

Gabapentin Suppresses Cutaneous Hyperalgesia following Heat-Capsaicin Sensitization

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Background: The anticonvulsant gabapentin, proven effective for neuropathic pain in two large, placebo-controlled clinical trials, is widely used for treatment of chronic pain. Preclinical studies have demonstrated analgesic and antiallodynic effects in models involving neuronal sensitization and nerve injury, without affecting acute pain transmission. The aim of the present study was to link data from animal models and clinical trials for chronic pain by investigating the effect of gabapentin on acute nociception and experimentally induced cutaneous hyperalgesia in healthy volunteers.

Methods: The human experimental hyperalgesia model, the heat-capsaicin sensitization model, was induced in 25 healthy male volunteers. Subjects received oral gabapentin (1,200 mg) or placebo after heat-capsaicin sensitization was established on the forearm. The primary outcome measures were the sizes of the areas of secondary hyperalgesia to von Frey hair and brush stimulation on the forearm. Secondary outcome measures were as follows: (1) size of secondary hyperalgesia area in response to brief thermal sensitization procedure on the thigh; (2) heat pain detection thresholds in normal and sensitized skin; and (3) painfulness of 1 min of 45°C stimulation in normal skin.

Results: Oral gabapentin profoundly suppressed established cutaneous sensitization on the forearm and prevented development of cutaneous sensitization on the thigh. Thermal nociception in normal skin was unchanged. Side effects were modest.

Conclusion: The results link preclinical findings with results from clinical trials of neuropathic pain. The results further suggest that gabapentin may prove effective in acute pain disorders involving neuronal sensitization, such as postoperative pain and acute herpetic pain, and could prove effective in prevention of chronic pain.

THE anticonvulsant gabapentin is widely used for treatment of chronic pain. Animal studies have shown that gabapentin does not alter acute nociception^{1,2} but suppresses experimentally induced hyperalgesia.²⁻⁴ Preclinical studies have also demonstrated that gabapentin re-

duces the allodynia and hyperalgesia associated with experimentally induced chronic nerve injury.^{1,5} Despite intensive investigation, the analgesic mechanism of action of gabapentin remains unsettled (for review, see Taylor *et al.*⁴).

Two large, placebo-controlled clinical trials demonstrated that gabapentin at a target dose of 3,600 mg/day reduced pain intensity in patients with postherpetic neuralgia and diabetic neuropathy.^{6,7} These studies did not investigate whether gabapentin reduced touch-evoked allodynia, which for many patients is the most disabling symptom. An open-label study of gabapentin at doses of up to 2,400 mg/day in 18 patients with chronic neuropathic pain of peripheral and central origin suggested improvement in daily pain, mechanical allodynia, and cold hyperalgesia but no effect on thermal and mechanical pain thresholds.⁸ No clinical studies of acute pain conditions have been reported.

Reliable and noninvasive human experimental pain models have been developed and have the potential to bridge the gap between animal models and clinical pain disorders. Available human experimental pain models test acute nociception and can produce neuronal sensitization but, for obvious ethical reasons, cannot involve actual nerve injury. Healthy volunteer models that use a prolonged or intense focal noxious stimulation to induce reversible cutaneous allodynia and hyperalgesia may replicate some aspects of clinical neuropathic pain. The extent to which human experimental pain models share underlying mechanisms with acute and chronic clinical pain conditions, especially of neuropathic origin, continues to be debated.⁹

To be of value in drug development, the profile of analgesic effects of a drug in human experimental pain model studies should be similar to the results in preclinical models and accurately predict results in clinical trials. An example is opioids, which have been proven effective in preclinical models and human experimental models involving acute pain and neuronal sensitization,⁹ as well as in controlled clinical trials of acute and chronic pain.¹⁰ Gabapentin has shown analgesic efficacy in preclinical models of neuronal sensitization, animal nerve injury models, and clinical trials of neuropathic pain. In two recent human experimental pain studies, gabapentin was without effect on cold pain tolerance¹¹ and the area of secondary hyperalgesia following an experimental burn injury, but it did reduce mechanical allodynia in sensitized skin.¹²

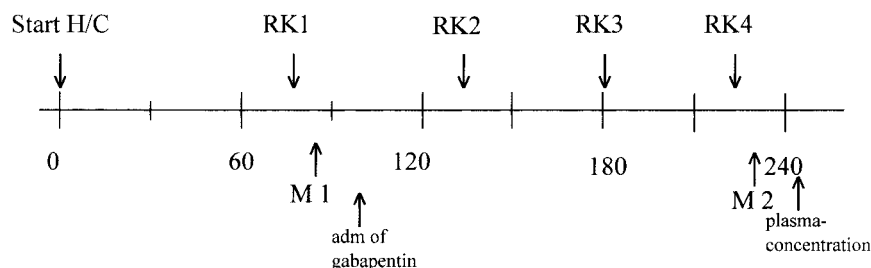
The aim of the present study was to use the heat-capsaicin sensitization model¹³ to investigate the effect

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Fig. 1. Time course of the study day in minutes. H/C = heat-capsaicin sensitization. RK = rekindling (40°C for 5 min). M1 = baseline measurements, including the following: (1) quantification of area of secondary hyperalgesia around heat-capsaicin-stimulated skin on the dominant forearm; (2) brief thermal sensitization on the thigh with 45°C for 3 min followed by quantification of area of secondary hyperalgesia; (3) heat pain detection thresholds (HPDT) in normal skin on the upper arm and in the heat-capsaicin-sensitized skin; and (4) long thermal stimulation (45°C for 1 min) in normal skin on the nondominant forearm. M2 = measurements as above (1–4) started 135 min after administration of study drug.



of gabapentin on acute nociception and experimentally induced neuronal sensitization in healthy volunteers. The results will suggest whether gabapentin should be further evaluated in acute clinical pain conditions involving neuronal sensitization, such as postoperative pain. Moreover, a study using this clinically effective compound will further test the validity of the heat-capsaicin sensitization model in testing of new analgesic compounds.

Materials and Methods

Subjects and Study Design

Subjects in this study were 25 pain-free and unmedicated adult male volunteers. Informed consent was obtained from all subjects, and the study was approved by the regional ethics committee and the Danish National Health Board (Copenhagen, Denmark). All study procedures were performed by the same investigator (J. Dirks) in a quiet room with subjects in a semisupine position, at least 1 week apart. Each subject had been familiarized with the study procedures on a separate day. All thermal stimulations were performed with a computer-controlled thermode (12.5 cm²; Thermotest; Somedic A/B, Hörby, Sweden).

The time line for study procedures is displayed in figure 1. Time 0 was the beginning of the heat-capsaicin sensitization procedure. The first set of study measurements (baseline, M1) took place before drug administration from $t = 75$ –90 min. Study drug administration took place at $t = 95$ min. The second set of study measurements (postdrug, M2) took place from $t = 225$ –240 min. Final study procedures were completed at $t = 245$ min.

Heat Pain Detection Thresholds and Pain during Long Thermal Stimulation

Heat pain detection threshold (HPDT), defined as the lowest temperature perceived as painful, was determined in normal skin on the nondominant upper arm and in heat-capsaicin-sensitized skin (in the area with primary hyperalgesia) on the dominant forearm. The starting temperature of the thermode was 32°C, and the rate of increase was 1°C/s. By pressing a button, subjects indicated when the threshold was reached. If the cutoff limit (52°C) was reached before the pertinent threshold,

the thermode returned automatically to the starting value, and 52°C was registered. Each threshold was calculated as an average of four stimulations; stimulations were 6–10 s apart.

Subjects were further asked to rate the painfulness of a 1-min-long 45°C heat stimulus (long thermal stimulation [LTS]) applied to normal skin on the nondominant forearm. Pain was rated on the electronic Visual Analog Scale (VAS), consisting of a vertical bar on a computer screen (sample rate, 2 Hz) anchored with the descriptors “no pain” (numeric value = 0) and “worst possible pain” (numeric value = 100). The subjects were able to see the VAS rating screen during each assessment, and each VAS measurement was independent of the previous measurement. Assessments of HPDT and LTS were performed at M1 and 140 min after administration of gabapentin or placebo after drug administration at M2.

Induction and Maintenance of Heat-Capsaicin Sensitization on the Forearm

Sensitization was produced by heating the skin of the dominant forearm to 45°C for 5 min with the thermode. Immediately thereafter, the skin was covered with capsaicin cream (0.075% capsaicin, Zostrix; Medicis Pharmaceutical Corp., Phoenix, AZ) for 30 min. The sensitization was rekindled four times by heating the treatment site with the thermode at 40°C for 5 min. The first rekindling was performed before drug administration at $t = 75$ (40 min after removal of capsaicin cream), and the fourth was performed at $t = 225$. Mapping of secondary hyperalgesia areas was performed after the first and fourth rekindlings.

Measurement of Secondary Hyperalgesia

The area of secondary hyperalgesia was quantified with a foam paint brush and with a 21.5-g von Frey hair. The borders of hyperalgesia were determined by stimulating along four linear paths arranged radially around the stimulation site in steps of 5 mm at intervals of 1 s. Stimulation started in normal skin and continued toward the stimulation site until subjects reported a clear change in sensations (“burning,” “tenderness,” “more intense pricking”). The borders were marked with a felt

pen, and the distances were measured for later surface area calculations.

Induction of Brief Thermal Sensitization on the Thigh

Brief thermal sensitization was produced at $t = 85$ and $t = 235$ min. Sensitization was induced with the thermode placed on the center of the anterior side of the dominant thigh at 45°C . After 3 min of heating, the borders of hyperalgesia were determined in the same manner as described above before the thermode was removed.

Study Medication and Safety

For this two-session, double-blind, randomized, placebo-controlled, crossover study, gabapentin was purchased by the investigators and prepared by the hospital pharmacist (D. L.) into identical capsules containing either 300 mg gabapentin or placebo. On the study days, the subjects received 1,200 mg oral gabapentin or placebo immediately after the first rekindling and baseline measurements ($t = 95$ min, fig. 1) according to a computer-generated randomization schedule prepared by the pharmacy. Side effects (lightheadedness, drowsiness, headache, decreased coordination, visual disturbances, and nausea) were rated by the subjects on a four-point verbal scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) at 90 and 135 min after drug administration.

Plasma Concentration of Gabapentin

Peripheral blood was collected from the cubital vein on the nondominant arm 150 min after drug administration to determine the plasma concentration of gabapentin. Samples were obtained in serum tubes, and plasma was separated by centrifugation at room temperature and stored at -80°C until drug assay. Assay of plasma was performed by high-performance liquid chromatography, at neutral pH, after derivatization with 2,4,6-trinitrobenzenesulphonic acid. All samples were performed in the same series to avoid analyze dispersion between series. Assay was performed by the laboratory Kolonien Filidelfia (Dianalund, Denmark).

Statistical Analysis

A power calculation indicated that 25 subjects were necessary to achieve 80% power to detect a 20% treatment difference in the area of secondary hyperalgesia, with $\alpha = 0.05$ (two tailed). The painfulness of LTS was calculated as area under the curve and then converted to mean VAS values (0–100). Data are presented as median (lower and upper quartiles). Variables were evaluated with the Wilcoxon test for paired data. All significant P values were corrected with the Bonferroni test for repeated measurements. Before entering statistical analyses, data from each subject were normalized in relation to data obtained before administration of study drugs

(baseline), to achieve the same point of reference. $P < 0.05$ was considered statistically significant. Calculations were performed using SPSS 10.0 for Windows (SPSS, Chicago, IL). The statistical analysis was performed by the investigators.

Results

All 25 male subjects, aged 20–30 yr, completed the study.

Heat-Capsaicin Sensitization and Brief Thermal Sensitization

Combined sensitization with heat and capsaicin, and brief thermal sensitization, produced areas of secondary hyperalgesia to von Frey hair and brush stimulation that could be mapped easily in all subjects. The size of the areas of secondary hyperalgesia to heat-capsaicin sensitization was maintained throughout the study day. In contrast, the areas of secondary hyperalgesia after the brief thermal sensitization procedure lasted only shortly after the thermode was removed, and there were no spontaneous sensations or sensitization in the skin prior to the next brief thermal sensitization.

Baseline areas of secondary hyperalgesia to von Frey hair stimulation were comparable on the two study days after both heat-capsaicin sensitization (gabapentin: 127 [range, 103–157] *vs.* placebo: 97 [75–144] cm^2 ; $P = 0.08$) and brief thermal sensitization (201 [128–299] *vs.* 150 [117–278] cm^2 ; $P = 0.53$). In contrast, baseline areas of secondary hyperalgesia to brush stimulation were significantly larger on the gabapentin day compared with the placebo day after both heat-capsaicin (54 [43–82] *vs.* 36 [31–58] cm^2 ; $P = 0.004$) and brief thermal sensitization (121 [65–188] *vs.* 70 [53–132] cm^2 ; $P < 0.001$).

Effect of Gabapentin on Established Heat-Capsaicin Sensitization

The established areas of secondary hyperalgesia to von Frey hair and brush stimulation were reduced to 24% (20–32%) and 31% (25–39%) of baseline size 135 min after gabapentin administration, whereas the areas were maintained at 96% (91–114%) and 109% (93–121%) of baseline size after placebo administration (fig. 2). These differences between gabapentin and placebo were significant ($P < 0.0001$).

Effect of Gabapentin on Induction of Brief Thermal Sensitization

The areas of secondary hyperalgesia to von Frey hair and brush stimulation induced by brief thermal sensitization 140 min after gabapentin administration were 25% (20–35%) and 23% (18–34%) of the areas induced at baseline, while after placebo, brief thermal sensitiza-

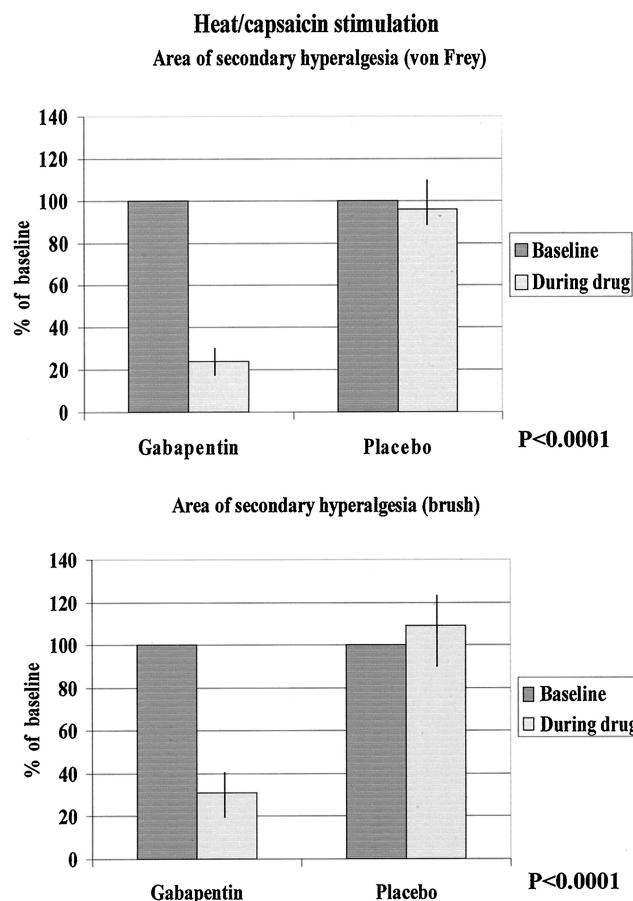


Fig. 2. Area of secondary hyperalgesia after heat–capsaicin sensitization expressed percentage of baseline to von Frey hair and brush stimulation. Baseline: Area of secondary hyperalgesia after rekindling 1 (before drug administration). During drug: Area of secondary hyperalgesia after rekindling 4, median lower and upper quartiles (135 min after administration of study drug).

tion-induced areas similar to baseline (von Frey hair: 100% [90–124%] and brush stimulation: 107% [90–146%]; fig. 3). These differences between gabapentin and placebo were significant ($P < 0.0001$).

Heat Pain Detection Thresholds and Pain during Long Thermal Stimulation

After study medication, HPDTs in sensitized skin were significantly higher on the gabapentin day compared with the placebo day (43.9 [42.4–45.0] *vs.* 42.8 [41.8–44.3]°C; $P = 0.02$). HPDTs in normal skin were not significantly different after administration of gabapentin *versus* placebo (44.1 [42.9–45.2] *vs.* 43.1 [41.5–44.7]°C; $P = 0.06$). Baseline values of VAS pain during LTS were not significantly different between the gabapentin day and the placebo day (51 [37–71] *vs.* 46 [38–62] mm; $P = 0.35$). The painfulness of LTS was not different after administration of gabapentin *versus* placebo (50 [42–62] *vs.* 60 [32–72] mm; $P = 0.34$).

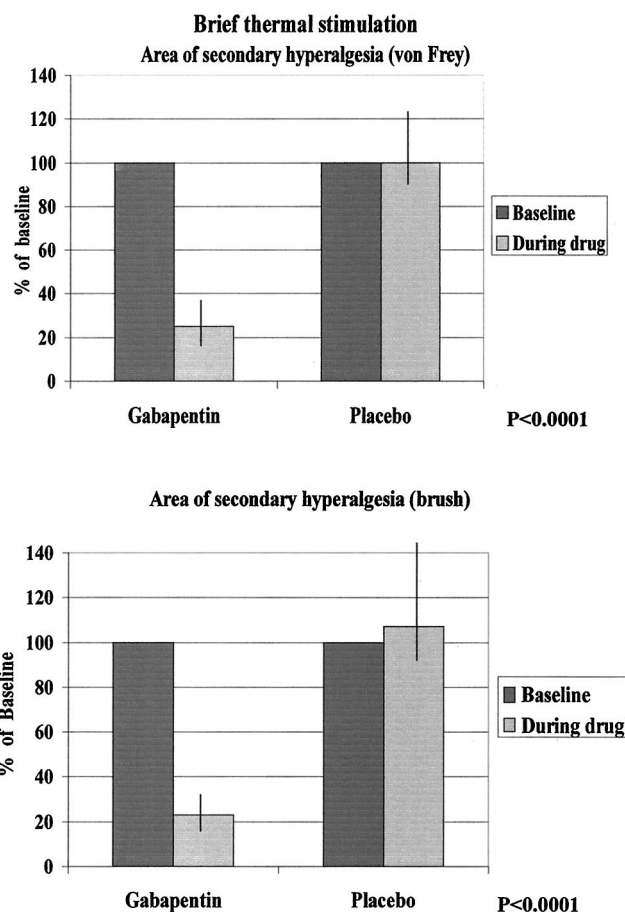


Fig. 3. Area of secondary hyperalgesia after brief thermal sensitization on the thigh in percent of baseline to von Frey hair and brush stimulation. Baseline: Area of secondary hyperalgesia after rekindling 1 (before drug administration). During drug: Area of secondary hyperalgesia after rekindling 4, median lower and upper quartiles (140 min after administration of study drug).

Side Effects

Lightheadedness was observed more frequently after administration of gabapentin than with placebo (seven *vs.* two subjects; $P < 0.05$), and was rated as “mild” to “moderate” by all who experienced it. The incidence of other side effects (drowsiness, headache, decreased coordination, visual disturbances, and nausea) was not significantly different between gabapentin and placebo. All subjects were able to cooperate fully during the various assessments. No blistering, skin pigmentation, or any other changes of the skin were observed in any of the subjects.

Plasma Concentration of Gabapentin

The median plasma concentration of gabapentin 150 min after drug administration was 29 M (range, 15–47 M).

Discussion

Oral gabapentin profoundly suppressed established secondary hyperalgesia on the forearm to less than 30%

of baseline and substantially prevented development of secondary hyperalgesia on the thigh. These effects are strong evidence that gabapentin prevents development of neuronal sensitization and reverses established neuronal sensitization. The observed magnitude of hyperalgesia suppression is comparable to that observed with intravenous administration of the potent opioid remifentanyl in a previous study using the heat-capsaicin sensitization model.¹⁴ Remifentanyl also suppressed responses to noxious heat in normal skin. However, in the present study, thermal pain thresholds and acute suprathreshold stimulation in normal skin were unchanged, suggesting that gabapentin does not reduce acute nociceptive transmission. The characteristic of oral gabapentin in reducing primary and secondary hyperalgesia without affecting acute nociceptive transmission is analogous to intravenous administration of the *N*-methyl-D-aspartate (NMDA) antagonist ketamine demonstrated in a previous study in human volunteers.¹⁵

Our data corresponds closely with gabapentin data obtained in preclinical and clinical trials. In rat studies, systemic and intrathecal gabapentin dose-dependently reduced thermally induced experimental secondary hyperalgesia, formalin phase 2 response, and substance P- and NMDA-induced hyperalgesia^{3,2,15} but had no effect on thermal withdrawal thresholds.^{1,2,16} Gabapentin relieved neuropathic pain in two large, placebo-controlled clinical trials of postherpetic neuralgia and diabetic neuropathy^{7,6} and reduced allodynia in an open-label study of neuropathic pain of peripheral and central origin.⁸ No studies of clinical acute pain conditions have been performed. Two studies have been performed in healthy volunteers. Eckhardt *et al.*¹¹ demonstrated that 600 mg gabapentin and 60 mg morphine (controlled release) in combination increased pain tolerance to cold stimulation by 75%. Morphine alone increased the pain tolerance by 40%, and gabapentin alone insignificantly increased cold tolerance by 19%. The small effect of gabapentin in that study could be due to the small number of subjects or the lower dose of 600 mg gabapentin. There are no animal studies using measures analogous to cold tolerance. In another study, Werner *et al.*¹² examined the effect of 1,200 mg gabapentin on acute thermal pain, thermal and mechanical pain thresholds in normal and sensitized skin, and areas of secondary hyperalgesia following an experimental burn injury. Gabapentin significantly reversed mechanical allodynia in sensitized skin and insignificantly attenuated other study parameters, including the area of secondary hyperalgesia to von Frey hair stimulation. Study medication was administered 3 h before the burn injury, and outcome measures were followed for 3 h after sensitization. As side effect scores peaked 3 h after administration, it is possible that measurements may have been performed after the peak analgesic effect of gabapentin, which may

explain the modest effect of gabapentin on study measures.

Corresponding results across preclinical, human experimental, and clinical trials have also been demonstrated for intravenous opioids and sodium channel blockers.^{14,17} The analgesic effects of opioid medications are consistent across preclinical models of acute pain, sensitization, and nerve injury. In healthy volunteers, opioids reduce pain in models of acute pain and sensitization,⁹ and in clinical trials, perioperative, postoperative, and chronic neuropathic pain are all relieved.¹⁰ In contrast, intravenous sodium channel blockers, such as lidocaine, have little effect in preclinical models of acute pain, modest effect at higher doses in models of neuronal sensitization, and profound effect at relatively low doses in models of nerve injury.¹⁸ Likewise, lidocaine has little effect on human experimental models of acute pain and sensitization,¹⁷ a very modest effect on perioperative and postoperative pain (for review, see Petersen and Rowbotham¹⁹), but a sometimes dramatic effect on chronic neuropathic pain (for review, see Kalso *et al.*²⁰). These similarities spanning preclinical, human experimental, and clinical trials in response to different pharmacologic agents validate the role of the heat-capsaicin sensitization model in phase I testing of new analgesic compounds that are thought to have a potential in pain conditions involving neuronal sensitization.

The similarity in gabapentin effect on secondary hyperalgesia associated with heat-capsaicin sensitization and the allodynia associated with neuropathic pain suggest that experimental cutaneous hyperalgesia has mechanistic similarities to chronic neuropathic allodynia. This is further supported by a recent study of the mechanisms underlying postherpetic neuralgia, showing that in some patients, the allodynia appears to be a form of chronic secondary hyperalgesia maintained by input from intact and possibly "irritable" primary afferent nociceptors to a sensitized central nervous system.²¹

The ability of gabapentin to reverse established sensitization suggests that gabapentin may relieve pain in a variety of pain disorders involving acute neuronal sensitization, such as postoperative pain and acute herpetic pain. Gabapentin also prevented development of neuronal sensitization, suggesting that gabapentin could help prevent development of chronic pain conditions, such as postoperative pain and postherpetic neuralgia.

In summary, these results provide a link between preclinical animal pain models and clinical trials in patients with chronic neuropathic pain. The results are consistent with evidence that chronic neuropathic allodynia has mechanistic similarities to experimental cutaneous hyperalgesia. They also suggest that gabapentin may prove effective in acute pain disorders involving neuronal sensitization, such as postoperative pain and acute

herpetic pain, and may help prevent development of chronic pain.

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