This Week in The Journal

Brevican Levels Fluctuate with Learning

Hartmut Niekisch, Julia Steinhardt, Julia Bergher, Sara Bertazzoni, Erika Kaschinski, et al.

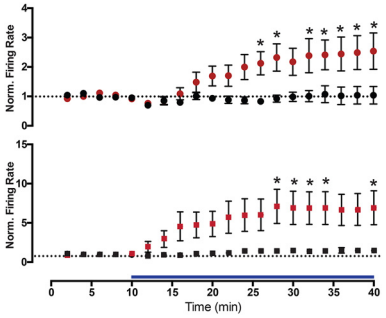
(see pages 7049–7060)

The extracellular matrix (ECM) is a scaffold of glycoproteins and proteoglycans that stabilizes cells and synapses, thereby limiting synaptic remodeling. The appearance of specialized ECM structures called perineuronal nets closes the critical period of elevated synaptic plasticity during development. But assembly and disassembly of ECM occurs locally in adults, and this might regulate the balance between retention of old memories and formation of new ones.

To test this hypothesis, Niekisch et al. trained mice on an auditory discrimination task in which one sound preceded the administration of an electric shock and a different sound indicated that no shock would be administered; mice learned to move to another part of the cage to avoid shock in response to these signals. The authors measured levels of the ECM protein brevican at multiple stages of learning: the avoidance stage, ending when mice learned that sound predicted shock but did not yet discriminate between the two sounds; the acquisition stage, ending when mice began to discriminate the sounds; the retrieval stage, after mice had discriminated sounds for several days; and the long-term recall stage, 4 weeks after successful learning. They also measured protein levels in mice that failed to learn the task and mice that were exposed to unpaired sounds and shocks.

Brevican levels differed across training stages, and the pattern of changes differed depending on brain area (hippocampus or auditory cortex), protein state (full-length or cleaved), and localization (soluble or associated with cell membranes). The level of membrane-associated cleaved brevican was reduced in both the auditory cortex and hippocampus during all stages of training, but not at the long-term recall stage. Levels of soluble fragments were significantly reduced only in animals that failed to learn the task. In contrast, levels of soluble full-length brevican increased during the retrieval stage selectively in auditory cortex. The level was positively correlated with the degree to which animals discriminated sounds and did not change in animals that failed to learn.

These data are consistent with the hypothesis that ECM remodeling occurs during learning. In particular, reduced levels of membrane-associated brevican during a salient event may enable synaptic plasticity. The production and secretion of new full-length brevican may then stabilize synaptic changes, enabling consolidation and long-term retention.



A D_2 receptor agonist (applied during the time indicated by blue bar) increases the activity of striatal cholinergic interneurons in mice with dystonia-linked mutations in *THAP1* (red, top) or *GNAL* (red, bottom), but not in wild-type mice (black, both panels). See Jaunarajs, Scarduzio, et al. for details.

D_2 Receptors Activate Cholinergic Interneurons in Dystonia

Karen L. Eskow Jaunarajs, Mariangela Scarduzio, Michelle E. Ehrlich, Lori L. McMahon, and David G. Standaert

(see pages 7195–7205)

In dystonia, involuntary muscle contractions produce abnormal movements and postures. Numerous genetic mutations have been linked to this condition, but how the mutations cause the symptoms remains poorly understood. Neurodegeneration and structural abnormalities are uncommon in people with dystonia, suggesting that abnormal function of motor-control circuits in the basal ganglia, cortex, and/or cerebellum is responsible. Such abnormal functioning can stem from the disruption of dopaminergic signaling and from excessive activity in striatal cholinergic interneurons (Balint et al., 2018, Nat Rev Dis Primers 4:25).

One common dystonia-causing mutation occurs in *TOR1A*, which encodes an ATPase of unknown function that resides in the endoplasmic reticulum. When *TOR1A* mutations are introduced in mice, striatal function is altered in several ways. For example, activation of dopamine D2 receptors increases spiking in striatal cholinergic interneurons in mutant, but not in wild-type mice. This effect results from excessive activation of muscarinic acetylcholine receptors, which causes D2 receptors to couple with β-arrestin instead of their normal partner, inhibitory Gi/o proteins. Blocking muscarinic receptors prevents these effects and reverses deficits in long-term depression at corticostriatal synapses in *TOR1A*-mutant mice.

Jaunarajs, Scarduzio, et al. asked whether other dystonia-causing mutations have similar effects on striatal function. They first examined mice with mutations in *THAP1*, which encodes a transcription factor that regulates *TOR1A* expression. Unsurprisingly, the effects of *THAP1* mutations were similar to those of *TOR1A*: extracellular acetylcholine levels were higher than normal, a D2 receptor agonist increased activity in cholinergic interneurons, a muscarinic antagonist reversed the effect of D2 agonist, and amphetamine-induced dopamine release was reduced.

Mutations in *GNAL*, which encodes $G\alpha_{olf}$, also caused D2 receptor agonist to increase the firing of cholinergic neurons. But in these mice, extracellular acetylcholine levels were lower than normal, the effect of D2 receptor agonist was potentiated rather than attenuated by a muscarinic antagonist, and amphetamine-induced dopamine release was unaffected. Instead, an antagonist of A_{2A} adenosine receptors, which promote D2-receptor coupling with β-arrestin, prevented the D2-receptor-induced increase in cholinergic interneuron activity in *GNAL* mutants.

These results suggest that the activation of striatal cholinergic interneurons via D2 receptors is a common consequence of dystonia-causing mutations, but it can occur through different mechanisms. Targeting the specific mechanisms in different individuals may therefore be beneficial.

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