MICROSCOPÍA DE SÚPER RESOLUCIÓN DE RECEPTORES Y PROTEÍNAS DE ANDAMIAJE DE LAS SINAPSIS INHIBITORIAS COMO OBJETIVOS FARMACOLÓGICOS. SUPER-RESOLUTION IMAGING OF RECEPTOR-SCAFFOLD INTERACTIONS AT INHIBITORY SYNAPSES AS PHARMACOLOGICAL TARGETS.

The function of synapses is closely controlled by the number, distribution and activity of postsynaptic neurotransmitter receptors. These biophysical properties depend on molecular interactions between the receptors and scaffold proteins, insofar as the availability of binding sites controls the clustering of the receptors at synapses. To understand the regulation of synaptic strength, it is therefore essential to know the precise copy numbers as well as the spatial arrangement of receptors and scaffold proteins on the molecular scale under normal conditions and during pathological processes. Using conventional and super-resolution fluorescence microscopy I will describe how the distribution of inhibitory glycine and GABA receptors (GlyR, GABAAR) in spinal cord neurons is controlled by the synaptic scaffold protein gephyrin, and how the receptors in turn shape the clustering of gephyrin at postsynaptic sites. In addition to its high spatial resolution, single molecule localisation microscopy (SMLM) has the unique capacity to gain precise quantitative information about complex biological systems. SMLM thereby gives access to absolute copy numbers and packing densities of GlyRs and gephyrin proteins in spinal cord synapses. The close relationship between glycine and GABA receptors with gephyrin makes receptor-scaffold interactions the target of post-translational regulations that contribute to inhibitory synaptic plasticity. In the same way, receptor-gephyrin interactions can be directly targeted using novel, cell-permeable affinity probes. When applied in living cells, these competing probes can displace neurotransmitter receptors from their synaptic binding sites, raising the prospect of pharmacological intervention to dynamically regulate the strength of inhibitory neurotransmission.

Autores: Specht C. G. 1

Afiliación: DHNS, Inserm, Université Paris-Saclay

Área de la Farmacología: Molecular pharmacology
Dirección de Correo: christian.specht@inserm.fr
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SIMPOSIO / SYMPOSIA 4

Coordinador Dr. Luis Constandil (USACH), auspiciado por A. Hernández y T. Pellisier "Surgical pain: Monitoring and strategies to prevent chronifcation)". Expositores: L. Constandil (USACH), F. Flores (MIT), JI Egaña (UCh), P. Brumovsky (U. Austral Arg).

ESTRATEGIAS FARMACOLÓGICAS PARA PREVENIR EL DOLOR CRÓNICO POSTOPERATORIO. PHARMACOLOGICAL STRATEGIES TO PREVENT POSTOPERATIVE CHRONIC PAIN.

One pain area of recent special interest is postoperative chronic pain. This type of pain refers to acute pain that appears as a result of surgery, which is strictly related to direct tissue damage. However, this acute pain could be transformed in chronic pain because of procedures that can lead to a process called sensitization, which can lead to allodynia and hyperalgesia, a pain that will not respond analgesics. For this reason, the pre-emptive administration of analgesics can reduce central and peripheral sensitization, which in turn reduces postoperative chronic pain. Pre-emptive analgesia is a therapeutic treatment that is initiated before the onset of a pain stimulus (nociceptive stimulus), a concept aimed to prevent and completely block pain signals from surgical wounds from the very first incision of the skin. This pre-emptive analgesia reduces the physiological consequences of nociceptive transmission induced by the procedure, including both the severity of postoperative pain and the possibility of converting acute pain into chronic pain. Currently, nonsteroidal anti-inflammatory drugs combined with opioids are the commonly used protocol, but opioids are under scrutiny due to the opioid epidemic crisis. Our laboratory has identified three important signals involved in the induction of central sensitization and studied how to block them: BDNF overexpression, glial activation, and pannexin-1 channel excitation. Using behavioral studies in rodents, we found that administration of TRkB receptor antagonists, glial inhibitors, or pannexin-1 blockers administered prior to induction of neuropathic pain, can prevent sensitization of pain responses observed in those chronic pain models. Some of these compounds are currently being tested in clinical trials for other purposes, opening future possibilities for their use as pre-emptive agents for chronic postoperative pain.

Autores: Constandil L1; Hernández A1.
Afiliación: Laboratory of Neurobiology, Deparment of Biology, Faculty of Chemistry and Biology, University of Santiago de Chile.

Área de la Farmacología: Neuropharmacology
Dirección de Correo: luis.constandil@usach.cl
Agradecimientos: Fondecyt Nº 1181622 and Basal/Conicyt, CEDENNA, AFB180001, and Proyecto USA1899 – 021943CC-PAP Universidad de Santiago de Chile.

HACIA UN MODELO ANIMAL DE ACTIVIDAD NOCICEPTIVA INTRAOPERATORIA DURANTE ANESTESIA GENERAL. TOWARDS AN ANIMAL MODEL OF INTRAOPERATIVE NOCICEPTIVE ACTIVITY DURING GENERAL ANESTHESIA.

The opioid epidemic is one of the most significant public health crises affecting the United States, a situation only worsened by COVID-19. The number of opioid-induced overdoses in 2020 was higher than in 2019 and close to the peak of 2016. One of the main drivers behind the opioid epidemic is the overuse of opioids for management of pain and nociception. In fact, one of the primary goals of general anesthesia is the proper management of intraoperative nociception, which is typically done by administration of opioids. However, both over- and under-administration of opioids can result in short- and long-term issues. Over-administration can slow recovery in the post-operative period and in extreme cases can contribute to the development of central sensitization and increased opioid requirements after discharge. On the other hand, under-administration of opioids could result in an ineffective to control of nociception and increased risk for development of chronic pain. In all cases, mismanagement of intraoperative nociception might increase post-surgical opioid requirements and contribute to longer-term dependence. In this talk I will explore the possibility of developing an animal model to study the extent to which nociceptive signaling is preserved in peripheral and central nervous pathways during general anesthesia, how opioids can affect nociceptive signaling in those pathways at different doses, and the use of a novel pharmacological strategy to potentiate or even dispense of the use opioids during general anesthesia. This research program has the potential to uncover the nature of nociceptive signaling during anesthesia and provide experimental evidence for decreasing the use of opioids in the operating room.

Autores: Francisco J. Flores

Afiliación: Massachusetts General Hospital

Área de la Farmacología: Neuropharmacology
Dirección de Correo: fflores@mgh.harvard.edu
Agradecimientos: MGH Executive Committee on Research ISF grant # 235552 MIT-Usach MISTI Grant 2022.

MONITORIZACIÓN DE LA NOCICEPCIÓN EN EL INTRAOPERATORIO. INTRAOPERATIVE NOCICEPTION MONITORING.

General anesthesia is a pharmacologically induced, reversible state in which several goals must be achieved. The most prominent (unconsciousness, amnesia and analgesia) are a consequence of the effect of anesthetic drugs on the nervous system. Until a few decades ago, brain monitoring during general anesthesia was based solely on clinical observation and hemodynamic variables. Today, using data derived from electroencephalography (EEG), depth of anesthesia (DoAM) monitors allows clinicians to assess the hypnotic component (unconsciousness and amnesia) while the patient is anesthetized. This has determined that medications are currently administered in a more individualized manner, which has resulted in safer anesthesias and better results. For a long time, the monitoring of nociception followed a much slower pace than that of its "brother" the hypnotic component. Nevertheless, in recent years new technologies have been developed to estimate the nociceptive component during surgery as well as the efficacy of the analgesic intervention. Unlike DoAMs, nociception monitoring is not based solely on EEG recording and analysis. Different manufacturers have developed tools that use other physiological variables to account for the measurement. In this symposium I will review the several of these new technologies, the different physiological principles in which they based their measurements and the clinical data available regarding their use.

Autores: Egaña J. I.

Afiliación: Laboratorio Neurosistemas/CICA, Facultad de Medicina/Hospital Clínico, Universidad de Chile.

Área de la Farmacología: Clinical pharmacology
Dirección de Correo: jiegana@uchile.cl

PREVENCIÓN DEL DOLOR POST-QUIRÚRGICO MEDIANTE EL USO DE UN OLIGODEOXYNUCLEÓTIDO INMUNOMODULADOR - EVIDENCIA PRE-CLÍNICA. PREVENTION OF POSTSURGICAL PAIN THROUGH USE OF AN IMMUNOMODULATING OLIGODEOXYNUCLEOTIDE – PRE-CLINICAL EVIDENCE.

Of the estimated 320 million people undergoing surgery each year, virtually all will develop acute postoperative pain, described as moderate, severe or extreme in 75% of the cases. Unsolved postoperative pain is detrimental for subsequent recovery and impacts the patient's quality of life. Moreover, it can lead to chronic postoperative pain in around 10% of patients with an estimated economic burden of US$43,000 per year/patient. In recent times, the role of the immune system in the mechanisms of pain is receiving serious attention, also for the development of new therapeutic agents. IMT504 is an oligodeoxynucleotide with immunomodulatory and tissue repair properties. Work in our laboratory for the past 15 years has exposed remarkable anti-allodynic and anti-inflammatory effects in various animal pain models. In the present talk, we will present novel data suggesting that, by targeting the immune system and MSCs, pre-emptive IMT504 modifies the response to surgical incision in an anti-allodynic and pro-resolution fashion. Moreover, we will reveal that this approach also results in opioid-sparing effects. Finally, we will address the steps taken thus far in relation to the validation of IMT504 as a therapeutic agent, with the aim of its future use in a variety of pain conditions.

Autores: Julia Rubione, Sandra Sbrascini, Bernardo Miguel, Candelaria Leiguarda, María Florencia Coronel, Carly McCarthy, Alejandro Montaner, Marcelo J. Villar, Pablo R. Brumovsky.

Afiliación: Instituto de Investigaciones en Medicina Traslacional, CONICET-Universidad Austral
Área de la Farmacología: Immunopharmacology
Dirección de Correo: pbrumovs@austral.edu.ar
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SIMPOSIO / SYMPOSIA 5

Coordinador Dr. Jorge Fuentealba (UdeC). Alzheimer Disease: an Update from basic to clinical research. Nibaldo Inestrosa (UMAG), Gonzalo Klassen (UdeC), Carlos Opazo (Florey Institute AU), Jorge Fuentealba (UdeC).

MENOPAUSIA Y DESARROLLO DE LA ENFERMEDAD DE ALZHEIMER. MENOPAUSE AND DEVELOPMENT OF ALZHEIMER´S DISEASE.

Late onset Alzheimer´s disease (AD) is a neurodegenerative disease with gender differences in its onset and progression. In fact, postmenopausal women are most frequently affected by sporadic AD in a ratio 3:1, differently from the incidence in the infrequent hereditary illness occurring in younger patients in a ratio 1:1. A particularly interesting aspect is the role of sex steroids on neuroprotection. Estrogen (E2) deficiency occurring in spontaneous or surgical menopause has been associated to cognitive decline; in this context, several studies have shown that early E2 replacement exerts neuroprotective effects. Here, we will address the role of estrogen deficiency and the role of Wnt signaling in the processes involved in the development of AD, including amyloid precursor protein (APP) processing to form senile plaques and Tau phosphorylation forming neurofibrillary tangles. Since AD is the most prevalent dementia and incurable disease, understanding its molecular pathogenesis could lead to the development of a specific therapeutic strategy.

Autores: Inestrosa NC.1,2 ; Villaseca P.1

Afiliación: 1Center of Excellence in Biomedicine of Magallanes (CEBIMA), University of Magallanes, Punta Arenas Chile, and 2Center for Aging and Regeneration (CARE), Pontifical Catholic University of Chile, Santiago, Chile.

Área de la Farmacología: Neuropharmacology
Dirección de Correo: ninestrosa@bio.puc.cl