Direct Evidence Indicating That a GABA-Mimetic Stimulates Acid Secretion through Central Mechanisms

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Abstract—Acid secretagogue effects of central and peripheral baclofen were compared in the rat. Intravenously (0.1–1.0 mg/kg) and intracerebroventricularly (0.1–1.0 µg) administered baclofen augmented acid output to the same degree in a dose-dependent manner. GABA microinjected into the lateral hypothalamus (200 and 400 µg) significantly increased acid output. These support the proposal that baclofen stimulates acid secretion through central mechanisms and also the possible role of GABA in central regulation mechanisms of acid secretion.

The lipophilic GABA-mimetic baclofen has been demonstrated to stimulate gastric acid secretion in several species including rats (1–4), dogs (5, 6) and humans (7). Since the increment in acid production by baclofen is markedly attenuated by both surgical and chemical vagotomies (1, 5), central or vagal dependent mechanisms seem to participate in part in the acid secretagogue action of this GABA-mimetic. In addition, the acid stimulatory effect of baclofen has been demonstrated in vagally denervated Heidenhain pouch of the dog (6). This evidence indicates that peripheral mechanisms may also account for this effect.

It is still unknown whether central mechanisms are mainly involved in the secretagogue action of baclofen, because there is no evidence to compare acid stimulatory effects of centrally and peripherally administered baclofen. In the present study, we compared acid secretory responses to intravenous and intracerebroventricular administration of baclofen in a standardized perfused rat stomach preparation. Furthermore, we also studied the acid secretagogue effect of central administration of GABA.

Male Sprague-Dawley rats weighing 230–270 g were used. Measurement of gastric acid secretion was carried out according to our previous method (8). Briefly, rats were deprived of food for 18 hr before the experiment but allowed free access to water ad libitum. Under urethane anesthesia (1.2 g/kg, i.p.), a dual polyethylene cannula was inserted into the gastric lumen and irrigated with saline solution at a flow rate of 5 ml/min by means of a peristaltic pump. The acid output was determined by titrating the perfusate collected every 2 min with 0.01 M NaOH to pH 5.5 using an automatic titrator (TOA Electronics Co., Ltd., Model HSM-10A, Japan). The amount of acid secreted was expressed in terms of µEq.H+*/2 min or µEq.H+*/2 hr. Intracerebral administration of compounds was carried out by using a stainless steel guide cannula (external diameter of 0.35 mm) which had been stereotactically implanted into the lateral ventricle or the unilateral hypothalamus. The following coordinates (millimeters) were used (atlas of Paxinos and Watson, 1986) (9): unilateral hypothalamus: A, 6.7; L, 1.8; H, 8.7; and lateral ventricle: A, 8.1; L, 1.4; H, 5.0. In our preliminary experiments, the intracerebral or intracerebroventricular injection of saline (1 µl or 10 µl, respectively) was found to have no significant effect on basal acid output. The location of the site of injection into the lateral hypothalamus or

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lateral ventricle was in all cases verified histologically by staining with Evans' blue. Acid output response in the rats whose injection sites were not confirmed to be in the area of the lateral hypothalamus was not counted for data analysis. Test compounds were microinjected at a volume of 10 μl in the case of intracerebroventricular injection and at a volume of 1 μl in the case of intrahypothalamic administration. Intravenous administration of test compound was performed through the femoral vein at the volume of 1 ml/kg b.w.

Baclofen (synthesized at Research Laboratories, Sumitomo Pharmaceuticals Co., Ltd.) (1 μg) injected into the lateral ventricle caused a significant increase in acid output with rapid onset. The response reached to the maximal level within 40 min and declined to the basal level about 2 hr after the treatment (Fig. 1). Intravenous application of baclofen at 1.0 mg/kg also stimulated gastric acid secretion with a somewhat smaller maximal response and a longer duration than intracerebral injection (Fig. 1). Net increments in acid output for

![Figure 1](attachment:image1.png)

**Fig. 1.** Typical recordings of gastric acid responses to intravenous and intracerebroventricular baclofen in urethane anesthetized rats. Baclofen (10 μl) was stereotaxically injected into the lateral ventricle, and the intravenous injection volume was 1 ml/kg. Each vertical deflection represents each 2-min acid output (μEq.).

![Figure 2](attachment:image2.png)

**Fig. 2.** Comparison of acid secretion in response to intravenous and intracerebroventricular baclofen in the rat. Each column indicates the mean±S.E.M. Numbers in the parentheses indicate the No. of experiments in each group.
2 hr after baclofen treatment were calculated to compare the secretagogue potencies of baclofen given by the central and peripheral routes. Intracerebroventricular injection of baclofen in the doses of 0.1–1.0 μg caused dose-dependent increase in gastric acid secretion. The 2-hr integrated increase in acid output after baclofen at 0.3 μg and 1.0 μg (corresponding values 34.8±5.0 and 139.2±44.0 μEq.H⁺/2 hr, respectively) were significantly higher than the saline control (−0.2±0.8 μEq.H⁺/2 hr) (Fig. 2). Acid secretagogue response to baclofen by the intravenous route at 0.3 and 1.0 mg/kg (corresponding values 28.2±8.2 and 126.8±30.4 μEq.H⁺/2 hr, respectively) were also significantly different from the saline control (−3.2±2.4 μEq.H⁺/2 hr) (Fig. 2). Since the average body weight of rats used in this experiment was about 250 g, intracerebral doses of baclofen at 0.1, 0.3 and 1.0 μg/rat are almost equivalent to 0.4, 1.2 and 4.0 μg/kg, respectively. According to our present result, the same acid output could be observed in the rats treated with baclofen intravenously (0.3 and 1.0 μg/kg) and intracerebroventricularly (0.3 and 1.0 μg/rat). Therefore, intracerebroventricular injection of baclofen seems to be 250 times as effective as intravenous injection with regards to acid secretagogue action. Furthermore, intravenous administration of 1.0 μg of baclofen, which could cause a massive acid response by intracerebroventricular application, had no influence on acid secretion (data not shown). Taking these results together, the main site of the secretagogue action of baclofen may be located in the central nervous system.

The lateral hypothalamus is well-known as a critical region in the central control of gastric acid secretion (10). In addition, a high concentration of GABA has been reported in the lateral hypothalamus (11). In this study, we also investigated the gastric acid response to baclofen injected into the lateral hypothalamus. It was clear that baclofen injected into the lateral hypothalamus definitely stimulated gastric acid secretion. The 2-hr integrated acid output responses to baclofen (0.1, 0.3 and 1.0 μg) injected into the lateral hypothalamus were 11.4±4.2, 23.6±9.6 and 117.4±32.0 μEq.H⁺/2 hr, respectively (N=8–9). It seems possible that GABA is important in the regulation of gastric acid secretion. Thus, we attempted to study the gastric secretagogue action of GABA micro-injected into the lateral hypothalamus.

GABA at the doses of 200 and 400 μg significantly increased the gastric acid secretion in a dose-dependent fashion. The corresponding values of net increments in acid output were 13.2±4.6 (N=7) and 24.2±4.4 μEq.H⁺/2 hr (N=9), respectively. These values were significantly higher compared with that in the saline control (−2.6±0.6 μEq.H⁺/2 hr; N=23). The acid secretory response to GABA seems to be equivalent to those induced by 0.1 and 0.3 μg of baclofen administered into the lateral hypothalamus. These data suggest that the lipophilic GABA-mimetic baclofen stimulates gastric acid secretion through central mechanisms, and that hypothalamic GABA plays a critical role in the regulatory mechanisms of gastric acid secretion.

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