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Editorial comment

Conditioned pain modulation: A useful test paradigm in research and in clinical practice

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In this issue of the *Scandinavian Journal of Pain*, Gullander et al. publish an interesting study [1] on how conditioning heat pain attenuate experimental muscle pain in men and women. Their main research question was whether the modulation of pain by a conditioning stimulus differed between males and females. Previous studies have shown conflicting results [2]. Conditioned pain modulation (CPM) [4] was previously called DNIC (diffuse noxious inhibitory control). The latter term is now reserved for specific lower brainstem mediated inhibitory mechanism that was described in animal research first by Le Bars et al. [3]. A number of different CPM-paradigms have been used, and in two recent articles it was shown how results can differ within the same subject depending on the choice of the conditioning stimulus (CS – that causes a CPM) or the test stimulus (TS – the effect of which is inhibited by the CPM) [5,6]. Several independent factors influence the CPM result, as reviewed by Matre [7].

Since muscular pain is common and a major reason for sick leave and disability, intramuscular stimulation as test stimulus has special interest. Gullander and her colleagues induced muscle pain with electrical stimulation via needles inserted in the tibialis anterior muscle, and they used 30 s of painful contact heat to the contralateral volar forearm as the conditioning stimulus. They carefully chose and executed their methods; thus, the conditioning stimulus was calibrated for each person to match pain intensity of 50 on a 0–100 Visual Analogue Scale and the test stimuli were a fixed ratio (1.1 and 1.6) of each individual's pain threshold. Such individualization of the CPM paradigm must be important but is not in general use. Often all subjects in a study of CPM receive the same conditioning stimulus. This could mean that the conditioning stimulus is only slightly painful to some subjects and intolerable to others.

It is well known that excitatory and inhibitory effects on pain perception vary in women during their menstrual cycle [8]. Therefore, Gullander and colleagues were also careful and examined all women in the ovulatory phase of their menstrual cycle, i.e. days 12–14 after the first day of a menstruation [1].

Gullander and colleagues did not find any difference in CPM effect between men and women. This is in contrast to the majority of previous studies [2]. One reason for this discrepancy could be the CPM paradigm used by Gullander and her colleagues with an intra-muscular test stimulus. Another reason could be their careful testing of female subjects only during the ovulatory phase, the phase of the menstrual cycle that is expected to give highest CPM in women [8].

An additional interesting finding is the fact that 6 of 40 healthy volunteers were CPM non-responders. Are these subjects at risk for developing chronic pain because they have ineffective pain inhibiting mechanisms? We know that chronic pain patients in general when tested show less CPM than controls, but that CPM is particularly lacking in patients suffering from fibromyalgia, irritable bowel syndrome, and temporomandibular pain syndrome [9–11]. CPM – testing has been used to identify patients at high risk of having chronic pain after surgery and therefore should receive intensified treatment before, during, and after surgery [12]. Very interestingly, a recent article found that CPM was increased in pain patients after treatment with ketamine and to a lesser degree after morphine and placebo [13].

Gullander and her colleagues found that non-painful conditioning stimuli also caused a detectable, but smaller CPM-effect. This underscores the fact that CPM is a complex paradigm, and that emotional and contextual factors play important roles [14,15]. We need careful research, like the present study by Gullander et al. in order to find how CPM can be used in both research and in clinical practice.

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