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The effect of dopamine on rat gastric motility

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Summary: The inhibitory mechanism of dopamine (DA) on rat gastric motility was investigated in association with DA receptors. Gastric movement was assessed according to the method of Jacoby et al and was expressed with the system of Ludwick et al. (1968). DA inhibited gastric movement in both the corpus and antrum in a dose-dependent manner. Domperidone, a specific antagonist of DA_2 receptor, suppressed DA-induced inhibition of gastric movement in a dose-dependent manner. SCH23390, a specific antagonist of DA_1 receptor did not affect DA-induced inhibition of gastric movement. LY171555, a specific agonist of DA_2 receptor, inhibited gastric movement in both the corpus and antrum in a dose-dependent manner. SKF38393, a specific agonist of DA_1 receptor, did not affect gastric movement. These results indicate that DA plays an important role in the inhibitory regulation of gastric motility, through DA_2 receptor but not DA_1 receptor. *Gastroenterol Jpn 1992;27:482-487.*

Key words: *gastric motility; dopamine; dopamine receptor.*

Introduction

Neurotransmitter dopamine (DA) plays important roles in the peripheral organs[1,2]. As domperidone (Dmp) particularly suppresses DA's effect on gastric motility, it is suspected that a specific DA receptor exists in the stomach[3].

There are many views regarding the mechanism of the effect of DA. According to some investigators, it is mediated by α- or β-adrenergic receptors, while others suggest that it is mediated by specific DA receptors. In a previous study, the effect of DA was investigated on gastric motility in vitro and in vivo, and it was concluded that DA suppressed the motility of rat stomach. It is possible that the release of acetylcholine (Ach) from nerve endings is suppressed by DA, mediated by specific DA receptors on cholinergic postganglionic nerves present in the gastric wall[4].

Materials and Methods

1. Animals

Male Wistar strain rats weighing 220–250 g were used. Rats were housed in wire-bottomed cages and were on a 12 hr. light-dark cycle. They were randomly grouped for experimentation, and each group consisted of 7 rats. Food was withheld the night before each experiment but they had free access to water.

2. Chemicals

The following chemicals were prepared: dopamine hydrochrolide (DA, Kyowa Hakko Co., Tokyo), domperidone (Dmp, DA_2 antagonist, Kyowa Hakko Co.), SCH23390 (SCH, DA_1 antagonist, Schering, Berlin), LY171555 (LY, DA_2 agonist, Eli Lilly and Co., Indianapolis), SKF38393 (SKF, DA_1 agonist, Smith Kline & French Laboratories, Philadelphia). DA was administered

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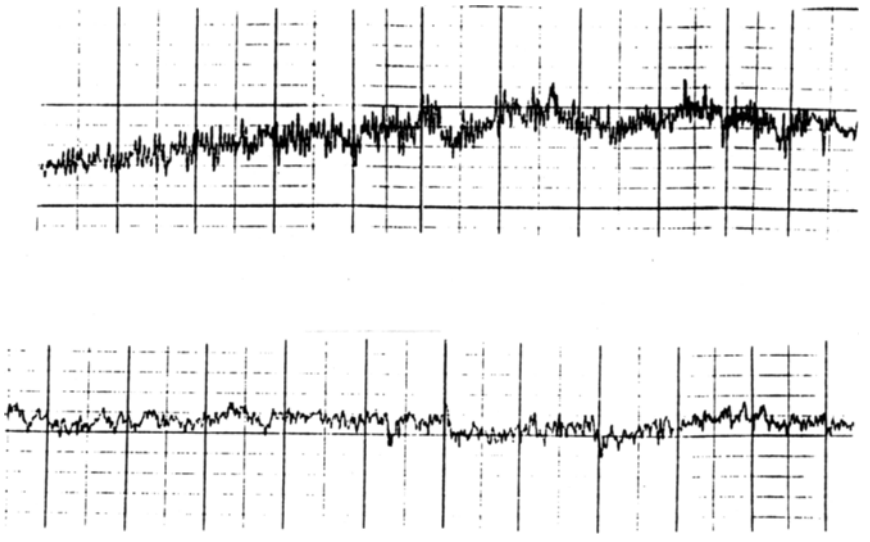

Figure 1. Records of rat gastric movement in the gastric corpus (upper) and antrum (lower).

Table 1. Definition of motility index (Ludwick et al.[6])

Milligrams force per level	~100	100~200	200~400	400~800	800~
Arbitrary value	1	2	4	8	16
Number of contractions per level	L_1	L_2	L_3	L_4	L_5
Period of Contractions observed			N (min)		

$$\text{Motility Index}=\frac{1\times L_1+2\times L_2+4\times L_3+8\times L_4+16\times L_5}{N}$$

intravenously (via jugular vein) for an hour at a rate of 1~50 μg/kg/min. Dmp (0.5~5.0 mg/kg), SCH (0.5~5.0 mg/kg), LY (1~1000 μg/kg) and SKF (1~1000 μg/kg) were administered intravenously (via caudal vein) by single injection.

3. Determination of the gastric motility index

Gastric motility was assessed according to the method of Jacoby et al[5]. A silicon-resin-covered waterproof strain gauge (Showa Sokki Co., Tokyo) was fixed in the anterior wall of the gastric corpus and antrum, and gastric movements were recorded with a polycorder (Medical Corder PMP3004, Nihon Kohden Co., Tokyo) (**Figure 1**). The data obtained were converted into gastric motility index values using the scoring system of Ludwick et al[6] (**Table 1**).

4. Data analysis

Data were expressed as means± SD. Statistical analysis was performed using multiple comparison (Dunnet). Dose dependency of drugs were judged using Spearman rank correlation coefficient. $P<0.05$ was considered statistically significant.

Results

1. Effect of DA on the gastric motility index

DA decreased the gastric motility index in a dose-dependent manner in both the gastric corpus ($P<0.01$) and gastric antrum ($P<0.01$) as shown in **Figure 2**. At a dose of 1 μg/kg/min., there was a significant decrease (21.7% in the corpus and 15.7% in the antrum) from pretreatment values. At a dose of 10 μg/kg/min., the gastric motility indices were 1.1±0.2 in the corpus and 2.0±0.3 in the antrum. After 50 μg/kg/min DA was administered, almost complete gastric stasis was observed with gastric motility indices of 0.3±0.06

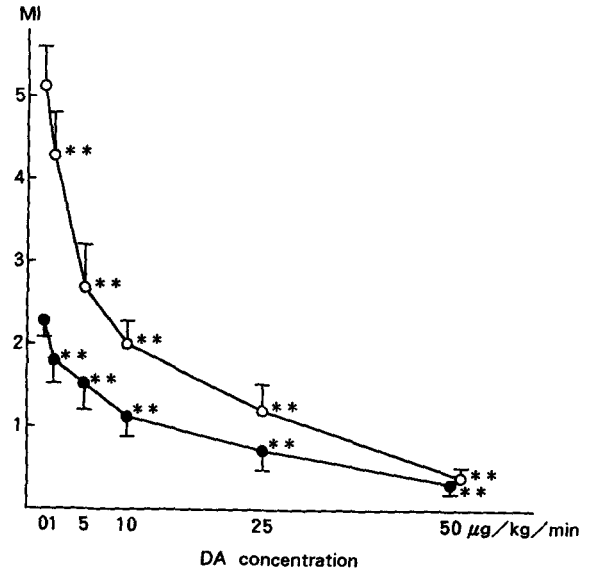

Figure 2. Inhibitory effect of dopamine on gastric motility. Dopamine (DA) reduced gastric motility index (MI) in a dose-dependent manner in the gastric corpus and gastric antrum. Solid dots represent the gastric corpus and circles represent gastric antrum. Each value is the mean±SD for 7 animals. Each **(P<0.01) shows a significant difference compared with each initial value.

Table 2. Effect of domperidone on dopamine-induced inhibition of rat gastric motility

DA	Dmp	Motility Index C	Motility Index A
0	0	2.3±0.2	5.1±0.5
10	0	1.1±0.2	2.0±0.3
10	0.5	2.4±0.4**	5.7±0.6**
10	1.0	3.2±0.3**	7.2±0.8**
10	2.0	4.6±0.7**	9.8±1.2**
10	5.0	5.3±0.6**	11.2±1.6**

DA: dopamine (μg/kg/min).
Dmp: domperidone (mg/kg).
C: gastric corpus, A: gastric antrum.
**: significant difference from basal value (DA 10 μg/kg/min and Dmp 0 mg/kg) (P<0.01).
(mean±SD). n=7.

in the corpus and of 0.4±0.09 in the antrum (**Figure 2**).

2. Effect of Dmp on DA-induced inhibition of the gastric motility index

When the gastric motility index fell significantly after DA treatment at 10 μg/kg/min., the animals were treated with 0.5 mg/kg of Dmp. This resulted in an increase of the gastric motility index to levels similar to the levels before DA treatment: 2.4±0.4 in the corpus and 5.7±0.6 in the antrum. With a larger dose of Dmp, the gastric motility index also increased at both sites. At a Dmp dose of 5.0 mg/kg, the indices were approximately twice as large as before DA treatment. Thus Dmp increased gastric motility index in a dose-dependent manner in both the gastric corpus (P<0.01) and the gastric antrum (P<0.01). No differences were noted at either site in response to Dmp treatment (**Table 2**).

Table 3. Effect of SCH23390 on dopamine-induced inhibition of rat gastric motility

DA	SCH	Motility Index C	Motility Index A
0	0	2.3±0.2	5.1±0.5
10	0	1.1±0.2	2.0±0.3
10	0.5	1.3±0.2	2.2±0.4
10	1.0	1.3±0.2	2.3±0.3
10	2.0	1.3±0.2	2.5±0.4
10	5.0	1.4±0.3	2.4±0.4

DA: dopamine (μg/kg/min).
SCH: SCH23390 (mg/kg).
C: gastric corpus. A: gastric antrum.
(mean±SD) n=7.

3. Effect of SCH on DA-induced inhibition of gastric motility index

After DA treatment at 10 μg/kg/min., SCH was given at doses of 0.5, 1.0, 2.0, 5.0 mg/kg. The gastric motility index after administration of SCH did not change significantly, recording 1.3~1.4 in the gastric corpus and 2.2~2.5 in the gastric antrum. There was no effect on gastric motility index at either site in response to SCH treatment (**Table 3**).

4. Effect of LY on the gastric motiliy index

LY decreased the gastric motility index in a dose dependent manner both in the gastric corpus (P<0.01) and in the gastric antrum (P<0.01). At an LY dose of 5 μg/kg there was a significant decrease from each pretreatment value at both sites. At a dose of 50 μg/kg, the gastric motility

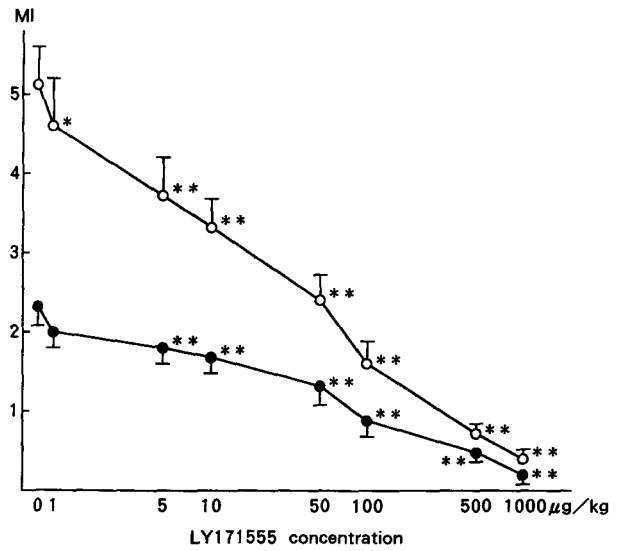

Figure 3. Dose response curves of LY171555 induced gastric motility index (MI). Solid dots represent the gastric corpus and circles represent the gastric antrum. Each value is the mean±SD for 7 animals. Each *(P<0.05) and **(P<0.01) shows a significant difference compared with each initial value.

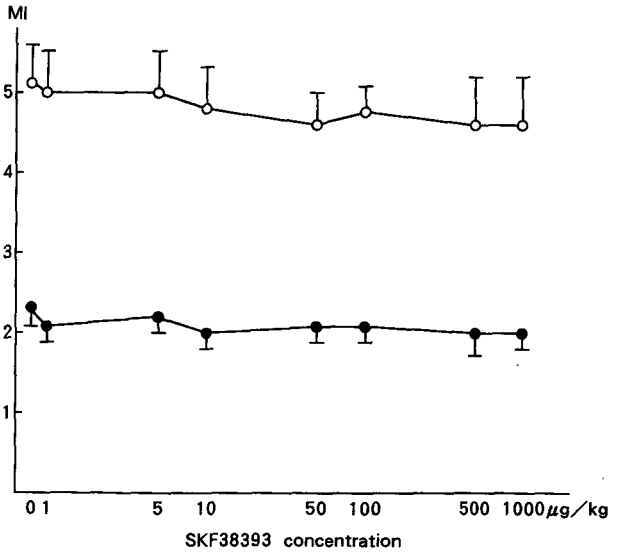

Figure 4. Effect of SKF38393 on gastric motility index (MI). Solid dots represent the gastric corpus and open circles represent the gastric antrum. Each value is the mean±SD for 7 animals.

indices were 1.3±0.2 at body and 2.4±0.3 at antrum. Almost complete gastric stasis was observed at doses above 500 μg/kg of LY (**Figure 3**).

5. Effect of SKF on the gastric motility index

SKF did not affect gastric movement at either site. The gastric motility index was 2.3±0.2 in the gastric corpus and 5.1±0.5 in the gastric antrum before SKF administration. After SKF administration the change of gastric motility index was insignificant (**Figure 4**).

Discussion

With advances in the study of DA, it has been revealed that DA works as a neurotransmitter in the peripheral tissue as well as in the central nervous system (CNS)[1,2]. Studies on specific DA receptors in the CNS and their classification have been increasing[7]. In the periphery some investigators have found that receptors specific to DA are present not only in blood vessels of the kidney and mesentery[8-10], but also in the pancreas[11] and esophagus[12,13]. DA subtypes are classified as DA_1 and DA_2 receptors in the periphery[14]. It is thought that D_1 and D_2 receptors in the CNS are similar to DA_1 and DA_2 receptors in the periphery. However some discrepancies have been reported between the DA receptors in the periphery and in the CNS[14]. Gastric mucosal level of DA, as high as 11.6±0.9 ng/g have been reported and it has some important effects on the stomach[15]. DA reduces gastric acid secretion[16], and increases gastric mucosal blood flow[17] and prostaglandin (PG) E_2 content in gastric mucosa[18]. Now DA is recognized as a potent agent against stress ulcer[19-21].

Beck et al[22,23] and other authors[14,24] found that DA suppresses gastric movements in dogs under stimulation with pentagastrin, and that the effect of DA is not affected by antagonists to α- or β-adrenergic receptors, although it is antagonized by DA-receptor antagonists such as Dmp and cisflupenthixol. Valenzuela et al[25] reported that DA reduced intragastric pressure in a dose-dependent manner, and that this effect was antagonized by Dmp. Fujii et al[26] and Shuto et al[27] suggested that Dmp affected the nerve plexus in the gastric wall. These studies suggest that the stomach has DA-specific receptors that are capable of suppressing gastric motility. In a previous paper from out insti-

tutions[28] it was suggested that postgaglionic cholinergic nerves in the gastric wall have receptors specific to DA and that the action of DA is mediated by these receptors.

In the present study DA suppressed gastric movement dose-dependently both in the gastric corpus and gastric antrum. DA at a dose of 50 μg/kg/min caused almost complete gastric stasis: 0.3±0.1 in the gastric corpus and 0.4±0.1 in the antrum. This suppressing effect of DA on gastric movement was antagonized competitively by Dmp which appears to be a specific antagonist for DA_2 receptor[24]. However the effect of DA on gastric movement was not affected by SCH, which is recognized as a specific antagonist for DA_1 receptor[29,30]. It is suspected that the suppressing effect of DA on gastric movement in the gastric corpus and gastric antrum is mediated via specific DA_2 receptor and there seems to be little effect from specific DA_1 receptor.

Next, the effect of LY on gastric movement was examined. LY is considered a specific DA_2 receptor agonist[31]. LY reduced gastric motility index in a dose-dependent manner both in the gastric body and gastric antrum. The effect of LY on gastric movement is not exactly similar to the effect of DA. Although LY is a specific DA_2 receptor agonist, the binding affinity for the DA_2 receptor of LY does not resemble that for DA. SKF, which is a specific DA_1 receptor agonist[32], did not affect gastric movement. It is thought that a specific DA_1 receptor has little effect on gastric movement. The effect of an agonist on an organ depends upon affinity, intrinsic activity and the number of receptors[33].

The interactions between gastric movement and gastric acid secretion, gastric mucosal blood flow and PGE_2 content are important. Increased gastric movement is considered to reduce gastric mucosal blood flow, though it has not been known how blood flow affected gastric motility. DA increases gastric mucosal blood flow[17,18], however increased blood flow has not been linked to gastric motility.

DA increases PGE_2 content in gastric mucosa[18]. PGE_2 has been considered to decrease gastric circular muscular tone and to increase gastric longitudinal muscular tone. If so PGE_2 would reduce gastric movement because circular muscle predonnates over longitudinal muscle in the gastric wall. It is not clear whether gastric movement supression is through reduction of increased endogenous PGE_2 content in gastric mucosa with DA administration or through direct action of DA.

DA is reported to suppress Ach release in gastric wall, and decrease of Ach release causes a decrease of both gastric movement and gastric acid secretion. However it is not clear how reduced gastric acid secretion affects gastric movement.

There are many unsolved issues concerning the association between gastric movement and gastric acid secretion, gastric mucosal blood flow and PGE_2 content.

In conclusion, DA appears to reduce rat gastric movement in a dose-dependent manner via specific DA_2 receptors. However it does not appear that DA_1 receptors have much effect on gastric movement.

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