ORAL COMMUNICATIONS

Day 2, 12:35 – 13:35 h, november 12, 2024 (tuesday)

1. IBUPROFEN OR PREGABALIN REDUCE THE HUMAN SPINAL CORD NEUROVASCULAR COUPLING RECORDED BY FUNCTIONAL NEAR-INFRARED SPECTROSCOPY (fNIRS). El ibuprofeno o la pregabalina reducen el acoplamiento neurovascular de la médula espinal humana registrada mediante espectroscopía funcional de infrarrojos cercanos (fNIRS).

Resúmen:
Neurovascular response (NVR) a vital coupling between neural activity and local blood flow is supposed to depends on neuronal Ca++ channels activation and glial prostaglandin release. Recently, fNIRS was applied for functional diagnosis of the spinal cord evaluating perispinal NVR triggered by peripheral nerve electrical stimulation. Here, pregabalin (PGL), an alpha2delta subunit blocker of the Ca++ channel, or Ibuprofen (IBU) a non-specific COX inhibitor was tested in healthy volunteers assigned to the IBU (n=38) or PGL (n=32) groups. Spinal NVR triggered by median nerve electrical stimulation was recorded by fNIRS optodes (750/850 nm) placed at cervical and lumbar level during basal condition and 60 minutes after a single oral dose of IBU 10 mg·Kg-1 or 75 mg PGL. Mann-Whitney and Kruskal-Wallis test were used at $p<0.05$. IBU decreases both NVR amplitude and rise time at the cervical (-45.2% and -17.1% respectively). However, more than 60.5% of the volunteers show lower lumbar NVR amplitudes and rise times after IBU. The NVR duration was reduced by IBU at both cervical (-24.4%) and lumbar (-18.3%) sites ($p<0.05$). PGL decreases NVR amplitude at cervical (-69.7%) but not at lumbar recording site. However, 84.4% of the volunteers of this group show lower lumbar NVR amplitudes and rise times respectively after IBU. The NVR duration was reduced by IBU at both cervical (-14.0%) and lumbar (-18.6%) sites ($p<0.05$). The resulting reduction of the NVR was probably due to the blocking of the Ca++ channel by PGL thus reducing neuronal excitability and prostaglandins release. The IBU non-specific COX synthesis inhibition results in a strongly NVR reduction. Additionally, fNIRS was able to monitor the pharmacological effects of these drugs.

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Socio Patrocinante: N/A

2. IDENTIFYING ALTERNATIVE CONCEPTIONS IN UNDERGRADUATE'S PHARMACOLOGY STUDENTS. Identificando concepciones alternativas en Farmacología de estudiantes universitarios.

Resúmen:
Introduction: One of the many challenges that affect students when learning sciences, is the presence of alternative conceptions (prior knowledge, preconceptions) about the content that will be taught. These ideas show characteristics that have been classified by neuroscience, sociology, history and education. Furthermore, they are deeply rooted in students' cultural heritage, significantly hindering the conceptual change necessary for effective science education. Thus, studies have shown that pharmacological concepts are often not fully understood by students, posing serious risks in health education. For this reason, many experts have emphasized the need to adjust the pharmacology curriculum without adequately considering students' prior knowledge, which is essential for effective learning. Aim: To identify the most common prior knowledge about pharmacokinetics and pharmacodynamics core concepts among Chilean undergraduate students. Methods: Observational study with a cross-sectional design and primarily quantitative approach for a multiple-choice questionnaire on pharmacological concepts that will be applied to 150 Chilean students from three different universities and fields of study. Results: Although in the first pilot the reliability parameter was insufficient for the dimensions considered (Cronbach's alpha < 0.7), within the preliminarily measurement scales responses were obtained that suggest the existence of several strong prior ideas. Among these are those related to the excretion (72%), antibiotic resistance (70%) and the mechanism of action of widely used drugs (78%). Conclusion: Even though there is abundant literature regarding alternative conceptions in science teaching, very little of it systematically addresses prior ideas about pharmacology among university students. We believe that the instrument we will develop can be useful as a foundation for future research aimed at clarifying the preconceptions that students hold most firmly in this domain.

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Socio Patrocinante: Javier A. Bravo, Ph.D.

3. ALZYFINDER: AN ML-DRIVEN PLATFORM FOR LIGAND-BASED VIRTUAL SCREENING AND NETWORK PHARMACOLOGY. AlzyFinder: Una plataforma impulsada por ML para el cribado virtual basado en ligandos y farmacología de redes

Resúmen:
Neurodegenerative diseases, such as Alzheimer's disease (AD), are characterized by progressive cognitive, emotional, and behavioral losses, impacting daily activities. Central to these disorders is neuronal degeneration, which affects essential brain functions. AD, the most common form of dementia, primarily affects the elderly. Key pathological features include amyloid plaques from amyloid-β (Aβ) aggregation and neurofibrillary tangles (NFTs) from tau hyperphosphorylation. Neurodegeneration begins 10-20 years before noticeable cognitive decline. Despite advances, AD remains a significant challenge for the elderly. To address this, research in AD drug discovery must focus on therapies targeting multiple pathological mechanisms. In response, the Alzyfinder Platform was developed. This web-based tool employs machine learning models to virtually screen over 80 key targets linked to AD. Alzyfinder offers a user-friendly interface for ligand-based drug design and presents results through drug-protein interaction networks (DPIs), illustrating how potential therapies interact with AD-related targets. As the first open-access platform of its kind, Alzyfinder's models have been rigorously tested for accuracy in virtual screening. The platform not only predicts interactions between candidate molecules and key targets but also identifies multitarget ligands, offering insights into their therapeutic potential. Alzyfinder Platform represents a crucial advancement in AD drug research by addressing multiple pathological mechanisms. This tool has the potential to improve patient outcomes and is freely accessible at www.alzyfinder-platform.udec.cl, with all necessary resources available in its GitHub repository.

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4. IMPACT OF EXPOSURE TO AN OBESOGENIC DIET AND SUBSEQUENT WEIGHT LOSS ON THE GLP-1 SYSTEM IN THE LATERAL SEPTUM AND RE-FEEDING BEHAVIOR. Impacto de la exposición a una dieta obesogénica y posterior bajada de peso sobre el sistema GLP-1 en septum lateral y comportamiento de re-alimentación.

Resúmen:
Feeding control is regulated at the central level by hypothalamic and extra-hypothalamic areas such as the lateral septum (LS). Last years, the Glucagon-like peptide-1 (GLP-1) system has taken great relevance in controlling food intake, and LS expresses the GLP-1 receptor (GLP-1R). However, the potential alterations in the GLP-1 system in obesity, its effects on feeding behavior, and whether these changes can be reversed after weight loss remain unknown. To test this, we induced obesity by exposing Sprague Dawley rats at post-natal day (PND) 21 to a high-fat diet (HFD) plus 5% sucrose solution for six weeks. Then, we performed a dietary and pharmacological treatment for 10 days where all groups were fed with chow food plus water and were injected with saline (1 mL/kg/day), liraglutide (0.05 mg/kg/day), or phentermine (30 mg/kg/day). Re-feeding test and Westen Blot analysis were performed before and after the treatment, to evaluate GLP-1R levels in LS. The exposure to the obesogenic diet reduces GLP-1R levels in LS of males but not females, and the change in diet was sufficient to reverse this effect. Liraglutide and phentermine treatments did not alter GLP-1R levels in LS of obese males, however, these drugs led to an increased in the HFD consumption during the re-feeding test. In conclusion, chronic exposure to obesogenic diet affects GLP-1 system in LS and re-feeding behavior, and anorectic treatments do not impact GLP-1R levels but induce a preference for HFD during re-feeding, which could lead to weigh regain.

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5. DEVELOPMENT OF A PLATFORM FOR THE EVALUATION OF MOLECULES WITH ACTIVITY AGAINST CASTRATION-RESISTANT PROSTATE CANCER AND ABIRATERONE-RESISTANT CÁNCER. Desarrollo de una plataforma de evaluación de moléculas con actividad frente al cáncer de próstata resistente a la castración y resistente a Abiraterona.

Resúmen:
Castration-resistant prostate cancer (CRPC) is a significant public health problem, especially when patients develop resistance to Abiraterone, a last-line drug in the treatment of this disease. This thesis presents the development of a platform for evaluating compounds with potential therapeutic activity against Abiraterone-resistant CRPC (AbiR). Two Abiraterone-resistant cellular models were generated using the C4-2B and 22RV1 cell lines, by chronic treatment with increasing concentrations of Abiraterone. These models were validated through real-time proliferation and cell death assays, which demonstrated that the resistant cells exhibited greater survival and proliferation in response to the drug compared to the parental cells. Additionally, traditional crystal violet staining methods were compared with automated real-time analysis, revealing that the latter offers advantages in terms of accuracy, amount of data, and reduced experimental bias. Five compounds with potential activity were evaluated using an automated robotic platform that allowed for real-time cytotoxicity and cell proliferation assays. The results showed significant differences in the activity of these compounds against the AbiR models, providing crucial data to identify candidates that could reverse resistance or have therapeutic activity against this type of cancer. This platform represents a breakthrough in the development of tools for researching new therapies against Abiraterone-resistant CRPC, improving the evaluation process of potential new treatments.

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ORAL COMMUNICATIONS

Day 3, 12:35 - 13:35, november 13, 2024 (wednesday)

1. INVOLVEMENT OF TREK AND BKCA CHANNELS IN PROTEIN-PROTEIN INTERACTION NETWORK ASSOCIATED WITH PAIN. Participación de los de los canales TREK y BKCa en la red de interacción proteína-proteína asociada al dolor.

Resúmen:
Large-conductance calcium-activated potassium (K+) channels (BKCa channels) and TWIK-related K+ channels (TREK-1 and TREK-2) are present in nociceptive primary sensory neurons. Novel molecules that increase TREK or BKCa activity have been suggested as potential treatments for pain. In this study, a graph database was constructed to map the pain interactome (or protein-protein interaction network) and its modulating drugs, with a focus on TREK and BKCa channels as nodes in the graph. The graph was analyzed using centrality parameters such as degree, eccentricity, and radiality. These topological parameters, along with the pharmacology of TREK and BKCa channels, were compared to other relevant pharmacological targets like different ion channels, GPCRs, and kinases. Additionally, a functional enrichment analysis was performed for the first- and second-neighbor networks of TREK and BKCa channels to understand the biological processes and metabolic pathways involving these proteins. This study contributes to understanding the pain interactome, providing a framework for designing multitarget pain therapies that regulate TREK and BKCa channels.

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Socio Patrocinante: Wendy González

2. IDENTIFICATION OF DRUGGABLE BINDING SITES AND SMALL MOLECULES AS MODULATORS OF TMC1. Identificación de sitios de unión a fármacos y pequeñas moléculas moduladoras de TMC1

Resúmen:
Inner ear sensory hair cells use mechano-electrical transducer (MET) channels, formed by TMC1/2 proteins, to convert mechanical stimuli into electrical signals essential for hearing and balance. The non-selective cationic channels allow the permeation of ototoxic drugs into hair cells. Recently, the FDA approved sodium thiosulfate to reduce the risk of cisplastin-induced ototoxicity. Its mechanism of action is not fully understood and does not protect against aminoglycoside-induced damage. This underscores the need for structure-guided search for novel otoprotectants compunds to prevent hearing loss. Also, multiple studies have aimed to identify or modify compounds as potential otoprotectants against ototoxic drugs. Despite the understanding of the interaction mechanisms between these modulators and TMCs remains limited. In this study, we used computational and experimental methods to identify novel TMC1 modulators and developed the first in silico pipeline using a structure-based screening approach, integrating molecular pharmacophore modeling, molecular docking and free-energy estimations analysis coupled with AM1-43 loading as a screening pipeline. Our 3D pharmacophore model contains structural features necessary for ligands to bind and modulate TMC1 activity. Molecular docking and free-energy estimations identified three potential drug binding sites within the TMC1 pore, phospholipids and highlighted key amino acids for ligand interaction. This approach successfully identified several FDA and non-FDA compounds that demonstrated MET modulation activity by reducing dye uptake in cultured cochlear explants. Additionally, the computational methods provide a deeper understanding of the key structural elements and moieties required for hit-to-lead optimization with enhanced biological activities. Finally, our pipeline offers a broad application to discover small molecule modulators for a wide spectrum of mechanosensitive ion channels.

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Socio Patrocinante: Ramírez D.

3. IMPACT OF QUERCETIN ON CELL PROLIFERATION AND ENZALUTAMIDE SENSITIVITY IN CASTRATION-RESISTANT PROSTATE CANCER. Impacto de quercetina en la proliferación celular y la sensibilidad a la enzalutamida en el cáncer de próstata resistente a la castración.

Resúmen:
Castration-resistant prostate cancer (CRPC) is a condition where prostate cancer continues to progress despite castration-level androgen levels. One of the drugs used to treat CRPC is the androgen receptor antagonist enzalutamide. A key pathway in CRPC progression is the PI3K/AKT pathway, which leads to increased expression of androgen receptor (AR) and prostate-specific antigen (PSA), both critical in resistance and desensitization to enzalutamide. Currently, the search for molecules that could serve as adjuvants to chemotherapeutic agents has gained prominence in cancer research. Quercetin, a secondary metabolite with antioxidant activity, has shown antiproliferative effects in various cancer types. Here, we propose that quercetin could enhance sensitivity to enzalutamide by inactivating AKT and reducing the expression and activation of AR and PSA. To test this, quercetin treatments were conducted on CRPC cell lines C4-2B and 22RV1. AKT activation was analyzed through Ser473 phosphorylation via Western blot, and AR and PSA levels were assessed using Western blot and RT-qPCR. Finally, cytotoxicity and cell proliferation assays were performed using increasing doses of quercetin combined with enzalutamide doses of 20 µM and 40 µM (for C4-2B) and 40 µM and 80 µM (for 22RV1), monitored through the Incucyte cell-by-cell system. Our results show that quercetin inhibits cell proliferation, prevents AKT activation, and reduces AR and PSA expression and activation. Additionally, quercetin increased the sensitivity of these cells when combined with enzalutamide.

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Socio Patrocinante:

4. METABOLIC PROFILE AND BIOACTIVE EVALUATION OF Berberis microphylla G. FORST (CALAFATE) LEAF INFUSION. Perfil metabólico y evaluación bioactiva de la infusión de hojas de Berberis microphylla G. FORST (CALAFATE).

Resúmen:
Berberis microphylla G. Forst (Calafate) fruit have been used in traditional medicine since pre-Hispanic times in Patagonia, its consumption provides health benefits, particularly in protecting against various metabolic diseases[1]. However, the bioactive properties of the leaves, have been poorly studied. Recently, 108 compounds, mainly hydroxycinnamic acids, flavonols, and berberine, were identified in a methanolic extract of the leaves[2]. Based on this, we evaluated the bioactive capacity of a Calafate leaf infusion prepared in hot water. For this, the chemical characterization of the infusion was performed using HPLC-Q-TOF. Bioactivity was assessed through antioxidant capacity, cell cytotoxicity, and cell oxidative stress assays. The inhibition of Aβ aggregation for Alzheimer's disease and gastrointestinal enzymes for metabolic syndromes were also evaluated. The results show that the infusion is rich in hydroxycinnamic acids and other bioactive compounds. The infusion does not exhibit cytotoxic activity. Additionally, it can reduce intracellular reactive oxygen species in HUVEC cells and showed a reduction in Aβ aggregation. Finally, the infusion exhibited in vitro hypoglycemic and hypolipidemic effects. These results support the use of Calafate infusion as a new functional beverage.

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Socio Patrocinante: Jorge Fuentealba

ORAL COMMUNICATIONS

Day 4, 12:35 - 13:35, november 13, 2024 (thursday)

INCORPORACIONES / INCORPORATIONS

1. GENETIC VARIANTS AND CLINICAL FACTORS AFFECTING THE RESPONSE TO 5-FLUOROURACIL-BASED TREATMENT IN CHILEAN PATIENTS WITH ADVANCED COLORECTAL CANCER. Variantes genéticas y factores clínicos afectan la respuesta al tratamiento basado en 5-fluorouracilo en pacientes chilenos con cáncer colorrectal avanzado

Resúmen:

Colorectal cáncer (CRC) is the second most common cancer in Chile, with late diagnoses leading to about 25% of patients presenting with metastatic disease and a five-year survival rate around 14%. Standard treatment involves tumor resection and adjuvant chemotherapy, primarily 5-fluorouracil (5-FU) combined with oxaliplatin or irinotecan. However, responses to 5-FU vary significantly due to genetic polymorphisms in enzymes like thymidylate synthase (TYMS) and dihydropyrimidine dehydrogenase (DPD), influencing drug metabolism. Polymorphisms in genes related to oxaliplatin's efficacy also contribute, yet the relationship between genetic variants and treatment outcomes is often population- and stage-dependent. Notably, a comprehensive model to predict chemotherapy safety for Chilean CRC patients has not been established. This study aimed to identify relevant genetic variants in TYMS, TYMP, DPYD, GSTP1, MTHFR, ERCC2, ABCB1, ABCC2, ABCC4, and ABCG2 that, alongside clinical variables, could help create a predictive model for the safety of 5-FU-based chemotherapy in advanced CRC patients. A retrospective nested case-control study analyzed 82 advanced CRC patients and 16 genetic variants to assess their influence on adverse reactions (ADRs). Key findings included that the G allele of GSTP1 (rs1695) was protective against neuropathy but increased the risk of mucositis. The C allele of DPYD (rs1801265) raised neuropathy risk, while TYMS deletion (rs151264360) was protective against skin and hematological ADRs. Two multivariate models predicted anemia and pain development. This study is a step toward developing predictive models for ADRs related to 5-FU, potentially aiding in pharmacogenetic-based dose adjustments for Chilean patients.

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Socio Patrocinante: Dr. Luis Quiñones Sepúlveda, PhD

2. MODELING AND DYNAMICS OF THE MINERALOCORTICOID RECEPTOR IN ITS INACTIVE STATE: DEVELOPMENT OF A PHARMACOPHORE MODEL AND SCREENING OF NOVEL ANTAGONISTS. Modelado y Dinámica del Receptor de Mineralocorticoides en su Estado Inactivo: Desarrollo de un Modelo Farmacofórico y Búsqueda de Nuevos Antagonistas

Resúmen:

The mineralocorticoid receptor (MR) is a critical therapeutic target in cardiovascular and renal diseases. However, structural data on its inactive conformation remain limited. In this study, we employed molecular modeling to complete the recently published, yet incomplete, crystallographic structure of the MR-Esaxerenone complex, enabling the exploration of MR in its inactive state. To characterize binding patterns and derive a pharmacophore model of pure MR antagonists, molecular dynamics simulations were conducted. Clustering strategies were applied to identify prevalent binding modes and pinpoint key residues in the protein-ligand interactions. This analysis revealed critical anchoring points that determine antagonist affinity and specificity for MR. We conducted a virtual screening campaign of approximately 100 million compounds using the most representative binding mode. This effort led to the identification of several novel chemotypes with potential selective antagonist activity for MR. These compounds represent promising candidates for MR-targeted therapies, providing new opportunities in modulating this receptor for potential clinical applications. Through molecular modeling and dynamics, we generated a detailed model of MR's inactive state, identifying novel chemotypes for MR antagonists. This work underscores the potential of virtual screening and computational modeling in drug discovery for diseases modulated by MR.

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Socio Patrocinante: Dr. David Ramirez