Report on the Conference on Integrative Physiology held at the Pavlov Institute of Physiology of the Russian Academy of Sciences at Saint Petersburg, Russia on September 24, 2019

Professor Ludmila Filaretova, Director of the Pavlov Institute of Physiology warmly welcomed all participants from within and outside of Russia to the Conference on Integrative Physiology held in honour of the 170th birth anniversary of Ivan Petrovich Pavlov. In her Introduction L. Filaretova discussed a role of I.P. Pavlov in a foundation on Integrative Physiology. Pavlov was responsible for training a whole school of physiologists and psychologists who continued his ideas about integrative physiology and behaviour to future generation.

Professor Julie Chan warmly recalled the contributions of Ivan Pavlov as he had set the stage for physiological sciences in the 20th century for which he was awarded the Nobel Prize for Physiology/Medicine in 1904 becoming the first Russian Nobel laureate, but also for his immense contributions in psychology. In her lecture, J Chan elaborated on the integrated behaviour from cell to animal behaviour and human disease through her studies that examined the role of microRNA-195 (miR-195) in the regulation of blood brain barrier (BBB) integrity in health and disease. The study models included wild-type and miR-195 knockout (KO) mice as well as patients with and without dementia and cerebral small vessel disease. MiR-195 expressed in astrocytes and released via exosomes increased its expression in tight junctions of endothelial cells, in conjunction with claudin-5 and ZO-1 facilitated endothelial and BBB integrity. MiR-195 also found to regulate thrombospondin-1 (TSP-1) expression in hippocampus which in miR-195 KO mice also led to impaired cognitive function. Adequate level of miR-195 and low level of TSP-1 found important to keep blood brain barrier integrity and to reduce the risk of neurodegeneration associated with cerebral disease.

Professor S. Chan discussed his experiences on the successful execution of tractographic analysis by diffusion tensor imaging (DTI) of the medulla oblongata in mice and rats to evaluate baroreflex functionality. The passage of action potentials along the axon creates anisotropy, the reduction in fraction anisotropy taken to infer that disruption of impulse traffic within the baroreflex neural circuits occurs during the execution of cardiovascular regulatory functions. This when viewed in conjunction with radiotelemetric analyses of the baroreflex it was discovered that under pathophysiological conditions disrupted connectivity between key nuclei in the baroreflex circuits is reversible such as in neurogenic hypertension and amenable to remedial measures. However, fatality ensues when the connectivity between key substrates is irreversibly severed as in hepatic encephalopathy. These results sustain the notion that coupled with relevant physiological phenotypes, DTI can be an effective investigative tool for functional evaluations of brain stem activities.

Professor F. Essop explored the links between HIV and the onset of cardiovascular diseases. The development of cardiovascular diseases (CVD) in HIV infected individuals is considered to be a multi-factorial process where traditional risk factors (eg. smoking and diet), side effects of antiretroviral drug cocktails and persistent immune activation are implicated. The perturbations in CVD onset in HIV infected individuals may be caused by increased immune-activation and oxidative stress as pivotal drivers of this process through metabolic re-

programming of immune cells that can contribute to coagulation pathway activation providing a putative mechanistic link between HIV and CVD development.

Professor V. Antunes discussed the purinergic signalling mechanisms operating at hypothalamus level in the control of salt-induced hypertension. Circumventricular organs (CVOs) of subfornical organ, and the vascular organ of lamina terminalis lying outside the blood brain barrier have the ability to sense signals in blood, then pass that information neurally to the paraventricular (PVN) region of the hypothalamus, an integrative centre for autonomic functions that modulate sympathetic nerve activity (SNA) and blood pressure homeostasis. Of numerous neurotransmitters that act within the PVN to regulate the SNA - adenosine -5-triphosphate (ATP) is one such. ATP-gated purinoreceptor (P2X) belongs to a cation channel family of membrane ion channels preferably permeable to sodium, potassium and calcium that open within milliseconds of the binding of ATP. An increase in plasma osmolality activated PVN neurones in an awake animal model led to increased expression of FOS protein in neurons that express P2X2 receptor subunit, and the increase in SNA induced by hyperosmolality involved P2 receptor activation in PVN. These results support the notion that purinergic signalling is involved in the control of salt-induced sympatho-excitation in PVN neurons via the activation of P2X receptors.

Professor G. Baffy elaborated on the risk assessment modalities in complex diseases such as hypertension and diabetes that result from the interaction of multiple genetic and environmental factors. In precision medicine the prediction of disease outcomes and success of therapeutic interventions depend upon the genetic, metagenetic, clinical laboratory and imaging data for deep phenotypic employing system biology approaches. In nonalcoholic fatty liver diseases (NAFLD) associated with obesity and diabetes for example individuals can express simple liver steatosis, while in others it may develop into steatohepatitis and in some cirrhosis and may ultimately progress to hepatocellular carcinoma which has poor prognosis. Applying principles of complexity and network science could allow for the mapping of an individual's phenotype in a multidimensional phase space by accounting a myriads of factors to predict and to prevent disease outcomes.

Professor D. Zelena discussed the use of ultrasound vocalisation (USV) induced by foot shock in rats as a study model of pathological anxiety. The role of vasopressin in stress-related disturbances such as anxiety was confirmed in natural vasopressin-deficient Brattleboro rat using foot-shock induced USVs. The role of vasopressin in the emission of separation-induced USVs via the V1a and V1b receptors has been confirmed from genetic and pharmacological studies. Monitoring the emission of USVs may play useful role in the development of new treatment strategies for anxiety, schizophrenia and autism.

Professor I. Zhdanova discussed the latest advances in the biology of sleep appreciating its role in normal cognitive functions and physical performance. Recent advances have led to understanding the regulation of sleep process *per se* by the homeostatic mechanism and the circadian clock. The use of animal models that include zebrafish, drsosophila, cell culture systems and mathematical modelling shall help to provide newer insights into the molecular mechanisms of sleep.

Professor J. Sengupta included in her discussion the role of stress as one predisposition factor that *in utero* may trigger the emergence of endometriosis in adult life. The aberrant role of eutopic endometrium of ovarian endometriosis in the progression of this disorder through

seven cardinal mechanisms that include homeostatic stress response, epithelial-mesenchymal transition (EMT), cellular and extracellular matrix, cell proliferation, angiogenesis, inflammatory cytokines, apoptosis and autophagy were highlighted. Endometriosis a disorder with no known medical cure, and with high rates of recurrence following ablation of ectopic lesions is associated with greatly compromised health and quality of life with primary infertility experienced in more than 50% women diagnosed with this disease. Being a chronic inflammatory disease it is associated with comorbidities that include cardiovascular diseases, fibromyalgia and chronic fatigue syndrome, multiple sclerosis and systemic lupus erythromatosus. Ovarian endometrioma, but not deep infiltrating endometriosis, via transition through atypia is associated with the onset of ovarian cancer – clear cell carcinoma and endometrioid carcinoma as well as non-ovarian cancers that include, endometrial cancer, breast cancer , melanoma and thyroid cancer. Based on available data from her own laboratory and from others, a network of oncogenes, growth factors, transcription factors and miRNAs described to decipher how through cell proliferation, angiogenesis, EMT and inhibition of apoptosis fibrogenesis and oncogenesis may be initiated in ectopic lesion of ovarian endometrioma. The presence of higher Y-chromosome transcripts (validated by RNA-seq, qRT-PCR, DNA inserts and WB) in eutopic endometrium of ovarian endometriosis raised a question on its putative role in fecundability.

Professor I. Abraham highlighted the non-classical actions of estrogen in the brain. Estrogen is known to play a role in determining the vulnerability of cholinergic neurons that degenerate in Alzheimer's disease, and estrogen through its feedback action plays a major role in altering the function of GnRH neurons that function as a 'central processor' in the regulation of fertility. The use of immunohistochemistry, transgenic technology, calcium imaging, single-cell electrophysiology and single molecule detection the role of estrogen-induced, 'non-classical' effect on signalling molecules in cholinergic and GnRH neurons were discussed.

These discourses comprised the first day of the Conference on Integrative Physiology at the Pavlov Institute of Physiology, Russian Academy of Sciences, Saint Petersburg Russia.