대한생리학회지 : 제20권 제 1 호

Effect of Dopamine on Propagation and Frequency of Slow Wave in Cat Isolated Stomach Muscle*

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=국문초록=

적출한 고양이 위(胃) 근절편에서 서파의 전파 및 발생빈도에 미치는 Dopamine의 영향

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조양혁 · 심상수 · 김명석 · 김정진 · 최 현

위(胃) 전기활동(서파)의 전파(傳播) 및 발생빈도에 미치는 dopamine의 영향을 구명하기 위하여 145마리의 고양이를 사용하여 다음의 실험을 실시하였다. 위의 복측부분을 적출하여 종주근의 주행방향으로 대만쪽에서 길이 5 cm, 폭 1.2 cm인 근절편을 만들어, 95% O_2와 5% CO_2가 계속 공급되는 Krebs-Ringer 용액(pH 7.4, 온도 36±0.5°C)내에 두고 가느다란 은선이 들어있는 모세관 전극(Ag-AgCl)을 사용하여 단극성으로 서파를 기록하였다. dopamine의 첨가후 위서파의 전파방향은 첨가한 농도에 비례하여 전환이 많아졌으나, dopamine의 영향은 domperidone의 전처치로 유의하게 억제되었다. dopamine은 또한 농도가 증가함에 따라 불규칙한 위서파의 발생빈도를 증가시켰으며 이 현상은 domperidone 및 phentolamine에 의하여 억제되었으나 propranolol, hexamethonium 및 tetrodotoxin에 의하여는 억제되지 않았다. 그러므로 dopamine은 고양이 위에서 dopamine receptor와 일부 α-adrenergic receptor에 작용하여 이상적(異常的)서파를 발생시킨다고 사료된다.

INTRODUCTION

Dopamine was proposed as a possible neurotransmitter for gastric relaxation (Valenzuela, 1976) because of its ability to inhibit gastric motility in guinea-pigs (Van Nueten & Janssen, 1980), in dogs (Bech & Hovendal, 1982) and in man (Lanfranchi et al., 1978; Thompson & de Carle, 1982). Moreover, the discovery of the fact that domperidone, a specific peripheral dopamine antagonist (Baudry et al., 1979; Laduron & Leysen, 1979), completely reverses the inhibitory effect of dopamine on gastric motility and gastric emptying (Jacobs et al., 1981) suggested the presence of dopamine receptors in the stomach (Van Nueten & Janssen, 1978). The inhibitory effect of dopamine was not blocked by α- and β-receptors antagonists but by domperidone and metoclopramide, two known dopaminergic antagonists (Valenzuela, 1976; Schuurkes & Van Nueten, 1981 & 1984; Bech & Hovendal, 1982).

In conscious dogs, Lee et al. (1985) recen-

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tly observed that dopamine and dopamine agonists produced retching and vomiting. Gastric dysrhythmia regularly occurred in these dogs during bouts of vomiting. Similar observation was made in man (Lanfranchi et al., 1978). The occurrence of these symptoms and gastric dysrhythmia was prevented by intravenous administration of domperidone (Chey et al., 1983; Lee et al., 1985).

In the present study, we investigated whether dopamine produced gastric myoelectrical abnormalities by an action on dopamine receptors in isolated stomach muscle strips of cats.

MATERIALS AND METHODS

One hundred forty-five adult cats of either sex, weighing between 2.1 and 3.0 kg, were anesthetized with 20% urethan (5 ml/kg, i.p.). The whole stomach was removed and the mucous membrane was peeled off from the specimen. The muscle strip including lower portion of corpus and antrum (5 cm in length, 1.2 cm in width) was excised parallel to the greater curvature from the ventral part of the stomach. The muscle strip was pinned down on the paraffin covering the bottom of a recording chamber (40 ml of capacity) containing Krebs-Ringer solution. The solution of chamber was kept at 36±0.5°C and gassed with 95% O_2 and 5% CO_2, giving a pH of 7.4.

After stabilization of muscle strip for 30 min, the slow waves (SWs) of gastric electrical activity were recorded with four capillary electrodes of which two (C_1, C_2) were placed on the corporal part and the other two (A_1, A_2) were on the antral part of the muscle strip. Each electrode was a glass capillary containing a silver chloride wire (Ag-AgCl electrode) and was apart 1 cm from each other. The SWs were recorded with a pen recorder (San-ei, Type 8S) through the preamplifier (San-ei, Type 1205C, Japan).

Changes in the propagative direction and frequency of gastric SWs of the muscle strip were measured for 20 min after adding dopamine (IMS) and/or domperidone (Janssen). For the control period, acetic acid, solvent for dissolution of domperidone, was added. Phentolamine (CIBA), propranolol (Ayerst), tetrodotoxin (Sigma), hexamethonium (Sigma) dissolved in saline were used. These antagonistic drugs were added 5 min before dopamine addition.

All results obtained were represented as mean±SEM and analyzed statistically by χ^2, Fisher or Student's t test, or regression analysis. The level of significance was set at 5%.

RESULTS

In almost all of muscle strips, typical gastric SWs were recorded from the corpus and the antrum. In the control study, the SWs occurred at a frequency of 4.05±0.13 cycles per min (cpm) and regularly propagated from the corpus to the antrum. Each range of the SW frequency was from 3.3—3.8/min to 4.2—4.9/min with a coefficient of variation of 3.5 (1—6)%.

After addition of dopamine, the propagation of the SW became irregular, as if pacemaker of the SW had shifted to the distal part of corpus (C_2 electrode) or to the antrum (A_1) from the mid-corpus (C_1) (Figure 1). Dopamine, at concentrations of 10^{-6}, 3×10^{-6}, 10^{-5} and 3×10^{-5} M concentration-dependently increased the occurrence of the irregular propagation in the SWs ($\chi^2=$

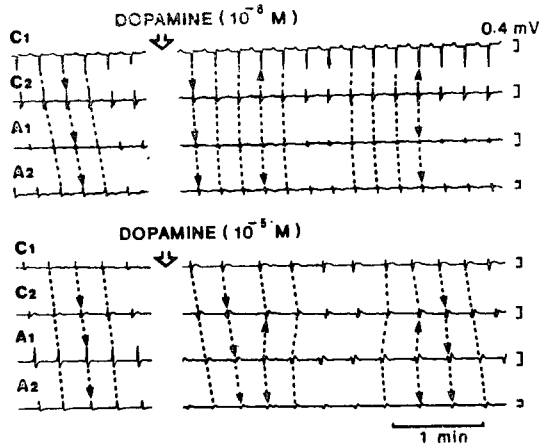

Fig. 1. The electrical recordings after dopamine addition show shifting pacemaker of gastric SW. The broken lines indicate the directions of propagation.

Table 1. Occurrence of irregular propagation in gastric SW in response to addition of dopamine with or without pretreatment with domperidone

Treatments	Dopamine (M)			
	10^{-6} (%)	3×10^{-6} (%)	10^{-5} (%)	3×10^{-5} (%)
DA	4/13 (31)	7/13 (54)	8/11 (73)	10/10 (100)
DMP+DA	0/ 8 (0)	2/13* (15)	4/13* (31)	9/10 (90)

DA: Dopamine, DMP: Domperidone(10^{-5} M)
* : Significantly different from dopamine group ($p<0.05$, Fisher test).

12.21, df=3, $p<0.01$) (Table 1). As shown in Table 1, domperidone (10^{-5} M) significantly decreased the occurrence of this irregularity in the SWs, but the effect of dopamine at a high concentration (3×10^{-5} M) was hardly inhibited by domperidone. Phentolamine (10^{-5} M), propranolol (10^{-5} M), tetrodotoxin (10^{-7} M) and hexamethonium (10^{-5} M) did not influenced the dopamine-induced irregularity (Table 2).

Total duration of the irregular propagation

Table 2. Occurrence of irregular propagation in gastric SW in response to addition of dopamine with pretreatment of various antagonists

Treatments	Occurrence	(%)
DA	8/11	(73)
PL+DA	5/ 8	(63)
PPR+DA	4/ 6	(67)
TTX+DA	6/10	(60)
HM+DA	6/11	(54)

DA: Dopamine (10^{-5} M), PL: Phentolamine (10^{-5} M), PPR: Propranolol (10^{-5} M), TTX: Tetrodotoxin (10^{-7} M), HM: Hexamethonium (10^{-5} M)

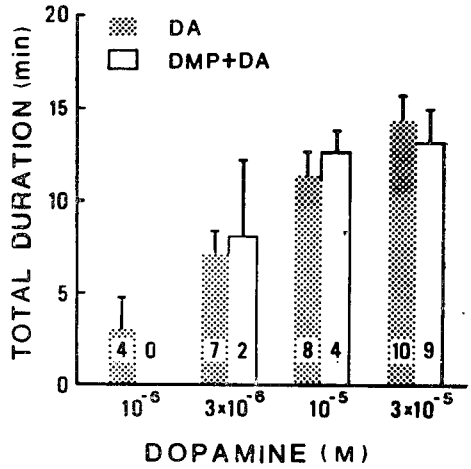

Fig. 2. Total duration of the irregular propagation in gastric SW by dopamine with or without pretreatment of domperidone during the 20 min recording period.
DA: Dopamine, DMP: Domperidone.
Numerals printed in each bar represent a number of strips propagated irregulary.

occurred by dopamine increased in a concentration-dependent manner by showing a positive correlation ($r=0.70$, df=27, $p<0.01$). The duration was not shortened by domperidone (Figure 2).

The addition of dopamine decreased and/or increased the SW frequency. Although the amplitude of the SW was not distinguishably

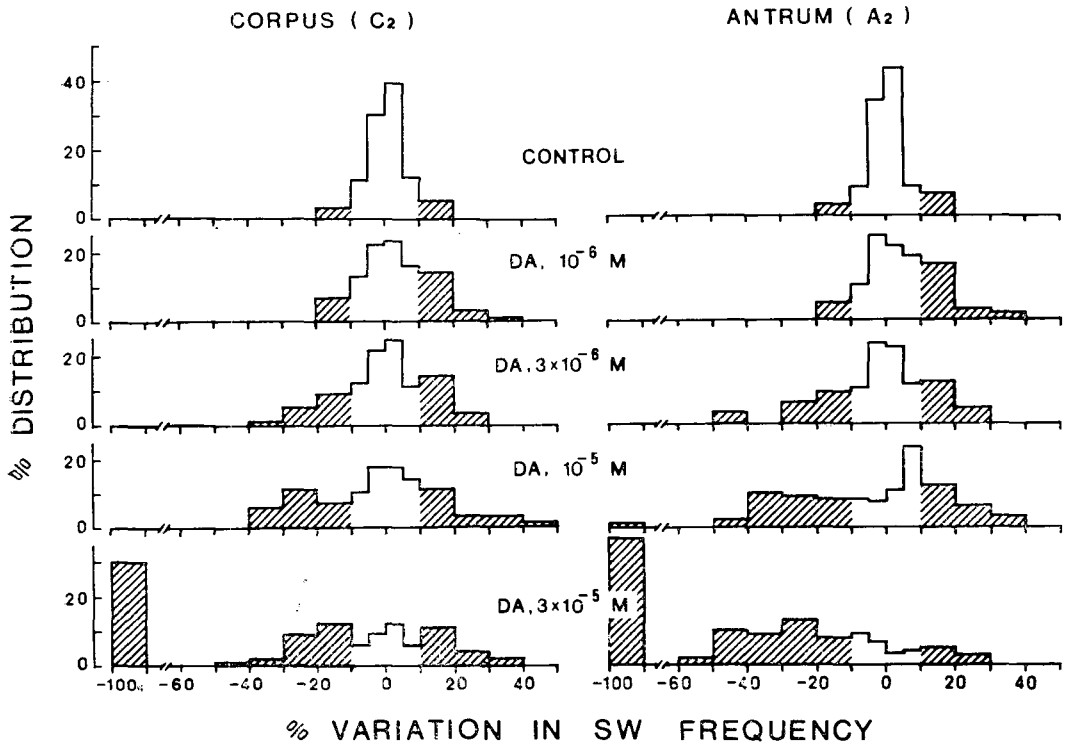

Fig. 3. Distributing pattern of percent variation in SW frequency in response to various concentrations of dopamine.
DA: Dopamine.
Dashed area indicates the percent variation of 10% or more.

altered by dopamine, in some cases the amplitude decreased in the antrum when the retropropagation occurred but it tended to increase during the period of tachyarrhythmia. After addition of various concentrations of dopamine, difference between mean control frequency and the SW frequency obtained at every min during the 20 min experimental period was expressed as percent to mean control frequency. The mean control frequency was obtained for 3 min during the control peroid before testing additions. Dopamine-induced percent variation of SW frequency was increased in proportion to its concentration added ($r=0.54$, $df=898$, $p<0.01$) (Figure 3). The variation in SW frequency induced by dopamine (10^{-5} M) was significantly decreased by the pretreatment with domperidone (10^{-5} M) or phentolamine (10^{-5} M). However, the pretreatment with propranolol (10^{-5} M), tetrodotoxin (10^{-7} M) or hexamethonium (10^{-5} M) did not show any significant effect on the variation induced by dopamine (Table 3). Domperidone, phentolamine, propranolol, tetrodotoxin or hexamethonium alone did not affect the variation.

DISCUSSION

The effect of dopamine on the gastric SW

Table 3. Effects of pretreatments with various antagonists on percent variation in gastric SW frequency

Treatments	% variation		(n)	Treatments	% variation		(n)
	C_2	A_2			C_2	A_2	
Control	3.55±0.23	3.38±0.22	(280)	DA	10.76±0.76*	14.91±0.96	(180)*
DM	2.94±0.27	2.89±0.28	(100)	DM+DA	6.70±0.67†	8.08±0.85	(180)†
PL	2.78±0.34	3.04±0.35	(60)	PL+DA	5.97±0.47†	5.76±0.45	(160)†
PPR	3.72±0.43	3.50±0.43	(60)	PPR+DA	10.29±0.73	13.68±0.81	(80)
TTX	3.58±0.33	3.42±0.28	(60)	TTX+DA	9.93±0.64	12.68±0.98	(160)
HM	2.76±0.27	2.81±0.30	(80)	HM+DA	12.95±1.33	14.95±1.64	(220)

Control: Acetic acid (10^{-5} M), DA: Dopamine (10^{-5} M), DM: Domperidone (10^{-5} M), PL: Phentolamine (10^{-5} M), PPR: Propranolol (10^{-5} M), TTX: Tetrodotoxin (10^{-7} M), HM: Hexamethonium (10^{-5} M).
n: Values were obtained from multiplying the 20 minutes of recording period by the number of samples.
* Significantly different from control group ($p<0.001$, Student's t test)
† Significantly different from dopamine group ($p<0.001$, Student's t test)

frequency has already been evaluated by Lanfranchi et al. (1978). They observed that dopamine changed the frequency of SW and its interval irregularly.

In the present study the gastric SW recorded from the muscle strips of isolated cat stomach aborally propagated from the corpus to the antrum in the control state. Its average SW frequency was 4.05 (3.3—4.9) cpm which coincides well with the result of Kim et al. (1985). By the addition of dopamine, the SW irregularly propagated and showed a dysrhythmia, that is, the retropropagation occurred and its frequency changed into 3 cpm or less and/or 5 cpm or more. These irregularly propagated SW responses to dopamine were significantly inhibited by domperidone, a specific peripheral dopamine antagonist, not by phentolamine, propranolol, tetrodotoxin and hexamethonium.

In conscious dogs with implanted electrodes in the stomach, a myoelectric abnormality of the antrum was occurred prior to or at the onset of retching and/or vomiting induced by dopamine or dopamine agonists, such as apomorphine, morphine or copper sulfate (Lee et al., 1985). The myoelectric abnormality was prevented by domperidone treatment with simultaneous cessation of retching and/or vomiting.

The present study showed that the percent variation of SW frequency and retropropagation of SW produced by dopamine subsided following domperidone pretreatment. It is thus concluded that dopamine produces abnormal electrical activities and domperidone plays a antagonistic role to dopamine preventing production of abnormal electrical activities in cats.

The changes of the SW frequency after dopamine addition were variable. The tachygastric, bradygastric or tachyarrhythmic pattern was produced and the intervals of SWs were varied by dopamine. Gastric contraction has been already proven to be paced and directed by the SW (Carlson et al., 1966; Kelly & Code, 1971) and the antral phasic contraction was recently reported to disappear during the period of gastric dysrhythmia induced by epinephrine infusion in dogs (You & Chey, 1984). Chey and his colleagues (1984) have observed that gastric dysrhythmia was

detected in patients with symptoms of severe nausea, vomiting, epigastric bloating and pain. It is known that myoelectric abnormalities of the lower part of stomach may play a role in the mechanism of upper gastrointestinal distress, such as nausea and vomiting.

It has reported that dopamine inhibited gastric motility (Lanfranchi et al., 1978; Van Nueten & Janssen, 1980; Thompson & de Carle, 1982) and delayed gastric emptying (Jacobs et al., 1981) in animal and in man. The inhibitory effect of dopamine was not blocked by α- and β-receptors antagonists but by domperidone and metoclopramide, two known dopaminergic antagonists (Valenzuela, 1976; Schuurkes & Van Nueten, 1981 & 1984; Bech & Hovendal, 1982). But our results showed that percent variation of SW frequency induced by dopamine was blocked not only by domperidone, but also by phentolamine. Such a discrepancy is so far yet unknown. There is a report that phentolamine antagonize dopamine-caused contraction of stomach circular smooth muscle in guinea-pig (Costall et al., 1981).

From the results of this study, it is inferred that dopamine plays a role in the genesis of gastric electrical abnormality acting on dopamine receptor and partly acting on α-adrenergic receptors in cats.

SUMMARY

The effect of dopamine on the propagation and the frequency electrical activities (slow wave) of the stomach was studied in isolated stomach muscle strips of 145 cats. The gastric slow wave was monopolarly recorded by four capillary electrodes (Ag-AgCl) in Krebs-Ringer solution (pH 7.4, temperature 36± 0.5°C) bubbled with 5% CO_2 in O_2. Dopamine caused concentration-dependent changes of direction of slow wave propagation with decline in development of irregular propagation by domperidone pretreatment. Dopamine also increased the variation of slow wave frequency concentration-dependently. The variation of slow wave frequency induced by dopamine was significantly inhibited by pretreatments with domperidone and phentolamine but not with propranolol, hexamethonium and tetrodotoxin.

It is therefore suggested that dopamine plays a role in the genesis of gastric electrical abnormality acting on dopamine receptors and partly on α-adrenergic receptors in cats.

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REFERENCES

Baudry, M., M.P. Martres and J.C. Schwartz: *^{3}H-Domperidone: a selective ligand for dopamine receptors. Naunyn-Schmiedebergs Arch. Pharmacol., 308:231-237, 1979.*

Bech, K. and C.P. Hovendal: *Effect of dopamine on bethanechol-stimulated gastric antral motility in dogs with gastric fistula. Scand. J. Gastroenterol., 17:945-951, 1982.*

Carlson, H.C., C.F. Code and R.A. Nelson: *Motor action of canine gastroduodenal junction: a cineradiographic, pressure and electric study. Am. J. Dig. Dis., 1:155-172, 1966.*

Chey, W.Y., C.H. You, K.Y. Lee and R. Menguy: *Gastric dysrhythmia: clinical aspects. In Functional Disorders of the Digestive Tract,*

W.Y. Chey (ed). New York: Raven Press, 1983, p.175-181.

Costall, B., R.J. Naylor and H.A. Sahyoun: *Catecholamines have a dual action on stomach strips: the relaxation component is selectively inhibited by domperidone. Br. J. Pharmacol., 72:558P-559P, 1981.*

Jacobs, F., L.M.A. Akkermans, O. Hong Yoe and P. Wittebol: *Effects of domperidone on gastric emptying of semi-solid and solid food. In Progress with Domperidone, A Gastrokinetic and Anti-emetic Agent: Royoal Society of Medicine, International Congress and Symposium Series No. 36, G. Towse (ed). London: Royal Society of Medicine and Academic Press, 1981, p.37-42.*

Kelly, K.A. and C.F. Code: *Canine gastric pacemaker. Am. J. Physiol., 220:112-117, 1971.*

Kim, M.S., Y.L. Lee, Y.H. Jo, S.S. Sim and H. Choi: *Effect of prostaglandin E_2 on the electric activity of cat isolated stomach muscle. Prostaglandins, 30:99-108, 1985.*

Laduron, P.M. and J.E. Leysen: *Domperidone, a specific in vitro dopamine antagonist, devoid of in vivo central dopaminergic activity. Biochem. Pharmacol., 28:2161-2165, 1979.*

Lanfranchi, G.A., L. Marzio, C. Cortini, L. Trento and G. Labó: *Effect of dopamine on gastric motility in man: evidence for specific receptors. In Gastrointestinal Motility in Health and Disease, H.L. Duthie (ed). Lancaster: MTP Press, 1978, p.161-172.*

Lee, K.Y., H.J. Park and W.Y. Chey: *Studies on mechanism of retching and vomiting in dogs: effect of peripheral dopamine blocker on myoelectric changes in antral and upper small intestine. Dig. Dis. Sci., 30:22-28, 1985.*

Odaibo, S.K., W.Y. Chey and K.Y. Lee: *Presence and role of local dopamine receptors on antral motility in the isolated perfused rat stomach. Gastroenterology, 84:1962, 1983.*

Schuurkes, J.A.J. and J.M. Van Nueten: *Effects of dopamine and its antagonist domperidone cannot be explained by an effect of α_1-adrenergic receptors. Arch. Int. Pharmacodyn., 250: 324-327, 1981.*

Schuurkes, J.A.J. and J.M. Van Nueten: *Domperidone improves myogenically transmitted antroduodenal coordination by blocking dopaminergic receptor sites. Scand. J. Gastroenterol., 19 (Suppl. 96):101-110, 1984.*

Thompson, B.K. and D.J. de Carle: *The effect of dopamine on human gastric smooth muscle. Aust. J. Exp. Biol. Med. Sci., 60:123-127, 1982.*

Valenzuela, J.E.: *Dopamine as a possible neurotransmitter in gastric relaxation. Gastroenterology, 71:1019-1022, 1976.*

Van Nueten, J.M. and P.A.J. Janssen: *Is dopamine an endogenous inhibitor of gastric emptying? In Gastrointestinal Motility in Health and Disease, H.L. Duthie (ed). Lancaster: MTP Press, 1978, p.173-181.*

Van Nueten, J.M. and P.A.J. Janssen: *Effect of domperidone on gastric relaxation caused by dopamine, secretin, 5-hydroxytryptamine, substance P, and adenosine triphosphate. In Gastrointestinal Motility, J. Christensen (ed). New York: Raven Press, 1980, p.225-231.*

You, C.H. and W.Y. Chey: *Study of electromechanical activity of the stomach and in dogs with particular attention to tachygastria. Gastroenterology, 86:1460-1468, 1984.*