CONFERENCIAS / LECTURES

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EFECTOS DE ETANOL EN LA NEUROTRANSMISION INHIBITORIA EN EL CEREBRO. Effects of ethanol on inhibitory neurotransmission in the brain.

Recent studies have reported the presence of glycine receptors (GlyRs) in higher brain regions, including the nucleus accumbens (nAc), ventral tegmental Area (VTA) and prefrontal cortex (PFC). These receptors have been linked to neurological and mental disorders, including autism spectrum, dementia, and alcohol abuse. However, it is largely unknown how their pharmacological properties are affected by the presence of selective subunit composition and if this is important for ethanol sensitivity. We studied four genetically modified mice models: GlyR alpha1 and alpha2 KI, GlyR alpha2 KO mice, and double KI. We used western blot, immunohistochemistry, GCaMP6s fluorometry, AAV-mediated gain/loss of function and electrophysiological techniques in brain slices, dissociated neurons (2-3 months), and in situ to learn about the properties of GlyRs in these brain regions and how they contribute to ethanol drinking. Compared to WT, the genetically modified mice presented less sedation after ethanol. Picrotoxin partially blocked the glycine-activated current in all brain regions, indicating that all these regions express heteromeric alpha/beta receptors. Interestingly, GlyRs in VTA neurons, but not in PFC neurons, were potentiated by low concentrations of ethanol and GTP-gamma-S. However, we found that the effect of ethanol was significantly attenuated in VTA neurons in the alpha1 KI, suggesting a role for ethanol potentiation. Finally, we rescued a lower drinking phenotype in the alpha1 KI by overexpressing the WT GlyR in the nAc. In conclusion, VTA neurons express predominantly ethanol-sensitive alpha1-containing GlyRs, whereas PFC neurons express ethanol-insensitive GlyRs that are most likely composed of alpha1/alpha2 subunits. On the other hand, the nAc expressed alpha1, alpha2 and beta subunits. These supraspinal GlyRs seem to play a role in the rewarding and sedative actions of ethanol.

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VITAMINA C EN LA ENFERMEDAD DEL CÁNCER: ¿DÓNDE ESTAMOS 50 AÑOS DESPUÉS? VITAMIN C IN CANCER DISEASE: WHERE ARE WE 50 YEARS LATER?

Vitamin C is a powerful antioxidant that has an intricate relationship with cancer and has been studied for more than 60 years. Numerous reports have shown that elevated concentrations of vitamin C selectively kill cancer cells in vitro and decrease the growth rates of several human tumor xenografts in immunodeficient mice. However, up to the date there is still doubt regarding the therapeutic efficacy of vitamin C in cancer treatment, mainly because cancer patients subjected to high-dose administration has not showed a clear antitumor activity. The specific mechanisms facilitating the uptake, metabolism, and compartmentalization of vitamin C by malignant cells remain unclear. Two different transporter systems are responsible for its acquisition, the glucose transporters GLUTs which uptake the oxidized form, and the sodium-coupled ascorbic acid transporters SVCTs which uptake the reduced form of vitamin C. We study in vitro tumors from different origins and analyze the capacity of cells to acquire vitamin C and found that cancer cells do not express SVCTs in the plasma membrane and are able to acquire vitamin C only in its oxidized form through GLUTs. However, and interestingly, cancer cells express a mitochondrial form of SVCT2, raising questions about the development of this capacity for transporting vitamin C within mitochondria. The revelation that cancer cells have developed the ability to transport reduced vitamin C within the mitochondria, shows that understanding the role of vitamin C physiology in tumor survival, could be key to unraveling the controversies in its relationship with cancer.

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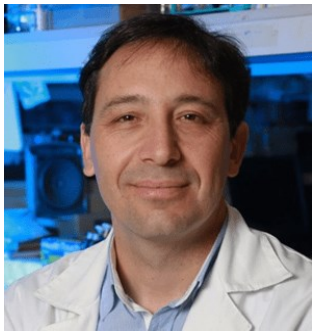

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BASES CIENTÍFICAS PARA EFICACIA DE VACUNAS Y EL CONTROL DE LA INMUNIDAD DE LA PANDEMIA COVID-19. The scientific basis for vaccine efficacy and the immunity controlling the COVID-19 pandemic.

Respiratory viruses are a leading public health burden worldwide due to inefficient viral immunity in the host. By inducing an excessive inflammatory response, these viruses can cause severe symptoms in the respiratory and nervous tissues, such as bronchiolitis and encephalopathy. In addition, some respiratory viruses impair T cell and dendritic cell function by suppressing the immunological synapse assembly. This could be a significant virulence factor to evade host immunity and enhance susceptibility to reinfection. Respiratory viruses can also cause learning impairment due to alterations in the blood-brain barrier and inflammation in the central nervous system after infection and the entry of immune system components to the CNS, damaging the function of neurons and astrocytes. These data have contributed to novel vaccine approaches to strengthen the immunological synapse leading to a safe and efficacious immunity capable of protecting against respiratory pathogens, such as RSV and SARS-CoV-2. The immunity triggered by these vaccines can also reduce CNS damage caused by respiratory viruses.

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EL INFLAMASOMA NLRP3 COMO DIANA FARMACOLÓGICA VASCULAR: DE LA SENESCENCIA ENDOTELIAL AL COVID-19. NLRP3 inflammasome as a vascular pharmacological target: from endothelial senescence to COVID-19.

Chronic inflammation is at the basis of a wide variety of clinical conditions, including vascular diseases such as hypertension or atherosclerosis or even premature vascular ageing. Understanding the cellular mechanisms that promote a sustained inflammation is essential to understand, prevent and treat such vascular disorders. In this context, we have focused in the role of the NLRP3 inflammasome, a critical protein complex of the innate immune system, whose over-activation has been linked with a number of diseases. While the priming of the NLRP3 inflammasome consists on the expression and subsequent production of some protein components of the complex, the activation phase leads to their assembly with the subsequent cleavage and activation of caspase-1 leading in turn to the production of active pro-inflammatory cytokines like interleukin (IL)-18 and IL-1beta. In the context of vasculopathies associated to cardiometabolic diseases, we have reported that some adipokines released by the adipose tissue, such as visfatin, also known as nicotinamide phosphoribosyl transferase (Nampt), or dipeptidyl peptidase-4 (DPP-4) are capable of both priming and activating the NLRP3 inflammasome in human endothelial cells, as a key cell type in vascular homeostasis. This favors vascular disease features like premature endothelial cell senescence and defected microvascular relaxation. Also, IL-1beta itself activates the NLRP3 inflammasome thus amplifying its own production. Moreover, external stimuli such as anti-cancer drugs (doxorubicin) or SARS-CoV-2 viral elements (S protein) also converge into the priming and activation of the NLRP3 inflammasome. Interestingly, pharmacological approaches that block the extracellular stimuli that trigger NLRP3 activation (adipokines, cytokines), directly prevent NLRP3 assembly or mimic endogenous molecules that promote the resolution of inflammation prevent the deleterious vascular signaling pathways elicited by the NLRP3 inflammasome.

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ESTUDIOS DE PRIMERA VEZ EN HUMANOS: LA EXPERIENCIA DE LA SECCION FARMALOGIA CLINICA DEL HOSPITAL ITALIANO DE BUENOS AIRES. First-time studies in humans: the experience of the Clinical Pharmacology Section of the Hospital Italiano de Buenos Aires.

La Sección Farmacología Clínica del Hospital Italiano de Buenos Aires ha sido pionera en Argentina en el desarrollo integral de estudios de primera vez en humanos, lo cual ha dejado muchas experiencias. Cada una de las tecnologías o medicamentos que fueron evaluados y eventualmente terminaron en un ensayo clínico pasaron por un proceso que incluye un análisis detallado de aspectos no tan tradicionales en la farmacología clásica pero que son fundamentales a la hora de la viabilidad del proyecto. Estos incluyen aspectos tradicionales como los planes de experimentación preclínica, sus resultados y su coherencia con los marcos regulatorios a los cuales ira destinado el producto, el diseño del estudio anticipando los riesgos y creando un marco de cuidado adecuado para los mismos como también si la indicación es la mejor dado el marco estratégico del desarrollo, el financiamiento, el marco regulatorio, la evolución del mercado y la competencia de otras tecnologías similares. Una evaluación integral permite que los riesgos asociados a este tipo de proyectos ya de por sí muy elevados se gestionen y permitan que avancen a la clínica aquellas con más mejores chances de éxito.

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LA ADMINISTRACIÓN DE PEPTIDOS POR VÍA ORAL: ¿HEMOS HECHO ALGÚN PROGRESO EN LOS ÚLTIMOS 30 AÑOS? The administration of peptides by the oral route: have we made any progress over the past 30 years?.

The oral administration of peptides and proteins remains one of the greatest challenges in pharmaceutical sciences. Efficacy depends firstly on patients committing to take essential medicines and this is built upon the convenience of a dosing regimen using a patient-friendly route of administration. Large molecules have problems negotiating the GI tract to achieve systemic delivery due to instability against metabolizing enzymes and inherent low permeability across the epithelium. To date, just five linear peptides for systemic delivery have been approved by the US FDA, the most recent being oral semaglutide (Rybelsus, Novo Nordisk, 2019) and oral octreotide (Mycappsa, Chiasma Ltd, 2020). These approvals heralded a renewed interest in the field, built largely around developing Glucagon-1-like peptide 1 (GLP-1) as a franchise for Type II diabetes and obesity, alone or as a dual agonist with other gut peptides. My group has been working on the mechanism of action of the intestinal permeation enhancers that typically are used to enable these formulations, albeit that oral bioavailability with the above products is less than 1%. We have focussed on comparisons between sodium caprate and SNAC, both medium-chain fatty acid derivatives, and found that they have multimodal actions suggesting a dual effect on tight junctions and the intestinal epithelial plasma membrane. We also have led the search for other permeation enhancers that can be used with peptides in oral dosage forms including the Gattefosse excipients, Labrasol and Labrafac. We have also researched a concept based on nanotechnology, where we achieved 7% bioavailability for insulin in a rat model using a core-shell construct based on silica coating over a core of peptide and the excipients, L-arginine and zinc, in precise ratios. Finally, we have been working on a new EU-funded HORIZON consortium project, BUCCAL-PEP, where we are investigating non-injected buccal administration of peptides using enhancers in a layered patch to avoid the food effect and the liver first pass effect. Relative success to date for oral peptides has been achieved with standard oral dosage forms made with permeation enhancers, but these will only work for niche peptides with high potency and long half-lives. Nanotechnology and devices may eventually be able to increase the oral bioavailability of peptides by an order of magnitude over permeation enhancers according to data from animal models, but clinical testing is at an early stage and the toxicology and the regulatory pathway for these types of technologies have yet to be addressed.

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BÚSQUEDA Y PERFIL FARMACOLÓGICO DE NUEVOS CANDIDATOS PARA EL TRATAMIENTO DEL ASMA. Searching and pharmacological profiling of novel candidates for treating asthma.

Asthma is defined as a chronic inflammation of the lung airways caused by environmental factors in genetically predisposed individuals. Episodic airway obstruction and bronchial hyperresponsiveness to nonspecific irritants are the major symptoms of this disease, which is on the increase in many countries and can be fatal. Inflammation is central to the pathogenesis of asthma. The antigens activate mast cells and TH2 lymphocytes in the airways, releasing preformed and neosynthesized inflammatory mediators, including vasoactive amines, lipid mediators, and cytokines, such as IL-4, IL-5, and IL-13. A marked feature of this process is the massive infiltration of eosinophils. Numerous experimental and clinical observations have linked eosinophil derivatives with asthmatic dysfunction. Local anaesthetics (LAs) are known for blocking voltage-sensitive sodium channels, responsible for increased sodium permeability during the rapidly rising phase of the action potential in excitable cells, such as neurons and cardiac and smooth muscle cells. It is now well established that lidocaine also has significant effects on non-excitable cells, such as eosinophils and lymphocytes, raising the possibility of alternative clinical uses to control chronic inflammatory diseases, including asthma. Prior studies have shown the benefits of nebulized lidocaine to patients with moderate and severe asthma. Still, adverse effects related to the local anaesthetic action limit their use for this specific clinical application. My talk will focus on what we have learned so far, our preclinical strategies and achievements in the search and pharmacological profiling of novel local anaesthetic analogues planned and screened for reduced action in sodium channels and optimized anti-asthma properties.

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