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Balancing Nociception in Cycling Females

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Among the most important discoveries in the 60s is the now well-acknowledged fact that the central nervous system exerts a dynamic influence on nociceptive and other somatovisceral information processing. This discovery led to the Gate Control theory [9] and then to the discovery of descending control mechanisms, initially inhibition [2] followed later by facilitation (4). These discoveries from research in animals, were quickly adopted and applied to human pain. One such translated concept, in addition to Gate Control, was “descending noxious inhibitory control” (7,8), or “DNIC,” in which some neurons in the spinal cord are inhibited when a noxious stimulus is applied in a region outside that neuron’s excitatory receptive field. Although it was initially described in rats, methods to induce and assess DNIC in humans were soon developed [11]. In fact, DNIC provides a good explanation for the phenomenon of counter-irritation

This recognition that pain perception depends on a dynamic balance of inhibitory and excitatory mechanisms helps inform the problem of individual differences in pain. One of the most important of the many factors that contribute to individual differences is sex/gender; thus considerable research exists on the topic [5].

Obvious, but complex contributors to sex differences in nociceptive mechanisms are sex steroid hormones. Of particular and logical interest, therefore, are possible influences of the ovarian cycle. As reviewed in Sherman and LeResche [12], findings are decidedly mixed, with some showing significant cyclical effects, others none. Even when cyclical effects are found, patterns differ between studies.

In this issue of *Pain*, Tousignant-Laflamme and Marchand [13] address this problem uniquely. Instead of asking how experimental acute pain varies across the menstrual cycle, they engaged a deceptively simple, but insightful approach, asking whether DNIC varied. In a carefully controlled study in healthy women whose cycles were confirmed by hormone assays, the authors used immersion of the right arm in ice-cold water (i.e., the cold pressor test, CPT) to induce DNIC. They found that, whereas there were no cyclical changes in the painfulness of the CPT or in any measure of pain to acute thermal stimulation of the left arm (threshold, tolerance, mean pain), immersion of the right arm in cold water decreased thermal pain to a greater extent in the ovulatory phase than it did in other phases (menstrual and luteal). In other words, across the menstrual cycle in healthy women, the painfulness of a noxious stimulus A is influenced indirectly by cyclical variation in the ability of an extraneous noxious stimulus B to inhibit the central consequences of A. The resulting reduction in pain is greatest during the ovulatory phase.

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The findings raise at least five issues. First, do the results increase knowledge of estradiol and progesterone influences on DNIC? Tousignant-Laflamme and Marchand found that, during the ovulatory phase, the higher the progesterone levels, the weaker the DNIC. They rightly conclude, however, that modulation of DNIC by hormones needs further study, not only because some of their subjects were on combined oral contraceptives, but also because the issue is confounded by endogenous production of neurosteroids in various parts of the CNS.

Second, what is the significance of greater DNIC during the ovulatory phase? Tousignant-Laflamme and Marchand do not speculate, but perhaps greater DNIC when women are in their fertile period provides a mechanism to focus attention so as to facilitate conception. For example, in women and rodents, pain of the skin is decreased during vaginal stimulation, the central effects of which, in rats at least, is greater when the rats are fertile [1]. Such thinking raises several questions. Is DNIC greater during pregnancy? Does it change across the course of pregnancy? Is DNIC engaged or could it be engaged during labor/delivery to improve birth outcome?

Third, what happens to DNIC in chronic pain conditions? Is DNIC increased or decreased across the menstrual cycle or differentially affected in different parts of the cycle? Johannesson and colleagues [6] studied the DNIC mechanism in women who suffered from “provoked vestibulodynia.” DNIC mechanisms were intact in these women, all of whom were tested during their follicular phase. In reviewing the literature, the authors found, however, that DNIC is influenced inconsistently by different chronic pain conditions, which led them to suggest that the nature of the influence of chronic pain conditions on DNIC may depend on whether the condition is “regional (e.g., trapezius myalgia) or generalized (e.g., fibromyalgia),” as well as on whether the condition is “intermittent or more continuous.” Johannesson and colleagues did not know, of course, that DNIC might vary across the menstrual cycle. Thus, another factor that could contribute to inconsistencies across studies is when during the cycle DNIC is assessed.

Fourth, what happens when an individual suffers from two painful conditions, one or both of which may be influenced by the ovarian cycle? Could one condition be considered a “DNIC inducer” and the other a “DNIC recipient?” And could the influence of one or the other be affected by the cycle? For example, in female rats a relatively benign surgical procedure (partial hysterectomy) was found to eliminate symptoms produced by bladder inflammation in one stage of the rat’s cycle [10]; i.e., the procedure produced a “silent bladder inflammation” during that stage. Since, as reviewed in ref. 10, it is known that the severity of symptoms produced by bladder inflammation varies with estrous stage, it may be that the control surgical procedure acted to increase DNIC during that stage. While this possibility may sound farfetched, it addresses the important clinical seriousness of the lack of pain symptoms when potentially dangerous pathology occurs and how little this problem is recognized or understood. For example, could DNIC be involved in the common and potentially life-threatening problem in pregnant women of symptomless bladder infection [3]?

Fifth, and finally, what is the relevance of Tousignant-Laflamme and Marchand’s findings to sex differences in pain? Despite a field full of inconsistent results, virtually everyone agrees that, overall, females experience more pain than males. Much of the research that attempts to understand this fact generally seeks to understand sex differences in excitatory processes. Tousignant-Laflamme and Marchand’s interesting findings join those of the minority of others to remind us that an individual’s current pain experience is a result of a dynamic balance between central neural excitatory *and inhibitory* processes, some of which may be influenced by other dynamic processes such as the ovarian cycle.

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