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Influence of dopamine receptor agonists on gastric acid secretion induced by intraventricular administration of thyrotropin-releasing hormone in the perfused stomach of anaesthetized rats

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1 The influence of dopamine receptor agonists on gastric acid secretion stimulated by thyrotropin-releasing hormone (TRH) was studied in the perfused stomach of anaesthetized rats.

2 Intraventricular TRH produced a dose-dependent stimulation of basal gastric acid secretion.

3 Pretreatment with apomorphine, bromocriptine or methamphetamine inhibited the TRH-stimulated gastric acid secretion; these drugs did not influence bethanechol-induced acid secretion.

4 Haloperidol and metoclopramide prevented the antisecretory effects of apomorphine, bromocriptine and methamphetamine.

5 The present study suggests that central dopamine receptor stimulation inhibits intraventricular TRH-induced gastric acid secretion in rats.

Introduction

Pharmacological evidence indicates that several endogenous brain oligopeptides have been involved in the central nervous system (CNS) modulation of gastric acid secretion (Osumi, Nagasaka, Fu & Fujiwara, 1978; Rozé Duburasquet, Chariot & Vaille 1980; Taché, Vale, Rivier & Brown, 1980a; Tepperman & Evered, 1980; Taché, Rivier, Vale & Brown, 1981; Morley, Levine & Silvis, 1982). Taché, Vale & Brown (1980b) demonstrated that thyrotropin-releasing hormone (TRH), a tripeptide originally isolated from the hypothalamus, acted within the CNS to elicite a vagus-mediated stimulation of gastric acid secretion in rats and Morley, Levine & Silvis (1981a) also confirmed this finding. We previously found that bromocriptine, a dopamine agonist, inhibited 2-deoxy-D-glucose-induced gastric acid secretion by acting within the CNS in rats (Maeda-Hagiwara & Watanabe, 1982a). These facts have led us to examine the relationship between the TRH-stimulated gastric acid secretion and the central dopaminergic system. We show here that dopamine agonists inhibit the gastric acid secretion induced by intraventricular TRH in rats.

Methods

Assay of gastric acid secretion

Male Wistar rats (ST. substrain from Sankyo Lab. Co., Ltd.), weighing 190–250 g, were anaesthetized with urethane (1.25 g/kg i.p.) after a 24 h fast, but were allowed free access to water. A gastric acid secretion assay was performed following the procedure as described by Watanabe & Goto (1975) with a slight modification (Maeda-Hagiwara & Watanabe, 1982b). The trachea was exposed and cannulated. A dual polyethylene gastric cannula was inserted into the gastric lumen after ligation of the pylorus and oesophagus. The inlet and outlet tubes of the dual cannula were connected to a saline reservoir and the stomach was continuously perfused with a saline solution (adjusted to pH 4 with HCl) through the gastric cannula by means of a perfusion pump at the rate of 5 ml/min. The perfusate was titrated in the reservoir with 0.01 N NaOH at pH 4 using an automatic titrator (HS-2A, TOA Electronics Ltd., Japan) with a recorder. The acid output during the 2 min period in the perfusate was continuously recorded by use of a zero suppression adaptor (TOA

Electronics Ltd., Japan) as described in Figures 1 and 2. The total amount of the secreted acid was expressed in terms of μEq HCl/60 or 90 min per animal. Basal secretion was low and almost constant during the longer periods in the present experimental condition. Therefore, the data indicate values in which the corresponding basal secretion before treatment was deducted from the acid output due to the treatment. Intraventricular drug administration was performed by the technique of Noble Wurtman & Axelrod, 1967. The rat was placed in a stereotaxic apparatus (Type SR-6, Narishige Co. Ltd., Japan). A small hole was made in the right occipital bone, 1.5 mm lateral to the sagital suture and 1.5 mm posterior to the cornal suture, and the needle (0.35 mm, diam.) was inserted to a depth of 5 mm below the surface of the occipital bone. TRH dissolved in saline was injected twice at 1–2 h intervals into the lateral ventricle in a volume of 10 μl/rat in approximately 2 min. To minimize the leakage of the drug out of the ventricle, the needle was left in place for 2 min following injection. TRH was also administered into the tail vein to examine its peripheral effect. Bethanechol dissolved in saline was given subcutaneously. Apomorphine, methamphetamine and atropine dissolved in saline were administered intraperitoneally 15 min before the second TRH or the bethanechol injection. Bromocriptine suspended in a 1% carboxymethylcellulose (CMC solution was given intraperitoneally 30 min before the second TRH or the bethanechol injection. Metoclopramide (injection solution) and haloperidol (suspended in a 1% CMC solution) were administered subcutaneously and intraperitoneally 45 min before the second TRH injection, respectively. All drugs except TRH were administered in a 1 ml/kg volume. When the drug is a salt, the weight refers to that of the salt.

Drugs

Drugs used were apomorphine HCl (Dainippon, Osaka), atropine sulphate (Wako Pure Chem., Tokyo), bethanechol HCl (Eisai, Tokyo), bromocriptine mesylate (Sandoz, Tokyo), methamphetamine HCl (Dainippon, Osaka), metoclopramide HCl (Terperan, Teikokuzoki, Tokyo), haloperidol (Dainippon, Osaka), thyrotropin-releasing hormone (Protein Res. Foundation, Osaka) and urethane (Nakarai Chem. Tokyo).

Statistical analysis

All data are presented as means ± s.e.mean. The data were analyzed by Student's *t* test and the paired *t* test.

Results

Intraventricular (i.c.v.) TRH produced a dose-dependent (1–10 μg/rat) increase in gastric acid secretion (Figure 1 and Table 1). Saline (10 μl/rat i.c.v.) did not influence basal gastric secretion. The time course of the secretory response to TRH indicated that the acid stimulatory effect of TRH began immediately after the injection; thereafter the secretory response returned to the basal level (10.2 ± 1.7 μEq HCl/30 min, $n = 36$) within 1 or 1.5 h. The repeated administration of TRH induced reproducible acid secretion (Figure 1 and Table 1). The increase in acid output by the second TRH injection was significantly larger than that by the first injection as is shown in Table 1. Pretreatment with atropine (0.1 mg/kg i.p.) inhibited the gastric response to the second TRH (10 μg/rat i.c.v.) by about 90% as is shown in Table 1. Intravenous TRH (100 μg/rat) had no effect on gastric acid secretion. TRH (500 μg/rat i.v.) produced a slight and short-lasting (no more than 30 min) in-

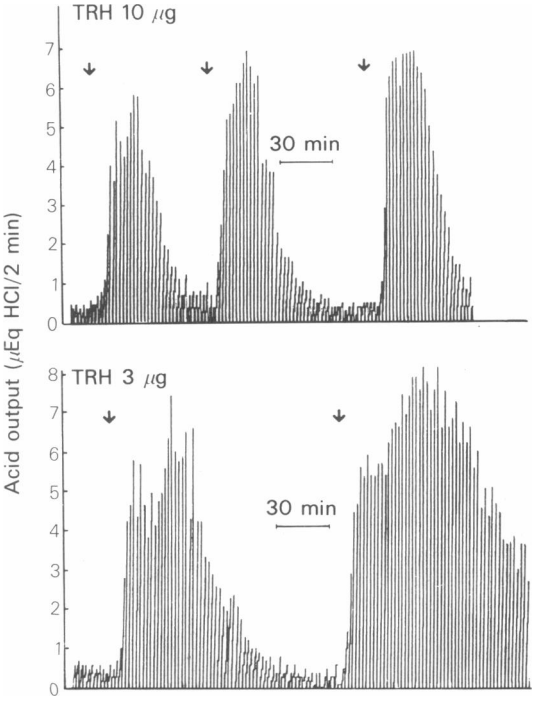

Figure 1 Intraventricular thyrotropin-releasing hormone (TRH) stimulates gastric acid secretion. Ordinate scale: rate of acid output per 2 min. Intragastric perfusate was titrated with 0.01 N NaOH. The titrated volume of the NaOH solution was recorded and was expressed in terms of μEq HCl/2 min. Abscissa scale: chart speed was 20 mm/30 min. TRH (3 or 10 μg/rat) was repeatedly injected into the lateral ventricle at arrows.

Table 1 Gastric secretagogue action of thyrotropin-releasing hormone (TRH)

Drugs	*Dose*	*No. of rats*	*Increase in acid output (μEq HCl/60 min)* 1st	2nd
TRH	1 μg/rat	9	24.1 ± 9.2	44.7 ± 12.2[a]
	3 μg/rat	9	54.6 ± 13.2	87.5 ± 20.3[b]
	10 μg/rat	9	98.1 ± 14.1	153.1 ± 12.5[b]
TRH + Atropine	10 μg/rat 0.1 mg/kg	9	106.4 ± 19.9	154 ± 8.1[b]**

The acid output values indicate the increase in acid output; basal secretion is deducted from the acid output stimulated by TRH, during 60 min after the TRH injection (intraventricular administration). Basal acid secretion before the TRH injection was 10.2 ± 1.7 μEq HCl/30 min ($n = 36$). Atropine was administered (i.p.) 15 min before the second TRH injection. [a]$P < 0.05$; [b]$P < 0.01$ vs. corresponding 1st value (paired t test).
**$P < 0.01$ vs 10 μg/rat of TRH (Student's t test).

Table 2 Effects of dopamine agonists on TRH-induced gastric acid secretion

Drugs	*Dose*	*No. of rats*	*Increase in acid output (μEq HCl/60 min)* 1st	2nd
TRH control	10 μg/rat	12	99.8 ± 11.5	146.3 ± 13.1[b]
Apomorphine	0.5 mg/kg	6	93.9 ± 14.3	33.5 ± 10.2**[b]
	1.0 mg/kg	6	102.7 ± 14.8	20.5 ± 8.8**[b]
Bromocriptine	2.5 mg/kg	6	116.2 ± 21.9	91.6 ± 23.5*
	5.0 mg/kg	6	104.5 ± 25.9	41.4 ± 9.8**[a]
Methamphetamine	0.5 mg/kg	6	107.4 ± 33.4	51.6 ± 10.9**
	1.0 mg/kg	6	96.3 ± 19.6	16.5 ± 7.4**[b]

Apomorphine and methamphetamine were given (i.p.) 15 min and bromocriptine was given (i.p.) 30 min before the second TRH injection (intraventricular administration).
[a]$P < 0.05$; [b]$P < 0.01$ vs corresponding 1st value (paired t test).
*$P < 0.05$; **$P < 0.01$ vs TRH control (Student's t test).

Table 3 Effects of dopamine agonists on bethanechol-induced gastric acid secretion

Drugs	*Dose (mg/kg)*	*No. of rats*	*Increase in acid output (μEq HCl/90 min)*
Bethanechol	0.5 s.c.	8	139.1 ± 22.2
+ Apomorphine	1.0 i.p.	5	148.1 ± 17.5
+ Bromocriptine	5.0 i.p.	5	135.1 ± 18.7
+ Methamphetamine	1.0 i.p.	5	148.8 ± 29.7
+ Atropine	0.1 i.p.	5	9.0 ± 6.9**

Test drugs except bromocriptine (30 min) were administered 15 min before the bethanechol injection. **$P < 0.01$ vs bethanechol.

crease in the acid secretion. The increased acid output in which the basal secretion was deducted from the acid output due to the TRH injection (500 μg/rat i.v.), was 15.7 ± 4.7 μEq HCl/30 min ($n = 3$).

Table 2 summarizes the influence of the dopamine agonists on TRH-stimulated acid secretion. Apomorphine (0.5 and 1.0 mg/kg i.p.), bromocriptine (2.5 and 5.0 mg/kg i.p.) and methamphetamine (0.5 and 1.0 mg/kg i.p.) all prevented the second TRH-stimulated gastric acid secretion in a dose-related manner. However, these dopamine agonists at doses which inhibited the TRH-induced acid secretion did not significantly influence the secretory response to the systemically administered

Table 4 Effects of dopamine antagonists on the antisecretory action of apomorphine

Groups	*Drugs*	*Dose*	*No. of rats*	*Increase in acid output* (μEq HCl/60 min) 1st	2nd	*Statistical significance* vs. Group 2	vs. Group 1
1	TRH control	10 μg/rat	12	101.4±13.9	151.9± 9.8[a]	—	—
2	+Apomorphine	1.0 mg/kg i.p.	6	101.4±13.9	21.2± 8.7[a]	—	$P<0.01$
3	+Apomorphine +Haloperidol	1.0 mg/kg i.p. 1.0 mg/kg i.p.	6	96.8±12.8	102.3±26.2	$P<0.01$	NS
4	+Apomorphine +Haloperidol	1.0 mg/kg i.p. 0.25 mg/kg i.p.	6	99.5±22.2	62.4±14.2	$P<0.05$	$P<0.01$
5	+Apomorphine +Metoclopramide	1.0 mg/kg i.p. 10 mg/kg s.c.	6	98.6±22.5	98.1±17.7	$P<0.01$	$P<0.05$
6	+Haloperidol	1.0 mg/kg i.p.	6	97.2±22.7	99.0±10.1	—	$P<0.01$
7	+Metoclopramide	10 mg/kg s.c.	6	102.2±16.8	140.0±18.6[a]	—	NS

Apomorphine was given 15 min before the 2nd TRH injection. Haloperidol and metoclopramide were administered 45 min before the 2nd TRH injection.
[a] $P<0.01$ vs corresponding 1st value (paired t test).
NS: not significant.

Table 5 Effects of dopamine antagonists on the antisecretory action of bromocriptine and methamphetamine

Groups	*Drugs*	*Dose*	*No. of rats*	*Increase in acid output* (μEq HCl/60 min) 1st	2nd	*Statistical significance* vs. Group 2 or 5	vs. Group 1
1	TRH control	10 μg/rat i.c.v.	10	100.9±13.0	159.0±10.6[a]	—	—
2	+Bromocriptine	5.0 mg/kg i.p.	10	108.6±18.2	49.9± 8.5[a]	—	$P<0.01$
3	+Bromocriptine +Haloperidol	5.0 mg/kg i.p. 1.0 mg/kg i.p.	6	112.6±26.8	131.9±17.1	$P<0.01$	NS
4	+Bromocriptine +Metoclopramide	5.0 mg/kg i.p. 10 mg/kg s.c.	6	91.2±21.7	88.7± 8.2	$P<0.01$	$P<0.01$
5	+Methamphetamine	1.0 mg/kg i.p.	6	102.4±17.6	16.7± 7.3[a]	—	$P<0.01$
6	+Methamphetamine +Haloperidol	1.0 mg/kg i.p. 1.0 mg/kg i.p.	6	103.3±11.7	51.3±13.7[a]	$P<0.05$	$P<0.01$

[a] $P<0.01$ vs corresponding 1st value (paired t test). i.c.v., intraventricular administration.
NS, not significant.

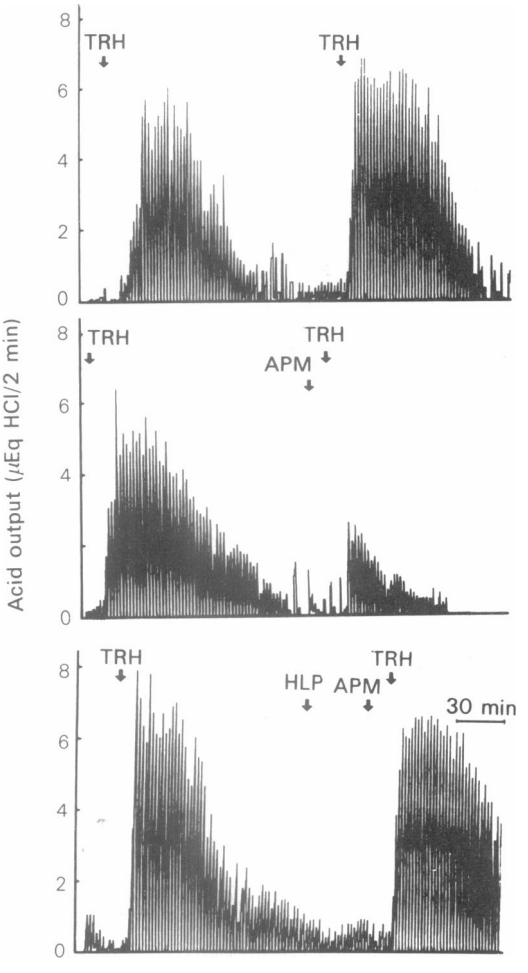

Figure 2 Effects of a dopamine agonist and an antagonist on thyrotropin releasing hormone (TRH)-stimulated acid secretion. TRH (10 μg/rat) was injected twice into one rat. Apomorphine (APM, 1 mg/kg i.p.) was given 15 min before the 2nd TRH injection and haloperidol (HLP, 1 mg/kg i.p.) was administered 30 min before apomorphine.

bethanechol (0.5 mg/kg s.c.) as is shown in Table 3. Atropine (0.1 mg/kg i.p.) prevented the bethanechol-induced gastric acid secretion by about 95%.

Figure 2 shows a typical pattern in which pretreatment with apomorphine (1.0 mg/kg i.p.) inhibits TRH-stimulated acid secretion and the inhibitory effect is reversed by haloperidol (1.0 mg/kg i.p.).

Tables 4 and 5 summarize the effects of dopamine antagonists concerning the inhibitory activity of apomorphine, bromocriptine and methamphetamine in TRH-induced acid secretion. Pretreatment with 0.25 and 1.0 mg/kg (i.p.) of haloperidol or 10 mg/kg (s.c.) of metoclopramide significantly reduced the antisecretory effect of apomorphine (Table 4). Metoclopramide (10 mg/kg s.c.) alone did not significantly influence the TRH-stimulated acid secretion, but haloperidol (1.0 mg/kg i.p.) alone produced a slight reduction of the secretion (Table 4). The inhibitory effect of bromocriptine (5.0 mg/kg i.p.) was also reduced by haloperidol (1.0 mg/kg i.p.) or metoclopramide (10 mg/kg s.c.) as can be seen in Table 5. The anti-dopamine activity of metoclopramide (10 mg/kg s.c.) was slightly weaker than that of haloperidol (1.0 mg/kg i.p.) regarding the bromocriptine-produced reduction of the TRH-induced acid secretion (Table 5). Haloperidol slightly but significantly reversed the antisecretory effect of methamphetamine (Table 5).

Discussion

Intraventricular TRH produced a dose-dependent gastric acid stimulation, while intravenous TRH did not produce stimulation in anaesthetized rats. Repeated intraventricular TRH induced reliable acid secretion. The gastric acid stimulation by the second intraventricular TRH was inhibited by pretreatment with apomorphine, bromocriptine or methamphetamine. That the antisecretory effects of these drugs are due to a specific dopamine agonistic action is demonstrated by the fact that dopamine antagonists (haloperidol and metoclopramide) reverse the inhibitory effects of apomorphine, bromocriptine and methamphetamine. The antisecretory effects of dopamine agonists might be due to the CNS, because apomorphine, bromocriptine and methamphetamine did not influence bethanechol-induced gastric acid secretion (Table 3). The gastric acid response to the electrical stimulation of the vagus or gastrin was not influenced by apomorphine and bromocriptine (Maeda-Hagiwara & Watanabe, 1982a).

Although the exact sites of the TRH action remain to be identified, the fact that high concentrations of TRH are present in the hypothalamus (Brownstein, Palkovits, Saavedra, Bassiri & Utiger, 1974), which has been shown in rats to participate in brain control of gastric secretion (Misher & Brooks, 1966, Davis, Brooks & Steckel, 1968), supports the possibilities that endogeneous TRH has physiological significance as a CNS chemical messenger, and that there is an interaction between the TRH and the hypothalamic monoaminergic neurone involved in brain modulation of the gastric secretion.

The involvement of the central dopaminergic system in TRH-stimulated gastric acid secretion has not been reported. However, inhibition of 2-deoxy-D-glucose-stimulated acid secretion by bromocriptine (Maeda-Hagiwara & Watanabe, 1982a) has been

recognized in rats. It has also been reported that intraventricular dopamine reduced the gastric distention-induced acid secretion mediated via the hypothalamus in rats pretreated with 6-hydroxydopamine, and apomorphine and methamphetamine prevented this acid secretion in intact rats (Maeda & Nakamura, 1978). TRH-induced release of growth hormone was suppressed after dopaminergic stimuli, such as bromocriptine therapy (Jackson, 1980). Dopamine has inhibitory effects on the TSH secretion induced by TRH in the thyrotrope (Scanlon, Weightman, Shale, Mora, Heath, Snow, Lewis & Hall, 1979). Further evidence for the dopaminergic inhibition of the TRH-TSH secretion was obtained in rats (Mannisto, Nattila & Kaakkola, 1981). However, the antisecretory action with dopamine agonists does not seem to be mediated through the hypophysis, because high intravenous doses of TRH which affect the hypophysis, produced almost no increase of acid secretion in the present study. It has also been shown that intraventricular TRH-induced decrease in food ingestion is not mediated through the hypophysis (Morley & Levine, 1980).

The central noradrenergic inhibition of acid secretion in electrical stimulation of the lateral hypothalamic area of rats (Osumi, Aibara, Sakae & Fujiwara, 1977) and the inhibitory effect of clonidine, a central α-receptor agonist, on gastric acid secretion in rats (Hoefke & Kobinger, 1966; Boissier, Giudicelli, Larno & Fichelle, 1970; Jennewin, 1977; Cheng, Gleason, Nathan, Lachamann & Woodward, 1981; Tacca, Soldani, Bernardini, Mastinotti & Impicciatore, 1982; Nakadate, Nakaki, Muraki & Kato, 1982) suggest the central noradrenergic inhibition of TRH-stimulated gastric acid secretion. Further studies are required to examine an interaction between the TRH action and the central noradrenergic system.

Calcitonin, a peptide hormone secreted from C cells within the mammalian thyroid, also inhibited TRH-stimulated gastric acid secretion in rats (Morley, Levine & Silvis, 1981b). Some authors examined the relationships between the TRH-stimulated gastric acid secretion and endogenous opiates and found an inhibitory action by β-endorphin and D-alanine-methionine-enkephalin (Morley *et al.*, 1981a). These facts suggest a relationship between the TRH action and other endogenous peptides in the central control of the gastric acid secretion.

In conclusion, the present study suggests that central dopamine receptor stimulation inhibits intraventricular TRH-induced gastric acid secretion in rats.

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