This Week in The Journal

Role of Spinal Microglia in Stress-Induced Pain Sensitivity

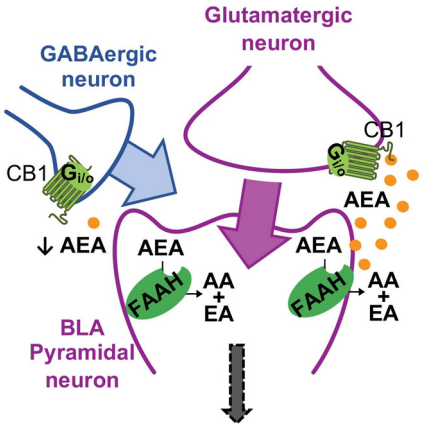
Caroline M. Sawicki, January K. Kim, Michael D. Weber, Timothy D. Faw, Daniel B. McKim, et al.

(see pages 1139–1149)

Stressful experiences activate the sympathetic nervous system, resulting in norepinephrine release in various tissues. Besides increasing heart rate and blood pressure to increase nutrient supply to muscles needed for fighting or flight, norepinephrine activates the immune system to enable quick responses to tissue damage. And prolonged or repeated stress alters the balance of different types of immune cells—including microglia, the primary immune cells of the CNS. Specifically, stress increases the proportion of cells with proinflammatory phenotypes. Proinflammatory cytokines released by such cells contribute to the psychological effects of stress, including the promotion of withdrawal from physical and social activity. These behaviors likely facilitate recovery from acute stressors, but they may become maladaptive after chronic stress, leading to depression and anxiety disorders (Weber et al., 2017 Neuropsychopharmacology 42:46).

In addition to psychological effects, both stress and inflammation have been linked to the development of chronic pain. Sawicki et al. therefore asked whether stress increases pain sensitivity by activating microglia. To answer this question, they subjected mice to repeated social defeat, which was previously shown to increase mechanical pain sensitivity, activate microglia in the brain, and produce anxiety-like behaviors. Repeated social defeat also increased labeling of P2Y12, a receptor involved in microglial chemotaxis, in the cap of the dorsal horn, the target of peripheral pain fibers. Levels of several proinflammatory cytokines and their receptors were also elevated in the spinal cord of stressed mice, but no peripheral immune cells were detected in the spinal cord. Importantly, after microglia were eliminated using a pharmacological agent, repeated social defeat no longer induced mechanical hypersensitivity, and some stress-induced increases in cytokines and receptors were attenuated.

These results indicate that social stress can increase pain sensitivity in the absence of injury by activating microglia in the spinal cord's dorsal horn. Elucidating the molecular mechanisms of this effect might therefore lead to improved treatments for stress-associated chronic pain conditions.



Increasing FAAH in BLA pyramidal neurons reduces AEA levels, leading to increases in presynaptic GABA release and reduced expression of fear and anxiety-like behaviors. See Morena et al. for details.

Effects of Amygdala Cannabinoids on Fear and Anxiety

Maria Morena, Robert J. Aukema, Kira D. Leitl, Asim J. Rashid, Haley A. Vecchiarelli, et al.

(see pages 1275–1292)

Cannabinoids influence emotions, including fear and anxiety, by acting on type 1 receptors (CB1Rs) in the amygdala, hippocampus, prefrontal cortex, and other brain areas. Neurons can produce two types of endocannabinoids, *N*-arachidonylethanolamide (AEA; released tonically) and 2-arachidonoylglycerol (2-AG; released when cells are highly activated). These molecules act on CB1Rs on presynaptic terminals of GABAergic, glutamatergic, and neuromodulatory neurons, and they reduce neurotransmitter release. CB1R activation usually reduces anxiety and relaxes people. Similarly, activation of CB1Rs in rodents typically reduces fear responses and anxiety-like behaviors (e.g., avoidance of bright rooms and open spaces), whereas reducing CB1R activity has the opposite effects. But sometimes people experience paranoia and panic attacks after using exogenous cannabinoids, and anxiety-like effects can be elicited in rodents when high doses of cannabinoids are administered (Lutz et al., 2015 Nat Rev Neurosci 16:705). These opposing effects might stem from differences in activation of CB1Rs across neuron types and brain areas.

To elucidate the role of endocannabinoid signaling in the amygdala, Morena et al. used a virus to overexpress fatty acid amide hydrolase (FAAH), an enzyme that breaks down AEA, primarily in pyramidal neurons of the basolateral nucleus of the amygdala (BLA) in rats. As expected, this transiently reduced AEA levels. Based on previous work, the authors predicted that overexpressing FAAH would increase stress responses and produce an anxiety-like state. They found the opposite: when FAAH was overexpressed, stress-induced elevation of blood corticosterone levels was attenuated and rats were less likely to avoid a lighted chamber or the open arms of an elevated plus maze. FAAH overexpression did not impair fear conditioning, but it reduced responses to fear-associated stimuli on subsequent days. Importantly, the reduction in fear responses was blocked by antagonists of $GABA_A$ receptors, but not of glutamate receptors, in the BLA.

These results suggest that pyramidal neurons in the BLA tonically release AEA, which reduces GABA release from inhibitory inputs. Overexpressing FAAH increases hydrolysis of AEA, thus disinhibiting GABA release. Consequently, pyramidal cells are inhibited and less likely to evoke fear and anxiety-like behaviors. Notably, previous work suggested that increases in FAAH during acute stress reduces the effects of AEA on glutamatergic inputs to BLA pyramidal cells, thus increasing these cells' output. Future work should determine how such synapse-specific effects of AEA might be achieved.

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