SIMPOSIOS / SYMPOSIA

SIMPOSIO / SYMPOSIA 1

Coordinador Dr. Waldo Cerpa (Umag/PUC) "Biomedical Sciences from the Magallanes region: Muscle, Heart, and Brain": W Cerpa (Umag/PUC), D. Rebolledo (Umag/PUC), R. del Río (Umag/PUC), Rodrigo Iturriaga (UAntof).

REGULACIÓN DE LA SEÑALIZACIÓN Y DISTRIBUCIÓN DE LOS RECEPTORES NMDA EN TRAUMA CEREBRAL REGULATION OF NMDA RECEPTOR SIGNALING AND DISTRIBUTION IN TRAUMATIC BRAIN INJURY.

Traumatic Brain Injury (TBI) mediates neuronal death through several events involving many molecular pathways, including the glutamate-mediated excitotoxicity for excessive stimulation of N-methyl-D-aspartate receptors (NMDARs), producing activation of death signaling pathways. However, the contribution of NMDARs (distribution and signaling-associated to the distribution) remains incompletely understood. The calcium entry through extrasynaptic NMDARs is linked to calcium overload in the mitochondria. Besides their role in ATP production in the cell, the mitochondria participate in calcium homeostasis. The disruption of mitochondrial calcium homeostasis has been linked to neuronal dysfunction and death. TBI causes central nervous system (CNS) damage under various mechanisms, including synaptic dysfunction, protein aggregation, mitochondrial dysfunction, oxidative stress, and neuroinflammation. Glial cells comprise most cells in CNS, which are mediators in the brain's response to TBI. In addition, astrocytes play critical roles in the brain's ion and water homeostasis, energy metabolism, blood-brain barrier, and immune response. Alterations at the mitochondrial level, and the role of glia in brain trauma, are cellular mechanisms that provide the reference framework for molecular alterations at the level of distribution and signaling of NMDA-type receptors, as well as their trafficking to the membrane of the cell. We propose a critical role of STEP61 (Striatal-Enriched protein tyrosine phosphatase) in regulating the phosphatase state of the GluN2B. An additional mechanism proposed includes the role of exocyst (Exo70), which are related to glutamate receptor constitutive trafficking/delivery towards synapses. We show the exocyst complex assembly and the increment of interaction with GluN2B under TBI conditions. Knowing new actors and specific cellular signals related to the cellular response to brain trauma is vital to generate possible diagnostic (early biomarkers) and therapeutic tools for this pathological condition.

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ALTERACIONES DE LA FUNCIÓN DEL MÚSCULO ESQUELÉTICO Y CARACTERÍSTICAS PATOLÓGICAS DEBIDO A LA ADMINISTRACIÓN DE ALCOHOL EN PATRÓN POR ATRACÓN. SKELETAL MUSCLE DYSFUNCTION AND PATHOLOGICAL FEATURES DUE TO BINGE-ALCOHOL ADMINISTRATION.

Among other health problems, chronic ethanol consumption causes alcoholic myopathy, a condition characterized by muscle weakness and atrophy. Nevertheless, little is known about the short- and long-term effects on skeletal muscle due to other patterns of alcohol consumption. Binge drinking, not necessarily associated with alcohol dependence, is defined as episodes of ingestion of large amounts of ethanol in a short time, typically ≤ 2 hours. Contrary to chronic dependent consumption, the risk perception for BD consequences in human health is low, which encourages consumption. BD affects a large population, especially adolescents and young people, and is also highly prevalent in amateur and professional athletes, especially in male group sports, with possible consequences in muscle function and physical performance. We have studied the effects of repetitive Binge-like alcohol administration in the skeletal muscle of murine models. We aimed to evaluate skeletal muscle contractile properties and the appearance of pathological markers two weeks after the last binge alcohol episode, seeking alterations that can persist in time and contribute to skeletal muscle dysfunction due to episodic BD. Our findings suggest that episodic binge alcohol decreases skeletal muscle strength and increases fatigability, which is associated with reduced fiber size and increased atrophy markers, the establishment of muscle fibrosis, and markers for inflammation and nitrosative stress. This work contributes to the knowledge of cellular mechanisms by which episodic BD causes muscle dysfunction. Furthermore, we show that pathological features upon binge-like alcohol administration, common to other neuromuscular diseases, remain in the tissue long after ethanol clearance, suggesting they arise as long-term consequences of binge alcohol on skeletal muscle.

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SEÑALIZACIÓN PURINÉRGICA MEDIA LA INCIDENCIA DE DESORDENES RESPIRATORIOS EN INSUFICIENCIA CARDIACA. PURINERGIC MEDIATED SIGNALING IN BRAINSTEM CHEMORECEPTOR NEURONS: ROLE IN DISORDERED-BREATHING DURING CARDIAC FAILURE.

Disordered breathing (DB) is a hallmark of heart failure (HF). The mechanisms underlying these alterations are not known. Interestingly, it has been described that purinergic signaling (PurS) in the retrotrapezoid nucleus (RTN), a main central chemoreceptor area, modulate ventilatory chemoreflex control in healthy conditions. However, nothing is known about the role of the RTN on DB in HF nor the precise molecular mechanisms underpinning the development/maintenance of DB in HF. Accordingly, we aimed to determine in HF rats: i) the contribution of the RTN on DB; ii) the alterations in PurS in the RTN; iii) the activation level of RTN chemoreceptor neurons/astrocytes; iv) the effects of chronic RTN chemogenetic manipulation using DREADDs on the maintenance of DB; and v) if astrocyte-targeted expression of the P2X7 receptor (P2X7r) normalizes breathing. Sprague-Dawley rats underwent volume overload to induce HF. DB was assessed by whole-body plethysmography. RTN micropunches were used to determine neuron/astrocyte activation, P2X7r gene/protein expression and ATP levels. Adeno-associated vector (AAV) expressing an excitatory Designer Receptor Exclusively Activated by Designer Drugs (DREADD) or an AAV carrying the P2X7r under the control of GFAP promoter were stereotaxically injected into the RTN of HF rats. Compared to control rats, HF rats displayed increases in the apnea/hypoapnea index (AHI), breath-to-breath interval variability and in the coefficient of variation (CV) of VT amplitudes (8.7±2 vs. 14.3±3 %). In addition, both ATP levels and P2X7r gene/protein expression were reduced in the RTN of HF rats. Importantly, we found that P2X7r expression was restricted only to astrocytes within the RTN. No chronic activation of RTN neurons were found in HF as evidenced by no changes in fosB expression compared to control rats. Contrarily, GFAP expression was significantly lower in the RTN from HF rats compared to controls. Chronic chemogenetic activation of RTN astrocytes in HF increases ATP levels and improve breathing regularity. Finally, increasing the expression of P2X7r in RTN astrocytes markedly reduced AHI and decreases breath-to-breath and VT variability. Our results show that the RTN is necessary for the maintenance of DB in HF and that RTN astrocytes play a pivotal role on breathing rhythm regulation by a mechanism encompassing ATP release and the P2X7r.

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FUNCIONES NORESPIRATORIAS DEL CUERPO CAROTIDEO EN SALUD Y ENFERMEDAD. NON RESPIRATORY FUNCTIONS OF THE CAROTID BODY IN HEALTH AND DISEASE.

The classical paradigm considers the carotid body (CB) as the main peripheral oxygen sensor that regulates blood gases and pH homeostasis. Hypoxia increases CB chemosensory discharge eliciting cardiorespiratory adjustments. However, the CB is a polymodal receptor that responds to other non-respiratory stimuli, including glucose, proinflammatory cytokines, reactive oxygen and nitrogen species, hormones, osmolarity, flow and temperature. In addition the CB has been involved in the regulation of cardiac output, regulation of peripheral resistance, hormonal regulation, insulin and glucose metabolism, renal function, exercise and thermoregulation. However, in last decade the idea that CB is implicated in sympathetic-related human diseases received much attention. Indeed, a growing body of new evidence support the novel idea that an abnormal enhanced CB chemosensory discharge triggers sympathetic overflow, which is associated with the autonomic and cardiorespiratory alterations in obstructive sleep apnea (OSA), resistant hypertension, congestive heart failure (HF) and metabolic diseases. In preclinical models, the enhanced CB chemosensory discharge elicits sympathetic hyperactivity, impairs baroreflex sensitivity and heart rate variability, induces breathing instability, hypertension, and insulin resistance. The ablation of the CBs reduces the autonomic alterations and sympathetic hyperactivity, the elevated arterial blood pressure in OSA and hypertensive models, reduces the breathing instability and improves animal survival in HF models, and restores insulin tolerance in metabolic models. In this symposium, In this symposium, I will discuss the evidence for a new role played by the CB in the autonomic dysfunction, and the pros and cons of the CB elimination as a therapy to reduce autonomic overflow.

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