PAIN IN EUROPE IV
4th Congress of the European Federation of IASP Chapters (EFIC)
September 2 – 6 / 2003 ■ Prague, Czech Republic

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Effects of localization and intensity of experimental muscle pain on ankle joint proprioception

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Accurate proprioceptive input is a prerequisite for balance control and coordination of movement. The present study investigated whether experimental muscle pain induced in healthy human subjects disturbed movement sense (detection of movement) or position sense (recognition of a reference position). Muscle pain was produced by infusion of 6% hypertonic saline simultaneously in m. tibialis anterior (TA) and m. soleus (experiment 1), by infusion of 6% hypertonic saline in TA (experiment 2) and by infusion of 9% hypertonic saline in TA (experiment 3). Control measurements were done with infusions of 0.9% isotonic saline. All infusions of 6% and 9% saline produced pain intensities significantly higher than the corresponding control infusions. Only infusion of 6% saline in two muscles (visual analogue scale = 4–5) produced an elevation in movement detection thresholds which was significantly higher, compared with before infusion. No other significant changes in movement and position sense were found during the painful or control infusions. Pain of relatively high intensity in two antagonist muscles is necessary to disturb the movement detection threshold. The ability to recognize a reference position is not disturbed by experimentally induced muscle pain. Whether the disturbed movement sense is caused by sensitivity changes in muscle spindle afferents or altered processing of proprioceptive input cannot be answered. The present findings indicate that human ankle proprioception is rather robust to muscle pain. © 2002 European Federation of Chapters of the International Association for the Study of Pain. Published by Elsevier Science Ltd. All rights reserved.

KEYWORDS: proprioception, movement, position, pain, hypertonic saline, human, muscle spindle.

INTRODUCTION

The general aim of the present study was to determine whether muscle pain may distort proprioception. The awareness of limb position and movement is referred to as proprioception (Sherrington, 1900). Accurate proprioceptive input is a prerequisite for balance control, body orientation and coordination of movements (Kavounoudias et al., 1999). Alterations in movement strategy and postural activity are often seen in persons suffering from different musculoskeletal pain syndromes (Lund et al., 1993; Sainburg et al., 1993). If alterations in movement and posture are results of disturbed proprioception, a vicious circle could be initiated, because increased postural muscle activity and unsound loading conditions may augment the pain. In clinical studies reproduction of position is found to be significantly less accurate in patients with cervical pain than in a control group (Revel et al., 1991), and Rogers (1997) found that both pain intensity and reproduction of position were improved with therapy. Lumbar reproduction of position is worse in low-back pain patients than in pain-free controls (Gill and Callaghan, 1998; Brumagne et al., 2000; Newcomer et al., 2000).
A recent study reported that movement sense is reduced with muscle fatigue (Pedersen et al., 1999). Causality cannot be determined in clinical cross-sectional studies. Experimental studies make it possible to compare intra-individual measurements before and during pain. Alterations in movement and posture have been reported during experimentally induced muscle pain in healthy subjects (Stohler et al., 1996; Arendt-Nielsen et al., 1996; Svensson et al., 1997; Madeleine et al., 1998). These reports are based on control of movement. Whether induced pain also disturbs the awareness of movement and position is not known.

The psychophysiological measurement of proprioception in humans depends on afferent input from the periphery and its integration with other afferent inputs in the spinal cord and in the brain. Proprioception may be disturbed at any of these levels, and in humans it is not possible to test one of these in isolation. Muscle spindles are considered the most important peripheral receptor to the sensation of position and movement in humans, although joint and skin receptors also contribute (McCloskey, 1978; Clark and Horch, 1986; Refshauge et al., 1995). Factors which alter muscle spindle sensitivity may therefore affect proprioception (Matthews, 1988). Several animal studies have found evidence for a connection between group III–IV afferent input (associated with muscle pain) and the γ muscle spindle system (see for example Schmidt et al., 1981; Appelberg et al., 1983; Mense and Skeppar, 1991; Johansson et al., 1993; Djupsjöbacka et al., 1995; Capra and Ro, 2000). However, the findings are not unequivocal and indicate both excitation and inhibition. Secondly, these are studies in animals and it is not proved that similar connections exist, and are functionally relevant, in humans (Knutson, 2000).

The general aim of the present study was to determine whether induced muscle pain distorts proprioception in humans. To focus on muscle spindle input, a method was developed in which joint input is kept constant across conditions and where cutaneous, tendon, auditory and visual inputs as well as variable descending control, are minimized. To reduce the influence of descending control, the methods developed were based on passive movements, because (1) the increased α–γ co-activation during muscle contraction may be a confounding factor when looking for a possible pain-related alteration in spindle sensitivity and (2) with active movement it is not possible to standardize the level of activation of the muscle studied or the pattern of contraction of the antagonists. The human stretch reflex shows a significant increase with pain in the relaxed, but not in the contracted, muscle, indicating that the γ muscle spindle system is most sensitive to pain without α–γ co-activation (Matre et al., 1998).

The subjective threshold to detect passive movement (movement detection) is a method to assess movement sense (McCloskey, 1978). Position sense is usually tested by active limb repositioning after presentation of a reference position (McCloskey, 1978). Because of the arguments presented above, the repositioning was done passively in the present experiments, i.e. recognition of the reference position is tested.

To investigate systematically whether pain per se disturbs proprioception, muscle pain was induced experimentally in healthy subjects by intramuscular infusions of small amounts of hypertonic saline (Kellgren, 1938; Stohler and Lund, 1994; Arendt-Nielsen et al., 1996). Two methods were developed, focusing on movement sense and on position sense. Three experiments were conducted to determine whether movement sense and position sense were disrupted by (1) pain of intermediate intensity induced in two antagonist muscles (tibialis anterior, TA, and soleus, SOL), (2) pain of low intensity induced in one muscle (TA) and (3) pain of intermediate intensity induced in one muscle (TA). The experiments were conducted on separate days, and movement sense and position sense were measured in all experiments before, during and after experimental muscle pain.

**METHODS**

**Subjects**

In experiment 1 (0.9% and 6% saline in TA and SOL), 11 healthy female subjects (age 22.5 ± 1.4 years; mean ± standard deviation (SD))
participated in the movement experiment, and nine healthy female subjects (age 23.6 ± 1.6 years) participated in the position experiment. In experiment 2 (0.9% and 6% saline in TA), 12 healthy female subjects (age 24.2 ± 5.6 years) participated in both the movement and the position experiments. In experiment 3 (9% saline in TA), 10 healthy female subjects (age 25.5 ± 2.5 years) participated in both the movement and the position experiments. All subjects were given a medical examination before participating. The exclusion criteria were any systemic illness (rheumatic, vascular or malignant disease) or a local ankle or knee disorder. No subjects had complaints of pain in the knee, lower leg or ankle at the time of recording. Subjects that had not reported the hypertonic infusion as painful (pain intensity rating below 1 cm on a 0–10 cm scale) were excluded from the data analysis (see Table 1). All subjects signed an informed consent form and the study was approved by the Local Ethical Committee and was conducted in accordance with the Helsinki Declaration.

Development of methods to assess ankle joint proprioception

Proprioception may be tested in basically all joints of the body, including the ankle, which have been investigated in a number of studies (for an overview see Refshauge et al., 1995). Two methods to test movement sense and position sense are detection of movement and recognition of a previously presented reference position. A test apparatus was developed with the intention to keep joint input constant across conditions and to minimize cutaneous, visual and auditory inputs. The subject was seated in a comfortable chair with head and arm support enabling relaxation of all muscles. The foot of the dominant leg was strapped to a platform and the axis of rotation was aligned with the ankle joint (Fig. 1A). With respect to the anatomical '0' position' the starting position of the ankle joint was slightly plantar flexed, and the knee joint was kept at an angle of approximately 70°. Dorsal and plantar flexion of the ankle were produced by rotating the platform with a computer-controlled (Tech 80, Minneapolis, USA) step motor (Zebotronic, Germany) driven by a power amplifier (SMD30C3, JVL Industri Elektronik, Denmark). Special care was taken to attenuate vibrations.
emerging from the step motor. A silicon linkage connected the motor to a planetary 36:1 gearbox (Technoigranaggi, Italy), and a toothed band (PowerGrip) connected the gearbox to the platform. Furthermore, the subject wore a 3 mm neoprene sock on the foot of the tested leg, which was surrounded by a vacuum cushion (AB Germa, Kristianstad, Sweden). Only a weak quivering could be felt at the sole of the foot in the present movement experiments owing to these precautions. In order to eliminate cues from this vibration at the beginning of each movement threshold test, the motor was stepped at identical rate before (3–5 s period) and throughout platform movements (Fig. 1B).

Electromyographic (EMG) activity was monitored from TA and SOL to ensure muscle relaxation during the recording procedure. To avoid visual cues a curtain blocked the subject's view of her legs, and white noise through headphones effectively masked any noise from the step motor. Rotation speed could be varied from 0.2% to 30%°. Maximum rotational torque of the platform is calculated to be approximately 250 N m. A stop button placed within the reach of the subject and the experimenter could terminate rotation immediately and electric switches would terminate rotation in case of rotation into extreme positions.

Calibration of the platform was performed using a laser beam aligned with the axis of rotation of the platform. A potentiometer was connected to the platform's axis of rotation and the output voltage (±5 V) was sampled (50 Hz; 12 bits) and stored on computer. The difference between programmed and measured velocities (0.35%/s, 2%/s, 4%/s, 5%/s, 10%/s) is estimated to be 1.2% ± 7.7%. The difference between programmed and measured positions (1°, 10°, 20°) is estimated to be <1%.

Movement sense

A threshold for detection of movement was determined after passive ankle joint rotation from the slightly plantar flexed starting position. After a random delay (3–5 s without movement) the motor continued at the same step rate, but in one direction at a speed of 0.35%/s. The subject indicated the perceived movement by pushing a button, after which the rotation was stopped (Fig. 1B). Immediately afterwards the subject indicated the direction (up/down), and the platform was returned to the starting position. Since movement generally is detected before direction (Laidlaw and Hamilton, 1937; Hall and McCloskey, 1983), the subject was instructed not to push the button until she was confident about the direction. It has been shown that a co-contraction of the muscles before movement gives lower thresholds for movement detection of the human elbow, probably because of a reduction of spindle slack (Wise et al., 1996). The idea is that after passive joint flexion (extensor muscles are stretched) and subsequent passive extension (extensor muscles are shortened) the spindles in the extensor muscle fall slack. This will happen only during passive movement without α–γ co-activation. Thus, to standardize the measurements, each test commenced with a short contraction (lasting less than 1 s), presumably co-activating α and γ motoneurones in the ankle extensor and flexor muscles. EMG feedback was provided from TA and SOL to make co-contraction easier and to ensure that the muscle was completely relaxed when the movement started. Between 10 and 20 tests were performed in each direction in random order. Between five and eight 'dummy movements' (0.01° steps in each direction) were included to discourage guessing. The number of false positives (subject response during a 'dummy movement') and the number of wrong directions indicated by the subject were counted. Mean thresholds for detection were calculated offline by averaging the thresholds in each direction.

Position sense

Repositioning of a previously presented reference position is considered a reliable parameter for proprioception (McCloskey, 1978; Smith and Brunolli, 1989). The repositioning procedure is performed either by active repositioning or by recognition of a passive positioning. The limb usually is moved from a starting position to a
reference position and back. Afterwards, the task of the subject is to reproduce or recognize the reference position. In the present experiments, passive positioning of the reference position and passive recognition of the limb to this reference position were used (Gross, 1987; Smith and Brunolli, 1989; Konradsen et al., 1993). Other studies have used active repositioning (Glencross and Thornton, 1981; Skinner et al., 1984; Marks et al., 1993; Lattanzio et al., 1997). The method used in the present study is illustrated schematically in Figure 1C. A weak co-contraction of the ankle extensor and flexor muscles was done to reduce spindle slack (Wise et al., 1996). The reference position was presented for the subject by a passive plantar flexion of the ankle. The subject was told to memorize this position, and the ankle was returned to the starting position. Immediately afterwards the ankle was plantar flexed again at a different speed (reproduction speed) to eliminate any cues from timing, passing the reference position by 4°, changing direction and returning to the starting position. Thus, the reference position was passed twice, once in the plantar direction and once in the dorsal direction. The task of the subject was to respond by pushing a button at the point when she felt that the ankle was aligned with the reference position (i.e. twice). Two error values, plantar error and dorsal error, were calculated by subtracting the reference position from the position when the subject responded in plantar and dorsal directions respectively (Fig. 1C). The errors were given a negative sign if the subject responded too early (undershoot) and a positive sign if the subject responded too late (overshoot). This was repeated four or five times for each combination of reference position, speed and reproduction speed. Two median values were calculated from the four or five plantar and dorsal errors. All position sense data were analysed separately for the plantar and dorsal errors. If the subject failed to push the button before the platform changed direction (at reference position +4°), the trial was counted as a miss and rejected.

Most studies of position sense have tested several reference positions, but little focus has been on the effect of the speed of rotation. In order to gain methodological information on position sense, the present study combined two reference positions (10° and 20° plantar displacement from the starting position), two rotation speeds (5°/s and 10°/s) and two reproduction speeds (2°/s and 4°/s), presented in random order.

Pain stimulus

Sterile hypertonic saline (6% or 9%) was infused to produce acute deep pain in the muscle. Sterile isotonic saline (0.9%) was infused at equal volumes and rates in separate control sessions. Infusions were always given unilaterally and were performed using a computer-controlled syringe pump (IVAC model P7000, UK) with a 10 ml plastic syringe (Graven-Nielsen et al., 1997a; Matre et al., 1998). A tube (IVAC G30402) was connected from the syringe to a catheter (Venflon, 22G, 25 mm), which was inserted in the muscle before the pre-infusion recordings and remained in the muscle for the rest of the recordings. For infusions in two muscles simultaneously, 10 ml was infused over 10 min. The tube was connected to two catheters via a three-way stopcock (Connecta, Sweden) with two 10 cm extension tubes (experiment 1 only). For infusions in one muscle, 5 ml was infused over 10 min. The infusion rate was modified during infusion to produce a constant pain intensity (Graven-Nielsen et al., 1997a; Matre et al., 1998).

The subjects rated the pain intensity on a 10 cm electronic continuous visual analogue scale (VAS) and the ratings were sampled (10 Hz; 12 bits) and stored on computer. The lower endpoint of the scale was marked ‘no pain’ and rated ‘0 cm’, and the upper endpoint was marked ‘most pain imaginable’ and rated ‘10 cm’. After infusion the subjects were instructed to indicate the distribution and quality of the most intense pain sensation on small-scale body maps and using a Norwegian version of the McGill Pain Questionnaire (MPQ) (Strand and Wisnes, 1991). The subjects were not asked to distinguish pain intensity during and between movements. Pain rating indices (PRIs) of the sensory (S), affective (A), evaluative (E) and total (T) dimensions were calculated (Melzack, 1975).
In experiment 2 the subjects were asked to fill in Spielberger’s anxiety test (STAI) to evaluate anxiety traits (form Y-2) and the anxiety level before and after each session in experiment 2 (form Y-1). In both forms minimum anxiety corresponds to score 20 and maximum anxiety to score 40.

Experimental protocols and data analysis

In experiment 1 (0.9% and 6% saline in two muscles) and experiment 2 (0.9% and 6% saline in one muscle), the subjects received the two saline concentrations in a single blind random order. In experiment 3 the subjects received 9% saline only. For each saline concentration, movement sense and position sense were tested in different sessions separated by at least 5 days. All tests were done between 8.30 am and 5.00 pm. Three measurements were performed: pre-infusion, during infusion and postinfusion. Measurements during infusion started 5 min after the last pre-infusion measurement. Measurements postinfusion started 5 min after VAS = 0 or 10 min after the last measurement during the non-painful infusions. For each saline concentration, the effects of the infusions were analysed by comparing measurements before, during and after infusion. For each subject, pain intensity was calculated as the average VAS score over the 10 min infusion period.

In order to evaluate test–retest reliability, two pre-infusion measurements were made before the infusions in experiment 2, making it possible to compare both inter-session reliability and intra-session reliability.

Statistics

Movement sense

Repeated-measures analyses of variance (ANOVA) were used to analyse the dorsal and plantar movement detection thresholds. When analysing test–retest reliability, session order (1 and 2) and order of pre-infusion measurement within session were used as factors (two-way ANOVA). The effect of the saline infusions (pre-infusion, during infusion and postinfusion) was analysed separately (one-way ANOVA) for the different saline concentrations (0.9%, 6% and 9%).

Position sense

Repeated-measures ANOVA were used to analyse the plantar and dorsal errors. When analysing test–retest reliability, order of pre-infusion measurement within session (1 and 2), session order (1 and 2), reference position (10° and 20°), rotation speed (5/s and 10/s), reproduction speed (2/s and 4/s) were used as factors (five-way ANOVA). When analysing the main effects of reference position, speed and reproduction speed, a three-way ANOVA was performed on the pre-infusion measurements. The effects of the saline infusions (pre-infusion, during infusion and postinfusion) were analysed separately for the different saline concentrations (0.9%, 6% and 9%) using reference position, rotation speed and reproduction speed as factors (four-way ANOVAs).

Pain intensity (VAS), pain quality (McGill Pain Rate Index, PRI) and anxiety (STAI) were compared using Wilcoxon’s test (paired comparisons) and Mann–Whitney U test (unpaired comparisons). In the repeated-measurements ANOVA tests, the Huynh–Feldt factor for correction of degrees of freedom was used, and if a major effect was found for one of the factors, or between factors, a post hoc test was performed using Student–Newman–Keul’s method. A probability of the null hypothesis of $p < 0.05$ was considered statistically significant in all tests.

RESULTS

Development of methods

Test–retest reliability was considered satisfactory because the statistical analysis showed no difference between the two pre-infusion measurements during detection of movement (plantar, $p = 0.92$; dorsal, $p = 0.36$) or during recognition of position (plantar error, $p = 0.29$; dorsal error, $p = 0.77$).
Thus, the second pre-infusion measurement was used as the pre-infusion measurement in the further analysis. Also when comparing pre-infusion measurements from separate days, there were no differences during detection of movement (plantar, $p = 0.9$; dorsal, $p = 0.55$) or during recognition of position (plantar error, $p = 0.19$; dorsal error, $p = 0.23$).

**Sensory effects of intramuscular saline infusions**

In most of the subjects, infusion of hypertonic saline (6% and 9%) produced a deep local pain sensation in the injected muscle (Fig. 2). The pain intensity ratings reflect the combined local and referred pain sensations. Three subjects had an average VAS rating <1, and were excluded from further data analysis (numbers in parentheses, Table 1). Infusion of hypertonic saline (6% or 9%) was always significantly more painful than infusion of 0.9% isotonic saline. Average pain intensity ratings during infusion of 0.9% and 6% saline in TA and SOL are shown in Figure 2A (movement experiment). Proprioceptive measurements were taken in the 60–660 s interval after infusion start (horizontal lines in Figs 2A–C). Infusion of 6% saline in two muscles simultaneously was not different in intensity from infusion of 9% saline in one muscle (Fig. 2C). However, both of these infusions were significantly more painful than infusion of 6% saline in one muscle (Fig. 2B). Table 1 gives a summary of the sensory effects. Pain distribution drawings show that infusions of 6% or 9% saline in TA produced local pain mainly in the same area; around

![Diagram](https://example.com/diagram.png)

**Fig. 2.** Mean ± SD pain intensity ratings during infusion of isotonic saline (○) or hypertonic saline (●, ▼) in (A) experiment 1 (infusion into TA and SOL; $n = 11$), (B) experiment 2 (infusion into TA; $n = 10$) and (C) experiment 3 (infusion into TA; $n = 9$). Measurements of proprioception were made in the 60–660 s period (horizontal bars). (D)–(F) Corresponding superimposed body map drawings of pain distribution during infusion in experiments 1, 2 and 3. Injections were done in the subject's dominant leg. Pain intensity scores and pain drawings are from the movement experiments. Drawings from the position experiments are similar.
TABLE 1. Summary of sensory effects after intramuscular saline infusions.

<table>
<thead>
<tr>
<th>Exp. 1 (0.9% and 6% saline in TA and SOL)</th>
<th>n</th>
<th>Saline (%)</th>
<th>VAS (cm), 50–660 s</th>
<th>Referred pain (number of subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Movement sense</td>
<td>11</td>
<td>0.9</td>
<td>0.3 ± 0.4</td>
<td>Dorsum 6/8 Knee 4/11 Heel 1/11</td>
</tr>
<tr>
<td>Position sense</td>
<td>8 (1)</td>
<td>0.9</td>
<td>4.3 ± 1.6b</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td></td>
<td>0.4 ± 0.6</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td></td>
<td>4.8 ± 1.8c</td>
<td>—</td>
</tr>
<tr>
<td>Exp. 2 (0.9% and 6% saline in TA)</td>
<td>10 (2)</td>
<td>0.9</td>
<td>0.1 ± 0.2</td>
<td>Dorsum 7/10 Knee 1/10 Heel —</td>
</tr>
<tr>
<td>Movement sense</td>
<td>10 (2)</td>
<td>0.9</td>
<td>2.8 ± 0.9b,d</td>
<td>—</td>
</tr>
<tr>
<td>Position sense</td>
<td>9 (1)</td>
<td>9</td>
<td>0.2 ± 0.5</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td></td>
<td>2.8 ± 1.2c,e</td>
<td>—</td>
</tr>
<tr>
<td>Exp. 3 (9% saline in TA)</td>
<td>9 (1)</td>
<td>9</td>
<td>4.3 ± 1.5d</td>
<td>Dorsum 7/9 Knee 2/9 Heel —</td>
</tr>
<tr>
<td>Movement sense</td>
<td>9 (1)</td>
<td>9</td>
<td>4.0 ± 2.2a</td>
<td>—</td>
</tr>
</tbody>
</table>

All values are mean ± SD, n, number of subjects excluded in parentheses (average VAS rating <1). *Anterior (A) or posterior (P) referred pain at knee level or slightly distal to knee level. Mann-Whitney U test results. Movement sense: **8% in two muscles vs 5% in one muscle, p = 0.007; **6% vs 9% in one muscle, p = 0.037. Position sense: *6% in two muscles vs 6% in one muscle, p = 0.021; **9% vs 9% in one muscle, p = 0.23.

The injection site (approximately 15 cm below the patella, indicated with ‘X’) and towards the ankle (Figs 2D–F). Referred pain at the dorsum of the foot was experienced by more subjects during 9% infusion than during 6% infusion (Table 1). Only few subjects experienced referred pain proximal to the injection site (‘knee’, Table 1). Infusions of 6% saline in SOL produced pain localized medially and laterally, distal and proximal to the injection site (Fig. 2D).

The above-mentioned results are from the movement experiments and are similar to results from the position experiments, although infusion of 9% saline in one muscle was not significantly different in intensity from infusion of 6% saline in one muscle when comparing the position experiments (note ‘c’ in Table 1).

The two experiments with matched distributions (6% and 9% saline in one muscle) and the two experiments with matched intensities (6% saline in two muscles and 9% saline in one muscle) made it possible to determine the relative importance of these two parameters in disturbing proprioception.

The affective pain rating index (PRI-A) was significantly higher during the 6% infusion in two muscles (3.9 ± 2.5) compared with the 6% infusion in one muscle (1.8 ± 1.7) in the movement experiment (Mann–Whitney U test: p = 0.03). The latter index was not different from that for the 9% infusion in one muscle (1.9 ± 2.7).

The pain rating indices in the position experiments were similar, but without any significant differences. The evaluative pain rating index (PRI-E) was significantly higher during 6% infusion in two muscles compared with the 9% infusion in one muscle (Mann–Whitney U test: p = 0.01). No other differences were found when comparing pain rating indices during the hypertonic infusions.

Effects of anxiety

Average trait anxiety score was 29.3 ± 5.5 (n = 8). Pearson’s two-tailed correlation test found no correlation between anxiety trait and VAS score (p = 0.83); hence, the subjects with a more anxious personality did not experience the experimental pain as more painful than subjects with less anxious personality. Also, there were no correlations between anxiety and the MPQ indices: PRI-S (p = 0.58), PRI-A (p = 0.13) and PRI-E (p = 0.37).

Average state anxiety score (n = 13) assessed before the subject participated in her first
experiment (29.8 ± 4.9) was higher compared with the score assessed after the first experiment was completed (27.0 ± 4.3; Wilcoxon, Z = -2.25, p = 0.024). This difference was not present when comparing anxiety states before and after the subsequent experimental sessions (Wilcoxon, Z = -1.40, p = 0.16).

Effects of experimental muscle pain on movement sense

In experiment 1 (0.9% and 6% saline in TA and SOL), there was a major effect of the 6% infusion, in both plantar and dorsal directions (Table 2; Fig. 3A). The average plantar movement detection threshold increased by >40% from pre-infusion to infusion (# in Fig. 3A). The average dorsal movement detection threshold increased by >30% during infusion (• in Fig. 3A). Average movement detection thresholds during the hypertonic infusion were not significantly different from before infusion (Table 2). The detection thresholds after the hypertonic and isotonic infusions were not different from before the infusions.

In experiment 2 (0.9% and 6% saline in TA), average plantar and dorsal movement detection thresholds during the 6% infusion were not significantly different from before infusion (Table 2, Fig. 3B). Also, there were no differences between the thresholds before and during the control infusion (Table 2). The detection thresholds after the hypertonic and isotonic infusions were not different from before the infusions.

In experiment 3 (9% saline in TA), average plantar and dorsal movement detection thresholds during the hypertonic infusion were not significantly different from before infusion (Table 2, Fig. 3C). The detection thresholds after the hypertonic infusion were not different from before infusion.

Effects of reference position, speed and reproduction speed on position sense

By combining different rotation speeds it was possible to investigate whether these movement-related components affected the ability to

| TABLE 2. Summary of main effects of saline infusions on plantar and dorsal movement detection thresholds and plantar and dorsal recognition errors. Statistical analysis was performed with repeated-measures ANOVAs. |
|---|---|---|---|---|---|---|---|
| n | Saline (%) | DF | F | p |
| Plantar | Dorsal | Plantar | Dorsal | Plantar | Dorsal |

Experiment 1 (0.9% and 6% saline in TA and SOL)

Movement sense

<table>
<thead>
<tr>
<th>Main effect of infusion</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

Position sense

<table>
<thead>
<tr>
<th>Main effect of infusion</th>
<th>8 (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

Interaction: during–after infusion, 20°

Experiment 2 (0.9% and 6% saline in TA)

Movement sense

<table>
<thead>
<tr>
<th>Main effect of infusion</th>
<th>10 (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
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Position sense

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<td>2</td>
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<tr>
<td>6</td>
<td>2</td>
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Experiment 3 (9% saline in TA)

Movement sense

<table>
<thead>
<tr>
<th>Main effect of infusion</th>
<th>9 (1)</th>
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<tbody>
<tr>
<td>9</td>
<td>2</td>
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Position sense

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<tr>
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<th>9 (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>2</td>
</tr>
</tbody>
</table>

n, number of subjects (number excluded, average VAS rating <1, in parentheses); DF, degrees of freedom; F, test statistics; p, level of statistical significance.
recognize the reference position. The analysis was performed on the pre-infusion measurements in experiment 1. A major effect of reference position was found for both error measurements. The plantar error was significantly smaller with a 10° reference position than with a 20° reference position ($p=0.004$; * in Fig. 4A). The dorsal error was significantly smaller with a 10° reference position than with a 20° reference position ($p=0.043$; $\#$ in Fig. 4B). A major effect of speed was found for the plantar error, which was significantly larger with rotation speed 10% than with rotation speed 5% ($p=0.025$). The dorsal error tended to be smaller than the plantar error ($p=0.059$). No significant differences were found between the different rotation speeds (plantar error, $p=0.12$; dorsal error, $p=0.09$) and reproduction speeds (plantar error, $p=0.27$; dorsal error, $p=0.43$).

Effects of experimental muscle pain on position sense

In experiment 1 (0.9% and 6% saline in TA and SOL), no differences in plantar or dorsal errors were found during any of the infusions, compared with before the infusions (Table 2, Fig. 4). The plantar and dorsal errors, where data from the two rotation speeds and the two reproduction speeds are averaged, are shown in Figures 4A and B. One interaction was found: the plantar error was significantly smaller after, compared with during, infusion of 6% saline for the 20° position (Table 2, in Fig. 4A). No interactions were found between any of the saline infusions and reference positions, rotation speeds or reproduction speeds.

In experiment 2 (0.9% and 6% saline in TA), no difference in plantar or dorsal errors was found during any of the infusions, compared with before the infusions. The errors after any of the infusions were not different from before the infusions.

In experiment 3 (9% saline in TA), no difference in plantar or dorsal errors was found during the infusion, compared with before infusion. The errors after the hypertonic infusion were not different from before infusion.

Undetected movements and missed positions

The numbers of wrong answers (wrong direction) and false positives (detected movement in the case of ‘dummy movement’) collected during the movement detection experiments were generally
low (<3%) and were not affected by the infusions. One of the subjects (former amateur ballet dancer) demonstrated a generally higher number of wrong answers than the rest of the group having 16 wrong answers alone. The median number of wrong answers for the whole group were 2. The proportion of misses in the reproduction experiment (not responding before the platform changed direction) was between 4% and 7% of the total number of responses and did not differ between the infusions.

**DISCUSSION**

In the present study, a reliable method was developed to test human ankle joint proprioception by means of detection of movement and recognition of joint position. Movement detection thresholds were determined by slow passive dorsal or plantar flexion of the ankle until movement was subjectively detected. A previously presented reference position was recognized by passive plantar and dorsal flexion of the ankle, yielding two error measurements. Pain was produced experimentally in one (TA) or two (TA and SOL) leg muscles and varied from low intensity (VAS = 2–3 cm) to intermediate intensity (VAS = 4–5 cm).

The general question addressed in the present study was to determine whether pain distorts proprioception. The present data indicate that human ankle proprioception seems rather robust against muscle pain. Despite the large spread of pain (Figs 2D–F), the ability to recognize a reference position was not distorted by pain at all. Only pain of intermediate intensity in two muscles disturbed the ability to detect movement changes. Movement detection was not disturbed with pain of similar intensity in one muscle.

**Sensory and affective measurements of experimental muscle pain**

The combination of two saline concentrations and two separate infusion sites made it possible to determine the relative importance of pain intensity and pain distribution in proprioceptive acuity. The pain intensities and distributions are similar to previous studies with infusion in TA and SOL (Graven-Nielsen et al., 1997a; Matre et al., 1998, 1999). Pain intensity and PRI-A (the affective pain rating index) were rated significantly higher during infusion of 6% saline in two muscles compared with infusion of 6% saline in one muscle. This indicates involvement of spatial summation and has been shown before for saline-induced muscle pain (Graven-Nielsen et al., 1997b).
Effects of experimental muscle pain on proprioception

Determining changes in proprioceptive input is a psychophysiological task depending on the information from the peripheral receptors and the spinal and central processing of this information. Thus, pain may modulate proprioceptive input at least three levels: (1) the information from the muscle receptors, (2) in the spinal cord and (3) during the supraspinal integration and evaluation of this information. From the present findings it is not possible to determine which of these that most likely explains the increased movement threshold; however, some speculations may be made.

**Disturbance of muscle receptors**

The importance of muscle spindles in signalling proprioceptive information is acknowledged (Matthews, 1988; Refshauge et al., 1995; Proske et al., 2000). If the observed pain-related increase in movement detection threshold should be related to changes in muscle spindle input, it seems to be most compatible with a reduced spindle sensitivity. In a recent study, Bergenheim and co-workers showed that an ensemble of muscle spindle input from several muscles contributes to encode ankle proprioception (Bergenheim et al., 2000). The present findings correspond to Bergenheim and co-workers' findings in that proprioceptive acuity is disrupted only with a large distribution of pain (disturbing a greater part of the muscle spindle ensemble). With the same intensity pain in a smaller area (disturbing fewer muscle spindles), the central neuronal system probably receives sufficient information from synergists, ago- and antagonists. Two cat studies supports a reduced information flow from the muscle spindle during nociceptive afferent input (Mense and Skeppar, 1991; Capra and Ro, 2000). Mense and Skeppar report a silent β-efferent activity after an artificial myositis, whereas Capra and Ro link their findings directly to proprioception by showing that the muscle nociceptive input (after injection of 5% hypertonic saline) produces a significant reduction in the information provided by brainstem neurones with 'muscle spindle secondary-like' properties. Whether these connections, where muscle nociceptive activity inhibits muscle spindle activity, are present in humans is not known. A recent study may provide support for this. Svensson et al. (2000) found that stretch-evoked reflexes in single-masseter motor units are reduced with ipsilateral experimental pain, and this reduction could stem from a reduced fusimotor drive that reduces the spindle firing. A similar mechanism could explain the increased movement threshold in the present study. Other studies do, however, report increased stretch-evoked reflexes during experimental pain when surface EMG is recorded, speaking for the opposite, an enhanced fusimotor drive during pain (Matre et al., 1998; Wang et al., 2000).

The only pain-related change to position sense in this study was a reduced plantar error after, compared with during, infusion of 6% saline for the 20° reference position (Fig. 4A). There is no obvious explanation for this improvement in position sense after pain in TA and SOL. It could indicate a non-nociceptive component of the saline stimulus that persists after the pain have vanished. The effect is seen only when moving in the plantar direction and with the most extreme position, which may suggest that the Golgi tendon organs are involved. Other studies have indicated that I\(b\) interneurones receive input from group III and IV muscle afferents (Kniffki et al., 1981).

**Spinal or supraspinal modulations**

An alternative explanation for the increased movement threshold could be found in an altered somatosensory processing in interneuronal circuits and central pathways during pain. Pain-induced sensitivity changes in dorsal horn neurones represent another potent source of modulation of proprioceptive input. Saline-induced muscle pain is associated with group IV afferent input (Mense, 1993; Laursen et al., 1999) that may cause sensitization of dorsal horn neurones (Hylden et al., 1989). The result may be an altered threshold to other stimuli (Hoheisel and Mense, 1989). Recently it has been reported that saline-induced muscle pain inhibits cutaneous touch perception, probably via temporal central
sensitivity changes in brainstem neurones (Stohler et al., 2001). A similar pain-induced inhibition of muscle or joint input could explain the reduced proprioceptive acuity in experiment I in the present study.

A possible confounding factor, that pertains to all experimental pain research, is a shift of attention during pain. Several studies have shown that strong pain takes priority of the attention (Eccleston and Crombez, 1999). One cannot exclude this as a contributing factor to the increased movement threshold with pain in two muscles. Indeed, the affective pain rating index (PRI-A) was significantly higher with intermediate intensity pain (6% saline) in two muscles, compared with low intensity pain (6% saline) in one muscle. PRI-A did not change between conditions with intermediate intensity and low intensity pain in one muscle. Thus, a significant change in PRI-A corresponds to a significant change in movement threshold. However, if simultaneous TA and SOL pain reduced the subjects' attention significantly, it seems strange that the ability to recognize reference positions was not affected at all.

Effects of reference position, speed and reproduction speed on matching errors

A general finding in the present study was a larger error with a 20° reference position, compared with a 10° reference position: this is compatible with other studies (Monter et al., 1973; Glencross and Thornton, 1981). There was a major effect of rotation speed; the subjects made larger errors when matching the reference positions at the highest speed. No effect of reproduction speed (during the recognition task) was found, although an effect of this parameter cannot be ruled out.

By using a passive recognition of position the subject could not 'tune in' on the reference position, as during reproduction with active movement of the limb. This method of testing revealed a rather large, although not significant, difference in magnitude between the two error measurements. The plantar error tended to be larger than the dorsal error for both reference positions (Figs 4A, B). It is not evident why the reference position is recognized more accurately during dorsal movement, but the relative contribution of spindle input from ankle extensors and flexors may play a role (Bergenheim et al., 2000).

Validation of methods

The present methods for testing position sense and movement sense for the human ankle joint seem valid and reliable. Both methods imply passive movement of the ankle, reducing α-γ co-activation. Cutaneous, visual and auditory cues are minimized. The average movement detection thresholds are comparable with thresholds from two other studies on the ankle (Gurfinke et al., 1979; Refshauge et al., 1995). Both higher (Clark et al., 1985) and lower (Laidlaw and Hamilton, 1937) thresholds have been found. Except for Laidlaw and Hamilton (1937), the other groups used a different procedure to determine the movement threshold (70% correct detection). The procedure used in the present experiment has previously been used to test movement sense in the knee (Barrack et al., 1984; Hall et al., 1994) and seems to be superior to methods with an arbitrary detection level because the movement is not stopped until a signal is given by the subject. Thus, no position cues may be used by the subject.

It has been demonstrated that if vibration is applied simultaneously to both the agonist and the antagonist muscles of a joint, no illusion of movement is felt (Gilibodes et al., 1986). If the muscle spindle endings were affected by vibration in the present experiments, they received the same disturbance before and during each movement sequence. The proportion of false-positive responses was less than 3%, and this mitigates against effects of vibration.

A well-known and reliable method for muscle pain induction, injection of hypertonic saline, has been used (Kellgren, 1938; Stohler and Lund, 1994; Graven-Nielsen et al., 1997a; Matre et al., 1998) and produced a stable pain intensity over 10 min. Injection of hypertonic saline into the muscle probably activates both nociceptive
afferents and low threshold mechanosensitive afferents (Iggo, 1960; Painal, 1960; Mense, 1993). It was recently reported that altered firing in muscle spindle afferents during saline are probably mediated via fusimotor neurones and not caused by direct effects on the receptor endings (Hellström et al., 1999).

CONCLUSION

To assess proprioceptive acuity of the human ankle joint, two reliable methods were developed to test passive movement detection and recognition of previously presented reference positions. Larger errors were made when approaching the reference position in the plantar direction than in the dorsal direction. Both error measurements were larger when recognizing the more extreme position, and there was an interaction between matching error and the speed of rotation.

Ankle joint proprioception seems robust to experimentally induced muscle pain. Pain disturbs detection of movement only when induced in two muscles simultaneously, at relatively high intensity, and with relatively large distribution. Possible explanations of the increased threshold are that relatively high intensity pain (located in an agonist-antagonist muscle pair) (1) reduces the sensitivity in muscle spindle receptors, (2) alters thresholds of spinal interneurones to sensory signals and (3) reduces the ability to interpret proprioceptive signals. However, the central nervous system seems to have enough information available from other afferents to identify changes in movement and position, even under relatively high intensity pain in one muscle. Whether other joints exhibit the same robustness to pain is not known and requires further investigation. A functional interpretation of the present findings is that pain is secondary to, and not causing, reduced proprioception. In patients with more widespread muscle pain, however, a reduced awareness of movement combined with a general motor system inhibition (Le Pera et al., 2001) could augment an impaired sensory–motor interaction.

ACKNOWLEDGEMENTS

We kindly acknowledge Peter S. Nicolaysen for skilful technical assistance, Janne Schiell for helping with the experiments and Drs Morten Waersted and Cecilie Roe for performing the medical examinations. All are affiliated with National Institute of Occupational Health, Norway. The Danish National Research Foundation and the Norwegian Research Council are kindly acknowledged for financial support.

REFERENCES


Gabapentin and pregabalin suppress tactile allodynia and potentiate spinal cord stimulation in a model of neuropathy

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Department of Clinical Neuroscience, Section of Neurosurgery, Karolinska Institutet, Stockholm, Sweden

Spinal cord stimulation (SCS) is an effective tool in alleviating neuropathic pain. However, a number of well-selected patients fail to obtain satisfactory pain relief. Previous studies have demonstrated that i.t. baeolofen and/or adenosine can enhance the SCS effect, but this combined therapy has been shown to be useful in less than half of the cases and more effective substances are therefore needed. The aim of this experimental study in rats was to examine whether gabapentin or pregabalin attenuates tactile allodynia following partial sciatic nerve injury and whether subeffective doses of these drugs can potentiate the effects of SCS in rats which do not respond to SCS. Mononeuropathy was produced by a photochemically induced ischaemic lesion of the sciatic nerve. Tactile withdrawal thresholds were assessed with von Frey filaments. Effects of increasing doses of gabapentin and pregabalin (i.t. and i.v.) on the withdrawal thresholds were analysed. These drugs were found to reduce tactile allodynia in a dose-dependent manner. In SCS non-responding rats, i.e. where stimulation per se failed to suppress allodynia, a combination of SCS and subeffective doses of the drugs markedly attenuated allodynia. In subsequent acute experiments, extracellular recordings from wide dynamic range neurones in the dorsal horn showed prominent hyperexcitability. The combination of SCS and gabapentin, at the same subeffective dose, clearly enhanced suppression of this hyperexcitability. In conclusion, electrical therapy and pharmacological therapy in neuropathic pain can, when they are inefficient individually, become effective when combined. © 2002 European Federation of Chapters of the International Association for the Study of Pain. Published by Elsevier Science Ltd. All rights reserved.

KEYWORDS: neuropathy, pain, gabapentin, pregabalin, spinal cord stimulation, rat.

INTRODUCTION

Chronic neuropathic pain caused by peripheral nerve injury is often associated with sensory abnormalities such as tactile allodynia, which can be described as pain induced by normally innocuous mechanical stimuli applied to the hypersensitive area. Such evoked pain is generally difficult to control. Hypersensitivity to innocuous stimuli is also present in rats with peripheral nerve lesions (Bennett and Xie, 1988; Seltzer et al., 1990) and thus resembles allodynia observed in patients with neuropathy.

Spinal cord stimulation (SCS) has been used since the late 1960s as a powerful tool in alleviating chronic pain (Meyerson and Linderoth, 2000b). Neuropathic pain following peripheral nerve injury is by many considered the best indication for SCS, but about 30% of well-selected patients fail to obtain satisfactory pain relief (Simpson, 1994). Despite research in recent years, the underlying mechanisms behind the positive effects of SCS are still unclear to a large extent (Linderoth and Foreman, 1999; Meyerson and Linderoth, 2000a).
As knowledge of the neurochemical mechanisms behind SCS and the pathophysiology of neuropathic pain has accumulated, it has been suggested that a combination of SCS and pharmacological agents might be useful to improve pain relief. To date, there are for example robust data showing that the development of neuropathic pain involves an impairment of the GABAergic (GABA, γ-aminobutyric acid) system in the spinal dorsal horn (e.g. Castro-Lopes et al., 1993; Cui et al., 1996, 1997b). It has been demonstrated that SCS induces an increase of GABA release as well as a decrease in the release of glutamate and aspartate in the dorsal horn of sciatic nerve injured allodynic rats (Stiller et al., 1996; Cui et al., 1997a). In line with these observations, studies in both animal models and patients show that the GABA, receptor agonist baclofen, when administered intrathecally, may potentiate the pain suppressing effect of SCS (Meyerson et al., 1997; Cui et al., 1998). However, this combined therapy is successful in less than half of the patients and there is a need for new and more effective drugs to be used in combination with SCS.

Gabapentin (Neurontin®) and pregabalin are two structurally related anticonvulsant drugs which have been shown to suppress tactile allodynia in rats induced by streptozocin (Field et al., 1999b), chronic constriction injury (CCI) as well as by spinal nerve ligation (Xiao and Bennett, 1995; Abdi et al., 1998; Field et al., 1999a). Gabapentin and pregabalin bind specifically, and with similar affinity, to the same site in central nervous system neurones (Taylor et al., 1998) identified as the α2δ subunit of voltage-dependent Ca2+ channels (Gee et al., 1996). It can therefore be assumed that the anti-allodynic effects of gabapentin and pregabalin involve the same central mechanisms. Regarding gabapentin, there are numerous animal studies suggesting that this drug may be useful for controlling acute nociceptive, as well as many different types of neuropathic, pain (Hunter et al., 1997; Jun and Yaksh, 1998; Partridge et al., 1998; Kayser and Christensen, 2000). Results from recent clinical studies have suggested that gabapentin is effective in the treatment of, for example, reflex sympathetic dystrophy (Mellick and Mellick, 1997), pain in diabetic neuropathy (Backonja et al., 1998) and postherpetic neuralgia (Rowbotham et al., 1998).

The present study was undertaken to first examine the abilities of i.v. and i.t. gabapentin and pregabalin to suppress tactile allodynia in rats subjected to ischaemic sciatic nerve injury. The principal aim was to analyse the capabilities of low or subeffective doses of these drugs to potentiate the SCS effect in rats with mono-neuropathy where the stimulation per se had no significant suppressing effect on the allodynia. Furthermore, we recorded neuronal activity of wide dynamic range (WDR) cells in the spinal dorsal horn following SCS and i.t. gabapentin infusion alone, as well as following SCS in combination with gabapentin.

MATERIAL AND METHODS

Animals

Male Sprague-Dawley rats (200–400 g, n = 66, B&K Universal AB, Sollentuna, Sweden), housed at the local animal department, were used. The animals were exposed to a 12 h light–dark cycle and were provided with food and water ad libitum. The experiments were carried out according to the recommendations of the Committee for Research and Ethical Issues of the IASP (1983) and were approved by the regional ethical committee for animal research. All efforts were made to minimise animal suffering and to reduce the number of animals used.

All surgical procedures were performed under general halothane anaesthesia and under sterile conditions. Briefly, anaesthesia was induced with 4% halothane and maintained with 1–2% in a 1 : 1 mixture of air and oxygen delivered at a rate of approximately 2 l/min. A heating pad was used to maintain a constant body temperature of 37°C during surgery.

Induction of nerve injury

A photochemically induced ischaemic nerve lesion (Gazelius et al., 1996) was used to produce mononeuropathy. The left sciatic nerve was
exposed by blunt dissection at the mid-thigh level and isolated from surrounding tissues. An arrow-shaped strip of aluminium foil was then inserted under the nerve in order to reflect the laser beam. A photochemically active dye, Erythrosin B (50 mg/kg, Sigma-Aldrich, Steinheim, Germany), was administrered by i.v. injection in a tail vein. Immediately after the injection, the sciatic nerve was irradiated for 20 min by a green low-energy laser (Laser-Compact Company Ltd, Moscow, Russia) with a wavelength of 532 nm and an output power of 5 mW. The wound was then sutured in layers and the animal was put back in its cage to recover. The choice of this ischaemic model of neuropathy for the present study was based on previous observations that the incidence of allodynia is very high and that hypersensitive animals exhibit an extremely low response rate to SCS (Cui et al., 1998). In total, 56 rats with ischaemic nerve injury were studied.

For comparison, 10 rats subjected to the CCI model (Bennett and Xie, 1988), where the sciatic nerve was loosely ligated four times approximately 1 mm apart with a 4-O catgut suture, were also included in the study.

**Implantation of spinal electrodes**

After exposure of the spine, a small laminectomy was carried out at the thoracic vertebra T12. The cathode (a thin solid silver rectangular plate: 3 mm × 1.5 mm × 0.25 mm) of the spinal electrode was introduced in the dorsal epidural space, whereas the anode (a solid silver disc, 6 mm in diameter) was placed subcutaneously on the left lateral side of the spine. A microcontact connected to the two poles via plaited insulated Teflon-coated stainless steel wires was then tunnelled subcutaneously and fixed to the skin. To avoid damage to the microcontact, the animal was put in a separate cage after surgery and allowed to recover for at least 24 h before further experiments.

**Implantation of intrathecal catheters**

Under halothane anaesthesia, a PE-10 catheter was inserted via a 21G needle used for puncturing the lumbosacral canal and advanced in a caudo-rostral direction up to the lumbar enlargement. The catheter was fixed to the fascia with tissue glue, tunnelled subcutaneously and fixed to the neck skin. In order to verify the position of the catheter physiologically, 500 μg of lidocain (Xylocain, AstraZeneca, Södertälje, Sweden) was injected, which induces a transient complete paralysis of the hind limbs.

**Spinal cord stimulation**

The parameters used for SCS in this animal model have been chosen to mimic those used in the clinic. Monopolar electrical stimulation was applied with a frequency of 50 Hz, a pulse width of 0.2 ms and a stimulation intensity individually set to 2/3 of the motor threshold. The parameters used here are the same as in previous studies (e.g. Linderoth et al., 1991). The motor threshold was recognized as slight twitching of the lower trunk muscles. For behavioural testing, SCS was applied for 30 min and the withdrawal thresholds to mechanical stimulation were assessed regularly with von Frey filaments. During the experiments, the animals were allowed to move freely in circular observation cages with wire mesh floors. Stimulation was started 60 min after i.v. administration and immediately after i.t. administration of gabapentin or pregabalin. For the electrophysiological experiments, SCS was applied twice for 5 min each time. First, SCS was given after identification of input properties of dorsal horn neurones and then gabapentin was injected i.t. 5–20 min after cessation of SCS. Secondly, additional SCS was applied 10–20 min following administration of gabapentin.

**Testing of withdrawal response to tactile stimuli**

In order to quantify the degree of alldynia, withdrawal thresholds to static tactile stimulation were evaluated with von Frey nylon monofilaments.

The animal was put in a Plexiglass cage with a metal mesh floor and allowed to adapt for at least
10 min before testing. The filaments were applied through the floor to the mid-plantar surface of the paw, so that the filament bent gently. Von Frey filaments with calibrated stiffnesses corresponding to 1, 2, 4, 5, 8, 11, 12, 17, 19 and 30 g were used. Testing was started with the softest filament and continued in ascending order of stiffness. The filament corresponding to 30 g was selected as cut-off. The withdrawal thresholds were compared for the same parts of the hind paw of the intact and the nerve-injured paw. Only animals that had developed tactile allodynia, defined as withdrawal from at least 5 out of ten applications of a filament corresponding to 8 g or less, were included in the experiment. All animals were subjected to von Frey testing every 30 min when given a drug i.v. and every 10 min when given a drug by i.t. administration.

Electrophysiological study

Subsequent to the behavioural experiments, acute electrophysiological experiments were conducted with SCS in combination with i.t. gabapentin in the same rats and the same subeffective doses that were used in the behavioural tests. These experiments were carried out under halothane anaesthesia and the heart rate was monitored through electrocardiogram electrodes implanted subcutaneously into the forepaws.

The spinal cord was exposed by a laminectomy of T11–L1. In order to avoid interference from breathing movements, the vertebral column was rigidly fixed in the horizontal position by clamps holding the spinal processes and lifting the animal, so that it was hanging in the experimental frame. The dura mater was then incised and reflected, and a pool using the skin flaps around the exposed spinal cord was created and filled with preheated (37°C) paraffin oil.

Recordings were made with tungsten micro-electrodes (impedance at 1000 Hz was 4–5 MΩ) (Frederick Haer, Brunswick, GA, USA) driven by an electronically controlled motor unit in steps of 2 μm (SCAT-01, Digitimer, Welwyn, Garden City, UK). Extracellular single-unit activity was recorded from WDR neurones in the spinal dorsal horn ipsilaterally to the nerve injury in segments L3–L5 medially to the dorsal root entry zone. Unitary activity was amplified and led to an analogue–digital system (Neurolog System, Digitimer Ltd, Welwyn Garden City, UK, and MacLab/4, Castle Hill, Australia) via a window discriminator for recording neuronal responses and construction of peristimulus time histograms. The distance between stimulating and recording sites varied between 5 and 10 mm depending on the position of the recording electrode.

Identification of a WDR neurone was carried out by testing its ability to respond, in a gradual manner, to various stimuli (brush < press < pinch) applied to the plantar surface of the nerve-injured paw (Yakhnin et al., 1999). After identification, the cell was tested with innocuous mechanical stimuli which consisted of gentle paw pressure with a flat-tipped forceps. Mechanical stimuli were applied for 10 s at least 60 s apart.

Drug administration

Gabapentin (Neurontin®) and pregabalin (CI-1008, S- (+)-3-isobutylGABA) were obtained from Parke-Davis, division of Warner-Lambert Co, Ann Arbor, MI, USA (now Pfizer Inc). Drugs were administered at an average volume of 2 ml/kg for i.v. injection and a volume of 10 μl for i.t. injection. In the first part of the experiment, both dose-response and time-response characteristics for the drugs were studied. Doses of 10–100 mg/kg and 5–50 mg/kg were used for i.v. injection of gabapentin and pregabalin respectively and the animals were tested for 5 h. For i.t. administration, doses of 25–200 μg were used for gabapentin and 1.8–60 μg for pregabalin, and the animals were tested for 3 h. In the second part of the experiment, individually screened subeffective doses of the drugs were given (both i.v. and i.t.) in combination with SCS. The subeffective dose for each animal was defined as the highest dose tested that did not suppress tactile allodynia (see definition above in ‘Testing of withdrawal response to tactile stimuli’). In the third part of the experiment, activity in WDR neurones was recorded before and after