This Week in The Journal

Cortical Suppression of Hippocampal Inputs to Striatum

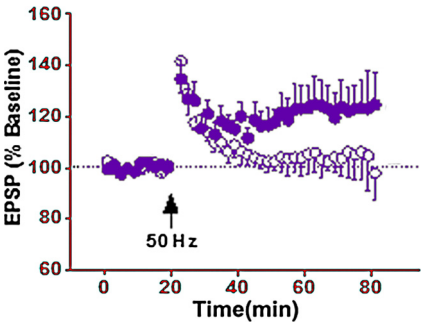
Julie M. Brooks and Patricio O'Donnell

(see pages 7140–7148)

The ventral striatum integrates information from multiple brain areas to motivate behaviors that are appropriate in a given situation. Contextual information is provided by the hippocampus, which drives ongoing oscillations in striatal medium spiny neurons (MSNs). When choices are made, projections from the prefrontal cortex (PFC) produce bursts of spikes and synchrony between the hippocampus and striatum is briefly interrupted. This interruption likely occurs at least in part because PFC bursts temporarily suppress MSN responses to hippocampal afferents. Some of this suppression is mediated by activation of $GABA_A$ receptors in the striatum (Calhoon & O'Donnell 2013 Neuron 78:181).

Brooks and O'Donnell report that kappa opioid receptors (KORs) also contribute to PFC-mediated suppression of hippocampal inputs to the ventral striatum. Whereas a KOR agonist reduced the amplitude of EPSPs evoked in MSNs by stimulation of either PFC or hippocampal afferents, a KOR antagonist blunted the suppression of hippocampal inputs after burst-like stimulation of PFC inputs. Moreover, suppression of hippocampus-driven EPSPs was completely blocked by a combination of KOR and $GABA_A$-receptor antagonists. In contrast, antagonists of $GABA_B$ or cannabinoid receptors had no effect on PFC-induced suppression of hippocampal inputs.

These results suggest that burst-like activation of PFC inputs to the ventral striatum temporarily reduce the influence of hippocampal inputs by triggering release of GABA and dynorphin, the endogenous ligand of KORs. KORs are expressed on glutamatergic and dopaminergic terminals in the ventral striatum, and their activation by dynorphin is thought to inhibit neurotransmitter release. Suppression of glutamate release from hippocampal terminals might increase the influence of PFC, which conveys information about task demands, relative to that of the hippocampus. This might facilitate production of appropriate behavioral responses as reward contingencies change. Given that dynorphin is expressed preferentially in MSNs that express D1 dopamine receptors, future work should address whether PFC bursts selectively attenuate hippocampal inputs to these neurons.



A stimulus that was insufficient to induce LTP in rats that had not undergone extinction training (open circles) was able to induce LTP in rats that underwent such training (filled circles). See Wang et al. for details.

A Pathway to Extinguish Memories of Withdrawal

Weisheng Wang, Yun-Yue Ju, Qi-Xin Zhou, Jian-Xin Tang, Meng Li, et al.

(see pages 7096–7110)

Exposure to cues associated with opiate use often promote drug-seeking behaviors and relapse. Perhaps counterintuitively, cues associated with withdrawal can also trigger drug seeking, because they produce a negative affective state. Breaking the association between cues and withdrawal through extinction training has therefore been proposed as a means to reduce relapse. A more thorough understanding of the molecular mechanisms underlying extinction of withdrawal-associated memories might reveal ways to increase the effectiveness of such training.

The extinction of memories associated with opiate withdrawal can be studied using conditioned place aversion (CPA). In such studies, naloxone is administered in one chamber of a cage, thus precipitating withdrawal symptoms in that context. Rats subsequently avoid the withdrawal-associated chamber. CPA is then extinguished by repeatedly confining the animal to the avoided chamber without precipitating withdrawal. Use of this paradigm (Wang et al. 2012 J Neurosci 32:13763) has shown that extinction of withdrawal-induced CPA requires upregulation of brain-derived neurotrophic factor (BDNF) in the ventromedial prefrontal cortex (vmPFC).

Wang et al. now describe a molecular cascade lying downstream of extinction-induced BDNF expression. Extinction training reduced surface expression of $GABA_A$ receptors ($GABA_A$Rs) in vmPFC without affecting expression of AMPA receptors. Extinction training also facilitated induction of long-term potentiation (LTP) in vmPFC, an effect that was mimicked by a $GABA_A$R antagonist. Importantly, extinction training occluded the effect of the $GABA_A$R antagonist, suggesting that the internalization of $GABA_A$Rs during extinction training underlies the facilitation of LTP.

Blocking the function of dynamin, a component of the endocytic machinery, prevented extinction-associated $GABA_A$R internalization and LTP facilitation while impairing extinction of CPA. Additional experiments suggested that activation of the small GTPase Rac1 and a resulting increase in synaptic levels of the activity-regulated cytoskeleton-associated protein (Arc) were also required for extinction-associated $GABA_A$R internalization and CPA extinction. Finally, reducing activation of the BDNF receptor—which prevents extinction—reduced both the internalization of $GABA_A$Rs and the facilitation of LTP during extinction training.

All together, these results suggest that BDNF promotes extinction of withdrawal-associated memories by activating Rac1, which leads to translocation of Arc to the synapse. There, Arc promotes dynamin-dependent internalization of $GABA_A$Rs, and the resulting decrease in inhibitory regulation facilitates subsequent induction of LTP. Which synapses might undergo LTP to enable extinction of inappropriate aversion should be investigated in future studies.

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