This Week in The Journal

Neuromuscular Junction Plasticity Underlies Motor Memory

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(see pages 9186–9209)

Animals quickly adapt motor behaviors in response to sensory feedback. For example, when leg extension causes pain, animals keep the leg flexed. This has been demonstrated in rats: if the tibialis anterior muscle is electrically shocked every time the leg is lowered, the animals learn to keep the muscle flexed for prolonged periods. This occurs even when the cervical spinal cord is severed, indicating it does not require input from the brain; but it requires activation of NMDA receptors in the spinal cord. Hoy et al. confirm that communication between the muscle and spinal cord is required for learning this response, but surprisingly, they show that maintenance of the response depends on postsynaptic plasticity at the neuromuscular junction (NMJ).

Like in previous work, rats with transected spinal cords learned to hold a hind-limb in a flexed position to minimize electric shock applied to the tibialis anterior muscle, and this learning was prevented by treating the spinal cord with lidocaine. Learning was also prevented by transecting the sciatic nerve or by removing the relevant section of spinal cord. Importantly, however, none of these treatments altered the prolonged flexion response after it was learned, suggesting the response was mediated by a peripheral change. Consistent with this, successful training increased the duration of muscle contraction evoked by sciatic nerve stimulation. Furthermore, an increase in flexion duration could be induced after the sciatic nerve was transected by pairing muscle stimulation with stimulation of the distal motor nerve. In addition, the area and intensity of acetylcholine receptor (AChR) staining increased at NMJs after training. Finally, vesicular glutamate transporters were found at NMJs, suggesting that motor nerves corelease glutamate and acetylcholine, and intramuscular injection of an NMDA receptor antagonist disrupted both new learning and maintenance of previously learned responses.

These results suggest that repeated pairing of motor nerve and muscle stimulation potentiates the postsynaptic muscle response by increasing the expression of AChRs at the NMJ. Like long-term potentiation at central synapses, this potentiation depends on the activation of NMDA receptors. Future work should determine whether similar plasticity occurs if animals are trained with a nonelectrical noxious stimulus.

Vesicular glutamate transporters 1 (blue, top left) and 2 (blue, top right) are coexpressed with the vesicular acetylcholine transporter (green, top) and acetylcholine receptors (red, top) at NMJs on the tibialis anterior muscle. After motor training (bottom right), the density of acetylcholine receptors at these NMJs was higher than in untrained NMJs (bottom left). See Hoy et al. for details.

Sleeping Sickness May Disrupt Adenosine Signaling

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(see pages 9306–9316)

Trypanosomiasis, commonly called sleeping sickness, is caused by single-celled parasites (trypanosomes) transmitted to people by tsetse flies. Trypanosomes proliferate in the blood, lymph, and, eventually, the CNS. This results in a variety of neurological symptoms, the most common of which is a change in sleeping patterns. Unlike

numerous other infectious diseases that induce fatigue, however, trypanosomiasis is not typically associated with increases in the total amount of sleep per day. Instead, it leads to sleep fragmentation, excessive daytime sleep, and nighttime insomnia. Rijo-Ferreira et al. previously showed that disruption of the circadian clock accounts for many sleep disturbances associated with trypanosomiasis. The authors now suggest that abnormal adenosine signaling also plays a role.

By 85 d after trypanosome injection, infected mice spent more time awake and less time in slow-wave or rapid eye movement (REM) sleep during the light period—the normal inactive period—than healthy mice. In addition, slow-wave sleep episodes were shorter and less likely to be followed by an REM episode in infected mice than in controls. Whereas slow-wave activity in healthy mice peaked after prolonged wakefulness in the dark period and declined throughout the light period as sleep drive decreased, such activity varied relatively little over 24 h in infected mice. Finally, sleep deprivation led to increases in slow-wave activity and the duration of slow-wave sleep in healthy mice, but these effects were diminished in infected mice.

These results suggest that trypanosome infection disrupts the regulation of sleep by sleep drive, which normally increases while an animal is awake. Because accumulation of extracellular adenosine in the brain during wakefulness is an important mediator of sleep drive, the authors asked whether adenosine signaling was disrupted in infected mice. To assess this, they examined the effects of an adenosine A1 receptor (ADORA1) antagonist on paired-pulse facilitation at hippocampal synapses. Whereas the antagonist reduces facilitation in normal mice, it had no effect in infected mice, where facilitation under baseline conditions was similar to that caused by ADORA1 antagonists in controls.

These results suggest that impaired sleep drive resulting from blunted adenosine signaling contributes to sleep disturbances in trypanosomiasis. Future work should examine the ability of ADORA1 agonists and other mediators of adenosine signaling to restore sleep drive in infected animals.

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