

# Intrathecal Gabapentin Enhances the Analgesic Effects of Subtherapeutic Dose Morphine in a Rat Experimental Pancreatitis Model

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**Background:** Morphine sulfate has long been used for analgesia, but clinical applications can be limited by side effects, tolerance, and potential for addiction at therapeutic doses. An agent that produces therapeutic analgesia when coadministered with low-dose morphine could have important clinical uses. The anticonvulsant agent gabapentin has been identified as having antihyperalgesic properties acting on the  $\alpha_2\delta_1$  subunit of N-type voltage-activated calcium channels on dorsal root ganglia neurons. In this study, intrathecal gabapentin, which by itself is ineffective when administered spinally, was combined with low-dose morphine and tested in an acute bradykinin-induced pancreatitis model in rats.

**Methods:** An intrathecal catheter was surgically inserted into the subarachnoid space of male Sprague-Dawley rats. A laparotomy was performed for ligation and cannulation of the bile-pancreatic duct. Rats were pretreated intrathecally with artificial cerebrospinal fluid, gabapentin, morphine, or combined gabapentin and morphine 30 min before bradykinin injection into the bile-pancreatic duct. Spontaneous behavioral activity (cage crossing, rearing, and hind limb extension) was monitored before drug injection (baseline) and after bradykinin injection into the bile-pancreatic duct to assess visceral pain.

**Results:** Spinal pretreatment with up to 300  $\mu\text{g}$  gabapentin alone was not effective in reducing hind limb extension in this model, but did restore some cage crossing and rearing behaviors. Spinal treatment with low-dose morphine reduced hind limb extension only. Spinal pretreatment with combined gabapentin and subtherapeutic doses of morphine sulfate resulted in restoration of all spontaneous behaviors to surgical baseline levels including elimination of hind limb extension.

**Conclusion:** Combined spinal administration of gabapentin and low doses of morphine significantly reduces pain-related behaviors in this acute rat pancreatitis model, whereas these agents were ineffective when used alone in this dose range. These data suggest that the  $\alpha_2\delta_1$  subunit of the N-type voltage-activated  $\text{Ca}^{2+}$  channels is involved in transmission of this visceral pain, likely through effects on primary afferent endings in the spinal cord. Thus, gabapentin may be an effective adjuvant to initial low dose spinal opioid therapy for clinical management of visceral pain.

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CONTROL of severe pain with administration of intrathecal medication is an important area in which much investigation has been done yet much remains to be done.<sup>1</sup> Whereas most studies have focused on postsurgical or neuropathic pain, visceral pain pathways and development of treatments for visceral pain in animal models that closely resemble human conditions remain relatively less well unexplored.<sup>2</sup> Pain is the primary manifestation and cause of suffering in patients with inflammatory conditions or cancer of visceral organs. Clinical management of acute and chronic visceral pain presents a number of challenges. For example, adequate doses of opioid drugs are often accompanied by significant undesirable side effects such as tolerance, constipation, sedation, and other mental status changes, and eventual habituation and dependence with long-term administration in many patients.<sup>3</sup> In addition to oral, transcutaneous, and intrathecal pharmacologic therapy to manage intractable pain, neurolytic blocks of the sympathetic axis are often recommended for temporary pain relief in patients with visceral pain.<sup>4,5</sup> Surgical disruption of nociceptive system components is the last line of therapy used as opioid medications become limited by tolerance and side-effects.<sup>6</sup> A midline dorsal column lesion has been shown to be an effective surgical treatment for the relief of pelvic or thoracic visceral pain in patients, although this approach has been limited to terminal cancer patients.<sup>7,8</sup> The paucity of basic pharmacological information about visceral pain hinders efforts to develop better treatment strategies for clinical use.<sup>9,10</sup>

Morphine sulfate, a  $\mu$ -opioid receptor agonist, and lidocaine, a sodium channel antagonist, have for decades been the primary pharmacological agents used for pain control *via* spinal administration. Morphine is the most widely used drug for chronic intrathecal infusion. Because of its undesirable side effects at therapeutic concentrations, numerous studies have been undertaken to find other medications that potentiate the effects of morphine so that a lower dose can be used to achieve satisfactory pain control or medications that can replace morphine altogether. Among the medications explored are N-methyl-D-aspartate receptor antagonists,<sup>11</sup>  $\gamma$ -aminobutyric acid (GABA) analogs and GABA-receptor agonists,<sup>12,13</sup> ion channel ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{++}$ , and  $\text{Cl}^-$ ) modulators,<sup>14</sup> and other classes of medications such as tricyclic antidepressants and antiepileptic drugs. The results of studies with some of these medications alone and in combination with morphine have been promis-

ing.<sup>1</sup> Use of intraperitoneal injection of a local anesthetic (such as ropivacaine) significantly decreases postoperative visceral pain<sup>15-17</sup> and has been used in combination with morphine. However, respiratory depression has been reported when the effects of bupivacaine wear off when combined with morphine.<sup>18</sup>

Gabapentin (1-[aminomethyl]-cyclohexaneacetic acid (Neurontin; Parke-Davis, Division of Warner-Lambert, Morris Plains, NJ) is a clinically safe, oral anticonvulsant medication approved by the United States Food and Drug Administration in 1994 that has been used to treat diabetic and other neuropathic pain effectively. Gabapentin is structurally related to the neurotransmitter GABA and was initially thought to act as a GABA analog. Further research has shown that gabapentin is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation and does not interact with GABA receptors. It is currently hypothesized that gabapentin binds to voltage sensitive calcium ion channels.<sup>19-23</sup> Several gabapentin analogs that bind with high affinity to the  $\alpha_2\delta_1$  subunit of voltage-dependent calcium channels possess anticonvulsant and antinociceptive effects.<sup>24</sup> Gabapentin can produce a reduction in calcium influx in presynaptic nerve terminal and inhibit the release of excitatory amino acid.<sup>25</sup> It has been shown that gabapentin increases blood serotonin concentrations,<sup>26</sup> which likely also contributes to decreases in pain.

Gabapentin is indicated in the treatment of seizure disorders and certain types of neuropathic pain but has been used safely in numerous cases for treatment of other types of pain and conditions.<sup>27-29</sup> The pharmacological effects of gabapentin have been explored in animal studies and clinical trials. Gabapentin has been shown to be a moderately effective antihyperalgesic by itself<sup>27-36</sup> and as an adjuvant to opioid therapy in cases of neuropathic or allodynic pain.<sup>37-40</sup> A recent study of the effects of gabapentin administered into the intraperitoneal space of the rat showed that it was effective in alleviating symptoms of visceral irritation after intraperitoneal administration of acetic acid.<sup>41</sup> Intrathecal administration of combined morphine and gabapentin is also reported to be effective in reduction of second phase nociception after orofacial formalin.<sup>42</sup>

Previous preclinical investigations evaluating gabapentin-opioid interactions have shown gabapentin enhances the analgesic effect of morphine,<sup>33,37,38</sup> and gabapentin significantly reduced postoperative morphine consumption after abdominal hysterectomy.<sup>43</sup> Also Gilron *et al.*<sup>44</sup> determined that gabapentin prevents and reverses chronic morphine tolerance in the rat paw-pressure and tail-flick tests. Our study was undertaken to explore the effects of combined spinal administration of gabapentin and minimally effective doses of morphine on visceral nociception. Potentiation of morphine effectiveness with initial low dosages and prevention of tolerance

with combined gabapentin treatment intrathecally may provide effective and prolonged therapy. In these studies, spontaneous behavioral activities were assessed in rats with visceral nociception arising after acute pancreatitis induced chemically with intraductal bradykinin.<sup>11</sup>

## Materials and Methods

### Preparation of Animals

This study was conducted under a protocol approved by the Animal Care and Use committee at our institution and in accordance with the *Guide for Care and Use of Laboratory Animals* of the National Institutes of Health. The 66 male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, IN) used in this study each weighed between 250–300g. Animals were housed individually and in groups up to three in conventional Lucite cages with soft bedding, given free access to food and water, and kept on a 12-h light:dark cycle in a climate-controlled environment.

### General Procedures

Each animal received an intrathecal catheter. After 4 to 5 days of recovery, a laparotomy was performed for ligation of the common bile-pancreatic duct and intraductal catheter placement. The next day, rats received intrathecal vehicle, gabapentin, morphine sulfate, or a combination of both drugs. Thirty min later, 0.5 ml of bradykinin ( $10^{-5}$  M, Sigma, St. Louis, MO) in lactated Ringer's solution (Baxter Healthcare Corporation, Deerfield, IL), was injected into the pancreas. Based on a previous physiologic study,  $10^{-10}$ – $10^{-4}$  M bradykinin is effective in producing nociceptive responses in this model without producing desensitization.<sup>45</sup> The response to bradykinin returns 45–60 min after intrathecally administered morphine in this acute pancreatitis model. Intraductal delivery of bradykinin served as the noxious visceral stimulus evoking nociceptive responses and inducing severe acute pancreatitis.

The spontaneous behavioral activity of the rats was observed during the first 10 min in a novel cage setting, and the number of these events was quantified as follows: 1) before any surgery (naïve), 2) after intrathecal surgery, 3) the next day after laparotomy (surgical baseline), and 4) after noxious activation of pancreatic afferent fibers with bradykinin in the case of either vehicle (0  $\mu$ g of drug) or a drug treatment. Animals were used for injection of bradykinin and drug testing only once.

### Intrathecal Catheter Placement

All animals had an intrathecal catheter implanted for vehicle or drug administration. Rats were put under general anesthesia with an ultra-short acting barbiturate administered intraperitoneally (Brevital; methohexital sodium, Jones Pharma Inc., St. Louis, MO; 40 mg/kg). A

**Table 1. Experimental Groups**

Drugs	Drug dosages ( $\mu\text{g}$ ) and number of rats			
aCSF		(n = 6)		
Morphine	0.1 (n = 6)	0.2 (n = 6)	0.5 (n = 6)	1.0 (n = 6)
Gabapentin	100.0 (n = 6)	200.0 (n = 4)	300.0 (n = 6)	–
Morphine + gabapentin (300 $\mu\text{g}$ )	0.1 (n = 5)	0.2 (n = 5)	0.5 (n = 5)	1.0 (n = 5)

aCSF = artificial cerebrospinal fluid.

45-mm intrathecal catheter (32-gauge, RecathCo, Allicon Park, PA) was inserted through a slit in the atlanto-occipital membrane into the subarachnoid space, and the tip of the catheter was carefully placed the T6–T7 level in a method described previously.<sup>11,46</sup> The catheter was linked to soft polyethylene tubing (PE10; inner diameter, 0.28 mm; outer diameter, 0.61 mm; Clay Adams Brands, Becton Dickinson Primary Care Diagnostics Becton Dickinson, Sparks, MD) and then stepped up *via* larger diameter polyethylene tubing for connection to a Hamilton syringe for administration of the pharmacological agents. The catheter was tunneled under the skin and allowed to remain subcutaneous at the neck until use. Total volume of the entire catheter assembly was less than 10  $\mu\text{l}$ . After implantation of the catheter, all animals were treated with topical antibiotic ointment at the wound site and 2 mg of intramuscular gentamycin injection to help prevent infection. Animals were observed for at least 4 days before experimental use. Animals exhibiting neurologic impairments or infection as a result of the implantation of the intrathecal catheter (n = 10) were not included in this study.

#### *Intraductal Catheter Placement*

After a recovery period of 4–7 days after intrathecal catheter placement, a second surgical procedure was performed to insert a catheter in the bile-pancreatic duct to cause ductal obstruction by ligation<sup>47,48</sup> and provide a route for administration of the chemical irritant, bradykinin. The animals were placed under general anesthesia with Brevital intraperitoneally, and a midline abdominal incision was made about 30 mm in length. The duodenum, pancreas, and the common bile-pancreatic duct were identified. Polyethylene tubing was inserted into the common bile-pancreatic duct. Proper placement of the catheter was confirmed by the appearance of bile progressing through the catheter. The free end of the polyethylene tubing was then tunneled subcutaneously to the neck, where it was secured with suture and sealed. The rats were allowed to recover overnight. Animals that developed a swollen abdomen or were inactive after laparotomy (n = 10) were not included in the study.

#### *Behavioral Study*

Behavioral testing was performed in a clean transparent homecage according to a method adapted by

Craft.<sup>11,49</sup> Immediately after introduction to a new cage, behavioral activity in three categories was observed and recorded every 10 s for a total of 10 min. These included cage crossing (forward locomotion across the centerline of the cage), rearing (standing on the hind limbs with or without support of the cage walls), and hind limb extension (stretching or twisting of the hind limbs behind or under the body). Decreases in the number of cage crossing and rearing events or the appearance of hind limb extensions are specific indicators of visceral pain. Every incident of these behaviors was recorded for each 10-s block, continuing for 10 min. The mean number of counts for each behavioral measure was used as the behavioral response to induction of pancreatitis. Responses were assessed to pretreatment with artificial cerebrospinal fluid (aCSF), gabapentin, morphine, or combined treatment. The experimenter analyzing animal behavior was blinded as to whether the animals had received a drug treatment or the aCSF vehicle as the drug control.

#### *Intrathecal Administration of Drugs*

Rats were randomized to experimental groups receiving vehicle (aCSF-treated drug control; n = 6), gabapentin (n = 16, a gift from Parke-Davis at Parke-Davis Research Laboratory), morphine (n = 24, Paddock Laboratories Inc, Minneapolis, MN), or combinations of the two agents (n = 20, table 1). The dose range was selected based on intrathecal doses effective for suppression of phase 2 behaviors in the formalin test (EC<sub>50</sub> rightward shift with 100  $\mu\text{g}$  dose).<sup>35</sup> A dose-response curve for each drug was generated by examining the effects after pretreatment with the drug in animals with pancreatitis. After the dose-response curve was generated for gabapentin, a single dose of gabapentin (300  $\mu\text{g}$ ) was selected for administration with various doses of morphine to examine the effectiveness of the combination on the behavioral measures. This dose was selected because it was the highest dose of gabapentin soluble in saline. All experiments were conducted at the same time of day to minimize effects of circadian rhythms. Drugs were dissolved in saline and injected to their final concentration in a 10- $\mu\text{l}$  volume of aCSF. The drugs were slowly injected into the intrathecal catheter with a Hamilton syringe (Reno, NV). An additional 10  $\mu\text{l}$  of pure aCSF was injected to ensure that the entire drug dose was propelled through the catheter and into the sub-

arachnoid space. At the end of the experiment, proper placement of the catheter was verified with intrathecal injection of 2% lidocaine (25  $\mu$ l), which temporarily paralyzed the hind limbs if the catheter was intact and properly placed.

### Statistical Analysis

Comparison of behavioral response values before (surgical baseline) and after drug treatment with different doses were analyzed using the Wilcoxon test. For behavioral changes with specific doses, comparisons were made between groups using the Mann-Whitney U-test. Comparisons were made between the aCSF treated drug control (0  $\mu$ g drug) and morphine alone, gabapentin alone, or combined drug treatment. Comparisons were also made between the group with combined drug treatment and either morphine alone or gabapentin alone. Data were expressed and plotted as means  $\pm$  SEM. A *P* value less than 0.05 was considered a significant difference.

## Results

### Intrathecal Catheter Placement Had No Effect on Spontaneous Behavior

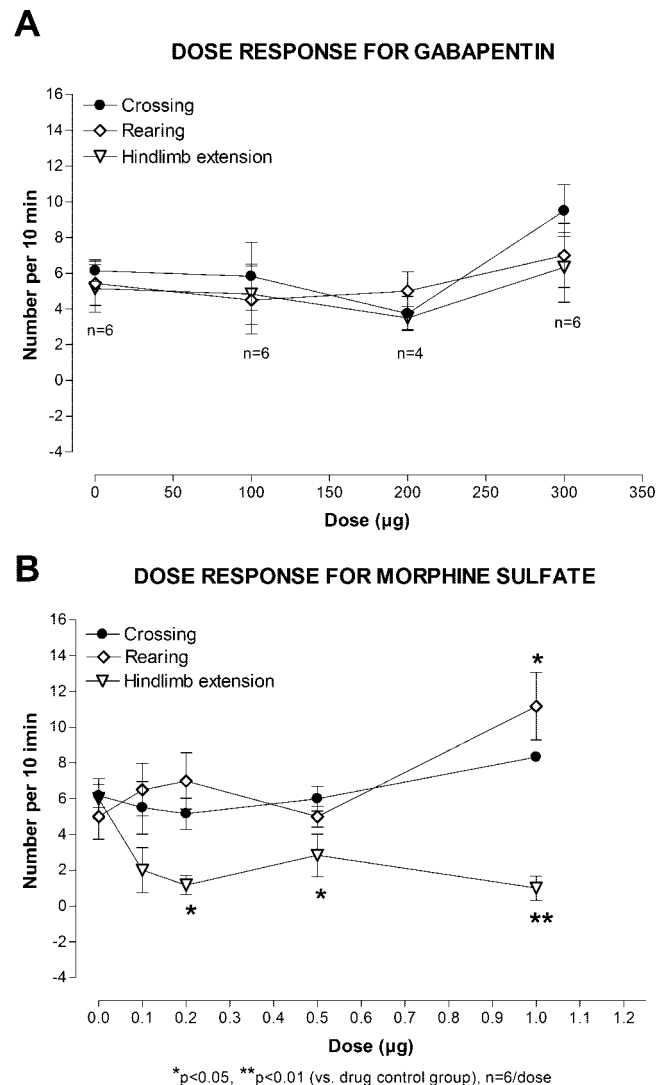
After a 4–5 day recovery period, behavioral testing revealed that intrathecal catheter placement did not affect rat spontaneous behavioral activities. The numbers of cage crossings and exploratory rearing were  $23.71 \pm 1.97$  (range, 16–31) and  $32.43 \pm 3.37$  (range, 22–43) in naïve rats and  $23.67 \pm 0.8$  and  $31.97 \pm 0.98$  in rats with intrathecal surgery, respectively. Hind limb extension was not evident in either naïve rats or in rats after intrathecal surgery. Because there were no significant differences in the spontaneous behavioral activities between the two groups of rats, these groups were combined as one control group for comparisons with other groups in this study.

### Spontaneous Behavioral Activity Changes Subsequent to Bile-Pancreatic Duct Obstruction

In the day after bile-pancreatic duct ligation and cannulation, hind limb extension behavior was increased significantly in comparison to naïve rats and those with intrathecal surgery ( $4.91 \pm 0.52$ ; range, 0–18; *P* < 0.01). The numbers of cage crossing and rearing events in rats with ductal obstruction were decreased to  $11.69 \pm 0.55$  (range, 4–24) and  $13.08 \pm 0.72$  (range, 1–28), respectively. These values are shown as the surgical baselines and used in the statistical comparisons.

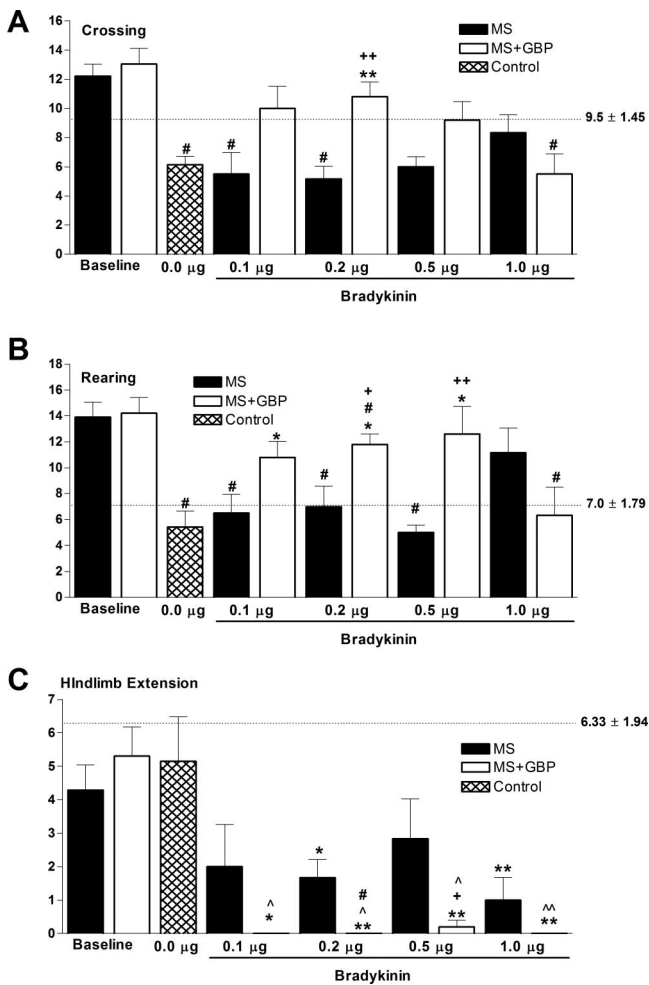
### Effect of Bradykinin Infusion into Pancreas on Spontaneous Behavior

Bradykinin was administered through the pancreatic intraductal catheter and the effects on behavior were



**Fig. 1.** (A) Dose-response curves illustrating the weak antinociceptive effect of intrathecal administration of gabapentin on behavioral activities in rats with acute pancreatitis induced by intraductal bradykinin infusion. Values are represented as the mean  $\pm$  SEM for initial 10-min activity in a novel cage experience. The 0- $\mu$ g dose represents the aCSF vehicle treated drug control group used for comparisons to the gabapentin treatment groups with Mann-Whitney U-tests (*n* = 6 for all doses, except *n* = 4 for the 200- $\mu$ g dose). No significant differences were found. (B) Dose-response curves illustrating the weak antinociceptive effect of intrathecal administration of morphine (for doses less than 1  $\mu$ g) on spontaneous behavioral activities in rats with acute pancreatitis induced by intraductal bradykinin infusion. Hind limb extension, a specific pain-related phenomenon, was significantly reduced at all doses. Values are represented as the mean  $\pm$  SEM for initial 10-min activity in a novel cage experience. The 0- $\mu$ g dose represents the aCSF vehicle treated drug control group. Comparisons were made between the vehicle and morphine treatment groups using Mann-Whitney U-tests. \**P* < 0.05; \*\**P* < 0.01; *n* = 6 per dose.

monitored. After bradykinin infusion into the pancreas, another significant reduction in cage crossing and rearing behaviors occurred. This is illustrated in fig. 1, A and B and fig. 2 as the 0  $\mu$ g dose, denoting the aCSF vehicle-treated drug control group after administration of brady-



**Fig. 2.** Bar chart illustrating the antinociceptive effects of intrathecal coadministration of a single ineffective dose of gabapentin (300 µg) with various low doses of morphine (white bar). Measures examined included cage crossing, rearing, and hind limb extension activities in rats with acute pancreatitis (n = 5 per dose) or for morphine alone (n = 6 per dose). Values are represented as the mean ± SEM for the initial 10 min of activity in a novel cage experience. Surgical baseline behaviors were tested for each of the animals in the drug studies for comparison to its own behavior after a single treatment (total n = 20 for the combined morphine plus gabapentin groups and total n = 24 for the morphine alone doses). The 0-µg dose (hatched bar) represents the aCSF vehicle treated control group in animals with intrathecal and intraductal catheters after bradykinin infusion (n = 6) used as controls combined for both studies. The dotted line illustrates the values for gabapentin alone (300 µg) from fig. 1A (9.5 ± 1.45 for crossing, 7.0 ± 1.79 for rearing, and 6.33 ± 1.94 for hind limb extension). Black bars indicate treatment with morphine alone (same data as in fig. 1B) for comparisons. Comparisons were made between surgical baseline and drug groups using the Wilcoxon test (#P < 0.05). Comparisons were made to the combined gabapentin and morphine treatment groups using Mann-Whitney U-tests versus the 0 µg aCSF vehicle treated control group (\*P < 0.05; \*\*P < 0.01); versus morphine alone (+P < 0.05; ++P < 0.01); and versus gabapentin alone (^P < 0.05; ^^P < 0.01). MS = morphine sulfate; GBP = gabapentin.

kinin. The effect of bradykinin, *i.e.*, the decrease in cage crossing and rearing behaviors, was significant in comparisons to surgical baseline behavior (P < 0.01, fig. 2).

No significant increase in hind limb extension events occurred in the drug control group compared to behaviors in rats with ductal obstruction only (surgical baseline, fig. 2).

*Effect of Gabapentin Pretreatment on Spontaneous Behavioral Activities*

Comparing behavioral activity of the aCSF-treated drug control group (0 µg) after bradykinin with that of rats receiving intrathecal preadministration of gabapentin, there was only a modest improvement in crossing and rearing behaviors at the highest 300-µg dose, but this was not a significant increase. Hind limb extension behavior was not statistically different in the gabapentin pretreated groups versus the aCSF-treated drug control group (0 µg) (fig. 1A). The 300-µg dose of gabapentin was used for studying the effect of combination with subtherapeutic doses of morphine.

*Effect of Morphine Pretreatment on Spontaneous Behavioral Activities*

The effects of morphine alone were monitored on spontaneous behavioral activities in rats with acute pancreatitis induced by intraductal bradykinin infusion. The morphine significantly reduced the number of hind limb extension behaviors at the 0.2- and 1.0-µg dose compared with aCSF-treated drug control rats (P < 0.05-0.01). Only at the highest 1.0-µg dose tested, was the number of rearing events increased significantly compared with the aCSF treated control group (0.0 µg) (fig. 1B).

*Coadministration of Gabapentin and Morphine*

Intrathecal coadministration of low doses of combined morphine (0.1-0.5 µg) and gabapentin (300 µg) in rats with intraductal bradykinin was associated with an improvement in cage crossing and rearing behavior equivalent to baseline (surgical baseline) (fig. 2). These values were significantly higher than the aCSF-treated drug control rats (0.0 µg) (P < 0.05-0.01). Furthermore, intrathecal coadministration of morphine (0.1-1.0 µg) with gabapentin (300 µg) significantly prevented development of hind limb extension activity in all groups (P < 0.01), comparable to the control group (naïve and intrathecal surgery only). Only the 0.2-µg dose of morphine improved all behavioral measures when combined with gabapentin. Thus, the low doses of morphine combined with gabapentin produced the same effects on spontaneous behavior as the higher-dose morphine alone (1 µg; fig. 1B) when used at fractions of this dose (1/5 to 1/2). At the highest dose tested, hind limb extension behavior remained well controlled but cage crossing and rearing activity did not improve and remained at levels equivalent to the aCSF-treated bradykinin stimulated animals (fig. 2). Selected doses of the combined drugs were significantly improved over morphine alone for crossing and rearing, whereas all doses of the combined drugs

were significantly improved over gabapentin alone (300  $\mu\text{g}$ ) for hind limb extension (fig. 1A).

## Discussion

The mechanisms for nociception arising from visceral organs continue to represent an area of research that requires much more exploration. Until recently visceral pain has received significantly less attention than post-surgical and neuropathic pain. Furthermore, the animal models that have been used to explore pain mechanisms and effective pharmacologic interventions have typically not resembled conditions encountered in humans. There has been a call to develop animal models for pain management that more closely simulate human ailments. There is also a need to further investigate the effects of intrathecal pharmacologic therapy both in acute and chronic models.<sup>1,2</sup> Gabapentin, an antiepileptic drug that has been shown to have efficacy in the treatment of neuropathic pain,<sup>19,23,50</sup> was used in the current study to examine its usefulness as an adjuvant to initial low dose morphine therapy.

In our study we sought to investigate the effects of combined intrathecal administration of two United States Food and Drug Administration approved drugs, gabapentin and morphine, in an animal model that closely simulates a relatively common condition that causes excruciating pain in humans, acute bouts of pancreatitis. The consistency of our results was assured by conducting all of the behavioral experiments at the same time of day and precisely adhering to a 30-min interval between the administration of the drugs and pharmacological induction of acute visceral pain. Our results were measured by observation of three types of spontaneous behavioral activity in the rats. This included numbers of cage crossings, rearing events, and hind limb extensions. Hind limb extensions are evoked in many visceral pain models. It was shown in the current study that the induction of acute visceral pain using our pancreatic inflammation method produces quantifiable pain-related behavioral measures including reduction of the number of cage crossing and rearing events and the appearance of hind limb extensions.

In the current study, we found that although intrathecal administration of gabapentin (300  $\mu\text{g}$ ) alone was ineffective in reducing hind limb extension behavior, it did increase the number of cage crossing and rearing events in the rats with pancreatitis compared with bradykinin-treated rats injected intrathecally with vehicle (aCSF) alone. Morphine was found to decrease hind limb extension but did not increase cage crossing and rearing behavior at doses less than 1  $\mu\text{g}$ . Co-administration of gabapentin potentiated the effect of low-dose morphine providing a leftward shift in efficacy and improving all of the pain-related behaviors, particularly the disappear-

ance of hind limb extensions. These results indicate that intrathecal gabapentin, while ineffective by itself on this visceral pain state in this dose range, can enhance the effects of coadministered low-dose morphine both qualitatively and quantitatively by approximately 10-fold. These results support previous clinical and animal experimental investigations using morphine/gabapentin for the treatment of pain.<sup>33,37,38,44</sup> It should be noted that the effect reverses at the 1- $\mu\text{g}$  dose of morphine for one of the behavioral measures, however.

The affinity of gabapentin for neuronal calcium channel subunits leads us to hypothesize that the effects of gabapentin may be related to blockade of calcium ion transmission at the spinal cord level. Gabapentin reportedly binds with high affinity to  $\alpha_2\delta_1$  voltage sensitive calcium channel subunits and is likely to potentiate the effects of morphine in a fashion similar to known calcium channel blockers. Therefore, its mechanism of action may be related to modulation of voltage-gated calcium channels in the central nervous system as has been shown in spinal cord slices<sup>51</sup> and dorsal root ganglia cells in culture.<sup>23,52,53</sup> It has been shown that other voltage-gated calcium channel blockers (verapamil and omega conotoxins),<sup>54,55</sup> when coadministered intrathecally with ineffective doses of morphine, have had significant antinociceptive effects while administration of the calcium channel blockers alone had mixed results depending on the type of calcium channel affected. These results are consistent with our findings that gabapentin enhances the effects of morphine and improves spontaneous activity levels.

In summary, the results of this study indicate that intrathecal infusion of gabapentin combined with a low dose of morphine can alleviate visceral pain to the same degree as administration of a higher dose of morphine by itself. In addition, the combined administration of gabapentin and low dose morphine increased behavioral activity levels for the rats with pancreatitis and eliminates visceral pain specific hind limb extensions. Intrathecal administration of gabapentin alone has limited effects on visceral pain. These results suggest that for clinical management of visceral pain such as pancreatitis, gabapentin may be an effective adjuvant to initial low dose opioid therapy improving both pain and daily activity measures.

This article commemorates completion of a study done by Matt Smiley, M.D. We dedicate this paper to Matt, his parents and friends to acknowledge his contributions as the first author of the manuscript, including the conception and lead effort on this project. It was a privilege to know him, an honor to work with him and a pleasure to enjoy his infectious enthusiasm. The authors also acknowledge assistance with the manuscript references and figures from Pat Gazzoli, Administrative Secretary, Department of Neurosciences and Cell Biology, University of Texas Medical Branch, Galveston, Texas.

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