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Original Reports

Expectations Modulate Heterotopic Noxious Counter-Stimulation Analgesia

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Abstract: The present study examined the contribution of expectations to analgesia induced by heterotopic noxious counter-stimulation (HNCS) in healthy volunteers assigned to a control group or 1 of 3 experimental groups in which expectations were either assessed (a priori expectations) or manipulated using suggestions (hyperalgesia and analgesia). Acute shock-pain, the nociceptive flexion reflex (RIII-reflex), and shock-related anxiety were measured in response to electrical stimulations of the right sural nerve in the baseline, HNCS, and recovery periods. Counter-stimulation was applied on the contralateral forearm using a flexible cold pack. A priori expectations were strongly associated with the actual magnitude of the analgesia induced by HNCS. In comparison to the control condition, suggestions of hyperalgesia led to an increase in RIII-reflex amplitude and shock-pain, while suggestions of analgesia resulted in a greater decrease in RIII-reflex amplitude, which confirms that the analgesic process normally activated by HNCS can be blocked or enhanced by the verbal induction of expectations through suggestions. Changes in shock-anxiety induced by these suggestions were correlated to changes in shock-pain and RIII-reflex, but these changes did not emerge as a mediator of the association between manipulated expectations and HNCS analgesia. Overall, the results demonstrate that HNCS analgesia is modulated by expectations, either from a priori beliefs or suggestions, and this appears to be independent of anxiety processes.

***Perspective:** This study demonstrates that a priori and manipulated expectations can enhance or block HNSC analgesia. Results also suggest that expectations might influence responses to analgesic treatments by altering descending modulation and contribute to observed deficit in pain inhibition processes of chronic pain patients.*

***Key words:** Expectation, heterotopic noxious counter-stimulation (HNCS), nociceptive flexion reflex (RIII-reflex), anxiety, descending modulation, analgesia.*

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A wide range of psychological factors is known to modulate pain perception as well as physiological responses to analgesic treatments. One such factor is expectations, or the positive or negative experiences anticipated as a result of a given intervention.[19,29] A well-recognized manifestation of this is placebo analgesia, during which a treatment that has no inherent therapeutic effect induces pain relief.[27,39,48,50] An individual's expectations can also lead to the development of adverse effects, as observed in nocebo hyperalgesia.[9,17]

Both positive and negative expectations are thought to be influenced by verbal suggestions as well as previous experiences and conditioning.[30,39,62,64] Substantial evidence supports the implication of the endogenous opioid systems in the mediation of placebo effects by expected analgesia.[1,5,8,25,36] As for nocebo hyperalgesia, anticipatory anxiety is thought to activate the cholecystokininergic system, which in turn facilitates pain transmission.[6,7,56]

Several studies support the possibility that placebo-induced pain inhibition and nocebo-induced facilitation occur in part through the activation of descending modulatory pathways. Some of these modulatory mechanisms can be activated experimentally by heterotopic noxious counter-stimulation (HNCS), during which a noxious stimulus (conditioning stimulus) inhibits another noxious stimulus (test stimulus) applied on a different part of the body[34,43] (see also[11] for review). The diffuse analgesic effect triggered by this experimental procedure is generally thought to reflect, at least in part, the activation of diffuse noxious inhibitory controls.[51,53,68,69] Also known as conditioned pain modulation, this experimental model has been used extensively in clinical studies to assess the integrity of pain regulatory systems in various chronic pain populations.[10,31,44,47,65,70]

Most relevant to the present study, it was shown that HNCS analgesia can be altered by psychological factors, including pain catastrophizing,[23] attention,[32,40,41] and expectations.[22] In this last study, individual a priori expectations were reinforced in a first group of participants expecting that HNCS (hand immersion in cold water) would decrease pain induced by noxious electrical stimulation (expectations of analgesia) and in a second group expecting that HNCS would increase this same pain (expectations of hyperalgesia). The authors reported that pain as well as the amplitude of the spinal nociceptive flexion reflex (RIII-reflex) was decreased in participants with expectations of analgesia but not in participants with expectations of hyperalgesia. This suggests that expectations can alter HNCS analgesia through descending modulation processes. However, the specific contribution of expectations remains to be determined, as these results have not yet been confirmed by a direct comparison with a control condition. In addition, the contribution of a priori expectations should be controlled for and tested independently in order to separate their effects from verbally induced expectations provided by an experimenter.

Therefore, the aim of the present study was to further investigate the impact of expectations on pain and analgesia induced by HNCS. We examined the modulatory effect of HNCS induced by cold pain on responses to electrical shocks administered to the sural nerve in healthy subjects randomly assigned to a control group or 1 of 3 experimental groups in which expectations were either assessed (1 group) or manipulated by suggestions (2 groups). Moreover, we explored the potential contribution of anxiety to the association between expectations and HNCS analgesia. In line with previous studies, we hypothesized that expectations will predict the magnitude of HNCS analgesia, as evidenced by changes in pain responses, and that anxiety will mediate this association.

Methods

Ethics and Subjects

All experimental procedures conformed to the standards set by the latest revision of the Declaration of Helsinki and were approved by the Research Ethics Board of the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM). Recruitment was done through flyers distributed throughout the CRIUGM and Université de Montréal's campus. A telephone contact was initiated with interested participants and a series of questions ensured they met all inclusion criteria (good health, no prior history of pain problems or psychiatric disorders, no previous exposure to experimental pain procedures). All participants gave written informed consent prior to the experimental session, acknowledged their right to withdraw from the experiment without prejudice, and received a compensation of $15 per hour for their travel expenses, time, and commitment.

Sixty-four healthy university students and young professionals volunteered to participate in the study. Pretests were done to assess pain and RIII-reflex thresholds and familiarize individuals with the pain sensation and visual analog scales (VASs). In 4 subjects (1 male and 3 females), extremely low pain tolerance made it impossible to reach 120% of RIII-reflex threshold (see below), which led to their exclusion. The final sample comprised 60 healthy subjects (38 females and 22 males) with a mean age of 24.1 $\pm$ 4.1 years. Subjects were pseudorandomly assigned to 1 of the following 4 groups: 1) Control; 2) Measure of Expectation; 3) Suggestion of Hyperalgesia; or 4) Suggestion of Analgesia.

Noxious Stimuli

Electrical Stimulation (Test Stimulus)

Degreased skin over the retromaleolar path of the right sural nerve was stimulated by a pair of custom-made surface electrodes (1 cm^2; 2-cm interelectrode distance). Transcutaneous electrical stimulation (trains of 10 $\times$ 1-ms pulses at 333 Hz) was delivered with an isolated DS7A constant current stimulator (Digitimer Ltd, Welwyn Garden City, Hertfordshire, UK) triggered by a Grass S88 train generator (Grass Medical Instruments, Quincy, MA) and controlled by computer with a stimulus presentation program (E-Prime 2; Psychology Software Tools, Sharpsburg, PA). Shock intensity was adjusted individually to produce a stable RIII-reflex and moderate pain.

Cold Pain (HNCS)

HNCS was produced by a flexible cold pack (15 $\times$ 20 cm) filled with 500 mL of frozen gel. The cold pack was applied for 2 minutes to the subject's left contralateral forearm and covered most of the anterior forearm surface. When applied, it was approximately $-12^{\circ}C$ and produced moderate pain (see Groups' Characteristics and Baseline Ratings below).