Acid Secretagogue Action of Structurally Gamma-Aminobutyric Acid (GABA)-Related Compounds in Rats

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Abstract—The properties of GABA related compounds on gastric function were studied in standardized perfused rat stomach preparations. Intravenous GABA (400 mg/kg) produced a rapid increase in acid secretion. Acid secretagogue actions of 3-aminobutyric acid and 2-aminobutyric acid were less potent than that of GABA. Intravenous injection of 5-amino-n-valeric acid (400 mg/kg) stimulated gastric acid secretion, but 6-amino-n-caproic acid was inactive. Isoguvacine (40 mg/kg, s.c.) stimulated acid output, whereas guvacine, an isomer of isoguvacine, did not. Systemically administered 3-hydroxy-GABA and \( \beta \)-(p-chlorophenyl)-GABA (PCPGABA) showed significant secretagogue actions. Acid responses to GABA-related compounds were significantly reduced by surgical truncal vagotomy and completely antagonized by atropine. The acid responses to PCPGABA and isoguvacine were partially augmented by yohimbine and propranolol. These results suggest that the secretagogue action of GABA is mimicked by structurally GABA-related compounds, which is mediated through cholinergic receptors, with slight implication of alpha-2 and beta-adrenoceptor mechanisms.

It is well-established that the central nervous system participates in the regulation of gastric acid secretion (1). The relationships between neurotransmitters and gastric acid secretion were widely studied with regard to aspects such as inhibitory effects of norepinephrine (2), dopamine (3), calcitonin-gene related peptide (CGRP) (4), nicotine (5), bombesin (6), neurotensin (7) and somatostatin (8) and secretagogue effects of nicotine (9) and thyrotropin-releasing hormone (TRH) (10). Gamma-amino-n-butyric acid (GABA) is well-established as an inhibitory transmitter in the CNS. We previously reported that GABA produced a dose-dependent increase in gastric acid secretion (11); and also a lipophilic derivative of GABA, \( \beta \)-(p-chlorophenyl)-GABA (PCPGABA), stimulated gastric acid secretion more potently at a small dose (2–8 mg/kg, s.c.) (12). The acid secretagogue effects of GABA and GABA-mimetics have been also confirmed in dogs and humans (13, 14). GABAergic mechanisms to stimulate acid secretion are, however, complicated because both types of GABA\(_A\)- and GABA\(_B\)-receptor agonists stimulate gastric acid secretion responses. There is no evidence to show that GABA mechanisms in the regulation of gastric secretion is selectively activated by GABA or a GABA-moiety. This led us to explore the effect of structurally GABA-related compounds on gastric secretion.

In the present study, we examined the effect of various types of GABA-related compounds on gastric acid secretion by the route of intravenous administration in most cases because of its quick or rapid onset to cause certain changes. We also compared the effect of GABA with those of other amino acids that have chemical structures similar to GABA, with special reference to structure-activity relationships, and also attempted to define the autonomic neuronal mechanisms involved.

Materials and Methods

Measurement for gastric acid secretion:

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Male Wistar rats weighing 180–240 g were fasted in metal cages with mesh bottoms for 18–24 hr prior to the experiment but were allowed free access to water ad libitum. Rats were anesthetized with urethane (1.25 g/kg, i.p.). A cannula was inserted into the trachea followed by the ligation of the esophagus to avoid the reflex of the perfusate. A laparotomy was performed, and the pylorus was ligated. Care being taken not to interfere with the vascular supply and neural connections to the stomach. A small incision on the forestomach was made, and the gastric lumen was gently rinsed with saline to remove the solid gastric contents. A dual polyethylene cannula was introduced into the gastric lumen through the forestomach. The stomach was perfused with saline, pH adjusted to 5.5 by HCl, using a peristaltic pump at a flow rate of 5 ml/min. Acid output was determined by titrating the perfusate with 0.02 N NaOH to pH 5.5 using an automatic titrator (Toa Electronic Co. Ltd, Japan. TSB-10A) and continuously recorded in terms of every 2 min response via a zero suppression adaptor (Toa Electronic Co. Ltd, Japan, C96667T). Acid output was expressed in terms of μ equivalents of hydrogen ions (μeq.). After stabilization of basal acid secretion for usually 30 min after the initiation of the gastric lumen perfusion, each compound was intravenously or subcutaneously given at a volume of 1 or 2 ml/kg.

The cervical ligation of the esophagus was followed by resections of the cervical truncal vagi. Vagotomy was performed 30 min prior to administration of GABA or GABA-related compounds.

**Drugs:** The drugs used were as follows: 4-amino-n-butyric acid (GABA), DL-2-amino-n-butyric acid (2A-BA), DL-3-amino-n-butyric acid (3A-BA), 5-amino-n-valeric acid (5A-VA), 6-amino-n-caproic acid (6A-CA), DL-4-amino-3-hydroxy-n-butyric acid (GABOB), atropine sulfate, yohimbine hydrochloride, and DL-propranolol hydrochloride, which were all purchased from Nacalai Tesque Ltd., Japan. Isoguvacine and guvacine were from Funacoshi Pharm. Co., Japan; and DL-4-amino-3-(p-chlorophenyl)-butyric acid (PCPGABA) was a generous gift from Ciba-Geigy, U.S.A. The chemical structures of these GABA-related compounds are shown in Fig. 1. The compounds dissolved in saline or distilled water were administered through the femoral vein or administered subcutaneously. Pretreatment with atropine, yohimbine or propranolol was performed 20 min before each secretagogue was administered.

**Statistical analysis:** Results are expressed as the mean±S.E. Basal acid output was very low and usually less than 2.0 μeq./10 min. For evaluation of drug effects, the net increase in gastric acid output was calculated...
by subtracting the basal response from the acid response to each compound. Statistical significances were determined by analysis of variance followed by Dunnett's test for multigroup comparison of parametric data.

**Results**

**Effect of GABA-related compounds on gastric acid secretion:** Typical responses of GABA-related compounds on basal acid secretion are shown in Fig. 2. GABA (400 mg/kg) given intravenously significantly increased the gastric acid production. The secretagogogue effect was observed with 15 min latency and maintained for more than 120 min. The maximal response to GABA was observed 60 min after the administration and was 8.4±1.2 μeq./10 min (N=7). The acid secretagogogue action of GABA was dose-dependent (100–400 mg/kg, i.v.). The effect of GABA in anesthetized rats was mimicked by 5A-VA, GABOB, isoguvacine and PCP-GABA. The results obtained with structurally related compounds are summarized in Fig. 3. 3A-BA, 2A-BA and 6A-CA, however, had little or no secretagogogue actions. Intravenous injection of 5A-VA (400 mg/kg) and GABOB (200 mg/kg) markedly stimulated gastric secretion, reaching maximal responses of 12.1±2.0 μeq./10 min (70 min after, N=6) and 7.2±1.5 μeq./10 min (60 min after, N=6), respectively. Isoguvacine also showed a potent secretagogogue effect at the dose of 40 mg/kg, s.c. (maximal response: 15.7±3.2 μeq./10 min at 90 min after the medication, N=6), while guvacine had no influence on gastric acid secretion. Dose-response relations of 5A-VA, GABOB and isoguvacine were also confirmed at the dose ranges of 100–400 mg/kg, i.v.; 50–200 mg/kg, i.v.; and 10–40 mg/kg, s.c., respectively. PCPGABA was more than 100-fold potent than GABA on a molecular basis. PCPGABA (4 mg/kg, s.c.) exhibited secretagogogue action and its peak response was obtained within 90 min (25.6±4.3 μeq./10 min (N=10)). Bethanechol (1 mg/kg) and histamine (10 mg/kg) given subcutaneously caused potent acid increments, and the peak responses were 16.6±1.8 (30 min, N=10) and 17.7±2.9 (70

**Fig. 2.** Typical secretory responses to GABA, 5-aminovalleric acid (5A-VA), 4-amino-3-hydroxybutyric acid (GABOB) and isoguvacine in stomach perfused rats.
Fig. 3. Secretagogue action of GABA-related compounds in rats. Each column represents the net increase in gastric acid output for 60 min. GABA (400 mg/kg, i.v.), 3A-BA (400 mg/kg, i.v.), 2A-BA (400 mg/kg, i.v.), 5A-VA (400 mg/kg, i.v.), 6A-CA (400 mg/kg, i.v.), GABOB (200 mg/kg, i.v.), isoguvacine (40 mg/kg, s.c.), guvacine (40 mg/kg, s.c.), PCPGABA (4 mg/kg, s.c.), bethanechol (1 mg/kg, s.c.) and histamine (10 mg/kg, s.c.).

Table 1. Influence of atropine and vagotomy on gastric acid response to GABA-related compounds in rats

| Compound          | Dose (mg/kg) | Net gastric output (μeq./60 min) |
|-------------------|--------------|----------------------------------|
|                   |              | control                          | with atropine 1 mg/kg, s.c. | with vagotomy |
| GABA              | 400, i.v.    | 39.7±4.1 (7)                     | 2.0±1.7 (6)*                 | 10.6±2.6 (7)* |
| 5A-VA             | 400, i.v.    | 40.8±8.8 (6)                     | 3.6±4.3 (4)*                 | 8.7±3.1 (6)*  |
| Isoguvacine       | 40, s.c.     | 30.1±5.2 (6)                     | 4.3±1.5 (6)*                 | 2.8±1.8 (4)*  |
| PCPGABA           | 4, s.c.      | 44.1±5.3 (10)                    | 6.2±2.3 (6)*                 | 1.7±1.7 (6)*  |
| Bethanechol       | 1, s.c.      | 66.3±6.2 (10)                    | 0.2±0.2 (4)*                 | 41.1±9.8 (4)  |
| Histamine         | 10, s.c.     | 60.1±6.7 (10)                    | 48.8±6.3 (4)                 | 38.3±8.1 (4)  |

Atropine was subcutaneously pretreated 20 min before administration of GABA-related compounds. Each value represents the mean±S.E. of the net increase of acid output (μeq./60 min). 5A-VA: 5-aminovaleric acid, PCPGABA: β-(p-chlorophenyl)-GABA. A significant difference was obtained from the secretagogue alone at the level of *: P < 0.05 by Dunnett’s test. The number of rats is indicated in parentheses.

Influence of cholinergic blockades on gastric acid response to GABA-related compounds: The results of the effectiveness of surgical and chemical vagotomy on the acid secretion in response to GABA-related compounds are shown in Table 1. Bilateral truncal vagotomy reduced the basal acid secretion compared to vagi-intact rats. When GABA (400 mg/kg, i.v.), 5A-VA (400 mg/kg, i.v.), isoguvacine (40 mg/kg, s.c.) and PCPGABA (4 mg/kg, s.c.) were given to vagotomized rats, the secretagogue actions of these compounds were significantly attenuated, while bethanechol and histamine given subcutaneously still exhibited marked effects to increase
Table 2. Influence of adrenergic blockers on gastric acid response to GABA-related compounds in rats

| Compound     | Dose mg/kg | Net gastric output (μeq./60 min) |
|--------------|------------|----------------------------------|
|              |            | saline (control) with propranolol 5 mg/kg, s.c. with yohimbine 5 mg/kg, s.c. |
| GABA         | 400, i.v.  | 39.7±4.1 (7)                      | 43.3±10.1 (7)                      | 45.3±5.7 (7)                      |
| 5A-VA        | 400, i.v.  | 41.2±8.8 (6)                      | 46.7±5.6 (6)                       | 48.6±10.9 (6)                     |
| Isoguvacine  | 40, s.c.   | 30.1±4.2 (6)                      | 43.3±3.4 (8)*                     | 47.2±4.0 (8)*                     |
| PCPGABA      | 4, s.c.    | 44.1±5.3 (10)                     | 63.5±3.5 (10)*                    | 78.8±9.1 (10)*                    |
| Bethanechol  | 1, s.c.    | 65.3±6.2 (10)                     | 61.5±9.5 (6)                       | 62.7±10.3 (6)                     |
| Histamine    | 10, s.c.   | 60.1±5.7 (10)                     | 63.5±7.1 (6)                       | 57.7±10.6 (6)                     |

Propranolol and yohimbine were subcutaneously pretreated 20 min before the administration of GABA-related compounds. Each value represents the mean ± S.E. of the net increase of acid output (μeq./60 min). 5A-VA: 5-aminovaleric acid, PCPGABA: β-(p-chlorophenyl)-GABA. A significant difference was obtained from the secretagogue alone at the level of *: P < 0.05 by Dunnett's test. The number of rats is indicated in parentheses.

acid output. Atropine (1 mg/kg) given subcutaneously had little influence on basal gastric acid secretion, but completely antagonized the secretagogue action of GABA-related compounds and bethanechol, and it had little influence on histamine stimulation.

Influence of adrenergic blockers on gastric acid response to GABA-related compounds: The effects of yohimbine (5 mg/kg, s.c.) and propranolol (5 mg/kg, s.c.) on the acid response to GABA-related compounds are shown in Table 2. The acid responses to PCPGABA and isoguvacine were significantly potentiated in both yohimbine or propranolol-treated animals. The responses to the other GABA-related compounds, GABA and 5A-VA, were slightly augmented in yohimbine- and propranolol-pretreated groups, and the responses were not significantly different from the control values.

The acid responses to bethanechol and histamine have, however, not been modified by both adrenergic receptor blockers.

Discussion

The present study shows that peripherally administered GABA and GABA-related compounds potently increased gastric acid secretion in anesthetized rat perfused stomach preparation. The maximal activity seemed nearly equal to that of bethanechol and histamine, and the durations lasted for more than 120 min. This is coincident to the findings that administration of the GABA-related compound muscimol, a GABA_A-agonist, resulted in a dose-dependent increase in gastric acid secretion (15). In contrast, Bhargava et al. (16) observed that intracerebroventricular administration of GABA reduced gastric secretion in Shay rats. This discrepancy may be at least in part due to differences in experimental conditions. A recent finding indicated that several neurotransmitters administered centrally stimulated the gastric acid secretion at very small doses (1). In this study, a large amount of these compounds was required to produce the secretagogue actions by intravenous administrations. Little penetration across the blood-brain barrier occurs since these compounds are amino acids. Indeed, PCPGABA, a lipophilic derivative of GABA, can cross the blood-brain barrier (17) and vigorously stimulated gastric acid secretion when it was given in small doses by the subcutaneous route.

In this experiment, only small numbers of GABA-related compounds were available for studying the quantitative structure-activity relationships. The acid stimulatory effect of 3A-BA, in which the amino group is situated at the 3-position, was markedly less potent than that of GABA. 2A-BA, in which the amino group is at 2-position, and 6A-CA, which has a 2 carbon longer chain than GABA, had little or no secretagogue effect. However, 5A-VA whose chemical structure contains 5 carbon atoms exerted an approximately equivalent effect to GABA. These results and effects of GABA taken together suggest that the terminal amino group and 3–4 carbon atoms
between the amino and carbonic acid moieties are necessary for the exhibition of secretagogue actions. Isoguvacine had a potent secretagogue effect, while guvacine, an isomer to isoguvacine, had no influence on gastric acid secretion. Krogsgaard-Larsen et al. (18) have been reported that the conformationally restricted analogue of GABA, isoguvacine, is a potent agonist at GABA receptors, and its activity was comparable with that of another analogue, muscimol. These compounds are potent as displacement ligands in receptor binding studies with $^3$H-GABA. There is, however, no evidence that guvacine acts on GABA-receptors, except for the inhibitory effect on GABA uptake (19). These relative potencies may reflect different molecular mechanisms of receptor interactions of GABA and suggest that steric factors are important for studying structure-activity relationships of GABA.

Although the mechanisms for how GABA stimulates acid secretion have not yet been completely understood, it seems that a central cholinergic pathway is involved in the secretagogue mechanisms, since these responses were antagonized by pretreatment with atropine and by truncal vagotomy. It is, however, still unclear whether this effect is accomplished by activating GABA receptors directly or by other mechanisms. In addition, the adrenergic pathways have been postulated to play a role in the inhibitory mechanisms involved in the regulation of gastric acid secretion (20, 21). Some researchers have obtained data showing the acid inhibitory effects of the alpha$_2$-receptor agonist clonidine (22–24) or showing a contradictory effect to stimulate acid secretion in the dog (25). A beta$_2$-stimulant also inhibited the gastric acid response to histamine (26). In the present study, the adrenergic neural activity was attenuated by pretreatment with adrenoceptor antagonists, yohimbine and propranolol. The acid responses to PCPGABA and isoguvacine were significantly augmented in the yohimbine-treated animals. Furthermore, significant potentiations of acid responses to GABA-related compounds were also observed in propranolol-treated animals as compared with the saline control, but the magnitude was smaller than that observed in the yohimbine-treated animals. The adrenergic blocking agents used in this study tended to modulate the secretagogue action of GABA and 5A-VA, although these effects were not significant. This postulates that sympathetic inhibitory mechanisms may be mediated by the adrenergic receptors in gastric acid responses to these compounds. There is no evidence to explain the potentiation by alpha$_2$- or beta-blockers of the acid response to GABA-related compounds. It may be assumed that this synergism is related to the inhibition of acid inhibitory mechanisms. GABA itself and 5A-VA did not stimulate acid output as potently as PCP-GABA and isoguvacine, suggesting the latter compounds are more active in GABA-mechanisms that seem to be affected by adrenergic inhibition.

It has been reported that GABA receptor agonists, including muscimol and baclofen, stimulate gastric secretion in the anesthetized rat (1, 11–15). The amino acids used in this study such as GABOB, one of the GABA metabolites (27, 28); isoguvacine, a GABA$_A$ agonist (29); PCPGABA, a GABA$_B$ agonist (30); and 5A-VA, a GABA$_B$ partial agonist (31), also stimulated gastric secretion with a potency similar to or greater than that of GABA. According to our previous finding, both GABA$_A$- and GABA$_B$-agonists, however, failed to suppress the acid response to baclofen (K. Yamasaki et al., unpublished data). Most studies on the subtypes of GABA receptors have been based on in vitro receptor binding assays. In the gastric acid secretion response in vivo, either an agonist of GABA$_A$-receptors or an agonist of GABA$_B$-receptors increased acid secretion through central cholinergic activation mechanisms (15). We have recently found that phaclofen, a GABA$_B$-receptor antagonist, had no significant effect on baclofen-induced acid response (32). Furthermore, a specific GABA$_A$-receptor antagonist, bicuculline, had no influence on the acid response to muscimol, whereas bicuculline antagonized the secretagogue action of GABA in isolated guinea pig stomach preparation (33). This suggests that the acid stimulatory effect of GABA-mimetics might be mediated through non-GABA$_A$- and non-GABA$_B$-receptors. The question that GABAergic mechanisms could
be activated by GABA or structurally restricted GABA analogues led us to investigate whether the effect of systemically administered GABA-related compounds on gastric acid secretion is specific to certain moieties of GABA-structures. The present result suggests that the in vivo effect of GABA-related compounds on gastric secretion is different from that in vitro, namely, the stimulatory effect of GABA-analogues might be activated by non-GABA₆- and non-GABA₈-receptors. Guvacine has been demonstrated to block the uptake of GABA to GABA-receptors. There are, however, no reports on the interactions between 2A-BA and GABA-receptors. None of the three compounds exerted any significant secretagogue action in this experiment.

In conclusion, GABA, 5A-VA, GABOB, PCPGABA and isoguvacine showed a significant increment in gastric acid secretion through the activation of central cholinergic mechanisms in rats. We concluded this from the observed complete inhibition by atropine and truncal vagotomy of the stimulatory actions of these agents.

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