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Experimental muscle pain impairs descending inhibition

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Abstract

In chronic musculoskeletal pain conditions, the balance between supraspinal facilitation and inhibition of pain shifts towards an overall decrease in inhibition. Application of a tonic painful stimulus results in activation of diffuse noxious inhibitory controls (DNIC). The aims of the present experimental human study were (1) to compare DNIC, evoked separately, by hypertonic saline (6%)-induced muscle pain (tibialis anterior) or cold pressor pain; (2) to investigate DNIC evoked by concomitant experimental muscle pain and cold pressor pain, and (3) to analyze for gender differences. Ten males and 10 age matched females participated in two sessions. In the first session unilateral muscle pain or unilateral cold pressor pain were induced separately; in the second session unilateral muscle pain and unilateral cold pressor pain were induced concomitantly. Pressure pain thresholds (PPT) were measured around the knee joint before, during, and after DNIC induction. Cold pressor pain increased PPT in both males and females with greater increases in males. Hypertonic saline-evoked muscle pain significantly increased PPT in males but not in females. When cold pressor and muscle pain were applied concomitantly the PPT increases were smaller when compared to the individual sessions. This study showed for the first time that two concurrent conditioning tonic pain stimuli (muscle pain and cold pressor pain) cause less DNIC compared with either of the conditioning stimuli given alone; and males showed greater DNIC than females. This may explain why patients with chronic musculoskeletal pain have impaired DNIC.

Keywords

Experimental muscle pain; Inhibition; DNIC; Cold pressor

1. Introduction

The inhibitory control of nociceptive neuronal excitability in animals is manifested through inhibitory circuits operating principally at the segmental level and pathways that originate at higher central nervous system sites, such as cerebral cortex, thalamus, and brainstem (e.g. periaqueductal grey; raphe nuclei, rostroventral medial medulla). One manifestation of such inhibitory influences is that associated with diffuse noxious inhibitory control (DNIC). DNIC is a reduction in pain in response to application of painful stimuli outside the area of pain. In general, painful heterotopic tonic stimuli decrease pain induced by phasic noxious stimulation applied extrasegmentally [2,4,18,19,39]. Initial studies showed that application of noxious heat to the arm results in decreased responses to painful stimuli in the legs [28]. More recent data

shows that in addition to descending inhibition, the same sites can also facilitate pain and activity of dorsal horn neurons [36,43,48]. Hence the excitability of the spinal circuitry is a result of a balance between descending inhibition and facilitation. There is increasing evidence that this balance may be disturbed in chronic pain conditions in human subjects [23,27] and plays a role in maintaining central sensitization and widespread hyperalgesia in animal models of pain [11,36,46,47]. The descending control is particularly inefficient in patients with chronic musculo-skeletal disorders such as osteoarthritis [24], fibromyalgia [24] and temporomandibular pain [5]. It would therefore be of basic mechanistic interest to study if DNIC can be impaired by experimentally induced musculoskeletal pain (e.g. hypertonic saline, glutamate, capsaicin).

In healthy volunteers and patients different techniques have used to induce DNIC. The most commonly used techniques to evoke DNIC are heat pain [34], cold pain [2,21,51,52], ischemic pain by a tourniquet applied to arms or legs [23,24] or muscle pain [10,18]. Age [10,50], but not gender in general [3,12,38] seems to influence DNIC. Further when muscle pain is used to induce DNIC more efficient DNIC is induced in males [14] which could be one mechanistic explanation for the female predominance in chronic musculoskeletal pain conditions.

Based on the above observations, the aims of the present experimental human study were (1) to compare DNIC evoked separately by hypertonic saline (6%)-induced muscle pain and cold pressor pain, (2) to investigate DNIC evoked by concomitant experimental muscle pain and cold pressor pain, and (3) to analyze if there were gender specific differences.

2. Materials and methods

2.1. Subjects

Ten healthy males (mean age: 22.6 years; age range: 20–30 years) and ten age matched healthy females (mean age: 22.6 years; age range: 21–26 years) participated in the current study. None of the subjects had previous injuries that interfered with normal somatosensory functioning in the assessed limbs. Informed consent was obtained from each subject. The study was approved by the local ethics committee (VN20060024).

2.2. Protocol

Subjects sat in a chair without armrest. Feet were on the floor with 90 degree in knee joint.

2.2.1. Pain rating—Subjects rated the pain intensity on a 10 cm electronic visual analog scale (VAS) and ratings were sampled and stored on a computer every 1 s (0 – no pain, 10 – worst imaginable pain). The area under the muscle pain intensity curve (VAS_{AUC}) was calculated (arbitrary units) as a sum of the values sampled every 1 s from start of the experiment until the pain ratings returned to zero.

2.2.2. Pressure pain—A pressure algometer (Somedic, Hörby, Sweden) was used to assess pressure pain thresholds (PPTs). The pressure was applied at a rate of 30 kPa/s, with a 1 cm [2] diameter probe. All participants were instructed to push a button when they felt that the pressure was just barely painful. PPTs from 5 test sites around both knee joints were measured before, during and after pain induction. The five test sites selected in randomized order were located (1) 2 cm proximal to the superior lateral edge of patella, (2) 2 cm proximal to the superior edge of patella, (3) 2 cm proximal to the superior medial edge of patella, (4) 2 cm distal to the inferior lateral edge of patella, (5) 2 cm distal to the inferior medial edge of patella. PPTs were collected when the tonic pain was above 4–5 on the VAS scale (approx. 0.5–1.0 min). PPT was measured again 5 min after the tonic pain had returned to zero. Once the baseline thresholds were known the pressure was increased rapidly up to approx 70% of the expected

threshold and then slowly increased by 30 kPa/s. This was done to have enough time for assessment during the pain session.

2.2.3. Muscle pain—A total of 0.5 ml 6% hypertonic saline was injected over 15 s into the left tibialis anterior muscle 5 cm from the lower rim of patella. Subjects rated the pain intensity on the visual analog scale. The tibialis anterior muscle was selected for the saline induction to mimic clinical studies where muscle pain was present in another segment than where DNIC was induced [23,24].

2.2.4. Cold pressor pain—The left hand up to the wrist was immersed into stirred ice water (1–2 °C) for 5 min. Subjects rated the pain intensity on the visual analog scale. When pressure pain threshold measurement was finished around right and left knee, subject withdrew the hand from the ice water and kept the hand at the level of heart until the pain returned to zero. Only volunteers who in the initial training session could maintain the hand in the water for 5 min were included. Technically it was difficult if less time was available for assessment.

The study consisted of two individual sessions. *In the first session* muscle pain and cold pressor pain were induced on two separate occasions. The sessions were randomized and at least 1 month elapsed between two experiments. *In the second session* muscle pain and cold pressor pain were induced simultaneously. To match the pain profiles the saline injection was started 60 s before the hand was immersed into ice water. The volunteers rated the total pain intensity of the saline and the cold evoked pains on a single VAS. Session 1 and 2 were separated by at least 1 month.

2.3. Statistical analysis

PPTs were analyzed by repeated measures ANOVA (RM-ANOVA) with within-group-factors of sites (5 sites), side (left and right), and time (before, during, and after pain). Gender was taken as between groups factors. The area under the VAS curve (AUC) which represents the overall pain intensity was analyzed by one-way ANOVA between genders. The AUC for muscle pain and cold pressor pain in the first session was compared with AUC in the second session by using RM-ANOVA. The increment of PPT was calculated by subtracting PPT before pain stimulation. The increment data was analyzed by RM-ANOVA with factors of session (muscle pain, cold pressor pain and combine pain) and gender. The Student–Newman–Keuls (SNK) test was used as post-hoc test in case of significant factors. $P < 0.05$ was considered significant.

3. Results

3.1. Pressure pain thresholds

Males had higher PPT than females (ANOVA: $F_{1,19} = 9.7$, $P < 0.01$). There were no significant differences in PPTs between left and right knee for either males or females.

There was a significant difference between sites (ANOVA: $F_{4,76} = 15.5$, $P < 0.001$; SNK: $P < 0.05$). The lowest PPT was obtained from the site 2 cm away the medial upper corner of patella.

3.1.1. The first session

Muscle pain: PPTs were higher during saline-evoked muscle pain than before or after pain for males (Time $\times$ gender: ANOVA $F_{2,38} = 17.1$, $P < 0.001$; SNK: $P < 0.05$). Females showed no significant increases in PPT during or after saline evoked muscle pain. The increases in PPT were significantly higher in males than females (ANOVA: $F_{1,19} = 19.6$, $P < 0.001$; SNK: $P < 0.05$) (Fig. 1).

Cold pressor pain: PPTs were higher during cold pressor pain than before and after pain in both males and females (Time $\times$ gender: ANOVA $F_{2,38} = 18.2$, $P < 0.001$; SNK: $P < 0.05$) and the increase in PPT was higher for males than for females (ANOVA: $F_{1,19} = 19.6$, $P < 0.001$). The increases in PPT occurred bilaterally during cold pressor pain; however, increases were greater for the knee ipsilateral to the cold pressor pain (ANOVA: $F_{1,19} = 8.7$, $P < 0.01$). The increases in PPT observed during cold pressor pain were higher than during saline evoked muscle pain (ANOVA: $F_{1,19} = 19$, $P < 0.001$; SNK: $P < 0.05$) (Fig. 2).

3.1.2. The second session—During concomitant muscle and cold pressor pain the PPT significantly increased compared to before and after pain (ANOVA: $F_{2,38} = 20.1$, $P < 0.001$; SNK: $P < 0.01$). The increases in PPT were similar between males and females, and between ipsilateral and contralateral sides. However, the increases in PPT during combined cold pressor and muscle pain were smaller than in the first session for males, but similar between sessions for females (ANOVA: $F_{2,38} = 11.6$, $P < 0.001$; SNK: $P < 0.05$) (Fig. 3).

3.2. VAS score

3.2.1. The first session—Pain intensity (VAS area under curve) was similar between males and females in response to the saline evoked muscle pain (males: 617 ± 128 (arbitrary units); females: 703 ± 134) or the cold pressor pain (males: 1632 ± 252 ; females: 2011 ± 264). However, subjects experienced greater pain to the cold pressor pain than of the saline evoked muscle pain (ANOVA: $F_{2,38} = 58.3$, $P < 0.001$; SNK: $P < 0.05$) (Fig. 4).

3.2.2. The second session—Combined application of muscle pain and cold pressor pain produced significantly higher pain intensity (3303 ± 324 (VAS area under curve in arbitrary units)) (SNK $P < 0.05$) than with muscle pain (660 ± 93 cm) or cold pressor pain (1822 ± 183 cm) also (first session). Pain was not different between males and females (males: 3398 ± 447 cm; females: 3208 ± 468 cm) (Fig. 5).

4. Discussion

The current study showed that both muscle and cold pressor pain can trigger DNIC in males and females with men showing the most potent inhibition. Cold pressor pain caused greater pain than hypertonic saline-induced muscle pain suggesting pain intensity relates to the level of DNIC observed. However, when the two conditioning pain stimuli were given concomitantly, the evoked DNIC was less effective despite a higher perceived pain intensity by the subjects.

4.1. Descending inhibition versus facilitation

The classical studies examining DNIC in animals show inhibition of spinal dorsal horn (SDH) neurons after a noxious stimulus applied to any body region remote from the excitatory receptive field of the neurons [9]. These studies parallel human studies which show analgesia in areas after a noxious stimuli has been applied to areas remote from the site of testing [28].

Supraspinal sites both facilitate and inhibit nociception and involve similar brain nuclei. Since both facilitation and inhibition of nociception occur simultaneously, the net output is measured as either predominately inhibition or facilitation. Human studies measuring 'DNIC' are actually measuring this balance between inhibition and facilitation. Therefore, the overall increase in 'DNIC' in the current study might be due to shift in the balance between the masking of facilitatory influences or enhancement of inhibitory influences or a combination of both.

4.1.1. Human experimental and clinical studies—The heterotopic character of endogenous analgesia in the spinal system has been demonstrated psychophysically [26,37,

53] and electrophysiologically [2,7,13,39,41,53] in healthy volunteers [18,54] and patients with neurogenic pain [4]. Decreased overall inhibition, i.e. less efficient DNIC, is suggested in people with a number of chronic pain conditions including myofascial temporomandibular disorder [5], chronic low back pain [34], fibromyalgia [23,27], complex regional pain syndrome [9], painful osteoarthritis (OA) [24] chronic tension-type headaches [40], and irritable bowel syndrome [52]. The current study, initiated the combined stimuli by first applying the painful stimulus to the muscle, followed by application of the cold pressor test suggesting that induction of the two concomitant conditioning painful tonic stimuli produces less DNIC than either of the individual conditioning stimuli given alone. Interestingly, in patients with a chronic musculo-skeletal pain condition (OA), that presented with a deficient DNIC showed normal DNIC after total knee replacement in a pain-free state [24]. Thus, the ongoing pain observed clinically, may result in less effective DNIC, or increased facilitation that is masking the DNIC.

Alternatively, the current study could be influenced by expectation of a painful response. Modulating expectation verbally prior to a DNIC stimulus showed that subjects who expected an analgesic effect from a DNIC stimulus indeed did get an analgesic response to a painful stimulus. However, in the group that expected an increased painful response to DNIC there was no analgesia [16]. Larivière et al. [25] showed that expectation partially explained the magnitude of DNIC response. Thus, it is possible that subjects familiar with the stimuli being presented expected an increased painful response to two simultaneously applied noxious stimuli and the loss of DNIC in our study reflected a change in expectation.

4.2. Pain intensity vs. DNIC

The current study measured pressure pain thresholds of deep tissue during application of a noxious stimulus to either the arm or the contralateral limb to either cold or to muscle pain induced by hypertonic saline. The cold pressor resulted in greater pain intensity than the muscle pain, and also greater DNIC suggesting that greater pain during the DNIC induction stimulus results in greater DNIC. However, the literature is not clear on whether there is a relationship between the intensity of the tonic stimulus and the magnitude of DNIC with some studies showing that the greater the pain intensity the greater the DNIC [13,29,49] while others do not show this relationship [3,38]. It is not clear if the different results can be explained by the different stimulus paradigms applied.

This difference could also be due to the experimental design where the PPTs were measured extrasegmentally to the cold pressor pain but segmentally to the muscle pain. The segmental effect of tonic muscle pain could activate supraspinal facilitatory pathways, in addition to the inhibitory pathways, which have bilateral inputs to the spinal cord [1,55]. Further in animal studies electrical or chemical stimulation of the RVM results in bilateral changes in the hindpaws [20,44] further supporting bilateral effects from supra-spinal pain modulation sites. Thus the overall magnitude of the DNIC observed would be less when compared to an extrasegmental stimulus. We specifically designed the experiment to mimic the clinical studies where DNIC evoked by noxious stimulation of the arm was impaired by osteoarthritic pain from the knee [23,24], i.e. extrasegmentally.

4.3. Pain stimulus vs. DNIC

The effects of DNIC are known to differ, depending on the magnitude and nature of the conditioning stimulation and stimulated nerve fibers [8,28,33,45]. The most commonly used techniques are heat [35], cold [2,21,52,52] ischemic pain [23,24] or muscle pain [14,18,19]. The current study showed a greater increase in DNIC with cold pressor pain than with muscle pain.

Differences between the effects of DNIC in the two tests could be related to the underlying neuroanatomical pathways that mediate cutaneous and muscle pain. Specifically cold pain, elicited by the cold pressor test, is a cutaneous stimulus that likely activates a thermal pathway involving lamina I spinothalamic tract neurons that project supraspinally to distinct regions of the posterior thalamic nuclei and to brainstem nuclei such as the parabrachial nucleus and dorsal PAG [6,15,22,31]. On the other hand, there is a substantial input from muscular afferents to the deep dorsal horn which then project supraspinally not only to the thalamus, but to brainstem nuclei such as the vlPAG that are under control of hypothalamic input [22,30,32].

4.4. DNIC and gender specific effects

The current study showed less efficient DNIC in females as compared to males after the cold-pressor test, or after muscle pain and is in agreement with prior studies [14,17,41,42]. However, other studies have found no gender differences in DNIC [3,12,37]. The differences between studies might be due to the DNIC stimulus applied, or to the outcome measure, but no comparative studies have verified this. Interestingly, Ge et al. [14] showed that repeated bilateral injection of hypertonic saline into trapezius muscles resulted in higher PPTs in males than females; and that the hypoalgesic effects were longer lasting in males as compared with females. Thus, males may be better able to activate DNIC pathways, and activation of DNIC may result in a longer-lasting effect.

These differences between genders could underlie some of the predominant chronic pain conditions in females. However, in the present study 10 males and 10 females participated. It could be argued that the lack of gender differences in some of the parameters could be due to lack of statistical power.

In conclusion this study for the first time showed that two concomitant conditioning tonic painful stimuli produce less DNIC than either of the individual conditioning stimuli given alone indicating that two concurrent tonic pain stimuli may counteract each other. Further, females seem to have less ability to recruit DNIC as compared to males. The study supports clinical data that ongoing musculoskeletal pain disturbs the balance between descending inhibition and facilitation and that this may be particularly important in females.

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Fig. 1.

PPT of test sites around both knees (R = Right, L = Left) before, during and after saline evoked pain for males and females. The five test sites were (1) 2 cm proximal to the superior lateral edge of patella, (2) 2 cm proximal to the superior edge of patella, (3) 2 cm proximal to the superior medial edge of patella, (4) 2 cm distal to the inferior lateral edge of patella, (5) 2 cm distal to the inferior medial edge of patella. *Significantly higher than before and after saline evoked pain.

Fig. 2.

PPT of test sites around both knees (R = Right, L = Left) before, during and after cold pain for males and females. The five test sites were (1) 2 cm proximal to the superior lateral edge of patella, (2) 2 cm proximal to the superior edge of patella, (3) 2 cm proximal to the superior medial edge of patella, (4) 2 cm distal to the inferior lateral edge of patella, (5) 2 cm distal to the inferior medial edge of patella. *Significantly higher than before and after cold pain.

Fig. 3.

PPT of test sites around both knees (R = Right, L = Left) before, during and after combined saline and cold pain for males and females. The five test sites were (1) 2 cm proximal to the superior lateral edge of patella, (2) 2 cm proximal to the superior edge of patella, (3) 2 cm proximal to the superior medial edge of patella, (4) 2 cm distal to the inferior lateral edge of patella, (5) 2 cm distal to the inferior medial edge of patella. *Significantly higher than before and after combined pain.

Fig. 4.

Increment of PPT of test sites during saline evoked muscle pain, cold pain, and combined saline/cold pain for males and females. *Significantly higher than females.

Fig. 5.

The VAS area under curve (arbitrary units) of males and females during saline evoked muscle pain, cold pain, and combined saline/cold pain. *Significantly higher than VAS area under curve during saline evoked muscle pain; +significantly higher VAS area during saline evoked muscle pain and cold pain.