Effects of GABA Antagonists and Structural GABA Analogues on Baclofen Stimulated Gastric Acid Secretion in the Rat

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Abstract—The effects of GABA receptor antagonists (bicuculline and phaclofen) and structural GABA-analogues on baclofen stimulated gastric acid secretion were studied in standardized perfused rat stomach preparations. Pretreatment with bicuculline, a GABAₐ-receptor antagonist, in the doses of 1 and 3 mg/kg, subcutaneously, had no influence on the gastric acid response to baclofen. In addition, phaclofen, a GABAₚ antagonid, in the doses of 3 to 30 mg/kg, intravenously, was found to have no significant effect on the acid response to baclofen. However, GABA-analogues (MOPS and ABA; 10–30 mg/kg, i.v.) and lipophilic GABA derivatives structurally related to beta-amino acids (APPA and APHA; 30 mg/kg, i.v.) significantly counteracted the secretagogue action of baclofen. Further experiments on APPA action showed that the antisecretory effect of APPA could be overcome by higher doses of baclofen. APPA did not affect bethanechol stimulated acid secretion. These results suggest that the secretagogue action of baclofen is independent to GABAₐ and GABAₚ-receptors and that APPA may interact with baclofen in regulation mechanisms of acid secretion, although further investigations are necessary to define the mode of action of APPA on the GABA-ergic system.

Gamma-aminobutyric acid is considered to be an important regulator of gastrointestinal functions in the central nervous system (1–5). There are some evidence that central administration of GABA agonists and antagonists caused significant alteration in gastric motility (5, 6), gastric secretion (1, 7, 8) and intestinal electrolyte transport (9). Particularly, baclofen, a lipophilic derivative of GABA has a marked stimulatory effect on vagal activity, gastric motility and acid secretion in anesthetized rats (2, 6, 7, 10–13), conscious dogs (4,14) and humans (15). These stimulatory effects of baclofen were completely abolished by surgical and chemical vagotomy (6, 10, 11, 14). Furthermore, we have shown that parenteral administration of baclofen induced gastroduodenal ulcers in the anesthetized rat (13). However, the effects of GABA receptor antagonists on gastric acid secretion in response to baclofen have not been studied yet. Blandizzi et al. (7) reported that bicuculline counteracted the acid secretagogue effect of baclofen. GABA receptors are generally classified into two subtypes, namely GABAₐ- and GABAₚ-receptors, and baclofen is well-established as a specific GABAₚ-receptor agonist that acts on the bicuculline-insensitive GABA receptor site (16, 17). Although baclofen obviously enhances gastric acid output through central mechanisms, possible functional implication of GABAₚ-receptors in its action has been obscure because of the lack of specific antagonists. However, phaclofen, the phosphono analogue of baclofen, was recently found to be a selective GABAₚ receptor antagonist albeit of low potency (18–22). This study investigated the effects of bicuculline and phaclofen on rat gastric acid secretory.
response to baclofen. We also compared the effects of several analogues of GABA (Fig. 1) on baclofen-stimulated acid secretion in the same preparation in order to compare their affinity to baclofen sensitive receptors.

Materials and Methods

Animal preparation and measurement of gastric acid secretion: Male Sprague-Dawley rats weighing 200–260 g were used. Rats were deprived of food for at least 18 hr before the experiment but allowed free access to water ad libitum. Under urethane anesthesia (1.2 g/kg, i.p.), two silicone cannulas were inserted into the gastric lumen through the cervical esophagus and pylorus. The ligature was made around the esophagus and pylorus to fix the cannulas. The gastric lumen was continuously perfused with saline from the esophagus to the pylorus at a flow rate of 5 ml/min by means of a peristaltic pump. The pH of irrigating saline was adjusted to 5.5. Acid output was determined by titrating the perfusate with 0.01 M NaOH to pH 5.5 using an automatic titrator (Toa Electronics Co., Ltd., Model HSM-10A, Japan). The acid output was recorded by every 2-min response via a zero-suppression adaptor. The amount of acid secreted was expressed in terms of ìEq. HCl per arbitrary period. Gastric acid secretion was stimulated by subcutaneous administration of baclofen (2 mg/kg). Phaclofen, GABA analogues or saline as a control was intravenously given 20 min prior to the gastric stimulant. Subcutaneous bicuculline frequently causes convulsions even under anesthetization. Respiratory obstruction observed during paralysis could have significant inhibitory effects on acid secretion. Therefore, bicuculline or saline as a control was subcutaneously given 60 min prior to the gastric stimulant in order to confirm the lower potency of the convulsive effect of this antagonist.

Drugs used: The following compounds were obtained from Aldrich Chem. Co., Milwaukee, WI, U.S.A.: 3-aminopropanesulfonic acid Na (APSA), 4-morpholinopropanesulfonic acid Na (MOPS), 3-aminobenzoic acid HCl (ABA), 4-imidazoleacetic acid HCl (IMAA) and 3-amino-3-phenylpropionic acid (APPA). Bicuculline was purchased from Sigma Chem. Co., St. Louis, MO, U.S.A. Baclofen, phaclofen, 4-amino-4-phenylbutyric acid (APBA), 5-amino-5-phenylvaleric acid (APVA), 6-amino-5-phenylcaproic acid (APCA) and 7-amino-6-phenylheptanoic acid (APHA) were synthesized at Research Laboratories, Sumitomo Pharmaceutical Co., Ltd. The stock solution for bicuculline in 0.1 M HCl was adjusted to pH 5.5 with 0.1 M NaOH. The other drugs were dissolved in saline. Doses of drugs tested were expressed as the amount of their salt.

Analysis of data: Results are expressed as the mean ± S.E. Net increment in gastric acid output was calculated by subtracting the

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**Fig. 1.** Chemical structures of GABA and GABA-related compounds tested in this study. The abbreviations are given in the text.
basal value from the estimated value with the gastric stimulant. Statistical significance was analyzed by Student’s t-test, and P<0.05 was regarded as significant.

Results

Effects of bicuculline and phaclofen: As shown in Figs. 2 and 3, subcutaneous administration of baclofen (2 mg/kg) caused a marked increase in acid output. Pretreatment with the GABA_A-receptor antagonist bicuculline (1 and 3 mg/kg, s.c.) had no influence on the secretagogue action of baclofen. Integrated increase in acid output for 2 hr after baclofen was 192.8±30.6 μEq. HCl in the saline-control rats (N=6). This response was not significantly modified by pretreatment with bicuculline at either 1 mg/kg or 3 mg/kg (corresponding values of 233.4±46.2 or 198.6±33.3 μEq. HCl, respectively) (Fig. 2). In addition, the GABA_B-receptor antagonist phaclofen at several doses ranging 3 to 30

Fig. 2. Effect of bicuculline on baclofen-stimulated gastric acid secretion in anesthetized rats. Left: Time course of acid secretion response to baclofen. Saline (○) or bicuculline (1 mg/kg ● and 3 mg/kg △) was subcutaneously administered 1 hr prior to baclofen. Right: 2 hr integrated increment response in acid output after baclofen. Each column indicates the mean±S.E. Numbers in the columns indicate No. of experiments in each group.

Fig. 3. Effect of phaclofen on baclofen-stimulated gastric acid secretion in anesthetized rats. Left: Time course of acid secretion response to baclofen. Saline (○) or phaclofen (3 mg/kg ● 10 mg/kg △ and 30 mg/kg △) was intravenously administered 20 min prior to baclofen (2 mg/kg). Right: 2 hr integrated increment response in acid output after baclofen. Each column indicates the mean±S.E. Numbers in the columns indicate No. of experiments in each group.
mg/kg, i.v., did not have any significant effect on gastric acid secretion in response to baclofen. As seen in Fig. 3, 2 hr integrated acid response to baclofen in the saline control group was 173.4±21.0 μEq HCl (N=6). The same responses in the phaclofen-treated groups at the doses of 3, 10 and 30 mg/kg were 229.0±20.6, 213.0±22.2 and 162.0±27.2 μEq HCl, respectively.

Effects of GABA-related compounds: The effects of four compounds related to GABA, APSA, IMAA, MOPS and ABA, are shown in Table 1. APSA and MOPS are aminosulfonic acids where the carboxylic moieties are substituted with the sulfonic group. IMAA and ABA are cyclic compounds and have three methylene groups between the amine and carboxylic group similar to GABA. APSA and IMAA potentiated the acid secretory response to baclofen in a dose-dependent fashion, whereas both compounds had only minor effects on basal acid secretion even at a high intravenous dose (10 or 30 mg/kg, respectively). The augmentation of acid output in response to baclofen with APSA (10 mg/kg) and IMAA (30 mg/kg) were significantly

| Treatment | Dose (mg/kg) | Route | No. of rats | Basal H⁺ Output (μEq./hr) | JH⁺ Output (μEq./2 hr) | Inhibition (%) |
|-----------|--------------|-------|-------------|--------------------------|------------------------|----------------|
| Saline    |              | i.v.  | 10          | 13.0±1.2                 | 135.2±18.4             |                |
| APSA      | 3            | i.v.  | 7           | 10.0±0.8                 | 228.4±57.8             | -68.6          |
|           | 10           | i.v.  | 8           | 16.6±3.8                 | 282.0±67.0*            | -108.6         |
| Saline    | i.v.         |       | 8           | 10.2±0.8                 | 168.4±37.4             |                |
| IMAA      | 10           | i.v.  | 5           | 14.4±2.4                 | 275.0±47.6*            | -63.3          |
|           | 30           | i.v.  | 6           | 15.8±3.0                 | 354.6±72.0*            | -110.6         |
| Saline    | i.v.         |       | 9           | 12.2±1.6                 | 167.0±24.4             |                |
| MOPS      | 10           | i.v.  | 5           | 15.6±1.2                 | 101.6±19.8             | 39.1           |
|           | 30           | i.v.  | 5           | 10.4±1.5                 | 71.4±11.6*             | 57.2           |
| Saline    | i.v.         |       | 8           | 11.6±2.0                 | 156.8±23.4             |                |
| ABA       | 10           | i.v.  | 7           | 11.4±0.4                 | 63.6±21.6*             | 59.5           |
|           | 30           | i.v.  | 5           | 10.6±0.4                 | 60.6±33.4*             | 61.3           |

Each compound or saline was intravenously administered 20 min prior to baclofen (2 mg/kg, s.c.) dosing. Each value represents the mean±S.E. *P<0.05, compared with the control group.

Table 2. Effects of beta-amino acids structurally related to GABA on baclofen-stimulated gastric acid secretion in anesthetized rats

| Treatment | Dose (mg/kg) | Route | No. of rats | Basal H⁺ Output (μEq./hr) | JH⁺ Output (μEq./2 hr) | Inhibition (%) |
|-----------|--------------|-------|-------------|--------------------------|------------------------|----------------|
| Saline    |              | i.v.  | 8           | 11.4±1.0                 | 151.0±20.2             |                |
| APPA      | 10           | i.v.  | 6           | 11.0±1.2                 | 76.0±38.2              | 49.7           |
|           | 30           | i.v.  | 6           | 10.8±1.6                 | 14.4±9.8***            | 90.5           |
| Saline    | i.v.         |       | 8           | 10.2±1.0                 | 177.8±34.2             |                |
| APBA      | 10           | i.v.  | 7           | 11.6±1.2                 | 123.0±35.0             | 30.8           |
|           | 30           | i.v.  | 6           | 9.0±1.0                  | 183.8±31.0             | 3.4            |
| APVA      | 10           | i.v.  | 6           | 11.4±1.0                 | 144.8±45.6             | 18.6           |
|           | 30           | i.v.  | 6           | 12.6±1.8                 | 209.6±41.6             | -17.9          |
| Saline    | i.v.         |       | 8           | 13.2±1.4                 | 183.4±33.8             |                |
| APCA      | 10           | i.v.  | 6           | 11.4±0.8                 | 216.5±66.2             | -18.1          |
|           | 30           | i.v.  | 6           | 12.2±2.4                 | 184.2±57.6             | -0.5           |
| APHA      | 10           | i.v.  | 6           | 14.0±1.8                 | 152.8±57.6             | 16.7           |
|           | 30           | i.v.  | 6           | 11.4±0.2                 | 52.4±9.8**             | 71.4           |

Each compound or saline was intravenously administered 20 min prior to baclofen (2 mg/kg) dosing. Each value represents the mean±S.E. **P<0.01, ***P<0.001, compared with the control group.
Fig. 4. Effect of APPA on acid secretory response to baclofen and bethanechol in the rat. Each panel indicates a typical experiment in three different animals. Each vertical deflection represents every 2-min acid output (µEq.). The acid inhibitory effect of APPA was overcome by a higher dose of baclofen, shown in the middle panel.

different from their own control (P<0.05).

Effects of structurally GABA-related beta-amino acids on baclofen-stimulated gastric acid secretion: GABA is classified as a beta-amino acid. Therefore, we extended the experiment to examine the effects of a series of beta-amino acids on acid secretion. Test compounds in this study have two to six methylenes between the carboxyl and amino terminals and one phenyl-ring proximal to the aminogroup in an attempt to make them lipophilic or to increase their affinity to the blood-brain barrier (Fig. 1). Intravenous administration of APPA at 10 and 30 mg/kg inhibited the acid response to baclofen in a dose-dependent fashion. APHA did not inhibit the acid output induced by baclofen at 10 mg/kg, i.v. This compound, however, showed a significant inhibitory effect at the high dose of 30 mg/kg, i.v. Other compounds, APBA, APVA and APCA, had no influence on the baclofen effect (Table 2).

Effect of APPA on baclofen- and bethanechol-stimulated gastric acid secretion: We also performed preliminary experiments to get some clues on the inhibitory mechanisms of APPA. APPA (30 mg/kg, i.v.) completely inhibited acid output in response to 2 mg/kg of baclofen, but additional administration at the dose of 6 mg/kg restored the acid response. However, ASPA at the same dose had no influence on bethanechol-stimulated acid secretion (Fig. 4).

Discussion

The results of the present study demonstrate that the acid secretagogue effect of baclofen is resistant to both GABAₐ and GABAₐₐ-receptor antagonists. Evidence for the physiological role of GABA in the regulation of gastric acid secretion comes from the immunohistochemical identification of GABA neurons in the hypothalamus (23). Furthermore, we have demonstrated that
baclofen, a lipophilic GABA derivative, is a potent stimulant of gastric acid secretion in the rat and dog (11, 14), and this secretagogue effect is totally abolished by surgical vagotomy and atropine medication, suggesting the existence of central mechanisms to stimulate gastric acid secretion. A critical step in assessing the activation of parasympathetic transmission has been studied by means of monitoring vagal efferent discharges (11, 24). Vagal activity evoked by baclofen had a prolonged duration of more than 90 min, which coincides with the gastric acid response. Similar responses in gastric acid secretion and vagal transmission have been confirmed with muscimol (a GABA<sub>A</sub>-receptor agonist) (18). Our interest was, however, to determine which types of GABA-receptors are linked in gastric function, especially acid secretion. Two different types of GABA-receptor antagonists are now available, bicuculline as a GABA<sub>A</sub>-receptor antagonist and phaclofen as a GABA<sub>B</sub>-receptor antagonist, based upon their in vitro receptor-binding assay activity. There is a little information on the effect of these antagonists on the gastric acid response, and it is also unclear whether the two classes of GABA agonists have similar effects on gastric function.

Recently Tsai et al. demonstrated the peripheral mechanisms of GABA to stimulate acid production in an isolated guinea pig stomach preparation (25). They showed that muscimol and GABA but not baclofen stimulated acid output, and bicuculline also antagonized the secretagogue effect of muscimol. This motivated us to study the antagonistic effect of phaclofen on baclofen-induced hypersecretion of gastric acid. In our experiments, bicuculline, however, had no effect on baclofen action. We used 1 and 3 mg/kg of bicuculline, subcutaneously. These doses seem to be sufficient to block GABA<sub>A</sub>-receptors in the whole animal preparation, as evidenced by the appearance of physical convulsion.

Blandizzi et al. (7) reported that intracerebroventricular injection of bicuculline suppressed the acid secretagogue actions of not only muscimol but also those of baclofen. Most of the receptor binding studies have, however, demonstrated that bicuculline failed to antagonize baclofen binding at GABA<sub>B</sub>-receptors (17). When we did infuse bicuculline (1 mg/kg, i.v., bolus injection), it was recognized that the acid output in response to baclofen was markedly inhibited, accompanied by serious convolution followed by respiratory insufficiency. This inhibition by i.v. bicuculline of acid output might be attributed to a non-specific effect rather than a pharmacological effect of the antagonist.

Phaclofen has been found to antagonize the biological effects of baclofen in rat brain slices (18, 20, 22), isolated guinea pig ileum (21), cat spinal cord (21) and intact mice (19). In our current study, systemic administration of phaclofen at doses up to 30 mg/kg, did not, however, antagonize the secretagogue action of baclofen. Furthermore, phaclofen injected into the cisterna magna (30 μg/rat) had no effect on the baclofen effect (data not shown). According to these observations, it might be concluded that the GABA<sub>B</sub>-receptor does not participate in the secretagogue action of baclofen.

We, therefore, attempted to find specific or novel types of GABA-receptor antagonists among GABA-related compounds to suppress the acid secretagogue response to GABA-mimetics. APSA is a derivative of GABA, where the carboxylic component is replaced with sulfonic acid, and it is a weak agonist on GABA receptors. MOPS is a morpholine derivative of APSA. APSA was found to augment the action of baclofen dose-dependently. On the contrary, a morpholino derivative of APSA did suppress the acid response to baclofen. ABA and IMAA are cyclic compounds possessing phenol or imidazole rings in their chemical structures. IMAA is generally considered to have partial agonistic effects on GABA receptors. In our study, IMAA stimulated gastric acid secretion, whereas ABA inhibited it. The effect of APSA and IMAA on basal acid output were also studied in the same preparation, and we did not see any significant change at the doses of 3 and 10 mg/kg, i.v. (in our preliminary study and the data not shown). These results suggest that APSA and IMAA have some interaction with the GABA-mimetic effect. The introduction of the morpholino-group
into the APSA and also that of the amino-group into the benzoic acid, MOPS and ABA, respectively, were found to result in compounds with significant inhibitory effects on baclofen-induced hyperacidity.

The interesting finding in this study was the antisecretagogue properties of APPA. Five beta-amino acid analogues which each contained a phenyl group were challenged against baclofen-stimulated acid secretion. APPA seems to be more potent in inhibiting the acid response to baclofen. Intravenous injection of 10 and 30 mg/kg of APPA resulted in 50 and 90% inhibition of baclofen stimulation, respectively. In isolated preparations, rat anococcygeus muscle and guinea pig distal colon (26–28), 5-aminovaleric acid has been shown to antagonize the effect of baclofen on GABA<sub>B</sub>-receptors. However, a lipophilic derivative of 5-aminovaleric acid produced by introducing a phenyl group at the delta position, APVA, had no effect on the secretagogue action of baclofen. We performed further studies to find some clues about the mechanism by which APPA suppresses acid secretion. The inhibitory effect of APPA was surmounted by an excess amount of baclofen. APPA did not block the action of bethanechol. These suggest the specificity of the antisecretory effect of APPA on GABA-mechanisms. Although further investigation is necessary to find the mode of action of APPA, including whether the antagonistic effect of this compound is competitive against GABA-mimetics, APPA seems to be one of the prototypical GABA-antagonists with respect to gastric secretory mechanisms.

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