Gabapentin Activates Spinal Noradrenergic Activity in Rats and Humans and Reduces Hypersensitivity after Surgery

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Background: Gabapentin has been reported to inhibit various acute and chronic pain conditions in animals and humans. Although the efficacy of gabapentin depends on the $\alpha_2\delta$ subunit of voltage-gated calcium channels, its analgesic mechanisms *in vivo* are still unknown. Here, the authors tested the role of spinal noradrenergic inhibition in gabapentin's analgesia for postoperative pain.

Methods: Gabapentin was administered orally and intracerebroventricularly to rats on the day after paw incision, and withdrawal threshold to paw pressure was measured. The authors also measured cerebrospinal fluid concentration of norepinephrine and postoperative morphine use after surgery in patients who received oral placebo or gabapentin.

Results: Both oral and intracerebroventricular gabapentin attenuated postoperative hypersensitivity in rats in a dose-dependent manner. This effect of gabapentin was blocked by intrathecal administration of the α_2-adrenergic receptor antagonist idazoxan and the G protein–coupled inwardly rectifying potassium channel antagonist tertiapin-Q, but not by atropine. In humans, preoperative gabapentin, 1,200 mg, significantly increased norepinephrine concentration in cerebrospinal fluid and decreased morphine requirements.

Conclusions: These data suggest that gabapentin activates the descending noradrenergic system and induces spinal norepinephrine release, which produces analgesia *via* spinal α_2-adrenoceptor stimulation, followed by activation of G protein–coupled inwardly rectifying potassium channels. The authors' clinical data suggest that gabapentin activates the descending noradrenergic system after preoperative oral administration at the time of surgery. These data support a central mechanism of oral gabapentin to reduce postoperative pain and suggest that this effect could be magnified by treatments that augment the effect of norepinephrine release.

ONE could argue that postoperative pain represents an unmet medical need, because pain during the first days after surgery is rated as intense or very intense in one out of two patients.[1] Several approaches have been used to reduce postoperative pain, including systemic opioids and nonsteroidal antiinflammatory drugs, epidural or spinal infusion of local anesthetics, and peripheral nerve block. These approaches, however, are fraught with side effects and expense, which limit their effective application.

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Gabapentin was licensed as an antiepileptic drug in 1993 and was rapidly recognized to be effective in patients with neuropathic pain.[2] This clinical experience is paralleled in the laboratory, where gabapentin has been shown to possess analgesic properties in a wide range of chronic pain models.[3–5] Gabapentin binds with high affinity to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, which modulate the release of excitatory amino acids at the level of the spinal dorsal horn.[6] $\alpha_2\delta$ Subunits are up-regulated after nerve injury in animals,[7] and gabapentin blocks voltage-gated calcium channels in transgenic mice with up-regulated $\alpha_2\delta$ subunits of the $\alpha_2\delta_1$ subtype but not in normal mice,[8] suggesting that the efficacy of gabapentin depends on this subunit. In addition, several recent clinical and animal studies have reported efficacy of gabapentin to treat or prevent postoperative pain.[9–11] This is surprising because one might not expect an up-regulation of the $\alpha_2\delta$ subunit in such a short time.

Because it is well known that spinal plasticity and sensitization play pivotal roles in pain transduction after peripheral nerve injury and inflammation, most studies have focused on a spinal site of action of gabapentin. Tanabe *et al.*[5] recently demonstrated, however, that gabapentin acts supraspinally to activate the descending bulbospinal noradrenergic pathway in mice with peripheral nerve injury. Norepinephrine is released in the spinal dorsal horn by descending inhibitory noradrenergic axons, which mainly originate from the locus ceruleus and adjacent nuclei in the brainstem, and suppresses the activation of spinal nociceptive neurons *via* activation of α_2 adrenoceptors.[12] Peripheral inflammation enhances this descending inhibitory pathway and increases the sensitivity of spinal neurons to descending noradrenergic inhibition.[13] We hypothesized that gabapentin activates the descending noradrenergic system not only in neuropathic pain but also postoperatively, and we tested this hypothesis with oral gabapentin in rats after paw incision surgery, an animal model of postoperative pain and hypersensitivity.[14] To further separate the supraspinal from spinal actions of gabapentin, we also examined its effects after intracerebroventricular administration. Intrathecal injection of α_2-adrenoceptor agonists stimulates G protein–coupled inwardly rectifying potassium channels (GIRKs) for acute thermal antinociception[15] and also activates a spinal cholinergic circuit in animal models of neuropathic pain.[16] We therefore hypothesized and tested whether GIRKs and muscarinic receptors are involved in gabapentin analgesia in postoperative pain. Finally, to determine whether gabapentin stimulates spinal norepinephrine release in humans, we

gave oral gabapentin or placebo to patients preoperatively and measured norepinephrine content in cerebrospinal fluid (CSF) just before spinal anesthesia.

Materials and Methods

Animal Study

Animals. Male Sprague-Dawley rats (Harlan Industries, Indianapolis, IN), weighing 200–250 g, were used in this study. Animal surgery conformed to the Wake Forest University Guidelines on the ethical use of animals, and studies were performed under Animal Care and Use Committee approval from Wake Forest University School of Medicine, Winston-Salem, North Carolina. Animals were housed under a 12-h light–dark cycle, with food and water available *ad libitum*.

Surgical Preparations.

Paw Incision Model. Paw incision was performed as previously described.[14] Animals were anesthetized with halothane, the plantar surface of the right hind paw was prepared with 70% ethanol, and a 1-cm longitudinal incision was made through the skin and fascia, starting 0.5 cm from the edge of the heel and extending toward the toes. The plantaris muscle was elevated and incised longitudinally. The wound was then closed with two silk sutures. Behavior tests were performed 24 h after paw incision.

Intrathecal Catheterization. Animals were anesthetized with halothane, and intrathecal catheters were implanted as previously described.[17] Animals were placed prone in a stereotaxic frame, and a small incision was made at the back of the neck. A small puncture was made in the atlanto-occipital membrane of the cisterna magnum, and a polyethylene catheter, 8.5 cm, was inserted so that the caudal tip reached the lumbar enlargement of the spinal cord. The rostral end of the catheter was exteriorized at the top of the head, and the wound was closed with sutures.

Intracerebroventricular Catheterization. During anesthesia with an intraperitoneal injection of sodium pentobarbital (50 mg/kg) and atropine (0.1 mg/kg), animals were placed securely into a stereotaxic device (KOPF, Tujunga, CA), and a 1-cm midline incision was made to expose the skull surface. A sterile stainless steel guide cannula (22-gauge needle shaft; Plastics One, Roanoke, VA) was implanted into the left lateral cerebral ventricle. The coordinates for placement of the tip of the guide cannula were 0.80 mm posterior and 1.5 mm lateral to the bregma, and 3.5 mm ventral from the surface of the dura mater, according to the rat brain atlas.[18] Each cannula was kept in place with acrylic dental cement secured by two stainless steel skull screws and was fitted with a dummy cannula to maintain patency, and then the wound was closed with sutures.

After implantation of the intracerebroventricular and/or intrathecal catheters, rats were housed individually with free access to food and water. Animals were allowed at least 5 days to recover from the surgery, and

those displaying signs of motor dysfunction (forelimb or hind limb paralysis) were to be excluded from the study and killed immediately. No animal in the current study was excluded for these reasons.

Behavior Test. Nociceptive mechanical thresholds, expressed in grams, were measured with the Randall-Selitto test using an analgesimeter (Ugo Basile, Comerio, Italy). The test was performed by applying pressure to the hind paw. By pressing a pedal that activated a motor, the force increased at a constant rate on a linear scale. When the animal withdrew the paw or vocalized, the pedal was immediately released and the nociceptive threshold was read on a scale. A cutoff of 250 g was used to avoid potential tissue injury.

Drugs and Their Administration. All drugs were purchased from Sigma (St. Louis, MO) except gabapentin solution (Neurontin, 50 mg/ml; Park-Davis, New York, NY). For oral administration, gabapentin solution was diluted with sterilized water and given to the animals with a feeding tube (30–300 mg/6 ml/kg). For intracerebroventricular administration, gabapentin hydrochloride was dissolved in saline and injected (30–100 μg/5 μl/rat). For intrathecal administration, atropine sulfate, idazoxan hydrochloride, and tertiapin-Q trifluoroacetate were dissolved in saline and were injected in a volume of 10 μl followed by 10 μl saline at 1.5 h after oral gabapentin or at the same time as intracerebroventricular gabapentin administration. Drug doses and timing of administration were determined in preliminary experiments or from previously published ranges.

Human Study

After approval was obtained from the Institutional Review Board of Wake Forest University School of Medicine, 44 patients with American Society of Anesthesiologists physical status I–III who were scheduled to undergo orthopedic or urogenital surgery during spinal or combined spinal–epidural anesthesia were recruited. All patients provided written informed consent. Patients taking or allergic to gabapentin were excluded, as were those with leukopenia or renal insufficiency or failure. On the day of surgery, patients were randomly assigned to receive, approximately 90 min before surgery, 1,200 mg gabapentin (n = 21) or placebo (n = 23) using pills prepared by our research pharmacy. The study was double blind. At the time of anesthesia initiation, a 25- or 27-gauge Whitacre needle was inserted in a mid or lower lumbar interspace, and 3 ml clear CSF was aspirated for norepinephrine assay. Intraoperative anesthesia was provided with spinal or spinal epidural anesthesia with sedation or general anesthesia. CSF samples were stored at −80°C until norepinephrine assay. Patients were visited on the first postoperative day and asked to provide a global pain score since surgery, using a 10-cm visual analog scale. We did not control the method of postoperative analgesia, but recorded morphine use during the first 24 h.

Norepinephrine content of CSF was determined as previously described.[19] After treatment with 0.1 M perchloric acid, the CSF samples were centrifuged. Supernatants were collected, and norepinephrine content was measured by high-pressure liquid chromatography with electrochemical detection.

Statistical Analysis

Unless otherwise indicated, data are presented as mean ± SEM. Differences among groups for withdrawal threshold were determined using an unpaired t test, one-way analysis of variance for repeated measures followed by the Dunnett *post hoc* test within groups, or two-way analysis of variance for repeated measures followed by the Holm-Sidek *post hoc* test among groups. CSF concentrations of norepinephrine were not normally distributed, are presented as median ± 25th and 75th percentiles, and were compared using the Mann–Whitney rank sum test. The significance level was set at $P < 0.05$.

Results

Animal Study

Paw incision decreased mechanical withdrawal threshold of the incised paw from 191 ± 25 g (mean ± SD) to 81 ± 17 g, accompanied by swelling of the paw 24 h after surgery. Withdrawal threshold of the contralateral paw did not change after surgery (data not shown).

Oral (30–300 mg/kg) and intracerebroventricular gabapentin produced a dose-dependent increase in withdrawal threshold (fig. 1). Oral gabapentin increased withdrawal threshold compared with vehicle 1–4 h after administration (fig. 1A), whereas intracerebroventricular administration of 30 and 100 μg/rat of gabapentin increased withdrawal threshold compared with vehicle only 15–60 min after administration (fig. 1B). Based on these data, we used 100 mg/kg gabapentin orally and 100 μg/rat intracerebroventricularly in subsequent experiments.

Intrathecal administration of the α_2-adrenergic receptor antagonist idazoxan (30 μg/rat) alone did not change withdrawal threshold of the incised paw but significantly blocked oral gabapentin analgesia (fig. 2A). Similarly, intrathecal idazoxan (3 and 30 μg/rat) reduced analgesia from intracerebroventricular gabapentin (fig. 2B).

Intrathecal administration of the non–subtype-selective muscarinic receptor antagonist atropine (30 μg/rat) was used to test whether a cholinergic component is involved in gabapentin analgesia. This dose of atropine, which diminished the effect of intrathecal α_2-adrenergic receptor agonists on hypersensitivity after surgery,[20] did not change withdrawal threshold of the incised paw when administered alone and did not reverse the effect of gabapentin (fig. 3).
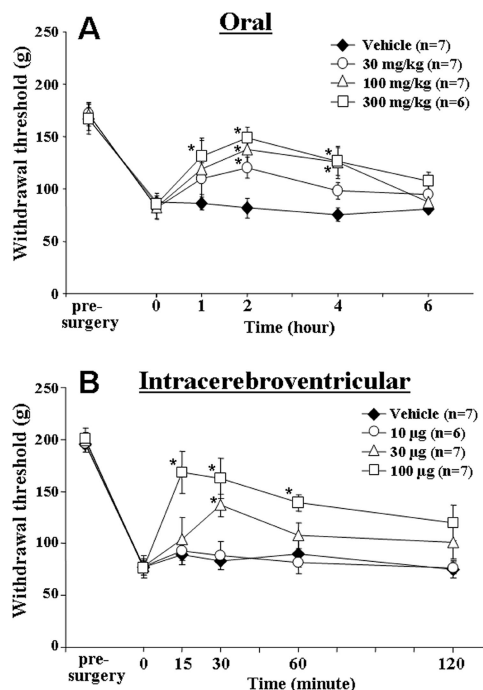

Fig. 1. Effects of orally and intracerebroventricularly administered gabapentin after surgery in rats. The mechanical withdrawal threshold is presented over time. Both oral (*A*; 30–300 mg/kg) and intracerebroventricular (*B*; 10–100 μg/rat) gabapentin produced a dose-dependent increase in withdrawal threshold compared with vehicle. * $P < 0.05$ *versus* time 0 by one-way analysis of variance. Groups differ by two-way analysis of variance with 300 mg/kg > 100 mg/kg > 30 mg/kg > vehicle in *A* and with 100 > 30 > 10 = vehicle in *B*.

Because α_2-adrenoceptor activation stimulates GIRKs,[15] we used the GIRK blocker tertiapin-Q[21] to test this potential downstream mediator of gabapentin analgesia. Intrathecally administered tertiapin-Q (1.0 μg/rat) alone did not change withdrawal threshold of the incised paw (fig. 4A) but dose-dependently inhibited oral gabapentin analgesia (fig. 4B). Higher doses than 1.0 μg/rat were not tested because they resulted in continual tail-flick behavior (data not shown).

Human Study

The group did not differ in demographic variables, with the study population as a whole 57 ± 2.4 yr in age, 92 ± 3.6 kg in weight, 171 ± 1.3 cm in height, and 43% female. The group also did not differ in surgery type, with 86% orthopedic and 14% urogenital procedures in the study population as a whole. Of the orthopedic procedures, 24% overall were hip replacement and 76% were open knee procedures. Groups did not differ in preoperative pain score (overall 4.3 ± 0.4 cm), and only two patients, one in each group, had no pain before surgery.

The CSF concentration of norepinephrine was greater in patients treated with gabapentin (median [25th–75th percentile], 461 [400–864]) than in patients who received placebo (329 [238–432]; $P < 0.005$). The groups
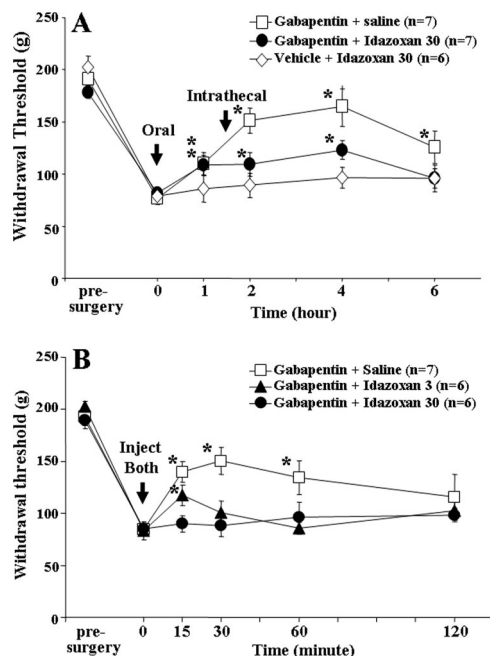
Fig. 2. Effects of intrathecal idazoxan on oral and intracerebro-ventricular gabapentin analgesia. The mechanical withdrawal threshold is presented over time. (*A*) *Arrows* indicate oral gabapentin (100 mg/kg) or vehicle, and intrathecal idazoxan (30 μg/rat, 1.5 h after gabapentin administration) or saline. (*B*) The *arrow* indicates coadministration of intrathecal idazoxan (3–30 μg/rat) or saline with intracerebroventricular gabapentin (100 μg/rat). * $P < 0.05$ *versus* time 0 by one-way analysis of variance. Groups differ by two-way analysis of variance with gabapentin + saline > gabapentin + idazoxan > vehicle + idazoxan in *A* and with gabapentin + saline > gabapentin + idazoxan 30 μg = gabapentin + idazoxan 3 μg in *B*.

did not differ in time from oral intake of study drug until CSF sampling (105 ± 8 min in the gabapentin group *vs.* 143 ± 13 min in the placebo group), and there was no significant correlation between this time and CSF norepinephrine concentration in either group or in the population as a whole.

The purpose of this study was not to determine the effect of oral gabapentin on postoperative pain, and we did not control the method of postoperative pain treatment. As such, postoperative analgesia was provided using a variety
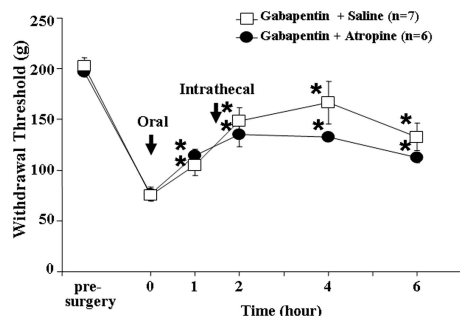

Fig. 3. Effect of intrathecal atropine on oral gabapentin analgesia. The mechanical withdrawal threshold is presented over time. *Arrows* indicate oral gabapentin (100 mg/kg) and intrathecal atropine (30 μg/rat, 1.5 h after gabapentin administration) or saline. * $P < 0.05$ *versus* time 0 by one-way analysis of variance. Groups do not differ by two-way analysis of variance.
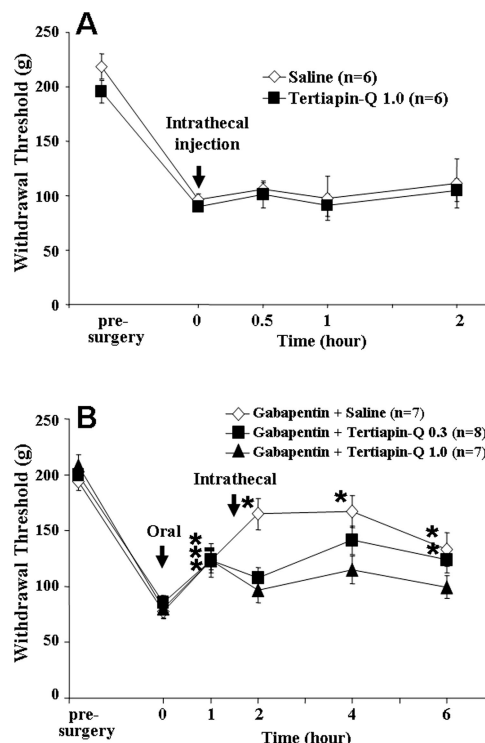
Fig. 4. Effects of intrathecal tertiapin-Q on mechanical hypersensitivity and oral gabapentin analgesia after surgery in rats. The mechanical withdrawal threshold is presented over time. (*A*) Intrathecal tertiapin-Q (1.0 μg/rat) did not show any difference of withdrawal threshold compared with the saline group. (*B*) *Arrows* indicate oral gabapentin (100 mg/kg) and intrathecal tertiapin-Q (0.3–1.0 μg/rat, 1.5 h after gabapentin administration) or saline. * $P < 0.05$ *versus* time 0 by one-way analysis of variance. Groups differ by two-way analysis of variance with gabapentin + saline = gabapentin + tertiapin-Q 0.3 μg/rat > gabapentin + tertiapin-Q 1.0 μg/rat.

of methods, with sustained-release epidural morphine (n = 7), peripheral nerve catheter infusion of local anesthetic (n = 21), epidural catheter infusion of local anesthetic with opioid (n = 3), or systemic analgesic (n = 11), with a similar distribution between gabapentin and placebo groups. Despite this variability, the amount of opioid administered in the first 24 h was lower in gabapentin-treated patients (32 ± 5.2 mg morphine equivalents) than in patients who received placebo (50 ± 9.3 mg; $P = 0.05$). Postoperative pain score, however, did not differ between groups (4.1 ± 0.5 *vs.* 4.4 ± 0.6 in the gabapentin and placebo groups, respectively).

Discussion

Our understanding of postoperative pain has been considerably advanced by the recent development of animal models of incisional[14] and deep tissue[22] surgical injury. Studies in these models have shown that postoperative pain, once considered akin to acute inflammation, rather reflects mechanisms that overlap with, but also differ from those of inflammation and nerve injury. It was therefore only slightly surprising that gabapentin,

a drug used to treat chronic neuropathic pain, also reduced hypersensitivity from incisional surgery in rats[9,11] and postoperative analgesia in humans.[10] The current study adds significantly to our understanding of the mechanisms by which gabapentin is effective in the postoperative setting.

Gabapentin Activates Descending Noradrenergic Inhibition in Postoperative Pain

Gabapentin reduces hypersensitivity from nerve injury in rodents[3–5] and patients,[2] and its mechanisms of action in this setting have been extensively studied. Because spinal plasticity and sensitization are recognized as critical components in pain amplification after peripheral nerve injury and inflammation, most studies have focused on peripheral afferents and spinal cord neurons. Recently, Tanabe et al.[5] demonstrated that gabapentin acts on supraspinal structures to stimulate the descending noradrenergic system after nerve injury in mice. Norepinephrine is released in the spinal dorsal horn by descending noradrenergic axons, which mainly originate from the locus ceruleus and adjacent nuclei in the brainstem, and produces analgesia by stimulating α_2 adrenoceptors.[12] Peripheral inflammation enhances descending noradrenergic inhibition and increases sensitivity of spinal neurons to α_2-adrenoceptor agonists such as clonidine.[13] Incision of the paw also activates descending noradrenergic inhibition, as evidenced by efficacy of intrathecal administration of norepinephrine transporter inhibitor Xen2714 after incisional surgery.[23]

The current study indicates that incisional surgery also alters the ability of gabapentin to activate descending noradrenergic inhibition, because systemic or intracerebroventricular gabapentin did not produce antinociception in normal animals,[5,24] but reduced hypersensitivity after surgery. The rapid onset of effect from intracerebroventricular gabapentin (15 min) is consistent with a supraspinal site of action, although we cannot absolutely exclude the possibility that gabapentin was distributed to the spinal cord during this period of time. Consistent with studies in a neuropathic pain model,[5] the antihypersensitivity effect of both systemic and intracerebroventricular gabapentin was significantly blocked by intrathecal injection of the selective α_2-adrenoceptor antagonist idazoxan. Intrathecal idazoxan alone did not affect hypersensitivity in this model, consistent with a lack of tonic descending inhibition, or with a floor effect of hypersensitivity after surgery. Blockade of intracerebroventricular gabapentin's effect by intrathecal idazoxan in the current study, and its blockade by depletion of spinal norepinephrine after 6-hydroxydopamine after nerve injury,[5] argues strongly that gabapentin acts at supraspinal sites primarily to stimulate the descending noradrenergic system. Although we could not administer intrathecal idazoxan to humans, the current study, which showed increased norepinephrine concentra-

tions in CSF after gabapentin compared with placebo, supports the clinical relevance of these observations in rats.

The mechanisms by which gabapentin activates noradrenergic neuron in the brainstem are still unknown. A direct effect seems unlikely, both because gabapentin does not exert direct excitatory effects on neurons and on previous observations that gabapentin inhibits rather than excites norepinephrine release in other sites in the brain.[25] Gabapentin binds with high affinity to $\alpha_2\delta$ subunits of voltage-gated calcium channels,[6] and its efficacy depends on the presence of $\alpha_2\delta$ subunits.[7,8] Because gabapentin has no antinociceptive effects against acute pain,[5,24] $\alpha_2\delta$ subunits or other heretofore uncharacterized gabapentin binding sites in supraspinal structures may be up-regulated or novelly expressed after incisional surgery. Further studies are ongoing in our laboratory to clarify the supraspinal mechanisms of gabapentin to treat postoperative hypersensitivity.

Role of Muscarinic Receptor and GIRKs in Gabapentin Analgesia

Stimulation of spinal cholinergic circuits by activation of spinal α_2 adrenoceptors is widely documented in humans and animals.[26] We hypothesized that gabapentin analgesia in the postoperative model might rely on this circuit, because intracerebroventricular gabapentin analgesia is completely blocked by systemic or intrathecal pretreatment with atropine after peripheral nerve injury.[27] This hypothesis was not supported, because atropine did not block the effect of gabapentin after paw incision. Sensitivity to atropine inhibition of spinal α_2-adrenoceptor activation differs between neuropathic and postoperative pain models. We previously reported that clonidine increased acetylcholine release in spinal cord slices from nerve-injured but not normal rats.[28] This agrees with the observation that the antihypersensitivity effect of intrathecal clonidine to mechanical stimuli is abolished by intrathecal atropine in nerve injured rats, but its antinociceptive effect is not inhibited by atropine in normal rats.[16,29]

G protein–coupled inwardly rectifying potassium channels have been identified in the spinal dorsal horn and play an important role in analgesia induced by various drugs, including α_2-adrenoceptor, muscarinic, and opioid receptor agonists.[15,21,30] We observed in the current study that oral gabapentin analgesia was strongly blocked by intrathecal administration of the GIRK blocker tertiapin-Q, consistent with gabapentin-induced activation of G protein–coupled receptors in the spinal cord which interact with GIRKs. Because gabapentin does not directly affect GIRK activity,[31] these data suggest that gabapentin-induced norepinephrine and acetylcholine release in the spinal cord causes GIRK activation, which participates in its antihypersensitivity effect.

Gabapentin Activates Descending Noradrenergic Inhibition in Humans

To our knowledge, this is the first report to test a mechanism of gabapentin action in humans. Oral gabapentin, in a dose previously demonstrated to produce postoperative pain relief,[10] significantly increased norepinephrine concentration in CSF compared with placebo group, consistent with our animal data of activation of the descending noradrenergic pathway by gabapentin. Nearly all of the patients in the current study had chronic pain, primarily from orthopedic causes, so we do not know whether similar results would be obtained in patients without pain before surgery. Oral gabapentin efficacy in a variety of surgical populations, however, argues that its action does not depend on the presence of pain before surgery. Gabapentin reduces pain intensity and opioid consumption after surgery,[10] whereas the current study only observed a reduction in opioid consumption in patients treated with gabapentin. This slight discrepancy likely reflects the fact that we did not control the method of postoperative analgesia. In addition, although oral gabapentin was associated with higher concentrations of norepinephrine in CSF at the time of surgery than placebo, whether this was sustained during the postoperative period and accounted for or contributed to analgesia from gabapentin is not determined by the current study.

Summary

In summary, oral and intracerebroventricular gabapentin reduces hypersensitivity in a rat model of postoperative pain. This effect is completely blocked by intrathecal idazoxan, suggesting that gabapentin analgesia is mainly mediated by spinal α_2 adrenoceptors as has been previously reported in animals after nerve injury. Gabapentin efficacy after incisional surgery is also reduced by intrathecally administered muscarinic antagonist and a GIRK inhibitor, consistent with spinal activation of α_2 adrenoceptors and a cholinergic circuit. The clinical relevance of these observations is supported by increased CSF concentration of norepinephrine in patients receiving oral gabapentin before surgery. These data suggest that gabapentin produces postoperative analgesia in part by activating descending noradrenergic inhibition, and that its effect may therefore be augmented by drugs that further amplify the consequence of norepinephrine release.

References

1. Chauvin M: Postoperative patient management: Pain after surgical intervention [in French]. Presse Med 1999; 28:203–11

2. Wiffen PJ, McQuay HJ, Edwards JE, Moore RA: Gabapentin for acute and chronic pain. Cochrane Database Syst Rev 2005; CD005452

3. Chen SR, Pan HL: Effect of systemic and intrathecal gabapentin on allodynia in a new rat model of postherpetic neuralgia. Brain Res 2005; 1042:108–13

4. Chen SR, Eisenach JC, McCaslin PP, Pan HL: Synergistic effect between intrathecal non-NMDA antagonist and gabapentin on allodynia induced by spinal nerve ligation in rats. ANESTHESIOLOGY 2000; 92:500–6

5. Tanabe M, Takasu K, Kasuya N, Shimizu S, Honda M, Ono H: Role of descending noradrenergic system and spinal alpha2-adrenergic receptors in the effects of gabapentin on thermal and mechanical nociception after partial nerve injury in the mouse. Br J Pharmacol 2005; 144:703–14

6. Gee NS, Brown JP, Dissanayake VU, Offord J, Thurlow R, Woodruff GN: The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2delta subunit of a calcium channel. J Biol Chem 1996; 271:5768–76

7. Luo ZD, Calcutt NA, Higuera ES, Valder CR, Song YH, Svensson CI, Myers RR: Injury type-specific calcium channel alpha 2 delta-1 subunit up-regulation in rat neuropathic pain models correlates with antiallodynic effects of gabapentin. J Pharmacol Exp Ther 2002; 303:1199–205

8. Li CY, Zhang XL, Matthews EA, Li KW, Kurwa A, Boroujerdi A, Gross J, Gold MS, Dickenson AH, Feng G, Luo ZD: Calcium channel alpha(2)delta(1) subunit mediates spinal hyperexcitability in pain modulation. Pain 2006; 125:20–34

9. Cheng JK, Pan HL, Eisenach JC: Antiallodynic effect of intrathecal gabapentin and its interaction with clonidine in a rat model of postoperative pain. ANESTHESIOLOGY 2000; 92:1126–31

10. Dahl JB, Mathiesen O, Moiniche S: "Protective premedication": An option with gabapentin and related drugs? A review of gabapentin and pregabalin in the treatment of post-operative pain. Acta Anaesthesiol Scand 2004; 48:1130–6

11. Whiteside GT, Harrison J, Boulet J, Mark L, Pearson M, Gottshall S, Walker K: Pharmacological characterisation of a rat model of incisional pain. Br J Pharmacol 2004; 141:85–91

12. Jones SL: Descending noradrenergic influences on pain. Prog Brain Res 1991; 88:381–94

13. Vanegas H, Schaible HG: Descending control of persistent pain: Inhibitory or facilitatory? Brain Res Brain Res Rev 2004; 46:295–309

14. Brennan TJ, Vandermeulen EP, Gebhart GF: Characterization of a rat model of incisional pain. Pain 1996; 64:493–501

15. Mitrovic I, Margeta-Mitrovic M, Bader S, Stoffel M, Jan LY, Basbaum AI: Contribution of GIRK2-mediated postsynaptic signaling to opiate and alpha 2-adrenergic analgesia and analgesic sex differences. Proc Natl Acad Sci U S A 2003; 100:271–6

16. Pan HL, Chen SR, Eisenach JC: Intrathecal clonidine alleviates allodynia in neuropathic rats: Interaction with spinal muscarinic and nicotinic receptors. ANESTHESIOLOGY 1999; 90:509–14

17. Yaksh TL, Rudy TA: Chronic catheterization of the spinal subarachnoid space. Physiol Behav 1976; 17:1031–6

18. Paxinos G, Watson C: The Rat Brain in Stereotaxic Coordinates. San Diego, Academic Press, 2005

19. Eisenach JC, Dobson CE II, Inturrisi CE, Hood DD, Agner PB: Effect of pregnancy and pain on cerebrospinal fluid immunoreactive enkephalins and norepinephrine in healthy humans. Pain 1990; 43:149–54

20. Duflo F, Conklin D, Li X, Eisenach JC: Spinal adrenergic and cholinergic receptor interactions activated by clonidine in postincisional pain. ANESTHESIOLOGY 2003; 98:1237–42

21. Marker CL, Stoffel M, Wickman K: Spinal G-protein-gated K+ channels formed by GIRK1 and GIRK2 subunits modulate thermal nociception and contribute to morphine analgesia. J Neurosci 2004; 24:2806–12

22. Martin TJ, Buechler NL, Kahn W, Crews JC, Eisenach JC: Effects of laparotomy on spontaneous exploratory activity and conditioned operant responding in the rat: A model for postoperative pain. ANESTHESIOLOGY 2004; 101:191–203

23. Obata H, Conklin D, Eisenach JC: Spinal noradrenaline transporter inhibition by reboxetine and Xen2174 reduces tactile hypersensitivity after surgery in rats. Pain 2005; 113:271–6

24. Field MJ, Oles RJ, Lewis AS, McCleary S, Hughes J, Singh L: Gabapentin (Neurontin) and S-(+)-3-isobutylgaba represent a novel class of selective antihyperalgesic agents. Br J Pharmacol 1997; 121:1513–22

25. Dooley DJ, Donovan CM, Pugsley TA: Stimulus-dependent modulation of [³H] norepinephrine release from rat neocortical slices by gabapentin and pregabalin. J Pharmacol Exp Ther 2000; 295:1086–1093

26. Eisenach JC: Muscarinic-mediated analgesia. Life Sci 1999; 64:549–54

27. Takasu K, Honda M, Ono H, Tanabe M: Spinal alpha(2)-adrenergic and muscarinic receptors and the NO release cascade mediate supraspinally produced effectiveness of gabapentin at decreasing mechanical hypersensitivity in mice after partial nerve injury. Br J Pharmacol 2006; 148:233–44

28. Obata H, Li X, Eisenach JC: α_2-Adrenoceptor activation by clonidine enhances stimulation-evoked acetylcholine release from spinal cord tissue after nerve ligation in rats. ANESTHESIOLOGY 2005; 102:657–62

29. Paqueron X, Conklin D, Eisenach JC: Plasticity in action of intrathecal clonidine to mechanical but not thermal nociception after peripheral nerve injury. ANESTHESIOLOGY 2003; 99:199–204

30. Ocana M, Cendan CM, Cobos EJ, Entrena JM, Baeyens JM: Potassium channels and pain: Present realities and future opportunities. Eur J Pharmacol 2004; 500:203–19

31. Cheng JK, Lee SZ, Yang JR, Wang CH, Liao YY, Chen CC, Chiou LC: Does gabapentin act as an agonist at native GABA(B) receptors? J Biomed Sci 2004; 11:346–55