This Week in The Journal

Sodium Pump Modulates Locomotor Activity in Mice

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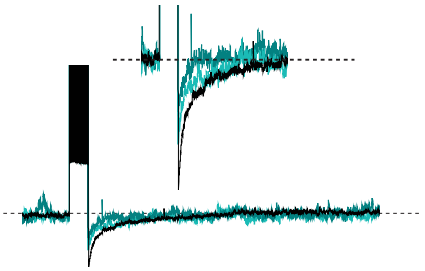
(see pages 906–921)

The Na^+/K^+ ATPase creates and maintains a hyperpolarized resting membrane potential in neurons by exchanging three intracellular Na^+ ions for two extracellular K^+ ions. The rate of pumping depends on the intracellular Na^+ concentration, and when Na^+ concentrations increase during strong neural activity, robust pump activity can cause neurons to become hyperpolarized below normal resting membrane potential. This effect has been documented in several types of neurons. In spinal neurons of *Xenopus* tadpoles, for example, activation of the Na^+/K^+ pump during swimming produces an ultraslow afterhyperpolarization lasting ~1 min. This afterhyperpolarization dampens subsequent activity: swim bouts evoked during the afterhyperpolarization are shorter and weaker than the preceding bout, and this effect is eliminated by the Na^+/K^+ ATPase inhibitor ouabain (Zhang and Sillar 2012 Curr Biol 22:526).

Picton et al. report that the Na^+/K^+ ATPase also regulates burst rate in mouse spinal cord locomotor circuits. The second of two closely spaced locomotor epochs evoked in isolated mouse spinal cords was shorter and weaker than the first. Ouabain prevented reductions in burst frequency and duration, suggesting the reduction depended on Na^+/K^+ pump activity. Furthermore, induction of repetitive spiking produced an ultraslow afterhyperpolarization lasting >20 s in many motor neurons; this afterhyperpolarization was also blocked by ouabain. Notably, the input resistance of cells didn't change during the ultraslow afterhyperpolarization, suggesting it was not mediated by opening of ion channels.

Interestingly, dopamine—which decreases the frequency and increases the amplitude of locomotor-related bursting in ventral nerve roots—increased the duration of the ultraslow afterhyperpolarization, suggesting dopamine regulates Na^+/K^+ pump activity in these neurons. Consistent with this, ouabain increased the frequency of motor neuron bursts during fictive locomotion in isolated spinal cords treated with dopamine, whereas increasing pump activity with monensin decreased burst frequency. Ouabain had no effect on burst frequency in the absence of dopamine, suggesting the Na^+/K^+ pump does not contribute significantly to locomotor activity under baseline conditions.

These results are intriguing because they suggest that neuromodulators influence Na^+/K^+ ATPase function in neurons in ways that alter neuronal excitability. Given that Na^+/K^+ ATPase-dependent afterhyperpolarization has been found in many neurons, the pump may contribute to activity-dependent regulation of more circuits than previously appreciated.



A burst of spikes in a motor neuron is followed by an ultraslow afterhyperpolarization (black traces), which is reduced dose-dependently by ouabain (green traces). See Picton et al. for details.

Accumbens nNOS Neurons Promote Drug Seeking

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(see pages 742–756)

Addictive drugs modify neural circuits involved in motivation and reward, and these changes contribute to relapse after abstinence. In rodents, cocaine and other addictive drugs downregulate glial glutamate transporters in the nucleus accumbens core (NAcore), resulting in increased spillover of synaptically released glutamate. In addition, several classes of addictive drugs increase the activity of matrix metalloproteinases MMP-2 and MMP-9 in the NAcore, and this leads to transient synaptic potentiation and increased drug seeking in the presence of drug-associated cues. Importantly, enhancing glutamate uptake or inhibiting MMPs reduces cue-induced reinstatement of cocaine seeking (Mulholland et al. 2016 Trends Neurosci 39:472).

Smith et al. have uncovered a pathway linking cocaine-induced glutamate spillover and MMP activation. Rats were trained to press a lever to receive cocaine paired with a cue. Lever pressing was extinguished by withholding cocaine and cues and then reinstated by presenting the cue alone. Consistent with previous results, cue presentation increased glutamate levels in the NAcore and promoted lever pressing. An antagonist of metabotropic glutamate receptor 5 (mGluR5) reduced lever pressing, whereas an mGluR5 agonist increased lever pressing in the absence of conditioned cues.

Because cocaine downregulates mGluR5 in principal neurons of the NAcore, the authors hypothesized that the receptors responsible for relapse were expressed on interneurons that express neuronal nitric oxide synthase (nNOS). Indeed, mGluR5 agonist increased extracellular levels of NO, and an nNOS inhibitor reduced agonist- and cue-evoked lever pressing. Furthermore, selective activation of NAcore nNOS-expressing interneurons caused S-nitrosylation of MMP-2 and increased lever pressing in the absence of conditioned cues. Finally, nNOS inhibition prevented cue-evoked increases in MMP-2 and -9 activity, and killing nNOS-expressing neurons reduced cue-induced lever pressing.

Together with previous work, these results suggest that increased glutamate spillover at NAcore synapses activates mGluR5 on nNOS-expressing interneurons, stimulating NO production. NO S-nitrosylates MMP-2, increasing its activity, which may in turn increase activity of MMP-9. Together, these effects help to elicit transient potentiation of excitatory synapses on medium spiny neurons, thus promoting drug-seeking in the presence of drug-associated cues. Inhibition of nNOS, as well as MMPs and mGluR5 (which appears to contribute to addiction more broadly) might therefore prevent cue-triggered drug seeking, a major cause of relapse in addicts.

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