This Week in The Journal

Dopamine Removes Spike-Time Rules for LTP in Spinal Cord

Jie Li, Theodore J. Price, and Mark L. Baccei

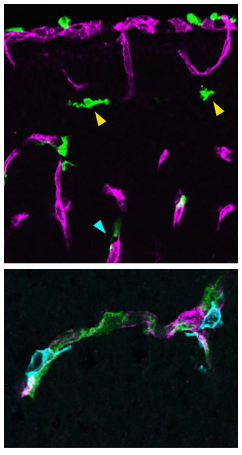
(see pages 350–361)

Like other neural circuits, those transmitting nociceptive information to the brain undergo use-dependent synaptic plasticity. Thus, strong activation of nociceptive pathways can produce long-term potentiation (LTP) that contributes to chronic pain. Such plasticity occurs even at the first synapse in the pathway, where afferent sensory fibers synapse with projection neurons in lamina 1 of the spinal cord dorsal horn. Normally, LTP at these synapses occurs only if postsynaptic neurons spike a few milliseconds after afferent fibers. But in some situations, including after early-life injuries, this spike-timing requirement is lost. Li et al. show that dopamine can cause such a switch from spike time-dependent plasticity (STDP) to spike time-independent plasticity.

Using spinal cord slices, the authors recorded from lamina 1 neurons that project to the parabrachial nucleus, a brainstem structure involved in the transmission of nociceptive signals. Consistent with previous results, synaptic strength did not increase when afferent nerve fibers were stimulated 50 ms before or 10–20 ms after a spike was evoked in the recorded neuron. After an agonist of D1/D5 dopamine receptors was applied, however, stimulation with the same parameters induced LTP. In fact, nerve stimulation alone was sufficient to induce LTP in the presence of the agonist.

Notably, blocking NMDA receptors, which are required for STDP under baseline conditions, did not block LTP induction in the presence of D1/D5 agonist. In contrast, the effect of agonist was eliminated by blocking activation of D5 receptors (D5Rs), G-proteins that act downstream of D5Rs, type 5 metabotropic glutamate receptors (mGluR5), or ryanodine receptors that mediate release of calcium from intracellular stores. Notably, whereas mGluR5 and D5R agonists did not by themselves alter synaptic strength between afferent fibers and spinoparabrachial neurons, adding both agonists led to the potentiation of these synapses. Finally, genetic deletion of D5R not only prevented the removal of STDP rules in the presence of D1/D5 agonists, but also prevented the loss of these rules after neonatal injury.

These results suggest that dopamine acting on D5Rs enables afferent nerve activity to induce spike time-independent LTP by activating mGluR5. This plasticity might sensitize nociceptive circuits, so that previously innocuous stimuli become painful. Therefore, blocking D5Rs may help prevent the development of chronic pain. Future work should identify the source of dopamine in the spinal cord, how its release is triggered, and whether other G-protein-coupled receptors have similar effects.



Embryonic microglia (magenta, top; cyan, bottom) travel along capillaries, where they nearly always contact pericytes (magenta, bottom) rather than vascular endothelial cells (green, both panels). See Hattori et al. for details.

Embryonic Pericytes Stimulate Microglial Proliferation

Yuki Hattori, Haruka Itoh, Yoji Tsugawa, Yusuke Nishida, Kaori Kurata, et al.

(see pages 362–376)

During embryonic development, neural progenitors, postmitotic neurons, glia, and vascular cells cooperate to build the complex architecture of the brain. For example, neurons secrete growth factors that promote the proliferation of endothelial cells that form blood vessels, and endothelial cells in turn produce molecules that promote neural progenitor proliferation and differentiation. Microglia travel along blood vessels as they migrate into the developing brain from the yolk sac, and they produce molecules that regulate neural proliferation, differentiation, migration, synapse formation, and myelination. In return, neurons secrete molecules that can shape microglial gene expression profiles. Adding to these interactions, Hattori et al. report that pericytes—contractile cells that line the outside of blood vessels, providing stability and helping to form the blood–brain barrier—secrete factors that stimulate microglial proliferation.

The authors noted that in the cerebral wall of mouse embryos, slightly more than half of all microglia were attached to capillaries, and nearly all of these microglia contacted pericytes rather than endothelial cells. Depletion of pericytes *in vivo* using a monoclonal antibody greatly decreased microglial proliferation and thus reduced the density of microglia without inducing microglial apoptosis. Conversely, adding pericytes to microglial cultures increased microglial proliferation in the absence of direct contact between cell types.

Consistent with previous work showing that microglia promote the generation of intermediate progenitor cells (IPCs) from neural stem cells (NSCs), *in vivo* depletion of microglia resulted in an increase in the number of NSCs and a complementary decrease in the number of IPCs. Importantly, pericyte depletion led to similar changes in NSC and IPC numbers without substantially increasing microglial phagocytic activity, decreasing endothelial cell proliferation, or altering vascular permeability.

These results suggest that pericytes secrete molecules that enhance microglial proliferation and thus indirectly affect NSC differentiation during brain development. Future work should determine the molecular mechanisms mediating the proliferative influence of pericytes on microglia and explore the possibility of direct effects of pericytes on neural proliferation and differentiation.

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