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8-OH-DPAT stimulates gastric acid secretion through a vagal-independent, adrenal-mediated mechanism

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Abstract

Serotonin (5-hydroxytryptamine, 5-HT) is a neuroendocrine component of the gastrointestinal tract. 5-HT_{1A} receptors exist both in the brain and have been demonstrated autoradiographically in high density in the rat stomach. However, the physiologic role of 5-HT_{1A} receptors in modulating gastric function is not known. The effect of the selective 5-HT_{1A} receptor agonist, (±)-8-hydroxy-2-(*n*-dipropylamino)tetralin (8-OH-DPAT), on gastric acid secretory function was compared to 5-HT in acute, urethane-anesthetized gastric-fistulated rats during pentagastrin infusion. 5-HT inhibited, but 8-OH-DPAT stimulated, gastric acid secretion in a dose-dependent manner. Bilateral cervical vagotomy or celiac ganglionectomy did not reverse the effect of 8-OH-DPAT on acid secretion. However, the enhancement of acid by 8-OH-DPAT was attenuated by acute adrenalectomy or close intra-arterial administration of spiperone, but not idazoxan. Thus, the data suggest that the selective 5-HT_{1A} receptor agonist 8-OH-DPAT may augment gastric secretory function via an adrenal-dependent mechanism.

Keywords: 8-OH-DPAT ((±)-8-hydroxy-2-(*n*-dipropylamino)tetralin); Adrenal gland; Gastrointestinal system, rat; 5-HT_{1A} receptor; Acid

1. Introduction

The gastrointestinal tract contains approximately 90% of the total body stores of serotonin (5-hydroxytryptamine, 5-HT). This biogenic amine is present in entero-endocrine cells, myenteric neurons and in mast cells of the rodent gastrointestinal tract (Dhasmana et al., 1993; Gershon, 1991). 5-HT produces effects on many gastrointestinal functional parameters, including gastric acid secretion (Cho and Ogle, 1986; LePard and Stephens Jr., 1994). Evidence suggests that 5-HT inhibits gastric acid secretion (Canfield and Spencer, 1983; Ormsbee and Fondacaro, 1985; Evans and Gidda, 1993), and produces an inhibitory tone on vagally stimulated acid output (LePard and Stephens Jr., 1994). Serotonin acts on heterologous receptors in the mammalian gastrointestinal tract; there is evidence for the existence of at least four receptor families (5-HT_1, 5-HT_2, 5-HT_3 and 5-HT_4) (Dhasmana et al., 1993). In regard to receptors of the 5-HT_1 family in the rat stomach, autoradiographic studies have indicated the presence of a high concentration of 5-HT_{1A} receptors in the lamina propria and myenteric ganglia (Kirchgessner et al., 1993). However, the role of mucosal or enteric 5-HT_{1A} receptors in modulating gastric function has not been delineated. A recent report revealed that in contrast to 5-HT or 5-HT_1 receptor agonists, infusion of the selective 5-HT_{1A} receptor agonist (±)-8-hydroxy-2-(*n*-dipropylamino)tetralin (8-OH-DPAT) close intra-arterially to the gastric circulation results in stimulation of gastric acid output (LePard and Stephens Jr., 1994). The present study was designed to further characterize this novel action of a 5-HT_{1A} receptor agonist to augment gastric acid secretion in the rat.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (200-250 g, Harlan Industries, Indianapolis, IN, USA) were maintained ad

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libitum on Purina Laboratory Chow and tap water. They were housed under controlled conditions of temperature (22 ± 1°C) and illumination (6 a.m. to 6 p.m.). All experiments were performed in animals deprived of food but not water 18–24 h before the experiment.

2.2. Measurement of gastric acid secretion

Gastric secretion was collected in urethane-anesthetized rats (1.5 g/kg i.p.). The trachea was cannulated, a midline laparotomy was performed and the pylorus was exposed and ligated. A double lumen cannula was then inserted through a small incision in the forestomach. Gastric acid secretion was collected by flushing the lumen with a 5 cc bolus of normal saline followed by a 5 cc bolus of air at 10 min intervals. Acid output was determined by titration of the flushed perfusate with 0.01 N NaOH to pH 7.0 on an automatic titrator (Radiometer, Copenhagen, Denmark).

2.3. Cannulation of the splenic artery

In some studies, either vehicle or various compounds were selectively infused into the gastric circulation through the splenic artery. The spleen was placed on moist gauze and the splenic artery was identified utilizing a stereomicroscope and was surgically isolated from the vein. The cannula (30 gauge needle attached to PE 10 tubing) assembly was inserted into the artery, tied and glued in place utilizing cyanoacrylate. The drug was infused in a volume of 0.1 ml over the time course of 1 min.

2.4. Vagotomy

In some experiments the vagi were cut bilaterally at the cervical level 30 min before the start of experiments, while littermates were exposed to sham vagotomy only. After ligation and section of the nerve, respiration was maintained through a tracheal cannula connected to a small animal ventilator (SAR-830; CWE, Ardmore, PA, USA).

2.5. Celiac ganglionectomy

Celiac ganglionectomized rats were obtained commercially (Zivic-Miller Laboratories, Zellenopie, PA, USA). The animals were utilized in experiments 2 weeks after the surgical procedure.

2.6. Adrenalectomy

Bilateral adrenalectomy was performed via a midline incision in rats under urethane anesthesia. The adrenals were isolated and carefully removed with forceps. In the sham controls, the abdomen was incised, the adrenals were exposed but not excised, and the incision was closed. The animals in each group were treated according to the protocol of 8-OH-DPAT challenge (described below) 3 h after surgery.

2.7. Protocol for dose-response studies

After three 10-min basal periods, pentagastrin (24 μg/kg/h i.v.) was infused via the femoral vein. After nine 10-min periods, the animal was treated i.v. with either 5-HT (0.1, 1, 3, 3.5 and 10 μmol/kg) or 8-OH-DPAT (0.1, 0.2, 0.28, 0.35, 1, 3.5 and 4.3 μmol/kg). Acid secretion was collected for six additional 10-min periods.

2.8. Protocol for antagonist studies

After three 10-min basal periods, pentagastrin (24 μg/kg/h i.v.) was infused via the femoral vein. After six 10-min periods, the animal was pretreated with either vehicle or the compounds of interest given close intra-arterially (close i.a.) to the gastric circulation via the splenic artery. After three more periods, the animals were challenged with 8-OH-DPAT (3.5 μmol/kg i.v.). Acid secretion was collected for six additional 10-min periods (1 h).

2.9. Drugs

Serotonin creatine sulfate (Sigma, St. Louis, MO, USA), (±)-8-hydroxy-2-(*n*-dipropylamino)tetralin HBr (8-OH-DPAT), *nor*-binaltorphimine dihydrochloride (*nor*-BNI), and idazoxan HCl (Research Biochemicals, Natick, MA, USA) were dissolved in distilled water. Spiperone HCl (Research Biochemicals, Natick, MA, USA) was suspended in 0.1% Tween 80. Pentagastrin (Ayerst Laboratories, New York, NY, USA) was diluted using normal saline to the appropriate concentration.

2.10. Data and statistical analysis

In the time-course data (Fig. 1 and Fig. 3) each time point is expressed as a percent change ± S.E.M. of the average of the three acid secretory measurements taken just before systemic vehicle or drug administration. With respect to the dose-response and the antagonist studies (Fig. 2 and Fig. 4) data are expressed as a percent change between the average of the three acid secretory measurements taken 30 min before treatment and the largest incremental change in 10 min acid output during the 30 min period after treatment. The data were analyzed utilizing the one-way analysis of variance (ANOVA) with post-hoc Student-Newman-Keuls (dose-response data) or Bonferroni test (time-

course data). Differences between groups were considered significant if $P < 0.05$.

3. Results

3.1. Comparison of the effect of systemic 5-HT and 8-OH-DPAT on pentagastrin-stimulated acid secretion

Basal acid output was low in all groups (pooled basal periods, mean ± S.E.M.: 4.8 ± 0.7 μEq/10 min). An equimolar dose (3.5 μmol/kg i.v.) of 5-HT or 8-OH-DPAT produced inhibition and stimulation, respectively on gastric acid secretion stimulated by pentagastrin infusion (24 μg/kg/h i.v.) (Fig. 1). Pentagastrin-stimulated gastric acid output reached a plateau 70–90 min after the start of infusion (pooled 70–90 min samples, mean ± S.E.M.: 27 ± 1 μEq/10 min). The inhibitory effect of 5-HT (3.5 μmol/kg) peaked at 30 min postinjection and the maximal effect was a 78% reduction in acid output (mean ± S.E.M.: 6.0 ± 0.7 μEq/10 min). In contrast, the stimulatory effect of 8-OH-DPAT (3.5 μmol/kg) peaked at the 20 min perfusate analyzed for acid content and a 60% augmentation from the plateau was produced (45 ± 10 μEq/10 min). In both cases the response was prolonged for the 60 min period analyzed after challenge with these agents. The effects of 5-HT administration were dose-dependent over the range of 0.1–10 μmol/kg) (Fig. 2A). The peak effect observed (72% inhibition) occurred after the 10 μmol/kg dose. In contrast, 8-OH-DPAT administration produced a steep dose-response profile to stimulate acid secretion (Fig. 2B). In the dose range of 0.1–0.28 μmol/kg, the full range of 8-OH-DPAT-stimulated acid secretion was observed, with the peak effect (90% stimulation) occurring at the 0.28 μmol/kg dose. Doses exceeding 0.28 μmol/kg produced stimulation ranging from 66 to 88% greater than pretreatment levels.

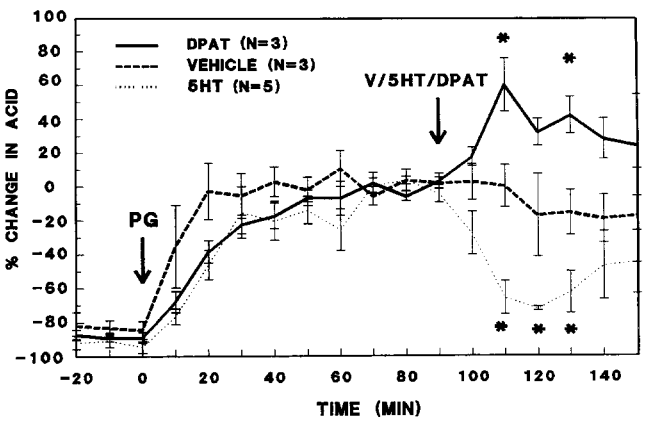

Fig. 1. Time course of the effect of systemic vehicle, 5-HT or 8-OH-DPAT on pentagastrin-stimulated gastric acid secretion. Pentagastrin (24 μmol/kg i.v.) infusion began after three 10-min basal periods. After an additional nine 10-min periods, the animals were given either systemic vehicle, 5-HT or 8-OH-DPAT at equimolar doses (3.5 μmol/kg i.v.). The acid secretory response was measured for six additional 10 min periods. Data are expressed as percent mean ± S.E.M. basal acid output for the number of animals indicated within the graph, as described in the Materials and methods section. * $P < 0.05$.

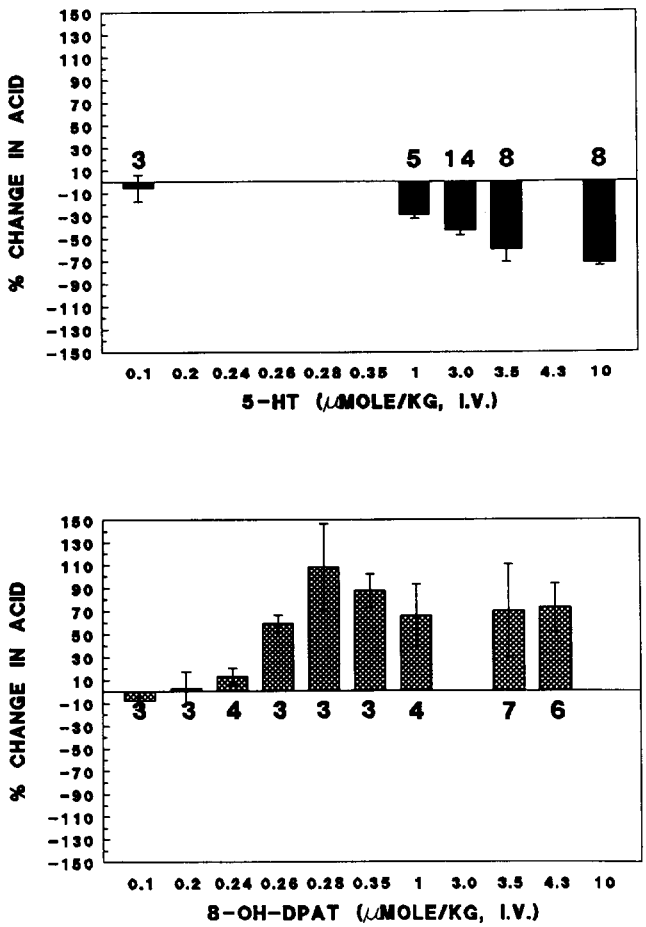

Fig. 2. Dose-response profile of the effects of systemic 5-HT or 8-OH-DPAT on pentagastrin-stimulated gastric acid secretion. Pentagastrin (24 μmol/kg i.v.) infusion began after three 10-min basal periods. After nine 10-min periods, the animals were given either systemic vehicle, 5-HT (0.1–10 μmol/kg) or 8-OH-DPAT (0.1–4.3 μmol/kg). The percent change in acid occurring within 30 min after 5-HT or 8-OH-DPAT administration is calculated as described in the Materials and methods section. Data are expressed as mean ± S.E.M. for the number of animals indicated above or below each bar.

3.2. Effect of vagotomy or celiac ganglionectomy on 8-OH-DPAT-induced stimulation of gastric acid secretion

Characterization of the novel stimulatory effect of 8-OH-DPAT was performed. Bilateral cervical vagotomy or celiac ganglionectomy did not attenuate the effect of 8-OH-DPAT (3.5 μmol/kg i.v.) to augment gastric acid secretion stimulated by pentagastrin (per-

cent change in acid after 8-OH-DPAT (mean ± S.E.M.): sham ($n = 3$) $+61 \pm 16$, vagotomy ($n = 3$) $+78 \pm 10$, celiac ganglionectomy ($n = 3$) $+147 \pm 74$).

3.3. Effect of 8-OH-DPAT in adrenalectomized rats

In contrast to its effect in sham-treated controls, bilateral adrenalectomy abolished the stimulatory effect of 8-OH-DPAT (3.5 μmol/kg i.v.). Indeed, a net inhibitory effect was produced as compared to the pretreatment control period (Fig. 3) (percent change in acid after DPAT; 30 min period (mean ± S.E.M.): sham ($n = 3$) $+38 \pm 11$, adrenalectomy ($n = 4$) -21 ± 16, $P < 0.05$). Between 30–60 min after 8-OH-DPAT administration, the disparity between the sham and adrenalectomized animals increased (percent change in acid after DPAT; 60 min period (mean ± S.E.M.): sham ($n = 3$) $+55 \pm 23$, adrenalectomy ($n = 4$) -58 ± 6, $P < 0.01$.

3.4. Effect of close intra-arterial spiperone or idaxozan on 8-OH-DPAT-stimulated gastric acid secretion

Since 8-OH-DPAT can produce actions mediated by both 5-HT_{1A} and α_2-adrenergic systems (Crist and Surprenant, 1987), its effect after close intra-arterial administration of the 5-HT_{1A} antagonist spiperone or selective α_2-adrenoceptor antagonist idazoxan was examined. The doses utilized were effective to reverse 5-HT-induced effects or interact with α_2-adrenoceptors in the rat after systemic administration (Murphy and Zemlan, 1990; Gartside and Cowen, 1990; Harland and Brown, 1988). Close i.a. pretreatment with the two agents had no significant effect on pentagastrin-stimulated acid secretion (Fig. 4A). However, spiperone (2.5 μmol/kg) pretreatment reversed the 8-OH-DPAT (0.35 μmol/kg)-induced stimulation by 60% (Fig. 4B) ($P < 0.05$). In contrast, idazoxan pretreatment resulted in a propensity for an enhanced acid response to 8-OH-DPAT ($P = 0.06$) (Fig. 4B).

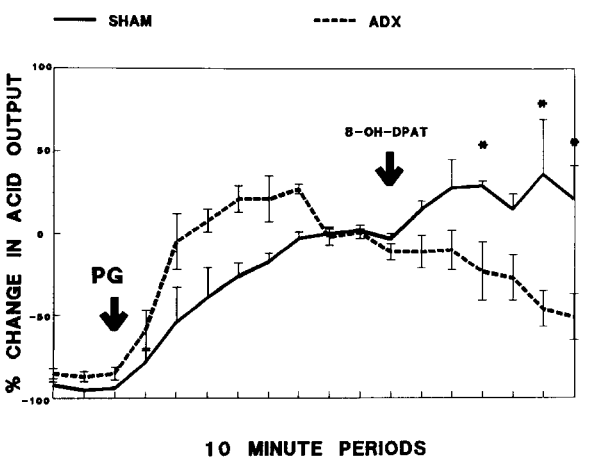

Fig. 3. Comparison of the effect of systemic 8-OH-DPAT (3.5 μmol/kg) on pentagastrin-stimulated gastric acid secretion in acute adrenalectomized ($n = 5$) versus sham-treated ($n = 4$) animals. Pentagastrin (24 μmol/kg i.v.) infusion began after three 10-min basal periods. After an additional nine 10-min periods, the animals were given 8-OH-DPAT. The acid secretory response was measured for six additional 10 min periods. Data are expressed as percent mean ± S.E.M. basal acid output as described in the Materials and methods section for the number of animals indicated above or below each bar. * $P < 0.05$.

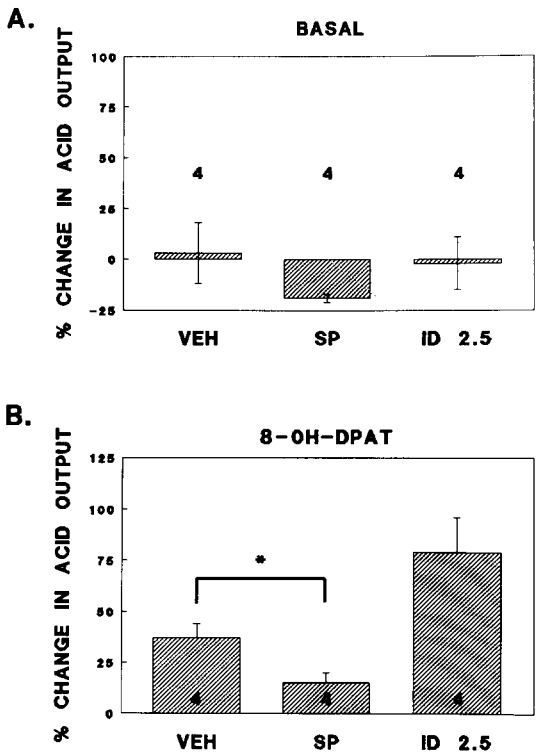

Fig. 4. A: Effect of local gastric infusion of vehicle, spiperone (2.5 μmol/kg) or idazoxan (2.5 μmol/kg) on pentagastrin-stimulated (24 μg/kg/h i.v.) gastric acid secretion (denoted 'BASAL'). Pentagastrin (24 μmol/kg i.v.) infusion began after three 10-min basal periods. After an additional nine 10-min periods, the animals were given either vehicle, spiperone or idazoxan via the splenic artery. Data are expressed as percent change of acid output after close intra-arterial injections as described in the Materials and methods section for the number of animals indicated above each bar. B: Effect of local gastric infusion of vehicle, spiperone (2.5 μmol/kg) or idazoxan (2.5 μmol/kg) on 8-OH-DPAT-induced stimulation of gastric acid secretion. Three 10-min periods after close intra-arterial administration of the tested agents, 8-OH-DPAT was administered intravenously at a 0.35 μmol/kg dose. Data are expressed as percent change of acid output after 8-OH-DPAT administration as described in the Materials and methods section for the number of animals indicated above or within each bar. * $P < 0.05$.

3.5. Effect of pretreatment with the selective κ-opioid antagonist nor-binaltorphimine on 8-OH-DPAT-induced stimulation of gastric acid secretion

Release of adrenal-derived endogenous opiates is a plausible mechanism of 8-OH DPAT-induced stimula-

tion of gastric acid output. κ-Opioid agonists produce stimulatory effects on gastric acid output (Fox and Burks, 1988). However, pretreatment with the selective κ-opioid antagonist *nor*-binaltorphimine (*nor*-BNI) (Takemori et al., 1988) at a dose effective to attenuate the effects of κ-opioid agonists (5 mg/kg s.c. (Alcaraz et al., 1993)), did not reduce the effect of 8-OH-DPAT (3.5 μmol/kg i.v.) to augment gastric acid secretion (percent change in acid after 8-OH-DPAT (mean ± S.E.M.): vehicle pretreatment ($n = 3$) $+81 \pm 37$, *nor*-BNI ($n = 3$) $+149 \pm 40$.

4. Discussion

The principal findings of this study were (1) the disparate effect of systemic 8-OH-DPAT (stimulatory) and 5-HT (inhibitory) on gastric acid secretion, (2) 8-OH-DPAT-induced stimulation of acid output was independent of sympathetic or parasympathetic innervation of the stomach, and (3) the novel stimulatory effect of 8-OH-DPAT required an intact adrenal gland. It is well documented that systemic 8-OH-DPAT stimulates adrenal catecholamine and steroid release (Bagdy et al., 1989; Durcan et al., 1991; Chaouloff and Jeanrenaud, 1987; Chaouloff, 1993), indeed many of the metabolic and cardiovascular effects of 8-OH-DPAT are mediated by the adrenal gland (Mir and Bouhelal, 1990). However, the site of 8-OH DPAT action remains controversial, with evidence supporting both central and direct effects of this compound on the adrenal (Chaouloff, 1993). Accordingly, the site of the spiperone-sensitive receptor mediating the response in this report may be peripheral, central or both. The local route of spiperone administration (close gastric intra-arterial) assures initial drug exposure to the stomach; however, the appearance of spiperone in the central nervous system or other peripheral site(s) cannot be excluded after intra-arterial administration.

Given the adrenal sensitivity of the stimulatory effects of systemic 8-OH-DPAT on gastric function, and the high concentration of 5-HT_{1A} receptors in the rat stomach (Kirchgessner et al., 1993), several possibile mechanisms exist to explain the effects of 8-OH-DPAT: (a) a constitutive adrenal-derived factor and 8-OH-DPAT act concomitantly at the level of the stomach to enhance gastric acid output, (b) 8-OH-DPAT facilitates adrenal release of a factor which is solely responsible for stimulating gastric acid output, or (c) 8-OH-DPAT facilitates adrenal release of a factor which acts concomitantly with 8-OH-DPAT on the stomach to stimulate gastric acid output. Extra-gastric sites of 8-OH-DPAT action are inferred by the ineffectiveness of a high dose of 8-OH-DPAT (0.88 μmol/kg) when administered close interarterially to the gastric circulation (LePard and Stephens Jr., 1994). Adrenal-derived catecholamines or dopamine probably do not solely mediate the stimulatory effects of 8-OH-DPAT on gastric function because each is associated with inhibitory influences on gastric acid output (Burks, 1994). Moreover, epinephrine administration at doses that mimic plasma concentrations reached after cerebroventricular CRF administration does not alter pentagastrin-stimulated gastric acid output (Druge et al., 1989). By contrast, other non-opioid peptides found in the adrenal medulla can activate receptors which produce stimulatory effects on gastric acid output, for example atrial natriuretic factor (Stapelfeldt et al., 1988). Clearly, further work will be required to delineate the mechanism of 8-OH-DPAT-induced stimulation of gastric acid output.

It has been reported that systemic 8-OH-DPAT produces hyperglycemia by activating peripheral α_2-adrenoceptors (hyperglycemia presumably mediated by enhanced adrenal-derived plasma catecholamines) (Chaouloff and Jeanrenaud, 1987). However, in the present report, the α_2-adrenoceptor antagonist idazoxan augmented the effect of 8-OH-DPAT (Fig. 4B) without changing the acid response in the 30 min before 8-OH-DPAT administration. The latter finding is strong evidence that in contrast to the case of adrenal catecholamine release, activation of peripheral α_2-adrenoceptors does not mediate the effect of 8-OH-DPAT on acid output.

Thus, a spiperone-sensitive receptor mediates 8-OH-DPAT's effect on gastric acid output. In addition to being a potent 5-$HT_{1A/2A}$ receptor antagonist, spiperone can also interact with α_1-adrenoceptors or D_2 dopaminergic systems (Leysen, 1985). Antagonism of α_1-adrenoceptors or dopamine D_2 receptors alone results in inhibition (Pascaud et al., 1982) or is ineffective (Glavin, 1989) in modulating gastric acid output. Spiperone pretreatment in this study produced no significant change in acid output as compared to vehicle in the 30 min before 8-OH-DPAT challenge. However, a combined interaction between 5-HT_{1A} receptors and/or adrenergic and/or dopaminergic systems activated by 8-OH-DPAT resulting in enhanced acid cannot be excluded.

Systemic administration of 5-HT_{1A} agonists is associated with inhibition of gastric acid secretion in one report (Farre et al., 1995). However, this study utilized conscious pylorus-ligated rats, a model characterized by elevated acid output, indicative of a stomach under the influence of enhanced vagal tone (Brodie, 1966). Thus, the effects of systemic 5-HT_{1A} agonists may be different on the stomach dependent on the magnitude of vagal tone. Disparities in pharmacological effects dependent on the rat model utilized have been demonstrated before in the study of adrenergic systems (Bernardini et al., 1986). The present investigation suggests that activation of 5-HT_{1A} receptors results in

stimulation of gastric acid secretion in the gastric fistula rat through an adrenal-mediated mechanism.

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