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Cardiac Pharmacology

Gabapentin Reduces Blood Pressure and Heart Rate through the Nucleus Tractus Solitarii

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Background: Oral and intravenous gabapentin can markedly attenuate blood pressure (BP) in hypertensive rats. The nucleus tractus solitarii (NTS) is the primary integrative center for cardiovascular control and other autonomic functions in the central nervous system. However, the signaling mechanisms involved in gabapentin-mediated cardiovascular effects in the NTS remain unclear. We investigated whether the nitric oxide synthase (NOS) signaling pathway was involved in gabapentin-mediated BP regulation in the NTS of spontaneously hypertensive (SHR) rats.

Methods: SHR rats were anesthetized with urethane at age 10-12 weeks. Arterial pressure and heart rate (HR) were monitored through a femoral artery catheter. For stereotaxic intra-NTS microinjection, the dorsal surface of the medulla was exposed by limited craniotomy. We observed that unilateral microinjection of gabapentin into the NTS whether to change dose-related BP and HR. Then, unilateral microinjection of gabapentin into the NTS before and after N(ω)-nitro-L-arginine methyl ester (L-NAME) treatment whether to change blood pressure and heart rate.

Results: Unilateral microinjection of gabapentin into the NTS produced prominent dose-related depressor and bradycardic effects in SHR rats. The cardiovascular effects of gabapentin were attenuated by the prior administration of the NOS inhibitor, L-NAME.

Conclusions: Gabapentin modulated central BP and HR control in the NTS of SHR rats in this study through NOS signaling.

Key Words: Central cardiovascular regulation • Gabapentin • Nitric oxide synthase • Nucleus tractus solitarii

INTRODUCTION

Gabapentin is an analog of gamma-aminobutyric acid (GABA), however its mechanism is unclear.[1] Gabapentin does not bind to GABA(A) or GABA(B) receptors (or benzodiazepine, opioid, or cannabinoid receptors), but it can increase GABA and decrease glutamate concentrations.[2,3] Its mechanisms of antiepileptic and analgesic actions are unknown, although in the latter it may reduce the release of pain-related peptides and decrease opioid-induced hyperalgesia.[4] However, a unique gabapentin-binding protein has been identified[5,6] which is a subunit of the voltage-dependent calcium channel complex,[7] suggesting a less specific mechanism of action through modulation of neurosignaling.

Gabapentin was initially approved in 1993 by the US

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Food and Drug Administration for the treatment of epilepsy as an adjunct to anticonvulsant therapy, and in 2004 it was also approved as an analgesic for postherpetic neuralgia.[8] The European Medicines Agency approved gabapentin in 2006 for epilepsy and certain types of neuropathic pain,[9] and the UK National Institute for Clinical Excellence recommends gabapentin as a first-line treatment for all neuropathic pain.[10] Because its mechanism of action is unclear and it is assumed to have no potential for abuse, gabapentin is used widely off-label to treat an array of disorders, including insomnia, various neuropathic pain conditions, drug and alcohol addiction, anxiety, bipolar disorder, borderline personality disorder, menopausal conditions, vertigo, pruritic disorders, and migraines. In fact, estimates of the off-label usage of gabapentin are reported to range from 83 to 95%.[11,12]

Hypertension is one of the most common chronic diseases and public health problems worldwide.[13,14] Our previous study indicated that oral gabapentin can markedly attenuate blood pressure in chronic kidney disease-induced hypertension.[15] Another study showed that the intravenous administration of gabapentin decreased blood pressure in hypertensive rats.[16] Endotracheal intubation is the standard method for securing the airway before surgery. However, this procedure can produce activation of the sympathetic nervous system and result in a hemodynamic response which, in high-risk patients, may lead to cardiovascular instability and myocardial ischemia. Many studies have demonstrated that gabapentin 800 mg in a single or double dose is equally effective in attenuating the hypertensive response to laryngoscopy and tracheal intubation in treated hypertensive patients.[17-19] In addition, gabapentin treatment for 4 weeks has been shown to result in an 82% improvement in symptom severity of restless legs syndrome, which may be associated with cardiovascular mortality and survival in uremic patients.[20,21] Using staged dose increases, Yamada et al. reported that treatment with gabapentin and propranolol gradually reduced paroxysmal sympathetic hyperactivity (PSH), with no further breakthrough PSH attacks, even in response to stimuli.[22] Gabapentin may play an important role in cardiovascular regulation in the central nervous system.

The nucleus tractus solitarii (NTS) is located in the dorsal medulla of the brainstem, which is the primary integrating center for cardiovascular regulation and other autonomic functions of the central nervous system. Our previous studies demonstrated that several neuromodulators, including adenosine,[23] angiotensin II,[24] angiotensin III,[25] carbon monoxide,[26] insulin,[27] renin,[28] neuropeptide Y,[29] nicotine[30] and nitric oxide,[31] are involved in cardiovascular control through the NTS. Moreover, many medicines such as simvastatin[32] and resveratrol[33] improve blood pressure through their effect in the NTS. In this study, we examined the pharmacological mechanisms using microinjection of gabapentin into the NTS and observed regulatory effects on blood pressure (BP) and heart rate (HR).

METHODS

Experimental chemicals

All experimental chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA), unless otherwise indicated.

Animals

Male spontaneously hypertensive (SHR) rats weighing 250-300 g were obtained from the National Laboratory Animal Center and housed in the animal room of Kaohsiung Veterans General Hospital (Kaohsiung, Taiwan, ROC). The rats were kept in individual cages in a room in which lighting was controlled (12 h on/12 h off), and temperature was maintained at 23 °C to 24 °C. The rats were acclimatized to the housing conditions for 1 week, and were given normal rat chow (Purina, St. Louis, MO, USA) and tap water *ad libitum*. All animal research protocols were approved by the Research Animal Facility Committee of Kaohsiung Veterans General Hospital.

Intra-NTS microinjection

Rats were anesthetized with urethane (1.0 g/kg intraperitoneal and/or 0.3 g/kg intravenous injection if necessary). The preparation of the animals for intra-NTS microinjection and the methods used to localize the NTS have been described previously.[34] Briefly, a polyethylene cannula was inserted into the femoral artery for fluid supplementation, and arterial pressure and pulse were continuously monitored through a PE-50 catheter inserted in the femoral artery and connected to a pres-

sure transducer (ADInstruments, Colorado Springs, CO, USA). This experimental method is different from clinical monitoring methods.[35] To verify that the needle tip of the glass electrode was in the NTS, L-glutamate (0.154 nmol/60 nL) was microinjected to test induction of a characteristically abrupt decrease in BP (BP ≥ 35 mmHg) and HR (HR ≥ 50 bpm). The gabapentin (3.3, 10, and 33 nmol/60 nL) we used in this study was dissolved in artificial cerebrospinal fluid (aCSF; 142 mmol·L-1 NaCl, 5 mmol·L-1 KCl, 10 mmol·L-1 glucose and 10 mmol·L-1 HEPES, pH 7.4). Gabapentin in doses of 3.3, 10, and 33 nmol/60 nL was microinjected into the rat's NTS to determine whether there was a dose-response relationship. We also investigated whether nitric oxide synthase (NOS) signaling participated in the depressor effect of gabapentin in the NTS by filling the electrode with the non-selective NOS inhibitor, N(ω)-nitro-L-arginine methyl ester (L-NAME, 33 nmol/60 nL). Involvement of NOS in the gabapentin-induced cardiovascular effects was determined by prior microinjections of L-NAME into the NTS, and the same dose (33 nmol/60 nL) of gabapentin was microinjected into the NTS before and 10, and 90 min after L-NAME administration.

Statistical analysis

All data are expressed as means ± standard error of the mean (SEM). The Mann-Whitney *U*-test or Kruskal-Wallis one-way analysis of variance was used to compare differences between groups. $p < 0.05$ was considered to be statistically significant.

RESULTS

Gabapentin modulated the central cardiovascular effect in the NTS

We initially investigated the central cardiovascular effects of gabapentin in the SHR rats by microinjection into the NTS. Unilateral microinjection of increasing doses of gabapentin (3.03 to 33 nmol) into the NTS produced dose-dependent depressor and bradycardic effects (Figure 1A). Microinjection of gabapentin at a dose of 3.03 nmol did not change the BP or HR in the SHR rats. A dose of 10 nmol slightly reduced the BP and HR (-7 ± 2 mmHg and -18 ± 5 bpm) (Figure 1B), while microinjection at a dose of 33 nmol induced dose-dependent increases (-13 ± 2 mmHg and -38 ± 3 bpm) in the SHR rats (Figure 1B). Therefore, 33 nmol of gabapentin was chosen in subsequent studies to investigate the central cardiovascular effects of gabapentin in the NTS of the SHR rats.

Gabapentin induced systemic vasodepressor effects through NOS in the NTS

We further investigated whether NOS contributed to the depressor effects of gabapentin in the NTS of the SHR rats. Pretreatment with the non-selective NOS inhibitor, L-NAME (33 nmol), attenuated the depressor effect of gabapentin (Figure 2A). The depressor and bradycardic responses to gabapentin in the NTS were attenuated 10 min after L-NAME treatment (-29 ± 2 versus -8 ± 2 mmHg and -35 ± 7 versus -13 ± 3 bpm; Figure 2B). The depressor effect of gabapentin in the NTS recovered gradually over 90 min after L-NAME treatment (-8 ± 2 versus -20 ± 3 mmHg and -13 ± 3 versus -36 ± 8 bpm; Figure 2B). These results indicated that gabapentin may have induced NOS to induce hypotension and bradycardia in the NTS of the SHR rats.

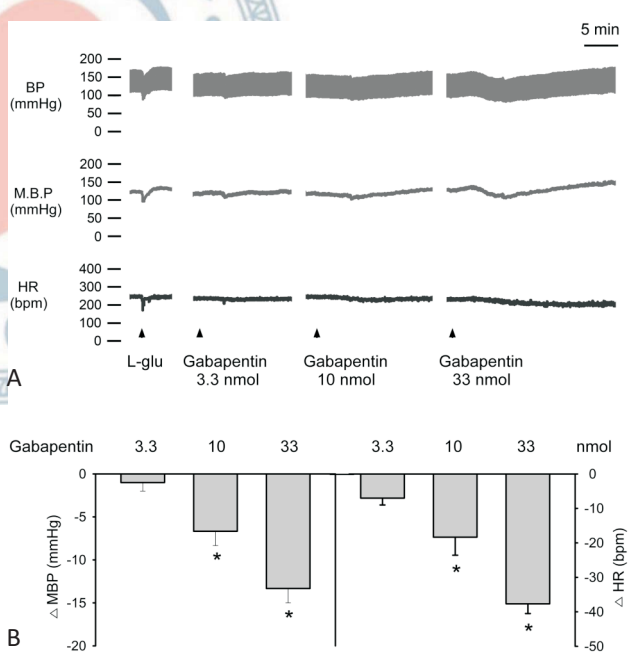

Figure 1. *Cardiovascular effects of different doses of gabapentin microinjected into the NTS in rats. (A) Representative tracings demonstrating the cardiovascular effects of different doses (3.3-33 nmol/60 nL) of gabapentin in anesthetized rats. (B) Effects of unilateral NTS microinjection of gabapentin on MBP and HR. BP, blood pressure; MBP, mean blood pressure; HR, heart rate recorded at paper speed of 3 mm/min. Horizontal bar represents recording during 5-min intervals. * $p < 0.05$ vs. vehicle group, n = 3.*

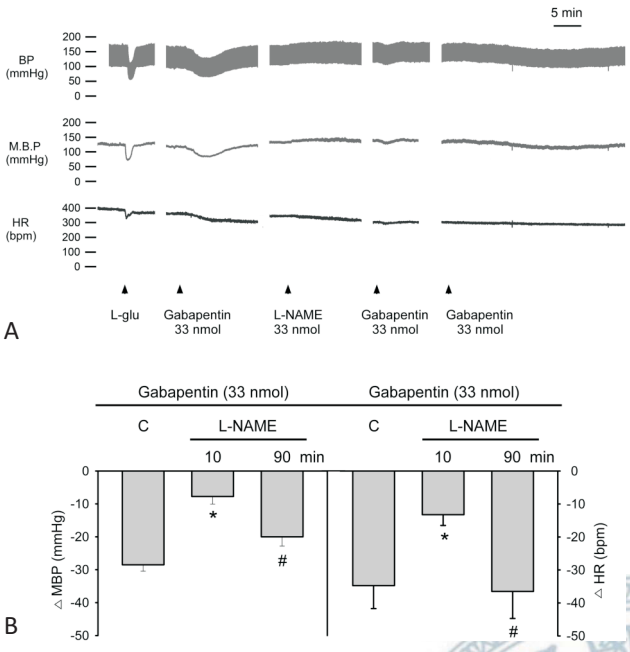

Figure 2. *Cardiovascular effects of gabapentin microinjected into the NTS before and after administration of an NOS non-selective inhibitor, L-NAME. (A) Representative tracings demonstrate cardiovascular effects of microinjection of gabapentin (33 nmol/60 nL) into unilateral NTS before and 10 min after pretreatment with L-NAME (33 nmol/60 nL) in anesthetized SHR rats. The depressor and bradycardic effects of gabapentin were significantly attenuated by L-NAME. As L-NAME washed out, the cardiovascular responses of gabapentin recovered. (B) Graph reveals the effects of pretreated L-NAME on MBP and HR after microinjection of gabapentin into unilateral NTS. Both the MBP and HR effects of gabapentin were significantly attenuated by L-NAME. Values shown are mean difference ± SEM. * $p < 0.05$ vs. vehicle group, # $p < 0.05$ vs. 10 min after pretreatment with L-NAME, n = 4. BP, blood pressure; HR, heart rate; L-NAME, L-arginine methyl ester; MBP, mean blood pressure; NOS, nitric oxide synthase; NTS, nucleus tractus solitarii; SEM, standard error of the mean; SHR, spontaneously hypertensive.*

DISCUSSION

Clinical side effects associated with gabapentin include hypotension and bradycardia; however, these side effects can evolve into antihypertensive treatment. Bala et al. showed that pretreatment with gabapentin 800 mg in single or double doses was equally effective in attenuating the hypertensive response associated with laryngoscopy and tracheal intubation in treated hypertensive patients.[17] The mechanism by which gabapentin attenuates the pressor response to laryngoscopy and intubation is unknown. We hypothesized that hypotension and bradycardia associated with gabapentin may occur through NTS regulation. Moreover, we found that microinjection of gabapentin into the NTS induced depressor and bradycardic effects in the hypertensive SHR rats (Figure 1).

Gabapentin was introduced in 1993 as an adjuvant anticonvulsant drug for the treatment of refractory partial seizures. It was subsequently shown to be effective in treating a variety of chronic pain conditions, including postherpetic neuralgia, diabetic neuropathy, complex regional pain syndrome, inflammatory pain, central pain, malignant pain, trigeminal neuralgia, human immunodeficiency virus-related neuropathy, and headache.[36] In 2002, gabapentin was approved by the US Food and Drug Administration for the treatment of post-herpetic neuralgia. In the UK, gabapentin has a full product license for the treatment of all types of neuropathic pain. Moreover, gabapentin is extensively distributed in human tissues and fluid after administration. Concentrations of gabapentin in cerebrospinal fluid are approximately 5-35% of those in plasma, whereas concentrations in brain tissue are approximately 80% of those in plasma.[37]

Gabapentin is a water-soluble drug that is active in the central nervous system because it crosses the blood-brain barrier on large neutral amino-acid transporters[38] such as L-type amino acid transporter 1 (LAT1). The affinity of gabapentin for LAT1 is unexpected, because gabapentin is a γ-amino acid, and LAT1 only has an affinity for α-amino acids. However, gabapentin is a cyclic form of a γ-amino acid, which places the amino and carboxyl groups in a conformation that mimics α-amino acids. In addition, gabapentin, which is used to treat epilepsy, increases GABA concentrations in the brain.[3] Rodent studies have suggested that gabapentin enhances glutamic acid decarboxylase activity at clinically relevant drug levels, whereas much higher drug levels than are typically obtained in the clinical setting are required to inhibit GABA-transaminase.[39] Moreover, inhibition of calcium influx has been shown to lead to reduced cytosolic calcium and overall neuronal excitability,[40] suggesting that the antiepileptic mechanism of action of gabapentin has little to do with acute increases in GABA concentration. Therefore, it is unclear how gabapentin injection into the NTS induced depressor and bradycardic effects when GABA increased. Although gabapentin has been proven to be effective, its mechanisms of action are far from clear. However, a previous study suggested

that among other potential mechanisms, the effects of gabapentin may be partially mediated through the nitric oxide (NO)/cGMP signaling pathway in antinociception.[41] NO plays an important role in the regulation of basal vascular tone and cardiac myocyte function.[42] In addition, NO-producing neurons in the rat medulla oblongata project to the NTS and modulate autonomic responses generated by nucleus tractus neurons in response to peripheral sensory stimuli, and thus ultimately regulate sympathetic and/or parasympathetic outflow. Moreover, NO has been shown to modulate the cardiovascular responses to electrical stimulation-induced muscle contraction within the NTS, subretrofacial nucleus, and periaqueductal gray.[43] In the present study, we demonstrated that microinjection of gabapentin into the NTS induced depressor and bradycardic effects through regulation of NOS in hypertensive SHR rats (Figure 2).

Gabapentin may have multiple therapeutic uses. Possible pharmacologic targets of gabapentin include selective activation of heterodimeric GABA(B) receptors that consist of GABA(B1a) and GABA(B2) subunits,[44] enhancement of the N-methyl-d-aspartate current at GABAergic interneurons,[45] blocking of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor-mediated transmission in the spinal cord,[46] binding to the l-α-amino acid transporter,[47] activating adenosine triphosphate sensitive K+ channels,[48] activating hyperpolarization-activated cation current (Ih) channels,[49] and modulating Ca2+ current by selectively binding to [3H]gabapentin (a radioligand), the α2δ subunit of voltage-dependent Ca2+ channels (VGCCs).[1] Conversely, Jensen et al. showed that the anticonvulsive effects of gabapentin arise from GABA(B) receptor-independent mechanisms.[50] Currently, VGCC is the most likely antinociceptive target of gabapentin. The proposed consequence of gabapentin binding to the α2δ subunit is a reduction in neurotransmitter release and hence a decrease in neuronal hyperexcitability. Gabapentin has been shown to inhibit the evoked release of glutamate,[51] aspartate,[52] substance P, and calcitonin gene-related peptide[53] from the spinal cord of rats. Interestingly, recent studies have demonstrated that the descending noradrenergic system, spinal α2 adrenergic receptors, and an intact spino-bulbo-spinal circuit are crucial elements influencing the analgesic effects of gabapentin in addition to α2δ interaction.[54] In addition, Li et al. show that type D personality could cause a high risk of cardiovascular morbidity and mortality among patients with hypertension.[55] This pattern of stress response could be attributed to dysregulation of the sympathetic-adrenal-medullary system and hypothalamus-pituitary-adrenal axis.[56] A number of mechanisms may be involved in the actions of gabapentin. In the present study, we demonstrated that gabapentin may have reduced BP and HR through NOS in the NTS of the SHR rats. Moreover, gabapentin may exhibit multiple therapeutic benefits in patients with hypertension[57] and psychotic disorders.

CONCLUSIONS

This is the first study to demonstrate the mechanism by which gabapentin regulates central cardiovascular depressor effects via the NTS. Our study suggests that gabapentin may modulate BP and HR via centrally located NOS in the NTS. Our findings suggest new insights into the regulation of BP by the central nervous system, and may be of help for further developing therapy for cardiovascular diseases.

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CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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