Experimental Knee Pain Evoke Spreading Hyperalgesia and Facilitated Temporal Summation of Pain

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Authors’ contributions
TSJ: main author of the manuscript; data collection, data analysis and writing. MH: contributed to the analysis and discussed and commented on the whole paper. BDS: discussed and commented on the whole paper and protocols. HB: discussion and commented on the whole paper and protocols. TGN: main responsible for outlining the manuscript, discussing, and commenting on the paper during the whole process.

Summary
Experimental knee pain leads to hyperalgesia at the knee and facilitated temporal summation of pain outside the knee, indicating involvement of peripheral and central sensitization, in subjects with no history of knee pain. Experimental models of knee pain in healthy subjects may be advantageous to investigate mechanisms of the nociceptive system related to joint pain without any unwanted variability.

Abstract

Objectives. This study evaluated the deep-tissue pressure pain sensitivity and temporal summation of pain within and around healthy knees exposed to experimental pain.

Design. The study was designed as a randomized crossover trial, with each subject tested on 1 day.

Setting. All tests were carried out at the Laboratory for Musculoskeletal Pain and Motor Control, Center for Sensory-Motor Interaction, Department of Health Science and Technology at Aalborg University, Denmark.

Subjects. Seventeen healthy subjects (10 males) participated in this study.

Interventions. Experimental pain model. Pain was induced in the infrapatellar fat pad by injection of hypertonic saline and the contralateral infrapatellar fat pad was injected with isotonic saline as control.

Outcome Measures. Pressure pain thresholds, temporal summation of pressure pain, and cutaneous mechnosensitivity were assessed on three occasions: baseline, immediately after the injection, and when pain had vanished. Assessments sites were located in the peripatellar region, vastus lateralis, and tibialis anterior muscles.

Results. The experimental knee pain model demonstrated 1) hyperalgesia to pressure stimulation on the infrapatellar fat pad during experimental pain, and 2) facilitated temporal summation of pressure pain at the infrapatellar fat pad and knee-related muscles.
Knee OA, Knee Pain, Hyperalgesia, and Facilitated Temporal Summation

Conclusion. The increased sensitivity and temporal summation found in this study were exclusive to deep-tissue with no contralateral decreased pain sensitivity. The study showed that acute knee joint pain leads to hyperalgesia and facilitated temporal summation in the infrapatellar fat pad and in muscles located distant to the injection site, in subjects with no history of knee pain.

Key Words. Knee Pain; Knee OA; Hyperalgesia; Temporal Summation; Pressure Algometry

Introduction

Despite the high prevalence of knee osteoarthritis (OA), it remains one of the most frequent knee disorders without a cure. Pain and disability are prominent clinical features of knee OA [1,2]. Hyperalgesia and spontaneous pain in knee OA [3] is most likely related to increased sensitivity of nociceptors located in deep tissue (peripheral sensitization) and/or by increased responses in dorsal horn or supraspinal neurons (central sensitization) [1,3–6]. In conditions of central sensitization, the central integrative mechanism is up-regulated resulting in facilitated temporal summation of pain, expanded referred pain areas, and increased neuronal responses to external stimuli [4,6]. Recently, Arendt-Nielsen et al. [7] reported decreased pressure pain thresholds (PPTs) on knees and arms and facilitated temporal summation in knee OA patients compared with healthy controls. The sensitization phenomenon is typically related to the presence of local inflammation in a joint [8,9]. Although there is growing consensus that knee OA is a low-grade inflammatory disease, inflammation is not clinically detectable in most patients. Thus, it is possible that other factors than inflammation may contribute to pain sensitization.

Knee OA is a chronic pain condition but also characterized by other factors (e.g., inactivity and joint degeneration). By consequence, it is difficult to assess the isolated effects of pain on pain sensitivity in a patient population. Experimental models of knee pain in healthy subjects may be advantageous to investigate mechanisms of the nociceptive system related to joint pain without any unwanted variability.

A limited number of human experimental knee joint pain models exist among which injection of hypertonic saline into the infrapatellar fat pad [10–15] is adequate for studies of sensory manifestations related to knee pain. The infrapatellar fat pad is an intra-articular structure, sensitive to mechanical stimulation, and densely innervated by nociceptors [16]. Changes in magnetic resonance imaging-detected synovitis in the infrapatellar fat pad are associated with changes in knee OA pain [17]. The infrapatellar fat pad is an important structure to consider in the etiopathogenesis of knee OA and knee OA pain [18]. Still, it is unknown whether pain in the infrapatellar fat pad, without presence of inflammation, leads to peripheral and/or central sensitization in healthy subjects similar to that previously observed in knee OA patients [7].

The aim of this study was to investigate deep-tissue pain sensitivity to pressure stimulation within and around healthy knees exposed to experimental knee pain. It was hypothesized that experimental pain induced in the infrapatellar fat pad in healthy subjects would lead to 1) hyperalgesia in the infrapatellar fat pad (peripheral sensitization), in the painful knee and the periarticular muscles (central sensitization), and 2) facilitated temporal summation of pain (central sensitization).

Methods

Subjects

Seventeen healthy subjects (10 males) with a mean age: 23.8 years and age range: 20–29 participated in this study. None of the subjects had a history of injuries or medical conditions that could interfere with normal somatosensory functioning. The study was approved by the local ethics committee (N 20090058), was conducted in accordance with the Declaration of Helsinki, and all subjects provided written informed consent.

Protocol

The study was designed as a randomized crossover trial, with each subject tested on 1 day. Pain was induced in the infrapatellar fat pad by injection of hypertonic saline, and the contralateral infrapatellar fat pad was injected with isotonic saline as control (sequence randomized). PPTs, temporal summation of pressure pain, and cutaneous mechanosensitivity were assessed on three occasions: baseline, immediately after the injection (after approximately 30–60 seconds including a period with moderate pain), and when pain had vanished (post pain). Assessment sites were located on the knee and on leg muscles.

Saline-Induced Infrapatellar Fat Pad Pain

Hypertonic saline (0.5 mL, 5.8%) was injected into the infrapatellar fat pad, randomized to either the right or left side. The subjects received an injection of isotonic saline (0.5 mL, 0.9%) in the contralateral infrapatellar fat pad. At baseline, the subjects were blinded to the type of injection. All injections were made into the medial fat pad region (equivalent to assessment site 1—see later) using a 27G × 25 mm needle. The needle was inserted at an angle of 30° in a superolateral direction to a depth of ~20 mm. The subjects rated the saline-induced pain on an electronic visual analog scale (VAS) in which “0 cm” represented no pain and “10 cm” represented “maximal pain.” The VAS signal was sampled every 2 seconds in 20 minutes. The subjects adjusted the VAS in-between the somatosensory sensitivity assessments.

To ensure moderate pain intensity, the subjects had repeated injections if the pain decreased below 3 on the electronic VAS scale. This was done to have sufficient time for assessment during the pain session. All subjects received two injections of isotonic saline separated by 10 minutes.
After the pain had vanished, the subjects were asked to mark the evoked pain areas on an anatomical map and describe the quality of the pain on the McGill Pain Questionnaire [19].

**Assessment Sites**

The eight sites on each knee were located in relation to bone landmarks (Figure 1). Site 1: 2 cm distal to the inferior medial edge of patella (injection site); site 2: 2 cm distal to the inferior lateral edge of patella; site 3: 3 cm lateral to the midpoint on the lateral edge of patella; site 4: 2 cm proximal to the superior lateral edge of patella; site 5: 2 cm proximal to the superior edge of patella; site 6: 2 cm proximal to the superior medial edge of patella; site 7: 3 cm medial to the midpoint on the medial edge of patella; and site 8: at centre of patella. On the contralateral knee, site 1 was used as a control site, when injecting the ipsilateral side. The two sites outside the knee were located on the vastus lateralis muscle 7 cm from the lateral upper rim of patella, and on tibialis anterior muscle 10 cm below tibial tuberosity.

**Manual Pressure Algometry**

A hand-held pressure algometer (Algometer Type II, SBMEDIC Electronics, Solna, Sweden) was used to assess manual PPTs. The pressure was applied at a rate of approximately 30 kPa/s, with a 1 cm² probe. All participants were instructed to push a button when they felt that the pressure was just barely painful. PPTs from the eight test sites around the injected knee and the contralateral control site were recorded. PPT was measured twice on each site, and the mean of the two measurements was used in the statistical analysis. An interval of minimum 20 seconds was kept between each PPT assessment.

**Temporal Summation of Pressure Pain**

A computer-controlled pressure algometer (Aalborg University, Denmark) was used for measuring computer-controlled PPTs and temporal summation of three sites (site 1, m. vastus lateralis, and m. tibialis anterior). The computer-controlled pressure algometer applied the mechanical stimuli perpendicular to the skin surface [20]. A round aluminum probe with a padded contact surface of 1 cm² was fixed to the tip of the piston. The pressure stimulation was feedback controlled via recordings of the actual force. The computer-controlled pressure stimulus, with an ascending pressure gradient of 30 kPa/s, was applied continuously until the subject reported pain and pressed a button. This recorded pressure pain was defined as the baseline PPT. The PPT of each assessment site was recorded three times, averaged, and used for further analysis.

The degree of temporal summation of pain was assessed by sequential stimulation consisting of 10 pressure stimuli (1 second duration and 1 second interval) at the PPT level [21]. The intensity of sequential stimulation was the mean of the three baseline PPT measurements for each site. For each site the 10 sequential stimuli were repeated twice. The sequential stimulation was applied randomly to the three assessment sites with a 1-minute interval in-between. Skin contact between the individual pressure stimuli was ensured by keeping a constant force of 10 kPa; i.e., during the series of sequential stimulation the probe was in contact with the skin and withdrew after 10 stimulations. The contact force of 10 kPa between two stimuli does not evoke pain. The subjects rated the pain intensity continuously during the sequential stimulation on an electronic VAS where “0 cm” and “10 cm” were

![Figure 1](http://painmedicine.oxfordjournals.org/)

The eight assessment sites over the peri-patellar region, m. vastus lateralis and m. tibialis anterior. Injections of saline were given at site 1. The contralateral site 1 (mirror to injection site) was used as control site for the ipsilateral assessments.
anchored to “no pain” and “maximal pain,” respectively. The VAS signal for each stimulus was sampled by a computer at 200 Hz. VAS scores were extracted immediately after the individual stimulations (i.e., 10 VAS scores are analyzed after sequential stimulation). The average VAS score from duplicate recordings was used for further analysis. The increment of VAS was normalized to the first stimulus VAS score by subtraction.

Cutaneous Mechanosensitivity

A Von Frey hair (Stoelting, Wood Dale, IL, USA; corresponding to a bending force of 279.4 g) was used to stimulate the skin to assess cutaneous sensitivity changes at assessment site 1, vastus lateralis and tibialis anterior at the injected knee, and the contralateral control site. The subjects rated the Von Frey-evoked pain intensity on a manual VAS on which 0 and 10 cm were anchored to “no pain” and “maximal pain,” respectively.

Statistics

The data are presented as mean and standard error (SE). To assess the peak pain intensity following the injection of hypertonic and isotonic saline, a paired t-test was used, testing the peak pain intensities during the pain/control conditions. In the analysis of the manual PPTs, of the temporal summation, and the cutaneous mechanosensitivity, a longitudinal data model was applied to assess multiple repeated measures on the same subject using the MIXED procedure of the SAS® system (v. 9.1.3 Service Pack 4; SAS Institute Inc., Cary, NC, USA) with random effect for subject (random intercept model). The analyses focused on the fixed effects analyses, analyzing whether there were Time ¥ Saline interactions (Time: baseline, immediately after, post; Saline: hypertonic, isotonic) and main effects. Post hoc tests were used to explore the pairwise differences comparing saline solutions at baseline, immediately after, and post injection. To assess

Figure 2

Pain intensity and distribution of saline-induced pain. (A) Mean visual analog scale (VAS) scores (N = 17) of the pain intensity (VAS scores) measured after hypertonic (solid line) and isotonic (broken line) saline injected into the infrapatellar fat pad in healthy subjects. Thin lines illustrate the mean +/− standard error (SE) VAS scores. Note that the maximum VAS scores on this graph does not reflect the average of individual VAS peaks as this is a time independent measure. (B) The individual experimental pain distribution superimposed on anatomical drawings (N = 17). The pain was relatively localized to the medial region of the fat pad. Note that the injection side was randomized but the drawings were all superimposed on left side and mirrored if needed.
for carryover effects, the analyses were done with the randomization order added as a covariate. Statistical significance accepted at \( P < 0.05 \).

Results

Saline-Induced Infrapatellar Fat Pad Pain

The pain intensity profiles following hypertonic and isotonic saline are illustrated in Figure 2A. The average VAS peak following hypertonic saline was 6.7 cm (SE 0.4) and 3.1 cm (SE 0.6) after isotonic saline. There was a significant difference in VAS peak measured after the injections of 3.6 cm (95% confidence interval: 2.5–4.7, \( P < 0.0001 \)) showing that hypertonic saline caused a significantly higher peak pain intensity than isotonic saline. Seven subjects received one injection of hypertonic saline whereas 10 subjects received two injections to maintain moderate pain intensity (VAS > 3) during the assessment procedures.

The saline-induced pain was distributed around the knee with dominance in the medial area of the fat pad, and two subjects perceived referred pain to the thigh (Figure 2B). The quality of pain was described as shown in Table 1.

\[
PPT
\]

The mixed linear model showed a significant Time \( \times \) Saline interaction (\( F_{2,1518} = 3.92; P = 0.02 \)). Post hoc analyses revealed a significantly lower PPT at site 1 and 2 at the knee injected with hypertonic saline compared with baseline and with the PPT after isotonic saline injections (\( P < 0.04 \); Figure 3). The peak pain intensity due to the injections was not correlated to the change in PPT during experimental knee pain.

Temporal Summation of Pressure Pain

For both isotonic and hypertonic saline injections, VAS scores progressively increased in response to the sequential pressure stimuli for the three assessment sites and at all three assessment times (Figure 4).

Sequential pressure stimulation on the infrapatellar fat pad revealed VAS scores with a significant Time \( \times \) Saline interaction in the linear model (\( F_{2,1687} = 47.75; P < 0.0001 \); Figure 4A, B). VAS scores after the 5th to the 10th pressure stimuli on the infrapatellar fat pad injected with hypertonic saline were higher compared with isotonic saline; both during and postpain (\( P < 0.04 \)). Within the knees injected with hypertonic saline, significantly increased VAS scores from the baseline were observed during and postpain from stimulation number 4 to 10 (\( P < 0.04 \); Figure 4A).

At the vastus lateralis muscle, sequential pressure stimulation resulted in VAS scores with a significant Time \( \times \) Saline interaction (\( F_{2,1697} = 11.39; P < 0.0001 \), Figure 4C, D). Post hoc analyses showed that during pain by injection of hypertonic saline in the infrapatellar fat pad, the 5th to 10th pressure stimuli on the vastus lateralis muscle evoked higher VAS scores compared with injections of isotonic saline (\( P < 0.02 \)). Within the knees injected with hypertonic saline, a significantly increased VAS score from the baseline was observed during pain at stimulus 10 (\( P < 0.037 \); Figure 4E).

At the tibialis anterior muscle, sequential pressure stimulation resulted in VAS scores with a significant Time \( \times \) Saline interaction (\( F_{2,1688} = 10.87; P < 0.0001 \); Figure 4E, F). An increase in VAS scores during pain by injection of hypertonic saline in the tibialis anterior compared with baseline was observed for the 7th to the 10th pressure stimuli on the tibialis anterior muscle (\( P < 0.04 \), Figure 4E).

Cutaneous Mechanosensitivity

There was no significant difference in the VAS scores to cutaneous Von Frey hair stimulation when comparing hypertonic and isotonic saline for the three assessment sites (Table 2).

Discussion

The experimental knee pain model demonstrated 1) hyperalgesia to pressure stimulation on the injected infrapatellar fat pad during pain, and 2) facilitated temporal summation of pressure pain at the infrapatellar fat pad and knee-related muscles. The increased sensitivity was
exclusive to deep tissue, and there were no changes in contralateral decreased pain sensitivity. This is the first study to demonstrate augmented peripheral and central sensitization in healthy subjects induced by experimental pain in the infrapatellar fat pad.

Figure 3 Mean pressure pain thresholds (PPTs) (+/- standard error [SE], N = 17) from assessment site 1–8 and the contralateral control site 1 (1 c.l.) at baseline, immediately after (During) and post injection of hypertonic (triangles) and isotonic saline (circles). *: PPT was significantly reduced after hypertonic saline compared with isotonic saline (P < 0.04).

experimental Knee Joint Pain

There are only a few studies on experimental pain in the infrapatellar fat pad [10–12,14,15]. Bennell et al. [10] showed that experimental pain induced in the medial

Table 2 Von Frey hair stimulation (cutaneous mechanosensitivity)

<table>
<thead>
<tr>
<th>VAS (cm)</th>
<th>Hypertonic Saline</th>
<th>Isotonic Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infrapatellar fat pad</td>
<td>Baseline (3.1 (2.2–3.9))</td>
<td>Immediately after (3.0 (2.2–3.8))</td>
</tr>
<tr>
<td>Vastus lateralis</td>
<td>3.4 (2.5–4.3)</td>
<td>3.0 (1.9–3.6)</td>
</tr>
<tr>
<td>Tibialis Anterior</td>
<td>3.7 (2.9–4.5)</td>
<td>3.0 (2.1–3.8)</td>
</tr>
</tbody>
</table>

Mean VAS scores (95% confidence interval, N = 17) after Von Frey hair stimulation (cutaneous mechanosensitivity) in response to injection of isotonic and hypertonic saline into infrapatellar fat pad.
infrapatellar fat pad, with referred pain to the thigh, produced strong knee pain in region similar to those in patients presenting with anterior knee pain and of similar quality. All subjects described local pain in the region medial to the patellar tendon around the injection site. This is corroborated by the present study, although the subjects reported medial, central, and lateral pain, as well as referred thigh pain (Figure 2B). Experimental pain may not replicate “real” OA pain although several studies [10,12–15] found that experimental pain induced into the infrapatellar fat pad produced strong knee pain in regions similar to those in patients with knee OA which is in line with the current findings. Other studies have found that experimentally induced pain into the infrapatellar fat pad lead to altered motor unit recruitment and changed gait pattern similar to that observed in patients with knee OA indicating widespread motor adaptation [11–13].

Experimental pain is acute and transient and does not necessarily reproduce knee OA pain, but for obvious reasons, it is not possible to induce chronic pain experimentally. Nevertheless, the infrapatellar fat pad accommodate nociceptors [16], and is a source of pain in knee OA [18]. The healthy subjects included were significantly younger than the knee OA patients. However, asymptomatic, elderly people may have radiographic or other age-related changes that may confound any findings related to the experimental pain. Therefore, studying subjects who are as “healthy as possible” is advantageous when the isolated effects of pain are to be assessed, and the present study design allows for such assessment. Furthermore, experimental approaches using healthy subjects provide a unique opportunity to study the pain pattern arising from nociceptive stimulation of specific structures without any influences from other conditions related to knee pathology (e.g., inflammation, comorbidities, central sensitization etc.).

**Hyperalgesia Due to Experimental Infrapatellar Fat Pad Pain**

The present findings of hyperalgesia induced by experimental knee pain are in line with the observation of lower PPTs in knee OA patients compared with healthy subjects [7]. In patients with severe knee OA, the pressure pain (>6 cm VAS) thresholds in the peripatellar region of the knee were significantly lower than those of healthy subjects [7] in line with the present findings of hyperalgesia caused by experimental knee pain. It has been suggested that knee OA pain may result from mild inflammation in structures such as synovial layers [9], and the infrapatellar fat pad may also be involved [18]. The pain induced by hypertonic saline occurs immediately and is not associated with tissue damage or toxicity [22] and thus inflammatory reactions in the tissue is not present. Accordingly, the present study shows that inflammation does not have to be present to reduce the knee pain threshold. This is further supported by the fact that reduced PPTs is found immediately after onset of pain and the hyperalgesia disappears when pain vanishes. In contrast, the effects appear to be due to short-term sensitization of nociceptors due to the injection of hypertonic saline and less likely due to mechanical distortion effects because isotonic saline caused minimal pain and no hyperalgesia. Assuming that hypertonic saline and mechanical stimulation excite different populations of nociceptors, the hyperalgesia may also be due to a central summation or facilitatory mechanism. Spatial summation of neural activity and facilitation of previously ineffective dorsal horn synaptic connections might be of importance [23,24]. In the study by Arendt-Nielsen et al. [7], spreading of the sensitization in the knee OA patients to the contralateral knee was also observed. Spreading to the contralateral knee was not observed in the present study. The diverging results between knee OA patients [7] and healthy subjects in the present study is likely because most knee OA patients have bilateral symptoms or subclinical changes. It is also possible that, in chronic diseases such as knee OA, central neuronal systems are sensitized bilaterally, which is not likely to happen during acute experimental pain.

Experimental muscle pain leads to a variety of changes in deep and superficial tissue sensitivity in the local muscle pain area [10,23,25]. In several human studies (for review, see Graven-Nielsen [26]), it was demonstrated that sensitization of muscle nociceptors using algesic substances or external nociceptive stimuli induced muscle hyperalgesia. In line with experimental tendon pain [24], the present study shows that hyperalgesia is not only seen after experimental muscle pain, but can also be induced experimentally in other deep tissues (i.e., the infrapatellar fat pad, tendon, and tendon bone).
Facilitated Temporal Summation of Pressure-Induced Pain

This study demonstrated that experimental pain in the infrapatellar fat pad facilitated temporal summation of pressure pain in the infrapatellar fat pad and in muscles located distant to the actual experimental pain. This indicates an enhanced sensitivity of the central mechanisms responsible for temporal summation of pain. Plastic changes or central sensitization within the neural organization of the spinal cord occur during development of joint inflammation [8,9], which leads to facilitation of the spinal neuronal processing of the afferent inputs from group III and IV afferent fibers. This leads to increased sensitivity or reduced thresholds to non-noxious pressure on the inflamed joint and, with some delay, to the adjacent and noninflamed tissue, the latter indicating that spinal neurons expand their receptive fields [8,9]. The findings in the present study shows that pain without interference from inflammation can elicit facilitation of central mechanisms.

Recently, facilitated temporal summation in both the same segment and the neighboring segment (tibialis anterior), and at the contralateral site, in patients with knee OA has been shown [7]. The results in the present study contrasts this, which might be because central sensitization in neighboring segments occur over time [4], and the fact that most patients with knee OA have bilateral involvement. It is likely that the initial excitation and sensitization of nociceptors, due to tissue damage, cause sufficient nociceptive input to the central pain systems to initiate central sensitization of dorsal horn neurons, higher brain centers, or both. The timescales involved in this working hypothesis are not clear, but it has been shown that a few hours of muscle soreness can cause facilitated temporal summation [27] and extended areas of deep-tissue hyperalgesia [28], probably related to central sensitization. The present study shows however that signs of central sensitization occur shortly after acute pain and are sustained in the immediately following period when the pain has vanished.

Clinical Implications

The infrapatellar fat pad has been shown to be an active osteoarthritic joint tissue that is able to produce and excrete important inflammatory mediators directly into the knee joint [18], which can explain the role of the infrapatellar fat pad in the disease process of knee OA [18]. Furthermore, Hill et al. [17] have shown that the infrapatellar fat pad is a significant source of knee pain suggesting that the treatment of painful OA of the knee is targeted at synovitis, which may improve pain [17]. The enhanced peripheral and central sensitization in painful but otherwise healthy knees reported in this study has not been shown before indicating that infrapatellar fat pad pain may contribute significantly to the hyperalgesia and sensitization phenomena seen in knee OA patients.

Conclusion

This study shows that acute experimental knee joint pain leads to hyperalgesia and facilitated temporal summation in the infrapatellar fat pad and in muscles located distant to the injection site, in subjects with no history of knee pain. Furthermore, the changes observed in this study suggest involvement of both peripheral and central sensitization similar to those observed among knee OA patients. The experimental knee pain model is valuable for assessing the effects of pain modulation of both peripheral and central mechanisms related to knee OA and can possibly contribute to the development of rational pain therapies.

Acknowledgments

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Statement: The authors have no conflicts of interest to declare.

References

10 Bennell K, Hodges P, Mellor R, Bexander C, Souvilis T. The nature of anterior knee pain following injection of...


