SIMPOSIO / SYMPOSIA 3

Coordinardor Dr. Gonzalo Yévenes (UdeC), "New insights in the pharmacological modulation of central synapses". Expositores: G. Yévenes (UdeC), B. Muñoz (U. Indiana), Christian Specth (U. Paris-Saclay)

MODULACIÓN FUNCIONAL DE SINAPSIS INHIBITORIAS MEDIANTE NUEVAS HERRAMIENTAS FARMACOLÓGICAS. FUNCTIONAL MODULATION OF INHIBITORY SYNAPSES BY NOVEL PHARMACOLOGICAL TOOLS.

The inhibitory synapses of the central nervous system are one of the main control systems of neuronal excitability. Both GABAergic and glycinergic neurotransmission contribute to the neuronal inhibition through different mechanisms, which may include fast synaptic inhibition, activation of tonic currents and presynaptic modulation. In line with its critical importance, the mechanisms of action of many clinically relevant drugs, including general anesthetics, anxiolytics, hypnotics, and novel anti-depressive agents, involves the modulation of the inhibitory neurotransmission. Most of the therapeutical actions of these drugs are linked to direct actions on post-synaptic GABAA receptors. On the other hand, the pharmacological modulation of the glycinergic neurotransmission has been not yet translated into clinical applications. Nevertheless, recent evidence has shown that the enhancement of key proteins of the glycinergic transmission, including glycine receptors (GlyRs) and glycine transporters, have beneficial actions against pain. This concept has been highlighted by data from our group and others showing that GlyR modulators displayed analgesic effects on behavioral models of chronic pain. Our recent data show that GlyR subtypes are differentially modulated by molecules of diverse chemical natures, including tricyclic sulfonamides, cannabinoids, natural alkaloids, and tert-butyl phenol analogs. In addition, our studies revealed that the actions of these modulators on GlyRs are related with diverse putative binding sites and allosteric mechanisms. Moreover, we found that these compounds target different elements of the glycinergic neurotransmission. Finally, we determined that the GlyR subunits contribute asymmetrically to chronic pain and to the analgesia induced by glycinergic modulators. Ongoing studies will define a more complete picture of the key neurophysiological targets of the glycinergic neurotransmission, contributing to pave the path for novel therapeutics.

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MECANISMO DE LA PLASTICIDAD SINÁPTICA MEDIADA POR EL RECEPTOR OPIOIDE MU EN EL ESTRIADO DORSAL. MECHANISM OF MU OPIOID RECEPTOR-MEDIATED SYNAPTIC PLASTICITY IN THE DORSAL STRIATUM.

Mu opioid receptors (MORs) are expressed in the dorsal striatum, a brain region that mediates goal-directed (via the dorsomedial striatum), and habitual (via the dorsolateral striatum, DLS) behaviors. Our previous work indicates that glutamate transmission is depressed when MORs are activated in the dorsal striatum, inducing MOR-mediated long-term synaptic depression (MOR-LTD) or short-term depression (MOR-STD), depending on the input. In the DLS, MOR-LTD is produced by MORs on anterior insular cortex (AIC) inputs and MOR-STD occurs at thalamic inputs, suggesting input-specific MOR plasticity mechanisms. Here, we evaluated the mechanisms of induction of MOR-LTD and MOR-STD in the DLS using pharmacology and optogenetics combined with patch clamp electrophysiology. We found that cAMP/PKA signaling and protein synthesis are necessary for MOR-LTD expression, similar to previous studies of cannabinoid-mediated LTD in DLS. MOR-STD does not utilize these same mechanisms. We also demonstrated that cannabinoid-LTD occurs at AIC inputs to DLS. However, while cannabinoid-LTD requires mTOR signaling in DLS, MOR-LTD does not. We characterized the role of presynaptic HCN1 channels in MOR-LTD induction as HCN1 channels expressed in AIC are necessary for MOR-LTD expression in the DLS. These results suggest a mechanism in which MOR activation requires HCN1 to induce MOR-LTD, suggesting a new target for pharmacological modulation of synaptic plasticity, providing new opportunities to develop novel drugs to treat alcohol and opioid use disorders.

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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.

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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.

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