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REVISTA DE
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¡BIENVENIDOS AL CONGRESO ANUAL DE LA SOCIEDAD DE FARMACOLOGÍA DE CHILE!

CONCEPCIÓN 2019

EL EVENTO CIENTÍFICO CONTARÁ CON LA PARTICIPACIÓN DE 5 CONFERENCISTAS INTERNACIONALES, 70 EXPOSITORES EN SIMPOSIOS Y MINI SIMPOSIOS, JUNTO A CERCA DE 200 JÓVENES CIENTÍFICOS QUE EXHIBIRÁN LOS AVANCES OBTENIDOS EN SUS DIFERENTES LÍNEAS DE INVESTIGACIÓN.

SOFARCHI
SOCIEDAD DE FARMACOLOGÍA DE CHILE

5. ALZHEIMER'S DISEASE: NEW TARGETS AND DRUGS.

INTRODUCTION.

García, A.G.
Instituto Teófilo Hernando, Departamento de Farmacología y Terapéutica, Facultad de Medicina, Universidad Autónoma de Madrid, Spain.

Alzheimer's disease (AD) is becoming a devastating health, social, and economical problem. Burden to society will increase as population ages. The search of disease-modifying drugs has focused on over 30 distinct targets, most of them linked to amyloid beta (Aβ) aggregation or hyperphosphorylated tau. Anti-oxidant, anti-inflammatories, neurotransmitter receptors, or growth factors have been explored as targets to develop a medicine to delay disease progression. Ligands for those targets have been explored in cell and murine models of AD. Although many of them have shown efficacy in this preclinical set-up, they have failed in dozens of clinical trials performed during the last 20 years in AD patients. It is interesting that the Alzheimer's Foundation for Drug Discovery (AFDD) is not supporting any more clinical trials with compounds targeted to Aβ or tau. So, new targets and ideas are urgently needed. In this symposium on new targets and drugs for AD, four scientists from the Institute "Teófilo Hernando for Drug Discovery", at the Universidad Autónoma de Madrid, Spain, will present their work on new approaches to the search of new targets beyond conventional (Manuela García López), multitarget compounds (Rafael León Martínez), and Phosphatase PP2 (Raquel López Arribas). A last communication focus on altered neurotransmission processes in AD (Luis Gandía Juan). It is expected that only with these and other new strategies, we can find out the way to a medicine capable of slowing down the natural course of the disease; and what it is even more challenging, if administered at presymptomatic AD stages, in patients at risk diagnosed with biomarkers, this medicine be capable of delaying disease

NON CONVENTIONAL TARGETS FOR THE TREATMENT OF ALZHEIMER´S DISEASE.

López M.G. 1, Luengo E. 1, Trigo P. 1, Fernández-Mendivíl C. 1, Franco F. 1, del Sastre E. 1, Cuadrado A. 2, Rodriguez-Franco M. I. 3 y León R. 1 4.
1.Instituto Teófilo Hernando. Departamento de Farmacología. Universidad Autónoma de Madrid. 2.Instituto de Investigaciones Biomédicas "Alberto Sols" Departamento de Bioquímica. Facultad de Medicina. Universidad Autónoma de Madrid. España.3. Instituto de Química Médica. CSIC. Madrid. España. 4. Instituto de Investigación La Princesa. Hospital Universitario La Princesa. Madrid, España.

Alzheimer´s disease (AD) is the most common form of dementia with still no effective treatment. From a histopathological point of view, AD is characterized by extracellular aggregates of betaamyloid and, intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. During the last twenty years great effort has been made to develop therapeutic strategies, mostly based on beta-amyloid pathology, but without success. On the other hand, AD shares with other neurodegenerative diseases pathological mechanisms like oxidative stress, subchronic inflammation, mitochondrial dysfunction and proteinopathy. Given this scenario, our group seeks to identify new therapeutic targets focused on the regulation of oxidative stress and neuroinflammation, processes that precede the accumulation of aberrant proteins and cognitive impairment. We have therefore centered out attention on two targets: (1) the NADPH oxidases enzymes (NOXs), which are the enzymes responsible for the production of reactive oxygen species such as superoxide and hydrogen peroxide, and more specifically, in its NOX4 isoform and, (2) in the transcription factor NRF2 (Nuclear factor (erythroid-derived 2) -like 2), master regulator of the antioxidant response, which also regulates the expression of genes that participate in the anti-inflammatory response and autophagic processes. To validate NOX4 as a possible target, we have used transgenic mice that do not express this enzyme and a model of taupathy by injecting i.c.v. adeno viruses containing the human tau protein mutated in P2301L, under the promoter synapsin. In this model we have been able to determine that animals that do not express NOX4 have less oxidative stress and less neuroinflammation which results in an improvement in the cognitive tests. For our second target, we are looking for compounds that inhibit the interaction Keap-1 (NRF2 repressor protein) and NRF2. To do this, we have performed an in-silico screening of large libraries using docking and molecular dynamics, as well as the synthesis of new compounds. In the latter case, we want to obtain multitarget compounds with complementary activities to the induction of