Molecular Interaction between Stress and Pain

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CHRONIC pain and stress are common bedfellows. Pain is stressful. Stress is painful. We use the words "pain" and "stress" in overlapping ways to describe the subjective experience of each. We know from personal experience that we get headaches when we are experiencing a stressful situation. Saying "My landlord is a headache" means you find dealing with your landlord stressful. Is this just language, or is there a physiologic basis linking pain to stress? In this issue of Anesthesiology, Ciszek *et al.*[1] report on the molecular details that underlie the interaction between stress and pain as manifested by chronic elevation of catecholamines and nociceptive behaviors in rats.

"… patients living in a setting where stress is chronic … [experience] a higher prevalence of chronic pain."

The "stress response" involves local and systemic enhancement of signaling through the release of catecholamines and corticosteroids from the adrenal glands. Norepinephrine and epinephrine are released from the adrenal medulla in response to sympathetic activation in a pulsatile manner throughout the day. In the setting of stress, both the frequency and the amplitude of catecholamine boluses released increase.

Acutely, extreme stress is associated with analgesia—"stress-induced analgesia" related, at least in part, to the enhancement of descending inhibitory systems.[2] This phenomenon is manifested when a soldier is acutely injured in the field or an athlete is injured during a sporting event, but they do not remember experiencing pain during this period.

Paradoxically, in patients living in a setting where stress is chronic, such as in patients with chronic anxiety and post-traumatic stress disorders, there is a higher prevalence of chronic pain. This association has been demonstrated in many pain conditions, including arthritis, fibromyalgia, temporomandibular disorders, low back pain, chronic postoperative pain, and irritable bowel syndromes.[3] The physiology linking long-standing chronic pain and stress is not well understood. Some evidence suggests that long-standing chronic stress may be associated with increased plasma levels of epinephrine although it is not clear whether this relationship is generalizable.[3] Also, several important chronic pain conditions, including Chronic Regional Pain Syndrome, arthritis, and low back pain, seem to involve dysregulated catecholamine signaling in the periphery.[3–5]

In this work, the authors demonstrated that inhibition of catechol-*O*-methyltransferase (COMT, the enzyme that metabolizes catecholamines) results in upregulation of systemic and central nervous system concentrations of catecholamines and nociceptive behaviors in previously normal rats. By inhibiting the metabolism of catecholamines, the basal concentrations are increased. After treatment with a COMT inhibitor, these rats demonstrated increased nociceptive responses. They withdrew from being poked with small von Frey filaments (light hairs that are normally not painful). The rats also had an exaggerated response to stimuli that would be expected to be mildly troublesome. Rats that had their adrenal glands removed did not develop enhanced nociceptive responsiveness when COMT was inhibited, pointing to the importance of systemic catecholamines released by the adrenal glands rather than sympathetic neurons in this phenomenon. This state of catecholamine excess induces a situation that in some way mimics clinical syndromes of complex widespread pain, such as fibromyalgia and migraine that are often associated with increased responsiveness to stimuli. In this study, the rats even avoided bright lights, which is similar to the photophobia associated with migraine. However, it does not physiologically mimic stress-induced catecholamine release because it is only the basal concentrations that are elevated due to reduced metabolism rather than the amplitude and frequency of the pulses that are increased during stress.

Perhaps the experimental paradigm of inhibition of catecholamine metabolism is more representative of genetically induced differences in COMT enzyme activity. COMT enzyme activity is one element that contributes to individual variability in catecholamine metabolism. It varies, in part, because of differences in the COMT genotype that result in differences in enzyme expression and activity.[6] The variability

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in COMT enzyme expression and function is likely a significant factor in the manifestation of human pain conditions. Patients with COMT genotypes that result in proteins that do not metabolize catecholamines well experience increased pain in labor, burn, trauma, and surgery.[6] Human genetic variants that are associated with poor enzyme activity are also linked to chronic pain syndromes. It is not known on a molecular level how increased catecholamines exacerbate pain. In this article, Ciszek *et al.*[1] shed light on a potential mechanism.

Epinephrine activates α_1-, α_2-, β_1-, β_2-, and β_3-adrenergic receptors (ARs). At physiological concentrations, the effects on βARs predominate. Previous studies in animals have shown that blockade of β_2- and β_3ARs prevents the increased nociceptive responsiveness caused by COMT blockade. This finding may be translatable to clinical care. In clinical studies, the nonspecific β-blocker propranolol improves pain report in various pain syndromes, including fibromyalgia and temporomandibular disorders.[7] This association is not universally applicable. COMT genotype-based treatment of burn patients showed worsened rather than improved pain scores when propranolol was administered.[8] In addition, treatment with propranolol is limited by bradycardia, hypotension, sedation, and sexual dysfunction. Selective antagonists for β_2AR (butoxamine and ICI-118551 used in this study) and β_3AR (SR 592230A) exist but have not found clinical utility to date. Perhaps, this study presages an increased interest in these and related compounds.

βARs are important for signaling in both central and peripheral neurons, as well as in multiple other cell types. The findings reported by Ciszek *et al.* are particularly exciting because they provide evidence that receptors in peripheral, not central, locations are important for the enhancement of nociceptive responses by excess β-adrenergic signaling. In this study, peripheral β_2- or β_3AR antagonists prevented the increased responsiveness to the normally not noxious von Frey fiber poke, whereas intrathecal and intracerebroventricular administration of the drugs proved ineffective. This finding is important because the use of peripherally restricted drugs would prevent central side effects, such as the sedation observed with propranolol. The compounds used in this study are not peripherally restricted but did not have obvious central side effects in the animals studied by Ciszek *et al.* The cell types expressing the β_2-/β_3ARs responsible for the pain effect remain to be identified. Their identification will provide important information as to the mechanism of their effects, as well as potential targets for new drug development.

A surprising finding in these studies was that sex made no difference. Previous studies of preclinical and clinical COMT-dependent pain have shown that the effects are increased in female animals and women.[6] Many generalized pain disorders have female predominance. In this model, blockade of catecholamine breakdown led to equal nociceptive enhancement in rats of both sexes. It may be that the specific changes found in existing mutations in COMT have sex-specific expression or that there is sex-dependent epigenetic modulation. There is emerging evidence for congruent modulation of CpG island methylation in the promoter regions of genes for estrogen and COMT.[9] This type of methylation is important for the expression of estrogen and the COMT enzyme. This work raises many interesting questions about the role of peripheral adrenergic activation in chronic pain that await further clarification.

The modulation of pain by catecholamines has a long history but one that continues to grow as we explore the functions of catecholamines in local, regional, and widespread pain conditions. Much of the recent interest has focused on the role of catecholamines in the brain and spinal tissue. The report by Ciszek *et al.* reminds us that the stimulation of peripheral ARs may constitute a pain-supporting site of action amenable to novel treatments, which potentially avoid many of the troublesome central side effects that have plagued recent analgesic development efforts.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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