This Week in The Journal

Cellular/Molecular

Opioids Induce Hyperalgesia by Multiple Means

Céline Heinl, Ruth Drdla-Schutting, Dimitris N. Xanthos, and Jürgen Sandkühler

(see pages 16748–16756)

Opioids produce analgesia by activating μ-opioid receptors (MORs) on the central terminals of nociceptive C-fibers and ultimately reducing glutamate release onto dorsal horn neurons. But long-term use or abrupt withdrawal of opioids paradoxically increases pain sensitivity by potentiating C-fiber-evoked responses in spinal neurons. Surprisingly, the mechanisms underlying opioid-induced hyperalgesia vary. Heinl et al. reported that long-term potentiation (LTP) of spinal responses induced by withdrawal of the MOR agonist remifentanil was prevented by NMDA receptor (NMDAR) antagonists. But NMDAR antagonists only partially reduced LTP produced by withdrawal of morphine or fentanyl. These MOR agonists also seemed to activate extraspinal descending serotonergic neurons that facilitate C-fiber-evoked responses. Facilitation increased throughout opioid infusion and continued after opioid cessation, thus contributing to post-withdrawal potentiation. Withdrawal of fentanyl, but not of remifentanil, also enhanced vesicle release at C-fiber terminals. Infusion of both NMDAR and serotonin receptor antagonists eliminated post-withdrawal enhancement of nociceptive responses and thus might reduce opioid-induced hyperalgesia.

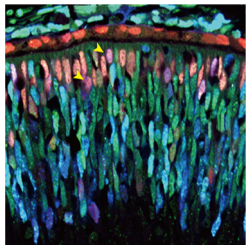
Development/Plasticity/Repair

RAX Activates Otx2 *Transcription in Photoreceptor Precursors*

Yuki Muranishi, Koji Terada, Tatsuya Inoue, Kimiko Katoh, Toshinori Tsujii, et al.

(see pages 16792–16807)

Specialized cell types arise through precise developmental sequences of gene expression and suppression orchestrated by networks of transcription factors. With each step, cells become restricted to fewer possible fates, until they are fully differentiated. Retinal neurons arise sequentially from retinal progenitor cells (RPCs) in a specific order, and generation of photoreceptors is initiated by the transcription factor OTX2. But what triggers *Otx2* transcription? Muranishi et al. identified a portion of the *Otx2* untranslated region—an embryonic enhancer locus for photoreceptor *Otx2* transcription (*EELPOT*)—that drove spatially and temporally appropriate gene expression. RAX, another transcription factor expressed in differentiating photoreceptors, bound to *EELPOT* and initiated transcription. At earlier developmental stages, HES1, a transcriptional repressor activated by NOTCH signaling, bound to *EELPOT*, thus preventing RAX binding. The authors suggest that just before photoreceptor generation, an extracellular signal that activates NOTCH signaling turns off, causing HES1 to vacate *EELPOT*, thus enabling transcriptional activation by RAX.



Otx2 (red) is first expressed in RPCs in the final cell cycle before postmitotic photoreceptors are generated, whereas one of its targets (white) is not produced until after the final cell division. Blue and green label cells undergoing DNA synthesis. See the article by Muranishi et al. for details.

Behavioral/Systems/Cognitive

Striatal Learning Inhibits Hippocampal Learning

Mathieu Baudonnat, Jean-Louis Guillou, Marianne Husson, Matthias Vandesquille, Marc Corio, et al.

(see pages 16517–16528)

Memory systems comprising different brain structures are thought to mediate different types of learning. For example, spatial learning requires the hippocampus, whereas reward-driven instrumental learning involves the striatum. Although these memory systems are largely independent, Baudonnat et al. suggest that activation of striatal memory systems impairs hippocampus-dependent learning. When a visual cue indicated which arm of a maze provided food or morphine, learning-associated phosphorylation of cAMP response element-binding protein (CREB) increased in the striatum and mice learned which arm was rewarded. When lack of overt cues forced mice to engage spatial learning, food reward promoted CREB phosphorylation in the hippocampus rather than the striatum, but mice still identified the rewarded arm. When the spatial task was rewarded with morphine, however, CREB phosphorylation increased in the striatum rather than hippocampus, and mice performed at chance levels. Blocking striatal CREB phosphorylation in this task rescued CREB phosphorylation in the hippocampus, and mice again learned which arm was rewarded.

Neurobiology of Disease

Phosphorylation of Ser129 Increases α-Synuclein Toxicity

Hiroyasu Sato, Shigeki Arawaka, Susumu Hara, Shingo Fukushima, Kaori Koga, et al.

(see pages 16884–16894)

In Parkinson's disease (PD), α-synuclein accumulates in intracellular inclusions in dopaminergic neurons of the substantia nigra (SN), eventually causing cell death. Most aggregated α-synuclein is phosphorylated at serine 129 (Ser129), whereas Ser129 phosphorylation is minimal in normal brain, suggesting that this phosphorylation contributes to α-synuclein accumulation and/or toxicity. To test this, Sato et al. virally expressed a PD-associated form of α-synuclein (A53T) and G-protein-coupled receptor kinase 6 (GRK6)—which phosphorylates α-synuclein on Ser129—in rat SN. A53T α-synuclein was minimally phosphorylated on Ser129 when expressed by itself, but it nonetheless accumulated in granule deposits in SN neurons and caused dopaminergic neurons to degenerate. Coexpression of GRK6 increased Ser129 phosphorylation of A53T α-synuclein and accelerated the loss of dopaminergic neurons without increasing α-synuclein deposits. Neuron loss was not accelerated by catalytically inactive GRK6 or when Ser129 was mutated to prevent phosphorylation. Therefore, phosphorylation of Ser129 does not contribute to α-synuclein aggregation, but potentiates its toxicity.