Volumen 12
Número 3
Año 2019
ISSN Nº 0718-8811
www.sofarchi.cl

REVISTA DE FARMACOLOGÍA DE CHILE

Órgano oficial de la Sociedad de Farmacología de Chile

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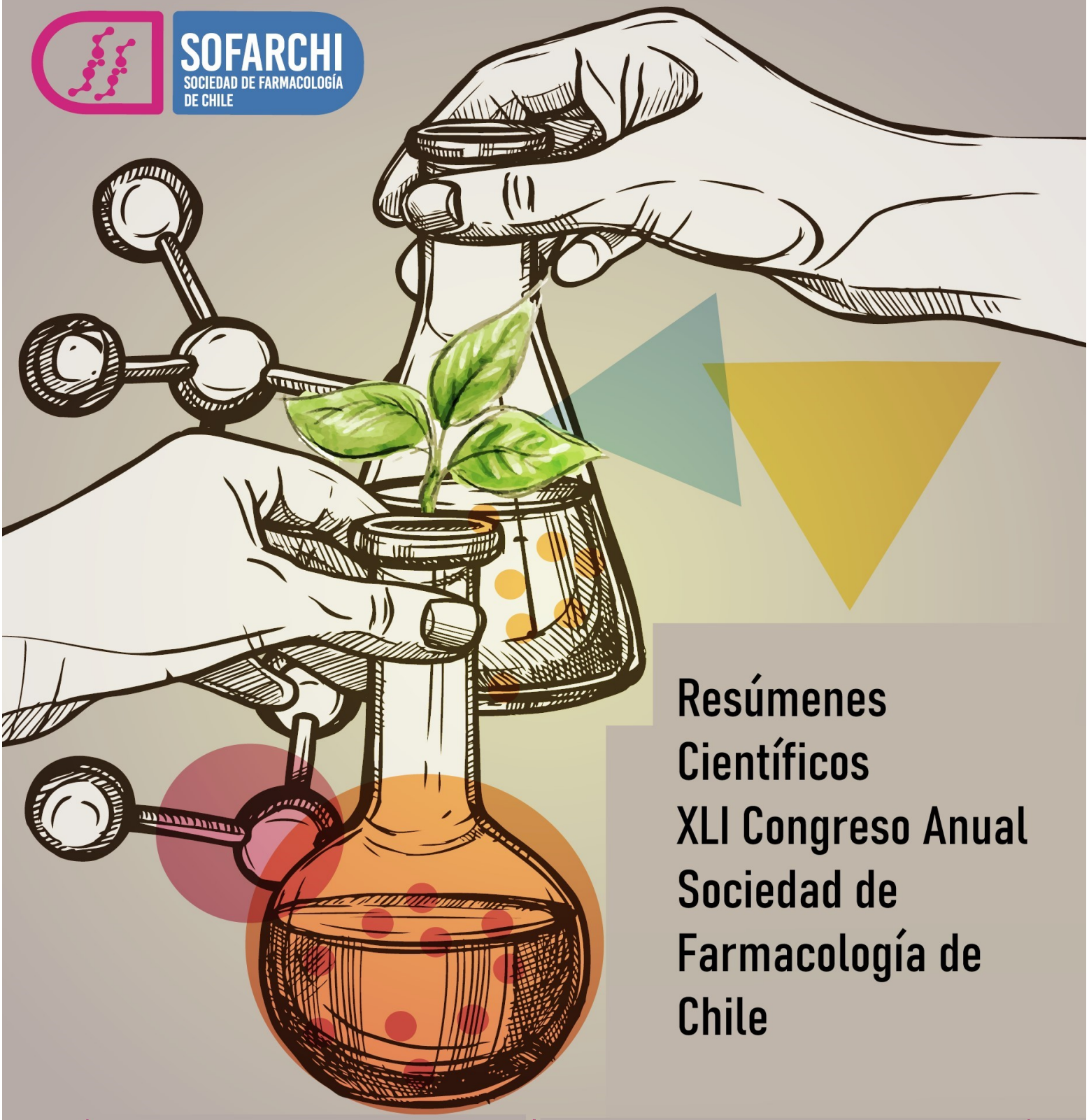
SOCIEDAD DE FARMACOLOGÍA DE CHILE



Resúmenes Científicos XLI Congreso Anual Sociedad de Farmacología de Chile

4 al 8 de Noviembre de 2019,
Universidad de Concepción,
Concepción Chile.

PANEL DE EDITORES

La Revista de Farmacología de Chile tiene un panel de editores conformado por connotados farmacólogos nacionales que son miembros de la Sociedad de Farmacología de Chile y académicos de las principales universidades chilenas.

Comité Editorial:

Evaluadores Asociados:

Revista de Farmacología de Chile es publicada por la Sociedad de Farmacología de Chile

ISSN 0718-8811 versión impresa
ISSN 0718-882X versión digital

ABSTRACTS FOR XLI OF THE CHILEAN SOCIETY OF PHARMACOLOGY

CONFERENCES

1. THE EMOTION OF SCIENTIFIC DISCOVERY.
Antonio G. García
Instituto Teófilo Hernando, Departamento de Farmacología y Terapéutica, Facultad de Medicina, Universidad Autónoma de Madrid, Spain

Stephen Hawking said that "science is not only a matter of reason; it is also a matter of romance and passion". This was already written by Santiago Ramón y Cajal in his famous book "Reglas y Consejos sobre Investigación Científica", a hundred years ago. More recently, the National Academy of Sciences of the USA wrote a short guide entitled "ON being a scientist", that summarizes the emotions that a scientist may feel along his carrier when pursuing a problem and finding the response sometimes after years of hard work. I will illustrate the way science is practiced with some experimental findings on the topic of calcium signaling and exocytosis in adrenal chromaffin cells. In doing so, I will focus first on basic science, describing how we arrived to the concept of a functional triad that includes the voltage-gated calcium channels (VGCCs), the endoplasmic reticulum (ER) and mitochondria (MIT). Such triad shapes the cytosolic calcium signals that control both pre-exocytotic and exocytotic responses, the basis of the fight-or-flight stress response of W. Cannon. Then, I will focus on more recent translational research done in chromaffin cells from mouse models of neurodegenerative diseases. I will comment on dysfunctions of Ca2+ and exocytosis occurring even at pre-symptomatic disease stages. I will next make some comments on the failure of clinical trials in AD, to end with some hints on the pressure to "publish-or-perish" and how science is becoming just a mere business for editorials and else.

Recent and ongoing work from AGG'S laboratory is being founded by
1. European Union Horizon 2020 Research and Innovation Programme under the Marie Skoldowska-Curie Grant Agreement 766124);
2. Grant SAF-2016-48892-R, from Ministerio de Ciencia, Innovación y Universidades, Spain; and
3. Fundación Teófilo Hernando, Madrid, Spainen un contexto general y discutiré su importancia con relación a la salud y a la enfermedad.

2. THE PLEASURE OF SCIENCE: MY LIFE IN PHARMACOLOGY.
Salvador Moncada
Manchester Cancer Research Centre, The University of Manchester, U.K.

I will describe the work that opened several fields of investigation. From the mechanism of action of non-steroidal anti-inflammatory drugs, to the discovery of thromboxane synthase and prostacyclin, to the identification of nitride oxide and its metabolic pathway of synthesis. I will finish with a reference of the role of mitochondria in oxidative stress. I will put all this work in a general context and its importance in health and disease will be discussed.

3. DIRECT C–H FUNCTIONALIZATION OF CYTISINE. NICOTINIC RECEPTOR SELECTIVITY AND MECHANISM OF ACTIVATION.
Tim Gallagher
University of Bristol, UK

The talk will cover the application of subtype-selective nicotinic partial agonists to manage nicotine addiction, with a focus on the chemistry of cytisine. Already used for smoking cessation, cytisine (and varenicline) target subsets of nicotinic receptors, and the opportunity to generate novel structural variants of cytisine raises the question of whether more subtype selective ligands are available and of value or indeed are even desirable. The talk will cover recent work in this area, much of which is underpinned by development of C-H functionalisation chemistry that provides very direct and efficient access to new C-10 cytisine derivatives, which in turn, offer more selective subtype profiles. Recent studies (in collaboration with Henry Lester and Dennis Dougherty) have probed the influence of steric vs. electronic factors in determining the binding mode of cytisine. We have also pursued extensive molecular dynamics simulations to probe the mechanism (timing) of signal propagation through the protein scaffold that occurs on ligand association to the receptor, and addressed the question of the applicability and generality of that mechanism across other receptors.

4. GENETIC, PROTEIN AND PHARMACOLOGICAL MODULATION OF HUMAN α7 NICOTINIC RECEPTORS.
Cecilia Bouzat
Instituto de Investigaciones Bioquímicas de Bahía Blanca, INIBIBB (CONICET-UNS), Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur, Bahía Blanca, Argentina.

The α7 nicotinic acetylcholine receptor is a pentameric ligand-gated ion channel. It is widely expressed in the central nervous system where it is involved in cognition, attention, and memory. It is also expressed in many non-neuronal cells and its activation has anti-inflammatory and neuroprotective roles. Enhancement of α7 activity is emerging as a therapeutic strategy for cognitive, neurodegenerative and inflammatory

disorders. We have focused on understanding α7 function and its different mechanisms of modulation associated to physiological, pathological and therapeutic situations. By single-channel recordings we determined that positive allosteric modulators (PAMs) enhance α7 activation by increasing open-channel lifetime and inducing prolonged activation episodes, and we also identified novel PAMs. Although α7 has been considered the homomeric member of the family, heteromeric α7β2 receptors have been detected in human brain. We generated α7β2 receptors with different stoichiometries and determined how the β2 subunit modifies α7 kinetics and its allosteric modulation. This information is required to decipher the role of α7β2 receptors in native cells. In humans, there is a truncated α7 subunit (dupα7) that lacks part of the ACh-binding site and results from partial duplication of the α7 gene. We demonstrated that dupα7 acts as a negative modulator and can assemble with α7 into functional heteromeric receptors. Deciphering the molecular basis underlying α7 function has implications for the design of novel therapeutic compounds as well as for clarifying its pleiotropic actions.

5. IRON AND FERROPTOSIS IN AGING AND AGE-RELATED NEUROLOGICAL DISEASES.

Ashley Bush
The Melbourne Dementia Research Centre, The Florey Institute of Neuroscience and Mental Health and the University of Melbourne, Australia.

Recent research has implicated increased brain iron as a trait that can propel various neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Motor Neuron disease and the complications of stroke. Ageing itself causes iron to increase in the brain to a point where it is "too much of a good thing" and can set up conditions that lead to neurodegeneration. During childhood and reproductive life, iron recruitment is geared towards avoiding iron deficiency, but there is no natural mechanism for off-loading excess iron. After reproductive life the systems that harvest iron so efficiently do not turn off, and lead to accumulation in tissues that are not normally shed, like brain. In the C. elegans model of ageing, we find that such iron elevation limits lifespan. In Alzheimer's disease brain iron elevation is associated with the rate of cognitive loss, lipid peroxidation products and features of the regulated cell death mechanism, ferroptosis. Anti-ferroptosis agents have been effective in animal models of neurodegenerative disease, and a recent phase 2 clinical trial of the anti-ferroptotic chelator deferiprone in Parkinson's disease lowered nigral iron and improved clinical readouts. We are currently testing this drug in a phase 2 RCT in Alzheimer's disease. CuATSM, has recently reported benefits in phase 1 studies of Parkinson's disease and Motor Neuron Disease, and we have identified that it possesses potent anti-ferroptotic properties.

References:

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