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Characterization of Dopamine Receptor Subtypes Involved in Experimentally Induced Gastric and Duodenal Ulcers in Rats

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Abstract

There are conflicting reports about the role of dopamine in gastric and duodenal ulcers. This investigation was undertaken to characterize the specific subtypes of dopamine receptor involved in gastric and duodenal ulceration.

Administration of dopamine D_1 agonist fenoldopam and dopamine D_2 antagonist sulpiride elicited a significant decrease in acid secretion, total acid output, pepsin output and histamine content in the gastric juice, and reduced ulcer-index values, in pylorus-ligated rats. However, dopamine D_1 receptor antagonist SCH 39166 ((−)-*trans*-6,7,7a,8,9,13b-hexahydro-3-chloro-2-hydroxy-*N*-methyl-5H-benzo (d) naptho - (2,1-b) azepine) and the D_2 receptor agonist quinpirole led to significant augmentation of these parameters compared with respective controls. In the restraint plus water-immersion stress model the score for intraluminal bleeding and the cumulative gastric lesion length was significantly lower for rats treated with fenoldopam and sulpiride. The opposite effects were observed after pretreatment of rats with SCH 39166 and quinpirole. In the cysteamine-induced duodenal ulcer model the mean ulcer area and the score for intensity were significantly lower for fenoldopam and sulpiride and higher for SCH 39166 and quinpirole.

Our data suggest that the dopamine D_1 and D_2 receptors have opposite effects on gastric and duodenal ulcers. Whereas stimulation of dopamine D_1 receptors inhibits the formation of gastric and duodenal ulcers, stimulation of dopamine D_2 receptors has a pro-ulcerogenic effect.

It has been suggested that dopamine imbalance is one of several factors that might contribute to the pathogenesis of gastric and duodenal ulcers (Szabo 1979). Whereas specific dopamine-receptor agonists such as lergotrile, apomorphine, amphetamine and methylphenidate are reported to have anti-ulcer activity, dopamine receptor antagonists such as pimozide, spiperone, metoclopramide and haloperidol have a pro-ulcerogenic effect in several models of gastric and duodenal ulcers (Sikiric et al 1986). However, many reports conflict with this view. Treatment of duodenal ulcer patients with the specific dopamine D_2 receptor antagonists sulpiride and domperidone is beneficial (Lam et al 1979; Weihrauch & Ewe 1981) and these drugs have been successfully used as adjuncts in the therapy of peptic ulcer disease. The different observations after administration of the various drugs cited above might be because of specific dopaminergic receptor subtypes present in the gastrointestinal tract—both central and peripheral—modulating cytoprotective or ulcerogenic effects in erosive gastroduodenal disease. Since the first suggestions of two distinct dopamine receptor subtypes (D_1 and D_2 receptors; Kebabian & Calne 1979), much interest has focused on determining the relative contribution of each subtype to various physiological functions. Sandrock (1981) suggested that dopamine receptors in the gut are of the D_1 subtype, because of the absence of specific [^{3}H]haloperidol binding (D_2 ligand). Competitive binding studies were not performed, however. In the light of the current controversy on the effects of dopaminergic agents on gastric and duodenal ulcers, the objective of this study was to characterize the dopamine receptor subtypes involved in gastric and duodenal ulcers by use of selective dopamine D_1 and D_2 receptor agonists and antagonists.

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Materials and Methods

Wistar albino rats of either sex, 200–220 g, fed standard rat chow diet, were divided into groups of 8–10 animals. The distribution of animals in groups, the sequence of trials and the treatment of each group were randomized. Gastric ulceration was induced by the pylorus ligation and the restraint plus water-immersion models. Animals used for these models were fasted for 36 h before experiments. Coprophagy was prevented by fasting the animals in cages with gratings as floors. Duodenal ulceration was induced by administration of cysteamine. In this model fasting is not required and food and water were freely available until the start of the experiment. After completion of the experiments the animals were killed by anaesthetization with ether; the stomachs were removed, opened along the greater curvature, washed with saline and examined with a 6·4 binocular magnifier. Lesions were assessed by two observers unaware of the experimental protocol.

Drug treatment schedule

The drugs used were fenoldopam (5 and 10 mg kg^{-1}), SCH 39166 ((−)-*trans*-6,7,7a,8,9,13b-hexahydro-3-chloro-2-hydroxy-*N*-methyl-5H-benzo(d)napth-(2,1-b)azepine) (10 and 20 mg kg^{-1}, p.o.), quinpirole (1 and 5 mg kg^{-1}, p.o.) and sulpiride (5 and 10 mg kg^{-1}, p.o.). They were administered as subacute treatment once daily for six consecutive days. On the sixth day animals were subjected to any ulcerogenic procedure 30 min after drug treatment. In the interaction studies, atropine sulphate was administered 1 h before the pyloric ligation.

Pylorus-ligated rats

Rats were anaesthetized with ether and a portion of the abdomen was opened by a small midline incision below the xiphoid process. The pylorus portion of the stomach was lifted and ligated. During this process care was taken to avoid the traction to the pylorus or damage to its blood supply. The stomach was replaced carefully and the abdominal wall closed by interrupted sutures (Shay et al 1945). Nineteen hours after ligation the animals were killed by ether overdose. The stomach was isolated from the body and its contents were collected, measured and centrifuged. The supernatant was stored at 4°C for biochemical analysis, next day, for total acidity (Hawk 1965), pepsin activity (Debnath et al 1974) and histamine levels (Komatsu 1978). Immediately after removal of their contents the stomachs were examined for lesions and these were measured and expressed in terms of an ulcer index calculated as the total ulcerated area divided by the total mucosal area.

Restraint plus water immersion-induced ulcers

The animals were immobilized in a restrainer and immersed to the level of xiphoid process in a water bath maintained at 20 ± 0·5°C (Hayase & Takeuchi 1986). After 16 h restraint the animals were killed by ether overdose. The stomachs were removed and examined for the severity of intraluminal bleeding according to the arbitrary scale (Chiu et al 1984): 0, no blood detectable; 1, thin blood follows the rugae; 2, thick blood follows the rugae; 3, thick blood follows the rugae with blood clots in some areas; 4, extensive coverage of the whole gastric mucosal surface with thick blood.

After removal of the blood by wiping, the intensities of the lesions were scored by measuring their maximum continuous length (mm).

Cysteamine hydrochloride-induced duodenal ulcers (Szabo 1978)

Duodenal ulcers were induced by two administrations of cysteamine hydrochloride (400 mg kg^{-1}, p.o.) in 10% aqueous solution at an interval of 4 h. The drugs under study were administered 30 min before each dose of cysteamine HCl. All animals were killed 24 h after the first dose of cysteamine and the duodena were excised carefully and opened along the antimesenteric side. The mean duodenal ulcer area was determined by measuring the dimensions of the ulcer(s) (mm^2). The duodenal ulcers were scored for intensity on a scale of 0 to 3: 0, no ulcer; 1, superficial mucosal lesion; 2, deep ulcer or transmural necrosis; 3, perforated or penetrated ulcer (into the pancreas or liver). The ulcer index (UI) was calculated from the equation:

$$\begin{aligned} UI = {} & \text{arithmetic mean of the intensity in a group} \\ & + [(\text{number of ulcer-positive animals})/ \\ & (\text{total number of animals})] \times 2 \end{aligned} \quad (1)$$

Expression of results and statistics

The results were analysed statistically by use of Student's unpaired *t*-test as described by Ghosh (1984). Values of *P* less than 5% ($P < 0{\cdot}05$) were considered to be indicative of statistical significance. Data for the incidence of intraluminal bleeding and mortality were analysed statistically by use of Fischer's exact test.

Results

Effect on ulcer index, volume of gastric acid secretion, total acid and pepsin output in pylorus-ligated rats

Pylorus ligation for 19 h induced accumulation of gastric secretory volume and an increase in the total

Table 1. Effect of dopamine-receptor agonists and antagonists on gastric secretion, acid output, pepsin output and intensity of gastric lesions in pylorus-ligated rats.

Treatment ($mg\,kg^{-1} \times$ days)	Volume of gastric contents (mL/100 g)	Total acid output ($\mu equiv.\ h^{-1}$)	Pepsin output ($\mu mol\,h^{-1}$)	Ulcer index
Fenoldopam				
Control (10)	14·31 ± 0·91	58·96 ± 6·60	46·93 ± 1·29	2·67 ± 0·17
5 × 6 (10)	9·83 ± 1·13**	38·20 ± 3·83*	20·56 ± 1·46***	1·28 ± 0·11***
10 × 6 (10)	7·62 ± 0·84***	28·61 ± 1·94***	13·50 ± 1·04***	0·77 ± 0·07***
SCH 39166				
Control (10)	10·33 ± 0·64	54·70 ± 4·44	39·82 ± 2·55	2·34 ± 0·19
10 × 6 (10)	19·13 ± 1·16***	87·89 ± 4·36***	125·58 ± 11·28***	3·55 ± 0·15***
20 × 6 (10)	21·26 ± 0·84***	88·95 ± 3·39***	146·64 ± 7·17***	3·94 ± 0·23***
Quinpirole				
Control (5)	11.80 ± 0·72	64·72 ± 0·83	36·09 ± 1·71	1·93 ± 0·11
1 × 6 (5)	12·50 ± 0·77	93·53 ± 2·12*	63·36 ± 1·38***	3·23 ± 0·14**
5 × 6 (5)	12·10 ± 0·86	95·61 ± 1·99**	61·22 ± 3·50***	3·53 ± 0·22**
Sulpiride				
Control (8)	11·05 ± 1·03	73·86 ± 6·45	33·49 ± 1·44	2·38 ± 0·29
5 × 6 (8)	4·15 ± 0·85***	30·36 ± 1·86***	14·08 ± 1·83***	0·12 ± 0·03***
10 × 6 (8)	6·60 ± 0·60***	34·25 ± 1·36***	15·87 ± 1·90***	0·21 ± 0·01***

Values are means ± standard errors of the means. $*P < 0{\cdot}05$, $**P < 0{\cdot}01$, $***P < 0{\cdot}001$, significantly different from control result. Drugs were administered orally; the values in parentheses denote the number of animals.

acid and pepsin content of the gastric juice (Table 1).

Fenoldopam and sulpiride elicited a dose-dependent decrease in ulcer index (Table 1). Six days treatment with fenoldopam significantly reduced the volume of the gastric contents and total output of acid and pepsin. Similarly, D_2 receptor antagonist sulpiride had significant anti-ulcer effects. Six days pretreatment with sulpiride (5 and $10\,mg\,kg^{-1}$) significantly reduced the volume of the gastric contents, total acid output and the value of the ulcer index, compared with control values. Pepsin output was also found to be significantly reduced but it was observed only after six days pretreatment with a $10\,mg\,kg^{-1}$ dose of sulpiride (Table 1).

SCH 39166 augmented the intensity of gastric ulcers and the volume of the gastric contents, the total output of acid and pepsin, and the ulcer index. Quinpirole (both doses) significantly increased the ulcer index (Table 1), with a concurrent increase in the acid and pepsin output, without altering the volume of gastric content in pylorus-ligated rats.

Effect on gastric juice histamine levels

Histamine levels were $20{\cdot}60 \pm 1{\cdot}2\,\mu g\,mL^{-1}$ in the gastric juice obtained from control untreated rats subjected to 19 h pylorus ligation. Six days pretreatment with fenoldopam ($10\,mg\,kg^{-1}$) or sulpiride ($10\,mg\,kg^{-1}$) elicited a significant decrease in gastric juice histamine levels whereas similar pretreatment with SCH 39166 ($20\,mg\,kg^{-1}$) or quinpirole ($5\,mg\,kg^{-1}$) markedly increased gastric juice histamine levels compared with those of control pylorus-ligated rats. (Table 2).

Interaction with atropine sulphate

Pretreatment of animals with intraperitoneal atropine sulphate ($0{\cdot}5\,mg\,kg^{-1}$) 1 h before pyloric ligation significantly inhibited the formation of gastric lesions compared with control pylorus-ligated rats. As observed earlier in the pyloric ligation model, the D_1 antagonist SCH 39166 and the D_2 agonist quinpirole had significant pro-ulcerogenic effects (Table 1). Pretreatment of rats with atropine not only reversed the pro-ulcerogenic effect of these agents but led to a significant decrease in the severity of gastric lesions after pylorus ligation in rats (Table 3).

Table 2. Effect of specific dopamine-receptor agonists and antagonists on gastric juice histamine levels in pylorus-ligated rats.

Treatment ($mg\,kg^{-1} \times$ days)	Number of animals	Concentration of histamine in gastric juice ($\mu g\,mL^{-1}$)	Percentage of control
Control	8	20·60 ± 1·2	100
Fenoldopam (10 × 6)	10	11·53 ± 0·8*	56
SCH 39166 (20 × 6)	10	43·71 ± 3·8*	212
Quinpirole (5 × 6)	5	34·68 ± 2·7*	168
Sulpiride (10 × 6)	8	3·06 ± 0·2*	15

Values are means ± standard errors of the means. $*P < 0{\cdot}001$, significantly different from control result. Drugs were administered orally.

Table 3. Effect of interaction between atropine (0·5 mg kg^{-1}) and six days pretreatment with dopamine-receptor agonist (SCH 39166) or antagonist (quinpirole) on the ulcer index in pylorus-ligated rats.

Treatment	Ulcer index	
	Pylorus ligation	Atropine + pylorus ligation
Control	2·18 ± 0·11	0·47 ± 0·03**
SCH 39166 (20 mg kg^{-1})	3·94 ± 0·23*	0·39 ± 0·05**
Quinpirole (5 mg kg^{-1})	3·54 ± 0·22*	0·56 ± 0·03**

Values are means ± standard errors of the means of results from eight experiments. *$P < 0·01$, **$P < 0·001$ compared with respective controls.

Effect on gastric lesion length and score for intraluminal bleeding in the restraint plus water-immersion stress model

Animals subjected to restraint plus water-immersion developed not only considerable ulcers but also intraluminal bleeding in the glandular portion of the stomach. Fenoldopam significantly reduced not only the score for intraluminal bleeding but also the gastric lesions in the restraint plus water-immersion stress model. Sulpiride markedly reduced the intraluminal bleeding score but only after six days pretreatment with the higher dose (10 mg kg^{-1}). Gastric lesions however, decreased markedly after six days pretreatment with both doses of sulpiride (Table 4).

SCH 39166 (10 and 20 mg kg^{-1}) significantly increased the intraluminal bleeding and gastric lesion scores (Table 4). Unlike the dopamine D_1 agonist, the dopamine D_2 agonist quinpirole (5 mg kg^{-1}) markedly increased the intraluminal bleeding score and the length of gastric lesions (Table 4). A smaller dose of quinpirole (1 mg kg^{-1}) had no significant effect on either intraluminal bleeding or gastric lesions.

Effect of various dopamine-receptor agonists and antagonists on the cysteamine-induced duodenal ulcer model

Fenoldopam (5 and 10 mg kg^{-1}) significantly reduced the mean ulcer area and the ulcer score when administered for 6 days. Administration of cysteamine resulted in 25% mortality within 24 h. The rats which died had perforated ulcers. Mortality was reduced by treatment of the animals with fenoldopam. Administration of SCH 39166 significantly increased the ulcer score and the mean ulcer area (Table 5). Pretreatment with quinpirole markedly increased the mean ulcer area and the ulcer score (5 mg kg^{-1} dose only). Mortality increased after pretreatment with SCH 39166 and quinpirole. Administration of sulpiride significantly

Table 4. Effect of dopamine-receptor agonists and antagonists on restraint plus water-immersion stress model.

Treatment (mg kg^{-1} × days)	Intraluminal bleeding				Gastric lesions			
	Incidence		Score	Percentage of control	Incidence		Score	Percentage of control
	No.	%			No.	%		
Fenoldopam								
Control	8/8	100	2·71 ± 0·17	100	8/8	100	25·33 ± 1·99	100
5 × 6	7/8	88	1·53 ± 0·14†	56	8/8	100	15·35 ± 1·31†	61
10 × 6	6/8	75	1·13 ± 0·33†	42	8/8	100	12·55 ± 1·37‡	50
SCH 39166								
Control	8/8	100	2·67 ± 0·23	100	8/8	100	33·63 ± 3·11	100
10 × 6	8/8	100	3·86 ± 0·08‡	145	8/8	100	49·63 ± 1·94†	148
20 × 6	8/8	100	3·87 ± 0·09‡	145	8/8	100	54·37 ± 3·08‡	162
Quinpirole								
Control	8/8	100	2·51 ± 0·31	100	8/8	100	32·84 ± 1·98	100
1 × 6	8/8	100	2·93 ± 0·26	117	8/8	100	36·61 ± 4·03	ill
5 × 6	8/8	100	3·61 ± 0·32†	144	8/8	100	47·88 ± 5·11*	148
Sulpiride								
Control	7/7	100	2·20 ± 0·33	100	7/7	100	47·40 ± 4·03	100
5 × 6	7/7	100	1·75 ± 0·22	80	7/7	100	17·43 ± 1·56‡	37
10 × 6	4/7	57	1·29 ± 0·44†	59	7/7	100	18·70 ± 2·61‡	39

*$P < 0·05$, †$P < 0·01$, ‡$P < 0·001$ compared with control. Drugs were administered orally.

Table 5. Effect of dopamine-receptor agonists and antagonists on cysteamine-induced duodenal ulcer model.

Treatment ($mg\,kg^{-1} \times$ days)	Ulcer incidence		Ulcer score	Percentage of control	Mortality		Mean ulcer area (%)	Ulcer index
	No.	%	Score		No.	%		
Fenoldopam								
Control	8/8	100	2·88 ± 0·60	100	2/8	25	16·84 ± 1·17	4·88
5 × 6	8/8	100	1·38 ± 0·17*	48	1/8	13	5·07 ± 0·85***	3·38
10 × 6	8/8	100	1·48 ± 0·19	51	0/8	0	7·98 ± 0·54***	3·48
SCH 39166								
Control	10/10	100	1·97 ± 0·75	100	1/10	10	25·36 ± 1·17	3·97
10 × 6	9/10	90	3·62 ± 0·22*	184	2/10	20	46·64 ± 2·03***	5·42
20 × 6	10/10	100	3·86 ± 0·27*	196	3/10	30	49·85 ± 3·25***	5·86
Quinpirole								
Control	8/8	100	2·45 ± 0·29	100	1/8	13	30·38 ± 2·87	4·45
1 × 6	8/8	100	2·98 ± 0·36	122	1/8	13	50·58 ± 4·01**	4·98
5 × 6	8/8	100	3·43 ± 0·26*	140	2/8	25	53·62 ± 6·11**	5·43
Sulpiride								
Control	8/8	100	1·43 ± 0·28	100	2/8	25	22·31 ± 2·01	3·43
5 × 6	4/8	50	0·50 ± 0·25*	38	1/8	13	4·77 ± 2·50***	1·50
10 × 6	3/7	43	0·66 ± 0·30	46	1/7	14	6·06 ± 4·14**	1·51

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with control. Drugs were administered orally.

reduced the ulcer score (except $10\,mg\,kg^{-1}$ for 6 days) and the mean ulcer area (Table 5). A decrease in mortality was also observed after sulpiride pretreatment.

Discussion

These results indicate that dopamine D_1 and D_2 receptors have opposing roles in peptic ulceration. Whereas an anti-ulcer effect was observed with the specific dopamine D_1 receptor agonist fenoldopam and the selective dopamine D_2 receptor antagonist, sulpiride, a pro-ulcer effect was observed for SCH 39166, a selective D_1 antagonist, and quinpirole, a selective D_2 receptor agonist. Similar results have been reported with these and other drugs. Glavin (1989) reported that the D_1 antagonist SCH 23390 worsened experimentally induced gastric lesions and augmented gastric acid secretion. Parmar et al (1984) reported that bromocriptine, another D_2 receptor agonist, had a pro-ulcerogenic effect on gastric lesions induced with NSAIDs (aspirin and phenylbutazone) and reserpine.

In the pylorus ligation model it has been proposed that the digestive effect of accumulated gastric juice and interference with gastric blood circulation are responsible for the induction of ulcers (Brodie 1966). Thus, the gastroprotective and pro-ulcerogenic effects of dopamine receptor modulators could be partly a result of their effects on the volume of the gastric contents and the total acid and pepsin output of the gastric juice. Pyloric ligation induces a substantial release of histamine from the gastric mucosa with simultaneous elevation in the rate of histamine formation, events which seem to be associated with an increase in free histamine levels in the gastric juice (Johansson et al 1972). In the current experiments gastric juice histamine levels were reduced by fenoldopam and sulpiride, which had anti-ulcer activity, and increased by SCH 39166 and quinpirole, which were found to be pro-ulcerogenic drugs. Thus, it seems that activation of dopamine D_2 receptors stimulates the release of histamine whereas activation of D_1 receptors inhibits release of histamine.

The role of the autonomic nervous system in stress-induced gastric pathology has been widely documented (Glavin 1980; Maeda-Hagiwara et al 1986). Analysis of the factors which regulate gastrointestinal dynamics and stress-ulcerogenesis has revealed a facilitatory cholinergic involvement (Henke 1983). Atropine pretreatment is known to prevent the mechanical rubbing of the mucosa which results from inhibition of gastric motility, distension of the stomach, and the increase in gastric mucosal blood flow seen after exposure to water immersion (Takeuchi et al 1976). In the current study also atropine was found to significantly reverse the gastric mucosal damage induced by the D_1 antagonist SCH 39166 and the D_2 agonist quinpirole after pylorus ligation. The involvement of a cholinergic mechanism might be either at the central level, interfering with the vagal outflow, or peripherally, at the muscarinic receptor level.

Our observations indicate a potential gastrointestinal pharmacotherapeutic target in each dopa-

mine receptor subtype. The results of the study provide a rationale for the clinical effectiveness of selective D_1 receptor agonists and dopamine D_2 receptor antagonists as adjuncts in the treatment of peptic ulcer disease. Fenoldopam, a potent renal vasodilator, is one of the novel and highly selective, orally active, dopamine D_1 receptor agonists (Lokhandwala 1987) developed for clinical use in the treatment of hypertension and ischaemic renal disease. Because fenoldopam is mainly used clinically as an antihypertensive agent (Lokhandwala 1987), it might be suggested that fenoldopam can be safely used for patients with gastroduodenal ulcers.

Dopamine D_1 receptor antagonists such as haloperidol, SCH 23390, SCH 39166 and butaclamol are commonly used as antipsychotic agents. Similarly, dopamine D_2 receptor agonists such as bromocriptine are commonly used clinically to treat Parkinsonism. Both these groups of drugs have pro-ulcerogenic activity and so should be used cautiously in patients with a potential threat of gastroduodenal disease.

In conclusion, the results of this study strengthen the hypothesis that dopamine D_1 and D_2 receptors have opposing effects on peptic ulceration. Whereas dopamine D_1 receptor stimulation can inhibit the formation of gastric and duodenal ulcers, stimulation of dopamine D_2 receptors has a pro-ulcerogenic effect. These results also indicate that in addition to histamine-induced gastric acid secretion, cholinergic mechanisms are also involved in alteration of gastric acid secretion by dopamine.

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