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NEUROPSYCHOPHARMACOLOGY

Symposium Neuropsychopharmacology «Inaugural Symposium of the **Master in Physiology and Pharmacology**: New frontiers in nucleus accumbens pharmacology».
Chair: **Dr. Ramón Sotomayor-Zárate**

MODULATING THE REWARD SYSTEM: VASOPRESSIN'S IMPACT ON AMPHETAMINE ADDICTION IN MALE AND FEMALE RATS VIA THE LATERAL SEPTUM. Modulación del sistema de recompensa: impacto de la vasopresina en la adicción a anfetamina en ratas macho y hembra a través del septum lateral.

Resúmen:
Drug addiction is a chronic brain disease characterized by compulsive use of drugs. Amphetamine (AMPH) is a psychoactive substance commonly used as a recreational drug by young people, and there is a lack of effective medications for the treatment of AMPH or other psychostimulant addiction. Recent studies have shown that the vasopressin (AVP) system plays a significant role in drug addiction, making it an interesting therapeutic target. The lateral septum (LS) is a brain structure implicated in addictive behaviors, regulating the activation of dopamine (DA) neurons in the ventral tegmental area (VTA), therefore modulating the reward system. Extended amygdala vasopressin (AVP) projections to LS are sexually dimorphic and could be responsible for the vulnerability to addiction in a sex-dependent manner. Our work aimed to study the effect of LS AVP system modulation on AMPH-induced behavioral and neurochemical responses in female and male rats. We showed that AVP microinjection in LS reduces the expression of AMPH-induced conditioned place preference (CPP) in male and female rats. However, this behavior is only associated with lower nucleus accumbens (NAc) DA release in male rats. Also, intra-LS AVP administration increases LS GABA release and decreases VTA DA release only in male rats. Interestingly, our data demonstrate that intra-LS AVP reduces AMPH-induced CPP in rats of both sexes; however, at the neurochemical level, we observed sex differences. This research contributes to the knowledge about sex differences in the role of AVP in LS in regulating the reward circuit and addictive-like behaviors.

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IDENTIFICATION OF SPECIFIC RESIDUES WITHIN THE C-TERMINUS OF DOPAMINE TRANSPORTER INVOLVED IN AMPHETAMINE-MEDIATED DOPAMINE EFFLUX. Identificación de residuos específicos dentro del extremo C-terminal del transportador de dopamina involucrados en el eflujo de dopamina mediado por anfetamina.

Resúmen:
The dopamine transporter (DAT) plays a crucial role in the regulation of brain dopamine (DA) homeostasis through the re-uptake of DA back into the presynaptic terminal. In addition to re-uptake, DAT is also able to release DA through a process referred to as DAT-mediated DA efflux. This is the mechanism by which potent and highly addictive psychostimulants, such as amphetamine (AMPH) and its analogues, increase extracellular DA levels in motivational and reward areas of the brain. Recently, we discovered that G protein βγ subunits (Gβγ) binds to the DAT, and that activation of Gβγ results in DAT-mediated efflux – a similar mechanism as AMPH. Previously, we have shown that Gβγ binds directly to a stretch of 15 residues within the intracellular carboxy terminus of DAT (residues 582–596). Additionally, a TAT peptide containing residues 582 to 596 of DAT was able to block the Gβγ-induced DA efflux through DAT. Here, we use a combination of computational biology, mutagenesis, biochemical, and functional assays to identify the amino acid residues within the 582–596 sequence of the DAT carboxy terminus involved in the DAT-Gβγ interaction and Gβγ-induced DA efflux. Our in-silico protein-protein docking analysis predicted the importance of F587 and R588 residues in a network of interactions with residues in Gβγ. In addition, we observed that mutating R588 to alanine residue resulted in a mutant DAT which exhibited attenuated DA efflux induced by Gβγ activation. We demonstrate that R588, and to a lesser extent F5837, located within the carboxy terminus of DAT play a critical role in the DAT-Gβγ physical interaction and promotion of DA efflux. These results identify a potential new pharmacological target for the treatment of neuropsychiatric conditions in which DAT functionality is implicated including ADHD and substance use disorder.

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SEXUAL DIMORPHISMS IN ADDICTION AND SOCIAL BEHAVIOURS OF RATS EXPOSED TO ANTIBIOTICS EARLY IN LIFE. Dimorfismos sexuales en adicción y comportamientos sociales de ratas expuestas a antibióticos en etapas tempranas de la vida.

Resúmen:
Neonatal gut colonization begins as the newborn passes through the birth canal and later comes into contact with the mother (e.g., through breastfeeding). Alterations in the maternal gut microbiota, such as those induced by antibiotic use during the perinatal period, can affect the infant's microbiota. Moreover, it has been shown that changes in the gut microbiota influence human and animal behaviour. In Sprague-Dawley rats, early life exposure to antibiotics (ELEA) has been demonstrated to modify the mesocorticolimbic circuit in a sex-dependent manner, promoting addiction-like behaviours in adult male rats but not in females, while inducing neurochemical alterations in females but not in males. One possible explanation for these differences involves sex hormones. Research has shown that oestrogen in females regulates brain dopamine levels and release, and oestrogen circulation is, in turn, regulated by the gut microbiota, contributing to the observed effects on the brain. This presentation will highlight the effects of ELEA on addiction-like and social behaviours, as well as the role of sex hormones in these outcomes. To explore this further, we performed gonadectomies on the offspring of Sprague-Dawley dams exposed to antibiotics and analysed their social behaviour, revealing only a few sex-specific behavioural traits, which will be discussed in this presentation. Overall, findings from our group suggest that the gut microbiota contributes to some of the behavioural changes observed in dopamine-related neuropsychiatric conditions, opening possibilities for novel pharmacological and/or nutritional interventions

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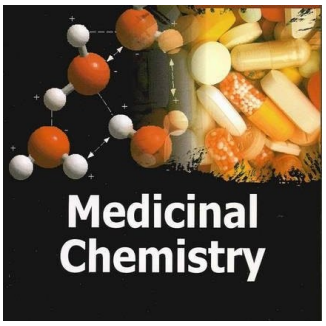

Symposium Medicinal Chemistry «Medicinal Chemistry in Chile: From design to experimental pharmacology".
Chair: Dr. Patricio Iturriaga-Vásquez

MEDICINAL CHEMISTRY IN CHILE: FROM DESIGN TO EXPERIMENTAL PHARMACOLOGY. Química Medicinal en Chile: Desde el diseño a la Farmacologia Experimental

Resúmen:
Medicinal chemistry is an interdisciplinary discipline that combines principles of chemistry, biology, and pharmacology for the design, synthesis, and development of new drugs. Its main objective is to create compounds that interact specifically with biological targets, such as proteins or nucleic acids, to treat different pathologies. The drug discovery process begins with identifying a therapeutic target, which may be a protein involved in a pathological process. From there, studies are carried out to design molecules that modulate the activity of this target. This design may involve computational chemistry methods, which allow the interaction between the compound and its target to be predicted. In addition, medicinal chemistry is influenced by advances in areas such as structural biology and biotechnology, which facilitate the understanding of how molecules work at the molecular level. This has allowed the development of more targeted and effective therapies. In short, medicinal chemistry is essential for the creation of new treatments, contributing significantly to the improvement of human health and the treatment of complex diseases. Its interdisciplinary approach makes it a dynamic and constantly evolving field. In this symposium, we present the work of three prominent Chilean Medicinal Chemistry Researchers and their work on the design and synthesis of new substances with biological activity. Dr. Carlos D. Pessoa-Mahana, Benzimidazole: A suitable framework for synthetic cannabinoids, Dr. Christian Espinosa-Bustos, Synthesis of histamine 3 receptor ligands: our six-year journey and Dr. Cristian Salas, Purine as a privileged scaffold for designing new Bcr-Abl inhibitors as potential leukemia drugs.

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BENZIMIDAZOLE: A SUITABLE FRAMEWORK FOR SYNTHETIC CANNABINOIDS. Benzoimidazol: Un heterociclo dúctil para la construcción de moduladorers cannabinoides.

Resúmen:
The endocannabinoid system (ECS) constitutes a broad-spectrum modulator of homeostasis in mammals, providing therapeutic opportunities for several pathologies. Its two main receptors, cannabinoid type 1 (CB1) and type 2 (CB2) receptors, mediate anti-inflammatory responses and their different patterns of expression make the development of selective ligands therapeutically attractive. The benzimidazole ring can be considered a privileged scaffold in drug discovery and has demonstrated its versatility in the development of molecules with varied pharmacologic properties. Here, we present a summary of the main results obtained in our laboratory where we focuse on the synthesis of benzimidazole derivatives and their application as suitable chemical modulators of the ECS. Our initial efforts focused on the study of the benzimidazole system as a useful framework to develop novel high-affinity CB1R synthetic cannabinoids. We then extended our investigation to the CB2R and worked to obtain benzimidazole derivatives with selective CB2R agonist activity. Additionally, we have explored the endocannabinoid degrading enzyme FAAH target through the synthesis and 3D-QSAR studies of FAAH inhibitors.
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Socio Patrocinante: Patricio Iturriaga-Vásquez

SYNTHESIS OF HISTAMINE 3 RECEPTOR LIGANDS: OUR SIX-YEAR JOURNEY. Síntesis de ligandos del receptor de histamina 3: nuestro recorrido en estos 6 años

Resúmen:
Histamine is released predominantly from the tuberomammillary nucleus of the hypothalamus in the central nervous system (CNS) and acts as a neurotransmitter. H3 receptors as presynaptic autoreceptors on histaminergic nerve terminals, they are unique members of the histaminergic receptor family (H1-H4) and show higher densities in the CNS in comparison to peripheral tissues (e.g, basal ganglia, globus pallidus, cortex and hippocampus) and are involved in the modulation of a wide range of physiological effects (e.g. neurotransmitter release, regulation of cognitive processes, attention and/or arousal, appetite, food and water intake and many hypothalamic functions). As H3 receptors are negatively coupled to adenylyl cyclase via Gi/o proteins, their activation results in the inhibition of cAMP production, leading to a wide range of signalling events. Due to their constitutively active nature in vitro and in vivo, H3 receptors tonicly inhibit histaminergic (and possibly other) neuronal activity. Therefore, antagonism/inverse agonism of the H3 receptor increases histaminergic neuronal activity and CNS histamine levels, which in turn stimulate neurotransmitter release and contribute to the overall physiological effects of H3 blockade. The anatomical localisation and favourable properties of H3 receptors make them a viable target for CNS-related drug discovery. In view of the above, our research group has focused in recent years on the design, synthesis and evaluation of heterocyclic compounds as H3R ligands. Therefore, in this symposium we will show our main results in terms of affinity for this receptor as well as results of the search for multi-target ligands directed against H3R and other therapeutic targets involved in neurodegenerative diseases.

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PURINE AS A PRIVILEGED SCAFFOLD FOR DESIGNING NEW BCR-ABL INHIBITORS AS POTENTIAL LEUKEMIA DRUGS. Purina un privilegde scaffold para el diseño de nuevos inhibidores de Bcr-Abl como potenciales fármacos contra la leucemia

Resúmen:
Bcr-Abl is an oncoprotein with aberrant tyrosine kinase activity involved in the progression of chronic myeloid leukemia (CML) and has been targeted by inhibitors such as imatinib and nilotinib. Despite their efficacy in the treatment of CML, a mechanism of resistance to these drugs associated with mutations in the kinase region has emerged. Since the most potent inhibitors of Bcr-Abl are those that bind directly to the ATP-binding site, the purine core has been chosen as a privileged scaffold in the development of new inhibitors of this kinase. In this address, we have been working on the design and synthesis of new 2,6,9-trisubstituted purine derivatives as Bcr-Abl inhibitors. From our most promising results, we identified several purines that showed enhanced inhibition with IC50 values of 4.6 – 14 nM and were more potent than imatinib and nilotinib (IC50 = 327 and 47 nM). Structure-activity relationships and in silico studies were able to explain the differences in potency and selectivity between some kinases by our compounds. Likewise, our Bcr-Abl inhibitors exhibited low micromolar cytotoxicity in CML-cancer cell lines (KCl22, K562, KBM5, and BV173) and decreased the phosphorylation of downstream proteins in the signaling pathways of Bcr-Abl in K562 cells at lower concentrations than imatinib. In addition, some purine derivatives have shown antiproliferative effects in a panel of subclones of KCL22 cells expressing different mutations in Bcr-Abl. Finally, one compound is being considered for in vivo testing. Therefore, we demonstrated that certain purine derivatives are promising compounds for the development of new drugs for CML treatment.

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Symposium Argentina-Brazil-Chile (ABC) Pharmacology «The ABC of South American Pharmacology: Addiction Research".
Chair: Dr. Mario Rivera-Meza

COCAINE INDUCED HIPPOCAMPAL NEUROADAPTATIONS: UNRAVELLING THE ROLE OF PHOSPHODESTERASE 5 INHIBITORS IN THE VULNERABILITY TO SUBSTANCE USE DISORDERS. Cambios neuroadaptativos inducidos por cocaina en el hipocampo: develando la influencia de los inhibidores de la fosfodiesterasa 5 en la vulnerabilidad a los trastornos por consumo de sustancias.

Resúmen:
Behavioral sensitization to the hyperlocomotion effect of psychostimulants is a useful model for studying addiction, the most severe form of substance-use-disorders-SUD. The hippocampus-HP and prefrontal cortex-mPFC participate in the neuropathological mechanisms underlying addiction. Nitric oxide-NO is involved in neuronal excitability, synaptic plasticity, and sensitization to psychostimulants. Phosphodiesterase-5 inhibitors-PDE5i potentiate NO-activated signaling pathways. Our work aims to characterize the role of NO in development and expression of cocaine-COC sensitization, the brain areas involved and the effect of sildenafil-SILD on sensitization. Behavioral procedures were performed in male Wistar rats to observe COC sensitization in presence of inhibitors or activators of the NOS1/NO/sGC/cGMP signaling pathway. Electrophysiological tools were used to determine HP synaptic plasticity and mPFC-neuronal activity ex-vivo. The effects of SILD upon the dopamine-DA system were determined by amperometry ex-vivo and of-silico methods. Systemic administration of NO signaling pathway inhibitors reduced the proportion of sensitized rats and the increased neuronal activity in HP and mPFC. Conversely, its activation by sildenafil-SILD increased the proportion of sensitized animals and HP synaptic plasticity. Inhibition of NO signaling within the HP, but not mPFC, reversed COC sensitization. On the other hand, reduced function of DAT was observed in HP and nucleus accumbens of SILD-treated animals. Furthermore, molecular docking, dynamics and free-energy of binding analyses showed that SILD binds to the DAT allosteric regulatory site. We can conclude that upregulation of NO signaling pathway in HP may initiate or exacerbate SUD in humans. Considering the widespread prescription and misuse of PDE5i, we demonstrated here that they may increase susceptibility to drug abuse, describing a novel mechanism of action for SILD via direct action on the DA system.

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Socio Patrocinante: Mario Rivera-Meza

PREVENTING DEFICITS FROM PRENATAL ALCOHOL EXPOSURE THROUGH ENVIRONMENTAL ENRICHMENT DURING PREGNANCY: THE POTENTIAL ROLE OF OXYTOCINERGIC MECHANISMS. Prevención de déficits por exposición prenatal al alcohol mediante enriquecimiento ambiental durante el embarazo: el potencial rol de los mecanismos oxitocinérgicos

Resúmen:
Fetal Alcohol Spectrum Disorders (FASD) encompass a range of conditions arising from prenatal alcohol exposure, impacting physical, cognitive, and behavioral development. The severity of FASD varies with the timing, frequency, and amount of alcohol exposure, as well as environmental factors like stress. Early diagnosis and intervention are crucial for improving outcomes. Prenatal alcohol exposure disrupts oxytocin (OT) system development, leading to FASD-related deficits in social interaction, anxiety, and depression. Environmental enrichment (EE) offers diverse stimuli that enhance social, cognitive, and physical activity. Previous findings indicate that EE modulates the oxytocinergic system by increasing OT levels and mRNA expression in the hypothalamus and reducing OT receptor binding and phospholipase C (PLC) activity in specific brain regions. In this study, pregnant mice exposed to ethanol were housed in EE or standard conditions (SC). Ethanol exposure impaired maternal behaviors in SC, while EE mitigated these deficits, with increased OT-immunoreactive cells in the paraventricular nucleus (PVN) and elevated OT gene expression. Offspring from ethanol-exposed dams in SC showed delayed physical and reflex development, reduced social interaction, and heightened anxiety, regardless of sex. Female offspring displayed increased ethanol consumption and reduced maternal aggression, while males showed increased aggression compared to their EE-exposed counterparts. Gestational EE exposure attenuated these ethanol-induced impairments.These findings underscore the complex interplay between environmental factors and prenatal ethanol exposure, highlighting EE's potential to counteract the detrimental effects of alcohol during gestation. Additionally, they identify the OT system as central in FASD pathophysiology, suggesting OT modulation as a promising therapeutic approach.

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HCN ION CHANNELS AS A POTENTIAL PHARMACOLOGICAL TARGET TO REDUCE THE ADDICTIVE EFFECTS OF ETHANOL. Canales iónicos HCN como un potencial blanco farmacológico para reducir los efectos adictivos del etanol

Resúmen:
A key target for the addictive properties of ethanol is the dopaminergic circuitry within the ventral tegmental area (VTA). Ethanol enhances the activity of VTA dopamine neurons, leading to increased dopamine release in the nucleus accumbens (NAc). The excitability of these neurons is primarily regulated by hyperpolarization-activated cyclic nucleotide-gated (HCN) ionic channels. In vitro studies indicate that ethanol can activate HCN channels, and blocking these channels inhibits ethanol's effects. Among the four HCN channel genes (HCN1-4), HCN2 is the most prevalent in the VTA. Our research demonstrated that overexpressing HCN2 in the VTA significantly increases ethanol consumption and amplifies ethanol-induced locomotor activity, dopamine release, and place preference compared to control rats. Conversely, reducing HCN2 expression in the VTA resulted in a substantial decrease in voluntary ethanol intake. Recent experiments showed that administering various HCN blockers—ZD7288 (non-selective), MEL55A (moderately selective for HCN2), and 4e (highly selective for HCN2)—to rats led to a significant dose-dependent reduction in ethanol-induced dopamine release in the NAc, with 4e exhibiting the highest potency. These neurochemical changes correlated with a notable decline in voluntary ethanol consumption among the animals. These findings suggest that HCN2 channels may serve as a promising molecular target for addressing the rewarding effects of ethanol.

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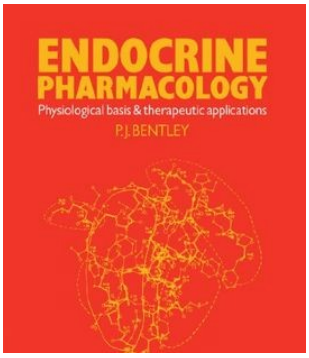

Symposium Endocrine Pharmacology and Metabolism «From Obesity to Diabetes: Pathophysiological Mechanisms and Therapeutic Options».
Chair: Dr. Rafael Barra

NUTRITIONAL PROGRAMMING OF HYPERTENSION. CENTRAL ROLE OF THE HYPOTHALAMIC PVN. Programacion nutricional de la hipertension. Rol central del nucleo paraventricular del hipotalamo.

Resúmen:
The literature supports that undernourishment is one of the leading nutritional issues remaining in the world. Prenatal exposition to undernourishment has permanent and severe effects on the adult health of the offspring. In this context, chronic hypertension has been described as one of the most relevant conditions manifested. Our research groups have characterized a higher neuronal activity in the Paraventricular Nucleus of the hypothalamus (PVN) through electrophysiological recordings and using pharmacological manipulations to blockade and activate excitatory and inhibitory control on the neuronal activity of the PVN. Mainly, the noradrenergic connections from the Locus Coeruleus (LC) are excitatory and reciprocal with the PVN, and the connections from the Subiculum ventral (vSUB) are inhibitory for the neuronal activity of the PVN. We have demonstrated a chronic increase of the Noradrenergic input from the LC to the PVN and its subsequent effect on blood pressure control. Additionally, we found coherent changes in the expression levels of glucocorticoid receptors in the PVN. Our research allows us to identify the status of neuronal excitatory and inhibitory controls over the PVN and correlate them with cardiovascular parameters, like blood pressure and Heart frequency. The research associated with this prenatal nutritional impairment model will allow the development of better pharmacological and therapeutic strategies for diminishing the harmful effects of prenatal nutritional programming and help to unravel the pathognomonic of persistent hypertension in prenatal malnutrition.

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Socio Patrocinante: Dr. Rafael Barra Pezo

STUDY OF NEW PHARMACOLOGICAL TARGETS IN THE CONTEXT OF CARDIAC FIBROSIS INDUCED BY DIABETES AND OBESITY. Estudio de nuevos blancos farmacológicos en el contexto de la fibrosis cardiaca inducida por diabetes y obesidad

Resúmen:
Cardiac fibrosis is a pathological condition characterized by excessive extracellular matrix (ECM) that slowly replaces functional tissue, decreasing the heart's contractile, relaxation, and conduction capacity, leading to cardiac dysfunction. Many diseases progress to cardiac fibrosis, from hypertension to myocardial infarction. Lately, interest has been focused on metabolic diseases, such as diabetes, dyslipidemia, and obesity, as essential promoters of cardiac fibrosis and myocardial dysfunction. However, the cellular and molecular targets for cardiac fibrosis promoted by these last pathologies are not yet fully known. Cardiac fibroblasts (CF) are mesenchymal cells responsible for synthesizing, secretion, and degradation of ECM components, such as collagen I and III. Under normal conditions, CF have minimal basal activity, while pathological stimuli such as high glucose (HG) or hypoxia increase their ECM secretory activity, leading to cardiac fibrosis. Fibrotic and inflammatory activation of CFs induced by metabolic stimuli has not been extensively studied. Our results have determined that members of the FoxO family are critical for HG-induced CF activation, where FoxO1 promotes fibrosis and inflammation, whereas FoxO3a demonstrates antifibrotic effects. On the other hand, SGK1, an aldosterone-activated kinase involved in renal and cardiac inflammatory pathologies, is activated in CFs, inducing fibrosis and inflammation of CF by inhibiting FoxO3a, and its gene targets SOD2 and catalase. Finally, through an in vitro obesity model, we demonstrated that conditioned medium obtained from adipocytes induces fibrosis and CF inflammation of CFs by activating SGK1 and inhibiting FoxO3a. Similarly, similar results were obtained in an in vivo obesity model. The heart of obese animals presents a higher expression of fibrotic markers and SGK1 than control mice. In comparison, a lower expression of FoxO3a was observed. Our results point to SGK1 and FoxO3a as novel antifibrotic.

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ROLE OF THE NLRP3 INFLAMMASOME AND CHOLESTEROL IN SKELETAL MUSCLE DURING OBESITY-INDUCED INSULIN RESISTANCE. Papel del inflamasoma NLRP3 y del colesterol en el músculo esquelético durante la resistencia a la insulina inducida por la obesidad.

Resúmen:
Chronic inflammation is a critical factor in the development of insulin resistance (IR), a key precursor to type 2 diabetes mellitus. The NLRP3 inflammasome, which regulates the release of pro-inflammatory myokines IL-1β and IL-18, has been implicated in the impairment of insulin sensitivity associated with IR. Skeletal muscle is the primary site for insulin-stimulated glucose uptake via GLUT4, a process predominantly occurring in transverse tubules (TT). However, in the context of IR, the translocation of GLUT4 to TT is disrupted. Insulin-resistant animals exhibit elevated cholesterol levels and reduced expression of the ATP-binding cassette transporter A1 (ABCA1) in TT. Nevertheless, the specific role of cholesterol accumulation in activating the NLRP3 inflammasome - and its contribution to low-grade inflammation and impaired glucose homeostasis during the progression of IR- remains poorly understood. We investigated the effects of cholesterol dysregulation on low-grade inflammation and the development of IR in skeletal muscle. Compared to chow-fed mice (NCD-fed), high-fat diet-fed mice (HFD-fed) displayed significantly reduced ABCA1 expression and increased cholesterol content in flexor digitorum brevis (FDB) muscle. Elevated levels of NLRP3, ASC, caspase-1, and IL-1β were observed in homogenized FDB muscle from HFD-fed mice. Importantly, pre-incubation with T0901317, a selective liver X receptor (LXR) agonist, enhanced ABCA1 expression, reduced membrane cholesterol, and improved insulin-mediated glucose uptake. This treatment also decreased NLRP3 inflammasome components in muscle fibers from HFD-fed mice. In conclusion, these findings indicate that targeting cholesterol accumulation and NLRP3 inflammasome activation may provide promising therapeutic strategies for mitigating insulin resistance and type 2 diabetes mellitus.

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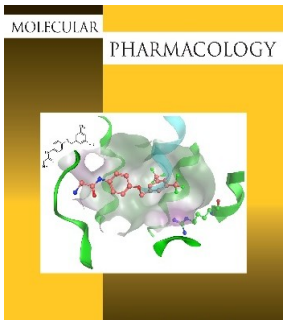
SIMPOSIO / SYMPOSIUM



Symposium Molecular Pharmacology «The problem of the 3 elements: receptor, ligand and AI. Pharmacological approaches in purinergic transmission». **Chair: Dr. Jorge Fuentealba**

ROLE OF THE P2X2 RECEPTOR IN THE CELLULAR MECHANISMS OF NEUROGENERATION, THE EXAMPLE OF ALZHEIMER'S DISEASE. Papel del RECEPTOR P2X2 en los mecanismos celulares de neurogeneración, el ejemplo de la Enfermedad de Alzheimer.

Resúmen:
One of the main toxic agents in Alzheimer's Disease (AD) are the soluble oligomers of the Aβ peptide (AβOs). In our laboratory, we have demonstrated that AβOs induce an intracellular Ca2+ increase, ATP leakage, changing the modulation of ionotropic purinergic receptors (P2XR). We have also shown that AβOs induce an increase the expression of P2X2, further reinforcing the Ca2+ overload in the cytoplasm that modulate several proteins and pathways, including the AMP-activated protein kinase (AMPK), CALP-1, TG2, which plays diverse roles in protein, energy, and mitochondrial metabolism. In our hands, We have shown that in AD, overexpression of the P2X2 receptor generates the activation of a vicious circle that enhances the generation of the amyloid beta peptide, alters mitochondrial functionality and dynamics, altering its interaction with the ER and promoting an alteration of calcium homeostasis that results in synaptic failure in the excitatory terminals. The main findings of this project are corroborated in human samples, providing the first confirmed evidence of the role of this receptor in the disease, which opens a new space for pharmacological development for AD.

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PURINERGIC AND GLUTAMATERGIC CROSSTLAK IN THE NEURAL TUVE FORMATION. DECIPHERING THE ROLE OF ANTISEIZURE MEDICATION (ASM). Interacción purinérgica y glutamatérgica en la formación del tubo neural. Descifrando el papel de los medicamentos anticonvulsivos.

Resúmen:
Neurulation is crucial for the central nervous system (CNS) formation, which initiates with the folding and fusion of the neural plate generating the Neural Tube and subsequently the brain and spinal cord. Paracrine signals like FGF participate in Neurulation wherein others signals such us purinergic (ATP) and glutamate has been recently described, which are required for the cellular responses like migration and proliferation necessary for the process. Environmental factors like anti-seizure medications (ASM) alter Neurulation promoting Neural Tube Defects (NTDs) and others latter alterations of neural function. Our group investigate the pharmacological modification of purinergic and glutamate signaling analyzing their synthesis, release and P2X4/NMDAR activity during Xenopus laevis Neurulation, evaluating the phenotypic and the cellular and molecular consequences. We found the presence and functionality of glutamate synthesis enzyme, GLS1 and even though expression levels remains constant, its catalytic activity increases significantly (~66%) between early and middle to late stages of Neurulation. We increased the appearance of NTDs reducing GLS activity (~36%) using the competitive inhibitor 6-diazo-5-oxo-L-norleucine. Related to purinergic signaling, we demonstrate the expression and functionality of connexin hemichannels (HCs), including Cx46, which are associated with the release of ATP. Furthermore, applications of FGF2 and/or changes in intracellular redox potentials (DTT), well known HCs-Cxs modulators, transiently regulated the ATP release in our model. Importantly, the blockade of HCs-Cxs by carbenoxolone (CBX) and enoxolone (ENX) reduced ATP release and increases NTDs. Additionally, the potentiation of P2X4 with ivermectin during Neurulation generates NTD with a significantly reduced motor behavior associated with a neuromuscular junction alteration. All together could contribute to a comprehensive view of how ASM affects the neural development.

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MODELLING THE ACTIVE SITE OF PURINERGIC RECEPTORS. Modelando el sitio activo de receptores purinérgicos

Resúmen:
Purinergic P2X receptors (P2XRs) are a family of ligand-gated ion channels (LGICs) composed of seven different subunits that can assemble into homo- or heterotrimeric channels activated by ATP. Each subunit consists of an extracellular loop, two transmembrane domains (TM1-2), and intracellular N- and C-termini. Three ATP-binding sites are located at the interfaces between subunits; however, two ATP molecules are sufficient to activate the channel and allow the passage of cations. P2XRs have been implicated in neurological disorders, including Alzheimer's disease, where overexpression of P2X2, P2X4, and P2X7, along with their activation by ATP released into the extracellular medium, have been reported. Despite the therapeutic potential, efforts to develop modulators targeting P2XRs have yielded limited success, with only a few receptor structures and specific modulators described to date. The structures of human P2X2 (hP2X2) and P2X4 (hP2X4) receptors are not yet available, complicating the design of more selective and effective modulators. To address this, we generated models of both receptors through comparative modeling and performed structure-based virtual screening to identify potential modulators. For protein-ligand docking, interaction grids were created at the ATP-binding sites, and ligand were obtained from the Molport database. Resulting complexes were analyzed and ranked by docking scores and delta Gbind. Promising candidates with values comparable to ATP were selected from various chemical families for in vitro testing. Electrophysiological evaluations revealed active molecules capable of modulating the P2X2 and P2X4 receptors expressed in HEK293 cells. In conclusion, our in-silico approach demonstrates a valuable strategy for characterizing interactions between P2X receptors and ATP and for screening novel, selective compounds with potential modulatory activity.

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DEVELOPING SELECTIVE DRUG BY NANO IMPRESION – NANOMIPS – THE NEXT GENERATION. Desarrollo de fármacos selectivos mediante nanoimpresión – NanoMIPs – la próxima generación

Resúmen:
The advancement of nanotechnology has opened the way for innovative approaches in drug development, particularly through the use of nano-imprinted materials known as nanoMIPs (Nano Molecularly Imprinted Polymers). This study highlights the potential of nanoMIPs as the next generation of selective drugs, emphasizing their ability to replicate biological recognition processes with high specificity and efficiency. By employing nano-imprinting techniques, we can create customized molecular recognition sites that enhance drug targeting and minimize side effects. It is also a review on the synthesis, characterization, and application of nanoMIPs in the pharmaceutical field, highlighting their advantages over traditional drug delivery systems. The findings suggest that nanoMIPs can significantly improve diagnosis and therapeutic outcomes by enabling precise drug interactions at the molecular level, ultimately contributing to the development of more effective and safer therapeutic agents. Future directions include exploring the scalability of this technology and its integration into clinical practices for personalized medicine.

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SIMPOSIO / SYMPOSIUM

Symposium «Women in Pharmacology» **Chair: Dr. Mabel Catalán**

CARDIAC FUNCTION AND REMODELING DURING SIMULATED MICROGRAVITY: INVESTIGATING THE HIPPO PATHWAY AND THERAPEUTIC POTENTIAL OF VERTEPORFIN. Función y remodelamiento cardiaco durante la microgravedad simulada: Investigando la vía Hippo y el potencial terapéutico de la Verteporfina

Resúmen:

Changes in hydrostatic pressure due to prolonged bed rest and microgravity conditions, such as those experienced during spaceflight, have profound effects on cardiovascular function and structure. These effects include reduced cardiac workload, myocardial atrophy, and impaired contractile function, ultimately leading to significant cardiac remodeling. Despite advances in understanding these phenomena, the molecular mechanisms driving these changes remain unclear. The Hippo signaling pathway, a key regulator of organ size, has recently emerged as a critical player in cardiac remodeling. Under physiological conditions, the Hippo pathway helps maintain cardiac homeostasis and normal cardiac function. However, its role in response to microgravity-induced cardiac stress remains unexplored. We are studying the impact of simulated microgravity and prolonged bed rest on cardiac function and remodeling, with a specific focus on changes in cardiac T-tubules and the Hippo pathway. Using a preclinical model of hindlimb suspension unloading (HSU), we evaluate the molecular and structural changes in the myocardium. Additionally, we assess the therapeutic potential of Verteporfin, a drug known to inhibit the transcriptional co-activators YAP/TAZ, which are downstream effectors of the Hippo pathway. By targeting YAP/TAZ, we aim to mitigate the deleterious effects of Hippo pathway dysregulation in microgravity-induced cardiac remodeling. Our findings will contribute to a better understanding of the molecular pathways of cardiac remodeling during spaceflight and prolonged physical inactivity. Furthermore, this study explores the potential of Verteporfin as a therapeutic intervention, which may lead to the development of new strategies to protect cardiovascular health in astronauts and bedridden patients.

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MIRO1: AT THE HEART OF EMERGING MITOCHONDRIAL PHARMACOLOGICAL TARGETS. Miro1: en el corazón de los nuevos blancos farmacológicos dirigidos a la mitocondria.

Resúmen:

Mitochondrial dynamics, including fission and fusion processes, are vital for maintaining cellular homeostasis, particularly in high-energy-demanding cells like cardiomyocytes. These dynamic processes allow mitochondria to adapt to changing energy needs, repair damaged regions, and remove dysfunctional mitochondria through mitophagy. In the heart, where continuous energy production is essential for contractile function, disruptions in mitochondrial dynamics can lead to severe cardiac dysfunction. Recent studies have highlighted the mitochondrial Rho GTPase 1 (Miro1) as a critical regulator of mitochondrial movement and positioning within cells, particularly in neurons. However, emerging evidence indicates that Miro1 also plays a significant role in cardiac pathophysiology, especially under conditions of stress and injury. This presentation will explore the functions of Miro1 in cardiomyocytes, focusing on its involvement in cardiomyocyte hypertrophy and its contributions to mitochondrial dynamics and localization. Our research demonstrates that Miro1 expression is upregulated in hypertrophic cardiomyocytes, suggesting a potential role in the pathological remodeling of the heart. Beyond its established influence on mitochondrial fission, Miro1 appears to affect the spatial distribution of mitochondria within cardiomyocytes, which is crucial for efficient energy distribution. By investigating Miro1's dual role in mitochondrial dynamics and positioning, we aim to uncover novel pathophysiological mechanisms underlying cardiac diseases, ultimately paving the way for innovative therapeutic strategies targeting Miro1 and mitochondrial function.

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MICROFLUIDICS AS A NANOTECHNOLOGICAL TOOL FOR EARLY CANCER DIAGNOSIS. La microfluídica como herramienta nanotecnológica para el diagnóstico temprano del cáncer.

Resúmen:
Tumor-derived extracellular vesicles (EVs) are emerging as crucial biomarkers for cancer diagnosis, prognosis, and therapeutic monitoring. These nanoscale particles, secreted by cancer cells, facilitate cell-to-cell communication, making their detection in body fluids a promising tool for non-invasive diagnostics. However, capturing and analyzing EVs, especially in early disease stages, is challenging due to their small size and low abundance. Traditional methods like ultracentrifugation and Western blotting are labor-intensive, time-consuming, and require large sample volumes, often yielding low sensitivity. To address these issues, we developed a 3D self-assembled nanostructured SiO_2 microfluidic chip, designed to enhance EV capture efficiency. This chip was functionalized with antibodies targeting exosomal markers CD63 and CD81 and tested using conditioned media from breast cancer cell lines (MCF7, MDA-MB-231, and MCF10A). Results showed that the 3D SiO_2 nanostructured chip successfully captured EVs from the conditioned media with high sensitivity and specificity. Fluorescence microscopy revealed a significant increase in the detection of EVs expressing CD63 and CD81 compared to conventional methods. The chip demonstrated a detection limit capable of identifying even low-abundance EVs, which is critical for early cancer diagnosis. Additionally, the platform required minimal sample volumes and allowed for rapid analysis, making it suitable for high-throughput applications. These findings highlight the platform's potential as a liquid biopsy tool for cancer detection, providing a faster, more efficient, and non-invasive alternative to traditional biopsy methods. This technology could significantly improve early cancer detection and patient outcomes by enabling real-time monitoring of tumor-derived EVs.

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Socio Patrocinante: Dra. Mabel Catalán

OBESITY AND CANCER: THE LINK THROUGH THE MITOCHONDRIAL MODULATION. Obesidad y cáncer: El link a través de la modulación mitocondrial

Resúmen:
Chronic conditions such as cardiovascular diseases, obesity, and cancer are prevalent in the world. In this context, pharmacological research has progressively focused on providing novel alternatives for managing these diseases, with the awareness of solving these health problems with increasing effectiveness and safety. From the pharmacology point of view, cancer and obesity have been struggling with novel and effective alternatives to be included as part of the treatment. Both situations involve the search for novel therapeutic targets. In this context, the mitochondrion emerges as an attractive target from the pharmacological perspective, given the distinctive characteristics that allow different pharmacophores to be directed into this organelle. Additionally, both obesity and cancer have a similar background of mitochondrial dysfunction; thus, restoring function or taking advantage of this abnormality could result in a novel therapeutic strategy for the treatment of these pathologies. In this sense, we have studied different lipophilic cations derived from polyphenols that have been shown as antineoplastic agents in many cancer cellular models without evident toxicity in normal cells and tissues. Additionally, these new drugs could improve the functioning of adipocytes in vitro and in vivo models, making them metabolically active. Different concentrations of these new lipophilic cations can modulate cellular effects. In conclusion, our background in designing, synthesizing, and evaluating novel mitochondrial agents could offer an alternative as a therapeutic for mitochondrial dysfunction in prevalent diseases.

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SIMPOSIO / SYMPOSIUM

Inaugural Symposium of the Master in Physiology and Pharmacology: «Empowering Science by Women in Valparaíso» **Chair: Dr. Marcela Julio-Pieper**

ROLE OF DYNAMINS IN CENTRAL EXCITATORY SYNAPTIC TRANSMISSION: A POTENTIAL NEW THERAPEUTIC TARGET IN THE SYNAPTOPATHY OF ALZHEIMER´S DISEASE. Rol de las dinaminas en la transmision sinaptica excitatoria central: un potencial nuevo blanco terapeutico en la sinaptopatia de la Enfermedad de Alzheimer.

Resúmen:

Dynamins are large GTP-ases implicated in membrane and cytoskeleton remodeling in different cell types. They are expressed in the Central Nervous System (CNS), playing key functions at pre and post-synapses. At presynapses dynamins modulate the endocytic recycling of synaptic vesicles; at post-synapses dynamins regulate the insertion and turnover of neurotransmitter receptors. We recently demonstrated that dynamin-2, the only ubiquitous dynamin´s isoform, is critical for neuronal morphology, synaptic transmission and plasticity. In neurons that express pathogenic mutations in dynamin-2 that impair its catalytic activity, dendritic arborization and formation of dendritic spines are significantly impaired, leading to synaptic and cognitive defects in mice. These results suggest that dynamin´s dysfunction at the CNS might lead to neurological disorders. It has been demonstrated that dynamin´s expression is reduced in postmortem brains of Alzheimer´s disease (AD) patients, suggesting that dynamins are involved in the pathogenesis of AD, the most prevalent for of dementia in elderly. Our in-progress work has been aimed to evaluate the impact of the pharmacological and genetic modulation of dynamins on the neuronal morphology, and functional synapses in neurons from APP/PS1 and 3xTg mice, murine models of AD. Additionally, we have also evaluated the impact of the pharmacological modulation of dynamin´s activity on cognitive functions in adult APP/PS1, 3xTg and wildtype (WT) mice. Our data suggest that promoting dynamin´s GTPase activity enhances dendritic arborization and dendritic spine formation in hippocampal neurons, preventing the loss of spatial and recognition memory in mouse models of AD. Our work contributes to positioning dynamins as new actors, and potential therapeutic target in Alzheimer´s disease.

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IMPACT OF DOPAMINE D2 RECEPTORS AND DOPAMINE LEVELS IN COMPULSIVE BEHAVIOR. Impacto del receptor D2 y los niveles de dopamina sobre la conducta compulsiva

Resúmen:
The repeated administration of Quinpirole (QNP), a dopamine D2 receptor (D2R) agonist, induces locomotor sensitization, a sustained increase in locomotor activity. Although QNP-induced locomotor sensitization is very robust in rats, this effect is poorly observed in mice. The mesolimbic dopamine system, composed of ventral tegmental (VTA) dopamine neurons projecting to the Nucleus Accumbens (NAc), underlies the induction of locomotor sensitization. QNP activates D2R in medium spiny and dopamine neurons, promoting locomotion and decreasing dopamine release. Previously, we found that rats showing QNP locomotor sensitization have decreased basal dopamine release in the NAc. We hypothesize that the chronic reduction of extracellular dopamine levels facilitates QNP-induced locomotor sensitization. To induce a chronic decrease of NAc dopamine levels independently of D2R activation, we expressed the inhibitory DREADD, hM4Di, selectively in the mesolimbic dopamine pathway in mice and repeatedly administered its agonist C-21. In these mice, we found increased sensitivity of D2R inhibition of DA release measured by fast-scan cyclic voltammetry, suggesting sensitized D2R presynaptic function. Then, we assessed whether repeated QNP administration affects locomotion in our hands. Interestingly, mice repeatedly treated with QNP did not develop locomotor sensitization. However, QNP administration in mice with previous chemogenetic inhibition of mesolimbic DA activity induced a sustained and enhanced locomotion, suggesting that chronic reduction of tonic dopamine in the NAc facilitates QNP-induced locomotor sensitization. We are assessing whether this chronic inhibition impacts D2R levels in the VTA and NAc. We intend to contribute to understanding the mechanisms that underlie compulsivity by studying the involvement of D2R in dopamine neurons.

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RESOLUTION OF VASCULAR INFLAMMATION: EXPLORING THE IMPACT OF SPECIALIZED PRO-RESOLVING MEDIATORS. resolucion de la inflamación vascular: explorando el impacto de los mediadores especializados proresolutorios

Resúmen:
Cardiovascular diseases are the leading cause of death in Chile and worldwide, placing a significant burden on healthcare systems. These conditions, such as hypertension and atherosclerosis, are characterized by vascular deterioration driven by high levels of angiotensin II, vasoconstriction, and chronic inflammation, which lead to the formation of atherosclerotic plaques. Conventional therapies focus on reducing cholesterol and the effects of angiotensin but do not address chronic inflammation. Endogenous pro-resolving mediators of inflammation and chronic damage, such as resolvins, maresins, lipoxins and protectins, have been identified as being reduced in patients with cardiovascular damage, suggesting their therapeutic potential. However, it remains unclear whether their exogenous administration in combination or sequence is more effective and whether they involve the NF-κB and NLRP3 pathways, which are key in chronic inflammation. This study evaluated the effects of RvE1, RvD2, and MaR1, administered alone, in sequence, or in combination, on inflammation and vascular damage using in vitro models of multicellular spheroids and in vivo models of vascular damage induced by angiotensin II. RvE1 and its combination significantly reduced neutrophil adhesion and pro-inflammatory cytokines, while RvD2 decreased the proliferation of muscle cells. A reduction in the expression of p65 was observed, but its localization in the nucleus was minimal. All conditions, except for RvD2, reduced the expression of NLRP3, correlating with decreased levels of IL-1β and IL-18. In vivo results indicated that the mediators decreased arterial hypertrophy, edema, and leukocyte infiltration, as well as serum levels of MCP-1, IL-1β, IL-6, VEGF, and TGF-β. These findings highlight the potential of pro-resolving mediators to resolve inflammation and promote vascular repair, suggesting their use in chronic inflammatory diseases.

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THE GUT NEUROCHEMICAL CODE AND PLASTICITY AS INSIGHTFUL THERAPEUTIC TARGETS FOR GASTROINTESTINAL DISORDERS. El código neuroquímico y la plasticidad entérica como blancos terapéuticos de interés para desórdenes gastrointestinales.

Resúmen:
Current gastrointestinal drugs are directed against a variety of cell types and molecular targets, but traditionally, they modify gastrointestinal motility and liquid absorption and many of them act on effector cells. More recently, the possibility of targeting regulatory –rather than effector– cells within the gut has received increasing attention. This is how enteric neurons, glia, immune cells and microbial communities have been shown to provide a wide array of molecular targets that are worth investigating. The gut submucosal plexus is a notoriously plastic tissue, located at the interphase of mucosal and muscular layers, with access to signals from the luminal compartment, the lymphatic vasculature and the bloodstream. The type of signalling molecules and receptors expressed by neurons in the submucosal plexus, also known as their neurochemical code, readily adapt to their microenvironment. We and others have described the responses and involvement of colonic submucosal neurons in the context of both physiological processes and pathological conditions. This talk will address some of the features that make submucosal neurons as well as their mechanisms, targets of interest for developing pharmacological strategies to treat gastrointestinal related disorders.

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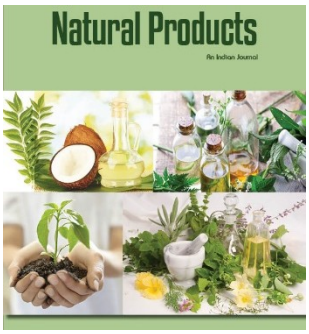

Symposium Natural Products «Medicinal and Food Plants in Chile: Status, Opportunities and challenges"
Chair: Dr. Raquel Bridi

ANTI-INFLAMMATORY PROPERTIES AND CHEMICAL COMPOSITION OF NATURAL PRODUCTS: INFLUENCE OF GENOTYPE AND DRYING. Propiedades 34nti-inflamatorias y composición química de productos naturales: influencia del genotipo y el secado.

Resúmen:
A wide range of factors can influence the production of bioactive compounds in natural products and, consequently, the pharmacological activities of the resulting extracts. Key factors include the plant genotype and the drying process of the plant material used to produce extracts. Regarding genotype, studies on Chilean endemic plants, such as Ugni molinae Turcz. (commonly known as murtilla), conducted by our research group, have evaluated the anti-inflammatory activity and chemical composition of extracts from the leaves and fruits of 10 different murtilla genotypes (INIA), all cultivated under the same edaphoclimatic conditions. Significant differences were observed in the profile of phenolic compounds and pentacyclic triterpenes, quantified by HPLC-UV/MS, as well as in the anti-inflammatory activity, assessed in an in vivo mouse ear edema model. Among the genotypes studied, genotype 19-1ha stood out with higher anti-inflammatory activity and greater bioactive compound content (1,2). Regarding the drying process, research conducted by our group in collaboration with researchers from the University of La Serena and the University of Chile has demonstrated that the content of active compounds and pharmacological properties, such as in vitro antioxidant and in vivo anti-inflammatory activities, can vary depending on the drying method used. In plant species such as Ugni molinae, Aristotelia chilensis, and Fuchsia magellanica, among others, freeze-drying, vacuum drying, and low-temperature vacuum drying have proven superior in preserving bioactive compounds compared to convection or infrared drying methods. These results highlight the importance of selecting an appropriate drying method for plant material intended for medicinal use (3,4).
References (DOI/LINK): 1. 10.1016/j.foodchem.2016.07.159 2. https://www.redalyc.org/articulo.oa?id=85647558001 3. 10.3389/fpls.2023.1095179 4. 10.3390/foods13193162

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UNRAVELING THE HEALTH-PROMOTING AND DISEASE-PREVENTATIVE BENEFITS OF TRADITIONAL FERMENTED BEVERAGES FROM CHILE. Desentrañando los beneficios para la salud y la prevención de enfermedades de las bebidas fermentadas tradicionales de Chile.

Resúmen:
Ethnohistorical and ethnographic information in Chile has shown that fermented beverages have an important role beyond the social or ritual use linked to their function as alcoholic beverages. This is evident, based on the extensive documentation of their use as foods and medicines. In South America, especially in the Andean regions, indigenous communities prepared chicha based on practically all plant materials, including fruits, grains, starchy tubers, and even mushrooms. As food, chicha has been used as an energy source providing calories, proteins, vitamins, minerals, and different bioactive compounds. Among the health-beneficial properties reported are: diuretic, treatment of respiratory and digestive infectious diseases, anti-inflammatory, antineuralgic, to treat extreme fatigue and thinness, to relieve menstrual pain, to treat hemorrhoids, as a tonic, astringent, emollient, and to improve appetite. The notion that consuming fermented beverages is associated with health benefits is widespread and even survives to the present day. However, health claims are mostly based on ethnographic reports and traditional knowledge, while the experimental evidence is still incomplete. Yet, besides the limited scientific information, the existing research on plant-raw materials, phenolic compounds, in general, and fermented beverages of different plant-raw materials, indicate that Chilean traditional fermented beverages may possess a promising potential yet to be investigated and fully exploited. This talk provides scientific evidence that permits validation that fermentation results in changes in the chemical profile of the initial plant raw materials and that these modifications are associated with an increase in antioxidant capacity, bioaccessibility, bioavailability, and pharmacological activities against metabolic syndrome and gastrointestinal cancers.

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HEPATOPROTECTIVE POTENTIAL OF IRIDOIDS AND POLYPHENOLS. Potencial hepatoprotector de iridoides y polifenoles

Resúmen:
Liver disease accounts for approximately 2 million deaths per year worldwide. Regular usage of medicines, increased consumption of western-type diets (high in fructose, lipids, and cholesterol), alcohol, and also exposure to radiation, viral infections, lipid peroxidation products, and other toxic chemicals are considered to be the main causative factors to liver disorders. Since currently available synthetic drugs may not be effective and may have limitations due to their negative side effects, there is a vast need for new and alternative approaches to find novel hepatoprotective agents. Accordingly, much attention is focused on developing novel drugs for treating liver diseases derived from medicinal plants. Active extracts, fractions, or isolated compounds of plants may prove very effective drugs for liver diseases. Some secondary metabolites like polyphenols and iridoids showed hepatoprotective activity. Iridoids are secondary metabolites recognized by their intense bitter taste. Several plants containing iridoids are used as hepatoprotective agents, and some studies confirmed this effect. On the other hand, polyphenols from a wide range of foods and medicinal plants have demonstrated therapeutic effects in a range of liver diseases. The hepatoprotective effect of iridoids and polyphenols is mainly attributed to their antioxidant activity. Our studies using extracts rich in these compounds obtained from medicinal plants, legumes, and bee products showed protection in hepatic cells against oxidative damage triggered by AAPH-derived free radicals. This effect can be credited to the ability of the iridoids and phenolic compounds present in the extracts to protect the liver cells from chemical-induced injury, which might be correlated to their free radical scavenging potential. Additionally, some extracts reduce lipid accumulation in a cellular model of steatosis.

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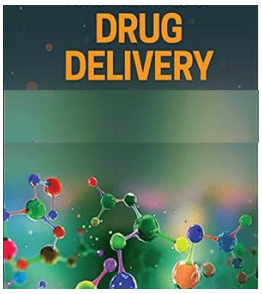

Symposium Drug Delivery "Breaking Barriers for Drug Delivery"
Chair: Dr. Tania Bahamondez

DRUG DELIVERY STRATEGIES THROUGH MUCOSAL MEMBRANES. Estrategias de entrega de activos a través de membranas mucosas

Resúmen:
Mucosal membranes form a barrier between the body's internal systems and the environment. This route offers several advantages over traditional routes of administration, such as rapid absorption due to their rich blood supply, resulting in a faster onset of action and avoiding first-pass metabolism. Mucosal delivery is typically non-invasive, improving patient compliance. Furthermore, mucosal delivery allows localized treatment using formulations such as sprays, gels, and films, targeting specific tissues such as the respiratory or gastrointestinal tracts. This can be particularly beneficial for managing localized infections while minimizing systemic side effects since these membranes provide a moist, nutrient-rich environment for pathogens. In susceptible patients, bacteria can adhere and grow into biofilms—structured communities encased in a protective matrix that resists antibiotics and immune defenses. However, this route poses unique challenges, including limited permeability, rapid clearance, and risk of degradation by mucosal enzymes. Overcoming these barriers is crucial for effective treatment. Recent strategies focus on integrating bioactive compounds, such as essential oils, due to their ability to perfuse through these membranes, exert antimicrobial, antioxidant, and antifungal effects, and improve mucociliary clearance. Essential oils can disrupt biofilm structure and inhibit bacterial growth. Additionally, oxygen delivery agents, such as perfluorooctyl bromide (PFOB), are being explored to enhance oxygenation in lung tissues. PFOB can dissolve significant volumes of oxygen, making them suitable for addressing the hypoxic conditions typical within biofilm environments. By improving oxygen levels, PFOB promotes tissue regeneration and boosts the effectiveness of antimicrobial agents, which often require oxygen to function optimally. These combined approaches help overcome the challenges of mucosal drug delivery in managing chronic mucosal infections.

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THE IDEAL FILTER DOES EXIST: OVERCOMING MECHANICAL, CHEMICAL, AND AERODYNAMIC OBSTACLES IN RESPIRATORY DOSING. El filtro ideal sí existe: Superando obstáculos mecánicos, químicos y aerodinámicos en la dosificación respiratoria

Resúmen:
This presentation explores the delivery of drugs to the lungs, highlighting the advantages and challenges associated with this route compared to traditional oral administration. In terms of benefits, pulmonary drug delivery allows for rapid absorption and bypasses hepatic first-pass metabolism, making it an ideal route for drugs intended to act locally within the lungs. It also requires lower dosages than oral administration for local pulmonary action, potentially minimizing systemic side effects. However, significant biological and aerodynamic barriers challenge the effective delivery of drugs to the lungs. Key obstacles include the branching structure of the respiratory tract, which affects particle distribution and aerodynamics; inertial impact within the oropharyngeal region, where many particles are lost before reaching the lungs; and lung barriers, such as mucociliary escalator action and macrophage activity, which effectively remove foreign particles, including respirable drugs, from the lungs. These barriers act as "ideal filters," presenting hurdles to achieving efficient pulmonary dosing. This presentation will discuss strategies designed to overcome these natural lung barriers, aiming to enhance drug deposition in the lungs and improve therapeutic outcomes in respiratory dosing.

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NANOCARRIER DESIGN FOR INTACT BARRIER PERMEATION FOLLOWED BY TARGETING. Diseño de nanocarriers para la permeación intacta a través de barreras seguida de direccionamiento.

Resúmen:
Nanocarrier development for targeted drug delivery has advanced considerably, with promising strides in lipid-core micelles (LCMs) tailored to permeate biological barriers and respond to disease-specific biomarkers. Our recent work highlights the potential of MMP-9-responsive LCMs designed to release therapeutic payloads upon encountering elevated enzyme levels typical in cardiovascular pathologies, followed by specific cardiomyocyte targeting. Extending this strategy, our ongoing research investigates buccal administration as a non-invasive route for peptide-loaded nanocarriers, designed to bypass gastrointestinal and hepatic barriers, thus enhancing systemic bioavailability of labile biomolecules. Utilizing inkjet-printed mucoadhesive films, we are exploring intact nanocarrier permeation through the buccal epithelium, focusing on the role of film polymer hydration in modulating permeability and achieving controlled release. Preliminary data shows that optimized inkjet-printed films loaded with nanostructured lipid carriers can achieve stable permeation, as confirmed by NTA and TEM imaging. This research is exploring physicochemical parameters such as particle size, zeta potential, and deformability, alongside the impact of permeation enhancers, including bile salts, in promoting intact nanocarrier passage. Findings aim to delineate the synergy between nanocarrier design and buccal film hydration dynamics, establishing a robust platform for targeted and sustained peptide delivery via buccal administration. This presentation will cover the integration of bioresponsive nanocarriers with non-invasive delivery platforms, showcasing how advanced formulation and characterization techniques pave the way for more efficient and patient-conscious targeted drug delivery systems.

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