This Week in The Journal

● Cellular/Molecular

CaMKII-Dependent Modulation of T-Type Channels

A Mechanism for the Direct Regulation of T-Type Calcium Channels by Ca^{2+}/Calmodulin-Dependent Kinase II

Philip J. Welsby, Hongge Wang, Joshua T. Wolfe, Roger J. Colbran, Michael L. Johnson, and Paula Q. Barrett
(see pages 10116–10121)

The biophysical properties of low-voltage-activated (LVA), or T-type, calcium channels underlie their role in dendritic excitation, burst firing, and rhythmic activity in several brain circuits. Compared with their high-voltage-activated cousins, modulation of LVA channels has been relatively unexplored, perhaps because LVA channels were cloned only a few years ago. It is known that calcium/calmodulin-dependent kinase II (CaMKII) enhances α_{1H} but not α_{1G} LVA channel activity by shifting their activation to more negative membrane potentials and increasing their voltage sensitivity. In this week's *Journal*, Welsby et al. demonstrate in recombinant LVA channels that CaMKII regulation of α_{1H} is direct, resulting from phosphorylation of a serine residue in the II–III cytoplasmic linker domain. Because CaMKII does not affect the α_{1G}-type channel, the authors created "G/H" chimeras by exchanging the II–III cytoplasmic linker domains; the α_{1H} II–III domain was required for CaMKII modulation. Glutathione *S*-transferase fusion proteins of the linker domain and functional studies of site-directed mutants identified Ser^{1198} as the critical phosphorylation site. The α_{1H} II–III domain also binds G-protein $\beta\gamma$ subunits leading to channel inhibition. Thus the II–III linker is likely to coordinate multiple regulatory signals for LVA channels.

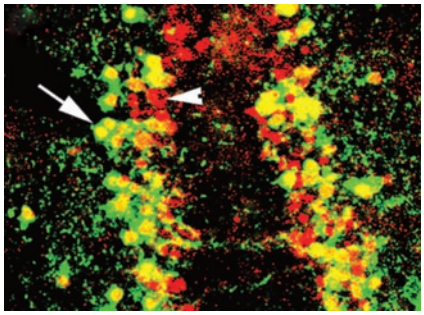
▲ Development/Plasticity/Repair

Lmx1b + Pet-1 + Nkx2.2 = 5-HT

Lmx1b, Pet-1, and Nkx2.2 Coordinately Specify Serotonergic Neurotransmitter Phenotype

Leping Cheng, Chih-Li Chen, Ping Luo, Min Tan, Mengsheng Qiu, Randy Johnson, and Qiufu Ma
(see pages 9961–9967)

Serotonergic neurons require the expression of transcription factors Nkx2.2 and Pet-1, as well as an additional previously undefined factor. Now experiments by Cheng et al. point to the Lim homeobox gene Lmx1b as the third factor necessary for development of the hindbrain serotonergic system. Lmx1b−/− hindbrain neurons lacked expression of genes critical to serotonin synthesis and transport. The authors used electroporation to express Lmx1b, Pet-1, and Nkx2.2 in chick neural tube at embryonic day 2 (E2). Predictably, ectopic expression of any one factor was not sufficient, but combinations of two factors rescued 5-HT-fated cells in some areas, providing clues to the interdependence of the factors. Expression of all three factors rescued the hindbrain serotonin phenotype. End of story? Sorry, it's yet more complicated. The authors propose two unidentified Nkx2.2 cofactors: one to activate expression of Pet-1 and Lmx1b and a second that allows Pet-1 and Lmx1b to direct serotonergic gene expression.



Coronal section through the ventral pons (mouse, E14.5) shows immunostaining of Lmx1b (red) and 5-HT (green). Lmx1b was expressed in all 5-HT cells (yellow nuclei, arrow). A subset of Lmx1b-positive cells was 5-HT negative (arrowhead).

■ Behavioral/Systems/Cognitive

κ-Opioid inhibition in the VTA

κ-Opioid Agonists Directly Inhibit Midbrain Dopaminergic Neurons

Elyssa B. Margolis, Gregory O. Hjelmstad, Antonello Bonci, and Howard L. Fields
(see pages 9981–9986)

Opiate addiction is thought to involve activation of dopamine (DA) neurons in the ventral tegmental area (VTA). Although μ-opioid receptors (MORs) and κ-opioid receptors (KORs) are expressed in the VTA, they have opposing behavioral effects. For example, MOR activation in the VTA produces conditioned place preference in rats, whereas KOR activation produces conditioned place aversion. MOR agonists enhance dopamine release in the nucleus accumbens, whereas KOR agonists reduce dopamine release. MOR agonists are thought to enhance DA indirectly by disinhibition of VTA dopamine neurons, via MORs located on GABAergic nerve terminals. However, the action of KORs is less clear. In this issue, Margolis et al. tested whether KORs directly inhibit dopamine neurons in the VTA. Using voltage recording in brain slices, the authors first classified VTA neurons according to their size and physiological responses as principal, secondary, and tertiary. KOR agonists inhibited a subset of principal cells by activation of G-protein-coupled inwardly rectifying potassium channels. Secondary cells, presumably GABAergic interneurons, were unaffected by KORs. Subsequent immunohistochemistry revealed that KOR-responsive cells were tyrosine hydroxylase-positive, and thus dopaminergic. Given the presence of dynorphin-containing inputs to the VTA, these experiments suggest that endogenous KOR activation can oppose the action of MORs and thus modulate the circuitry involved in motivation and reward.