This Week in The Journal

Pedunculopontine Tegmental Nucleus Role in Active Avoidance

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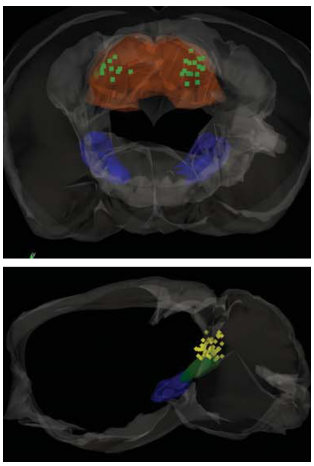
(see pages 4576 – 4594)

Animals learn cues that signal upcoming dangers and respond by performing passive or active defensive behaviors. Tones that predict electrical shock, for example, can induce mice to freeze (a passive behavior) or to exit to a safe chamber (active avoidance). Recognition of cues that elicits passive or active responses depends on the lateral amygdala. From there, however, the circuits controlling passive and active responses diverge: whereas activation of the central amygdala leads to freezing, activation of the nucleus accumbens, a part of the basal ganglia, is required for signaled active avoidance.

How the nucleus accumbens promotes active avoidance is unclear, but inhibition of neurons in the substantia nigra pars reticulata (SNr), one of the main output nuclei of the basal ganglia, might be involved. Indeed, activation of SNr can suppress signaled active avoidance, possibly by inhibiting the superior colliculus, an area that is activated during cue-triggered escape and that drives escape when stimulated. Alternatively, the SNr might inhibit signaled active avoidance through its projections to the thalamus or the pedunculopontine tegmental nucleus (PPT), a midbrain nucleus that contributes to locomotor control.

Hormigo et al. used optogenetic tools to investigate the roles of SNr, PPT, superior colliculus, and thalamus in signaled active avoidance. Activation of SNr terminals in the thalamus did not affect avoidance responses, but activation of terminals in the PPT suppressed these responses. Stimulation of SNr terminals in superior colliculus sometimes suppressed avoidance, but this stimulation also led to the inhibition of PPT neurons, likely by activating SNr collaterals. Therefore, SNr likely suppresses signaled active avoidance primarily by inhibiting neurons in PPT. Consistent with this, inhibiting glutamatergic PPT neurons reduced the proportion of cue-triggered escapes and increased the escape latency, whereas exciting these neurons enhanced escape. In contrast, inhibiting GABAergic PPT neurons increased the proportion of escapes and reduced latency, whereas exciting these neurons suppressed escape.

These results suggest that SNr suppresses signaled active avoidance by inhibiting glutamatergic neurons in the PPT that drive locomotor behaviors. What activates PPT neurons to promote escape in the presence of threat-associated cues remains unclear, but, given that the amygdala and ventral striatum send direct projections to the PPT, these are likely candidates.



Projections from SNr (blue) have terminals (green diamonds, top; yellow diamonds, bottom) in the superior colliculus (orange, top) and PPT (green, bottom). See Hormigo et al. for details.

Astrocyte Fatty Acid Metabolite and Depression-Like Behavior

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(see pages 4606 – 4623)

Astrocytes support nervous system function by regulating extracellular levels of ions and neurotransmitters, providing nutrients to neurons, and releasing neurotrophic factors and gliotransmitters. Disruption of these functions can contribute to various neurological and psychiatric conditions. Several studies have suggested that astrocytes play a role in major depressive disorder. These include postmortem studies showing reduced numbers and altered morphology of astrocytes in people with depression, as well as studies showing altered astrocyte function in animal models of depression. For example, in brain slices from mice that were susceptible to chronic social defeat stress (as indicated by subsequent avoidance of a caged aggressor), astrocyte release of ATP was reduced. Stimulation of ATP release from astrocytes reduced social avoidance in these mice by promoting activation of P2X2 receptors (Cao et al., 2013, Nat Med 19: 773). Xiong, Cao, et al. extend these findings, providing evidence that reduced ATP release stems from decreases in 14,15-epoxyeicosatrienoic acid (14,15-EET), a fatty acid derived from arachidonic acid.

Activation of soluble epoxide hydrolase (sEH), an enzyme that reduces EET effectiveness, was elevated in the prefrontal cortex (PFC) of people with major depressive disorder and in mice that were susceptible to chronic social defeat stress. Consistent with this, levels of 14,15-EET were reduced, while levels of the metabolite 14,15-DHET were elevated, in PFC of defeated (but not resilient) mice. Treatments that increased 14,15-EET levels in the PFC—including injecting the molecule, inhibiting sEH, and knocking out the gene that encodes sEH in astrocytes—reduced social avoidance after defeat and reduced immobility in the forced swim test, another model of depression. In contrast, treatments that decreased 14,15-EET levels promoted these depression-related phenotypes. Importantly, increasing 14,15-EET levels also increased release of ATP from astrocytes, whereas reducing EET signaling reduced ATP release. Finally, preventing activation of P2X2 receptors reduced the antidepressant-like effects of knocking out the sEH gene.

These results support the hypothesis that ATP release from astrocytes in the prefrontal cortex promotes resilience to stressful situations and thus reduces depression-related behaviors stemming from stress. Future work will need to elucidate the molecular mechanisms linking stress to sEH and EET levels, linking EET to ATP release, and linking P2X2 receptor activation to resilience.

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