generate a loop of stimuli/response/stimuli to maintain the homeostasis.

OP.134

Copper Dyshomeostasis In Neurodegenerative Diseases

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Copper (Cu) homeostasis is required for a number of processes included brain development. Cu dyshomeostasis and oxidative stress play a pivotal role in several neuropathologies such as Parkinson disease (PD). In such diseases, metal accumulation in the central nervous system could result in loss-of-function of proteins involved in copper metabolism and in a copper redox cycling that generates reactive oxygen species. Moreover, neurodegenerative disorders imply the presence of an excess of misfolded proteins known to lead to neuronal damage: in PD, copper accumulates in the brain, binding alpha-synuclein and initiating its aggregation. In this work, we assessed the correlation between neuronal differentiation and copper homeostasis regulation, in both physiological and pathological conditions. At this purpose, we used SHSY5Y neuroblastoma cell line, treated with retinoic acid and brain derived growth factor (BDNF) in order to induce neuronal differentiation, and rotenone, able to cause neuron degeneration. Upon Cu treatment, we analyzed transcriptional and metabolic levels of proteins directly or indirectly involved within copper homeostasis such as Cu transporters and chaperones, together with α-synuclein and the prion protein (PrP). Aberrant conformations of these soluble proteins facilitate their precipitation and the tendency to form insoluble and toxic deposits: identifying Cu dependent alterations in the pathways responsible for the protein-misfolding may potentially offer new opportunities for clinical intervention.

OP.135

The Effect of Growth Hormone and/or Swimming Exercise on PI3K/AKT/mTOR Signaling Pathway and Bone Mineral Density in Rats Skeletal Muscle

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Athletes misuse recombinant human growth hormone (r-hGH) to enhance their performance. The aim of this study was to investigate possible effects of r-hGH use and/or exercise on phosphatidylinositol 3-kinase(PI3K)/protein kinase B(Akt)/Mammalian target of rapamycin(mTOR) signaling pathway and bone mineral density in rats skeletal muscle. 36 Sprague-Dawley male rats were divided into control (C,n=9), swimming exercise (E,n=8), r-hGH (GH,n=10) and swimming exercise+r-hGH (E+GH,n=9) groups. Exercise groups completed a 1-h swimming exercise 5 times a week for 8 weeks. Subcutaneous r-hGH was administered as 0.3 mg/kg/day. Protein expression of PI3K, AKT1, mTOR were assessed by immunohistochemistry. Total body bone mineral content(BMC), bone mineral density(BMD), lean mass(LM) and fat(%fat) were performed using Dual-energy X-ray absorptiometry. One-way ANOVA and Tukey post-hoc test were used for statistical comparisons. PI3K, AKT1 and mTOR protein expression were higher in the GH, E and E+GH groups compared with in C group ($p<0.05$, <0.05 and <0.005, respectively). Average values of BMC, GH and GH+exercise groups were found to be lower than those of only exercise groups (p:0.001). Growth hormone administered coupled with swimming exercise appeared to affect the PI3K/AKT/mTOR signaling pathway. On the contrary to the common opinion, GH didn't increase lean mass but caused only a partial decrease in adipose tissue.

OP.136

Mechanotransductive signaling pathway in human islets of Langerhans: implications for β-cell survival and function.

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Pancreatic β-cells are constantly exposed to mechanical stimuli arising from the surrounding extracellular matrix (ECM), neighboring cells and blood flow, but whether and how these stimuli contribute to β-cell differentiation and function is largely unknown. By exploiting cluster-assembled zirconia substrates with tailored roughness to mimic the nanotopography and stiffness of the ECM, we investigate the effect of mechanical forces on human islet of Langerhans

survival and function. Human β-cells viability and function are improved on nanostructured substrates: β-cells contain several dispersed insulin granules and show increased glucose-sensitive calcium currents and insulin secretion. Quantitative immunofluorescence analysis reveals reorganization of the cell-substrate adhesion complexes, the actin cytoskeleton and the nuclear architecture. Proteomic analysis demonstrate protein changes that are congruent with the functional and morphological results and shows that β-cells respond to mechanical forces through the activation of a certain number of mechanosensors, including mechanosensitive ion channels and integrins (Gene Ontology GO terms: 0005925). Their activation causes remodeling of the actomyosin cytoskeleton (GO: 0005856) and nuclear architecture (GO: 0031891) and is conveyed to the nucleus where it modulates gene expression. The characterization of the mechanotransduction signaling pathway may offer a unique possibility to understand how beta cells work and can lead to the identification of new targets of pharmacological intervention in diabetes mellitus.

OP.137

Hyper-excitability and hyper-plasticity disrupt cerebellar signal transfer in the IB2 KO mouse model of autism

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Autism spectrum disorders (ASD) are pervasive neurodevelopmental conditions that often involve mutations affecting synaptic mechanisms. Recently, the involvement of cerebellum in ASD has been suggested but the underlying functional alterations remained obscure. Thus, we exploited a combination of whole-cell patch-clamp recordings with voltage sensitive dye imaging (VSDi) in acute cerebellar slices in WT and IB2 KO mice to investigate single-neuron and microcircuit properties. The IB2 gene (chr22q13.3 terminal region) deletion occurs in virtually all cases of Phelan–McDermid syndrome, causing autistic symptoms and a severe delay in motor skill acquisition. The granular layer of these mice revealed severe alterations in synaptic transmission, neuronal excitation and long-term synaptic plasticity. A 2.5-times larger NMDA receptor-mediated current in IB2 KO granule cells enhanced synaptic plasticity (WT = 20.4±4.2%, n=12 vs. IB2 KO = 107.7±44.4%, n=9; p<0.05) along with the excitatory/inhibitory (E/I) balance (WT = 0.98±0.27, n=6 vs. IB2 KO = 2.78±0.32, n=7; p<0.01). At the same time, the spatial organization of granular layer responses to mossy fiber inputs shifted from a "Mexican hat" to a "stovepipe hat" profile, with stronger excitation in the core (WT = 12.9±1.7 μm vs. IB2 KO = 29.5±4.9 μm, n=5 for both; p<0.01) and limited inhibition in the surround (WT/KO ratio IWT/KO = 2.83±0.17, n=5). The IB2 KO mouse model therefore configures a complex cerebellar synaptopathy centered on NMDA receptor gain of function, that in several respects resembles alterations also observed in cortical minicolumns. The profound changes of signal processing at the cerebellar input stage unveil a possible new mechanism contributing to the pathogenesis

Workshop

EXERCISE AND CARDIOVASCULAR PHYSIOLOGY

Oral presentations

OP.138

Cardiovascular kinetics during moderate3intensity arm and leg exercise: a preliminary report.

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The phase I cardiovascular response to exercise implies an instantaneous cardiac output ($\dot{Q}$) increase, due to the effect of sudden vagal withdrawal on heart rate (fH) and of sudden venous return increase, due to muscle pump action, on stroke volume (SV). If the latter is the case, we would expect that, when exercise is performed with small active muscle mass, the cardiovascular responses at exercise are depressed. On 8 healthy young subjects, we measured beat3by3beat fH, SV and $\dot{Q}$ during arm ergometer and cycle ergometer exercise transitions, from rest to 50W. A double exponential model was applied to the transient phase, and we computed amplitudes and time constants of phase I (A1 and T1). For arm cranking, steady state fH was 65.2±7, and 102.3±7.8 bpm, at rest and 50 W exercise, respectively V corresponding SV was 106.1±16.5, and 112.9±13.4 mL, so that $\dot{Q}$ was 6.6±0.8, and 11.8±1,4 L/min. For leg cycling, fH was 68.4±7.8, and 92.7±6 bpm, SV was 101.8±14.4, and 117.1±16 mL, and $\dot{Q}$ was 6.9±0.6, and 10.8±1.2 L/min, at rest and exercise, respectively. For fH, A1 and T1, for arm exercise (18.4±8.1 bpm and 7.5±5 s, respectively) were greater (p<.05) than the corresponding values for leg exercise (9.1±2.2 bpm and 3.2±2 s, respectively). No significant differences appeared in A1 and T1 for SV and $\dot{Q}$ between the two