This Week in The Journal

A Marker for Septum-Projecting Dopamine Neurons

Shabana Khan, Simon Stott, Audrey Chabrat, Anna M. Truckenbrodt, Bradley Spencer-Dene, et al.

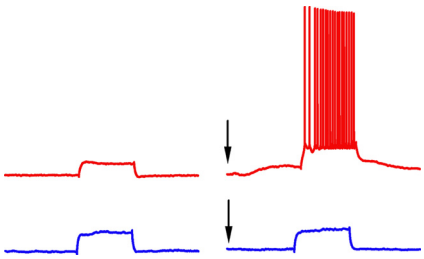
(see pages 2305–2316)

Dopaminergic projections from the midbrain regulate many neural functions, including motor control, motivation, aversion, emotion, and learning. The neurons are divided into two broad populations, residing in the substantia nigra pars compacta and the ventral tegmental area (VTA). Each of these regions is divided into several subnuclei that contain heterogeneous populations of neurons, differing in gene expression profiles, projection patterns, and, presumably, function. Defining the functions of different subpopulations has been difficult, however, because most known markers are expressed in multiple subpopulations. Therefore, identifying genes with more restricted expression would be beneficial.

Kahn et al. have described one such gene, Neurod6, which encodes a transcription factor involved in neuronal fate specification and survival. Neurod6 is expressed along with tyrosine hydroxylase (the rate-limiting enzyme for dopamine synthesis) in several subnuclei of the VTA. All neurons that expressed Neurod6 also expressed the transcription factor OTX2, the calcium binding protein calbindin 1, aldehyde dehydrogenase 1, and gastrin-releasing peptide. Co-expression of these four genes along with two others was previously used to define one of four subpopulations of VTA neurons based on single-cell expression profiling data (Anderegg et al. 2015 FEBS Letters, 589:371). Unlike those genes, however, expression of Neurod6 appears to be restricted to this subpopulation.

Knocking out Neurod6 caused an ~30% reduction in the number of neurons expressing a fluorescent protein (YFP) under the control of the Neurod6 promoter, suggesting that some, but not all, Neurod6-expressing neurons require NEUROD6 for survival. Knocking out Neurod6 also eliminated dopaminergic projections from the VTA to the intermediate lateral septum; projections to other brain areas were not noticeably affected. Retrograde labeling of axons innervating the lateral septum in wild-type animals indicated that Neurod6-expressing VTA neurons project to dorsal, as well as intermediate regions. But not all Neurod6-expressing VTA neurons were retrogradely labeled, and some retrogradely labeled VTA neurons did not express Neurod6.

These results suggest that most Neurod6-expressing dopamine neurons in the VTA project to the lateral septum, and those that project to intermediate regions depend on Neurod6 expression for survival. By enabling selective expression of light-sensitive proteins and designer receptors exclusively activated by designer drugs, this discovery will facilitate future investigation into the functions of dopaminergic projections to the septum.



Under baseline conditions (left traces), injection of a 50 pA current is insufficient to elicit spiking in PFC layer 5 pyramidal neurons. After addition of acetylcholine (arrow, right traces), a 50 pA current elicits spiking in uninjured animals (top traces), but not in animals subjected to peripheral nerve ligation (bottom traces). See Radzicki et al. for details.

Reduced Cholinergic Signaling in PFC during Chronic Pain

Daniel Radzicki, Sarah L. Pollema-Mays, Antonio Sanz-Clemente, and Marco Martina

(see pages 2292–2304)

Damage to peripheral nerves can induce plasticity throughout the nervous system, leading to chronic pain. Injury-induced plasticity is not limited to areas targeted by the affected nerve or even to nociceptive circuits, but extends to brain areas involved in emotion and cognitive function. Thus, chronic pain is typically accompanied by depression and impaired attention, working memory, and decision-making.

Chronic pain in patients and animal models is associated with hypoactivation of the prefrontal cortex (PFC), which has prominent roles in attention and working memory. The cellular and molecular underpinnings of this hypoactivation are poorly understood, but given the importance of acetylcholine in cortical activation and cognitive function, Radzicki et al. hypothesized that alteration in cholinergic signaling is involved. To test this hypothesis, they examined cholinergic modulation of layer 5 pyramidal neurons in slices taken from medial prefrontal cortex of rats subjected to peripheral nerve ligation, a model of chronic pain.

In control neurons, acetylcholine elicited a slow inward current that was blocked by an M1 receptor antagonist. Acetylcholine also elicited an inward current in neurons from injured animals, but the current was smaller than in controls. Furthermore, while acetylcholine increased excitability of control neurons, neuronal excitability was unaffected by acetylcholine in injured rats. In addition, whereas spiking often persisted after stimulation ceased and spike trains were followed by a slow afterhyperpolarization in acetylcholine-treated control slices, persistent spiking was rare and the amplitude of the slow afterhyperpolarization was reduced in injured animals. Finally, although acetylcholine evoked long-lasting depolarization that was sometimes preceded by a hyperpolarizing response in slices from both control and injured animals, the depolarization was smaller and the hyperpolarizing response was larger and more common in neurons from injured animals.

These results suggest that peripheral nerve injury causes hypoactivation of the prefrontal cortex in part by reducing the ability of acetylcholine to increase excitability in layer 5 pyramidal neurons. Additional experiments suggested that this effect stems partly from reduced surface expression of M1 acetylcholine receptors. Additional mechanisms are also likely to be involved, however. Regardless of the mechanisms, restoring the ability of acetylcholine to promote prefrontal activation may boost attention and working memory in chronic pain patients.

This Week in The Journal was written by Teresa Esch, Ph.D.