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Neural discharge can be modulated by carotid arterial injection of gastrin-17 in rat hypothalamic paraventricular nucleus

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Abstract. Neural discharge in the hypothalamic paraventricular nucleus (PVN) was examined after gastrin-17 injection into the carotid artery in anesthetized rats. Neural discharge was increased by gastrin-17 injection into the carotid artery close to the cranium, and the response due to the gastrin was dose-dependent. No discharge response was seen when gastrin was injected into the jugular vein. These results suggest that gastrin circulating in the arterial blood can penetrate the blood brain barrier, and modulate neural PVN activity which is responsible for gastric acid secretion.
Key words. Gastrin; hypothalamus; gastric acid secretion.

It has been well documented that gastrin enhances gastric acid secretion by stimulating the parietal cells in the stomach[1,2]. Recently, it has also been shown that gastrin enhances gastric acid secretion by stimulating the gastrin-sensitive cells in the hypothalamic paraventricular nucleus (PVN) or in the lateral hypothalamic areas (LHA) when administered directly to the corresponding regions[3–5]. These observations suggest that gastrin stimulates gastric acid secretion by activating not only the gastric parietal cells but also a central mechanism sensitive to gastrin[6]. However, there are no reports as yet showing that gastrin circulating in the blood influences neural activity in the brain. Recently we observed that gastrin-17 injected into the carotid artery changes the neural activity of the PVN.

Materials and methods

Thirty-nine male Wistar rats weighing about 250 g were used. They were deprived of food for 22 h before the experiments. The animals were anesthetized with urethane (1.2 g/kg, i.p.) and put into a stereotaxic frame in a prone position. The exposed cerebral cortex was covered with warm agar solution. The anal temperature was maintained at 36.0 ± 0.5 °C.

Neural discharge was recorded by the methods described previously[7,8]. Briefly, extracellular potentials were recorded by means of glass micropipettes. The recording barrel was filled with 2% brilliant blue. Focal staining was carried out by applying a 20 nA DC current for 5 min. Neural discharges were observed on an oscilloscope and were plotted on an X-Y recorder.

Gastrin-17 (gastrin; human, sulfated form, Cambridge Research Biochemicals, Ltd., UK) and gastrin-34 ("big gastrin"; human, Peninsula Laboratories, Inc., USA) were used. The agent was dissolved in 154 mM NaCl and adjusted to pH 8.0 with NaOH. The right side of the internal carotid artery was interrupted, and a test solution was injected into the cranial cut side of the artery. Another catheter for injection was placed in the right jugular vein. A 28-guage tube was used and 500 nl was injected each time, over a period of 10 s, with an infusion pump. Arterial and venous injections were performed in the same animal.

After the experiment, the brain was fixed with 10% formalin, and 50 μm frozen serial sections were cut in the frontal plane and stained with cresyl violet.

Data were collected from the PVN portion where discharge responses occurred with different concentrations of a test agent. The data were analyzed by ANOVA, and the specific values were evaluated by Duncan's multiple range test.

Results and discussion

Neural discharge responses were obtained from 20 out of 294 recording sites where spontaneous discharge of less than 15/60 s was observed. Gastrin (400 pM) injected into the carotid artery increased the discharge rate of the PVN neurons (fig. 1A). The discharge response reached its maximum 45 s after the injection, then returned to the control level within another 60 s. NaCl (154 mM) injection failed to cause a discharge response (fig. 1B). When data at 45 s after the injection of different concentrations of gastrin were compared, the threshold concentration of gastrin was found to be 200 pM, and the discharge response to gastrin was dose-dependent. Dose-dependency measurement were made on the same cell. No discharge response was induced when the same dosage of gastrin was injected into the jugular vein. It was also noted that neural PVN activity in response to gastrin was not reproduced when

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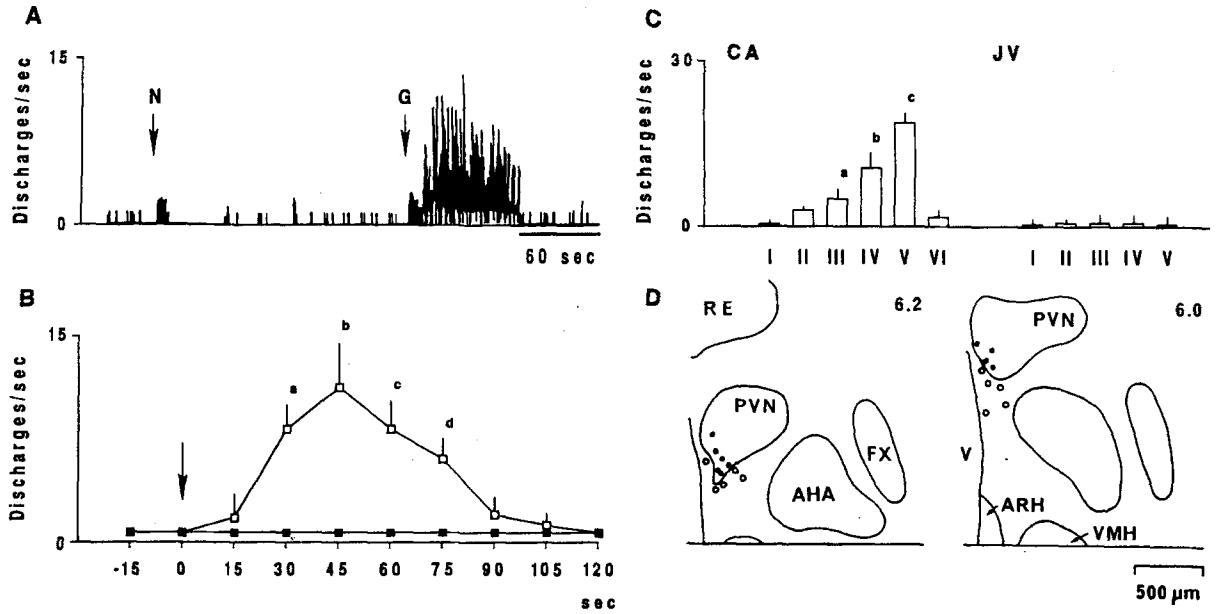

Figure 1. *A*) Changes in neural discharge in the hypothalamic paraventricular nucleus after gastrin injection. Gastrin (G, 400 pM) or NaCl (N, 154 mM) was injected into the carotid artery. Arrows indicate the time of injection.
B) Neural discharges after gastrin (□, 400 pM) or NaCl (■, 154 mM) injection into the carotid artery. Arrows indicate the time of injection. Values are the mean ± SE (n = 6). $^{a-d}p < 0.01$ vs ■.
C) Neural discharges 45 s after gastrin (II, 100 pM; III, 200 pM; IV, 400 pM; V, 600 pM) or "big gastrin" (VI, 600 pM) or NaCl (I, 154 mM) injection. The agents were injected into the carotid artery (CA) or into the jugular vein (JV). Values are the mean ± SE (n = 6). $^{a}p < 0.01$ vs I and VI. $^{b}p < 0.01$ vs III. $^{c}p < 0.01$ vs IV.
D) Tip positions of infusions in the hypothalamic paraventricular nucleus (PVN) in 21 rats. Effective (●) and ineffective (○) sites of infusions are shown. Numbers in the upper right corner of each panel indicate distances in mm from the vertical zero plane. AHA, anterior hypothalamic area; ARH, arcuate nucleus; FX, fornix; RE, reuniens nucleus; V, ventricle; VMH, ventromedial hypothalamic nucleus.

"big gastrin" was injected (fig. 1C). Effective sites for the recording barrel were located in or near the PVN (fig. 1D).

The present study demonstrated that gastrin circulating in the systemic blood can modulate neural activity of the PVN. The discharge response seemed to be specific to gastrin because the response due to gastrin was dose-dependent. Although the diffusion of gastrin has been considered to be limited by the blood-brain barrier (BBB)[9], in the organum vasculosum laminae terminalis (OVLT) the BBB is lacking so that peptides or peptide fragments can penetrate[10,11]. Our findings could therefore be interpreted as indicating that gastrin injected into the carotid artery penetrated the BBB at the OVLT, and stimulated gastrinergic fibers which originate in the PVN. Jugular injection of gastrin failed to change the rate of neural discharge. It appears that either there was no mechanism through which PVN neural activity could be affected, or that gastrin injected into the vein had been diluted to an ineffective concentration.

Neurohypophyseal gastrin occurs in all species in concentration of the same magnitude[12,13]. It was also noted that gastrin is synthesized in hypophyseal neurons, and that the concentrations were higher than those in other regions of the central nervous system[14]. Moreover, it was found that gastrin-17 stimulates gastric acid secretion when injected into the PVN or LHA[3,4]. Considering these reports, together with the present finding that gastrin injected into the systemic circulation changes the neural PVN discharge, it can be suggested that the PVN neuron can be activated not only by hypothalamic gastrin but also by gastric gastrin.

Gastrin is released into the systemic circulation immediately after food ingestion, and the gastrin concentration is maintained during food digestion[15]. If gastrin controls gastric acid secretion through the mechanism mentioned above, this means that there is a dual control system, involving the gastric parietal cells and a central mechanism.

Our observations lead us to suggest that gastrin in the systemic circulation can penetrate into the brain and modify neural PVN activity which stimulates gastric acid secretion.

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