This Week in The Journal

Cerebellar Inhibition Reduces Alcohol Consumption

Josh Steven Kaplan, Michelle A. Nipper, Ben D. Richardson, Jeremiah Jensen, Melinda Helms, et al.

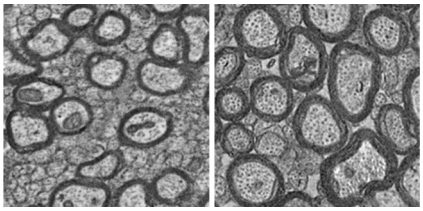
(see pages 9019–9025)

Susceptibility to alcohol abuse has a strong genetic component. Some of this susceptibility may result from genetic influences on physiological and behavioral responses to alcohol. For example, people with a family history of alcohol abuse are able to consume more alcohol without experiencing motor impairment than people with no such family history. A similar phenomenon occurs in mice: C57BL/6 mice are less sensitive to alcohol-induced ataxia than DBA/2 mice. Moreover, given free access, C57BL/6 mice consume more alcohol than DBA/2 mice. Studying these mice might therefore provide insights into the neural circuits involved in the genetic predisposition to alcohol abuse.

Such studies have revealed that alcohol has opposite effects on tonic currents mediated by $GABA_A$ receptors ($GABA_A$Rs) in cerebellar granule cells. Alcohol increased tonic inhibition in DBA/2 mice, but suppressed inhibition in C57BL/6 mice (Kaplan et al. 2013 Nat Neurosci 16: 1783). Because many genetic and phenotypic differences distinguish these mouse strains, however, whether the difference in granule cell responses cause differences in alcohol consumption remained unclear.

Kaplan et al. reasoned that if alcohol-induced increases in tonic inhibition of granule cells reduces alcohol consumption in DBA/2 mice, then increasing such inhibition with $GABA_A$R agonists in C57BL/6 mice should produce a similar effect. Indeed, THIP—a specific agonist of the extrasynaptic $GABA_A$Rs that mediate tonic GABA currents—reduced alcohol consumption in C57BL/6 mice to a level comparable to that in DBA/2 mice. Interestingly, THIP also reduced sucrose consumption in C57BL/6 mice, which were previously shown to have a greater sucrose preference than DBA/2 mice (Lewis et al. 2005 Physiol Behavior 85:546). Importantly, gross locomotor activity and water consumption were unaffected by THIP.

These results suggest that genetic differences in the effects of alcohol on granule cell inhibition influence the amount of alcohol consumed. Additional experiments showed that these effects were likely mediated by reduced excitation of Purkinje cells, the sole output neurons of the cerebellar cortex. This work adds to mounting evidence that cerebellar circuits contribute to reward processing and addiction—an exciting direction for new research.



Myelin (dark rings) in the corpus callosum was thicker 21 days after ERK1/2 was activated in mature oligodendrocytes (right) than in controls (left). See Jeffries et al. for details.

Mature Myelin Sheaths Can Grow Thicker

Marisa A. Jeffries, Kelly Urbanek, Lester Torres, Stacy Gelhaus Wendell, Maria E. Rubio, et al.

(see pages 9186–9200)

Myelination is a major determinant of axon conduction velocity, and thus influences neuronal communication. Not only does the extent and thickness of myelin determine how quickly information reaches a target, but differences in myelination can cause information to travel at different rates along different pathways, allowing information carried by long and short axons to reach a common target simultaneously. Therefore the degree of myelination must be finely tuned. Little is known about this tuning process, however. In particular, what causes the wrapping process to stop when the optimal thickness has been achieved, and whether wrapping can be re-initiated in mature oligodendrocytes to increase myelination are unknown. Although white matter volume certainly increases during skill learning in adults, it is unclear whether this results from generation of new oligodendrocytes or remodeling of pre-existing myelin.

To address these questions, Jeffries et al. activated extracellular-signal regulated kinase (ERK1/2), which promotes myelination, selectively in mature oligodendrocytes in adult mice. ERK1/2 activation increased myelin thickness in the spinal cord, corpus callosum, and optic nerve, without affecting the number of mature oligodendrocytes or the proportion of myelinated axons. The nodes of Ranvier of myelinated axons were shorter in these mice, while paranode regions—where the edges of myelin layers are staggered to allow each to bind to the axon—were longer. Thus, it appeared that ERK1/2 activation induced pre-existing oligodendrocytes to extend and make additional wraps around the axon. In addition, although pre-existing oligodendrocytes do not normally contribute to myelin repair after injury, increasing ERK1/2 activity enabled them to do so.

As expected, ERK1/2-induced hypermyelination resulted in increased axon conduction velocity. Surprisingly, this resulted in few behavioral changes. Cued fear memory, object-recognition memory, motor learning, and motor coordination were all normal in mutant mice. Contextual fear memory, which depends on the hippocampus, was enhanced, however.

These results demonstrate that mature myelinating oligodendrocytes can be induced to produce thicker myelin sheaths in the healthy adult brain, and that the same strategy can be used to enhance remyelination after demyelinating injuries. Whether ERK1/2 activation and growth of mature oligodendrocytes underlie the increases in white matter volume that occur during learning remains unknown. If they do, blocking this activity may reveal whether such increases are required for learning to occur.

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