This Week in The Journal

PPTg Contributes to Reinforcement

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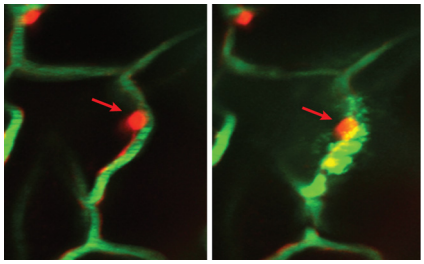
(see pages 38–46)

The pedunculopontine tegmental nucleus (PPTg) is a brainstem structure that has been proposed to have two primary roles: promoting arousal as part of the ascending reticular activating system and controlling movement as part of the mesencephalic locomotor region. The latter function has recently been called into question, however, as accumulating evidence suggests that the PPTg is a basal-ganglia-like structure involved in reinforcement-based learning, decision making, and action selection, rather than a pure locomotor center (Gut and Winn 2016 Mov Disord 31:615). In support of this reinterpretation, the PPTg and basal ganglia are extensively interconnected, and stimulation of the PPTg induces burst firing in midbrain dopaminergic neurons, which project to the striatum and shape reward learning.

The PPTg is distinctive for its large population of cholinergic projection neurons, which are thought to have an essential role in arousal. The nucleus also contains numerous glutamatergic projection neurons, however, and considerably less is known about the functions of these neurons. Yoo et al. now provide evidence that glutamatergic PPTg neurons contribute to reinforcement learning via projections to the dopaminergic neurons in the ventral tegmental area (VTA).

The authors first demonstrated that glutamatergic PPTg neurons project to the VTA, and that optically stimulating these projections produced EPSCs and increased firing rates in dopaminergic and other VTA neurons in brain slices. Optogenetic stimulation of glutamatergic PPTg neurons or their terminals *in vivo* also activated dopaminergic and nondopaminergic VTA neurons. Moreover, *in vivo* optical stimulation was reinforcing: when one of two nosepoke holes was paired with PPTg stimulation, mice showed a preference for the stimulation-paired hole. And remarkably, water-deprived mice preferentially licked a water sipper paired with stimulation of glutamatergic PPTg neurons even when the alternative sipper contained a highly desirable sucrose solution.

These results clearly establish a role for glutamatergic PPTg neurons in reinforcement and demonstrate that this function is mediated at least partly by activation of VTA neurons, including dopaminergic neurons. The work thus expands our understanding of the neural circuitry driving motivated behaviors, providing additional potential targets for treating drug addiction and other conditions involving maladaptive activation of reward pathways.



Pericytes (red, arrow) extend processes along capillaries (green). After blood flow in capillaries is blocked (right), fluid leaks out preferentially near pericyte somata. See Underly et al. for details.

Leaks Occur Near Pericytes after Capillary Occlusion

Robert G. Underly, Manuel Levy, David A. Hartmann, Roger I. Grant, Ashley N. Watson, et al.

(see pages 129–140)

The blood–brain barrier limits the movement of blood-borne molecules and cells into the CNS, thus helping to maintain the ionic balance within the brain and preventing infiltration of toxins and pathogens. The barrier is formed by specialized endothelial cells that are linked together by tight junctions and adherens junctions. Its construction is orchestrated by pericytes, which extend processes along blood vessels and promote expression of tight junction proteins. Pericytes, along with astrocytic endfeet, remain essential for maintaining the integrity of the blood–brain barrier throughout life.

Blockage of CNS blood vessels during ischemic stroke leads to opening of the blood–brain barrier, allowing extravasation of serum proteins and immune cells, which in turn exacerbate neuronal damage. The cellular and molecular mechanisms underlying stroke-induced blood–brain barrier breakdown remain unclear. Upregulation of the matrix metalloproteinases MMP-2 and MMP-9, which break down basal lamina and tight junction proteins, are important contributors to barrier opening, but the cellular source of these proteins is unknown (Jin et al. 2010 Neurobiol Dis 38:376). Loss of pericytes might also contribute to blood–brain barrier degradation, but the temporal relationship between pericyte loss and barrier breakdown is unclear.

To address this question, Underly et al. used two-photon microscopy to track leakage after cerebral capillary occlusion in mice that expressed a fluorescent marker selectively in pericytes. MMP-9 and MMP-2 activity increased around the somata of pericytes and non-pericyte glia cells, respectively, within 30 min of capillary occlusion. Capillary contents (indicated by a fluorescent dye) began leaking into surrounding tissue where MMP activity was elevated. Notably, ~80% of leakage sites were near pericyte somata, even though these somata covered only ~7% of the total capillary length. And inhibiting MMPs decreased capillary leakage selectively near pericyte somata.

These results indicate that upregulation and activation of MMP-9 near pericyte somata contributes to blood–brain barrier disruption after stroke. Whether MMP-9 is secreted by pericytes themselves or secreted by other cells (e.g., leukocytes or endothelial cells) surrounding pericytes is not yet clear. Nonetheless, these data provide additional evidence that inhibiting MMP-9 might improve stroke outcomes by preventing disruption of the blood–brain barrier.

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