

This Week in The Journal

Hypocretin Contributes to Morphine Withdrawal Symptoms

Ronald McGregor, Ming-Fung Wu, Brent Holmes, Hoa Anh Lam, Nigel T. Maidment, et al.

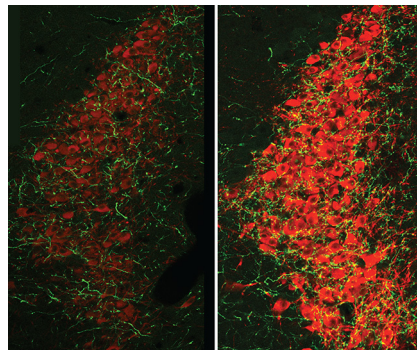
(see pages 255–263)

Repeated use of heroin, cocaine, or related drugs can produce long-lasting changes in multiple brain areas, thus promoting continued drug use despite negative consequences. One area affected by these drugs is the lateral hypothalamus, which houses neurons that produce hypocretin (also called orexin). These neurons help drive goal-directed behaviors in response to internal states (such as hunger) or external stimuli that signal the availability of reward, including drugs of abuse. Drug-associated stimuli increase the activity of hypocretin neurons, and remarkably, the number of hypocretin-expressing neurons is much higher in people addicted to heroin than in control subjects. Similarly, chronic morphine administration increases the number of hypocretin-expressing neurons in rodent hypothalamus, presumably by increasing hypocretin levels in neurons that previously produced this peptide at undetectable levels.

Given that hypocretin neurons project throughout the brain, increases in hypocretin expression may have wide-ranging downstream effects. Investigating these effects in mice, McGregor et al. focused on three brainstem areas that produce norepinephrine and are thought to contribute to unpleasant consequences of withdrawal: the locus coeruleus and the A1 and A2 clusters. Daily injections of morphine for 2 weeks approximately doubled the density of hypocretin-expressing fibers and significantly increased the expression of tyrosine hydroxylase (required for norepinephrine synthesis) in the locus coeruleus. In contrast, morphine did not affect hypocretin innervation or tyrosine hydroxylase levels in A1/A2 clusters. Importantly, tyrosine hydroxylase did not increase in the locus coeruleus if hypocretin neurons were killed before morphine treatment. Furthermore, although killing hypocretin neurons did not prevent mice from developing a preference for a chamber

paired with morphine administration, it reduced locomotor sensitization to morphine, reduced physical and affective symptoms of withdrawal, and prevented the development of conditioned aversion to a chamber paired with naloxone treatment after chronic morphine administration.

These results suggest that chronic morphine treatment increases hypocretin release and tyrosine hydroxylase production selectively in the locus coeruleus, possibly resulting in increased norepinephrine release in target areas. Future work should determine where norepinephrine release increases and the extent to which this is required for the development of withdrawal symptoms. Finally, the results add to evidence suggesting that targeting the hypocretin system may reduce withdrawal symptoms and thus reduce relapse in people addicted to opiates.



After mice receive morphine for 14 d (right), the density of hypocretin-expressing axons (green) and the expression of tyrosine hydroxylase (red) in the locus coeruleus are much higher than normal (left). See McGregor et al. for details.

Exercise Reduces Inflammatory Microglia in Brain

Kaitlin B. Casaletto, Cutter A. Lindbergh, Anna VandeBunte, John Neuhaus, Julie A. Schneider, et al.

(see pages 288–298)

Brain damage resulting from concussion, blood vessel blockage, infections, and even normal aging processes leads to activation of microglia, which initiate inflammatory responses. Although these responses are important for clearing debris and repairing damage, chronic inflammation is

detrimental and contributes to neurodegenerative diseases. Blocking the destructive effects of microglia while maintaining the beneficial effects may therefore help to slow disease progression and promote healthy aging. Remarkably, studies in animals have suggested that this goal might be achieved through exercise. In support of this, Casaletto et al. show that microglial activation in some brain areas is inversely correlated with physical activity levels, particularly in people with inflammatory conditions.

The authors examined postmortem brain tissue from elderly volunteers who had undergone yearly assessments of activity level, motor function, and cognition before they died. Immunostaining and morphological assessment were used to determine the proportion of microglia that were highly activated in different brain areas, and levels of synaptic proteins and pathological hallmarks of several neurodegenerative conditions were quantified. Bivariate correlation analysis indicated that activity levels were inversely related to the proportion of activated microglia in the caudate and the inferior temporal gyrus, and these relationships were strongest in brains with evidence of infarcts and high levels of Alzheimer's disease (AD) pathology, respectively. Microglial activation in the caudate was unrelated to synaptic protein levels or cognition, but microglial activation in the inferior temporal gyrus was inversely related to both of these measures. Moreover, mediation analysis indicated that reductions in the proportion of activated microglia in the inferior temporal gyrus partly accounted for the positive relationship between physical activity and both synaptic protein levels and cognitive function in people with high levels of AD-related pathology.

These results suggest that increasing physical activity can reduce detrimental microglial activation in people with AD pathology and thus can reduce synaptic damage and cognitive decline. Notably, many people exhibit AD-related pathology without behavioral symptoms; staying active may make such people resilient to cognitive consequences. Together with previous studies showing that exercise generally enhances cognition and mood, this work should help motivate people to keep their resolution to get more exercise.

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