme situations. Subsequently, training sessions have been organized from 2018 for every French nuclear power plant staff; the program includes: generalities regarding crisis factors, crisis common factors, crisis protagonists' traits, stress definitions and processes, reactions to stress, manifestation of stress, techniques for optimizing the potential (TOP; see Perreaut-Pierre, 2019). TOP include techniques or strategies for self-management of stress such as emotion regulation, stimulating breathing, relaxing

breathing or diaphragmatic breathing, square breathing, progressive muscle relaxation, internal dialogue or self-talk, mental rehearsal, reflex Adjustment Signal-Sign, power nap or caffeine nap. **RESULTS AND DISCUSSION:** In two years, more than 800 people were concerned by self-management training distributed over 65% of the nuclear sites. This took three different forms: training in classroom, conferences and integration within the professional program. All this being performed by an ex-military with a substantial experience of battlefields and the related acute stress, each TOP was illustrated by lived examples of militaries engaged in fights or emergency recues after catastrophes. Trainees conceded that, if a young psychologist freshly out of the university and without any experience would have given the same lecture, the impact would not have been the same: after hearing the ex-military trainer, trainees trusted him and were ready to try the TOP. Trainees' feedback also showed that speaking of acute AND chronic stresses was appreciated, and, as TOP could be applied at work as well as in daily life, this was really welcomed. As a perspective, other professionals and teams in and out of the company ask for the training program. **RESEARCH SUPPORT:** Electricité de France.

**THE PSYCHOLOGICAL NATURE OF ALEXITHYMIA AND FUNCTIONAL CONNECTIVITY REORGANIZATION.** SV Tukaiev, TV Vasheka, ON Dolgova, Research Institute, National University of Physical Education and Sports of Ukraine, Kiev, Ukraine. **INTRODUCTION:** The alexithymia construct is characterized by impairment of emotional processing and reduced interaction between different brain areas during various experimental conditions. Yet little known about permanent alteration of functional connectivity associated with alexithymia in resting state. We aimed to investigate the resting state cortical networks of alexithymic personality type. Another purpose of current study was to establish the psychological nature and mechanisms of the occurrence of alexithymia by analyzing its connection with the properties of the nervous system, mental states and characteristics of the emotional sphere of personality. **METHODS:** 232 volunteers, first-third year students from the Taras Shevchenko National University of Kyiv aged 18 to 24 years (Mage = 19, SD = 1.13) participated in this study. EEG was registered during the rest state (3 min). We estimated the interhemispheric and intrahemispheric average coherence across all EEG segments in all frequencies from 0.2-45 Hz. Psychological testing was performed before the registration of EEG. To determine the level of alexithymia we used 26-item Toronto Alexithymia Scale (TAS-26). In order to measure individual typological characteristics, emotional sphere and mental states of the respondents, we used the following psycho-diagnostic methods: Temperament Diagnostics Test by J. Strelau; Eysenck's Personality Inventory; Taylor Manifest Anxiety Scale; UN Scale (Questionnaire for express diagnostics of neurotization level by L. Wasserman); State-Trait Anxiety Inventory (STAI) by C.Spielberger and Y.Hanin; Syndrome of Emotional Burnout by V. Boyko (SEB) and Maslach Burnout Inventory (MBI), Leonova`s the Degree of Chronic Fatigue Syndrome Test; Lemur-Tessier-Fillion Psychological Stress Measure (PSM-25); Boston the Social Stress Test "Lifestyle Analysis"; Technique of Differential Diagnostics of Depression by V.A. Zhmurov; Aggressive Behaviour Test by E. Illyn and P. Kovalev; Aggression Test by A. Assinger (assessment of aggressiveness in the relationship); Diagnostics of Emotional Response to Environmental Stimuli by V. Boyko. The Mann-Whitney test was carried out to compare the data of independent samples. To determine the type of distribution, the Kolmogorov-Smirnov test is used. Based on the normality of the sample, Pearson's correlation coefficient and Spearman's rank correlation coefficient were applied. **RESULTS AND DISCUSSION:** Alexithymic personality type was found in 43 volunteers (TAS-26 total score ≥74, alexithymia group). A control group consisted 113 subjects with low alexithymia (TAS-26 total score ≤62,non-alexithymia group).85 participants formed intermediate group (TAS-26 total score 62>and<74). The main factors related to alexithymia were a weak nervous system, low stress resistance, such characteristics of the emotional sphere, as high level of trait anxiety, depression, neuroticism, indirect verbal aggression, low levels of aggression; with mental states as, chronic fatigue, depression, psychological stress. The emotional exhaustion and reduction of personal achievements (MBI), the Resistance Phase (SEB) were the most pronounced within the alexithymia group. In background EEG activity during the development of the alexithymia variations in EEG spatial synchronization were observed in low- and high-frequency EEG components. Alexithymic personality type includes breaking of interhemispheric anterior frontal-frontal (alpha1,2-subbands) and formation central-temporal links (alpha1-subband) (awareness and cognitive processing of incoming information). We demonstrated left lateralization of intrahemispheric links in alpha3 (occipital-parietal area) and beta (central area) subbands (inner image formation, external attention). Inter and intrahemispheric coherence in low-frequency EEG components (theta2-subband) indicates the influence of alexithymia on attention focusing, working memory, and emotional processes. It was demonstrated that the topographical reorganization of functional connectivity under alexithymia had specific features reflecting information and emotion-activating processes. The results obtained confirm the adaptation theory of the alexithymia development, according to which, due to the weakness of the nervous system and high trait anxiety, the persons adapt to stressful situations by avoiding and suppressing negative emotions, which eventually creates the impossibility of their verbal description and expression.

**GENDER DIFFERENCES IN EMOTION INDUCTION BY MANUPULATED FEEDBACK DURING DESICION MAKING TASK.** AT Kamzanova, V Pivkina, G Matthews, AM Kustubayeva**,** Center for Cognitive Neuroscience, al-Farabi Kazakh National University, Almaty, Kazakhstan, University of

Central Florida, Orlando, USA. **INTRODUCTION:** Emotion induction by manipulating positive and negative feedback during decision-making task performance may have gender differences. Gender differences in ERP waves during emotional tasks were observed in previous studies. The aim of this study was to define gender differences in ERP waves during emotion induction during a decision-making task with positive and negative feedback. **METHODS:** Sixty volunteers participated in the present study. The average age was 25,97 SD= 6,52 (average age 26.7 SD= 5.30, 30 males; average age 25.2 SD= 7.56; 30 females). The study was approved by the local Ethic Committee of the Medical Faculty of Kazakh National University. All participants signed a consent form, and completed a mood questionnaire (DSSQ, Matthews et al., 2002) before and after a decision-making task (Kustubayeva et al. 2010) with positive and negative feedback conditions in random order. After assessment and a task involving different rescue routes and choosing a route, participants received information about the result of the current decision-making set (Fbk_1) and a result from all previous sets (Fbk_2). EEG was recorded continuously during task performance by using the Neuron-spectrum-4 electroencephalograph. Peak amplitude and latency of the following ERP waves were analyzed using the EEGlab/ERPlab toolbox (Lopez-Calderon & Luck, 2014) in MATLAB: P100 (50 ms to 150 ms), P300 (250 ms to 600 ms), FRN (feedback related negativity, 200 ms to 250 ms). **RESULTS AND DISCUSSION:** Increased P100 amplitudes on Fbk_1 in Cz (F=5.63, p=0.02) and Pz (F=4.21, p=0.04) were found in females in comparison to males in the negative condition only. P300 amplitude to Fbk_2 was significantly higher in the female group in Pz (F=4.90, p=0.03) for negative condition and in Fz (F=4.82, p=0.03) for positive condition. P300 amplitude to hazards were increased in the female group (F=4.82, p=0.03). Latency results revealed that females were significantly slower in comparison to males in both conditions of the task (F=4.77 to 11.10, p=0.00 to 0.03). There was no difference in FRN parameters. Males paid more attention to benefits in negative condition (F=5.45, p=0.02) vs. females, and an opposite tendency was observed in the positive condition (F=4.72, p=0.03). Emotion induction by manipulated positive and negative feedback during decision-making task performance revealed gender differences supporting higher brain activation and lower reactivity to emotion induction in females. Females were more sensitive to hazards. **RESEARCH SUPPORT:** A grant from the Ministry of Education and Science of Kazakhstan to AM Kustubayeva (AP05135266).

**INITIALLY UNRECOGNIZED NEUROMYELITIS OPTICA SPECTRUM DISORDER WITH CONSEQUENT END-STAGE SPINAL CORD ATROPHY.** I Nosek, J Boban, D Vlahovic, B Radovanovic, D Tihomir, D Kozic**,** University of Novi Sad, Faculty of Medicine, Oncology Institute of Vojvodina, Novi Sad, Serbia. **INTRODUCTION:** Neuromyelitis optica spectrum disorder (NMOSD) represents an immune-mediated neuroinflammatoy syndrome, that was classified as a separate entity after discovery of aquaporin-4 immunoglobulin G antibodies (AQP4-IgG). The neuroimaging spectrum of NMOSD classically consisted of bilateral optic neuritis and longitudinally extensive transverse myelitis (LETM) but was broadened to include lesions in the area postrema, diencephalon, brainstem and the cerebellum, and extensive cord atrophy as a chronic sequelae. **METHODS:** Follow-up magnetic resonance imaging (MRI) studies were performed over the course of three years and correlated with laboratory and clinical findings. **RESULTS AND DISCUSSION:** AntiAQP4 positive 65–year old female patient initially presented with underappreciated LETM and two years later developed multiple cerebral and cerebellar lytic demyelinating lesions associated with acute long segment optic nerve involvement. Two atypical and novel MRI findings in NMOSD were evident: the involvement of complete cross-sectional area of pons and microhemorrhage in the pons and corpus callosum, potentially associated with corticosteroid therapy. Raising suspicion of NMOSD is of a crucial importance in cases with isolated LETM, even when no lesions in the brain and optic nerves can be detected, due to recent reports of the continuous immunosuppressive therapy in order to prevent relapses in Anti-AQP4 positive cases, improve patient outcome and recovery.

**PREDICTION OF AUTONOMIC DYSFUNCTION TO MOTOR SEVERITY IN PARKINSON'S DISEASE IN SOUTHERN CHINESE.** C Cui, East Hospital, Tongji University School of Medicine, Shanghai, China. **INTRODUCTION:** Parkinson's disease (PD) is a common movement disorder characterized by bradykinesia, resting tremor and rigidity. The aim of our study was to investigate whether autonomic dysfunction could predict the severity of the development of motor symptoms of Parkinson's disease (PD) in southern Chinese population. **METHODS:** 246 PD patients were recruited in this study. All patients were evaluated by Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire (SCOPA-AUT), Hamilton anxiety rating scale and Hamilton depression rating scale and Unified PD Rating Scale provided by movement disorders society (MDS-UPDRS). We re-evaluated them with MDS-UPDRS door to door after 2 years of baseline for assessing the status of PD. **RESULTS AND DISCUSSION:** 246 patients finished the follow-up. SCOPA-AUT scores were associated with total score and subparts of MDS-UPDRS. (Total: p: <0.001; p: <0.001, adjusted; Part I: p: 0.005; p: 0.005, adjusted; Part II: p: <0.001; p: <0.001, adjusted; Part III: p: <0.001; p: <0.001, adjusted) As for subparts of SCOPA-AUT, the subpart of gastrointestinal symptoms, urinary symptoms, and drug usage were associated with changes of total score and subparts of MDS-UPDRS. (Gastrointestinal symptoms: total: p: <0.001; p: <0.001, adjusted; Part I: p: 0.005; p: 0.006, adjusted; Part II: p: <0.001; p: <0.001, adjusted; Part III: p: <0.001; p: <0.001, adjusted; Urinary symptoms: total: p: <0.001; p: <0.001, adjusted; Part I: p: 0.021; p:

0.021, adjusted; Part II: p: <0.001; p: <0.001, adjusted; Part III: p: <0.001; p: <0.001, adjusted; Drug usage: total: p: 0.001; p: <0.001, adjusted; Part I: p: 0.032; p: 0.033, adjusted; Part II: p: 0.018; p: 0.014, adjusted; Part III: p: 0.004; p: 0.003, adjusted) Cardiovascular symptoms and skin symptoms were associated with changes of total scores of MDS-UPDRS and motor function parts of MDS-UPDRS (Part II, Part III). (Cardiovascular symptoms: Total: p: 0.001; p: <0.001, adjusted; Part II: p: <0.001; p: <0.001, adjusted; Part III: p: 0.005; p: 0.003, adjusted; Skin symptoms: Total: p: 0.001; p: <0.001, adjusted; Part II: p: 0.005; p: 0.004, adjusted; Part III: p: <0.001; p: <0.001, adjusted) . Our study found that higher involvement of autonomic symptoms could predict motor functions in PD. Higher involvement of autonomic symptoms could reflect wider spread of α-synuclein, which could influence faster progression of motor function.

**NOLDUS PRESENTATION: THE STANDARDIZATION PARADOX: BETTER DATA WITH NATURALISTIC BEHAVIORAL TESTS.** A Willemsen, Noldus IT, Wageningen, The Netherlands. Most animals, like humans, have a rich and varied behavioral repertoire. Which behavior they show depends on internal and external cues, and that makes it quite variable. Since most scientific research depends on finding reproducible statistically significant differences between groups, it is desirable to reduce random variation as much as possible. Many paradigms (e.g. mazes, treadmills) therefore attempt to create a straightforward situation, in which all animals are subjected to exactly the same procedure. Despite this rigorous approach, the unexplained variation in the data remains, both within and between groups. Experimental conditions appear less standardized than they seem, leading to noise and even potentially biased data. Naturalistic behavioral tests can offer a solution. The Cognition Wall paradigm, carried out in Noldus PhenoTyper cages, is an example of a hands-off memory test with low noise and high reproducibility. Voluntary walking on the CatWalk device offers better validity and less variation than forced walking in treadmills. A recent study carried out in PhenoTyper cages at three sites in Europe demonstrated that proper standardization of lab procedures actually leads to identical results across sites.

## SYMPOSIUM 4: ZUKOWSKA STRESS NEUROSCIENCE SYMPOSIUM

Chairs: AV Kalueff (China, Russia, USA) and VM Klimenko (Russia)

**INTRODUCTION: PROFESSOR ZOFIA ZUKOWSKA.** Prof. ZOFIA M. ZUKOWSKA (1949-2012) received her M.D. and Ph.D., trained in cardiovascular medicine at the Warsaw Medical Academy (Poland). She pursued post-doctoral training at the NIH, working with such renowned scientists as Irwin Kopin, Scientific Director of NINDS, and Julius Axelrod, a Nobel Laureate. During this research period, her interest in stress and neuropeptides became galvanized. For the 25 years, she was a professor (and, later Chair) of the Department of Physiology and Biophysics at Georgetown University, before moving to the University of Minnesota as the Director of Stress Physiology Center. Her research examined how stress affects cardiovascular and metabolic health and diseases, and the role of peptides, in particular neuropeptide Y (NPY), a sympathetic neurotransmitter and stress mediator. She was the first to determine that NPY mediates stress-induced prolonged vasoconstriction and vascular mitogenic and pro-atherosclerotic effects (via Y1 receptors) and potent angiogenic actions (via Y2 receptors), establishing the role of NPY in ischemia, retinopathy, tumors and obesity. Professor Zukowska (or Zosia, as she was known and admired by many) was a good friend and a strong supporter of the ISBS, serving as a regular plenary speaker at our conferences. Her scientific vision, extraordinary creativity, kindness to colleagues, and the talent to be daring, continue to inspire all her ISBS colleagues and their research. This regular ISBS symposium continues Zofia's scientific legacy in the field of biological psychiatry of stress.

**MODERN IMAGING IN CLINICAL AND BEHAVIOURAL NEUROSCIENCE.** D Kozić, University of Novi Sad Faculty of Medicine, Novi Sad, Serbia. **INTRODUCTION:** Novel developments in brain imaging, especially magnetic resonance imaging (MRI) and positron emission tomography (PET), offer us the remarkable opportunities of non-invasive investigation of physiologic brain ageing and detection of microstructural changes, even in presymptomatic stages of neurodegenerative disorders. **METHODS:** Structural (MRI) and molecular (PET) imaging, performed in our institution allowed us to obtain powerful insights into the structure and function of the healthy brain in different age groups and in numerous disorders affecting the brain. **RESULTS AND DISCUSSION:** Novel brain imaging modalities have given us remarkable evaluation of brain, not only in evaluation of common and rare diseases, but also the evaluation of presymptomatic stages of dementia, movement disorders, chemotherapy or radiotherapy - induced cerebral metabolic changes, affecting a large segments of the

population. These biomarkers could be used not only in establishing the correct diagnosis, but also, to monitor the treatment effects.

**BLOOD-BASED LIPIDOMICS OF SCHIZOPHRENIA AND OTHER PSYCHIATRIC DISORDERS.** D Petrova, A Tkachev, Ph Khaitovich**,** Skolkovo Institute of Science and Technology, Moscow, Russia. **INTRODUCTION:** Lipid metabolism reflects important aspects of healthy and pathological biological processes. Blood plasma lipids represent the pool of lipids that are utilized across different tissues, including nervous tissues, and are an important indicator of metabolic health. Differences in concentration of brain lipids have been reported for psychiatric disorders compared to healthy controls. On the other hand, psychiatric disorders have been shown to be associated with physical-health comorbidities such as cardiovascular disease, diabetes, obesity. For this study, we aimed to discover lipid alterations in blood plasma of psychiatric disorders using three independent sample cohorts. **METHODS:** For this study, blood sample were collected from 476 schizophrenia patients, 333 bipolar disorder patients, 256 major depressive disorder patients, and 529 control individuals representing three independent cohorts collected in Germany, China and Russia. We used untargeted mass spectrometry coupled with liquid chromatography to assess lipid abundances of a total of 1361 lipid features reproducibly quantified across the three cohorts. **RESULTS AND DISCUSSION:** Statistical analysis of the quantified lipid features revealed significant differences in lipid abundances between schizophrenia patients and control individuals, and these differences were reproducible across all three sample cohorts. Among these differences, the abundance levels of phospholipid plasmalogens and acylcarnitines were reduced in schizophrenia patients, while ceramides were consistently increased. Moreover, logistic regression classifier demonstrated that schizophrenia patients could be distinguished from control individuals with good accuracy based on blood lipid abundances. Comparison of lipid alterations observed in schizophrenia patients with the differences found in bipolar and major depression disorders further revealed extensive similarity of disease-related lipidome alterations among three disorders. **RESEARCH SUPPORT:** The Russian Science Foundation grant 19-74-00151.

**MATERNAL HYPERHOMOCYSTEINEMIA DISRUPTS NEUROPIL FORMATION IN RAT HIPPOCAMPUS INDUCING MEMORY DEFICIT IN ADULTHOOD.** DS Vasilev, AD Shcherbitskaia, NL Tumanova, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia. **INTRODUCTION:** The action of different stressors during pregnancy leads to various complications both in the maternal organism and developing fetus increasing risk of abnormal brain development and functioning via disturbance of the essential trophic factors balance. In this study we examined the effects of maternal HHC on structural abnormalities in dorsal hippocampus as well as on memory of rat offspring. We investigated the ultrastructure of neuropil and analyzed the distribution of synaptic marker proteins during first month after birth. **METHODS:** HHC was induced in female rats by per os administration of 0.15% aqueous methionine solution (0.10-0.15 g per animal) in the period of days 4-21 of pregnancy. The hippocampus structure was investigated in rat pups. The distribution of dendritic spines involved in long-term potentiation were analyzed by immunohistochemistry of marker proteins. The ultrastructure of synaptic terminals and contacts were studied using FEI Tecnai V2 (FEI, USA) transmission electron microscope. We tested short-term and spatial memory of adult offspring using the 8-arm maze test. **RESULTS AND DISCUSSION:** In HHC group of adult rat offspring, the number of erroneous runs in the 8-arm maze test was increased compared naive control, suggesting some memory impairment. The electronic microscopy of the CA1 hippocampus tissue of HHC pups on P5-P14 showed increased number of the intracellular spaces, growth cones, and undeveloped synapses compared to naïve control suggesting the delay in the development of cortical neuropil. Furthermore, prenatal HHC had a negative effect on the number of mature synaptopodin-positive dendritic spines in stratum radiatum-moleculare of CA1 area in P20 pups. These changes may reflect impaired afferentation of pyramidal neurons in CA1 of hippocampus and decreased neuronal network plasticity resulting in learning and memory deficits. Our data suggest that maternal HHC affects formation of hippocampus neuropil in early postnatal ontogenesis, leading to memory deficit in the adulthood. **RESEARCH SUPPORT:** RFBR 20-015-00388 and Russian state budget assignment AAAA-A18-118012290373-7.

**MODULATION OF DETRUSOR MUSCLE AND EXTERNAL URETHRAL SPHINCTER ACTIVITY BY SITE-SPECIFIC ELECTRICAL STIMULATION OF RAT SPINAL CORD.** Y Sysoev, E Bazhenova, V Lyakhovetskii, G Kovalev, P Shkorbatova, N Pavlova, O Gorskii, N Merkulyeva, D Shkarupa, P Musienko, Institute of Translational Biomedicine, St. Petersburg State University, Department of Pharmacology and Clinical Pharmacology, St. Petersburg State Chemical-Pharmaceutical University, Pavlov Institute of Physiology RAS, Russian Research Center of Radiology and Surgical Technologies, Ministry of Healthcare, Clinic of High Medical Technologies, St. Petersburg State University, St. Petersburg, Russia. **INTRODUCTION:** Spinal cord injury (SCI) is often accompanied by disturbances of lower urinary tract (LUT) function manifesting in as overactive bladder and/or detrusor sphincter dyssinergia. Promising approach for the treatment of LUT system disabilities can be a neuromodulation of the spinal neuronal networks contributing to the micturition control by epidural electrical stimulation of the spinal cord (EES). Up today the neuronal mechanisms underlying these modulatory effects have

been poorly investigated. The main purpose of the present study was to reveal the hypothetical mechanisms of EES effects to sympathetic, parasympathetic and somatic spinal visceral networks controlling normal detrusor (Detr) and external urethral sphincter (EUS) activity. **METHODS:** The study was performed on 4 adult male Wistar rats. We implanted stainless steel wire EMG electrodes into the EUS and Detr muscles. The thoracolumbar stimulating electrode was implanted on the VT12 vertebral level corresponding to T13-L1 spinal region. The sacral stimulating electrode was implanted on the VL2-VL3 vertebral level in close relation to S1 spinal root projecting afferent and efferent pathways to the corresponding spinal segment. After 3-4 weeks of the surgery the recorded motor evoked potentials generated by EES aiming to recruit various spinal pathways responsible for LUT control in thoracolumbar and sacral spinal cord regions. The reflex responses were recorded from EUS and Detr when the tested rat was sitting in the plastic box. The averaged latencies and peak-to-peak amplitudes of evoked responses were analysed. The hierarchical linear model with random intercept was used to compare latencies of EUS and Detr responses obtained from thoracolumbar vs. sacral regions of the spinal cord stimulation. The criterion level for the determination of statistical difference was set at $P < 0.05$. **RESULTS AND DISCUSSION:** The obtained results demonstrate that activation of detrusor muscle mainly occurs during the stimulation of the thoracolumbar spinal cord whereas external urethral sphincter was activated predominantly by sacral stimulation. These findings can be used for development of new neuromodulation approaches based on EES for recovery of autonomic functions after severe SCI. **RESEARCH SUPPORT:** The Russian Foundation for Basic Research (RFBR) grant 20-015-00568 and the SPbU internal grant ITBM_2019 (ID: 40986737/51134206).

**ACTIVATION OF STRESS- AND NEUROPLASTICITY-RELATED GENES IN THE HIPPOCAMPUS OF RATS FOLLOWING MORRIS WATER MAZE TRAINING.** PE Panchenko, HM Goss, KR Mifsud, EM Price, JMHM Reul, Neuro-Epigenetics Research Group, University of Bristol, Bristol Medical School, Bristol, UK. **INTRODUCTION:** Effective navigation in one's environment is crucial for survival. Adaptation to a changing environment involves complex molecular responses in different brain regions. Neuroplasticity in the hippocampus is required for the formation of spatial representations of the environment. It is known that the spatial memory formation requires changes in gene transcription within hippocampal neurons. However, whether the same genes are involved in memory formation during the initial acquisition of spatial information (learning) and relearning process (which occurs when the spatial environment changes) is currently unknown. In this study, we subjected rats to the Morris Water Maze (MWM) spatial learning test, followed by a reversal test during which the rats were forced to adapt to the new position of a hidden platform. The aim was to compare the effects of initial spatial learning and relearning on the expression of stress- and neuroplasticity-associated genes in the rat hippocampus. **METHODS:** MWM training was performed for three consecutive days with a hidden platform kept in a fixed position in a circular pool filled with water. On the fourth day, the reversal test was performed where the platform was moved to an opposite position within the pool. Time taken to find the platform (latency) was recorded, along with the number of crossings made of the previous platform location (platform zone). We compared Lister-Hooded male rats undergoing reversal test (MWM Reversal group) with rats trained only on the first day (MWM D1 group), naïve rats (baseline group, BL) and time-matched swim control rats (SC D1 and SC D4 groups) that swam in the same maze, but without a platform. Hippocampi were collected 90 minutes after the start of the first trial of the day. Messenger RNA expression levels of stress- and neuroplasticity-related genes Sgk1, Per1, Camk2a and Grin2b were evaluated by RT-qPCR. **RESULTS AND DISCUSSION:** The latency to the platform decreased significantly over three days of training, showing successful spatial learning. After the platform reversal, MWM-trained rats crossed the platform zone significantly more times than the control group rats (SC D4), indicating that trained rats were actively searching for the platform in its previous location. Therefore, this behaviour demonstrates the successful acquisition of spatial information. Expression of Per1 and Sgk1 was increased after the first day of training in both MWM D1 and SC D1 groups, compared with BL group. This response could be linked to the role of these genes in the stress response occurring in unknown and potentially life-threatening environment. After the platform reversal, Sgk1 gene activation was significantly attenuated. On the contrary, Per1 mRNA levels were significantly higher in MWM reversal group, compared with BL group. No significant alterations were found in the expression of Camk2a and Grin2b genes. Overall, our results support the hypothesis that spatial memory formation involves altered gene expression in the hippocampus. The exact role of Sgk1 and Per1 in relearning process remains to be revealed in future studies. Follow-up transcriptomic studies are necessary to assess changes happening during MWM reversal test on whole-genome level and to elucidate gene networks involved in the fundamental process of spatial memory formation and adaptation to a changing environment. **RESEARCH SUPPORT:** The Biotechnology and Biological Sciences Research Council (BBSRC) grant BB/P001653/1.

**INTEGRATING ELEVATED PLUS MAZE AND DARK/LIGHT BOX TO DETECT ANXIETY-RELATED BEHAVIOR DUE TO SYNERGISTIC EFFECT OF PSYCHOSOCIAL STRESS IN OBESE MALE MICE.** C Baroni, C Spalletti, J Agrimi, V Casieri, M Caleo, V Lionetti, Sant'Anna School of Advanced Studies, Neuroscience Institute, National Research Council (CNR), Pisa, Italy. **INTRODUCTION:** Obesity (Ob) and psychosocial stress (PS) are increasingly coexisting within the same individual affected by anxiety disorders. We have recently demonstrated that psychosocial stress impinging obese mice seriously

alters hippocampal structure leading to behavioral disorders. However, the dysfunctional impact of Ob and PS synergy on emotionl reactivity requires further investigations using different tests. In order to minimize the limitatons due to single test, we have compared results obtained by elevated plus maze (EPM) and dark/light box (DLB), two different gold standard anxiety tests, in obese stressed mice. **METHODS:** Hippocampal remodeling was induced in male wild-type C57BL6/J mice (n=8; 10 weeks old) fed with high-fat diet (HFD) for eighteen weeks and exposed to resident-intruder test (RIT) during the last two weeks of diet to spark off PS. Age-matched male mice fed with a standard diet (SD) served as controls (n=4). Mouse emotional reactivity was assessed through both EPM and DLB test. To assess hippocampal morphological alterations, laminae volume (Hoechst), neurogenesis (BrdU-positive cells), synaptic plasticity (PV-positive interneurons) and astrogliosis (GFAP expression) were analysed on perfused brain slices. Hippocampal Brain-Derived Neurotrophic Factor (BDNF) expression, whose lower levels are an index of anxiety vulnerability, was measured by Western blot. **RESULTS AND DISCUSSION:** In the same obese stressed mice with hippocampal remodeling and lower BDNF levels, EPM and DLB have revealed different magnitude of anxiety-related behavior. In particular, EPM showed zeroing of percentage of entries and time spent in the open-arms of the maze in obese stressed mice compared to SD animals. Conversely, DLB showed no significant difference in number of transition between the two zones in Ob+PS group compared to SD one; although, time spent in light side, number of rears, latency were significantly reduced by 76.3±1, 89.4±1 and 94.4±1 respectively, in Ob+PS mice compared to SD rodents. In conclusions, integration of EPM and DLB provides a more complete and reliable picture of emotional reactivity of stressed obese mice. Our data will be helpful to design further experimental protocol. **RESEARCH SUPPORT:** Internal funds of Sant'Anna School of Advanced Studies, Pisa, Italy.

**MOLECULAR ALTERATIONS IN BRAIN, BONE MARROW, TESTIS AND ADRENAL GLANDS OF STRESSED MICE.** MP Petrova, TS Glinin, VA Mamontova, V Shcherbinina, AB Volnova, PA Starshova, EV Daev, PE Khaitovich, CAS-MPG Partner Institute for Computational Biology, Shanghai Institutes for Biological Sciences CAS, Shanghai, China. **INTRODUCTION:** There absolutely clear now that psychogenic stress can have a variety of adverse effects throughout the body, but the most vulnerable systems are nervous and immune. Acute psychogenic stress induces DNA damage and chromosomal aberrations in dividing germline and somatic cells of the house mouse, leading to a decrease in the reproductive success and immunosuppression. High-throughput ‘omics’ approaches have made it possible to study in detail the changes that occur during stress in the nervous, endocrine, and immune systems at the cellular level. **METHODS:** Our study was designed to assess concordance between transcriptional responses induced by 2-h stress pheromone 2,5-dimethylpyrazine exposure and commonly used immobilization stress paradigm in mouse bone marrow and testis tissues of CBA mice using RNA sequencing. The lipidomic profile of the prefrontal cortex of the same CBA mice was evaluated by liquid chromatography and mass spectrometry. The same lipidome analysis approach was used for profiling large-scale differences in the lipid composition of the prefrontal cortex and adrenal glands of CBA and C57BL/6 mice subjected to 21 days of ultrasound stress. **RESULTS AND DISCUSSION:** RNA sequencing analysis identified genes showing statistically significant changes in response to immobilization in the bone marrow of CBA mice. Most of these genes demonstrated similar trends of expression changes across pheromonal and immobilization stress, with the strongest positive correlation for genes involved in unfolded protein response. LC-MS data analysis showed that chronic ultrasound stress affects primarily on the lipid profile of the adrenal glands of C57BL/6 mice and that adrenal lipid abundance alters in opposite directions in CBA and C57BL/6 strains. Meanwhile, prefrontal cortex lipidome responses correlated positively between these two mouse strains. The study provides preliminary evidence that psychogenic stress of different duration induces transcriptome and lipidome changes in neuroendocrine and immune tissues that may explain adverse physiological and cytogenetic effects previously shown by our group.

**ACUTE PAIN AS A POSSIBLE CAUSE OF A NEGATIVE STRESS REACTION THAT PROVOKES TACHYARRHYTHMIA IN ELDERLY PEOPLE.** VP Nesterov, AI Burdygin, KB Ivanov, SA Filenko, SV Nesterov, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia. **INTRODUCTION:** Previously it was suggested that a sudden action of a stressor on an elderly people can trigger negative stress-reactions in their cardiovascular system (CVS). Later this suggestion was confirmed in practice - in one of our elderly patients, whom we have been examining for over 18 years, twelfth left rib (*costa fluctuantes*) was broken in the fall, and the acute accompanying pain provoked the emergence of persistent paroxysmal atrial tachyarrhythmia. The report will present evidence confirming this fact and characterizing the functional state of his CVS for more than 15 years before the injury and for several months after it. This work is part of a comprehensive comparative study aimed at studying the features of the formation of peripheral mechanisms of autonomous (neuroendocrine) regulation of CVS muscular effectors in patients on the late stages of ontogenesis and subject to various stressful conditions. Individual differential diagnosis of patients is currently recognized as very relevant. **METHOD:** The main method of CVS diagnostics was piezopulsometry with a corresponding spectral analysis of the variability of parameters of arterial blood pressure pulse waves (APP; [mm Hg]). As the

universal parameter for evaluation of the nature of autonomous regulation of APP and heart rate (HR), we used the point of absolute positive extremum on the differential graph of APP (VmaxPP; [mm Hg/s]). The spectral power of the APP oscillations ([mm Hg/s]$^2$) was measured using VmaxPP parameter, as well as of the HR oscillations was measured using the TNN [ms$^2$] parameter. The regulatory effects of the autonomic (vegetative) nervous system (ANS; frequency ranges – HF and LF), as well as the action of humoral catecholamines (HC) of the endocrine system, which were limited to the frequency range ULF (0.003-0.03 Hz), were investigated. The central (*a.carotis*) arterial vessel of an elderly Mr. M. was investigated during 68-86 years old as part of a comparative study of 117 volunteers of different age groups. The advantage of the arterial piezopulsometry (APP-method), in contrast to ECG, is to evaluate not only changes in HR, but also the dynamics of changes in APP. **RESULTS AND DISCUSSION:** It is shown that acute pain in an elderly person can provoke a negative stress response in his organism, in particular in his CVS. The report provides data indicating that the impact of acute pain on the first day led to a sharp increase in heart rate (from 56-59 to 70-90 beats/min) and arrhythmias (from 0.12% to 7.3% of the number of registered cardiocycles, i.e. more than 60 times), mainly due to numerous extrasystoles. A reflection of these changes was the disappearance of the overlay on catakrot of systolic wave with the other APP wave reflected from the peripheral vascular resistance, as evidenced by the nullification of the augmentation index (AIx; [%]) of pulse waves of BP in this period, and the decline sympathovagal balance index (SVIx) from 0.6 to 0.19. Then, apparently, by mobilizing the protective resources of the autonomous regulation of the CVS muscular effectors, the normal (approximately as it was before the injury) level of cardiohemodynamics is restored. The results of spectral analysis show that a significant and rapid increase in the regulatory activity of the parasympathetic autonomic nervous system plays a crucial role in this. At the same time, there is a sharp drop in the activity of humoral catecholamines (a decrease of 10 times). In a more distant period (after two or more months), the protective resource of autonomous (vegetative) regulation is apparently exhausted. The function of maintaining normal hemodynamics is assumed by humoral catecholamines, which prevent an excessive increase in heart rate and the occurrence of arrhythmias, while replacing the influence of mediators of the sympathetic link of the autonomous regulation of CVS. **RESEARCH SUPPORT:** The Russian Government program project AAAA-A18-118012290142-9.

**NOREPINEPHRINE AND SEROTONIN IN THE DIFFERENT REGIONS OF THE CENTRAL NERVOUS SYSTEM OF DAT -/- RATS.** NS Pestereva, DS Traktirov, AZ Marshak, VS Artemova, ZS Fisenko, MN Karpenko, VM Klimenko, Pavlov Department of Physiology, Institute of Experimental Medicine, Peter the Great St. Petersburg Polytechnic University, Institute of Translation Biomedicine, St. Petersburg State University, St. Petersburg, Russia. **INTRODUCTION:** DAT-KO rats with genetically ablated DAT (dopamine transporter) gene have been developed to research diseases caused by the accumulation of extracellular dopamine with a simultaneous decrease in its intracellular content. An influence of knock-out DAT gene to content of dopamine is well-known, but influence of this mutation on content of other biogenetic amines, particularly norepinephrine and serotonin is not well-studied. The aim of this work was to analyze the content of norepinephrine, serotonin and its metabolite HIAA in various regions of the central nervous system of DAT-/- rats. **METHODS:** The study was performed by HPLC-ED using an external standard, the content of norepinephrine (NE), serotonin (5-HT), indoleacetic acid (HIAA) was expressed as ng / mg protein in the sample. The content of these monoamines was analyzed in the striatum, hippocampus, prefrontal cortex, olfactory bulbs, medulla oblongata, cerebellum and spinal cord in male DAT-/- rats (n = 5), the control group consisted of Wistar rats (n = 5). Data was expressed as mean ± SEM and analyzed using the t-test. **RESULTS AND DISCUSSION:** NE content in the cerebellum of DAT-/- rats was 1.6 times higher vs. control (3.4 ± 1.4 vs 5.6 ± 1.3, p = 0.045), in the olfactory bulbs of experimental rats the amount of NE was below the level of detection, while in the control it is 0.2 ± 0.1. We found 30% lower serotonin level with a simultaneous increasing indoleacetic acid level 3.8 times (0.8±0.2 vs 3.2±0.5, p=0.002) in striatal cells of DAT-/- rats. In the hippocampus, there was a 1.8-fold decrease of HIAA. The most pronounced changes were observed in the cerebellum: DAT-/- rat level of 5-HT decrease 12 times vs. DAT+/+ (0.07±0.01 vs 0.92±0.03, p=0.007) with unchanged HIAA level. In the medulla oblongata, 5-HT was below the level of detection, and 0.6±0.3 in control. There were no changes in other brain regions. Since serotonin enhances neurogenesis, we suggest that the pronounced decrease of the content of 5-HT that we revealed in the brain of DAT-/- rats indicates a decrease in the intensity of neurogenesis. An increase in the content of norepinephrine in the cerebellum was previously described in papers studying morphine intoxication at the stage of forming the addiction. Our results support facilitated sensitization to addictive drugs in rats, as already demonstrated by Morice et al. (2010) for DAT-KO mice. **RESEARCH SUPPORT:** The RFBR grant 19-34-90030.

**EMOTIONAL OVEREATING INDUCED BY BRAIN STIMULATON REWARD IN FREE-FED RATS.** NS Efimov, AA Lebedev, YuN Bessolova, ER Bychkov, VA Lebedev, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia.
**INTRODUCTION.** Emotional eating is a phenomenon in which a person consumes food for reasons other than being physically hungry. Because emotional eating is significantly related to clinical eating disorders like bulimia and binge eating disorder, as well as obesity and malnutrition, there is growing

interest in learning how to treat and prevent the issue. More specifically emotional eating is linked to a tendency to overeat in response to negative emotions, but little is known about emotional eating and positive emotions – like happiness or excitement. The purpose of this work was to prove that the reaction of food self-deprivation in "fed up" rats is a model for the study of emotional overeating in the experiment. **METHODS.** To date, the self-deprivation reaction, i.e. self-isolation of an animal from food during electrical self-stimulation of the brain, was studied in animals with food deprivation. To induce the self-stimulation of the lateral hypothalamus, male Wistar rats were trained to press the pedal in the Skinner box. After training, rats received a food deprivation, a feeder was placed in the Skinner box, and a conditioned reflex on food reinforcement was developed in rats for 5 days. **RESULTS.** The food self-deprivation reaction was observed in these rats with a stimulating current intensity of 10% and above the threshold for self-stimulation. "Hungry" animals pressed the pedal for hypothalamic self-stimulation and did not distract to the feeding trough. Food reactions were observed only when using the threshold current. Then rats received a free access to food, but the animals, pressing the pedal for self-stimulation, continued food intakes for many times and eat up to 60 pellets in 10 minutes of the experiment. To determine the sensitivity of the method, dopamine sulpiride receptor D2 antagonist at doses of 5 and 20 mg/kg ip, orexin receptor antagonists OX1R SB-408124 and OX2R TCS-OX2-29 0.5 mg/ml, 20 µl intranasally were used. Sulpiride administration in "fed" rats decreased both the eating behavior and the reinforcing properties of electrical stimulation in food self-deprivation testing. At the same time, SB-408124 administration induced only a decrease in the number of seeds eaten, while the number of pedal presses did not change. **DISCUSSION:** The conclusion was made about the selectivity of the orexin OX1R SB-408124 antagonist for emotional eating compared with orexin BOX2R TCS-OX2-29 and D2 receptor antagonist dopamine sulpiride. Because emotional eating is significantly related to clinical eating disorders like bulimia and binge eating disorder, as well as obesity and malnutrition, there is it seems promising to use drugs of the orexin system.

**ANTICONVULSANT PROPERTIES OF THE NEW GLUTAMATE NMDA-RECEPTOR COMPLEX ANTAGONISTS – 1,2-SUBSTITUTED IMIDAZOL-4,5-DICARBOXYLIC ACIDS.** EE Jakovleva, SP Foksha, MA Brusina, LG Kubarskaja, LB Piotrovskij, ER Bychkov, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** Antagonists of NMDA receptors exhibit anticonvulsant activity in various models of seizures. However, the application of current NMDA-blockers is limited by their toxic effects - the problem of mild regulation of the NMDA receptor function, and accordingly the safety of the therapy, is still unresolved. In this regard, the investigation and development of new effective and safe NMDA-targeted agents for modulation neuronal synaptic transmission, which plays a decisive role in the pathogenesis of convulsions, remains a relevant task of neuropharmacology. The aim of the study was to investigate the anticonvulsant effect of new ligands for the glutamate NMDA-receptor complex – imidazole-4,5-dicarboxylic acid derivatives. **METHODS:** The experiments were performed on male mice weighing 18-25 g. The effects of two derivatives (substances 1 and 2) of imidazole-4,5-dicarboxylic acid (IDCA), synthesized in the Department of Neuropharmacology of the Institute of Experimental Medicine were studied. The agents were dissolved in distilled water, adjusted using 0.5 n NaOH to pH=7.0 and was injected into the lateral ventricles of an awake mouse brain in a volume of 5 µl. As a convulsant, an NMDA solution was injected into the lateral ventricles of the brain (Sigma, USA, 5 µg in 5 µl). Test substances were administered in doses of 0.1-0.5 µmol in 5µl 15-20 min before NMDA, after that motor activity and animal behavior, as well as the intensity, duration of convulsions and the frequency of deaths due to introduction of NMDA were registered in each experimental group. **RESULTS AND DISCUSSIONS:** On the model of NMDA-induced seizures in the dose range from 0.1 to 0.5 mmol, the studied IDCA derivatives showed anticonvulsant activity of various degrees of severity. Administration of substance 1 at doses of 0.2-0.3 mmol reduced the percentage of deaths caused by NMDA convulsions from 100 to 50%. After the introduction of substance 1 at 0.4 mmol, there were no fatal outcomes, and the duration of convulsions decreased from 325 (at 0.3 mmol) to 125 s. In addition, sedative and muscle relaxant effects were revealed. Substance 2 also showed anticonvulsant activity in this test, reducing the percentage of animal mortality at 0.1 mmol from 100 to 16.7%, and at 0.2 mmol in 100% of cases, preventing deaths and completely protecting animals from the onset of seizures with concomitant sedative and muscle relaxant effects. At 0.3 mmol, anticonvulsant and muscle relaxant effects were less pronounced (tonic-clonic convulsions and death were observed in 37.5% of cases). With a further increase of substance 2 concentration subtoxic and toxic effects (increased respiratory rate, heart rate, convulsions and tremor) and 75% mortality were observed. Thus, the results of the study confirm dose-dependent anticonvulsant activity of new antagonists of the glutamate NMDA-receptor complex - 1,2-substituted imidazole-4,5-dicarboxylic acids, administered at 0.1-0.5 mmol into the lateral ventricles of the rodent brain, that indicates the promising aspect of further development of these substances and searching for new potential anticonvulsants agents among this pharmacological class.

**ROLE OF THE GRELIN SYSTEM IN ANXIETY AND STABILITY OF THE PERIPHERAL BLOOD GENOME AFTER VITAL STRESS.** GP Kosyakova, AG Pshenichnaya, KE Gramota, IV Kazurov, VA Lebedev, Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg State

University of Chemical Pharmaceuticals, St. Petersburg, Russia. **INTRODUCTION:** A change in the state of an organism of rats manifests itself after obtaining vital stress in order to study the effects of ghrelin and its receptor antagonist D-Lys3] -GHRP. In particular, this indicates a stress factor, which is reflected in the destabilization of the peripheral mononuclear cell genome blood of animals. This factor is not only of scientific, but also of practical interest: how much vital stress affects behavior and destabilization of the animal peripheral blood genome. In this regard, we continue research on the assessment of such an informative indicator characterizing the instability of the cellular genome, such as the frequency of red blood cells and lymphocytes with micronuclei. **METHODS:** Mental trauma was caused by a stressful effect, the essence of which was the animal experiencing the circumstances of the death of a partner from the actions of a predator. A group of rats was once placed in a terrarium to the tiger python. After the action of vital mental stress in rats, two associated behavioral phenomena were observed - a high level of anxiety and an increase in the number of buried balls. This was accompanied by a decrease in communicativeness. Peripheral blood in rats was taken from the tail vein, a drop of blood was applied to a glass slide, dried in air and fixed with 96% ethanol. Next, coloring was carried out according to Romanovsky-Giemsa. To determine the frequency of occurrence of mononuclear cells with micronuclei, at least 10 thousand cells from each individual were analyzed. The study processed only morphologically normal, intact cells. The number of genetically aberrant cells was expressed in ppm. Blood red blood micronuclei were detected by Romanovsky–Giemsa dye. The preparations were examined using an Olympus Vanox–T microscope. **RESULTS AND DISCUSSION:** The data obtained by the frequency of red blood cells and lymphocytes with micronuclei in the rat group after vital stress with and without drug administration are of undoubted interest. The drug ghrelin with an intranasal course (7 days, at 10 μg/20 μl), administration after the presentation of vital stress exposure reduced anxiety level and normalized compulsive behavior). Despite the low background frequency of the occurrence of mononuclear cells with micronuclei between the studied groups of animals, significant differences were recorded. The frequency of micronuclei in rat peripheral blood mononuclear cells after vital exposure without drugs amounted to an average of 1.12, whereas even with intranasal administration of ghrelin and its antagonist of the ghrelin receptor D-Lys3] -GHRP-6, a tendency to a decrease in the frequency of micronuclei in red blood cells could be detected peripheral blood up to 0.6 ‰. Thus, ghrelin and its antagonist ghrelin receptor D-Lys3]-GHRP-6 reduces the manifestation of compulsive behavior and can be considered as correctors caused by vital stress anxiety disorders of an obsessive-compulsive nature, emotional behavior and cognitive impairment. They also reduce the instability of the genome of peripheral blood mononuclear cells, reflected in fewer anormal cells. The use of intranasal administration of ghrelin and its analogues in the clinic may allow the use of small doses of substances and thereby reduce their possible toxic effects.

**DYNAMICS OF GLUTAMATE METABOTROPIC RECEPTOR GENES EXPRESSION IN THE RAT BRAIN IN THE MODEL OF TEMPORAL LOBE EPILEPSY.** AA Kovalenko, MV Zakharova, AP Schwarz, OE Zubareva, AV Dyomina, AV Zaitsev, Sechenov Institute of Evolutionary Physiology and Biochemistry, St. Petersburg, Russia. Temporal lobe epilepsy (TLE) is a severe neurological disease. About 30% of patients suffer from drug-resistant forms of the TLE, indicating the importance of new treatment approach development. The imbalance between inhibitory (GABA) and excitatory (glutamate) systems in various brain regions is considered to be the primary pathogenetic mechanism of epilepsy. Metabotropic glutamate receptors (mGluRs) modulating the activity of both excitatory and inhibitory synapse are believed to be promising targets for TLE treatment. This research aims to analyze the dynamics of gene expression of metabotropic glutamate receptors of the groups I and II in the dorsal and ventral regions of the rat hippocampus after lithium-pilocarpine seizures. Lithium-pilocarpine seizures were induced in Wistar rats at the age of 7-8 weeks by administration of LiCl solution (i.p., 127 mg/kg) and then after 24 h PC (i.p., fractional administration of 10 mg/kg every 30 min before reaching stage 4 severity of seizures on the Racine scale or to a maximum dose of 40 mg/kg). Half an hour before the first injection of PC, methylscopolamine was administered (i.p., 1 mg/kg). The control rats were injected with saline and LiCl. The relative gene expression of mGluRs of the group I (Grm1, Grm5) and II (Grm3) was measured by quantitative RT-PCR in the latent (3 and 7 days after PC-induced seizures) and the chronic (60 days after PC administration) phase of the model. We found that PC-induced seizures led to altered expression of both groups mGluR genes. Changes in the mRNA levels of Group I mGluRs are detected only in the latent phase: expression of the Grm1 gene was reduced 3 days after seizures in the dorsal hippocampus and 7 days in the ventral hippocampus, Grm5 mRNA was upregulated in the ventral and dorsal hippocampus on the 3rd day. The Grm3 mRNA expression in the dorsal hippocampus changed bidirectionally in the latent (increased expression) and in the chronic (decreased expression) phase. Thus, the mRNA expression of mGluRs changes after pilocarpine-induced seizures. The revealed changes in the expression of the Grm1 and Grm3 genes can lead to a decrease in the activity of NMDA receptors and the risk of excitotoxicity, which is probably one of the neuroprotective mechanisms that start after the induction of status epilepticus, which, however, no longer works in the chronic phase of the model. **RESEARCH SUPPORT:** The RSF grant 16-15-10202.

## SYMPOSIUM 5: ZNRC ZEBRAFISH NEUROSCIENCE SYMPOSIUM

Chair: AV Kalueff (Russia, USA, China)

**METHODS FOR MODELING PTSD IN ZEBRAFISH: A PILOT STUDY.** AV Zhdanov, SL Khatsko, KN Zabegalov, AV Kalueff, Ural Federal University, Yekaterinburg, Russia. **INTRODUCTION:** Post-traumatic stress disorder (PTSD) is a severe neuropsychiatric disease, affecting approximately 10% of the world's population and developing in nearly 40% of traumatized people. Despite rich clinical and preclinical data, there are no generally accepted pharmaceutical treatments for this disorder. Here, we used zebrafish (Danio rerio), as an effective and relatively inexpensive model organism, to develop novel PTSD models based on long-term predator (*Cichlasoma nigrofasciatum*) stress and chronic unpredictable stress. Hence, the aim of our study was to compare the effect of a 2-week unpredictable chronic stress, a stressful response to predator presentation, and the 2-week discontinuation of these stressors. **METHODS:** The experiment involved wild-type short fin adult zebrafish randomly divided into 5 groups: control (n = 22), experimental group with predator presentation (n = 12) and with chronic stress (n = 20), and similar experimental groups with 2-weeks discontinuation (n = 15 and 22). Animal behavior was assessed in the novel tank test (NT). Statistical analysis utilized Kruskal-Wallace test, followed by a Dunnett post-hoc test. In all analyses, significance was set at $p<0.05$. **RESULTS AND DISCUSSION:** NT observations revealed the significant decrease in the number and total duration of top entries, as well as an increase in its latency in all experimental groups vs. control. Experimental groups also displayed significantly more erratic movements, indicating anxious state and low exploratory activity. Freezing was also increased vs. controls. The developed stressing protocols evoked high anxiety in experimental groups with acute stressors and in stress discontinuation groups, thus showing some success in modeling PTSD-like behaviors. **RESEARCH SUPPORT:** Ural Federal University, Ekaterinburg, Russia.

**NON-PHARMACOLOGICAL AND PHARMACOLOGICAL APPROACHES FOR PSYCHIATRIC DISORDERS FROM ZEBRAFISH MODELS.** MS de Abreu, ACVV Giacomini, R Genario, N Rech, J Carboni, AM Lakstygal, TG Amstislavskaya, KA Demin, BE Leonard, M Vlok, BH Harvey, A Piato, LJG Barcellos and AV Kalueff, Bioscience Institute, Postgraduate Program in Environmental Sciences, University of Passo Fundo, Passo Fundo, Brazil, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Center, St. Petersburg, Institute of Physiology and Basic Medicine, Novosibirsk, Russia, University College Galway, Pharmacology Department, Galway, Ireland, Center of Excellence for Pharmaceutical Sciences, School of Pharmacy, North-West University, Potchefstroom, South Africa, Postgraduate Program in Neurosciences, Federal University of Rio Grande do Sul, Porto Alegre, Postgraduate Program in Pharmacology, Federal University of Santa Maria, Santa Maria, Brazil, School of Pharmacy, Southwest University, Chongqing, China. Acute and chronic stressors are common triggers of human mental illnesses. Experimental animal models and their cross-species translation to humans are critical for understanding of the pathogenesis of stress-related psychiatric disorders. Mounting evidence suggests that both pharmacotherapy and non-pharmacological approaches can be efficient in treating these disorders. Here, we analyze human and zebrafish (*Danio rerio*) data to compare the impact of non-pharmacological and pharmacological therapies of stress-related psychopathologies. Emphasizing the likely synergism and interplay between pharmacological and environmental factors in mitigating daily stress both clinically and in experimental models, we argue that environmental enrichment (EE) emerges as a promising complementary therapy for stress-induced disorders. We also demonstrated that EE increased top activity (time in top of the novel tank) and time near conspecifics (in the social preference test), thereby demonstrating robust anxiolytic-like and prosocial effects in zebrafish. Overall, this research calls for a broader use of novel model organisms, such as zebrafish, to study such treatments and their potential interplay.

**MODELING ANTIDEPRESSANT DISCONTINUATION SYNDROME (ADS) VIA REPEATED WITHDRAWAL FROM PAROXETINE TREATMENT IN ZEBRAFISH.** KN Zabegalov, AV Zhdanov, SL Khatsko, and AV Kalueff, Ural Federal University, Ekaterinburg, Russia, School of Pharmacy, Southwest University, Chongqing, China. **INTRODUCTION:** Previously mentioned antidepressant discontinuation syndrome (ADS) occasionally develops within a period after treatment discontinuation. It often happens after abrupt drug cessation and presents a complex of adverse symptoms. However, these symptoms can relapse in case of repeated treatment, and every last ADS episode is more deleterious than previous one. Hence, the aim of our study was to observe severe paroxetine withdrawal in zebrafish after a number of short discontinuation episodes. **METHODS:** A total of 81 adult wild type zebrafish with 50/50 male-female ratio were kept in group of 40 in 40-L tank filled with filtered water in accordance with zebrafish care standards. Zebrafish behavior testing included 5 min video recording in novel tank test after a week of chronic paroxetine treatment at 0.01 (n=18) and 0.05 mg/L (n=15), as well as after a week of daily episodes of 6h drug withdrawal at the above doses (n=18 for 0.01 mg/L, and n=15 for 0.05 mg/L). Behavioral markers included the latency (s) and number of top and bottom entries, time spent in the upper half (top) of the tank, duration and frequency of freezing and the number of anxiety-like erratic movements. **RESULTS AND DISCUSSION:** The fish from 0.01 mg/L repeated withdrawal group less

frequently entered the top zone and had a longer bottom latency in comparison with untreated control. Moreover, the fish of this group was the only one exhibiting freezing behavior. The higher dose (0.05 mg/L) paroxetine repeated withdrawal group did not exhibit freezing, though the fish of this group spent much more time in the upper half, than untreated fish. Regarding chronic treatment groups, the fish, undergone higher dose (0.05 mg/L) similarly to the withdrawal group spent most of the recording time at the upper half of the tank. Hence, together with our previous paroxetine study, paroxetine has prominent anxiolytic effect in high dose in zebrafish, as well as in mammals (Bourin, 2018). The resembling behavior of fish from 0.05 mg/L paroxetine withdrawal group may be explained as the result from incomplete drug washout within a 6-h cessation (Shrestha, et al., 2019). According to zebrafish anxiety hallmarks - bottom preference, freezing and erratic movements - the fish repeatedly withdrawn from 0.01 mg/L paroxetine, displayed anxiety like behaviors (rare top entries, and freezing). Hence, we observed paroxetine anxiolytic properties in higher dose (0.05 mg/L). The signs of ADS (anxiety) were presented in group, repeatedly withdrawn from the lower paroxetine dose (0.01 mg/L), apparently because lower dose washes out entirely from the fish body. **RESEARCH SUPPORT:** Ural Federal University, Ekaterinburg, Russia.

**DEEP LEARNING-BASED APPLICATION FOR PREDICTION OF DRUG-INDUCED BEHAVIOR IN ZEBRAFISH.** DV Bozhko, GK Galumov, AI Polovjan, SM Kolchanova, VO Myrov, VA Stelmakh and AV Kalueff, ZebraML, St. Petersburg, Russia, School of Biological Sciences, University of Queensland, Queensland, Australia, Neuroscience Center, Helsinki Institute of Life Science, University of Helsinki, Department of Neuroscience and Biomedical Engineering, Aalto University, Helsinki, Finland, Skolkovo Institute of Science and Technology, Center of Life Sciences, Moscow, Russia, School of Pharmacy, Southwest University, Chongqing, China. **INTRODUCTION:** Translational biomedicine aims to accelerate the integration of innovative preclinical research, such as novel drug screenings, into clinical practice and therapy. Zebrafish (*Danio rerio*) is a rapidly emerging and highly promising model organism for both CNS disease modeling and drug discovery. A growing number of studies are using this model organism in assays involving behavioral profiling. Use of AI (artificial intelligence) for behavioral pattern recognition tasks is a cutting-edge approach which will facilitate and dramatically accelerate the research in this field in the nearest future. In this project, we take advantage of innovative neural network-based algorithms and a convenient model organism system in order to develop a new tool for reliable movement pattern categorization in zebrafish exposed to various psychotropic substances. **METHODS:** In the present study we have applied neural network-based algorithms to an extensive dataset of adult zebrafish locomotor tracks recorded in a series of controlled experiments with various psychotropic drugs. Locomotor tracks of adult zebrafish were obtained by video recording fish exposed to different concentrations of several classical CNS-affecting compounds (e.g. ethanol, THC) with well-established pronounced in vivo CNS and behavioral effects and distinctive drug-specific features, which enable AI learning. Raw data were collected in Prof. Kalueff's laboratory using Noldus Ethovisikn software recorded in the novel tank apparatus. We employed a neural network approach with CNN (convolutional neural networks) for track classification. To avoid time-consuming training from scratch we used pretrained models to extract visual features of movements, replaced the decision layer with an appropriate structure and retrained it. For better generalization we augmented our dataset through superimposition of noise on the original tracks and subsequent removal of the random parts. To estimate the performance of our model we adapted the k-fold approach: the dataset was split into 6 equal subsets and each of them was interchangeably used for validation, while the rest was simultaneously used for training. To prevent possible mixing of the training and validation samples, we used different zebrafish individuals for training and validation. **RESULTS AND DISCUSSION:** This is one of the few pioneering applications of neural networks and AI-based neurophenotyping in zebrafish. The developed algorithm has the ability to distinguish behavioral patterns not only between different CNS drugs, but also between different concentrations of a specific drug. Classification accuracy for 16 classes (10 substances + control) was 82%, for 5 classes (dose-dependent THC + EtOH) it was 92%. Use of this automated approach in novel drug screenings will help identify similarities between test drug action profiles and already known drug profiles (e.g. pro/antidepressants, anxiolytics, convulsants) which have previously been classified. This will help accelerate preclinical research, mitigate human errors in results' interpretation of drug screening experiments on zebrafish, reveal shortcomings of experimental settings and methodology.

## Day 3. Friday, September 18, 2020

**Venue: Oktiabrskaya Hotel, 10 Ligovsky Prospect, St. Petersburg, Russia**

### CONFERENCE POSTER SESSION

**FIGHT, FLIGHT OR FREEZE? MECP2 INVOLVEMENT IN CHOOSING THE STRATEGY TO COPE WITH STRESS.** L Cosentino, F Zidda, S Witt, L Di Crescenzo, H Flor, B De Filippis, Center for Behavioral Sciences and Mental Health, Istituto Superiore di Sanità, PhD Program in Behavioral Neuroscience,

Sapienza University of Roma, Italy, Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany. **INTRODUCTION:** Coping is a behavioral response aimed at reducing the allostatic overload produced by stressors. The inability to cope successfully is a major determinant of stress-related disease vulnerability. Methyl-CpG binding protein 2 (MeCP2), an X-linked epigenetic modulator, was recently proposed as a crucial player in programming stress axis responsiveness, and alterations in its functionality have been associated to increased vulnerability to traumas, suggesting an involvement of MeCP2 in regulating the aptitude of adaptively respond to stress. In the present work, we sought to investigate the impact of MeCP2 deficiency on the ability to effectively cope with stress. **METHODS:** MECP2 mRNA was measured in healthy humans' blood samples; participants also filled a questionnaire on coping style (SVF78). Mice carrying truncated MeCP2 (MeCP2-308) and wild type (wt) controls underwent a test battery aimed at identifying the strategy employed to face different stressors (inescapable or escapable). **RESULTS AND DISCUSSION:** In humans, the use of negative coping strategies, including avoidance, escape tendency, rumination, resignation and self-accusation, correlated negatively with MECP2 mRNA levels in males only. MeCP2-308 male mice showed a preference for using maladaptive strategies, regardless of the stressor type, compared to wt. Mutants showed increased impulsivity and decreased emotionality in novel environments, spent more time struggling in inescapable situations, and used less active strategies in escapable conditions compared to wt. Present data suggest that MeCP2 alterations impair the ability to adaptively cope with stressors, increasing the risk of developing clinical conditions upon stress exposure. MECP2 blood levels may help identifying at-risk populations for disorders related to stress prior to disease onset.

**MORPHOLOGICAL ANALYSIS OF THE HUMAN STRIATAL NEURONS FOLLOWED BY A REVIEW OF THEIR ROLE IN MEDIATING BEHAVIOR.** B Krstonošić, NT Milošević, R Perić, University of Novi Sad, Faculty of Medicine, Department of Anatomy, Novi Sad, Serbia. **INTRODUCTION:** The striatum (putamen and caudate nucleus) is the input structure of the basal nuclei, which are involved in highly relevant behavior processes. Their role in the motor control is well known, but the basic scheme of their function has been radically supplemented over the years. They play the concert with the cortex, thalamus and brain stem centers to orchestrate and carry out planned behavior which requires motor, cognitive and limbic effects. The aim of this study was to interprete morphological characteristics of the striatal neurons in relation to their possible function. **METHODS:** Postmortem brain material was obtained from thirty adult human brains during medico-legal autopsies in the Centre for forensic medicine, toxicology and molecular genetics at the Clinical Centre of Vojvodina (Serbia). Tissue blocks, which contains precommissural putamen and caudate nucleus, were processed according to the modified Golgi impregnated technique. Striatal neurons were analyzed qualitatively and quantitatively. **RESULTS AND DISCUSSION:** In the sample of 652 neurons, 68.41% (446) were spiny and 31.59% (206) aspiny cells. Quantitative analysis confirmed qalitative, and classified neurons into five types (two types of spiny and three types of aspiny cells). Since the precommissural striatum is predominantly cognitive territory, which is related to complex neuronal circuits, high density of interneurons in the observed sample was expected. The results describe morphological differences between different types of neurons in the same part of the striatum, as well as between the same types of cells in different parts of the striatum. As the shape of neuron reflects its role in communication, in that manner the results of this study were discussed.

**MODELING WITHDRAWAL FROM CHRONIC PAROXETINE TREATMENT IN ZEBRAFISH.** KN Zabegalov, SL Khatsko, MV Bytov, I Yushchenko, and AV Kalueff, Ural Federal University, Ekaterinburg, Russia, School of Pharmacy, Southwest University, Chongqing, China. **INTRODUCTION:** Antidepressants are the most prescribed pharmaceuticals in the treatment of depression. Antidepressant discontinuation syndrome (ADS) is poorly studied set of adverse effects, which often occurs in patients after withdrawal of antidepressant treatment, and includes gastrointestinal disturbances, insomnia, headaches, anxiety and flu-like symptoms. ADS can last from several days to several weeks. However, such syndrome is not similar to classic drug withdrawal syndrome, as it is not related to drug addiction. As a logical continuation of our previous fluoxetine withdrawal studies, we tried to evoke ADS in zebrafish via chronic paroxetine treatment discontinuation, regarding more severe paroxetine withdrawal potential, than fluoxetine (Fava et al., 2015). **METHODS:** A total of 79 adult wild type zebrafish with 50/50 male-female ratio were kept in group of 40 in 40-L tank filled with filtered water in accordance with zebrafish care standards. Zebrafish behavior assessment included 5 min video recording in novel tank test after 2 weeks of chronic paroxetine treatment at 0.01 (n=17) and 0.05 mg/L (n=16), as well as 7 days after the cessation of 2-week paroxetine exposure at the above doses (n=16 for 0.01 mg/L, and n=15 for 0.05 mg/L). Major behavioral endpoints were the latency (s) and number of top and bottom entries, time spent in the upper half (top) of the tank, duration and frequency of freezing and the number of anxiety-like erratic movements. **RESULTS AND DISCUSSION:** The fish from all experimental groups, including untreated control, did not exhibit any freezing bouts. Chronic paroxetine treatment in dose of 0.05 mg/L significantly decreased the number of erratic movements. Moreover, the fish, exposed to this dose, spent

at the upper half of the tank most of the recording time in comparison with control untreated fish. These results are prominent hallmarks of anxiolytic behavior, which totally correlates with paroxetine therapeutic effects (Bourin, 2018). As far as anxiety state is highly remarkable symptom of ADS (Sah et al., 2012), we made a special emphasis on zebrafish anxiogenic responses to paroxetine withdrawal. Hence, the fish, undergone the 7-day cessation from 0.01 mg/L chronic paroxetine treatment, displayed reduced bottom latency of the fish, indicating the preference to the lower half of the tank. Increased bottom dwelling is a reliable anxiety endpoint in zebrafish, along with the increased freezing frequency and duration, and increased number of erratic movements (Cachat et al., 2011). To sum up, paroxetine treatment in higher chronic dose (0.05 mg/L) has anxiolytic effect. The discontinuation from the lower dose (0.01 mg/L) paroxetine treatment causes anxiety-like state that can be considered as a hallmark of ADS, probably related to entire drug removal from the fish body. **RESEARCH SUPPORT:** Ural Federal University, Ekaterinburg, Russia.

**NEUROCHEMISTRY OF THE ZEBRAFISH TAIL IMMOBILIZATION EXPOSURE.** NA Krotova, KA Demin, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare, St. Petersburg, Russia. **INTRODUCTION:** We previously proposed the Zebrafish Tail Immobilization (ZTI) test to study stress-related and antidepressant-related behavior in zebrafish. Here we evaluate the relationship between the despair-like behavior in the ZTI and neurochemical parameters in the zebrafish brain. For this, we determined brain concentration of serotonin (5-HT), dopamine (DA), norepinephrine (NE), 5-hydroxyindoleacetic acid (5-HIAA), 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in zebrafish using the high-performance liquid chromatography (HPLC) and we also assessed the 5-HIAA/5-HT, DOPAC/DA, HVA/DA, 5-HT/DA ratios. **METHODS:** Using high-performance liquid chromatography (HPLC) we studied neurochemical changes induced by nonpharmacological manipulations using experimental cohorts included control, ZTI-exposed and low voltage (0.1 V/cm of water) electric shock preexposure followed by ZTI fish (Experiment 1; n = 15). Furthermore, we studied antidepressants effects comparing ZTI-exposed and ZTI-exposed fish preexposed to 15 mg/L sertraline (Experiment 2; n=10) or 1 mg/L amitriptyline (Experiment 3; n=10) for 20 minutes. The fish were euthanized immediately after the exposure, and their brains dissected and stored in liquid nitrogen. On the day of analysis, they were extracted with 0.1 M perchloric acid, then HPLC was performed using CA-5ODS column with HTEC-500 chromatograph, mobile phase consisting of 0.1 M phosphate buffer, 400 mg/L sodium octylsulphonate, 50 mg/L EDTA, 17-% methanol and was adjusted to pH 4.5 by phosphoric acid. The concentrations data were normalized using individual DHBA as a standard and presented as pg/mg. Data were analyzed by the Kruskal-Wallis (KW; Experiment 1), followed by post-hoc Dunn's test (D-test) for pair-wise comparison for significant KW data or the Wilcoxon-Mann-Whitney U-test (Experiment 2-3). **RESULTS AND DISCUSSION:** Analyses of ZTI and fish preexposed to stress showed increased 5-HIAA/5-HT ratio in both experimental groups ($p<0.005$, KW test; $p<0.05$ vs. control, D-test), while other significant alterations were observed only in a stressed group, showing increased DOPAC ($H = 9.60$, $p<0.01$, KW test; $p<0.05$, vs. control, Dunn's test), 5-HIAA ($H = 11.85$, $p<0.005$, KW test; $p<0.05$, vs. control, D-test), DOPAC/DA ratio ($p<0.005$, KW test; $p<0.05$ vs. control, D-test) and reduced 5-HT/DA ratios ($p<0.05$ vs. control, D-test), without affecting NE, DA, 5-HT and HVA levels or the 5-HIAA/DOPAC and HVA/DA ratios. At the same time, sertraline action results in a reduction of both 5-HIAA/5-HT and DOPAC/DA ratio compare to the ZTI exposed drug-free group ($p<0.05$, U-test). Whereas 1 mg/L amitriptyline results in reduction of 5-HIAA/5-HT, DOPAC/DA ($p<0.05$, U-test) and 5-HIAA ($p<0.05$, U-test). Thus, neurochemical analyses show that ZTI activity in fish associated with altered monoaminergic (serotonergic and dopaminergic) signaling. ZTI pharmacological profiles and neurochemical changes are similar to those in rodent tests and in despair in humans. Therefore, we suggest that this test may be useful in the context of serotonergic drug research. However, note that the whole-brain approach is not sensitive enough to potential region-specific changes in brain neurotransmission, which requires further regional studies.

**DOSE-DEPENDENT EFFECTS OF SERTRALINE EXPOSURE IN ZTI ASSESSED USING AUTOMATED BEHAVIORAL VIDEO-TRACKING.** NA Levchenko, AS Taranov, NP Ilyin, KA Demin, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare, St. Petersburg, Russia. **INTRODUCTION:** Rodent despair-like behavior is widely used as a phenotype for antidepressant screening. At the same time, fish despair-like behavior remained unknown. Recently we proposed a new way of zebrafish (Danio rerio) behavioral phenotyping. The results of such studies (e.g. fluoxetine) strongly support the use of Zebrafish Tail Immobilization (ZTI) test to study and screening of antidepressants and suggest high sensitivity of this test. Here we study SSRI sertraline effects on the behavior of zebrafish using the ZTI test and automatic behavioral screening using Noldus Ethovision XT 11.5 and compare the results with former sertraline screening with the usage of ZTI test and manual scoring, reported earlier. **METHODS:** Wild-type naïve short-fin zebrafish (3-5 month-old) housed in standard care conditions were used in the study. Briefly, in ZTI, fish caudal half was immobilized for 5 min using the sponge that was placed right on the water surface in such a way that cranial part of the fish remained in a small tank filled water. Prior to test fish were pre-exposed to 2, 10, 50 mg/L sertraline

dissolved in DMSO (0.1%) or in a drug-free vehicle containing 0.1% ml/L DMSO in 0,25 L beakers filled with water for 20 min (n=15) or in drug- and DMSO free water. Trials were recorded on action camera and activity (relation of changing pixels to the arenas area, %) was studied. Fish that successfully escaped were excluded from further analyses. Data were analyzed by the Kruskal-Wallis ANOVA test between DMSO groups. The Mann-Whitney U-test was used to compare DMSO and control groups. **RESULTS AND DISCUSSION:** The data, analyzed using the Kruskal-Wallis ANOVA test, have demonstrated a statistically significant increase in percentage of activity for the 10 and 15 mg/L concentrations compared to the DMSO vehicle group (0.41 ± 0.08 and 0.52 ± 0.05 vs. 0.16 ± 0.06 %, respectively, with $p<0.0001$; Dunn's test for significant KW data. KW: 0,0259 and 0,0001 for the 10 and 15 mg/L respectively, with $p<0,0001$). The usage of DMSO as a solvent did not affect behavior in the ZTI when compared against the control drug-free group ($U=109$, $p=0.9$). Furthermore, the results allow for the activity threshold of sertraline in zebrafish to be established as being between 2 and 10 mg/L, as no statistically significant differences in mean activity were demonstrated by the KW test between 10 and 15 mg/L ($H = 0.83$, $p<0.0001$). Thus, sertraline exposure improves zebrafish performance in the ZTI test. Other assay methods (compared to the former study) prove the sensitivity of the ZTI to antidepressant screening and the efficiency of sertraline as an antidepressant. Since manual scoring was insensitive in assessing overall behavioral differences and relied on per-minute analyses automatic scoring may be seen as superior for studying ZTI behavioral responses. Finally, 0.1% DMSO did not affect zebrafish behavior in the ZTI, thus supporting its use as a solvent for insoluble in water drugs.

**BIDIRECTIONAL EFFECTS OF RESERPINE ON DESPAIR-LIKE BEHAVIOR IN THE ZEBRAFISH TAIL IMMOBILIZATION TEST.** M Seredinskaya, KA Demin, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare, St. Petersburg, Russia. **INTRODUCTION:** Reserpine is a natural plant alkaloid, which depletes monoamine neurotransmitters and induces pro-depressive effects in clinic and rodents and causes hypolocomotion and anxiety in zebrafish (*Danio rerio*). Thus, the reserpine model of depression has a high translational potential for the detection of antidepressants and antipsychotic drugs. At the same time, reserpine effects on depression behavior in zebrafish were not studied. Here is the first study examining the behavioral effects of chronic reserpine treatment on zebrafish using recently developed the Zebrafish Tail Immobilization test. **METHODS:** Wild-type naïve short-fin zebrafish housed in standard care conditions are used in the study. Prior to testing, fish were pre-exposed in a 0.5-L plastic beaker for 20 min to either 60 mg/L reserpine dissolved in 0.1 % of DMSO or drug-free water containing 0.1% of DMSO and then for 5 min tested behaviorally in the Zebrafish Tail Immobilization test. The testing (without additional compound exposure) was repeated with the same fish (n=14) on the first, second, seventh and 14th day. The behavior of the fish was recorded on camera and distance traveled by the center point of an animal (cm) and mobility time (s) was assessed in the program Noldus EthoVision XT. The two-factor ANOVA (Factors: Group and Day) were conducted to examine the correlation between behavioral effects and experiment day following the Fisher LSD test for pairwise comparison of groups on the same days. **RESULTS AND DISCUSSION:** There was significant ANOVA Day and Group*Day interaction effects in both behavioral endpoints ($F(4,130)=8.79$, $p<0.00001$ Day and $F(4,130)=5.94$, $p<0.0005$ Day* Group for distance and $F(4,130)=6.41$, $p<0.0001$ Day and $F(4,130)=5.30$, $p<0.001$ Day*Group for mobility). Fisher LSD revealed strong effects on acute exposure and the $14^{th}$ day. Such as distance was found to be reduced after acute exposure (211.61±42.99 cm control vs. 83.81±11.63 cm reserpine, $p<0.05$) and increase in both distance (178.92±32.54 cm control vs. 387.9±40.49 cm reserpine, $p<0.0005$) and mobility (60.35±13.16 s control vs. 134.18±17.4 s reserpine, $p<0.001$) at the $14^{th}$ day. Note fast-developing despair-like behavior followed by pronounced antidepressant-like activity that is similar to the phenotype observed following chronic stress (depressed after 1 week but less depressed at the 2nd week). The results are in contrast with rodents and clinical findings that often lack the acute reserpine effect associated with despair behavior and develop pronounced depression-related phenotypes weeks after exposure.

**IL-1RA THERAPY PARTIALLY PREVENTED EPILEPTOGENESIS AND BEHAVIORAL DYSFUNCTION IN RATS IN THE LITHIUM-PILOCARPINE MODEL OF TEMPORAL LOBE EPILEPSY.** AV Dyomina, OE Zubareva, IV Smolensky, AA Karepanov, AM Ishchenko, AV Zaitsev, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, Research Institute of Highly Pure Biopreparations, Federal Medical-Biological Agency, St. Petersburg, Russia. Epilepsy is a widespread chronic disorder often expressed by spontaneous seizures and may be accompanied by psychiatric comorbidities, such as depression, psychosis, cognitive impairment. Moreover, near 30 % of cases do not respond to drug therapy; therefore, prevention of epilepsy is a perspective therapeutic method. Neuroinflammation is thought to be one of the pathological mechanisms of epileptogenesis. Interleukin1-β plays a central role in inflammatory processes in the brain and is known to take part in cognitive function realization. The aim of this study was the investigation of interleukin-1 receptor antagonist treatment on epileptogenesis and comorbid behavioral dysfunctions in the epileptic model. The lithium-pilocarpine model of temporal lobe epilepsy in 6-week-old male Wistar rats was used in the study. The pilocarpine-induced status epilepticus (SE) was ceased by diazepam (5 mg/kg) in 75 min. Some animals were administrated with IL-1ra (100 mg/kg per day for 5 days, then 50 mg/kg for the next 5 days).

Behavior testing in the Open field and the Social interaction paradigm were performed in the latent and chronic phases of the model. Fear conditioning was done in the chronic phase only. Il-1ra treatment decreased the frequency and duration of spontaneous recurrent seizures in post-SE rats. Post-SE rats exhibited increased locomotor activity, which was corrected by IL-1ra treatment in the latent but not the chronic phase. Rats showed decreased social interaction time, and therapy partially recovered social behavior. We found cognitive impairments in rats in fear conditioning, manifesting in reduced freezing on an aversive stimulus and context. In IL-1ra treated group, we found a partial improvement of contextual memory. In conclusion, IL-1ra treatment reduces spontaneous recurrent seizures and partially prevented behavioral dysfunction in rats in the lithium-pilocarpine model of temporal lobe epilepsy. This research was funded by the Russian Science Foundation, grant number 16-15-10202.

**INVESTIGATION THE DOPAMINERGIC CONTROL OF POSTURAL FUNCTION.** D Kalinina, O Gorsky, V Lyakhovetskii, N Pavlova, R Gainetdinov, P Musienko, Institute of Translational Biomedicine, St. Petersburg State University, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, Russian Research Center of Radiology and Surgical Technologies, Ministry of Healthcare, Pavlov Institute of Physiology RAS, St. Petersburg, Russia. **INTRODUCTION:** The nigrostriatal dopamine pathway is the main element of the extrapyramidal system which is responsible for unconscious muscle tone control, body posture, facial expressions and plasticity during various forms of locomotor behavior. An impairment of the dopaminergic system leads to a decline in motor activity, a decrease of motor reactions rate, a state of stiffness, and muscle hypertonus. The key regulatory element of dopamine (DA) neurotransmission is DA transporter (DAT) which controls levels of extracellular DA and maintains DA stores by transporting released it back into neurons. **METHODS:** To study DA-ergic control of postural function we used rats with knockout of the gene encoding the DAT (n=3) and WT (n=3). The horizontal lateral shifts of the supporting platform were performed in three conditions: normal DA level (WT), mild DA deficiency (WT after injection 250 mg/kg of α-methyl-p-tyrosine - AMPT, inhibitor of tyrosine hydroxylase that blocked DA synthesis) and severe DA deficiency (DAT-KO after 250 mg/kg AMPT). To evaluate the postural correction responses in the hindlimbs the EMG electrodes were implanted to Gastrocnemius lateralis muscle. The EMG activity was analyzed before, and after the postural disturbance during standing. **RESULTS AND DISCUSSION:** The selective depletion of DA in DA-ergic terminals of DAT-KO rats by TH inhibitor AMPT resulted in almost immediate loss of locomotor activity and development of severe akinetic phenotype, which was previously described for DAT-KO mice (DDD mice) (Sotnikova et al., 2006). The WT rats had movement initiation disturbance after the injection of the AMPT. The horizontal shifts in rats with a normal DA level elicited a EMG corrective response soon after the platform displacement. In rats with mild DA deficiency the corrective response was delayed but had higher amplitude compared to normal DA level rats. The almost complete depletion of DA led to an earlier but significantly lower-amplitude response after the displacement. These observations suggest that different level of DA may cause appropriate severity of muscle rigidity and impairment of the postural corrective responses to lateral disturbance. **RESEARCH SUPPORT:** The Russian Foundation for Basic Research (RFBR) grant 17-29-01034-ofi_m and the SPbU internal grant ITBM_2019, ID: 40986737/51134206.

**THE INFLUENCE OF SOBER OR DRINKING RAT CAGE MATES ON ALCOHOL PREFERENCE.** EV Filatova, IV Demynko, SV Afanasyev, AA Orlov, AY Egorov, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia. **INTRODUCTION:** Social conditions are among of the main factors that determine alcohol consumption. The opposite tendency of alcohol preference was shown earlier in animal model with group or individual alcoholization of rats. It was revealed that individual consumption with sober cage mates did not lead to increase of ethanol preference in contrast to group mates under forced alcoholization. The purpose of the work was to analyze the social interactions in groups with individual and group alcoholization **METHODS:** Animals were randomized into two experimental groups: 1) all three rats had 15% ethanol solution and 2) only one rat received ethanol, while other rats received water. Video registration was performed immediately after drinking. Each rat coordinates were recognized automatically. Social interactions were verified manually during the process analysis up to video registration. **RESULTS AND DISCUSSION:** Neither expected signs of social neglect nor the increase in aggression towards to the ethanol-drinking rat were found. In contrast, after 1.5 months an increase in social interactions with drinking rat was observed. We assume that the main factor influencing to the formation of addiction is the anxiety as a result of forced alcoholization. The increase of social interactions toward to the ethanol drinking rats has blocked this anxiety. Thus, sober environment may have the protective effect on the formation of alcohol preferences in individually alcoholized individuals. **RESEARCH SUPPORT:** The Russian Foundation for Basic Research (RFBR) grant 18-013-00390A.

**BEHAVIORAL CHANGES CAUSED BY BISPHENOL A IN RESPONSE TO AN AVERSIVE STIMULUS IN FEMALE RATS.** NK Apraksina, IO Suchkova, TV Avaliani, NI Dergacheva, EL Patkin, SG Tsikunov, Pavlov Department of Physiology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** High prevalence of bisphenol A in the environment, the physical and chemical similarity with the female sex hormone estrogen, the cumulative effect, and the lack of data on the

minimum safe doses for human health, all necessitate studies of CNS effects of ecotoxicants, especially on learning and memory. The evaluation of behavioral changes in female rats after intraperitoneal exposure to 0.4 mg/ml and 4 mg/ml of bisphenol A was the purpose of the work. **METHODS:** The experiments were performed on the adult female rats of Wistar weigh 300 gram (n=20)., The experimental groups of animals were intraperitoneally injected with 0.3 ml of bisphenol A solution at a concentration of 0.4 mg/ml and 4 mg/ml, and the control groups injected with 0.3 ml of saline solution and a solution of dimethylsulfoxide in sesame oil for five days. A week before the introduction of bisphenol A, rats developed a conditional active avoidance reaction (CAAR) in a shuttle chamber with a metal rods floor with two platforms. CAAR retention was recorded one month after exposure. We estimated the average number of correct transitions (avoidance reaction - RA) before applying an electric pain stimulus, the total latent period of RA(TLRA), and the duration of the inter-pulse reactions (DIPR). For statistical processing of the obtained data, we used ANOVA analysis for repeated measurements, followed by posterior comparisons of Student t-test for independent samples, adjusted for multiple Bonferroni comparisons. **RESULTS AND DISCUSSIONS:** One month after CAAR production, we observed the suppression of active avoidance reflex to repeated exposure to a pain stimulus in female rats of control and experimental groups. After administration of bisphenol A at 4 mg/ml (TLRA- 143 ± 11.3 vs. 114 ± 6.2 control; $p < 0.05$) and (DIPR- 4.6 ± 1.2 vs. 10.2 ± 3.1; $p < 0.05$), the total latent period of RA and the number of inter-pulse reactions increased. There was a significant decrease in the number of RA after repeated presentation of an aversive stimulus (4 ± 1.3 vs. 8.7 ± 2.2; $p < 0.05$) compared with the control. Thus, the administration of high bisphenol A doses to female rats impairs memory consolidation in terms of the total latent period of RA and the number of correct answers and also suppresses emotionality, suggesitng potential amnestic and sedative properties of bisphenol A.

**THE EFFECT OF VITAL STRESS ON ANXIETY AND BRAIN GENOME WIDE DNA METHYLATION OF MALE RATS.** NK Apraksina, TV Avaliani, IO Suchkova, NI Dergacheva, EL Patkin, SG Tsikunov, Pavlov Department of Physiology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** Psychogenic effects of extreme nature lead to the development of neuropsychic diseases, including pathological anxiety. Epigenomic modifications, particularly changes in DNA methylation, can underlie long-term neurotic disorders caused by vital stress. Here, we identify the level of anxiety in the elevated plus-maze test (PM) and to determine brain-wide genome DNA methylation levels of CCGG sites of male rats on the 14th day after vital stress. **METHODS:** The study performed on the adult male rats of Wistar weigh 200-220 gram (n=20), the animals subjected to the vital stress caused by the threat to life experience within 20-30 min, death experience of the relative from predator actions (a tiger python) (Tsikunov et al., 2016). Anxiety levels of stressed and intact animals were assessed before and on the 14th day after vital stress by PM test. Genome DNA from structures of brain animal (hypothalamus, hippocampus, striatum, amygdala, nucleus accumbens, and prefrontal cortex) both groups emitted by phenol-chloroform method on the 14th day after stress. We use Methylation Sensitive Restriction-ImageJ Assay (MSR-IA) (Dergacheva et al., 2016; Suchkova, 2016) for a quantitative assessment of whole-genome DNA methylation. Genome DNA was processed endonucleases of restriction MspI and HpaII, following the recommendations of the producer. Then we produced 1% agarose gel electrophoresis and the densitometrical electrophoretic analysis in the ImageJ program. For the statistical processing of the obtained data, we used of nonparametric criteria of Kruskal-Wallis (H) and Bonferroni-Dunn post hoc test (Q) for paired comparison and Student's t-test for independent samples for multiple comparisons. Distinctions considered statistically significant at $p<0,05$. **RESULTS AND DISCUSSIONS:** In 80% of stressed males there was an increase in anxiety in the PM test, reducing the total duration of animals in the open sleeve (OS) (24.8±10.8 vs. 101.5±35.1; $P = 0.025$) as well as the period of "sit" in the OS (21.0±10.8 vs. 88.0±30.1; $P = 0.023$) vs. control. On the 14th day after vital stress, we found increased DNA methylation in the amygdala (76.7 to 10.8 vs. 55.6 to 6.6) and the striatum (83.6 to 3.5 vs. 67.5-12.0); $p<0.005$, of male rats with increased anxiety vs. controls. Thus, pathological anxiety of male rats, caused by vital stress, is accompanied by changes in the level of extensive genome DNA methylation in the striatum and amygdala, which in turn can disrupt gene expression in these brain regions and be one of the causes of long-term psychoneurological disorders.

**BLOOD CATALASE CONTENT IN CHILDREN WITH VARIOUS FORMS OF AUTISM SPECTRUM DISORDERS.** EM Malsagova, IS Ivleva, VA Maistrenko, SG Belokoskova, and SG Tsikunov, Pavlov Department of Physiology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** Autism spectrum disorder (ASD) is a group of complex disintegrative disorders of mental development characterized by an impaired ability to social interaction and verbal and nonverbal communication, stereotyped behavior leading to social maladaptation. Oxidative stress is involved in the pathogenesis of ASD (Kern and Jones, 2006). There is ambiguous information on the content of catalase, an intracellular enzyme, a component of the antioxidant system, in the blood of children with ASD. Some authors note its increase (Yenkoyan et al., 2018), while others show a decrease (Zoroglu et al., 2004). There are no data on the catalase content in children with different forms of ASD. The study aimed to determine the catalase content in the children's blood with separate types of ASD. **METHODS:** The object of the study was 28 patients who have ASD, including 23 boys and five girls aged 3 to 15 years.

ASD we diagnosed using generally accepted standard methods: interviews with parents (ADI-R), observation scales for diagnosing ASD (ADOS-2). The clinical manifestations of the disease were in line with F84, General Disorders of Psychological Development, ICD-10 (1995). The CARS scale used to assess the severity of clinical manifestations. All patients we divided into three groups. Group 1 included 13 children with early childhood autism; Group 2 – 8 children with atypical autism; Group 3 – 7 patients with other general developmental disorders (with elements of autism). The serum catalase content we measured by the colorimetric method. The significance of differences determines we use ANOVA, followed by the use of the Tukey criterion. Statistical dependence established by calculating the Spearman correlation coefficient. Differences were considered significant at $p \leq 0.05$. **RESULTS AND ITS DISCUSSION:** The serum catalase content in children of group 1 was 49.4±8.8 kE/L, group 2 – 65.1±14.8 kE/L, group 3 – 77.8±15.6 kE/L. Catalase content in patients of group 1 was lower than in patients of group 3 ($p < 0.05$). Patients of group 2 revealed a direct correlation between the severity of disorders of certain aspects of behavior (according to CARS) and catalase content ($r = 0.62$; $p < 0.05$); in patients of group 3, an inverse correlation dependence ($r = -0.5$; $p < 0.05$). For group 1, there was no relationship between these indicators. In children with early childhood autism, blood catalase levels were lower than in children with general developmental disorders. Low blood catalase levels in children with ASD, we believed to reflect a decrease in antioxidant system activity (Zoroglu et al., 2004). Elevated levels indicate the activity of compensation processes (Yenkoyan et al., 20018). Our data reflect distinct roles of oxidative stress in the pathogenesis of specific forms of ASD. Assessment of blood catalase in children with ASD can be used both for differential diagnosis of their multiple forms and in identifying promising areas of therapy.

**SERUM CYTOKINES LEVELS IN PATIENTS WITH PARKINSON'S DISEASE AND ESSENTIAL TREMOR.** ZM Muruzheva, DO Sholokhova, DS Traktirov, IS Ivleva, VA Maystrenko, MN Karpenko, VM Klimenko, Pavlov Department of Physiology, Institute of Experimental Medicine, Peter the Great St. Petersburg Polytechnic University, St. Petersburg, Russia. **INTRODUCTION:** Essential tremor (ET) and Parkinson's disease (PD) are the most common movement disorders. They can have overlapping features that make it difficult to differentiate between them both. The identification of peripherally accessible biomarkers could be a possible way to solve the problem. These biomarkers may be cytokines. Therefore, this study aimed to develop a method for differential diagnosis of the trembling form of PD and ET according to the serum cytokines levels. **SUBJECTS AND METHODS:** The study included two groups of patients. The first group included 7 men and 46 women (53 patients) with a diagnosis of "essential tremor", the median age of patients 61 (57-73) years. The PD group included 38 patients with a trembling form of the disease, with Hoehn and Yahr stage 1.0 or 2.0. Among patients of this group, there were 16 men and 22 women. The median age of the patients was 55 (51-67) years. We excluded patients with signs of the acute inflammatory process from both the ET and PD groups. All subjects signed informed consent for the study, which was approved by the Local Ethics Committee of the State Institute of Experimental Medicine. In the serum of patients with ET and PD, the concentrations of IL-1β, IL-2, IL-6, IL-10, and TNF, we measured by ELISA. Evaluation of diagnostic efficacy and calculation of threshold values for results with predictor value, used ROC analysis in the MedCalc Software v. 12.4.0. **RESULTS AND DISCUSSION:** The levels of IL-6 in the PD group and the ET group not different and were (0.8 ± 0.1) pg/ml and (1.1 ± 0.2) pg/ml, respectively. The levels of IL-1, IL-10 and TNF were higher in the PD group than in the ET group and were (6.5 ± 0.8) pg/ml, (7.3 ± 0.8) pg/ml and (3.1 ± 0.4) pg/ml respectively, vs (1.1 ± 0.3) pg/ml, (4.7 ± 0.6) pg/ml and (0.1 ± 0.03) pg/ml, respectively, $p < 0.01$. Based on the studied parameters, a logistic model we built to identify the most significant predictors of differential diagnosis. These predictors were IL-1 and TNF levels. For clarification, was performed ROC analysis with the construction of the ROC curve as a method of early differential diagnosis of BP and ET by the content of IL-1 and TNF in the blood, the optimal cut-point value was 0,5 pg/ml. AUC-ROC area under the curve IL-1 was 0.921 ($p<0.001$), AUC-ROC area under the curve TNF was 0.891 ($p<0.001$), which indicates the diagnostic effectiveness of this method. **CONCLUSION:** For the differential diagnosis of the trembling form, Parkinson's disease and essential tremor, the blood levels of IL-1 and TNF may represent potential biomarkers.

**THE EFFECTS OF GLIBENCLAMIDE ADMINISTRATION ON CNS CELLS IN NORMAL CONDITIONS AND UNDER ENDOTOXEMIA.** AS Zubov, AG Karaev, TV Tiutiunnik, MN Karpenko, VM Klimenko, Institute of Experimental Medicine, St. Petersburg Chemical Pharmaceutical University, Peter the Great St. Petersburg Polytechnic University, St. Petersburg, Russia. **INTRODUCTION:** Glibenclamide (GD) is a sulfonylurea-based sugar-lowering drug used in many countries as a treatment for type 2 diabetes mellitus. The effect of glibenclamide on CNS, especially neurotransmitter metabolism, remains poorly understood. Since type II diabetes mellitus mainly affects people of the older age group, who, as a rule, have a history of concomitant diseases associated with the development of a chronic inflammatory process, the aim of this study was to investigate the dose-dependent effect of chronic administration of GD on the dopamine (DA) and norepinephrine (NE) content in rat striatum and hippocampus in normal and with endotoxemia. **MATERIALS AND METHODS:** Four groups of male Wistar rats were used in the experiments - group 1 (daily ip administration of GD at 10 μg/kg for ten

days, n = 10), group 2, 3 (GD 25 μg/kg or 50 mg/kg, respectively, n = 10), and group 4 (daily i.p. administration of sodium chloride at 1 ml/rat for ten days). On Day 8 of the experiment, five animals from each group were injected with LPS i.p. at 1 mg/kg. At the end of the experiment, the animals were decapitated, the striatum and hippocampus were removed. The concentration of NE and DA in the samples was measured using HPLC-ED. Data are expressed as ng/mg of protein in the example and are represented by m ± SEM; MANOVA was used with the post hoc Tukey test. **RESULTS:** It was found that the introduction of GD according to the chosen scheme leads to a dose-dependent increase in the dopamine content in striatum cells from 65.4±7.8 in group 1, to 72.4±3.2 in group 2, 102.1±15.6 in group 3 and 121.5±9.0 in group 4 (ng/mg protein), p13 = 0.041, p14 = 0.004, p34 = 0.007, p32 = 0.041. The content of NE significantly differed from group 1 (4.3±0.9) only in group 3 (7.9±1.2, p13 = 0.039). Moreover, under LPS, the level of NE in the rat striatum in group 2+LPS was 12.5±2.0 higher than in group 2-LPS -3.3 ± 1.0, p = 0.022. The level of NE in the rat striatum in group 1+LPS was 2.7±1.0, p = 0.028 vs 5.7 ± 1.50 in group 1-LPS, p = 0.049. The level of DA in the striatum in group 3+LPS was 117.2 ± 14.5, which is higher than in the control group-LPS 57.6±11.4, p = 0.02. The level of DOPAC, a DA metabolite, in group 3+LPS (40.9±7.4) significantly increased vs. control-LPS (16.8±4.8), p = 0.006. In the hippocampus, the level of NE in group 3+LPS was 1.7±0.4, higher than in group 3-LPS 0.7±0.2, p = 0.016, also increasing vs. control-LPS 1.7±0.3, p = 0.042 and control+LPS 0.9±0.2, p = 0.015. **CONCLUSIONS:** Thus, the introduction of GD leads to an increase in the content of dopamine and norepinephrine in the striatum, norepinephrine in the hippocampus, and in the presence of endotoxemia, the effects of GD are preserved (similar). **RESEARCH SUPPORT:** The RFBR grant 20-015-00168.

**LINGERING EFFECT OF CHRONIC SLEEP RESTRICTION ON LONG-TERM MEMORY IN RATS.** MA Guzeev, NC Kurmazov, VV Simonova, YuF Pastukhov, IV Ekimova, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia. **INTRODUCTION:** Chronic sleep restriction (SR) is widespread in modern society due to social and cultural reasons. SR has a wide range of negative physiological consequences. One of the most significant effects of SR in humans is a cognitive deficit caused by impaired attention, learning, and memory. SR models in rodents give similar results: some studies have shown impairments in spatial and episodic memory during SR or immediately after it. However, the lingering effects of sleep deficiency on long-term memory are poorly studied. Therefore, using tests on spatial and episodic memory, we identified the disorders of long-term memory, which persist over two weeks after SR in rats. **MATERIAL AND METHODS:** SR was modelled in male Wistar rats using the 3/1 protocol (3 h of sleep deprivation by the orbital shaker, 1 h of sleep opportunity) for 5 days (SR group). The control group of rats did not receive SR. Two weeks after the end of SR, the rats were tested in novel objects recognition test (NOR) (control group = 20, SR group = 20) and in Barn's maze test (control group n = 10, SR group = 10). The NOR test was carried out in three stages (8 min each) with 24-h intervals: habituation, familiarization (T1), recognition (T2). The memory analysis was run on the data from rats that explored each item for at least 5 seconds in two tests (T1, T2). The Barn's maze test was carried out once a day for 4 days. **RESULTS:** NOR test showed that rats did not prefer exploring the novel object two weeks after the end of SR, while the control group did so. No significant differences were found in the time of exploration of objects between control and experimental group in tests T1 and T2. This suggests that exploration activity was not impaired, but episodic memory was lost. Both groups of animals found the target hole faster and examined fewer holes in Barnes maze test on the 3-rd and 4-th days compared to the 1-st and 2-d days, with significant differences between the groups. Consequently, there was no severe dysfunction in the formation of spatial memory and learning. **CONCLUSION:** Chronic sleep restriction has lasting effects on rat cognitive abilities, but this effect can be revealed only in some tests. Differences between tests may be related to distinct mechanisms of long-term memory formation. **RESEARCH SUPPORT:** The State assignment theme AAAA-A18-118012290427-7.

**INVESTIGATION OF CHRONIC SLEEP RESTRICTION EFFECT ON EMOTIONAL BEHAVIOUR IN RATS.** MB Pazi, KV Lapshina, DV Belan, MV Chernishev, IV Ekimova, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia. **INTRODUCTION:** Chronic lack of sleep is one of the most common stressors affecting the health of modern people, and can be a result of profession peculiarity (medical workers, military personnel, pilots, etc.), increased availability of computers and televisions or lifestyle. Chronic lack of sleep can cause a decrease in cognitive functions and an increase in emotional reactivity, as well as predispose to the development of neuropsychiatric, cardiovascular, and endocrine diseases. The fundamental reasons for these disturbances remain unclead. It remains unclear whether emotional behavior is fully restored after sleep deprivation, and how effectively the brain's molecular defense mechanisms work in response to such stressful factor. The aim of this study was to find out whether the development of signs of depression-like behavior associated with destructive changes in the limbic system occurs in rats after the procedure of chronic sleep deprivation. **MATERIALS AND METHODS:** The work was carried out on male Wistar rats aged 6 months. To perform total sleep deprivation (DS), the animal cage was placed on the SkyLine orbital shaker (ELMI, Russia). The following methodology of chronic sleep deprivation was used: 3 hours of DS and 1 hour of sleep break continuously for 5 days. To detect signs of depression-like behavior sucrose

preference test and Porsolt forced swim test were performed 2 weeks after the end of DS. Immunohistochemistry and immunoblotting assays were used to evaluate destructive changes in the ventral tegmental area (VTA) and locus coeruleus (LC). **RESULTS:** 2 weeks after DS, 56% of experimental group rats showed signs of anhedonia, which was evidenced by a 30% decrease in sucrose preference compared to the control values. In the Porsol test indicators of depression-like behavior were not detected. It was found that hedonistic deficit was associated with the development of neurodegenerative processes in the VTA and LC. It was found that stress of the endoplasmic reticulum (ER-stress; UPR) is involved in pathogenesis of neurodegeneration. In the surviving VTA neurons, a 41% increase in the UPR marker chaperone GRP78 as well as a 98% increase in the apoptosis marker CHOP protein were observed. This data indicated activation of the pro-apoptic branch of the ER-stress. In addition, VTA showed signs of neuroinflammation, evidenced by an increase in the number of activated microglyocytes; such changes were not observed in the LC. Our data suggest that chronic lack of sleep may be one of the reasons for the development of anhedonia, the pathomorphological basis of which are neurodegenerative and inflammatory processes in the mesolimbic system and the LC involved in the regulation of emotional behavior. **RESEARCH SUPPORT:** The State assignment theme AAAA-A18-118012290427-7.

**EFFECTS OF MELANOCORTIN MC4 RECEPTOR ANTAGONIST ML00253764 ON THE EMOTIONAL BEHAVIOR AND CONDITIONED PLACE PREFERENCE OF ETHANOL IN RATS.** ME Abrosimov, EA Vetlugin, AR Moskalev, AG Pshenichnaya, IYu Tissen, KB Abasova, PP Khokhlov, ER Bychkov, AA Lebedev, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** Alpha-melanocyte-stimulating hormone is an agonist of melonocortin receptors, activating melanocortin-signaling pathways, mediating stress-induced anorexia and increasing anxiety: acute restrictive stress, as well as forced swimming stress, was accompanied by an increase in the expression of mRNA with fos gene parts of pro-opiomelanocortin neurons of the arcuate nucleus of the hypothalamus. In this work, we investigated the actions of the antagonist of melanocortin-stimulating hormone MC4R ML00253764 on the emotional behavior and conditioned place preference of ethanol in rats. **METHODS**: The experiments were performed on 20 male Wistar rats (initial weight 200–220 g) using the open field, elevated plus-maze, Porsolt forced swim, “resident-intruder” and conditioned place preference (CPP) tests. Fifteen minutes before the behavior study the animals were injected with melanocortin MC4 receptor antagonist ML00253764, intranasally 20 µl, 1 mg/ml of a melanocortin stimulating hormone (ML) antagonist. The data were analyzed using Student t-test for independent samples. **RESULTS AND DISCUSSION:** After ML administration the peeping time increased in the “elevated plus-maze” test with a decrease in the time spent in the closed sleeve. After administration of ML the total number of acts and time immobilization decreased significantly ($p \leq 0.05$) in the forced swim test vs. control. In the "resident-intruder" test after ML administration, the frequency of protective behavior reduced. Thus, after the administration of ML, animals had lower levels of anxiety and depression with a slight increase in motor activity compared to the intact control. Control rats stayed in CPP 78.70 ± 15.4% of the time, and after administration of the peptide antagonist ML 00253764 - 82.02 ± 17.98%. Intranasal administration of the ML 00253764 antagonist, at a dose of 20 µg, did not block the expression of CPP ethanol.

**THE ALCOHOL WITHDRAWAL CHANGES EXPRESSION OF GENES OF TOLL-LIKE RECEPTORS IN THE STRUCTURES OF THE RAT BRAIN.** MI Airapetov, SO Eresko, ER Bychkov, AA Lebedev, PD Shabanov, Institute of Experimental Medicine, St. Petersburg State Pediatric Medical University, National Research ITMO University, St. Petersburg, Russia. **INTRODUCTION:** Much is known about the neurochemical mechanisms of alcohol intoxication, there are a sufficient number of publications regarding the study of the functional significance of the neurotransmitter and neuropeptide systems in the brain. However, in recent works there is convincing evidence that participants in the innate immune system are involved in the pathogenetic mechanisms of alcoholism, in particular, toll-like receptors (TLRs), which are expressed in the brain not only by microglia cells, as previously thought, but also by other types of glial cells, as well as neurons. TLR3, TLR4, TLR7 deserve special attention due to the fact that in experiments on rodents and in the study of post-mortem brain samples of people suffering from alcoholism, an increased level of their expression was shown. Moreover, the level of TLRs gene expression has not been studied previously in the brain of rats under conditions of alcohol withdrawal at different periods in different structures associated with the development of different forms of addiction to psychoactive substances, which was the purpose of this work. Studying the mechanisms of activation of the innate immune system through TLRs makes a new contribution to understanding the functional significance of TLRs in the brain in various pathological conditions. **MATERIALS AND METHODS:** In experiments withchronic alcoholization of mature rats (starting at 3–4months old), they were subjected to semi-forced alcoholization with a 20% ethanol solution asthe onlysource of fluid for 1 month, the control group of rats (n = 8) received water. Rats was decapitated: control group, alcoholization group (1 month), alcohol withdrawal groups on the 1st day., 7th day and the 14th day.The following brain structures were taken: hippocampus, amygdala (AMG), medial entorhinal cortex (mECIsolation of total RNA was performed using the TRIzol reagent (Ambion, USA). The cDNA synthesis is reproduced by RT using M-MuLV reverse transcriptase (Promega, USA). Real-time PCR (“Mx3005P”, “Stratagene”, USA)

present in the mixture have SYBR Green Mix (“Evrogen”, Russia). The data obtained are normalized to the level of expression of the Gapdh gene. For statistical data processing, the Graph Pad Prizm v.6 program is used. **RESULTS AND DISCUSSION:** In the long-term alcohol group, the TLR3 mRNA level decreases in the hippocampus, increases in mEC and remains unchanged in AMG. The TLR4 and TLR7 mRNA levels did not have statistically significant changes in any of the studied brain structures in the long-term alcoholization group. Ethanol withdrawal leads to an increase in the TLR3 mRNA level in the hippocampus at all studied withdrawal dates. In mEC, the mRNA level is reduced on the 1st day. It increases on the 7th and 14th day. In AMG, the mRNA level rises on the 1st day., On the 7th day. reaches the level of control on the 14th day. below control. The TLR4 mRNA level is increased in the hippocampus on the 7th and 14th day. In mEC and AMG, the mRNA level increased on the 1st day. Then it decreases in AMG and in mEC, reaching the control level on the 7th day. In AMG, the mRNA level decreases, acquiring a value below the control level on the 14th day. The level of TLR7 mRNA in the hippocampus decreases on the 1st day., Then increases on the 7th and 14th day. In mEC, there was no change in TLR7 at the mRNA level at all cancellation dates. In AMG, the TLR7 mRNA level does not change on the 1st and 7th day, but decreases on the 14th day. The obtained changes in the expression of TLRs genes during the period of alcohol withdrawal may be due to the fact that TLR signaling not only contributes to the development of a neuroinflammatory process in the brain, but is probably also involved in the regulation of the functional activity of neuropeptide and neurotransmitter systems.

**THE EXPRESSION OF POSTSYNAPTIC DENSITY PROTEIN-95 IN THE STRIATUM IN RAT MODEL OF PARKINSON’S DISEASE AND LEVODOPA-INDUCED DYSKINESIA.** ER Bychkov, EV Gurevich, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia, Vanderbildt University, Nashvile, USA. **INTRODUCTION:** *Parkinson's disease* is a progressive *degenerative disorder* of the basal ganglia, caused by degeneration of dopaminergic neurons. Abnormal signaling via dopamine receptors in the basal ganglia caused by dopamine depletion and subsequent dopaminergic therapy play an important role in the pathophysiology of motor disturbances in *Parkinson's disease* and levodopa-induced dyskinesia. Therefore, the studies of synapse-associated proteins, in particular role of postsynaptic density protein-95 (PSD-95) in the dopamine-depleted striatum may prove critical for the understanding of the pathology of *Parkinson's disease* and dyskinesia and for the success of the antiparkinsonian and/or antidyskinetic therapy. **METHODS:** We used unilateral 6-hydroxydopamine model of Parkinson’s disease. Rats received 10μg/ 5 μl 6-hydroxydopamine that was injected in medial forebrain bundle. Tree weeks after surgery rats received saline or levodopa (25mg/kg) for 10 days. Levels of PSD-95 in forebrain structures were determined by Western blotting. Subcellular fractions were prepared from rostral and caudal striatum dissected from 6- hydroxydopamine-lesioned rats, which had been treated with levodopa or saline. To estimate the degree of dopamine denervation, we measured tyrosine hydroxylase concentration in forebrain structures using rabbit polyclonal antibody (Chemicon). To measure PSD-95, mouse monoclonal antibodies (BD Biosciences) were used. **RESULTS AND DISCUSSION:** Chronic treatment with levodopa induced progressive increase in the rotation frequency indicative of the development of behavioral sensitization. Quantitative Western blotting for tyrosine hydroxylase revealed an almost complete loss in the rostral and caudal striatum (less than 5% of the values in the intact hemisphere). We have detected significant reduction in the concentration of PSD-95 in the lesioned hemisphere that was confined to rostral striatum and was not reversed by levodopa treatment. This indicates a complex mode of regulation of PSD-95 expression by dopamine. Therefore, differential changes in the PSD-95 availability in the rostral and caudal striatum observed in this study point to differential modifications of the plastic signaling mechanisms in these brain regions. One possibility is that reduced PSD-95 concentration produces supersensitivity of $D_1$ dopamine receptors in the rostral striatum, as PSD-95 reduces surface expression and signaling via $D_1$ receptors.

**EFFECTS OF CHRONIC TREATMENT WITH DOPAMINERGIC DRUGS ON ERK SIGNALING IN PARKINSONIAN RATS.** ER Bychkov, EV Gurevich, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** Parkinson’s disease is a neurodegenerative disorder caused by degeneration of dopaminergic neurons that provide dopamine to basal ganglia. The dopamine replacement therapy with levodopa remains the most efficacious treatment of Parkinson’s disease. However, motor complications such as dyskinesia are too common after a few years of therapy. Dopamine receptor agonists have lower probability of inducing dyskinesia than levodopa. It suggests that changes in ERK signaling may be implicated in levodopa-induced dyskinesia. Numerous studies have demonstrated ERK supersensitive responses to acute dopaminergic stimulation in the lesioned striatum. The aim of the study was to investigate effects of chronic levodopa and dopamine agonist pergolide treatment on ERK signaling in parkinsonian rats. **METHODS:** We used unilateral 6-hydroxydopamine model of Parkinson’s disease. Rats received 10μg/ 5 μl 6-hydroxydopamine injected into medial forebrain bundle. Tree weeks after surgery rats received saline, levodopa (25mg/kg) or dopamine agonist pergolide (0,25mg/kg) for 10 days. Twenty four hours after the last saline or drug injection, the animals were challenged with either saline or apomorphine (0.05 mg/kg) and sacrificed 30 min later. Levels of proteins in forebrain structures were determined by

Western blotting. To estimate the degree of dopamine denervation, we measured tyrosine hydroxylase concentration in forebrain structures using rabbit polyclonal antibody (Chemicon). To measure phosphorylated ERK1/2 mouse anti-phospho-p44/42 MAPK (Thr202/Tyr204) (Cell Signaling Technologies) antibodies were used. **RESULTS AND DISCUSSIONS:** Levodopa treatment for 10 consecutive days increases contralateral rotational behavior in unilateral 6-OHDA lesioned rats with respect to pergolide and saline treatment. DA depletion did not alter ERK2 phosphorylation in most regions. However, when the apomorphine challenge was applied, the increase in ERK2 phosphorylation was stronger in the lesioned striatum than in the control hemisphere. In nucleus accumbens, there was a small difference between the intact and lesioned hemisphere in the basal level of ERK phosphorylation in drug-naive animals, and ERK2 phosphorylation was only marginally increased by apomorphine challenge. Chronic treatment with both levodopa and pergolide reduced ERK2 activation in rat striatum in response to apomorphine challenge, thereby minimizing the difference between the intact and lesioned striatum. Neither levodopa nor pergolide had significant effect in nucleus accumbens. There were no differences in the concentration of total ERK2 in any brain region examined. Thus, chronic dopaminergic drugs reverse acute ERK super-sensitivity induced by dopamine depletion.

**ASSESSMENT OF DOSE-DEPENDENT EFFECTS OF ANXIOLYTIC DIAZEPAM IN *DANIO RERIO*.** AS Devyashin, AA Blazhenko, VA Lebedev, AA Lebedev, ER Bychkov, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** We have previously studied the effects of benzodiazepine anxiolytic phenazepam in zebrafish (*Danio rerio).* Here, we examine the effects of a benzodiazepine anxiolytic drug, diazepam, in zebrafish. **METHODS:** A stress test with novelty involved placing fish first in a beaker with a dissolved pharmacological substance (or water) and then into a novel tank for 6 min, where the trajectory, the path length, the number of movements to the upper part of the novel tank, the number and time of the pattern of “freezing” of the experiment were measured. **RESULTS:** In response to the novel tank, the fish reacted by submerging to the bottom, increasing freezing, and reducing the number of movements to the upper half of the tank. After diazepam exposure, the fish entered both parts of the novel tank. A pharmacological analysis of diazepam effect in zebrafish showed that in a certain dose range of 1-10 mg/l anxiolytic reduces (vs. the control group of fish) the number and time of freezing, increases the number of movements in the upper half of the tank and the swimming time in upper part of the tank. Diazepam causes a disinhibition of motor activity at doses of 1 and 5 mg/l, and at 20 mg/l has a motor-inhibiting effect. **DISCUSSION:** Diazepam acts in a higher dose range (1-10 mg/l) than phenazepam (0.1-1 mg/l) in zebrafish. Diazepam causes a disinhibition of motor activity at doses of 1 and 5 mg/l, which may be explained by the effect of small doses of tranquilizers on presynaptic GABA-A autoreceptors. However, diazepam is characterized by bell-shaped dose-dependent effects, unlike phenazepam. Thus, using zebrafish as an animal model or screen in behavioral pharmacology can be as efficient as rodent studies.

**FEATURES OF THE INVOLVEMENT OF THE DOPAMINE AND SEROTONIN BRAIN SYSTEMS IN POSITIVE AND NEGATIVE EMOTIONAL STATES IN RATS.** NS Efimov, ER Bychkov, AA Lebedev, IV Karpova, AE Kryukov, SS Pyurveev, NS Pavlov, BB Daliev, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** The aim was to study the effect of rewarding and aversive stimulation of lateral hypothalamus on the turnover of monoamines in the terminal structures of the mesocorticolimbic and nigrostriatal systems: the nucleus accumbens (NAc) and striatum (St). **METHODS:** The Wistar male rats were implanted electrodes in the lateral hypothalamus and further trained in self-stimulation test. Animals were also selected on aversive emotional reactions were observed after pressing the pedal for self-stimulation. Subsequently, forced stimulation was performed for 5 min, after which the animals were decapitated. The content of norepinephrine, dopamine (DA) and its metabolites 3,4-dioxiphenylacetic acid (DOPAC) and homovanilinic acid, serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) in the nucleus accumbens and striatum were determined by HPLC with electrochemical detection. **RESULTS:** Positive and aversive stimulation of lateral hypothalamus decreased the level of DA in the NAc, however, only stimulation of the positive emotiogenic zone increased the DA and 5-HT turnover in the NAc, as evidenced by an increase in the DOPAC/DA and 5-HIAA/5-HT ratios, respectively. Rewarding and aversive stimulation decreased the level of 5-HT in St, however, only rewarding stimulation decreased the St level of 5-HIAA compared to control and animals with aversive stimulation. Rewarding stimulation increased the turnover of serotonin in St, as evidenced by increased 5-HIAA/5-HT ratios. The activity of the noradrenergic system did not change after rewarding and aversive stimulation. **DISCUSSION:** Thus, both rewarding and aversive electrical stimulation increases the turnover of DA and 5-HT in NAc and St. However, these changes were more significant after rewarding stimulation. DA turnover increases more in NAc, and 5-HT turnover - in St. The data obtained indicate the specificity of the dopaminergic and serotonergic involvement for the formation of a modality of emotional reactions. Our findings may help developing treatment strategies for neuropsychiatric diseases related to aberrant reward system.

**EFFECTS OF NEW COUMARIN COMPOUNDS ON BEHAVIOR IN RATS.** AO Kashirin, AG Pshenichnaya, ER Bychkov, VA Lebedev, AA Lebedev, PD Shabanov, S.V. Anichkov Department of

Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** A study of the effects of coumarins has not received widespread use in medicine, largely due to the lack of optimal dosage forms, the creation of which is complicated by their poor solubility in water. The aim of this work was to study the central effect of new coumarin-based compounds: IEM-2262, IEM-2263, IEM-2266, IEM-2267 on emotional and research behavior in rats. **METHODS:** Studies have been carried out using battery of tests that are commonly used to study emotional and exploratory behavior: an open field test and an elevated plus maze in rats. A neuroprotector mexidol (200 mg/kg i.p., Farmasoft, Russia) was used as a reference substance. **RESULTS:** Coumarins (10-50 mg/kg ip) have been shown to have mild psychotropic, predominantly anti-anxiety and sedative, effects. 7-alkoxycoumarins (IEM-2262 and IEM-2266) and 4-aminocoumarins (IEM-2263 and IEM-2267) have different sensitivity in the open field compared with the effects in the elevated plus maze. Anxiolytic properties appeared in the elevated plus maze after the administration of 4-aminocoumarins (IEM-2263 and IEM-2267). The number of defecation boluses in the open field decreased as a result of the administration of 7-alkoxycoumarins (IEM-2262), which was associated not only with fear of novelty, but to a greater extent with anti-stress action. **DISCUSSION:** Thus, the new coumarin derivatives have mild tranquilizing and anti-stress effects and can be used in the future for post-traumatic stress disorders with panic attacks. Currently, studies are underway on the synthesis of macromolecules, combining various structural fragments, which will lead to increased biological activity of the synthesized coumarin derivatives compared to natural coumarins.

**ROLE OF OREXIN IN THE KARIOTYPIC STABILITY OF PERIPHERAL BLOOD MONONUCLEARS AND OBSESSIVE-COMPULSIVE BEHAVIOR IN ALCOHOLIZED RATS.** GP Kosyakova, IYu Tissen, PV Shalyapin, VA Lebedev, Department of Neuropharmacology, Institute of Experimental Medicine, St.Petersburg State University of Chemical Pharmaceuticals, St. Petersburg, Russia. **INTRODUCTION:** The participation of the brain orexin system and its antagonist OX1R receptor orexin SB-408124 in the formation of alcohol dependence and its withdrawal, which is expressed in the appearance of micronuclei in peripheral blood mononuclear cells, is being studied. **METHODS:** Laboratory animals were alcoholized by ethanol and divided into 10 groups as they received alcohol and drugs and into 4 groups after ethanol was withdrawn. 1 group — animals that received physiological saline (control group). 2 — group of animals with chronic alcoholization, 3 - after a 2-day cancellation of ethanol, 4 - after a 7-day cancellation of ethanol. Peripheral blood sampling was performed in alcoholized and control rats. Rats of 4 groups were observed after 2- to 7-day withdrawal of ethanol and also during chronic alcoholization, which received orexin A, a selective OX1R receptor antagonist of orexin SB-408124, which was intranasally injected at 20 μg. Cytogenetic analysis and morpho-functional changes in the cell nucleus of cells in animals from different cell populations were carried out using the AXIO Imager A1 hardware-software complex with Zeizz microscope (Germany). **RESULTS:** Orexin A and the OX1R antagonist of the orexin receptor SB-408124 have been shown to affect the emotional activity of rats and the karyotypic stability of peripheral blood cells and have a different dynamic profile during alcoholization and ethanol withdrawal. Of undoubted interest are the data obtained on the frequency of red blood cells and lymphocytes with micronuclei in the rat group forming alcohol dependence with intranasal administration of orexin (CHEM 0.77 ± 0.08 and CLM 1.15 ± 0.07) and its antagonist OX1R receptor orexin SB-408124 CHEM (0.21 ± 0.09 and CLM 0.57 ± 0.13) and without drug administration. **DISCUSSION:** Orexin A preparations and an OX1R receptor antagonist, Orexin SB-408124, when administered during alcohol abuse, reduced anxiety levels and normalized compulsive behavior. Despite the low background frequency of the occurrence of mononuclear cells with micronuclei between the studied groups of animals, significant differences were recorded. The frequency of micronuclei in rat peripheral blood mononuclear cells during alcoholization without drugs averaged 1.83 ‰, while even with intranasal administration of orexin A and an OX1R antagonist of orexin receptor SB-408124, a tendency to decrease the frequency of micronuclei in peripheral blood erythrocytes to 0.72 ‰. Karyotypic stability of mononuclear cells in chronically alcoholized animals at different periods of ethanol withdrawal: after 7-day ethanol withdrawal (CHEM 0.2 ± 0.09 and CLM 0.3 ± 0.10) is much less than with chronic alcoholism ethanol (CHEM 1.03 ± 0.09 and CHLM 1,5 ± 0,10). **CONCLUSIONS:** Thus, orexin A and its OX1R receptor antagonist, orexin SB-408124, reduce the manifestation of compulsive behavior and can be considered as correctors for alcohol withdrawal caused by ethanol-stress of an obsessive-compulsive nature, emotional behavior, and cognitive impairment. Also, orexin A and its OX1R receptor antagonist, Orexin SB-408124, reduce the instability of the peripheral blood mononuclear genome, which is reflected in fewer abnormal cells.

**ACTIVATION OF MITOCHONDRIAL KATP CHANNEL WITH URIDINE CAN LIMIT THE MYOCARDIAL STRESS CAUSED BY POSTISCHEMIC REPERFUSION.** IB Krylova, EN Selina, VV Bul'on, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** Thrombolytic therapy, coronary angioplasty, and aortic coronary bypass grafting significantly decrease the consequences of the cardiac ischemic stress. However, restoration of coronary blood flow provokes the development of pathological processes which can be classified as reperfusion stress (RS). The main metabolic changes of RS include pronounced oxidative stress which is accompanied with the increase in lipid peroxidation and decrease in antioxidant system activity. It can lead to impaired contractile function of the myocardium, the development of arrhythmias

and cardiomyocytes death. Mitochondrial KATP (mitoKATP) channel activation is known to play a key role in the myocardial resistance during ischemia/reperfusion stress. Investigation of mitoKATP channel openers as potential pharmacological agents involving in myocardial defense is of great importance. The aim of this work was to study the effect of uridine – the metabolic precursor of an endogenous activator of mitoKATP uridin diphosphate – on the system of biomarkers of oxidative stress in the model of myocardial stress caused by ischemia/reperfusion (I/R). **METHODS:** Postischemic reperfusion was created in male Wistar rats weighing 300-350 g by transitory ligation of the descending branch of left coronary artery (LCA). The time of occlusion was 30 min, the reperfusion period lasted 120 min. All animals were randomly divided into 4 groups (n=10-12): sham-operated animals received saline, control rats exposed to I/R without treatment, uridine 30 mg/kg given intravenously 30 min before LCA ligation and 5 min prior to reperfusion, the mitoKATP channel selective blocker 5-HD 5 mg/kg injected to the rats with I/R 5 min before uridine. Lipid hydroperoxides (LHP) and dienes conjugates (DC) as lipid peroxidation biomarkers, reduced glutathione (GSH) and activity of superoxide dismutase (SOD) as indicators of antioxidant system (AOS) activity were determined in myocardium of left ventricle. ATP and phosphocreatine (CrP) levels and the size of necrosis zone was measured to indicate the degree of myocardial stress. **RESULTS AND DISCUSSION:** The restoration of blood flow in the ischemic zone of the myocardium led to the decrease of ATP and CrP by 58% and 67%, respectively. The intensity of LPO significantly increased and was accompanied with AOS deficiency. It led to the formation of necrosis zone in myocardium. Uridine essentially decreased the manifestations of oxidative stress: LHP, DC, GSH content and SOD activity had the same meanings as in sharm-operated rats. It also maintained the initial level of ATP and CrP. As a result, the necrosis zone decreased by 36% vs. control. Application of mitoKATP channel selective blocker 5-HD before uridine treatment abolished its cardioprotective effect, indicating that uridine activity against I/R stress is mainly associated with activation of mitoKATP channel. Therefore, uridine is the promising pharmacological tool for correction of metabolic disorders developed in heart after its postischemic oxygenation, and for limiting the consequences of myocardial stress.

**CONSEQUENCES OF HYPOXIC-ISCHEMIC DAMAGE IN THE BRAIN OF INFANT RATS.** NN Kuznetsova, Institute of Experimental Medicine, St. Petersburg, Russia. Hypoxic ischemic brain damage in children is widespread and has multiple causes. Studying the dynamics of deviations of functional activity in the cardiovascular, respiratory and somatomotor systems is important for choosing the correct pharmacological correction of these deviations. Experiments were carried out on laboratory Wistar rats. In 7-day-old infant rats, perinatal hypoxic-ischemic brain damage (PHIBD) was modeled. Under inhalation ether anesthesia, animals were subjected to ligation of the left common carotid artery and then placed for 60 min into a chamber with a gas mixture of 8% oxygen and 92% nitrogen. Animals were examined 10 (i.e. on day 17 of postnatal development), 30, 60 and 90 days after surgery. The physiological parameters began to be recorded 30 min after placement of animals into a chamber and following adaptation to the environment. ECG, EMG of the gastrocnemius muscle, the respiratory rate (RR) was recorded. All recorded signals were fed into a computer using a L-card ADC E-14-440. Recorded signals were analyzed by PowerGraph 3.3.9. Cardiac activity was estimated by mean heart rate (HR) and heart rate variability (HRV). Motor activity (MA) of animals was assessed by integral EMG indices. Normal development of rats is characterized by a decrease in the heart rate (HR), which occurs by the end of the 2nd month. Analysis of HR dynamics in rats exposed to PHIBD has shown that since the first days post damage animals develop bradycardia, which persists during the following two months. Three months thereafter, bradycardia in this group is replaced by some increase in HR versus control animals. The HRV analysis has shown that 10 days after trauma animals demonstrate a shift in the vagosympathetic balance towards a parasympathetic prevalence. On day 30 in the experimental animal group the vagosympathetic balance shifts towards a humoral-metabolic and sympathetic prevalence. Two months after the beginning of the experiment, the HRV parameters in PHIBD rat group show no significant aberrations from those in control. After 90 days, rat pups with PHIBD exhibit an enhancement of parasympathetic and an attenuation of suprasegmental and humoral-metabolic influences. The (RR) in all experimental rat groups stays within the norm during the first month of the study. Beginning from the second month, in rats exposed to PHIBD RR decreases and becomes is significantly lower than in intact rats. Analysis of the integral parameters of MA has demonstrated that control and experimental animals have a similar age-dependent MA inhibition. Analysis of the EMG spectral structure indicates a disturbed electrical activity of skeletal muscles in rats exposed to PHIBD. In 3-month-old rats with PHIBD, the EMG spectrum is close to that in intact animals. Thus, it has been established that in rats under perinatal hypoxic-ischemic brain damage there occurs an impaired regulation of the cardiac and respiratory rhythms. PHIBD in rat pups leads to a parasympathetic prevalence the mechanisms of cardiac rhythm regulation.

**EFFECTS OF KRAMIZOLE ON THE EXPRESSION OF APO A-I, ApoC2, and SR-B1 GENES IN THE RAT'S HYPERCHOLESTEROL DYSLIPIDEMIA MODEL.** AV Lizunov, IV Okunevich, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of the Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** Atherosclerosis is a chronic multifactorial disease of vascular intima with the atherogenic dyslipoproteinemia (DLP) as a leading risk factor. Research indicates that

chronic psychological stress can increase the risk of atherosclerotic diseases. Prevention and treatment of atherosclerosis requires early intensive pharmacotherapy by means of effective lipid-lowering and anti-atherosclerotic agents. In order to correct atherogenic DLP, the search for new and safe drugs among aromatic heterocyclic compounds still represents an important biomedical task. In our work we used hypercholesterol model of dyslipidemia on rats to analyze the effect of kramizole injection on the expression of the main antiatherogenic genes and their regulators: Apo A-I, ApoC2, and SR-B1. **METHODS:** We had four groups of rats: intact control group, hypercholesterol diet group, phenophibrate group and kramizole group. During a 30 days we gave a per oral injections of carmizole for the kramizole group, phenophibrate (as a reference drug) for phenophibrate group and hypercholesterol diet for kramizole, phenophibrate and hypercholesterol diet groups. Liver tissue samples were used for RNA extraction and following RT-PCR (Real Time PCR) with primers for Apo A-I, ApoC2, and SR-B1 mRNA sequences. **RESULTS:** We have found, that Apo A-I mRNA level was not increased in the control and phenofibrate groups, but increased by 400% in the kramizole group respectively to the control group. Apo C2 mRNA level increased in the control group by 100%, decreased in phenofibrate group by 100% respectively to the control group, but increased by 250% in the kramizole group respectively to the control group. SR-B1 mRNA level was decreased in phenofibrate group by 40% respectively to the control group, and decreased in the kramizole group by 40%, respectively to the control group. **CONCLUSIONS:** Kramizole works like stimulator of Apo A-I and ApoC2 gene expression, and also like a repressor of SR-B1 gene expression. That modulating of the expression of antiatherogenic protein gene could be the base of the antiatherogenic effect of kramizole.

**THE EFFECTS OF KRAMIZOLE AND PHENOFIBRATE DRUGS ON TRYGLICERIDES IN RATS, TREATED WITH CHOLESTEROL DIET.** AV Lizunov, IV Okunevich, GP Kosyakova, LB Piotrovskiy, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** Since triglycerides in the blood are in the form of macromolecular complexes - lipoprotenes, as biomarkers of obesity, it is not surprising that the total level of triglycerides indicates the biological age of mammals. Triglycerides are the main lipids of fat deposits and comprise about 15-20% of body weight. Triglycerides are the main lipids of body fat and make up about 15-20% of body weight. The level of free fatty acids reflects the rate of breakdown of triglycerides and is also a biomarker of obesity, which is used in combination with readings of levels of lipoproteins of different densities. The purpose of this study is to study the effect of kramizole on triglycerides in serum. **MATERIALS AND METHODS:** A cholesterol model was used to study the effect of kramizole. This model increases the level of cholesterol in the blood, which creates the effect of hyperlipidemia. Male Wistar rats were divided into 4 groups: 1. intact control - rats not administered drugs or fed a cholesterol diet; 2. active control - rats were fed a cholesterol diet without drugs; 3. comparison drug group — rats were given a comparison drug (fenofibrate), fed a cholesterol diet; 4. experimental group - rats were injected with kramisol and cholesterol diet. On the 30th day after the administration animals were slaughtered and prepared with blood sampling and liver samples taken. All experimental animals were bled after decapitation, the liver was placed in trizol. Serum was taken from blood samplesand kept at -20 °C. The levels of cholesterol, triglycerides and HDL were then measured directly by standard kits (cholesterol-vital, triglycerides-vital, HDL-cholesterol-vital) using a spectrophotometer. **RESULTS AND DISCUSSION:** cholesterol level decreased in the experimental group compared with the cholesterol control group, approaching that in intact animals (1.77 vs. 2.31 μg/μl control, intact 0.78 μg/μl). The level of triglycerides decreased in the experimental group compared with the cholesterol control group (0.36 vs. 1.81 μg/μl control, intact 0.37 μg/μl). HDL levels have also increased. In the experimental group, HDL level increased compared to the cholesterol control (0.63 vs. 0.36 μg/μl in the cholesterol control, intact 0.32 μg/μl). In the experimental group with kramisole, the rate of destroyed nucleated cells in the peripheral blood decreased compared to the group of rats with the phenofibrate comparison drug. The lipid balance in the blood serum of experimental rats was disturbed in the cholesterol model. **CONCLUSIONS:** Kramizole increases rat high-density lipoproteins (HDL) and lowers triglycerides.

**MECHANISMS OF NEUROADAPTATION TO ACUTE STRESS INFLUENCE: UNEXPECTED EXPERIMENTAL DATA.** AV Lyubimov, IYu Thyssen, PP Khokhlov, AA Lebedev, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** One of the pressing issues of experimental medicine is the identification of markers of urgent and long-term adaptive reactions that occur in response to acute and chronic effects. In this case, one or another stressful effect can have both a maladaptive property and general adaptive properties, a particular variant of which is the phenomenon of preconditioning. The threshold level of stress exposure and its parameters are the determining factor the body is able to 'cope' with the stress factor. The aim of research was to study possible non-specific mechanisms of adaptation to acute non-hypoxic stress based on hypoxia-induced factor 1 in rats. **METHODS:** The experiments were performed on sexually mature awake male rats of the Wistar population weighing 200-250 g in three series of experiments. Immobilization of animals in individual plastic containers for 4 hours was used as a model of acute stress. The model of emotional-pain stress was electrocutaneous irritation (42 V for 15 seconds once). Hypothermic stress was modeled by placing animals in standard cages in a refrigerator at an ambient temperature of 4 ° C for 2 hours. At the end of the experiments, animals were decapitated, blood

was taken, the prefrontal cortex and amygdala were isolated, followed by homogenization and tissue extraction for ELISA. Quantification of the HIF1 peptide was performed using solid-phase ELISA. **RESULTS:** Various HIF1α concentrations were obtained in the studied brain regions before and after stress exposure and its complete absence in peripheral blood in response to various types of stress. The greatest increase in concentration occurred as a result of the application of cold stress and the tshok technique. An increase in the concentration of HIF1α in the prefrontal cortex was observed after application of all types of stress; changes in the concentration of HIF1 α were most pronounced after hypothermic exposure in the amygdala. **DISCUSSION:** The results suggest the presence of common non-specific mechanisms of adaptation to acute hypoxic and non-hypoxic stress, the starting point of which can be HIF1, namely, its subunit α is sensitive to hypoxia. The sensitivity of HIF1α in the organs and departments of the central nervous system, circulatory system is different and depends on the nature of the stress factor. The complete absence of HIF1α in peripheral blood is presumably related to the rate of development of the adaptive response to stress exposure.

**PHARMACOLOGICAL ANALYSIS OF THE EFFECT OF THE Y1R ANTAGONIST NEUROPEPTIDE Y BMS 193885 ON THE EMOTIONAL, INTRASPECIFIC BEHAVIOR AND REINFORCING PROPERTIES OF ETHANOL IN RATS.** AR Moskalev, ME Abrosimov, EA Vetlugin, AG Pshenichnaya, IYu Tissen, AS Ivankov, ER Bychkov, NR Evdokimova, AA Lebedev, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** Our previously data on orexigenic peptides (orexin, ghrelin) showed antagonists of peptides receptors as correctors of the emotional-motivational and cognitive spheres. Currently, a close relationship between ghrelin and orexin with neuropetide Y has been shown in feeding and emotional behavior. Here, we analyze the effects of the NPY antagonist Y1R BMS 193885 on emotional and intraspecific behavior, as well as on the reinforcing properties of ethanol in rats. **METHODS:** We used the open field, the elevated plus-maze, Porsolt's forced swim, “resident-intruder” and conditional place preference (CPP) tests. **RESULTS AND DISCUSSION:** BMS 193885 1 mg/ml, 20 µl intranasally did not cause an anxiogenic effect in the elevated plus-maze. In Porsolt's test, there was also no increase in the level of depression-like behavior. Moreover, there was a significant decrease in the number and time of dives, as an indirect indicator of a decrease in the level of depression. In the “resident-intruder” test, protective behavior decreased, suggesting lower stress of intraspecific interaction in the absence of aggression. Moreover, local movements increased in the open field test as an indicator of the animal’s activity impaired by fear. BMS 193885 had no effect on the expression of the CPP of ethanol. Thus, it was previously shown that the BMS 193885 is a powerful, selective, brain-penetrating Y1 receptor antagonist, it reduces food intake and body weight in animal models of obesity both after acute and chronic administration. Our data indicate that the decrease in food intake is not associated with the level of anxiety, depression, or with a change in intraspecific interaction. It has been previously shown that NPY reduces alcohol consumption. Our data indicate that the Y1R antagonist of the neuropeptide Y BMS 193885 does not alter alcohol CPP.

**PROTECTIVE ACTION OF TAUREPAR, URIDINE AND ITS NUCLEOTIDES UNDER FORCED SWIMMING AND COLD EXPOSURE.** AF Safonova, OM Rodionova, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** Taurepar, a derivative of taurine, synthesized in the neuropharmacology department of the Institute of Experimental Medicine, has antihypoxic and antioxidant properties, and uridine and its nucleotides support myocardial energy metabolism, especially in oxygen deficiency. The literature shows positive effects of some antihypoxants on physical activity of experimental animals under cold stress. Here, we study the effects of taurepar, uridine, and its nucleotides on physical endurance of rats under the forced swimming and cold exposure. **METHODS:** The experiments were performed on male rats (200-220 g) in the model of forced swimming with load (7% of the animal’s body weight) in a pool with a water at 14 °C until complete exhaustion. The influence of taurepar (25 mg/kg), uridine (30 mg/kg), uridine-5'-monophosphate - UMF (30 mg/kg) and comparison drug taurine (250 mg/kg) on physical endurance of animals was assessed as the duration of swimming (min). Single intraperitoneal introduction of substances and saline (control) was made 45 min before the test. Animals were tested in two stages. On the first day (without the introduction of substances), the rats swam until the first signs of fatigue appeared. In a day, the rats were subjected to repeated swimming (with the introduction of substances) until complete exhaustion (drowning). **RESULTS AND DISCUSSION:** The results of the study showed that in non-adapted animals, the first swimming served as a mobilizing factor, and maximum swimming duration was in the second episode. The physical endurance of rats administered withtaurepar, uridine, and UMF was higher than in control animals by 60, 20 and 40%, respectively. In animals treated with the comparison drug taurine, physical endurance did not change. Forced swimming with a water temperature of 14°C fatigue is known to cause fatigue much faster, and some antihypoxants increase working capacity under conditions of cold exposure. Thus, a single use of metabolic drugs (taurine, uridine, UMF) differently increases endurance of rats and their working capacity.

**LOPERAMIDE AND LACTITOL INTENSIFY THE PHYSICAL ENDURANCE OF RATS DURING EMOTIONAL-PHYSICAL STRESS.** AF Safonova, IB Krylova, KA Shemerovsky, S.V. Anichkov

Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** Sport activities are associated with multiple stress factors. The problem of competitive stress, which can lead to the development of functional disorders of various body systems, is particularly important. Digestive system is one of the most sensitive to the psychological and physiological stress factors the sportsmen deal with. The rhythm disturbance of the different parts of intestine leads to the development of diarrhea or constipation which can affect the endurance and sport results. Therefore, drug therapy is often used to overcome such conditions. The aim of this work was to study the influence of antidiuretic drug loperamide (LPR) and laxative drug lactitol (LT) on the physical endurance (PhE) of rats on the model of emotional-physical stress caused by forced swimming with load. **METHODS:** Wistar male rats (250-280 g) were randomly divided into 3 groups. 1 - control - subcutaneous injection of 2 ml of saline for 6 days; 2 - LPR 2 mg was dissolved in 2 ml of saline and injected subcutaneously daily for 6 days; 3 - LT 10 g was added to 200 ml drinking water daily within 6 days. On the 7th day all animals were subjected to emotional-physical stress - forced swimming with load 7% of body weight in the water 14°C. The physical endurance (PhE) was determined by the duration of the swimming up to the complete exhaustion. **RESULTS AND DISCUSSION**: The duration of the swimming up to the completer exhaustion in the control group in the test of forced swimming with load in the cold water was 136±8 s. LPR increased PhE by 1.94 times comparing with control. In LT group PhE was higher, than in controle by 1.44 times. Thus, both drugs administration resulted in the increase of PhE under conditions of emotional-physical stress. The most positive effect was observed after LPR treatment. The stress reaction is largely determined by the state of the stress-limiting systems of the organism. Important role belongs to opioid system. Recent data showed that LPR is the agonist of μ-opioid receptors. A mechanism of its positive effect on the endurance may be associated with the activation of these receptors. However, possible physiological consequences of both drugs (constipation or diarrhea) can be regarded as endogenous stress, which plays a role of the adaptogen factor and can increase resistance to stronger emotional-physical stress and enhances PhE of the animals.

**ANXIOLYTIC AND ANTIADDICTIVE EFFECTS OF MELANIN CONCENTRATING HORMONE ANTAGONIST 1R SNAP 94847 IN RATS.** EA Vetlugin, ME Abrosimov, AR Moskalev, AG Pshenichnaya, IYu Tissen, KG Konkova, PP Khokhlov, ER Bychkov, AA Lebedev, PD Shabanov, S.V. Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia. **INTRODUCTION:** Melanin concentrating hormone **(**MCH) affects food intake and lipid metabolism. It causes a dose-dependent increase in food intake by animals. Increased biosynthesis of hypothalamic MCH can make a significant contribution to the stimulation of appetite and the observed metabolic disorders. In the present work the effect of the selective non-peptide of melanin concentrating hormone antagonist 1R SNAP 94847 on the behavior in rats. **METHODS:** We used the open field, elevated plus-maze, Porsolt forced swim, “resident-intruder” and conditioned place preference (CPP) tests. 15 minutes before the behavior study the animals were injected with SNAP 94847, intranasally 20 μl, 1 mg/ml. **RESULTS:** Intranasal administration of SNAP 94847 significantly increased the number of crossed squares ($p \leq 0.05$) (30.80 ± 0.006) and sniffing (59.00 ± 4.59) in the open field vs. control group number of crossed squares (18.40 ± 2.38) and sniffs (45.20 ± 3.67). In the elevated plus-maze after SNAP 94847 administration, the time spent at the central platform (15.47 ± 3.36 s) and peeping (68.01 ± 20.52 s) increased while the time spent in the closed sleeve decreased (215.66 ± 24.58 s) vs. the control group of animals where the time spent on the central arena was (5.82 ± 2.53 s) vs. the closed arm (274.38 ± 9.13 s). In the “resident-intruder” test, SNAP 94847 induced reduction of probability of protective behavior. In the Porsolt's forced swimming test after administration of SNAP 94847, compared with the intact control (354.64 ± 67.38 s), the time of active swimming (126.94 ± 10.54 s) and immobilization significantly decreased with an increase in ($p \leq 0.01$) time of passive swimming. Control animals, which received intranasally 20 μl of physiological saline, spent an average of 50.0 ± 4% of the time in the CPP alcoholization chamber. Rats included in the experimental group were carried out in the chamber associated with ethanol 80.83 ± 10.21% of the experiment time ($p \leq 0.05$). Intranasal administration of an SNAP 94847 antagonist at a dose of 20 μg reduced the expression of CPP of ethanol to 46.33 ± 29.15% ($p \leq 0.05$). **DISCUSSION:** Thus, melanin concentrating hormone antagonist 1R SNAP 94847 reduces levels of anxiety and depression are observed in experimental animals compared with intact control rats. SNAP 94847 reduced the expression of CPP of ethanol. The data obtained indicate the prospect of studying MCH antagonists in drug addiction research.

**DISTRIBUTION OF LAYER-SPECIFIC MARKERS IN HUMAN NEOCORTEX DURING THE SECOND HALF OF GESTATION.** EA Kozubenko, NA Sidorova, LA Tkachenko, PA Zykin, EI Krasnoshekova**,** St. Petersburg State University, Russia, St. Petersburg State Pediatric Medical University, St. Petersburg, Russia. **INTRODUCTION:** Socially significant diseases such as ASD, schizophrenia, temporal lobe epilepsy, etc., are mostly attributed to disruptions of prenatal development of the neocortex. Study of normal prenatal development of human neocortex may help to identify critical developmental periods for area and layer specific neuronal populations. Those periods are important for predictive diagnosis of possible neurological abnormalities. We studied cytoarchitectonics and layer-specific populations of neurons in temporal and insular regions of human neocortex during the second half of gestation. **METHODS:** The study was approved by the ethics committee of SPbSPMU (IRB 00003875). Serial

paraffin embedded sections of temporal and insular lobes of human brain from 21 to 25 gestational weeks (GW) were used for immunofluorescence analysis for a set of layer-specific markers, adjacent sections were stained using the Nissl method. **RESULTS AND DISCUSSION:** We compared the distribution of MAP2 positive neurons (microtubule associated protein 2, marker of post-migratory neurons) with other functional specialization markers of neocortex: SATB2 (callosal pyramidal neurons, layers eII, eIV); CTIP2 (cortico-spinal pyramidal neurons, layers eV, eVI); FOXP1 (pyramidal cells of the lower complex of layers). The distribution of MAP2 at 21-23GW demonstrates that maturation of neocortex in studied areas begins from the lower temporal and insular regions. By 25GW neocortex of both regions has two layers of MAP positive mature cells (eV and eII-III). Other markers at 20-21GW had their own layer specific distribution patterns, without noticeable rostral-caudal difference or difference between studied neocortical regions. At 25GW marker distribution is more confined to specific layers. Dense layer of MAP2 positive neurons found in eV of insular and temporal regions was also positive for all other studied markers. Regional specificity of markers become prominent: middle temporal area has more FOXP1 positive cells in layer eVI, caudal part of upper temporal region has more SATB2 positive cells, CTIP2 positive cells vanish from layer eVI. While study of Nissl stained sections showed little difference between areas, MAP2 shows a clear gradient of maturation, other pyramidal neuron markers made it possible to detect distinct FOXP1 and SATB2-specific subpopulations of neurons in the developing neocortex. Our results determine the sequence and time of critical developmental periods for different pyramidal neurons in human neocortex. **RESEARCH SUPPORT:** SPbSU grant 1.38.333.2015, with the use of SPbSU “CM&CT” Research Park facility project 109-306.

**DETERMINATION OF THE OPTIMAL CONCENTRATION OF THE PROTEIN-ANTIGEN COMPLEX FOR THE DETECTION OF CORTISOL BY IMMUNOCHROMATOGRAPHY.** EV Panfilova, Institute of Biochemistry and Physiology of Plants and Microorganisms RAS, Saratov, Russia. **INTRODUCTION:** Cortisol is a biologically active steroid glucocorticoid hormone that plays a key role in responses to stress. It increases the concentration of glucose in the blood by increasing its synthesis and reducing utilization on the periphery. Currently, in medical practice, the study of cortisol is carried out in the blood and in the urine to diagnose diseases associated with an increase in the level of cortisol in the blood (Cushing's syndrome, Addison's disease). In addition, there are publications showing that an increase in cortisol levels accompanies the course of many diseases, including oncological, cardiovascular, gastrointestinal, endocrine, neurological and reproductive disorders. In this regard, the development of an immunochromatographic test to obtain the result of an analysis of cortisol directly in a short time for point-of-care use is an topical problem. For the detection of low molecular weight substances like cortisol, a competitive immunochromatographic analysis is used. Its essence lies in the competition of antigen molecules contained in the analyte and antigen molecules immobilized on the membrane in the form of an antigen conjugate with a carrier protein. A test strip for immunochromatography consists of several pads connected together and performing different functions. Briefly, the immunochromatography test strip contains a nitrocellulose membrane, conjugate pad, sample pad and adsorbent pad. Protein conjugated with analyte molecules and anti-species antibodies are preliminarily applied to the nitrocellulose membrane. Then an overlap of the conjugate pad is adhered, coated with a colloidal gold conjugate with antibodies to cortisol. Slightly above it - having retreated about 1 mm, attached the sample pad. An adsorbent pad is attached to the opposite edge of the membrane. When a sample is applied to the sample pad, the analyte molecules with a fluid flow rise up the membrane, interact with antibodies conjugated with a colloidal gold, forming an immune complex that, under the action of capillary forces, passes through the membrane, interacts with antispecies antibodies and we visually observe staining of the upper line (or, as in our case, spots). In the case when the number of cortisol molecules contained in the sample exceeds the number of molecules contained in the cortisol-BSA complex deposited on the membrane, the cortisol molecules contained in the protein complex do not bind to antibodies and only one red line (spot) can be visually observed, corresponding to anti-species antibodies-immune complex interaction. In the opposite case, when the number of cortisol molecules in the analyte is less than the number of molecules contained in the cortisol-BSA complex, the conjugate of colloidal gold with a-cortisol-Ab interacts with cortisol molecules contained in the cortisol-BSA complex. For this reason, the presence of 2 points is visually observed: both test and control. Thus, the staining of the test strip directly depends on the number of cortisol molecules deposited in the test zone of the membrane in the form of a complex with a protein. The aim of this work was the calculation and experimental confirmation of the optimal concentration of the complex cortisol-bovine serum albumin (cortisol-BSA), applied to the membrane, necessary for the detection of cortisol within its concentration in human biological fluids. **METHODS:** To create immunochromatographic test strips, we used the CNPF-SN12-L2-H50 nitrocellulose membrane, adsorbent pad AP 045, sample pad GFB-R7L (0.6), conjugate pad PT-R7 (all manufactured by Advanced Microdevices Pvt. Ltd., India). Colloidal gold with diameter 19±2 nm was used. The conjugate was made as follows: using 200 mM $K_2CO_3$, the colloidal Au was adjusted to pH 9, then mouse-a-cortisol antibody was added with a final concentration of 28 μg/ml. They were incubated for 1 h, then 8000 rpm 15 min were centrifuged, the precipitate was resuspended in the initial volume of phosphate buffer. 0.5 μl of the cortisol-BSA complex and 0.5 μl of goat-a-mouse Ab with concentration 550 mkg/ml were pipetted onto the membrane. After that, the membrane was dried for 2 h in an

desiccator at 37 °C. 10 µl of a colloidal gold conjugate with anti-cortisol antibodies was applied on the conjugate pad. Dried for 30 min in an desiccator. After that, a test strip containing a nitrocellulose membrane, conjugate pad, sample pad and adsorbent pad was collected. A fixed amount (60 µl) of the sample containing cortisol was applied on the sample pad. The cortisol concentration was determined by constructing a calibration graph of the dependence of the optical density of the solution at a wavelength of 248 nm on the concentration of cortisol. We obtained the equation of the approximating line Y = 0.032 * X-0.003. Using this equation, the cortisol content of the cortisol-BSA complex was calculated. It amounted to 18.6%. **RESULTS AND DISCUSSION:** Since in a competitive version of immunoassay, the antigen in the analyzed liquid is detected when the number of antigen molecules that have reacted with antibodies immobilized on the surface of gold nanoparticles exceeds the number of antigen molecules immobilized on the membrane as a complex with a protein, we calculated the amount of cortisol in analyte. Solutions with a cortisol concentration of 1, 10, 100 ng/ml contain 0.06, 0.6 and 6 ng cortisol/sample, respectively (a fixed sample volume of 60 µl was used in the experiment). To set up the analysis, we first performed an analysis with a concentration of the antigen-protein complex equal to 80 µg/ml (containment of cortisol is 7.5 ng), we expected to see a reduced color intensity (staining intensity was visually assessed) of the lower spot of the test with an analyte concentration of 100 ng/ml and an equally intense color of spots corresponding to concentrations of 10 and 1 ng/ml. Contrary to our expectations, staining was the same everywhere. Therefore, we reduced the concentration of the cortisol-BSA complex by a factor of 10 to a concentration of 8 µg/ml (containment of cortisol is 0.75 ng); no staining was observed in the analyte concentration range from 1 to 100 ng. This probably indicates that the concentration of the cortisol-BSA complex is too low for visual detection, that is, the number of colloidal gold nanoparticles bound to the antigen through antigen-antibody interaction is too small. Therefore, we chose an intermediate concentration of the complex at 40 µg/ml (containment of cortisol is 3.75 ng). The spot had a very weak intensity, while the spots corresponding to analyte concentrations 10 and 1 have an intense color. Our data suggest that 40 µg/ml is optimal for the analysis of samples with a cortisol concentration of about 100 ng/ml. **RESEARCH SUPPORT:** The Russian Science Foundation grant 19-73-00202.

**ACUTE BEHAVIORAL EFFECTS OF ASPIRIN (ACETYLSALICYLIC ACID) IN ADULT ZEBRAFISH.** DS Galstyan, KA Demin, TO Kolesnikova, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Ural Federal University, Ekaterinburg, Russia, School of Pharmacy, Southwest University, Chongqing, China. **INTRODUCTION:** Cyclooxygenase-1 (COX-1) is the key enzyme in the biosynthesis of proinflammatory thromboxanes and prostaglandins, expressed in glia and neurons. It is implicated in numerous CNS pathologies, including Alzheimer's, Parkinson's, depression, schizophrenia and autism. Here, we evaluated behavioral effects of acute treatment with acetylsalicylic acid (AS, aspirin), a common COX-1 inhibitor, in adult zebrafish. **METHODS**: A total of 52 adult wild type short-fin zebrafish were used for this study (0.1% DMSO control, 50, 75 and 125 mg/L) tested in the 50-min novel tank test and analyzed using Noldus EthoVision XT11.5. Data was analyzed by the Kruskal-Wallis (KW) test followed by Dunn's post-hoc testing ($P<0.05$). **RESULTS AND DISCUSSION**: Fish exposed to 125 mg/L AS showed reduced exploration and activity, including fewer top entries ($p=0.017$), distance traveled ($p=0.001$) and velocity vs. control ($p=0.001$). This AS group was also lower than all other groups in frequency ($p<0.001$-0.01) and cumulative duration ($p=0.001$-0.5) of high mobility, as well as the frequency of immobility ($p=0.003$-0.05), but showed more freezing duration ($p<0.001$-0.05). **CONCLUSIONS:** Although reduced top exploration may indicate anxiety, low activity endpoints observed here suggest that high doses of AS exert sedative and/or toxic (rather than anxiogenic) effects on fish. The results will be discussed in the context of clinical and rodent data on AS CNS effects.

**SCHIZOPHRENIA - MINOR PHYSICAL ANOMALIES OF HANDS AND FEET.** S Zigic, B Srdic Galic, SS Babovic, S Lovrencic, DJ Siladji Mladenovic, Z Gajic**,** University of Novi Sad, Faculty of Medicine, Serbia. **INTRODUCTION:** The brain disorders with relatively unclear etiology, such as schizophrenia, could have visible skin biomarkers, as these two organs have a common embrionic origin. Our aim was to identify the specific characteristics of the schizophrenia patients' hands and feet indicating environmental or endogenic prenatal stress during the first trimester pregnancy. **METHODS:** The study group included 126 schizophrenic patients (68 males and 58 females, aged 19-66) from the Psychiatry Clinic, Clinical Centre of Vojvodina, while the control group consisted of 124 healthy comparison subjects (61 males and 63 females aged 19-71). The following minor physical anomalies were assessed in areas of feet and hands by using a partially modified Waldrop scale: curved fifth finger, single transverse palmar crease, big gap between first and second toe, partial syndactily, hyperconvex fingernail and toenail, long thumb, fingers and toes lengths and presence of curved fifth toe. The fingers and toes lengths have been additionally put into the mutual ratios. **RESULTS AND DISCUSSION:** Our study showed significantly greater incidence of ambidextrous subjects in schizophrenia patients than in the control group ($p<0.001$). The thumb ratios were significantly greater in both hands in the study group, as well as the fingers ratios in left hand and incidence of hyperconvex fingernails ($p<0.001$). Toes in the study group were significantly shorter, with greater incidence of hyperconvex nails, syndactily of second

and first toe, as well as the big gap between first and second toe ($p<0.001$). The ratio of second and fourth toe (2D:4D), which was linked to some brain disorders in previous studies, did not significantly differed between examined groups. The results of the current study indicate potential clinical biomarkers in research and practice, supporting the neurodevelopmental concept of schizophrenia.

**DELAYED EFFECT OF ACUTE HYPOBARIC HYPOXIA ON ABSENCE EPILEPSY.** KR Abbasova, EA Volkova. Department of Human and Animal Physiology, School of Biology, Lomonosov Moscow State University, Moscow, Russia. **INTRODUCTION:** Epilepsy is a major neurological disorder. Experimental and clinical data associates the higher seizure susceptibility with impaired oxygenation during the prenatal period. Prenatal hypoxia is a particular case of stress response. There have been no studies so far of the influence of acute hypobaric hypoxia on absence epilepsy. Absence epilepsy is a specific epileptic syndrome characterized by generalized non-convulsive seizures concomitant with a cessation of activity and associated transient alteration of consciousness. Here, we examine whether prenatal acute hypobaric hypoxia influences the development of absence epilepsy and changes seizure susceptibility of adult brain of rats. **METHODS:** On day 14 of pregnancy (embryonic day 14 (E14)) six female WAG/Rij rats with spontaneous spike and wave discharges (SWDs) (9-11 Hz) were exposed to hypobaric hypoxia at 5% O2 (11500 m altitude, 145 mm Hg) in a decompression (altitude) chamber of 3.3 L volume. After closing the chamber, the air pressure inside decreased progressively during 1 min (200 m/sec) by the vacuum pump connected to the chamber. Six female WAG/Rij rats were not exposed to hypobaric hypoxia as control offspring. All male rat offspring (n=15) (control and experimental) at the age of 6 month were equipped with recording stainless-steel electrodes placed bilaterally over the frontal cortex. Baseline EEG was recorded for 4 h. Seizure susceptibility by injection i.p. of pentylenetetrazole (PTZ), a GABA-a receptor antagonist, at 25 mg/kg thrice every 15 min was then tested. The mean duration and number of SWDs, spectral power density of SWDs evaluated by Welch method using FFT was analyzed in baseline EEG and mean duration of PTZ induced discharges were calculated. **RESULTS AND DISCUSSION:** In the experimental group, we observed a significant increase of mean duration of SWDs as compared to the control. No significant changes of number of SWDs were found. Our results showed that prenatal hypoxia does not affect spectral power density of SWDs, whereas PTZ induced a significantly longer mean duration of discharges vs. control. The mean duration of seizures was longer in the experimental rats as compared to the control. Thus, the present study shows that prenatal acute hypobaric hypoxia has delayed effects on development of absence epilepsy. Prenatal hypoxia not only prolonged mean duration of SWDs, but also increased seizure susceptibility of adult brain of rats. We suggest that unaltered number of SWDs means no changes in the perioral zone of somatosensory cortex where absence seizures are initiated. The delayed effect of acute hypobaric hypoxia is due to changes of the functions of the hypothalamic-pituitary-adrenal system. Thus, acute hypobaric hypoxia as prenatal stress aggravates absence epilepsy and enhances seizure susceptibility in WAG/Rij rats.

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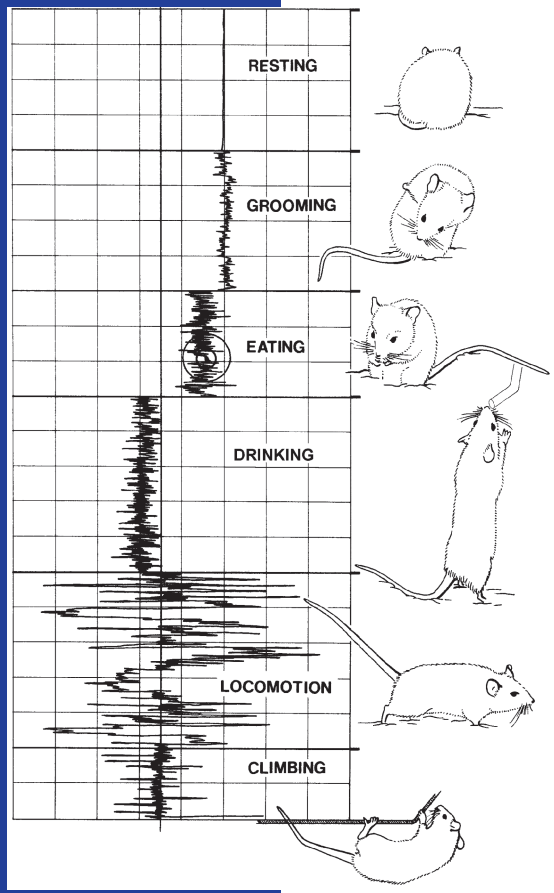


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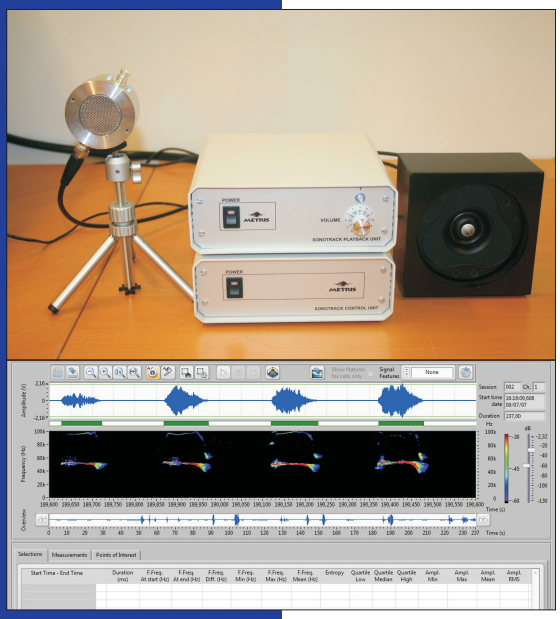
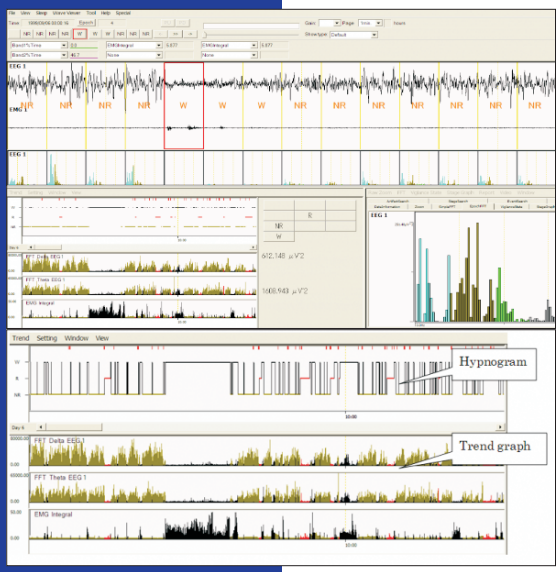
# Innovative Solutions, Instruments and Software for Animal Behavior Research



## SONOTRACK™

### Recording, Analysis and Playback of Ultrasonic Vocalisations (USV)

- Enables full spectrum analysis from 15 kHz to 125 kHz
- Multichannel continuous recording & playback functionality
- Fully automatic ultrasound vocalization (call) counting in user defined frequency bands
- Special System also designed for field use
- Highly valued for research in learning, anxiety, stress, pain, sexual related and social interaction experiments




## SLEEPSIGN™

### Automated Analysis of Sleep Stages in Laboratory animals

- Enables automated & manual sleep stage classification and scoring
- Integrated video & analysis of upto 6 vigilance stages
- Perform multi-animal staging with one step presetting
- Benefit from in-depth analysis using Hypnograms, Trend graphs, Stage graphs, FFT analysis, etc.

## Visit our booth!

**METRIS B.V.**
**The Netherlands**

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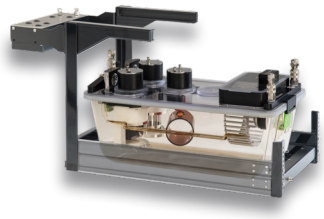
*Sophisticated Life Science Research Instrumentation*

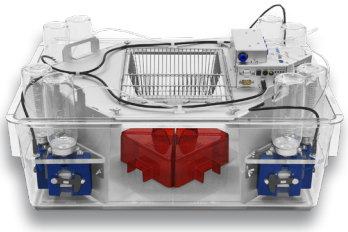
# TSE Systems - experienced supplier of life science research equipment for comprehensive solutions in the fields of **Metabolism, Behavior, Physiology, Inhalation Toxicology** and **Telemetry**

**Come and visit us at our booth!**



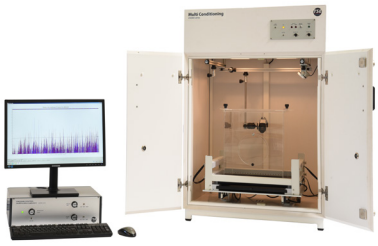
The **PhenoMaster** allows the assessment of metabolic, behavioral, cognitive and physiological parameters in the homecage.

For the evaluation of rodent models in a social context, the **IntelliCage** minimizes the necessity of human handling and increases reproducibility, while the assessment of cognition in a social context.




**Stellar Telemetry** monitors a wide range of physiological parameters in virtually any species.

The **Multi Conditioning System** is a multi-purpose modular test platform accommodating nine behavioral paradigms for the evaluation of learning, memory, emotion and stress-related behaviors in mice and rats.



We also offer complete solutions for a variety of **Inhalation** exposure studies (in-vivo and in-vitro) with aerosols and vapors for various application fields, e.g. pharmacology, toxicology.

**MotoRater** allows semi-automated evaluation of 4 different motion modalities – oveRground walking, skilled ladder walking, wading in water and swimming – and provides fine motor kinematic analysis tools to assess animals' motor performance with high precision.

www.TSE-Systems.com

info@TSE-Systems.com

Noldus
Information Technology

# EthoVision XT

## Video tracking and analysis software

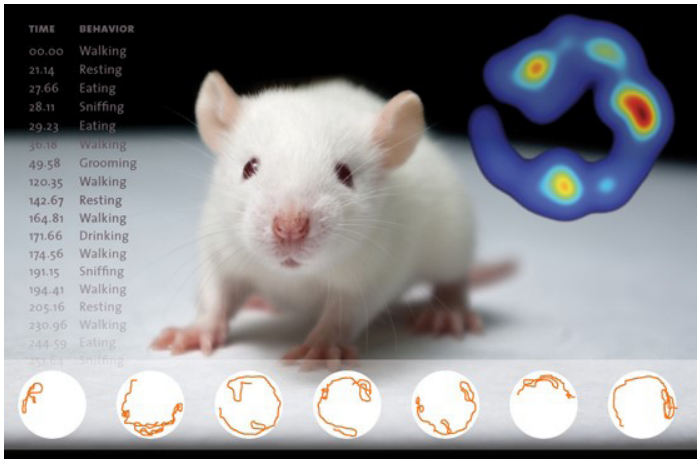
EthoVision® XT is the solution for automated tracking and analysis of animal activity and behavior, suited for everything from straightforward open field tests, to high-throughput research, to sophisticated protocols including external equipment control.

### ANY ANIMAL, ANY SET-UP

A versatile product in every sense of the word, EthoVision XT can be used to track any animal in any kind of test set-up. A basic EthoVision XT set-up allows you to automate standard behavioral tests such as the water maze, plus maze, and open field test. The modular approach makes it a platform to build on. You can create fully integrated systems with hardware control, useful in many contexts including sophisticated operant experiments. EthoVision XT is easily used to automate high-throughput experiments, such as monitoring zebrafish larvae activity in 96-well plates.

### WHY USE ETHOVISION XT?

- The industry standard with more than 7,500 peer reviewed publications and used at more than 2,000 sites worldwide.
- Automatic detection setting, superior detection methods, and powerful analysis.
- Cost effective solution.
- Flexible to fit your choice of hardware.
- External (such as physiological) data integration.
- Versatile to automate:
  - all standard behavioral tests
  - sophisticated set-ups with hardware control
  - high-throughput research



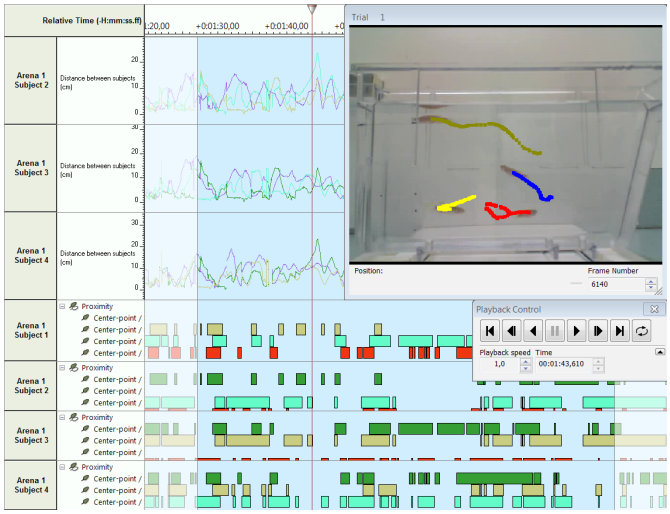

*From straight-forward video tracking to operant conditioning protocols and behavior recognition – EthoVision XT does it all!*

### THE BASICS

EthoVision XT can help in almost any step of your research. From setting up the trial list to the presentation of your results, templates and built-in tutorials make the program easy to use for first-time users, while extensive analysis options help you get most out of your data.

Analysis is made easy with EthoVision XT. Link areas of interest within your arena to tracking parameters so you can easily answer questions such as: What was the latency to enter of the outer zone? How much time does the animal spend near the new object? Visualize your data in heatmaps, track plots, and graphs. Dynamically plotted data streams alongside your video, which plays with superimposed tracking results, to give you the best representation of your data possible.

In addition to video tracking, EthoVision XT also allows for activity detection, where frame-by-frame changes at the pixel level give you data on, for example, freezing behavior in rodents. Flip the analysis parameters to examine high levels of activity, such as those seen during seizure bouts.



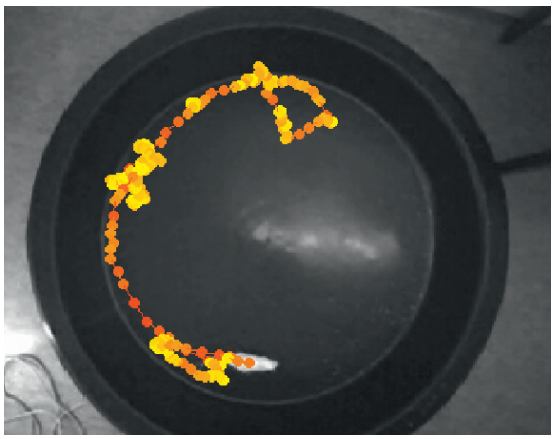

*Integrated visualization shows your video, the tracking of the animals and a dynamic representation of your data in one view.*

## INTEGRATION AND CONTROL OF OTHER TOOLS

Video tracking might be the core of what EthoVision XT does, but what truly sets it apart is the ability to integrate tracking data with other aspects of your experiment. This means that you can base the control of external hardware and software on the behavior of your animal(s).

How does this work? During tracking, EthoVision XT gathers information based on the coordinates of the animal and the zones or points of interest in the arena you have specified. This allows the software to tell, for example, when the subject has been immobile for 2 consecutive minutes, or when its nose point is in the feeding zone.

EthoVision XT can immediately use this information to control the action of other tools, such as starting a video to play, opening a door, turning on a light or audio signal, dropping a pellet, or triggering an optogenetic stimulus. In addition, EthoVision XT allows for the integration of video tracking data with physiological data.



*At the core of EthoVision XT: accurate tracking of any animal in any arena!*

## BEHAVIOR RECOGNITION

In addition to tracking and activity related data, EthoVision XT can also recognize specific rat and mouse behaviors.

- *Mice* - digging, drinking, eating, grooming, hopping, supported and unsupported rearing, sniffing, walking, and resting.
- *Rats* - grooming, jumping, supported and unsupported rearing, twitching, sniffing, walking, resting, eating, and drinking.

## FIND OUT MORE

There is much more to tell about EthoVision XT. Curious? Ask one of our representatives or go to www.noldus.com/ethovision.

## TRY IT OUT!

Request your free trial version online or talk to one of our representatives.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