Interesting Findings in an Initial Clinical Study of Neuropeptides and Pain

The article by Kilts et al. [1] in this issue of Pain Medicine explores new territory in clinical pain. As has been true for prior exploratory work, the initial maps of an area will likely be modified by additional studies. In addition, as is true for many worthy papers, this manuscript raises as many questions as it resolves. This article [1] is an initial clinical correlation study of pain with levels of neurosteroids. Neurosteroids are extremely interesting pain-modulating molecules that are produced within the central nervous system from cholesterol or progesterone. Neurosteroids join with endogenous opioids, serotonin, and other molecules as key components of the pain modulatory system. Neurosteroids can enhance gamma-aminobutyric-mediated neuronal inhibition, while reducing glycine-induced inhibition [2]. Understanding of the mechanism of action of endogenous opioids was enhanced by the recognition that the opioids act on different classes of receptors, which mediate different opioid effects [3]. In certain circumstances, different neurosteroids seem to have variant actions. Allopregnanolone and some other neurosteroids are often associated with elevated pain thresholds [2,4,5], whereas the sulfated form of dehydroepiandrosterone (DHEAS) has been associated with reduced pain thresholds and allodynia [6]. The role of serotonin in modulating pain [7] was enhanced by the recognition that different pain transmission pathways, such as the trigeminal nerve were more sensitive to serotonin [8,9]. Pain modulation became more complex with the recognition that chronic pain may be associated with alterations in the normal complement of pain-modulating transmitters and their receptors [10]. Emotional and physical stress also interface with pain modulation. The “gating model” provided a conceptual framework to consider the ways that emotional state could interact with pain modulation [11]. Acute stress may elevate pain thresholds [12] whereas repeated or chronic stress may lower pain thresholds [13,14].

The potential roles for neurosteroids in pain modulation are intriguing. Neurosteroids are produced rapidly in the brain from cholesterol or progesterone. Allopregnanolone, one of the neurosteroids discussed by Kilts et al. [1], is derived from progesterone and thus may be sensitive to changes in progesterone levels. Levels of neurosteroids vary with the estrus cycle in rodents [12] and likely with the menstrual cycle in women. Neurosteroids could contribute to some phenomena such as variations in migraine associated with menstrual phases. One could argue that a distinguishing feature of humans is relatively large head size at birth. Without elevation of pain threshold at the time of delivery, human child birth and hence survival of the species would be problematic. An area of future research is the variation of neurosteroid levels associated with acute and chronic stress and how possible variations in neurosteroid levels associated with stress relate to stress-induced changes in pain thresholds.

Kilts et al. [1] chose to correlate neurosteroid levels with perceived levels of pain in 90 veterans who served after September 11, 2001. Many were Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) combat veterans. This is a complex subject group. There is a frequent association of pain, posttraumatic stress disorder (PTSD) and prolonged post-concussion symptoms including headache among OIF/OEF combat veterans [15,16]. Consequently, markers of pain level such as neurosteroid levels can be confounded by coexistent stress, alteration in sleep [17], and residuals of traumatic brain injury [15,16]. In spite of the complexity of the study group, the authors did find correlations between pain levels and neurosteroid levels that were consistent with findings from animal studies. The findings that allopregnanolone levels were inversely associated with low back pain and chest pain, and that DHEA levels were inversely associated with muscle soreness are consistent with animal findings indicating that allopregnanolone and DHEA attenuate pain [2,4,5]. That DHEAS levels were positively associated with chest pain is consistent with animal studies indicating that DHEAS reduces pain thresholds [6]. Why the level of every neurosteroid did not correlate in an expected fashion with all of the pain types queried is the subject for future research.

A surprising finding was that neurosteroid levels did not correlate with headache pain levels. There are several reasons why the authors may not have observed a correlation between headache pain levels and neurosteroid levels. I will discuss a few of the possibilities. First, headache is a diverse category of pain disorders that includes primary and acquired headache disorders [18]. It is likely that many of the members of the study group who complained of headaches had posttraumatic headaches, which can have features of several primary headache...
types including tension headaches and migraine. Post-traumatic headaches among those who served in OIF/OEF usually have features of migraine [19–21] and may in part reflect sleep deprivation [17]. Therefore, it may be necessary to have a more detailed questionnaire about headache pain than was used in the aforementioned study [1] in order to delineate associations between different forms and intensities of headache pain that exist in combat veterans and neurosteroid levels. Understanding the lack of correlations between headache pain and neurosteroid levels is a challenge for future studies. Future studies might also consider the interactions between stress disorders such as PTSD, neurosteroid levels and different types of pain.

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References


