This Week in The Journal

Inhibiting Phosphodiesterase 2A Enhances Stroke Recovery

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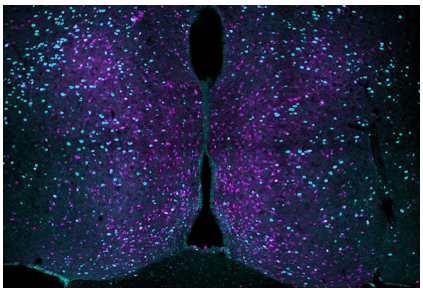
(see pages 8225–8236)

During ischemic stroke, loss of oxygen and nutrients leads to neuron death in the infarct zone. Subsequent disruption of the ionic balance, release of proteases from damaged cells, and increases in inflammatory molecules cause secondary neuronal degeneration in the peri-infarct zone. Left unchecked, this secondary damage can greatly increase functional impairment. Outcomes for stroke patients might be substantially improved not only by restoring blood flow quickly, but also by limiting harmful inflammation, neutralizing toxic molecules, and promoting sprouting of spared axons.

One way to promote neuron growth and plasticity is to activate cAMP response element-binding protein (CREB), which promotes transcription of plasticity-related genes. In fact, overexpressing CREB enhanced axonal sprouting in a mouse model of stroke. Neuronal plasticity can also be stimulated by elevating levels of cAMP or cGMP, either by increasing their synthesis or inhibiting their breakdown by phosphodiesterases (PDEs). Indeed, a selective inhibitor of PDE10A, a phosphodiesterase expressed predominantly in the striatum, promoted recovery in a mouse model of striatal stroke. Similarly, Bechay, Abduljawad, et al. report that inhibiting PDE2A, which is expressed predominantly in the cortex and hippocampus, speeds recovery in a model of cortical stroke.

The PDE2A inhibitor PDE2A-T1 was delivered via intraperitoneal injection starting 5 d after photothrombotic stroke was produced in the motor cortex of young adult or old mice. The treatment led to improved motor function measured after 1 or 9 weeks, increased axonal density in the peri-infarct zone, and greater coactivation of neurons (a measure of functional connectivity) in motor cortex. The inhibitor did not produce discernible effects on the generation of new blood vessels or glia or on microglial inflammatory responses, however. Furthermore, if treatment with the inhibitor was stopped after 4 weeks, recovery plateaued, and by 9 weeks, there was no statistically significant difference between mice treated with PDE2A-T1 and those treated with vehicle.

These results suggest that prolonged inhibition of PDE2A-T1 can improve functional recovery from stroke, perhaps by inducing axonal sprouting or by suppressing degeneration. Future work should determine how long the drug needs to be administered to produce lasting improvement and determine whether activation of CREB or other downstream molecules mediate the effects.



Exposure to pups activates neurons in PrlR-expressing neurons (magenta) in the MPN of sires, as indicated by c-*fos* expression (cyan). See Smiley et al. for details.

Prolactin Promotes Paternal Care

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(see pages 8308–8327)

Newborns of many species require substantial parental care. In mammals, most care is provided by mothers, but in some species, fathers also contribute. The neural circuits and hormones regulating paternal care remain poorly understood, but recent work revealed that prolactin, a hormone named for its role in promoting milk production, controls paternal, as well as maternal behaviors in mice. Smiley et al. sought to determine when and where prolactin acts in the male brain to promote paternal behaviors.

Virgin male mice housed with pups typically kill them. In contrast, males that have recently mated will retrieve and protect abandoned pups, even if the pups are not their own. Smiley et al. found that when sires engaged in paternal care, neurons that express prolactin receptors (PrlRs) were activated in several brain areas linked to paternal behavior, including the ventral bed nucleus of the stria terminalis (vBNST), the posteroventral division of the medial amygdala (MeApd), and the hypothalamic medial preoptic nucleus (MPN). PrlR-expressing neurons in MeApd were also activated in virgin males exposed to pups, but neurons in vBNST and MPN were not. Knocking out PrlR selectively in glutamatergic or GABAergic neurons had no apparent effect on paternal behavior. But knocking out PrlR selectively in neurons that express calcium/calmodulin-dependent kinase IIα (CaMKIIα), which includes both glutamatergic and GABAergic neurons in the MPN and MeApd, significantly reduced paternal behaviors.

Circulating prolactin levels are normally low in male mice, but there is a surge of prolactin release after copulation. No increase in prolactin levels occurred when sires were exposed to pups, however. This suggests that the surge during mating is required for subsequent paternal behavior. Surprisingly, however, blocking the prolactin surge had no effect on subsequent paternal behaviors. In contrast, blocking prolactin during pup exposure greatly inhibited paternal behaviors. Administering prolactin did not promote paternal behaviors in virgin males, however.

These results suggest that mating alters neural circuitry in male mice such that baseline prolactin levels promote paternal behavior, perhaps by promoting activation of neurons in vBNST and MPN. Future work should determine how mating primes circuits and how PrlR-expressing neurons in vBNST and MPN contribute to paternal behavior.

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