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Hemodynamic Effects of Gabapentin in Rats

Gabapentin has been known to elicit the antinociceptive effect. However, little has been known about the effect of gabapentin on the cardiovascular system. The author's aim of this experiment was to examine the hemodynamic effects of gabapentin. Male Sprague-Dawley rats were used. Intrathecal or intracerebroventricular catheters were implanted and gabapentin was delivered through each catheter or directly into the peritoneal cavity. For hemodynamic measurements, catheters were inserted into the tail artery. Blood pressure and heart rate were measured over 60 min following administration of gabapentin. Intrathecal and intraperitoneal gabapentin did not induce significant changes of hemodynamics over the 60 min compared to the baseline value. Intracerebroventricular gabapentin increased systolic and diastolic blood pressure, but there is no statistically difference in blood pressure change according to the dose.

Key Words : *Gabapentin; Hemodynamics; Injections, Spinal; Injections, Intraventricular; Injections, Intraperitoneal*

Myung Ha Yoon, Jeong Il Choi

Department of Anesthesiology and Pain Medicine
Chonnam National University, Medical School,
Gwangju, Korea

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Address for correspondence
Myung Ha Yoon, M.D.
Department of Anesthesiology and Pain Medicine,
Chonnam National University, Medical School,
8 Hakdong, Donggu, Gwangju 501-757, Korea
Tel : +82.62-220-6893, Fax : +82.62-232-6294.
E-mail : mhyoon@chonnam.ac.kr

INTRODUCTION

Gabapentin, a structural analogue to gamma-aminobutyric acid (GABA), is orginally developed as an anticonvulsant (1). It has been shown to reverse allodynia and hyperalgesia of many pain models in animal studies. Intrathecal gabapentin attenuates tactile-evoked allodynia in the Chung model of neuropathy (2) and thermal hyperalgesia in a rat model of painful peripheral neuropathy (3). Partridge et al. demonstrates its efficacy on substance-P induced thermal hyperalgesia (4). In studies on facilitated pain in rats following the formalin test, gabapentin suppress the pain behavior observed during the second phase (5, 6). Furthermore, its effectiveness for the treatment of neuropathic pain such as postherpetic neuralgia (7) and complex regional pain syndrome (8) has been reported in human studies.

Although some adverse effects have been noted, they were usually slight and disappeared within 2 weeks without interruption of the treatment, and the most serious adverse effect is convulsion (9).

Owing to these advantages and effectiveness, gabapentin has been widely used in the management of a variety of neuropathic pain, but there are lack of data or information about its effect on hemodynamics and no known cardiovascular side effects in human.

Therefore, the purpose of this study was to examine the changes of hemodynamics following administration of intrathecal (IT), intracerebroventricular (ICV), and intraperitoneal (IP) gabapentin in rats.

MATERIALS AND METHODS

All experiments were reviewed and approved by the Institutional Animal Care Committee, Research Institute of Medical Science, Chonnam National University.

Male Sprague-Dawley rats weighing 300-325 g were used. Rats were housed in groups of 4-6 with free access to food and water at all times.

For IT administration of the drug, rats were implanted with polyethylene (PE)-10 catheter (10). Briefly, under enflurane (3-4%)/O_2 anesthesia, the head of rats was placed in a stereotactic head holder. A skin incision was made along the dorsum of the skull, and dura mater was exposed by blunt dissection. The dura was incised, and a polyethylene (PE-10) catheter was advanced caudally to end at lumbar enlargement. The external catheter was tunneled under the skin and exited at the top of the head.

The ICV route for drug injection was constructed through skull (11). Placing the rat in a stereotactic holder under enflurane (3-4%)/O_2 anesthesia, a burr hole was made at 0.5 mm caudally from the coronal suture and 1.0 mm laterally from the sagittal suture. Through this hole, a stainless steel, thin-walled guide cannula was placed into the ventricle to a depth of 3 mm from dura mater and affixed to the skull with stainless steel screws and cranioplastic cement.

After surgery, rats were kept in individual cages. Animals showing neurologic dysfunction postoperatively were sacrificed immediately by excessive enflurane inhalation. Only rats that displayed no postsurgical motor or sensory deficits were assessed. Experiments were performed at least 4-5 days

following IT or ICV implantation.

For IP administration, the drug was injected into the peritoneal cavity directly.

In order to measure hemodynamic changes, a PE-50 catheter was inserted into the tail artery under enflurane (3-4%)/O_2 anesthesia and then the rats were restrained in a restraint cylinder. The catheter was flushed with 0.5 mL heparinized saline. The arterial line was connected to a pressure transducer of monitor (Datex-Ohmeda AS/3, Finland) for continuous recording of blood pressure and heart rate.

Rats were divided into three groups of IT (n=20), ICV (n=22), and IP (n=20) according to the route of drug administration. Each group was divided into four subgroups according to the dose of drug.

The doses of gabapentin for IT and ICV were 10, 30, 100, and 300 μg, respectively, and those for IP were 10, 30, 100, and 300 mg/kg, respectively. Gabapentin was dissolved in physiologic saline. A gear-driven microinjector was used to deliver the drug in IT and ICV groups, and the drug was given in 10 μL of saline. IT administration was followed by an additional 10 μL of saline to flush the catheter. In the IP group, the drug was injected into the peritoneal cavity with a volume of 3 mL/kg through the slit of the restraint cylinder. Blood pressure and heart rate were measured at 5, 10, 15, 20, 30, 40, 50, and 60 min after IT and ICV administration. After 30 min following IP injection, hemodynamics were measured at the same time intervals.

All data are presented as means±SEM. Baseline blood pressure and heart rate were compared by using one-way ANOVA. Stastistical analysis of hemodynamic changes was done using two-way repeated-measures ANOVA. A p value <0.05 was considered statistically significant.

RESULTS

The baseline systolic blood pressure, diastolic blood pressure, and heart rate were 127.8±1.5 mmHg, 92.6±9.4 mmHg, and 416.4±2.9 beats/min, respectively. The baseline blood pressure and heart rate in the several treatment groups did not differ. No changes of hemodynamics compared with baseline value were seen over the 60 min-period following administration of IT and IP gabapentin (Fig. 1, 3). However, systolic and diastolic blood pressure were gradually increased compared with baseline blood pressure after administration of gabapentin in all ICV subgroups (Fig. 2). And the change of heart rate was not statistically significant. Although the blood pressure was significantly increased after ICV injection, the extent of change was not different among ICV subgroups.

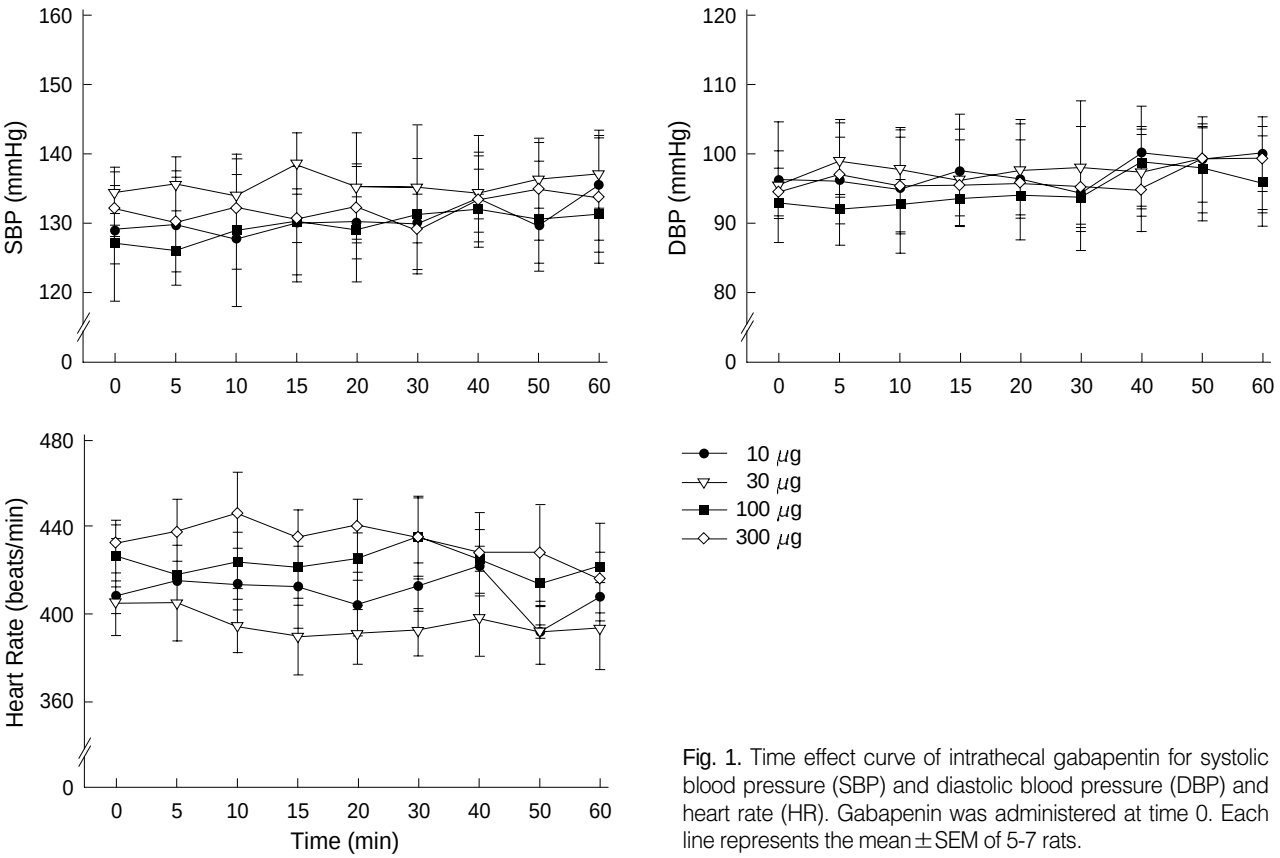

Fig. 1. Time effect curve of intrathecal gabapentin for systolic blood pressure (SBP) and diastolic blood pressure (DBP) and heart rate (HR). Gabapenin was administered at time 0. Each line represents the mean±SEM of 5-7 rats.

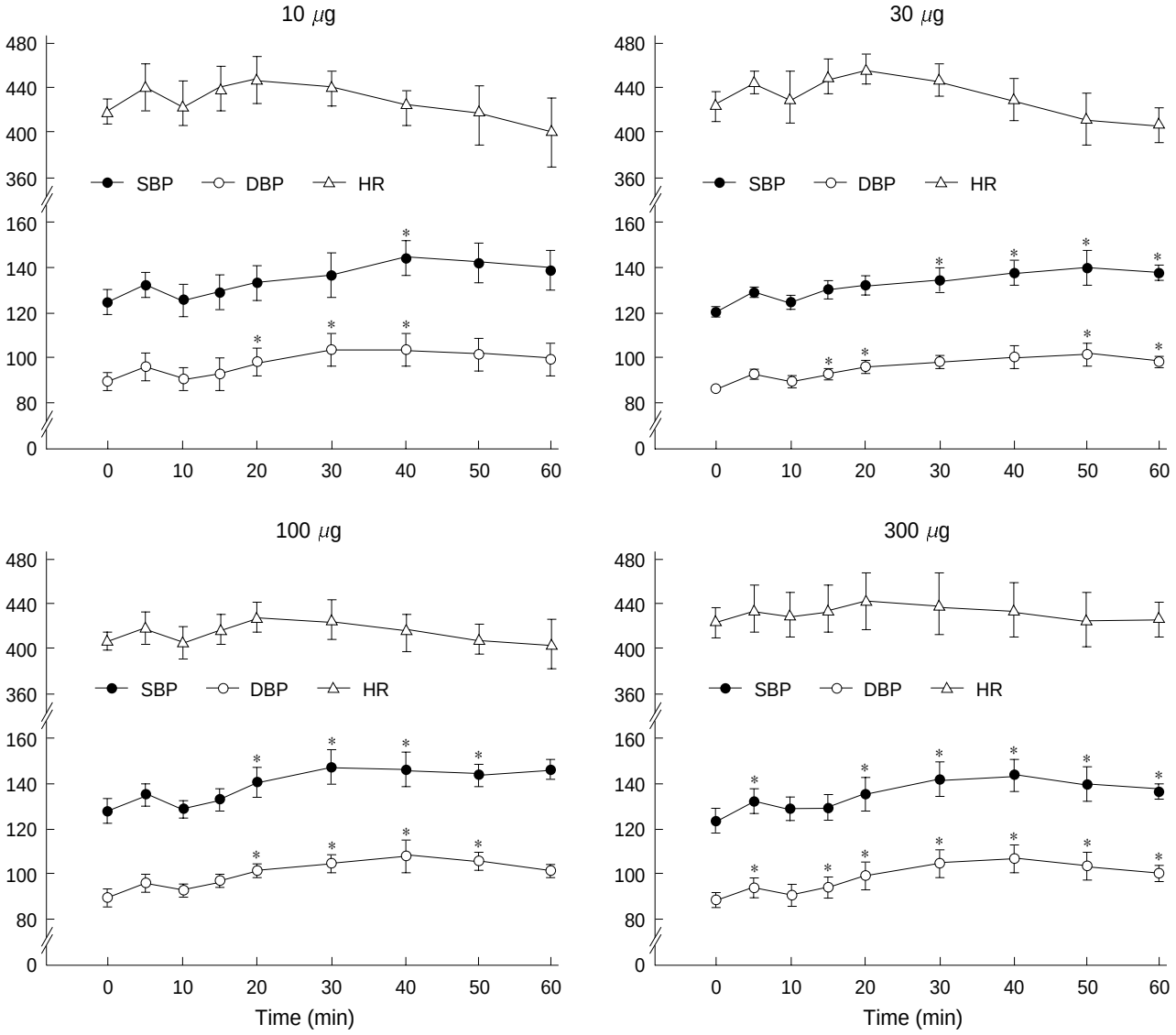

Fig. 2. Time effect curve of intracerebroventricular gabapentin for systolic blood pressure (SBP) and diastolic blood pressure (DBP) and heart rate (HR). Gabapenin was administered at time 0. Each line represents the mean±SEM of 5-7 rats. *Statistically significant compared with baseline value.

DISCUSSION

Gabapentin, administered via IT, IP, but ICV routes, did not affect the blood pressure or heart rate in the present study. These findings indicate that gabapentin may be given safely via IT and IP routes without the change of hemodynamics.

Numerous animal and human studies have shown that gabapentin is effective in a wide variety of pain syndromes. In human studies, it consistently provided relief of pain associated with various conditions including postherpetic neuralgia (7), diabetic peripheral neuropathy (12), and complex regional pain syndrome (8). Its efficacy on allodynia and hyperalgesia was also demonstrated in numerous animal studies (2-6). In these studies, gabapentin reduced the pain response of rat paw formalin test, thermal injury model, rat model of peripheral neuropathy and surgically induced neuropathic pain model.

Although there are many proposals for the mechanism of action of gabapentin, it has not been fully elucidated. Nonstrychnine site of NMDA receptor and the $\alpha 2\delta$ subunit of voltage-sensitive calcium channels have been suggested as the binding site of gabapentin (4, 5, 13). Clinically, the most common side effects of gabapentin are dizziness, somnolence, headache, and diarrhea (12). Side effects increase linearly with the increase of the daily dose, but the relative safety is supported in many studies including a case report of overdose of 48.9 g with lack of serious toxicity (14, 15). In addition, there has been no documentation of side effects on cardio-

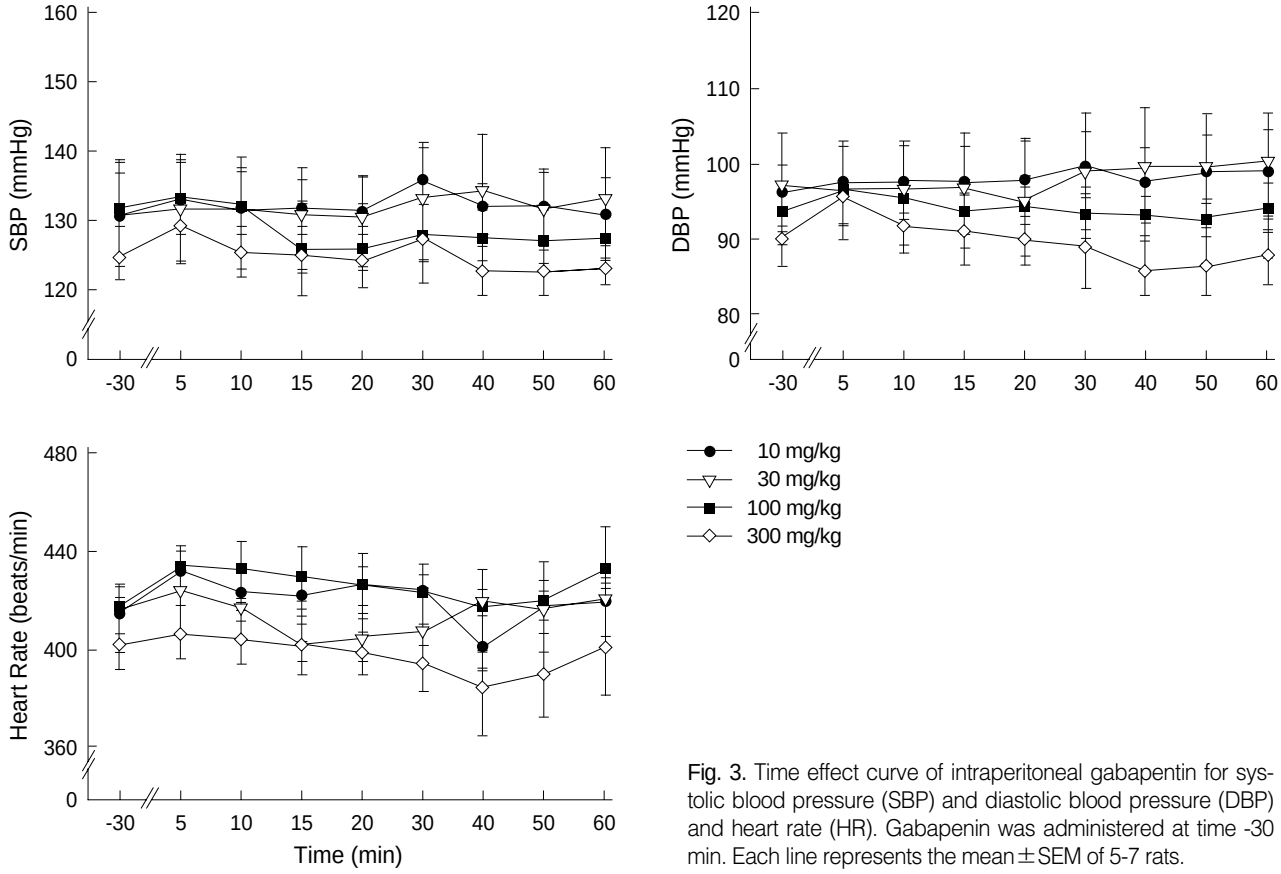

Fig. 3. Time effect curve of intraperitoneal gabapentin for systolic blood pressure (SBP) and diastolic blood pressure (DBP) and heart rate (HR). Gabapenin was administered at time -30 min. Each line represents the mean±SEM of 5-7 rats.

vascular system.

Although the current study was undertaken on animals, it showed that neither systemic nor intrathecal gabapentin affected the hemodynamics. These results are consistent with the previous findings (5, 6). Furthermore, intraduodenal gabapentin (100 mg/kg) produced no significant effects on the mean arterial blood pressure and heart rate (16), although animals in that study were pretreated with guanethidine and anesthetized owing to the invasiveness of the study. And 100 mg/kg gabapentin did not change the mean blood pressure within 60 min after intravenous administration in another study (17).

In our study, IT or IP administration of gabapentin did not affect blood pressure and heart rate. However, systolic and diastolic blood pressure were increased after ICV administration. Considering the minimal hemodynamic effect of IT gabapentin, increased blood pressure in ICV gabapentin was an unexpected result. Furthermore, dose-dependency was not observed in the ICV group. This different result might be related with very low volume of test drug, which could not have reached the brain when administered intrathecally. The unknown change of pharmacokinetics of ICV gabapentin could be thought of as one for the result, and the CNS side effects of gabapentin such as nausea, vomiting and headache might be attributed to the result. However, the reasons of these changes of blood pressure without dose-response relationship are uncertain and further studies for the side effects of ICV gabapentin including cardiovascular effects are required. The above mentioned findings jointly suggest that gabapentin does not affect cardiovascular responses when it is used via IT or IP but ICV route. Thus, if another preparation of IT or IP route is developed in the future, albeit only oral agents are clinically available now, it can be prescribed safely without cardiovascular side effects. But the result of increased blood pressure caused by ICV gabapentin suggests that it should be used cautiously, especially in patients with cardiovascular disease.

In conclusion, ICV gabapentin increased systolic and diastolic blood pressure, but IT and ICV gabapentin did not change hemodynamics.

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