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Gabapentin Markedly Reduces Acetic Acid–induced Visceral Nociception

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Background: **Gabapentin has recently been used clinically as an antihyperalgesic agent to treat certain neuropathic pain states. The aim of this study is to test whether gabapentin is able to inhibit responses to peritoneal irritation–induced visceral pain and to examine the effect of gabapentin on spinal cord amino acid release.**

Methods: **The acetic acid–induced writhing assay was used in rats to determine the degree of antinociception. The rats received an intraperitoneal injection of acetic acid 40 min after intraperitoneal administration of vehicle or gabapentin (50, 100, or 200 mg/kg). Cerebrospinal fluid dialysate was collected by microdialysis from the spinal subarachnoid space in anesthetized rats. Acetic acid–induced release of amino acids into the dialysate, including glutamate, aspartate, serine, glutamine, and glycine, following intraperitoneal injection of acetic acid was evaluated by measurements of changes in the concentrations of these amino acids. The effects of pretreatment with saline or gabapentin (100 mg/kg intraperitoneal) on amino acid release were compared.**

Results: **Gabapentin reduced writhing responses in a dose-related fashion. Dialysate concentrations of glutamate, aspartate, and serine increased significantly following intraperitoneal injection of acetic acid, while glutamine and glycine concentrations were not increased significantly. When compared to saline-treated rats, animals pretreated with 100 mg/kg gabapentin showed suppression of the acetic acid–induced increases in glutamate, aspartate, and serine concentrations.**

Conclusions: **These data demonstrate that gabapentin effectively inhibits acetic acid–induced nociception, and the antinociceptive effect of gabapentin correlates with the suppression of noxious-evoked release of excitatory amino acids in the spinal cord.**

GABAPENTIN is a novel, well-tolerated, anticonvulsant drug structurally related to γ-aminobutyric acid. Evidence obtained in a number of experimental models of neuropathic pain and inflammatory hyperalgesia[1–4] shows that gabapentin has an effective antinociceptive or antihyperalgesic action, in addition to being an anticonvulsant. Effects of gabapentin on the electrophysiological properties of dorsal horn neurons in the spinal cords of normal and hyperalgesic adult rats with diabetic neuropathy were investigated by Patel *et al.*[5]

Moreover, gabapentin monotherapy appears to be efficacious for the treatment of pain and sleep interference associated with diabetic peripheral neuropathy and exhibits positive effects on mood and quality of life.[6–8] Gabapentin has been used successfully to reduce neuropathic pain in a series of patients with reflex sympathetic dystrophy[9] and a patient with postherpetic neuralgia.[10]

The pharmacological safety profile of gabapentin has attracted more and more attention from basic and clinical investigators. Although the mechanism of action of gabapentin is still not understood, a highly specific gabapentin binding site in the brain has been described by Suman-Chauhan *et al.*[11] This is identified as the $\alpha_2\delta$ subunit of calcium channels. In addition, evidence from several laboratories has demonstrated that gabapentin treatment may involve glutamate metabolism and release.[12,13]

Gabapentin has been demonstrated to act within the spinal cord or brain to reduce sensitization of dorsal horn neurons. It is not effective in reducing immediate pain from injury, but it appears to reduce abnormal hypersensitivity induced by inflammatory responses or nerve injury. The acetic acid–induced visceral pain model is widely used in experimental research. It can produce not only abdominal contractions, but also gastrointestinal ileus.[14]

The excitatory amino acids, glutamate and aspartate, are likely neurotransmitter candidates for inflammatory nociceptive transmission. Both glutamate and aspartate are found in small myelinated and unmyelinated primary afferent neurons.[15] Although there are several case reports in which gabapentin is regarded as an adjunctive agent, assisting in refractory genitourinary tract pain control,[16,17] little is known about an action of gabapentin on visceral pain. Furthermore, its relation to excitatory amino acid release has not yet been demonstrated. The aim of this study is to test whether gabapentin is able to inhibit the responses of rats to peritoneal irritation–induced visceral pain and to examine the effect of gabapentin on the release of amino acids from the spinal cord.

Methods

Animal

Male Sprague-Dawley rats (weight, 300–350 g) were used for the experiments. The animals were housed individually in a temperature-controlled (21 ± 1°C) room with a 12-h light/dark cycle and were allowed free

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access to food and water. Surgical and experimental protocols used in this study were approved by the Animal Care and Use Committee at the University of Texas Medical Branch, Galveston, Texas.

Drug Preparation

Gabapentin (kindly donated by Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Co., MI) was dissolved in saline. Drugs and vehicle solutions were made up freshly in a volume of 1 ml before each experiment. To rule out the possibility that gabapentin worked by buffering the acetic acid, the pH values of the gabapentin solutions were tested. The body weight of the rats used in the experiments ranged from 300 to 350 g. We selected six concentrations of drug solutions according to three doses of gabapentin (50, 100, and 200 mg/kg) and two body weights (300 and 350 g). The pH values of different concentrations of gabapentin for the matched dose/body weight were 6.97, 6.88, 6.87, 6.94, 7.00, and 6.99, respectively, which were comparable to the average pH of saline (6.21).

Behavioral Tests of Antinociception

Each animal was initially allowed 30 min to habituate to laboratory surroundings. The rats were then placed in individual 30 × 50 × 30–cm polypropylene boxes. All randomizations were performed by drawing lots. At least three rats were tested simultaneously. The behavioral investigator was blinded as to what drug was injected intraperitoneally.

Visceral pain was scored according to a previously reported method.[18] The acetic acid–induced writhing assay was used to determine the degree of antinociception. Nociceptive responses were characterized by the presence of abdominal contractions, which consisted of the contraction of flank muscles associated with inward movements of the hind limb, a hind paw reflex, or whole-body stretching. The rats received an intraperitoneal injection of 0.6% acetic acid (4 ml/kg) 40 min after vehicle or gabapentin (50, 100, or 200 mg/kg) administration. Abdominal contractions were recorded by visual observation of the animals for 100 min following the intraperitoneal vehicle or gabapentin treatment.

Beam-balance Task

To test for a possible central nervous system inhibitory or sedative effect, which might influence antinociceptive behavior in tests using gabapentin, the beam-balance task was used. Beam balance is sensitive to motor cortical insults. This task is used to assess gross vestibulomotor function by requiring a rat to balance steadily on a narrow beam. The beam-balance task had been used to assess sensorimotor function and motor coordination following cerebral cortical injury in rats.[19,20] The rats were placed on a wood beam (60 cm length × 1.5 cm width) for up to 60 s. The time that rats remained on the beam was recorded and compared among the groups.

Dialysate Collection and Excitatory Amino Acid Analysis

For chronic implantation of an intrathecal microdialysis fiber in the form of a loop placed in the cerebrospinal fluid (CSF) space, the rats (weight, 300–350 g) were anesthetized with halothane, and the dialysis probe was inserted through an incision in the cisternal membrane and extended caudally until the active dialysis area (2-cm Hospal AN69, 200-μm OD, 45-kd cutoff) was placed at the level of the lumbar enlargement.

At least 4 days after recovery from implantation, rats were initially anesthetized with pentobarbital sodium (50 mg/kg intraperitoneal), and then anesthesia was maintained with 10% pentobarbital sodium administered at 20 μl/min through a tail vein. The animal's body temperature was maintained at 37°C by a servo-controlled heating blanket. The dialysis system was attached to a syringe pump and perfused with artificial cerebrospinal fluid (ACSF) at 10 μl/min. The ACSF consisted of 151.1 mM Na^+, 2.6 mM K^+, 0.9 mM Mg^{2+}, 1.3 mM Ca^{2+}, 122.7 mM Cl^-, 121.0 nM HCO_3, 2.5 mM HPO_4, and 3.5 mM dextrose. The ACSF was bubbled with 5% CO_2 in 95% O_2 to adjust the pH to 7.2. Samples were collected in polypropylene tubes on ice and frozen at −70°C until they could be analyzed for amino acids by high-performance liquid chromatography. Animals were dialysed for 30 min to achieve equilibrium. The mean concentrations of amino acids in samples collected preceding gabapentin or saline administration were designated as baseline, and three additional samples were collected after intraperitoneal injection of gabapentin (100 mg/kg) or saline at 10-min intervals. Then, 0.6% acetic acid was injected intraperitoneally (4 ml/kg). Consecutive samples were further collected at 10-min intervals for 60 min following the acetic acid injection. Samples were assayed for several amino acids, including aspartate, glutamate, glycine, glutamine, and serine.

Data Analysis

Each treatment group consisted of 12 rats, and each rat was used for only one treatment. The total number of writhing responses for each rat during 1 h was counted. Mean numbers of abdominal contractions were analyzed using one-way analysis of variance followed by the Dunnett *t* test to compare the responses after vehicle and after each drug dose.

The average times that rats stayed on the beam 40 min after treatment with gabapentin were analyzed using one-way analysis of variance followed by a least significant differences test to compare the effect of different doses of gabapentin on the central nervous system.

Each amino acid concentration was then expressed as a percentage of the baseline level to reduce the variation

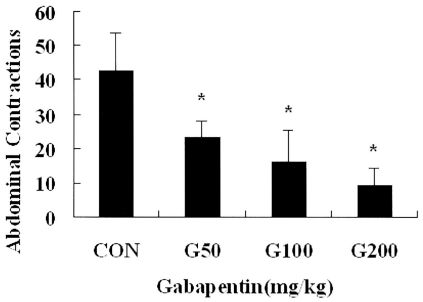

Fig. 1. Gabapentin attenuated abdominal contractions in a dose-related fashion following intraperitoneal injection of 0.6% acetic acid (mean ± SD). *$P < 0.05$ *versus* control group. CON = saline control; G50 = 50 mg/kg gabapentin; G100 = 100 mg/kg gabapentin; G200 = 200 mg/kg gabapentin.

among animals. Statistical analysis of the amino acid results was performed with repeated-measures analysis of variance followed by Mann–Whitney tests. $P < 0.05$ was regarded as significant.

Results

Antinociceptive Action of Gabapentin

Antinociceptive Action of Gabapentin on Writhing Responses Due to Peritoneal Irritation. Injection of either intraperitoneal saline or gabapentin by themselves did not alter the behavior of the animals. Frequent abdominal contractions were observed 10–20 min after intraperitoneal acetic acid injection in the saline pretreatment group. Gabapentin inhibited these abdominal contractions induced by peritoneal irritation in a dose-related manner (fig. 1).

Effect of Gabapentin on Beam-balance Test

Beam-balance time was significantly shortened after pretreatment with 200 mg/kg gabapentin when compared with either behavior in the absence of any treatment or after saline pretreatment ($P < 0.05$; fig. 2). Mild motor ataxia was noted in all rats at this dosage. However, intraperitoneal administration of gabapentin failed to have any effect on the beam-balance test at doses of 50 or 100 mg/kg.

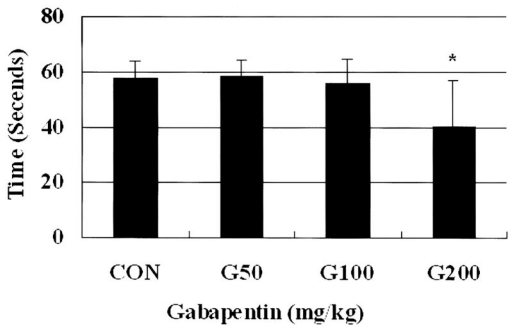

Fig. 2. The average time that rats stay on the beam bar 40 min after treatment with different doses of gabapentin. Systemic gabapentin, 200 mg/kg, significantly shortened the beam-balance time, $P < 0.05$. Bars indicate SD. CON = saline control; G50 = 50 mg/kg gabapentin; G100 = 100 mg/kg gabapentin; G200 = 200 mg/kg gabapentin.

Reduction of Excitatory Amino Acid Release by Gabapentin

Mean basal dialysate concentrations of amino acids (mean ± SE) in the control and gabapentin groups were as follows: aspartate: 0.04 ± 0.02 *versus* 0.07 ± 0.02 μg/μl; glutamate: 0.23 ± 0.026 *versus* 0.65 ± 0.49 μg/μl; serine: 0.43 ± 0.20 *versus* 0.61 ± 0.26 μg/μl; glycine: 0.66 ± 0.248 *versus* 0.70 ± 0.32 μg/μl; glutamine: 8.91 ± 0.2 *versus* 7.26 ± 5.02 μg/μl.

None of the amino acid concentrations changed significantly after intraperitoneal saline or gabapentin injection. Intraperitoneal acetic acid injection produced a significant increase in spinal dialysate concentrations of aspartate ($F = 4.64$, $P < 0.001$), glutamate ($F = 3.619$, $P = 0.003$), and serine ($F = 3.228$, $P = 0.004$). Dialysate concentrations of glycine and glutamine tended to increase, but there were no statistically significant differences (glycine: $F = 1.675$, $P = 0.124$; glutamine: $F = 0.945$, $P = 0.498$). The increased amino acid release induced by acetic acid alone reached a maximal level at 60 min after injection and remained unchanged for 2 h (data not shown). Pretreatment with gabapentin (100 mg/kg) significantly reduced the release of aspartate, glutamate, and serine in response to peritoneal irritation (fig. 3).

Discussion

In the current study, peritoneal irritation by acetic acid induced visceral nociceptive responses (abdominal contractions), which is in agreement with previous observations.[21] Intraperitoneal gabapentin effectively reversed these acetic acid–induced writhing responses in a dose-related fashion, even at doses that did not affect motor behavior, as determined by the beam-balance test.

Several lines of evidence have shown that excitatory amino acids, such as glutamate and aspartate, are important for the transmission of nociceptive inputs in a variety of nociceptive models, acting as direct or indirect neurotransmitters.[22–25] Profound changes may occur within the spinal cord in response to peripheral nociception or inflammation. These include changes in excitatory amino acid synthesis and release. For example, increased glutamate concentration in the spinal cord was found to correlate with noxious stimulation.[26] Acute arthritis caused a biphasic release of glutamate and aspartate in the dorsal horn.[27–29] Moreover, visceral pain caused by active labor in women induced a significantly increased concentration of the excitatory amino acid aspartate in lumbar CSF.[30] Our data clearly show, for the first time, that intraperitoneal injection of acetic acid induces an increased concentration of glutamate and

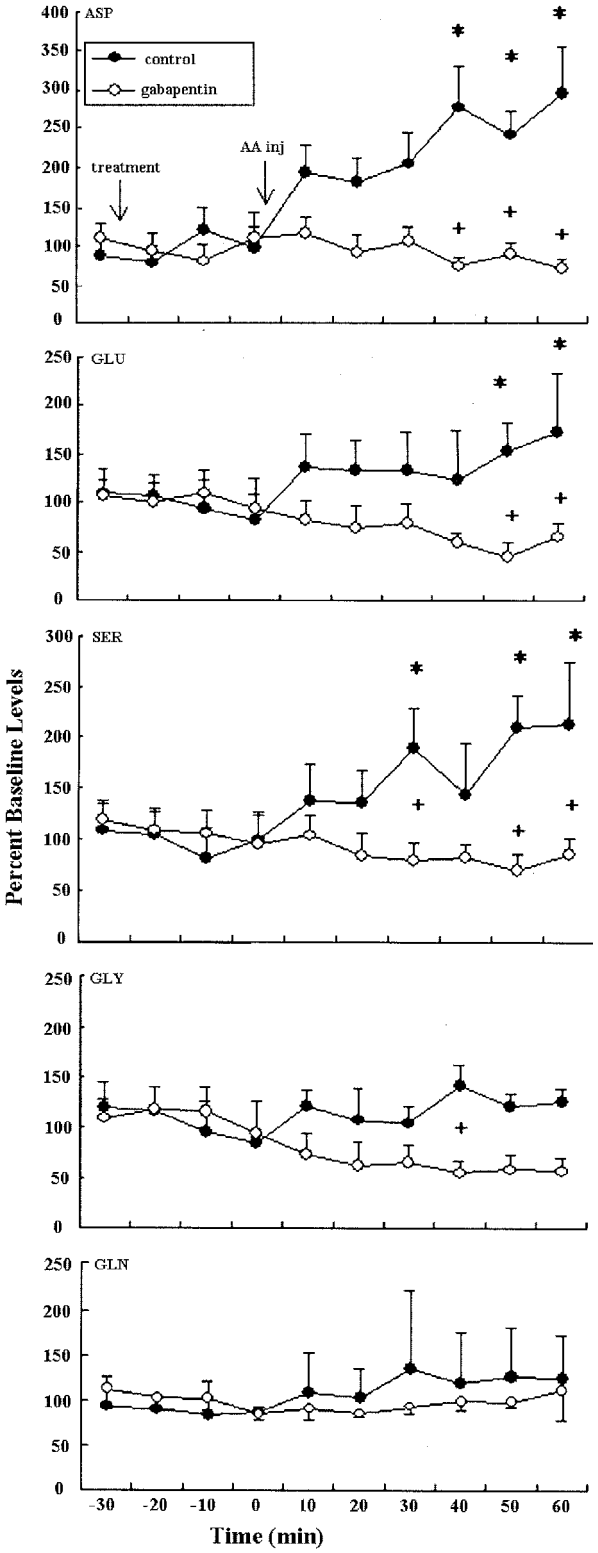

Fig. 3. Comparison of mean normalized intrathecal amino acid concentrations during 1 h between control and gabapentin groups (mean ± SE). *$P < 0.05$ *versus* baseline. +$P < 0.05$ *versus* control. Treatment: saline or gabapentin (100 mg/kg) intraperitoneal injection. AA inj = intraperitoneal injection of acetic acid; ASP = aspartate; GLU = glutamate; SER = serine; GLY = glycine; GLN = glutamine.

aspartate in the CSF. The results indicate that injection of an irritating agent intraperitoneally activates sensory neurons sufficiently to result in an increased release of excitatory amino acid into the CSF. Therefore, activation of the sensory nervous system and release of excitatory amino acid following acetic acid injection may be considered as a part of a host defense response. Presumably, intraperitoneal gabapentin effectively reversed the acetic acid–induced writhing responses through inhibition of this increase in excitatory amino acid release.

Although hypotheses have been put forward regarding the mechanism of action of gabapentin, how gabapentin may exert its effect on spinal and peripheral neurotransmitter release is currently unclear. One mechanism is that gabapentin might decrease the synthesis of the neurotransmitter and excitotoxin glutamate.[31–33] Since intracellular Ca^{2+} accumulation is important for the spread of epileptic discharges,[34] an effect of gabapentin on voltage-gated Ca^{2+} channels is possible. Although gabapentin is known to bind to the $\alpha_2\delta$ subunit of voltage-dependent calcium channels,[11,35] the functional significance of this action of gabapentin appears to be controversial. By using neocortical synaptosomal preparations, which contain mostly glutamatergic terminals, Flink *et al.*[36] found that gabapentin reduces Ca^{2+} influx into glutamatergic terminals, which is mainly mediated by P/Q-type voltage-gated Ca^{2+} channels, thus inhibiting the K^+-induced release of endogenous aspartate and glutamate. The inhibition of excitatory amino acid release conceivably leads to reduced postsynaptic excitability, providing one reasonable explanation for the antinociceptive efficacy of gabapentin. On the other hand, evidence shows that the antiglutamatergic properties of gabapentin are due to inhibition of cytosolic branched-chain aminotransferase, an enzyme that synthesizes glutamate in brain.[37]

In the current study, intraperitoneal acetic acid induced release not only in excitatory amino acids, but also in inhibitory amino acids, such as serine. The increased serine could be triggered by ascending transmission of nociceptive evoked activity, which in turn activates descending projection systems. The descending analgesia pathway excites inhibitory interneurons, which then release serine and glycine into the dorsal horn. The gabapentin pretreatment did not effect the concentrations of either excitatory or inhibitory amino acids. However, gabapentin significantly inhibited the acetic acid–induced serine increase.

Good clinical tolerance and a low incidence of side effects make gabapentin acceptable as a complementary analgesic by patients and physicians. In these experiments on rats, we did observe a sedative effect of gabapentin at higher doses, manifested as a shortened beam-balance time. This can be confused with analgesia.

In addition, it is not known which structures in the spinal cord are the sites of action of gabapentin. Thus,

the underlying mechanisms of the inhibitory effects of gabapentin on acetic acid–evoked excitatory amino acid release need further investigation.

Conclusion

Although the mechanism of gabapentin action remains unknown, the results of this study give direct evidence in support of the hypothesis that gabapentin has an antinociceptive effect on writhing responses that follow peritoneal irritation and that this antinociceptive effect corresponds to suppression of noxious-evoked release of amino acids from the spinal cord into the CSF.

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