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Chronic Oral Gabapentin Reduces Elements of Central Sensitization in Human Experimental Hyperalgesia

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Background: **In chronic pain, increased activity from intact or damaged peripheral nerve endings results in an enhanced response in central pain transmission systems, a mechanism known as *central sensitization*. Central sensitization can also be invoked in human experimental models. Therefore, these models may be useful to characterize novel analgesics in humans. The anticonvulsant gabapentin has demonstrated efficacy in patients with neuropathic pain, but its mode of action remains unclear. This study examined the effects of gabapentin on signs of central sensitization (brush and pinprick hyperalgesia) in a human model of capsaicin-evoked pain, using a gabapentin dosing regimen similar to that used in the clinic. The aims were to determine whether gabapentin, dosed in a manner similar to that used in the clinic, affected the various components of central sensitization and to assess the utility of this model for characterizing novel analgesics.**

Methods: **Intradermal capsaicin (100 μg/20 μl) was administered in the volar forearm of 41 male human volunteers to induce pain and clinical signs of central sensitization. Gabapentin (titrated to 2,400 mg daily) or placebo was given orally for 15 days in a randomized, double-blind, parallel-group design. The capsaicin test was conducted at baseline and after gabapentin or placebo. Endpoints were the size of areas of brush-evoked allodynia (with cotton gauze) and pinprick hyperalgesia (with von Frey filament), and the intensity of ongoing brush- and pinprick-evoked pain.**

Results: **Gabapentin significantly reduced the area of brush allodynia compared with placebo ($P \leq 0.05$) and insignificantly attenuated the area of pinprick hyperalgesia. Gabapentin had no significant effect on spontaneous and evoked pain intensity.**

Conclusion: **Oral gabapentin, administered to healthy volunteers in a regimen similar to that used in treating chronic neuropathic pain, reduces measures of central sensitization evoked by intradermal capsaicin. This suggests that the pain-relieving effect in chronic neuropathic pain condition is linked to the effect of gabapentin on central sensitization. The ability of the capsaicin model to detect the efficacy of this standard treatment of neuropathic pain suggests that it may have a predictive value for detection of efficacy in human subjects.**

CURRENT treatments for chronic pain are still insufficient for a large proportion of patients. In less than one third of chronic neuropathic pain, it is possible to obtain pain relief that is greater than 50%.[1,2] Therefore, there is a need for novel approaches to identify drugs, which may be more efficacious. A division of chronic pain based on mechanisms rather than on etiology or localization has recently been proposed as a new way of classifying pain and for identifying targets of drug therapy.[2–7] Sensitization of the peripheral or central nervous system is currently considered to be a key mechanism responsible for development and maintenance of chronic pain.[8] In neuropathic pain, nerve injury or similar insults result in an increased input from the periphery that sensitizes second- and higher-order neurons in the central nervous system (for review, see Jensen *et al.*,[4] Jensen and Baron,[7] Devor,[9] and Woolf and Salter[10]). There has been considerable interest in analyzing sensitization phenomena experimentally and clinically.

Signs of sensitization such as pinprick hyperalgesia, brush allodynia, and facilitated temporal summation, which are classic features in neuropathic pain, can also be evoked in experimental pain models.[11–16] The use of intradermal capsaicin injection in healthy subjects is a well-characterized model that has been shown to involve excitation of small afferent fibers resulting in central sensitization.[17] Therefore, this experimental model may be useful in humans for early characterization of novel compounds for the treatment of chronic pain, in particular neuropathic types of pain. In this model, allodynia/hyperalgesia surrounding the primary injured area can be reduced by acute intravenous administration of the sodium channel blocker lidocaine, the *N*-methyl-D-aspartate receptor antagonist ketamine, and various fast-acting opioids.[18–21] A recent study has reported effects of single oral dose administration of gabapentin on sensitization in healthy volunteers induced by topical capsaicin with heat rekindling.[22] Although single-dose administration may be used for acute pain, it is rarely of any value for the treatment of chronic types of pain that require long-term treatment. To determine the potential value of human experimental models of sensitization as seen in chronic pain, it is therefore necessary to demonstrate efficacy with drugs known to have an effect in chronic pain, using a dose regimen that has been proven to be effective and well tolerated. One of these compounds is gabapentin, which in the clinical setting is administered chronically after a stepwise up-titration over 2 weeks to maximize efficacy and minimize sedation and other side effects.[23] Gabapentin is efficacious in relieving pain in various types of neuropathic pain conditions (see Backonja *et al.*,[24] Rice and Maton,[25] Rowbotham *et al.*,[26] and Serpell and the Neuropathic Pain Study Group[27]; for

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review, see Backonja and Glanzman[23]). In these pivotal trials, the primary efficacy measure has been ongoing pain, but it has not been possible to conclude from these studies whether gabapentin can affect aspects of central sensitization. If capsaicin-induced allodynia, a manifestation of central sensitization,[16–20,28] is reduced by gabapentin using a clinical relevant dosing regimen, this will support that gabapentin exerts its clinical effect in part by reducing central sensitization.

The aim of the current study was therefore to investigate the effects of oral gabapentin on experimentally induced central sensitization in the capsaicin model, with a titration regimen that is commonly used in the clinic.

Materials and Methods

Subjects

Forty-one healthy subjects participated in this randomized, double-blind, placebo-controlled, parallel-group study. All volunteers were given oral and written information about the study and about the possible side effects of gabapentin. Informed written consent was obtained from each participant. The study was approved by the local ethics committee (Århus, Denmark) and by the Danish National Board of Health (Copenhagen, Denmark) and was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki.

Subjects were not included if they had a history or presence of clinical depression, psychotic illness, cardiac arrhythmias, asthma, atopy, drug or alcohol abuse (defined as daily intake > 3 units), or allergy to gabapentin. Subjects were excluded if they had received prescribed medication within 14 days before the first dosing day. No medication was allowed 48 h before first study day.

A screening session was conducted within 21 days before the start of the study. Screening included full medical examination, 12-lead electrocardiography, checking blood pressure and pulse rates, 24-h Holter electrocardiography, and laboratory screening including hematology, clinical chemistry, and urinalysis. The laboratory assessments were repeated on day 1 and day 15 and at follow-up. A blood sample was taken to screen for hepatitis B/C, and a urine drug screen was done for undeclared drugs. At the end of the screening session, an intradermal capsaicin test (50 μg, half of study dose) was given into the nondominant arm to familiarize the subject with the testing methods and to ensure that the subject developed brush allodynia and pinprick hyperalgesia.

Study Design

Subjects were randomized in a balanced manner, such that half of the subjects received 15 days' treatment of gabapentin orally, and the other half received matched placebo administered in the same manner. Randomization was performed by the sponsor (GlaxoSmithKline, Greenford, Middlesex, United Kingdom) using Coding Memo System software (GlaxoSmithKline Clinical Pharmacology Statistics and Programming, Harlow, Essex, United Kingdom). A capsaicin test was performed at baseline (on day 1 before the first dose) and on day 15. Subjects who withdrew were replaced.

Study Medication

Gabapentin or matching placebo capsules was prepared by the sponsor, by a pharmacist independent of the study in identical containers marked with the study number, subject number, and dosing instructions. Gabapentin, 300 mg, was given on day 1 and increased by 300 mg daily. The gabapentin dose on subsequent days was as follows: day 2, 300 mg twice a day; day 3, 300 mg three times a day; day 4, 400 mg three times a day; day 5, 500 mg three times a day; days 6–8, 600 mg three times a day; day 9, 700 mg three times a day; days 10–15, 800 mg three times a day. This titration regimen was applied to all subjects randomly assigned to receive gabapentin. During the washout period, gabapentin was reduced by 300 mg daily in the same manner. The medication was taken at home every 8 h: 7:00–8:00 AM, 3:00–4:00 PM, 11:00 PM-12:00 midnight. On day 15, subjects had their morning dose in the clinic 2 h before a capsaicin test was conducted. Because of possible sedative effect of gabapentin during the titrating period, all subjects were, for safety reasons, instructed not to drive any vehicle during the first 15 days of treatment. Adverse experiences were recorded during the titrating period by diary card and at specific time points *via* telephone. Adverse events were also recorded by interview before capsaicin injection on day 15. Severity of adverse experiences was rated as mild (easily tolerated by the subject, causing minimal discomfort, and not interfering with everyday activities), moderate (sufficiently discomforting to interfere with normal everyday activities), or severe (preventing normal everyday activities). A blood sample for assay of gabapentin was collected before dosing and at 2 h after dosing on day 15 to assess compliance during treatment and to investigate any relation between plasma concentration of gabapentin and its effects in the capsaicin model. Pharmacodynamic effects of gabapentin of individual subjects were plotted against their plasma gabapentin concentration. The plot was then visually inspected to decide whether formal analysis of the pharmacokinetic–pharmacodynamic relation was warranted.

Assay of Gabapentin Plasma Concentration

Plasma concentrations of gabapentin were assayed by GlaxoSmithKline using a method based on protein precipitation followed by liquid chromatography with dual mass spectrometry analysis using positive-ion electro-

spray ionization. Gabapentin was extracted from human plasma by protein precipitation using methanol containing [$^{13}C_3$]-gabapentin as an internal standard. Extracts were analyzed by high-performance liquid chromatography and double mass spectrometry using a TurboIonspray (Advanced Chemistry Development, Toronto, Ontario, Canada) interface and a Sciex API3000 mass spectrometer (Advanced Chemistry Development) with multiple reaction monitoring. The method has a lower limit of quantification of 50.0 ng/ml using a 50-μl aliquot of human plasma. Within- and between-run precision during the validation was better than 5%, while the accuracy was shown to vary from 102 to 105% across the concentration range of the assay (50–10,000 ng/ml).

Intradermal Capsaicin

Capsaicin (8-methyl N-vanillyl 6-nonamide) (Sigma, St. Louis, MO) was prepared as described previously[16] by the pharmacy at Aarhus University Hospital (Aarhus, Denmark). Capsaicin 100 μg (5 mg/ml, 20 μl) was injected intradermally using a 0.5-ml syringe fitted with a 27-gauge needle. All injections administered after screening were done on the volar surface of the dominant forearm. Each injection site was separated by 1 cm or more from previous sites.

Assessment of Pain and Pronociceptive Sensitization

Pain Assessment. The intensities of ongoing pain and evoked pain to brush (evoked by cotton gauze) and to pinprick (evoked by von Frey hair) were measured at multiple time points (2, 10, 15, 30, 45, 60, and 90 min after capsaicin injection) using a visual analog scale (VAS; 0–100 mm; 0 = no pain, 100 = unbearable pain). Pain unpleasantness was measured on a VAS (0–100 mm; 0 = no unpleasantness, 100 = unbearable unpleasantness). To evoke brush allodynia, cotton gauze was swept back and forth three times at the 3-cm point from the injection site, at a speed of 1–2 cm/s, as described previously.[18] Pinprick hyperalgesia was evoked by bending a fixed von Frey hair (744.9 mN) at a 3-cm point from the injection site twice, at a rate of 1 Hz.[18] Evoked pain intensity was scored on a VAS.

Areas of Allodynia and Hyperalgesia. Before capsaicin was injected, six radiating lines with ticks at 1-cm intervals were drawn on the skin. The angle between each line was 60° (fig. 1). The areas of brush allodynia and pinprick hyperalgesia were measured at specific time points (5, 10, 15, 30, 45, 60, and 90 min) after capsaicin injection. The area of brush allodynia was measured by stroking handheld cotton gauze from the skin with normal sensation toward the injection site at a rate of approximate 1 cm/s and at steps of 1 cm along six radiating lines drawn on the skin before injection of capsaicin. Subjects were asked to report when the sensation changed from slight touch to tenderness or pain,

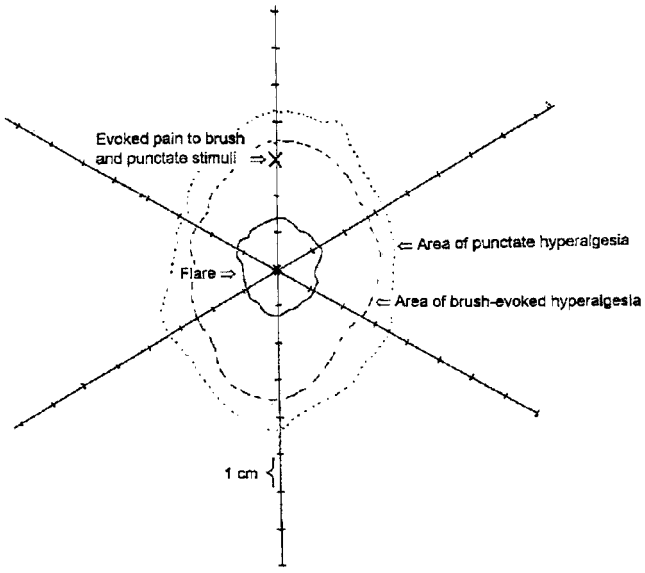

Fig. 1. The area was calculated from the average distance of the six points from the injection site. In the diagram, a, b, c, d, e, and f are the distances from the injection site, at which brush allodynia or pinprick hyperalgesia was perceived. Six new vector lines were calculated as follows: $a_1 = (a + b/2 + f/2)/2$; $b_1 = (b + a/2 + c/2)/2$; $c_1 = (c + b/2 + d/2)/2$; $d_2 = (d + c/2 + e/2)/2$; $e_1 = (e + d/2 + f/2)/2$; and $f_1 = (f + e/2 + a/2)/2$. The area was then calculated from the new vector lines as ⅙ of a circle with a radius $a_1 - f_1$: Area = $\pi((a_1)^2 + (b_1)^2 + (c_1)^2 + (d_1)^2 + (e_1)^2 + (f_1)^2)/6$.

and the point at which this change occurred was marked. The area was calculated from the average distance of the six points from the injection site. The area of pinprick hyperalgesia was measured in a similar way using a von Frey hair. More details are provided in Gottrup *et al.*[18]

Temporal Summation. As an additional measure of central excitability, we assessed temporal summation of pain evoked by repetitive pinprick stimuli.[29] A home-built microprocessor-controlled solenoid with an attached nylon filament (bending force, 1,234 mN) was used to apply pinprick stimuli at a frequency of 2.0 Hz over 60 s. This procedure was performed 20 min after injection of capsaicin at a site 3 cm proximal from the capsaicin injection site in the secondary hyperalgesic area. Evoked pain VAS was recorded every 10 s during the 60 s of stimulation. Pain VAS after stimulation had ceased (aftersensation) was recorded for 60 s after stimulation. A composite temporal summation score of the pain VAS during stimulation was derived as follows:

$$(VAS_{10s} + VAS_{20s} + VAS_{30s} + VAS_{40s} + VAS_{50s} + VAS_{60s}) - (6 \times VAS_{10s}),$$

where $VAS_{10\ s}$ = pain VAS at 10 s into stimulation. This represents the total change in VAS score in the latter part of stimulation from the VAS score early in stimulation. The $VAS_{10\ s}$, which was rated during filament application, was used as reference rather than the $VAS_{0\ s}$ (pre-

stimulation) because the $VAS_{0\ s}$ was rated without application of the filament.

In the 60 s after stimulation, a composite score of the pain VAS was derived as follows:

$$(VAS_{70s} + VAS_{80s} + VAS_{90s} + VAS_{100s} + VAS_{110s} + VAS_{120s}) - (6 \times VAS_{0s}),$$

where $VAS_{70\ s}$ = pain VAS at 70 s after start of stimulation (*i.e.*, 10 s after end of stimulation). This represents the total change in VAS score after stimulation stops from the prestimulation VAS.

Statistical Analysis

Given the exploratory nature of this study, the study was not formally powered. A retrospective power estimate was performed after the study using the observed variability in the areas of brush allodynia and pinprick hyperalgesia.

The primary endpoints of spontaneous pain intensity, unpleasantness of spontaneous pain, intensity and area of brush allodynia, and intensity and area of pinprick hyperalgesia were measured at multiple time points over 90 min after capsaicin injection. The area under the curve was determined over this 90-min period for each subject. The average area under the curve of each endpoint over this 90-min period was determined as weighted mean (area under the curve/t), where t is time. The weighted mean of each endpoint was calculated on day 1 and day 15. The change on day 15 from baseline (day 1) in weighted means (area under the curve/t) was calculated for each treatment group for each primary endpoint.

The change from baseline on day 15 for each primary pharmacodynamic endpoint was analyzed using analysis of covariance with terms for baseline and regimen in the model. Each subject's baseline (day 1 before dose test) weighted mean on the pharmacodynamic parameter of interest was included in the model as a covariate; this accounted for variation between subjects at baseline. Point estimates and 95% confidence intervals (CIs) for the differences between gabapentin and placebo were constructed using the residual variance from the analysis of covariance; *P* values of 0.05 or less were deemed significant.

Results

Forty-one male subjects (aged 20–32 yr; mean age, 25 yr) were included in the study. One subject withdrew during the treatment period because of an adverse event and was replaced by a new subject, who completed the study. Data were included in the analysis until the subject withdrew. Hence, the statistical analysis is based on complete session data from 40 subjects.

Effect of Gabapentin

Effect on Ongoing Capsaicin-evoked Pain. Capsaicin evoked ongoing pain in all subjects. In accord with the known profile of gabapentin, no reduction in the weighted mean of ongoing pain was observed in the gabapentin group compared with placebo: Its difference from placebo was 1.46 mm (95% CI, −2.89 to 5.82). Gabapentin did not reduce ongoing pain even when individual time points after capsaicin were examined (fig. 2A). Similarly, gabapentin did not have any effect on pain unpleasantness: Its difference from placebo was 0.48 mm (95% CI, −4.43 to 5.39).

Brush Allodynia. In the gabapentin group, the weighted mean area (SEM) at baseline (day 1) was 24.17 (2.92) cm^2; the change in the weighted mean area (SEM) on day 15 from baseline was −12.43 cm^2 (2.079), representing a 51% reduction. In the placebo group, the weighted mean area (SEM) at baseline (day 1) was 23.47 (3.16) cm^2; the change from baseline was −4.71 cm^2 (2.133), representing a 20% reduction. Gabapentin significantly reduced the weighted mean area of brush allodynia on day 15 compared with placebo by 7.72 cm^2 ($P < 0.05$; 95% CI, −13.75 to −1.68; fig. 2B), equivalent to a 31% drug effect. This effect of gabapentin was most prominent at 30 min after capsaicin, when it reduced the area of brush allodynia by 38% of baseline compared with placebo (fig. 2C). Gabapentin showed a trend to reduction on the intensity of brush allodynia, with a difference of −2.84 mm from placebo (95% CI, −7.25 to 1.57; fig. 2D).

Pinprick Hyperalgesia. In the gabapentin group, the weighted mean area (SEM) at baseline (day 1) was 45.17 (4.15) cm^2; the change in the weighted mean area (SEM) on day 15 from baseline was −14.78 cm^2 (3.119), representing a 33% reduction. In the placebo group, the weighted mean area (SEM) at baseline (day 1) was 44.35 (4.02) cm^2; the change from baseline was −6.04 cm^2 (3.2), representing a 14% reduction. Gabapentin showed a trend to reduction in the area of pinprick hyperalgesia of −8.75 cm^2 (95% CI, −17.80 to 0.31) compared with placebo (fig. 2B). This amounted to a 19% drug effect.

Gabapentin showed a trend to reduction on the intensity of pinprick hyperalgesia, with a difference of −4.17 mm from placebo (95% CI, −9.83 to 1.49; fig. 2D).

Temporal Summation. Gabapentin had no effect on the composite score during repetitive stimulation: Its difference from placebo was −2.77 (95% CI, −25.46 to 19.92). Similarly, gabapentin had no effect on the composite score after repetitive stimulation: Its difference from placebo was −22.05 (95% CI, −64.07 to 19.97).

Plasma Concentration of Gabapentin. On day 15, the mean trough plasma concentration of gabapentin taken before dose was 5.31 μg/ml (range, 3.70–7.35 μg/ml). At 2 h after dose, the mean plasma concentra-

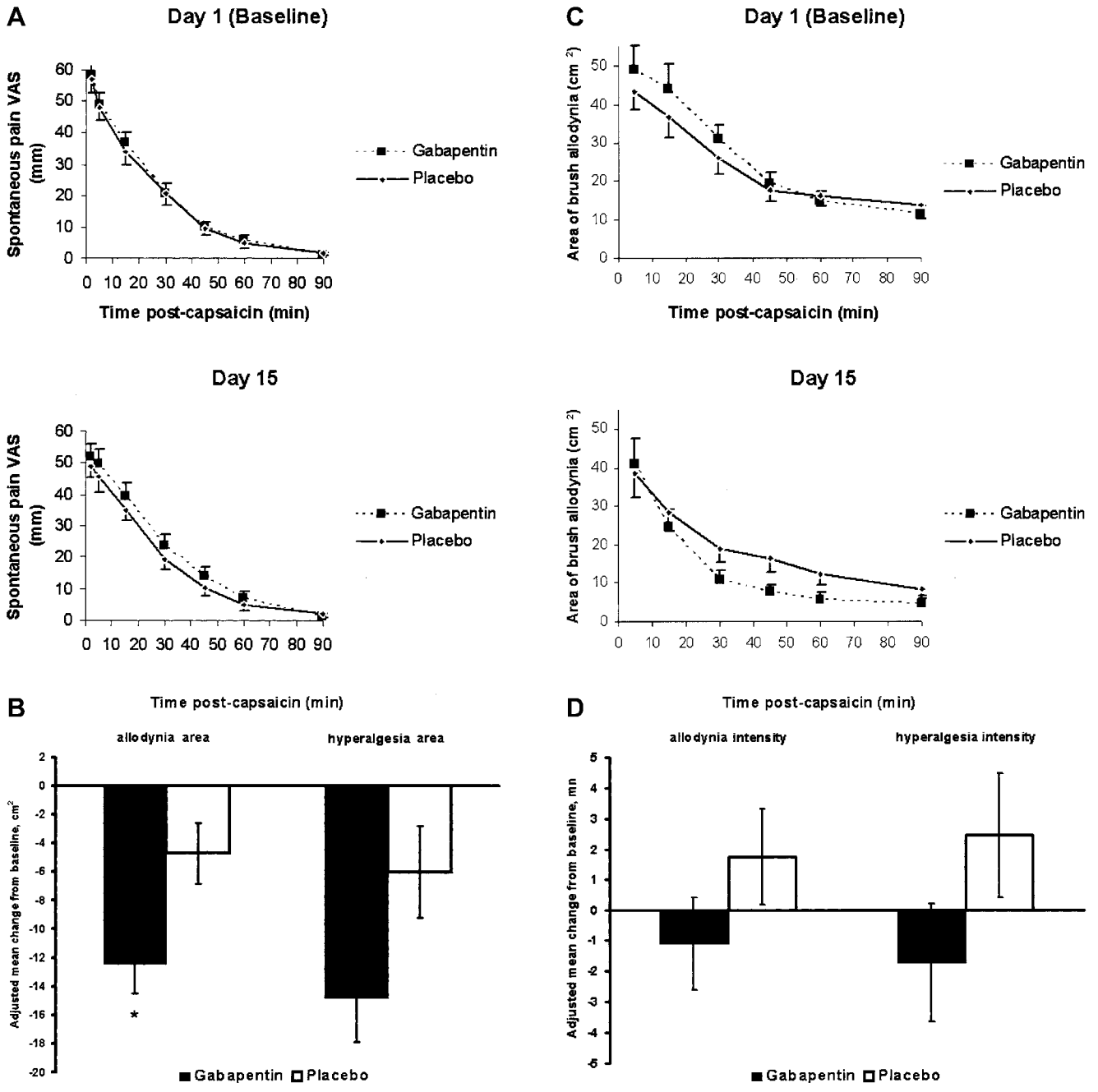

Fig. 2. (*A*) Effect of gabapentin and placebo on spontaneous pain visual analog scale (VAS) score on day 1 and day 15 over a 90-min period after capsaicin, plotted as mean (± SEM). (*B*) Effect of gabapentin and placebo on areas of brush allodynia and pinprick hyperalgesia; plotted as day 15 change from baseline of the weighted mean (± SEM). * Statistically significant difference between the groups ($P < 0.05$). (*C*) Effect of gabapentin and placebo on area of brush allodynia, on day 1 and day 15 over a 90-min period after capsaicin, plotted as mean (± SEM). (*D*) Effect of gabapentin and placebo on intensity of brush allodynia and pinprick hyperalgesia, plotted as day 15 change from baseline of the weighted mean (± SEM). No statistically significant difference between the groups.

tion was 7.65 μg/ml (range, 2.66–9.83 μg/ml). Visual inspection indicated there was no relation between gabapentin concentration and its pharmacologic effects in this study. This was not unexpected because all subjects reached the highest dose of gabapentin (800 mg three times a day) and were not taking a range of doses. Moreover, clinical trials in patients with neuropathic pain did not show a substantial increase in efficacy with increasing doses from 1,800 mg daily to 3,600 mg daily.[24–27]

Adverse Effects. One subject who received placebo withdrew during the study because of fatigue and muscle weakness. The most common adverse events in subjects dosed with gabapentin were fatigue, dizziness, and headache. Table 1 lists the frequency of adverse events in subjects dosed with gabapentin and those with pla-

Table 1. Adverse Events in Subjects Dosed with Gabapentin and Placebo

	Gabapentin	Placebo
Number of subjects with adverse events	17	16
Number of subjects exposed	21	20
Adverse events		
Fatigue	11	8
Dizziness	7	3
Headache	7	5
Somnolence	2	2
Concentration impaired	2	1
Rash	1	0
Nervousness	1	0
Paroniria (unpleasant dreams)	1	0

cebo. Overall, the adverse event profile is comparable to that seen in clinical trials. All adverse events were mild or moderate.

Discussion

This is the first demonstration that gabapentin in a dosing regimen similar to that used in clinical controlled trials can reduce experimental sensitization in a human model.[24–27] Given that brush allodynia and pinprick hyperalgesia in the intradermal capsaicin model are centrally mediated,[16–20,28] this suggests that gabapentin is able to inhibit elements of central sensitization in humans. These observations, together with the pain relief in pivotal clinical trials, suggest the inhibition of central sensitization as a potential mechanism for modulating neuropathic pain in patients.

Capsaicin is a selective agonist of vanilloid receptor type 1,[30] and its intradermal injection in humans apparently activates afferent fibers expressing these receptors, leading to a painful perception. Activation of capsaicin-sensitive, peripheral nociceptive afferents results in primary hyperalgesia at the site of injection,[31] with decreased threshold to noxious heat and an increased pain perception to such thermal stimulus.[17,32] As previously reported,[16] and as observed in this study, pinprick hyperalgesia (exaggerated pain to a mildly noxious pinprick stimulus) and brush allodynia (pain/unpleasantness in response to an innocuous touch stimulus) develop in the secondary zone surrounding the capsaicin injection site. The size of this secondary cutaneous hypersensitivity is believed to reflect the level of central sensitization of second-order (and potentially higher-order) neurons in the central nervous system brought about by input from the periphery.[17,33] Similar mechanisms are thought to be active in neuropathic pain states.[7] Therefore, central sensitization has been demonstrated in patients with postherpetic neuralgia and complex regional pain syndrome.[34,35] The intradermal capsaicin model has the sensitivity to detect efficacy of several important analgesic drug that are known to alleviate neuropathic pain. Therefore, we and others have demonstrated in single-dose studies that drugs such as lidocaine, ketamine, gabapentin, and adenosine have been found to reduce measures of sensitization in this model.[18,20,22,36] In this study, we have extended this evidence to one of the most frequently used treatments for neuropathic pain, chronic oral gabapentin.

Effect of Gabapentin

Gabapentin is an anticonvulsant serendipitously found to alleviate neuropathic pain, the finding later confirmed in several controlled studies.[24–27] Gabapentin was also found to reduce pinprick hyperalgesia and brush allodynia in several animal models of chronic pain.[37–39] The mechanism of its anticonvulsant and analgesic activity is unknown. Although a peripheral component of antiallodynic action of gabapentin cannot be excluded (see, *e.g.*, Pan *et al.*[40]), it is likely to be largely centrally mediated, potentially *via* binding to the $\alpha_2\delta$ subunit of voltage-gated calcium channels and inhibition of glutamate release presynaptically and postsynaptically in the central nervous system (see Field *et al.*[41]; for review, see Rose and Kam[42] and Taylor *et al.*[43]).

In this study, subjects in the placebo and gabapentin groups received intradermal capsaicin before and after treatment with the study medication. The intradermal capsaicin model has been shown to induce similar areas of allodynia/hyperalgesia on repeated administration,[44] in the absence of any drug treatment. In the placebo group, there was a reduction in the areas of allodynia and hyperalgesia with the second administration of intradermal capsaicin, which may represent adaptation of the pathways involved in central sensitization. It is assumed that this effect occurred to a similar degree in the gabapentin group.

The current results showed that compared with placebo, gabapentin reduced the area of brush allodynia. Gabapentin also reduced the area of pinprick hyperalgesia and intensity of brush allodynia and pinprick hyperalgesia, albeit insignificantly. We cannot exclude that the sample size was too small for demonstrating a significant effect on these latter endpoints. The study was based on feasibility and was therefore not powered to detect a difference. However, based on previously published data,[18] these data provided SDs of 6.1 and 10.2 cm^2 for the weighted mean of brush allodynia area and pinprick hyperalgesia area, respectively. The mean placebo responses after a capsaicin challenge for these endpoints were 4.4 and 26.1 cm^2, respectively. Using these data and given a sample size of 20 subjects receiving gabapentin and 20 subjects receiving placebo, it was estimated that the lower and upper bounds of the 95% CIs for the difference between gabapentin and placebo would have been within 4.4 and 7.4 cm^2 of the point estimates for brush allodynia area and pinprick hyperalgesia area, respectively. However, for the area of brush allodynia and

the area of pinprick hyperalgesia in the current study, we observed between-subject SDs of 8.58 and 8.90 cm^2, respectively. Using this observed variability, with a 5% significance level, we had 80% power to detect differences between treatment and placebo of 7.61 and 7.89 cm^2 for the area of brush allodynia and the area of pinprick hyperalgesia, respectively, which is very similar to the differences observed in this study.

The reduction of signs of sensitization and the lack of effect on capsaicin-evoked acute pain are consistent with the known profile of gabapentin in animal models.[37] Similarly, gabapentin reduced allodynia in a pilot clinical trial in patients with neuropathic pain.[45] The current findings also confirm the reduction of brush allodynia by Dirks *et al.*,[22] who reported that a single dose of 1,200 mg gabapentin reduced brush allodynia by 70% compared with placebo in the heat/capsaicin model. In this study, gabapentin reduced the area of brush allodynia by 31%. In the single high dose study,[22] pinprick hyperalgesia was also reduced, which is consistent with the trend toward a reduction of pinprick hyperalgesia seen in the current study. The smaller effects of gabapentin in our study may be partly due to the use of the weighted mean of the areas, which represents an average over 90 min after capsaicin (the size of the areas decline spontaneously after capsaicin; thus, any potential difference between the treatments is smaller toward the end of this period). When specific time points are examined, the effects of gabapentin are more pronounced, being maximum at 30 min after capsaicin.

Another factor that may explain the different magnitude of the effects seen in the two studies is different treatment regimens. The dosing regimen used in our study is the prevalent and recommended way of gabapentin dosing for the treatment of neuropathic pain in the clinic.[23] The stepwise escalation over 2 weeks from low doses to those required to achieve efficacy (between 1,800 mg and 3,600 mg daily) not only allows achievement of maximum efficacy, but also minimizes the occurrence of central side effects such as somnolence, dizziness, and ataxia.[23] These side effects are known to increase patients withdrawal rates in the clinic (*e.g.*, Backonja *et al.*,[24] Rice and Maton,[25] Rowbotham *et al.*[26]); in experimental settings such as those in our study, they may lead to "unblinding" of the subjects and investigator to treatment and compromise subjective endpoints. Importantly, in patients with neuropathic pain, gabapentin showed a reduction in pain and allodynia scores by 10–30%,[27,45] similar to the magnitude seen in the current experiment.

One further potential reason for the observed discrepancies is that in the experimental model used here, gabapentin is administered in a state where sensitization has not yet developed. Such states are at variance from clinical conditions where the nociceptive system already is activated. It may be speculated that gabapentin is only effective at the assumed $\alpha_2\delta$ calcium channel subunit, when the nociceptive system is already sensitized or alternatively that the dose has to be excessively high to obtain blockade of sensitization phenomena. The latter mechanism may possibly explain the greater effects seen in the heat/capsaicin model, where a single high dose of gabapentin was administered after the capsaicin challenge.[22] Nevertheless, in the current study, when gabapentin was given before the capsaicin test, it still reduced the sensitization with the magnitude comparable with that of the clinical effect in patients.

The relative balance of central *versus* peripheral sensitization in the heat/capsaicin model and the intradermal capsaicin model may also be different. For example, in burn injury models, heat hyperalgesia is seen not only in the primary hyperalgesic zone but also in the secondary hyperalgesic zone.[12,17] It is unlikely that any reduction of measures of central sensitization in this study was due to inhibition of afferent input by gabapentin because we did not observe any reduction of cutaneous flare (data not shown), which is believed to reflect the level of nociceptor activation.[46] Therefore, we believe that our findings are an important demonstration of the reduction of central sensitization in humans with a clinical dosing regimen of gabapentin.

In this study, we assessed different aspects of central sensitization by quantifying brush allodynia and pinprick hyperalgesia. Gabapentin had a somewhat greater effect on brush allodynia than pinprick hyperalgesia. The reason for this differential effect is not known, but differences in the mechanisms of these two types of mechanical hyperalgesia may play a role as found in previous studies.[44] Such differences in modulation of the two types of sensitization have previously been reported with other drugs (*e.g.*, Gottrup *et al.*[18]). Gabapentin also had a more prominent effect on the area of brush allodynia/pinprick hyperalgesia than on intensities. It is possible that areas of brush allodynia and pinprick hyperalgesia are more sensitive measures of central sensitization, rather than intensity of stimulation. From the current reduction of the area of allodynia, we cannot draw the conclusion that the area of brush-evoked allodynia is a manifestation of chronic pain. However, from previous studies using other substances, we have demonstrated significant reduction in areas of hyperalgesia, but with only some effect on intensity (*e.g.*, Gottrup *et al.*[18]). Furthermore, in patients with clinical neuropathic pain, reduction of allodynia simultaneously with diminished ongoing pain was observed, suggesting that area of allodynia does represent an aspect of chronic pain.[47]

Facilitated temporal summation is another characteristic phenomenon in chronic pain in particular in neuropathic pain.[4] This windup-like pain is thought to be a clinical equivalent to increasing neuronal activity after repetitive C-fiber stimulation at greater than 0.3 Hz (see Mendell[48]; for review, see Herrero *et al.*[49]). In patients

with neuropathic pain, a facilitated temporal summation is seen with increased pain evoked by repetitive stimuli and pain outlasting the stimulus (aftersensations).[50–52] We have recently demonstrated a correlation between evoked-pain pain intensity and aftersensations in allodynic skin in patients with neuropathic pain and in skin rendered hyperalgesic by a conditioning intradermal capsaicin injection in human volunteers, suggesting that aftersensations and evoked pain by repetitive stimuli share a common mechanism, both in the human experimental capsaicin model and in patients with peripheral neuropathic pain.[29] In the current study, gabapentin did not affect temporal summation and aftersensations, which is in contrast to its effect on brush allodynia. The difference cannot be explained by a failure of the capsaicin model to mimic the clinical temporal summation phenomena, because our previous study showed that pain evoked by temporal summation, time to pain onset, and aftersensations were similar in patients with neuropathic pain and in the capsaicin model.[29] Consistent with the current lack of effect on temporal summation and aftersensations, some animal data have shown lack of effect of gabapentin on windup.[53] These findings suggest that the mechanisms behind evoked pain by repetitive stimuli and mechanical hyperalgesia are different[54] and can be modulated in a pharmacologically specific fashion.

The main effect of gabapentin in the current human experimental model was on the area of brush allodynia, whereas the other measures only showed a trend toward reduction, and there was no effect on ongoing pain. The lack of effect of gabapentin on acute pain is compatible with findings in other human studies.[22,55,56] These findings are at variance from a number of clinical trials where gabapentin at an oral dose between 1,800 and 3,600 mg daily has been found to reduce spontaneous ongoing pain in postherpetic neuralgia, diabetic neuropathy, and other types of neuropathic pain.[24,26] The lack of pain relief on spontaneous pain in the current study may be due to the acute and severe nature of the capsaicin pain, which may be too vigorous to be modulated by gabapentin. Moreover, the spontaneous pain in the intradermal capsaicin model is most likely to be largely due to peripheral activation of sensitive fibers, and the lack of effect of gabapentin suggests its mode of action is predominantly on central sensitization. Consistent with this, other measures of peripheral sensitization in this model, such as heat detection threshold and heat pain threshold,[32,57] were not affected by gabapentin (data not shown).

In the current study, capsaicin was used twice to induce sensitization. It may be speculated that such repeated dosing desensitizes nociceptors in the periphery and thereby makes the model less sensitive to pharmacologic modulation in chronic treatment trials. Accordingly, additional experiments were performed in this group of subjects. Lidocaine administered intravenously has been shown to reduce hyperalgesia both experimentally[18,58] and clinically.[59–61] At the end of the current study, after a washout period of at least 7 days, all subjects were given an infusion of lidocaine (5 mg/kg during 30 min) or saline in a randomized manner. We found that lidocaine still was able to reduce signs of central sensitization (brush-evoked pain intensity and aftersensations; data not shown). These findings indicate that the capsaicin model was still sensitive to pharmacologic modulation other than gabapentin after multiple assessments and repeated capsaicin dosing.

Summary

The current findings are consistent with observations in clinical neuropathic pain trials of gabapentin. The similarities between the current experimental study and the clinical trials using a chronic oral gabapentin dosing regimen corresponding to that used in clinical trials suggest that the intradermal capsaicin model may represent a link between animal studies and clinical trials. So far, it has been difficult to analyze pain patients using a mechanism-based approach.[5] With a standardized method to induce sensitization, specific mechanisms can be studied in a controlled fashion. The capsaicin model may be useful for evaluating mechanism-based treatments in neuropathic pain in early phases of development.

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