

PROGRAM AND ABSTRACTS



IUPS-BRICS SYMPOSIUM ON STRESS

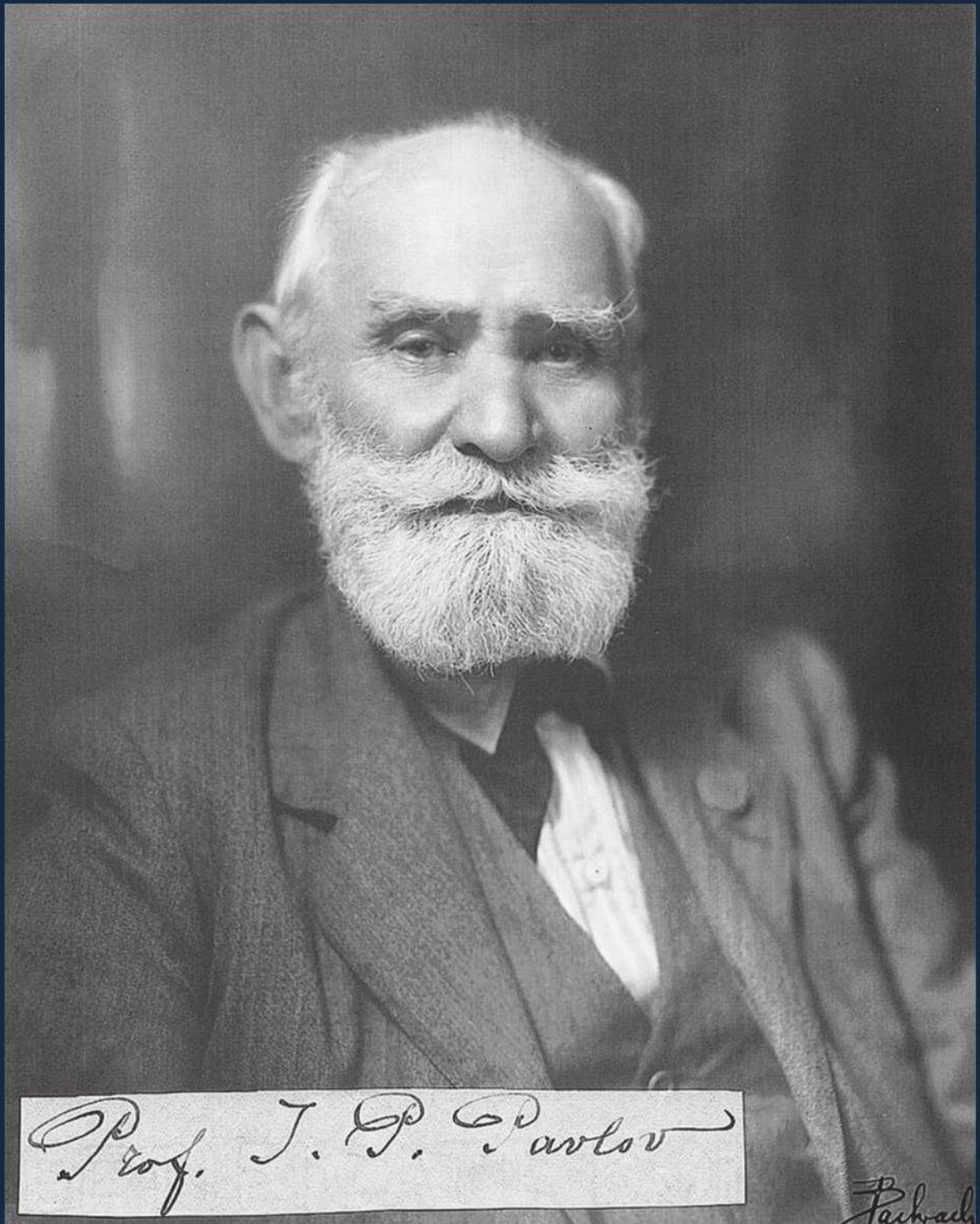
SEPTEMBER, 23, 2019

I.P. PAVLOV INSTITUTE OF PHYSIOLOGY
RUSSIAN ACADEMY OF SCIENCES

SAINT-PETERSBURG
RUSSIA

MY FAITH IS A BELIEF THAT SCIENTIFIC PROGRESS
WILL BRING HAPPINESS TO MANKIND

I.P. PAVLOV



I.P. Pavlov Institute of Physiology
Russian Academy of Sciences
International Union of Physiological Sciences (IUPS)

PROGRAM and ABSTRACTS

IUPS–BRICS SYMPOSIUM ON STRESS

September, 23, 2019

I.P. Pavlov Institute of Physiology
Russian Academy of Sciences

Saint-Petersburg
Russia

ORGANIZERS OF THE SYMPOSIUM

**I. P. Pavlov Institute of Physiology
Russian Academy of Sciences (RAS)
International Union of Physiological Sciences (IUPS)
Department of Physiological Sciences RAS
Russian Pavlov Physiological Society**

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Members of the Committee:

Vagner R. Antunes

Samuel H.H. Chan

Faadiel Essop

Debabrata Ghosh

On behalf of the Organizing Committee of IUPS-BRICS Symposium on Stress we welcome you to St. Petersburg. This symposium is held at the Pavlov Institute of Physiology of the Russian Academy of Sciences and is a celebration of Ivan P. Pavlov's 170th birthday anniversary and Pavlov's influence on integrative physiology.

Historical perspective & Venue: Pavlov Institute of Physiology of the Russian Academy of Sciences was founded in 1925. The first Director of the Institute of Physiology until 1936 was the first Nobel Prize winner in theoretical medicine Academician Ivan P. Pavlov.

Pavlov Institute is one of the largest physiological institutions of the country. By continuing traditional studies initiated by Ivan P. Pavlov and taking into account advances in modern physiology, the Institute goes on with development of fundamental and applied studies on mechanisms of the higher nervous activity, function of the sensory and visceral systems, understanding of processes of their regulation and adaptation. The Institute traditionally carries out extensive international cooperation. We hope that this symposium will promote scientific cooperation between IUPS, BRICS countries and Russia.

The Institute is partly located in very center of St. Petersburg, but its major part is a research campus founded by Ivan Pavlov and located in a village of Koltushi. Pavlovian Koltushi is the first scientific city of Russia and a UNESCO World Heritage site. The symposium program includes historical tour to Pavlov's original laboratory in Koltushi, "the capital of conditional reflexes" and his apartments in St. Petersburg.

The theme of this symposium is Stress. The topic is critically important for development of integrative physiology.

The Father of Stress concept Hans Selye foretold: "Stress in health and disease is medically, sociologically, and philosophically the most meaningful subject for humanity".

We hope that you enjoy your stay in Pavlov Institute of Physiology and in St. Petersburg, the beautiful city, the site of many museums, including the world-famous Hermitage.

Ludmila Filaretova
Chair of the Organizing Committee
Director of Pavlov Institute of Physiology RAS

September 23, 2019 Pavlov Institute of Physiology RAS (Nab. Makarova, 6)	
10.00–13.00 Morning Session Chairpersons: Ludmila Filaretova, Julie Y. H. Chan	
Opening of the Symposium	20 мин
Julie Y. H. Chan, Y. M. Chao (<i>Institute for Translational Research in Biomedicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan</i>) Maternal nutritional stress on the programming of hypertension and metabolic syndrome in young offspring	20 мин
Faadiel Essop (<i>Centre for Cardio-metabolic Research in Africa (CARMA), Stellenbosch University, Stellenbosch, South Africa</i>) An evaluation of stress-mediated cardiovascular pathology using a preclinical experimental system	20 мин
Samuel H. H. Chan (<i>Institute for Translational Research in Biomedicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan</i>) Interplay between brain-derived neurotrophic factor and oxidative stress in animal models of diseases	20 мин
Vagner R. Antunes (<i>Institute of Biomedical Sciences University of Sao Paulo, Sao Paulo, Brazil</i>) Hypothalamic-brainstem circuitry as the coordinator of autonomic functions and blood pressure control during osmotic stress	20 мин
Break, 20 min	

September 23, 2019
Pavlov Institute of Physiology RAS
(Nab. Makarova, 6)

10.00–13.00
Morning Session
Chairpersons: Ludmila Filaretova, Julie Y. H. Chan

Debabrata Ghosh (*All India Institute of Medical Sciences, New Delhi, India*)

To investigate the epigenetic landscape in endometriosis and its links to stress

20 мин

Irina V. Zhdanova (*CEO, BioChron LLC, Boston, MA, USA*)

Integrative role of the circadian clock in adult neurogenesis

20 мин

Dora Zelena (*Institute of Experimental Medicine, Budapest, Hungary; Medical School, University of Pécs, Pécs, Hungary*)

Posttraumatic stress disorder as a metabolic disorder in disguise

20 мин

Gyorgy Baffy (*VA Boston Healthcare System and Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA*)

Scholarly communication and scientific publishing: The emerging landscape

20 мин

Lunch time

September 23, 2019
Pavlov Institute of Physiology RAS
(Nab. Makarova, 6)

15.00–16.30
Afternoon Session
Chairpersons: Jayasree Sengupta, Yury Gerasimenko

Ludmila Filaretova (*Pavlov Institute of Physiology RAS, St. Petersburg, Russia*)

The HPA system is a key hormonal component of the brain–gut axis in stress

15 мин

Elizaveta Savochkina, Ludmila Gromova, Andrey Gruzdkov (*Pavlov Institute of Physiology RAS, St. Petersburg, Russia*)

Membrane digestion: Ugolev's discovery and new data on stress

15 мин

Elena Rybnikova (*Pavlov Institute of Physiology RAS, St. Petersburg, Russia*)

Hypoxic and psychoemotional stress: convergence and differences

15 мин

Yury Shelepin (*Pavlov Institute of Physiology RAS, St. Petersburg, Russia*)

The conscious and unconscious visual stress factors

15 мин

Yury Gerasimenko (*Pavlov Institute of Physiology RAS, St. Petersburg, Russia*)

Regulation of somatic-visceral interactions and emotional stress during spinal cord stimulation

15 мин

17.00–19.00

Visit to Ivan P. Pavlov's Apartment Museum,
tea party, discussion of joint scientific cooperation

Hypothalamic-brainstem circuitry as the coordinator of autonomic functions and blood pressure control during osmotic stress

Vagner Roberto Antunes

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Osmotic stress is a potent regulator of the normal function of cells that are exposed to osmotically active environments under physiologic or pathologic conditions. Despite large fluctuations in salt and water intake, mammals are able to maintain electrolyte concentrations, particularly sodium (Na^+) as the major determinant of osmolality of the extracellular fluid (ECF), within narrow physiological limits (~ 300 mOsm/kg). The two distinct sensory systems monitoring Na^+ -concentration and osmolality in the hypothalamic area of the brain are located outside the blood–brain barrier known as the subfornical organ (SFO) and the organum vasculosum of the lamina terminalis (OVLT), which have direct projections to parvocellular neurons located within the paraventricular nucleus of the hypothalamus (PVN) that in turn modulate sympathetic nerve activity (SNA), and consequently the level of blood pressure (BP). The SFO seems to be the primary locus of NaCl sensing for the control of salt-intake behaviour at the central level, identified as a sensory mechanism that relies on activation of a Na^+ channel (Na_x). The SFO is also involved in mediating the central Na^+ -induced pressor response, since administration of NaCl-rich in the artificial cerebrospinal fluid (aCSF) into the SFO caused an increase in BP, which was blunted by an angiotensin II type 1 (AT1) receptor antagonist at the same site. Not only SFO, but also the OVLT neurones are capable of detecting extracellular NaCl concentration to alter the sympathetic nerve discharge in order increase BP. Increases in $[\text{Na}^+]$ in body fluids activate Na_x channels in the OVLT. The Na_x signal in glial cells is transferred to the hypothalamic (PVN) and brainstem nuclei (rostral ventrolateral medulla – RVLM) controlling the sympathetic nerve activity (SNA), and BP levels. The brain circuitry involved in the sympathetic activation caused by high salt intake correlates with activation of hypothalamic neurons, more precisely those within the PVN, that projects to the brainstem, particularly to the RVLM and spinal cord, the main sympathetic outflow to control the BP level.

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Scholarly communication and scientific publishing: The emerging landscape

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Journal-based scientific publishing has been the fundamental form of scholarly communication ever since the first periodicals were launched in France and England almost simultaneously in 1665. Scientific publishing brings many stakeholders with conflicting interests under the same roof, including for-profit and not-for-profit publishers, government and private research funders, academic institutions and university libraries, along with investigators and other scholars who write and read the literature. Interestingly, academic authors offer their scholarly reports for publication without expecting to be paid by publishers. Despite this unique business model, scientific publishing has shown relentless growth with more than 2.5 million articles published each year in 42,000 scientific journals today. Digital communication has amplified the problems of traditional scientific publishing as evidenced by overwhelmed editors and peer reviewers, rising retraction rates, emergence of pseudo-journals and online piracy, strained library budgets and controversies about how to best recognize scholarly achievements. On the positive side, however, various forms of open access publishing represent a profound change from the traditional business model and offer opportunities for a globalized scholarly communication by providing readers with free access to scientific literature. These developments coincide with the acquisition and integration of large research databases and discovery services by several large for-profit publishers, raising the specter of oligopolization. Many financial, legal and ethical dilemmas complicate this technology-driven transition where successful innovations, new alliances and winning strategies remain difficult to predict. Since scientific publishing has been a highly profitable industry, financial interests will almost certainly continue to drive its transformation. However, the academic community has a fundamental interest in engaging in this process to protect traditional values, encourage positive trends, and promote an equitable and efficient system of scholarly communication.

References:

1. Tennant JP et al. The academic, economic and societal impacts of Open Access: an evidence-based review. *F1000Research*. 2016;5.
2. Johnson R, Watkinson A, Mabe M. The STM Report. An overview of scientific and scholarly journal publishing. In: STM: International Association of Scientific TaMP, ed. 5th ed. The Hague: International Association of Scientific, Technical and Medical Publishers; 2018.
3. Baffy G et al. Scientific authors in a new world of scholarly communication: What does the future hold? *Am J Med*. 2019; in press.

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Maternal nutritional stress on the programming of hypertension and metabolic syndrome in young offspring

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The term nutritional programming describes the process through which exposure to early-life nutritional stimuli brings about morphological changes and/or functional adaption in offspring. Nutritional programming is emerging as a critical risk factor for a number of non-communicable diseases in adult, including hypertension, cardiovascular disease, diabetes, obesity, allergic diseases, kidney disease, neurocognitive impairments, nonalcoholic fatty liver disease, and metabolic syndrome. The range of nutritional insults that have been utilized in animal models of nutritional programming can be grouped into models which restrict calorie intake, manipulate macronutrient intake, or restrict micronutrient intake. Despite the diversity in nutritional insults during gestation and/or lactation, similar disease phenotypes are witnessed in adult offspring; pointing to common mechanisms underpinning the pathogenesis of nutritional programming of disease. These may include nutrient-sensing signals, oxidative stress, inflammation, tissue remodeling, epigenetic regulation, and gut microbiota. Some of the proposed underlying mechanisms will be discussed in the presentation. Reprogramming strategies aim to reverse the programmed development and achieve normal development. In this regard, nutritional intervention, exercise, lifestyle modification and pharmacological therapy to mother or offspring have been adopted. In this presentation, pharmacological treatments with compounds targeting at nutrient-sensing signals, oxidative stress, and gut microbiota for reprogramming of disease in offspring will be highlighted.

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Interplay between brain-derived neurotrophic factor and oxidative stress in animal models of diseases

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Brain-derived neurotrophic factor (BDNF) is now known to possess nontrophic actions, one of which is amelioration of brain stem cardiovascular dysregulation via an antioxidant effects in rostral ventrolateral medulla (RVLM), a key nucleus of the baroreflex loop. In a neurogenic hypertension model, angiotensin II (Ang II) upregulates BDNF mRNA and protein, induces phosphorylation of cAMP response element binding protein (CREB) or p47phox subunit, suppresses mitochondrial electron coupling capacity, and increases mitochondrial uncoupling protein 2 (UCP2) in the RVLM. Superoxide dismutase mimetic (tempol), NADPH oxidase inhibitor (apocynin) or antisense CREB oligonucleotide blunts the Ang II-induced BDNF upregulation; and gene knockdown of BDNF or depletion of tropomyosin receptor kinase B (TrkB) attenuates UCP2 upregulation or potentiates Ang II-induced superoxide and pressor response. In a temporal lobe status epilepticus (TLSE) model, hypotension preceded by reduced baroreflex-mediated sympathetic vasomotor tone accompanies sustained hippocampal seizure; with concurrent increases in superoxide, phosphorylated p47phox NADPH oxidase subunit, BDNF mRNA or protein, TrkB, angiotensin receptor subtype 1 (AT1R), nitric oxide synthase II (NOS II) or peroxynitrite in the RVLM. Whereas tempol, apocynin or AT1R antagonist (losartan) blunts the elevated superoxide or phosphorylated p47phox subunit, hypotension and the reduced baroreflex, a recombinant TrkB-Fc fusion protein or an antisense bdnf oligonucleotide potentiates all those events without affecting NOS II. We conclude that BDNF acts as an endogenous antioxidant at the RVLM in neurogenic hypertension and TLSE.

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An evaluation of stress-mediated cardiovascular pathology using a preclinical experimental system

Faadiel Essop

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According to the World Health Organization more than 70% of global human mortality is attributed to non-communicable diseases, causing more than 38 million deaths each year. Although non-communicable diseases include debilitating conditions such as cancer, and respiratory diseases, the deadliest comprise cardio-metabolic complications. This includes both cardiovascular diseases (CVD) and metabolic disorders like Type II diabetes mellitus. Although a plethora of studies demonstrated that a number of well-known lifestyle-related factors are implicated in this process, the impact of chronic stress as a crucial contributing factor to CVD onset is increasingly being recognized. Here chronic stress can cause maladaptive changes in both the hypothalamic-pituitary-adrenal axis and the sympatho-adrenal medullary pathway, including elevated circulatory glucocorticoid levels, catecholamines and several growth hormones. The focus of this study was therefore to evaluate the detrimental effects elicited by chronic stress on the cardiovascular system. The literature gaps concerning the underlying molecular mechanisms driving stress-related CVD onset exist mainly due to the difficulty in establishing appropriate animal models to accurately simulate the stress response and related systemic effects. Although small rodents are a good choice due to their cost-effectiveness and physiological similarity to humans, there are also some fundamental differences between rodents and humans that can have a considerable impact on results generated and its eventual translation into clinical practice. In light of this, the present study employed the unpredictable chronic mild stress model (UCMS) model where rats were exposed to a daily stressor (in randomized fashion) over an 8-week time period and compared to matched controls. After the 8-week experimental period, rat hearts were subjected to ex vivo ischemia-reperfusion experiments using a Langendorff perfusion apparatus, while endothelial function was also assessed using isolated aortic rings. In addition, several markers of oxidative stress and inflammation were evaluated. Preliminary findings generated will be presented and further discussed.

The study was supported by the South African National Research Foundation.

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The HPA system is a key hormonal component of the brain–gut axis in stress

Ludmila Filaretova

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Bi-directional communication between the brain and the gut plays critically important role in health and disease. The first brilliant demonstration of the brain-gut communication was the cephalic phase of gastric and pancreatic secretion, discovered in Russia by Ivan Pavlov. The communication occurs through neuronal pathways including the vagus nerve, hormonal pathway as well as components of the immune system and the gut microbiota. Here we will provide data on the main hormonal component of brain-gut axis, namely the hypothalamic-pituitary-adrenocortical (HPA) system and emphasize its gastroprotective role. The results of our studies suggest that the activation of the HPA system is gastroprotective component of stress response and glucocorticoids released in response to stress are gastroprotective but not ulcerogenic factors as previously accepted for several decades. Contribution of glucocorticoids to protective influence of preconditioning mild stress on the gastric mucosa is further confirmation of physiological gastroprotective role stress-produced glucocorticoids. The fact that the disturbance of the normal stress reaction by the elimination of the HPA axis's functioning leads to negative effects on the body such as the development and aggravation of gastric ulcer disease proves that stress-induced activation of the HPA axis plays a leading role in maintaining the physical health of the body. Gastroprotective effects of glucocorticoids may be mediated by multiple actions, including maintenance of gastric mucosal blood flow, mucus production, and attenuation of enhanced gastric motility and microvascular permeability. Glucocorticoids may contribute to gastroprotection by maintaining general body homeostasis, including glucose levels and systemic blood pressure, which could be a basis for their beneficial influence on the gastric mucosal integrity. Glucocorticoids exert gastroprotective actions in co-operation with prostaglandins, nitric oxide and capsaicin-sensitive sensory neurons. The findings provide novel insight for understanding of the potential role of the HPA system as important hormonal branch of the brain-gut communication. According to the findings, activation of the HPA system is gastroprotective component of the brain–gut axis.

This study was supported by Russian Science Foundation (RSF) N 19-15-00430.

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Regulation of somatic-visceral interactions and emotional stress during spinal cord stimulation

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Any motor act is accompanying by somatic-visceral interactions. The goal of this study is to clarify the effects of spinal neuromodulation for somatic-visceral interactions and emotional stress regulation. We examined the neuromodulation of lower urinary tract function associated with acute epidural spinal cord stimulation and locomotion in adult rats. We show that spinal cord stimulation can effectively neuromodulate the lower urinary tract via frequency-dependent stimulation patterns. The data demonstrate that the sensorimotor networks controlling bladder and locomotion are highly integrated neurophysiologically and behaviorally.

In clinical studies we tested the capacity of electrical stimulation, applied transcutaneously over the spinal cord, to manage autonomic dysfunction in the form of orthostatic hypotension after SCI. During the orthostatic challenge, all individuals experienced hypotension, reduction in cardiac contractility, and reduction in cerebral blood flow along with severe self-reported symptoms. Electrical stimulation completely normalized BP, cardiac contractility, cerebral blood flow, and abrogated all symptoms. Thus, noninvasive transcutaneous electrical spinal cord stimulation may be a viable therapy for restoring autonomic cardiovascular control after SCI.

The development of acute and posttraumatic stress symptoms after a traumatic event is a typical for SCI patients. Experiments will be described which demonstrate that after complete paralysis the lumbosacral spinal circuitry can be functionally reorganized by repetitive practice of a given motor task, including standing and stepping as well as the recovery of standing and voluntary control and assisted stepping in humans that have been completely paralyzed for more than a year. Other effects that have been observed in paralyzed human subjects has been improved autonomic functions controlling multiple physiological systems. The most surprising observation has been the consistent recovery of voluntary function after complete paralysis of the lower limbs. The potential mechanisms that underlie these widespread changes motor and autonomic functions will be presented. Finally these results observed after paralysis suggest several neurophysiological phenomena that have not been previously recognize play a central role in the control movement.

How these physiological phenomena are related to emotional stress regulation will be discussed.

Supported by Program PRAN 42 project № 0134-2018-0001.

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To investigate the epigenetic landscape in endometriosis and its links to stress

Debabrata Ghosh

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Several lines of evidence that has gathered over quite some time links chronic cell stress to human diseases including cancer, atherosclerosis, diabetes and neurodegenerative disorders. Recent evidence points to epigenetic anomalies making substantial contributions to stress-induced pathologies. It appears that chronic stress can elicit changes in the chromatin landscape that 'lock' cells in dysregulated states. The adaptive pressure thus generated due to chronic stress may lead to the evolution of abnormal cell states causing system disorders and diseases.

One outcome of chronic stress is to establish cellular disorders that persist even if the stress exposure is removed or diminished due to anomalous chromatin compaction and organization. Chromatin compaction and organization are regulated by DNA methylation, histone variants, histone post-translational modifications and nucleosome remodelling help to determine the gene expression profile in cell- and state-specific manner. In fact, chromatin structure is controlled in cell-type and physiological state specific manner. Thus, particular cell types have specific epigenetic characteristics, and stem cells differ substantially from terminally differentiated cells. There is substantial evidence to suggest that the cells involved in several major human pathologies like cancer, cardiovascular disease and diabetes have aberrant patterns of epigenetic modifications due to chronic stress and, in many cases, the modified epigenetic landscape patterns may contribute substantially to the disease-causing cellular phenotypes.

In the presentation, I shall deliberate upon the hypothesis that stress may influence the cellular phenotypes of emigrated cells in the pelvis and other ectopic sites, as well as, the immune and endocrine responsiveness to those cells by influencing the epigenetic landscape untowardly. Such onslaught on epigenetic landscape leading combinatorial cellular heterostasis can result in endometriosis and infertility. However, there is no substantial study examining the putative role of stress-associated modifications in epigenetic landscape at global and local levels in ovarian endometriosis. We propose to undertake this study by adopting an integrative approach of employing related clinical physiology and cellular-molecular biology tools. A tentative study design shall also be presented.

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Hypoxic and psychoemotional stress: convergence and differences

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According to the classic concepts, stress is a condition when an organism is exposed to external or intrinsic factor (stressor) threatening its homeostasis. A complex of endogenous reactions to such exposures is called stress response of the organism. It is generally accepted that stress response is not specific for any kind of stressor and always includes similar activation of the hypothalamic-pituitary adrenal axis (HPA). In such terms, stressors of psychoemotional nature might be considered as most classical ones, and the profiles of HPA activation have been characterized in a detail for both acute and chronic exposures. In the first case, HPA response starts from rapid and sharp increase in glucocorticoid levels followed by the inhibition via negative feedback. In the second case, the feedback mechanisms are suppressed that results in the long-term maintenance of the elevated glucocorticoid levels. In both cases, injury to the organisms appears as a result of the toxicity of glucocorticoids, either over-release in acute stress, or chronic circulation of moderate concentrations in chronic stress. In such a frame, hypoxia also represents a kind of stressor and enables the hormonal mechanisms of stress response. For this reason, hypoxia is often called «hypoxic stress». Indeed, both acute and chronic hypoxia produces the activation of HPA, however the profiles of such activation differ significantly from the ones in psychoemotional stress. In particular, acute severe hypoxia leads to the lasting impairment of biphasic dynamics of HPA response. Chronic mild hypoxia up-regulates baseline levels of glucocorticoids and decreases HPA stress-reactivity. Principal difference of hypoxia from the classic stress is associated to the fact that in addition to HPA activation hypoxia induces specific molecular mechanisms to ensure cellular and systemic adaptation to low oxygen. They include inactivation of the prolyl-hydroxylases followed by stabilization of HIF-1 and activation of HIF-dependent adaptive processes, including the expression of multiple hypoxia-responsive genes. Delayed activation of HIF-1 has been also reported for the psychoemotional stressors but therein it correlates to the development of pathologic states, including depressive and anxiety disorders. Thus, it might be concluded that both stress and hypoxia engage the same mechanisms, including HPA and HIF-1, but in a very different manner. For this reason, it is incorrect to term hypoxia «hypoxic stress».

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Membrane digestion: Ugolev's discovery and new data on stress

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Academician Alexander Mikhailovich Ugolev (1926–1991) was one of the brightest representatives of national and world physiology in the last century. The most known of his achievements is a discovery in 1958 one of the basic types of digestion, previously unknown, which he named as membrane digestion.

Membrane digestion takes place at the external surface of the intestinal epithelium by the enzymes, adsorbed from the intestinal lumen, and by intrinsic intestinal enzymes, localized at the apical membrane of the enterocytes. A discovery of membrane digestion has led to reappraisal of many classic concepts, and has solved a number of serious contradictions in physiology of digestion. Many aspects of membrane digestion have been characterized in the investigations performed under A.M.Ugolev's supervision: the levels of organization of membrane hydrolysis, its spatial topography, organization and regulation of poly-substrate processes in the small intestine as well as well as the influence of various stress factors on functioning of membrane digestive enzymes.

In subsequent years, in the Laboratory of Physiology of Nutrition the researches of membrane digestion and glucose absorption at stress were continued. In particular, the effects of acute and chronic stress on the hydrolysis and absorption of nutrients in the small intestine of rats were studied. It has been found that the effect of acute immobilization stress leads to an increase in the absorption of glucose in the small intestine and to changes in the activities of enzymes involved in the membrane digestion.

In simulating chronic stress by administering corticosterone, a close correlation was shown between the rate of absorption of glucose in the small intestine and the level of glucocorticoids in the blood. At the same time, when the concentration of corticosterone in the blood was characteristic for moderate stress, the activity of membrane digestive enzymes did not change significantly compared to the effects observed with the concentration of the hormone in the blood in case of severe stress. It was also shown that the reactions of the glucose transport system and the activity of membrane digestive enzymes to chronic immobilization stress depend on the ambient temperature.

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The conscious and unconscious visual stress factors

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The significant for the observer properties of the environment are selected by the mechanisms of conscious and unconscious vision, and the part of the visual information works as a stress trigger, or stressors. The search of the visual stressors and investigation of their physical and semantic properties was the purpose of our work.

The description of the physical parameters of the perceived image of the scene, we provided by the spatial-frequency analysis of digital images of natural landscapes and humane faces. It has been established that certain spatial-frequency characteristics make it possible to predict the characteristics of perception during the conscious and unconscious operation mode. There are certain properties of images that have an emotionally positive or emotionally negative influence on a person. The single face or faces in the crowd giant cities sleeping areas have spatial-frequency characteristics featured aggressive influence, stressors for the person with very specific characteristics. A combination of the signals of «danger», which indicates the presence of the stressor, not only always appears in conscious perception, but it exists an optical space and it we found, be indicators, measuring components in the proper parts of the visual spatial - frequency range. The particular interest is the analysis of other usually unconscious, the semantic stress factors. For example we propose the subtle changes in the dynamic facial expressions of the interlocutors, and the mood of the crowd. Life circumstances, military actions or disasters, can leave an «age imprint» and provide an opportunity to track the impact of past by our «Emotional stress marker». New methods make it possible to identify, usually unconscious, anatomical changes in facial expressions, the search for which for many centuries inspired by the artists. We developed the stress experienced «Stranger Face» marker. The balance between the positive and negative «stressor» effects of the same semantic factor depends on the initial state of the brain. The importance of human brain neuronal nets interaction for face discrimination has been demonstrated.

Awareness and unconsciousness of the presence and influence of stress factors has been investigated. It works as unconscious operation mode for preparing to the physical and semantic factors of stressor. For stress experience markers we developed the new methods - stress anxiety and tension markers, as the result of accumulation of various stressors in observer mind. Our new methods for analyzing facial expressions made it possible to evaluate former stress and experienced emotions.

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Posttraumatic stress disorder as a metabolic disorder in disguise

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Posttraumatic stress disorder (PTSD) is a severe mental disorder that develops in some, but not all persons after exposure to extreme traumatic event. Since underlying neurobiological mechanisms are still not clear, available treatment options are not sufficient. Therefore, search for new tools are justifiable. Several studies indicate its high comorbidity with metabolic disorders, thus carbohydrate homeostasis seems to be an important area for identifying resilient versus vulnerable responders and determine new treatment targets. The similarity between human and rat carbohydrates supports the importance of rat studies with high translational value. Electric footshock induced PTSD-like symptoms was studied in rats. First, metabolic changes were followed during the development of symptoms. Trauma acutely increased food intake and energy expenditure, while in the long run they were decreased. During trauma reminder there was an increase in food intake without changes in energy expenditure. Next we were concentrating on the glycome and compared non-shocked controls to shocked vulnerable and resilient groups determined by behavioral z-score analysis. N-glycosylation occurs in all cells and enables adaptive response to environmental changes. More than 80% of its genetic problems leads to neurological abnormalities. We aimed to find new glycomic biomarkers for prevention and therapy. We checked pretrauma anxiety and N-glycan blood levels as well as behavioral and N-glycan profile of blood and brain samples 28 days after trauma exposure. Pretrauma anxiety did not determine vulnerability. The N-glycan measurement indicated the presence of the same N-glycans in all studied brain areas (prefrontal cortex, hippocampus, amygdala) with different types in blood. In blood the pretrauma blood samples showed similar profile and amount as posttrauma levels. However, there was no difference between the three groups in the concentration of any studied n-glycans. We can conclude that trauma with repeated reminders might lead to metabolic changes by increasing the energy expenditure. On the other hand, N-glycans do not seem to be predictive before trauma and did not change after trauma exposure.

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Integrative role of the circadian clock in adult neurogenesis

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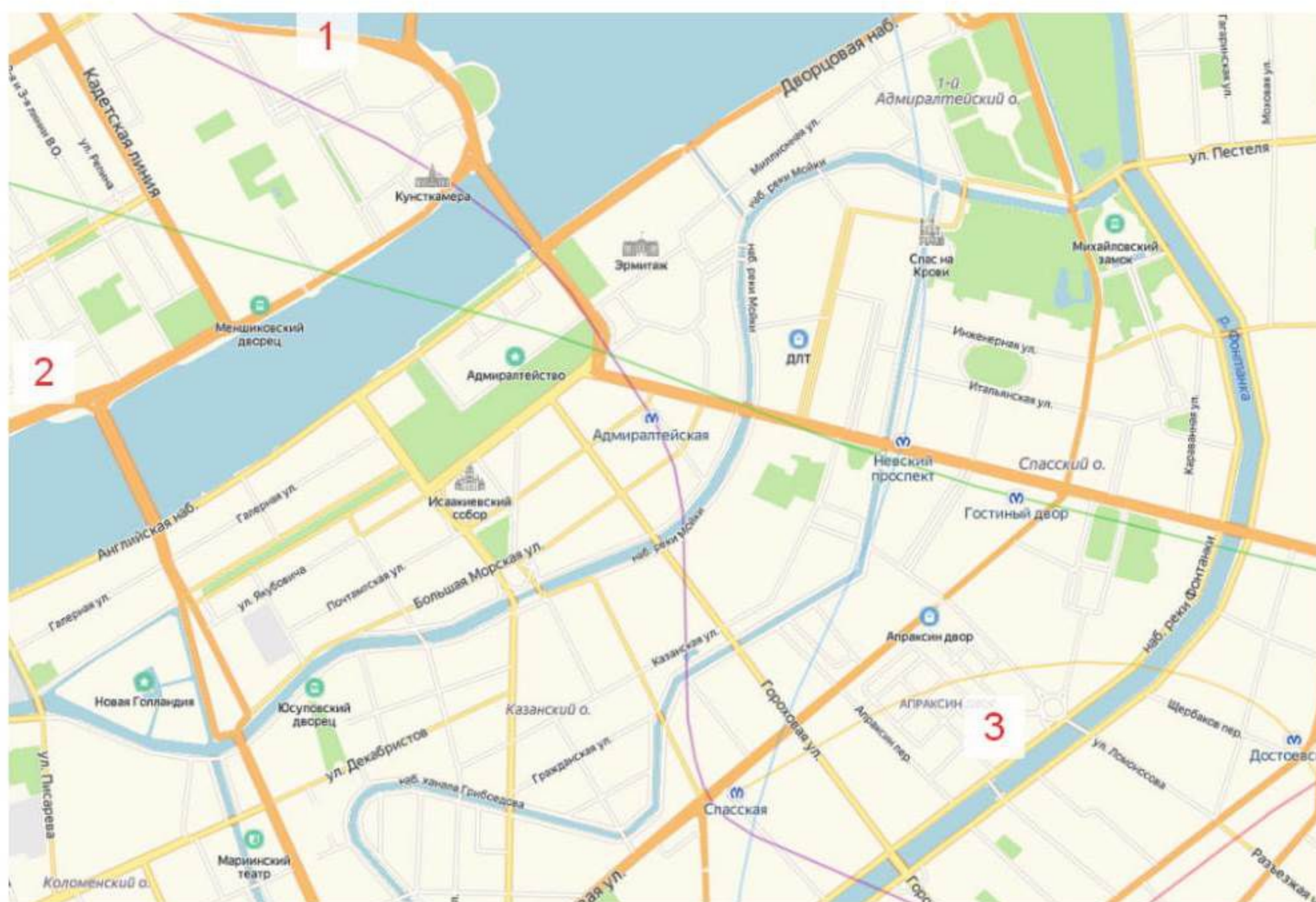
The circadian clock is one of the integrating molecular and physiological mechanisms. It is responsible for temporal mutual coordination of numerous internal processes and their adaptation to periodically changing external environment. While the most well appreciated circadian phenomena include sleep, metabolic or cardiovascular rhythms, the circadian clock regulates virtually all other known processes as well. The birth and maturation of new neurons as part of adult neurogenesis is no exception.

In mice, the circadian variation in neurogenesis was documented repeatedly but was found not to be very robust. This, in part, might be related to their nocturnal adaptation and/or polyphasic sleep patterns. We chose to study the role of the circadian clock on adult neurogenesis in diurnal animals displaying nighttime sleep by using zebrafish. One of the major advantages of this model is that zebrafish have exceptionally active proliferation throughout lifespan, generating thousands of new cells daily. Their brain contains 16 neurogenic niches distributed along the entire rostro-caudal axis, from the olfactory bulbs and telencephalon to cerebellum and hindbrain.

By focusing on 5 neurogenic niches, including those in the telencephalon, habenula, optic tectum, hypothalamus and cerebellum, we found robust circadian rhythm of adult neurogenesis in all of them. While the number of cells in S-phase of the cell division cycle was at peak by the end of the day in all the neurogenic niches studied, the kinetics of cell proliferation differed between the niches. This suggests that a combination of the circadian clock factors and specifics of niche environment define the proliferative patterns in adult brain. These findings open new opportunities for translational research into the regulatory mechanisms of adult neurogenesis, their modulation by pathological conditions and drugs, or changes throughout normal aging process.

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1. SYMPOSIUM VENUE: I.P. PAVLOV INSTITUTE OF PHYSIOLOGY (MAKAROVA NAB. 6)
2. I.P. PAVLOV APARTMENT MUSEUM (VASILEVSKIY ISLAND, 7TH LINE, 2)
3. SEPTEMBER 24, 19:00. WHIGHT NIGHT – (FONTANKA NAB. 59)

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