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The Role of Central Adrenergic Activity in Stress-induced Ulcerogenesis

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ABSTRACT

The role of central adrenergic activity in the genesis of stress ulcers was investigated by intracerebroventricular (i.c.v.) administration of catecholamines and clonidine in pylorus-ligated rats restrained for 4 hours at a temperature of 4℃.

1. The stress-induced ulceration was markedly decreased by the i.c.v. administration of norepinephrine, epinephrine, dopamine or low dose of clonidine.
2. After an i.c.v. administration of norepinephrine or epinephrine, the volume of gastric juice, and both acid and pepsin secretion were markedly decreased.
3. Dopamine or a low dose of clonidne decreased the volume of gastric juice and acid secretion but did not affect pepsin secretion.
4. Isoproterenol caused a decrease in the volume of gastric juice and acid secretion, however, the ulcerogenesis was similar to that of the control.
5. Gastric function as well as ulcerogenesis was little affected by a high dose of clonidine.

From the above results, it is suggested that central adrenergic activation inhibits cold-restraint induced ulcerogenesis via adrenergic alpha and dopaminergic receptors, and that this effect may be mediated by a decrease in gastric acid secretion. It is also suggested that other factors may be involved in this antiulcerogenic effect.

Key Words: Cold-restraint ulcer, Central adrenergic activity, Intracerebroventricular injection

INTRODUCTION

It has been well known for over a century that the central nervous system adversely influence the function of the upper gastrointestinal tract in response to diverse stress (Wolf, 1981).

It is understood that exposure to diverse stress produces gastric mucosal ulceration in rats within a short period of time via a central mechanism (Brodie and Valitski, 1963; Senay and Levine, 1967). Restraint with exposure to a temperature of 4℃ has been commonly employed to induce stress ulcers in rats (Senay and Levine, 1967; Dai and Ogle, 1974; Cho *et al.*, 1976).

Several lines of evidence indicate that changes in gastric acid and pepsin secretion are essential in the development of this type of gastric ulcer. But, the following pathogenic mechanisms are also involved (Silen, 1977), such as a decrease in mucus secretion, alterations in adrenal steroids and catecholamines secretion, disturbances of gastric mucosal circulation, and alterations in the synthesis of gut prostaglandins (Murakami *et al.*, 1985; Hernandez, 1986).

With regard to the control of gastric acid and pepsin secretion, the cholinergic mechanism has been widely studied. However, the adrenergic mechanisms have been neglected until the last decade. It is generally accepted that catecholamines have a gastric antisecretory effect in mammals (Daly, 1984). Yamaguchi *et al.* (1973) postulated that norepinephrine as well as chlor-

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promazine and imipramine inhibited gastric secretion by acting centrally rather than peripherally. In addition, Brodie *et al.* (1970) have shown that an intracerebroventricular injection of clonidine, an α_2-adrenergic agonist, inhibited gastric secretion in rats. Thus, it was suggested that central adrenergic receptors may be involved in the regulation of gastric secretion and are also responsible for the antisecretory effects of clonidine, chlorpromazine and imipramine.

However, controversy regarding the central adrenergic influence on gastric ulcerogenesis has been reported. Intracerebroventricular administration of epinephrine or norepinephrine ambivalently produced (Bhargava *et al.*, 1980) or suppressed (Hernandez, 1986) stress-induced gastric ulceration. Therefore, a paucity in information and some controversy concerning the roles of central adrenergic neurotransmitters in the regulation of gastric function need further investigation to verify them.

In this study, we attempted to investigate the role of central adrenergic activity in the genesis of stress ulcers by the intracerebroventricular administration of drugs which modify adrenergic mechanisms in rats.

MATERIALS AND METHODS

Animals

Albino rats of either sex weighing about 200 g were used. After a week adaptation period, rats were fasted for 48 hours prior to the experiment but allowed water ad libitum.

Intracerebroventricular cannulation

A polyethylene tube with bulb was prepared by cutting it at a distance of 3.5 to 4.0 mm from the bulb on one side and 1.5 cm from the bulb on the other side. The shorter end was inserted into the skull up to the bulb and the drugs were injected through the other side. For the implantation of a cannula into the lateral cerebral ventricle, rats were anesthetized with secobarbital (30 mg/kg, i.p.), and the head of the rat was fixed in a horizontal position using the stereotaxic apparatus. Then, the bregma was exposed through a mid-sagittal incision and two holes were made 1.4 mm lateral to the sagittal suture; one was 1.4 mm lateral to the bregma and the other was 2 mm anterior to the coronal suture. A screw (diameter: 0.5 mm) was inserted into the anterior hole to the depth of bone and the cannula was inserted into the posterior hole. The cannula was fixed to the screw by dental cement, and its free end was sealed with heat. The skin flaps were sutured. Each cannulated rat was placed in separate cage and the experiment was performed 7 days later.

Induction of the stress ulcer and assay of gastric secretion

Pylorus-ligated rats were prepared under light ether anesthesia by the method described by Shay et al. (1945). Immediately after pylorus ligation, saline or drugs were injected intracerebroventricularly through the polyethylene tube. After recovery from the anesthesia, these pylorus-ligated, previously cannulated rats were placed in plastic restraint cages and then placed in a cold room at 4℃. Four hours later, rats were decapitated and their stomachs were removed. Then, the stomachs were opened along the greater curvature, the gastric juice collected, and then the stomachs were examined under an optic magnifier ($\times 4$) for gastric lesions.

The volume, free acidity, total acidity and pepsin activity of the gastric juice of each rat were measured. Acidity measurements were carried out on a Automatic Titrator TTT2b (Radiometer, Copenhagen, Denmark) by titration with N/20 NaOH to pH 3.0 for free acid and pH 7.0 for total acid. Pepsin activity was measured by the modified method of Rick and Fritsch (1974).

The ulcer index was calculated by severity $\times$ length $\times$ number of ulcers each stomach. The following arbitrary scoring system was used to grade the severity and length. Severity: shedding of epithelium = 1; petechia = 2; shallow ulcer = 3; deep ulcer = 4. Length: spot = 1; 1-2 mm = 2; 3-4 mm = 3: above 5 mm = 4.

Intracerebroventricular (i.c.v.) administration of adrenergic agents.

Norepinephrine (Sigma, USA), epinephrine (Sigma, USA), isoproterenol (Sigma, USA), dopamine (Sigma, USA) or clonidine (Sigma, USA) was injected into the lateral ventricle through the polyethylene cannula immediately after pylorus ligation. The volume of the drug solution injected into the lateral ventricle did not exceed 20 μl. Twenty μl of saline was injected by the same procedure for the control.

RESULTS

Effects of the i.c.v. injection of adrenergic drugs on gastric lesion formation in pylorus-ligated, cold-restraint rats

Gastric ulcerogenicity was expressed by the ulcer index and incidence as described in the methods. After a 4 hour-restraint at 4℃, the resulting gastric ulceration demonstrated a close positive correlation ($r=0.85$) between ulcer incidence and the mean ulcer indices in the saline and drug treated groups (Table 1).

In the saline (20 μl/rat, i.c.v.)-treated group, gastric ulceration developed in 100% of the animals and the ulcer index was 89.0±19.1. Treatment of rats with norepinephrine (200 μg/kg, i.c.v.), epinephrine (200 μg/kg, i.c.v.), dopamine (200 μg/kg, i.c.v.) or a small dose of clonidine (15 μg/kg, i.c.v.) markedly decreased the ulcerogenesis in the cold-restraint rats, while isoproterenol (200 μg/kg, i.c.v.) or a large dose of clonidine (30 μg/kg, i.c.v.) caused little influence on the ulcerogenesis (Table 1).

Effects of the i.c.v. injection of adrenergic drugs on gastric function in pylorus-ligated, cold-restraint rats

The gastric juices collected during the 4 hours

Table 1. Effects of intracerebroventricular injection of adrenergic drugs on gastric ulceration induced by 4 hour-restraint at 4°C in rats

Group	Ulcer index †	Incidence (%)*
Saline (20μl/rat)	89.0 ±19.1	11/11 (100)
Norepinephrine (200μg/kg)	38.5 ± 11.7	8/13 (62)
Epinephrine (200 μg/kg)	39.0 ± 10.3	6/12 (50)
Isoproterenol (200 μg/kg)	90.0 ± 40.8	5/ 6 (83)
Dopamine (200 μg/kg)	49.9 ± 23.5	3/ 8 (38)
Clonidine		
(15 μg/kg)	18.1 ± 8.4	5/12 (42)
(30 μg/kg)	61.2 ± 23.7	4/ 5 (80)

† Values of ulcer index are means ± S.E. in arbitrary scale.

* Ulcer incidences are No. of rats with ulcer/No. of rats studied.

Table 2. Effects of intracerebroventricular injection of adrenergic drugs on the volume, acid and pepsin secretion of gastric juice in 4 hour-cold-restraint rats

Group	No. of Exp.	Volume (ml/100g/hr)	Free acid		Total acid		Pepsin	
			Concentration (μEq/ml)	Output (μEq/100g/hr)	Concentration (μEq/ml)	Output (μEq/100g/hr)	Concentration (unit/ml)	Output (unit/100g/hr)
Saline (20 μg/rat)	10	0.67 ±0.06	94.4 ± 5.1	64.9 ± 7.5	121.4 ± 5.9	84.7 ± 7.9	11,868 ± 1,110	7,937 ± 715
Norepinephrine (200 μg/kg)	10	0.31 ±0.04***	56.9 ± 8.8**	23.9 ± 4.6***	103.7 ± 7.4	36.9 ± 5.2***	6,716 ± 1,058**	3,318 ± 741***
Epinephrine (200 ug/kg)	7	0.37 ±0.03**	62.4 ± 7.0**	25.8 ± 4.2***	101.1 ± 6.0*	42.1 ± 5.2***	6,155 ± 597***	2,618 ± 702***
Isoproterenol (200 μg/kg)	6	0.32 ±0.04***	73.3 ± 7.2*	23.7 ± 3.7**	115.8 ± 4.9	36.8 ± 5.2**	19,087 ± 1,744**	6,036 ± 909
Dopamine (200 μg/kg)	5	0.28 ±0.06**	63.8 ± 8.3**	16.0 ± 4.5***	107.2 ± 4.3	28.6 ± 6.1***	16,566 ± 1,296*	6,266 ±1,019
Clonidine								
(15 μg/kg)	8	0.34 ±0.07**	78.7 ± 6.7	35.2 ± 7.8*	109.5 ± 7.8	44.4 ± 9.9**	19,497 ± 2,598**	6,458 ± 991
(30 μg/kg)	7	0.42 ±0.08*	77.1 ±13.3	50.0 ±13.3	110.9 ± 13.4	58.7 ±14.3	15,920 ± 1,230*	6,765 ±1,378

Values are means ± S.E.

* $P<0.05$, ** $P<0.01$, *** $P<0.001$ (Difference from saline-treated group)

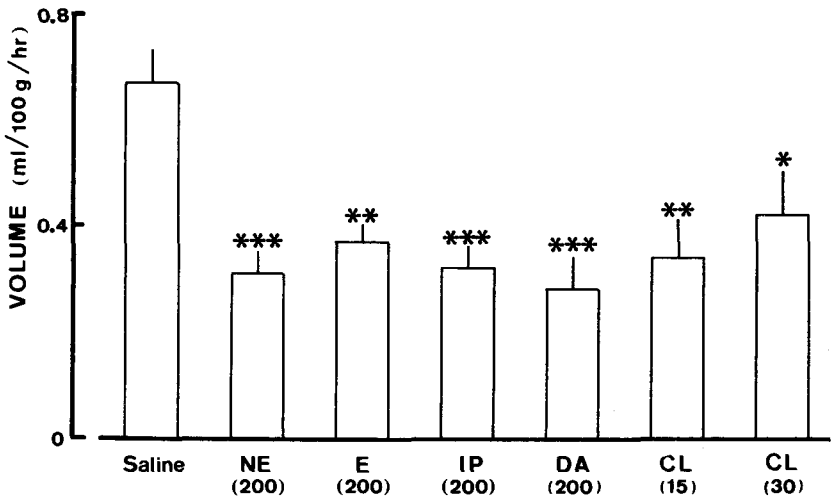

Fig. 1. Effects of i.c.v. injection of adrenergic drugs on the volume of gastric juice in 4 hour-cold-restraint rats. Parentheses are doses in μg/kg. NE = norepinephrine ; E = epinephrine ; IP = isoproterenol ; DA = dopamine ; CL = clonidine. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ (Difference from saline-treated group).

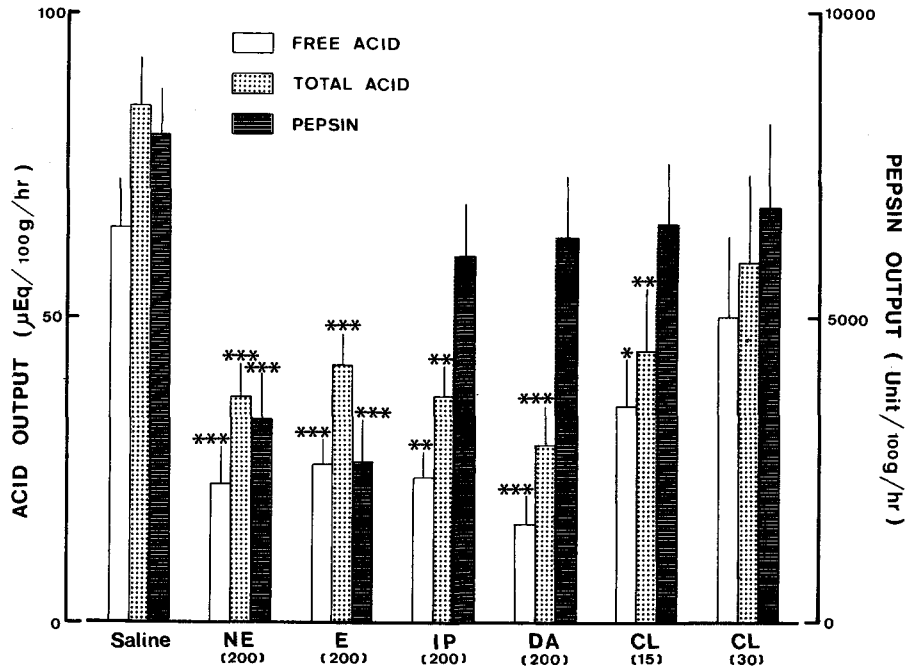

Fig. 2. Effects of i.c.v. injection of adrenergic drugs on the gastric acid and pepsin output in 4 hour-cold-restraint rats. Parentheses are doses in μg/kg. NE = norepinephrine ; E = epinephrine ; IP = isoproterenol ; DA = dapamine ; CL = clonidine. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ (Difference from saline-treated group).

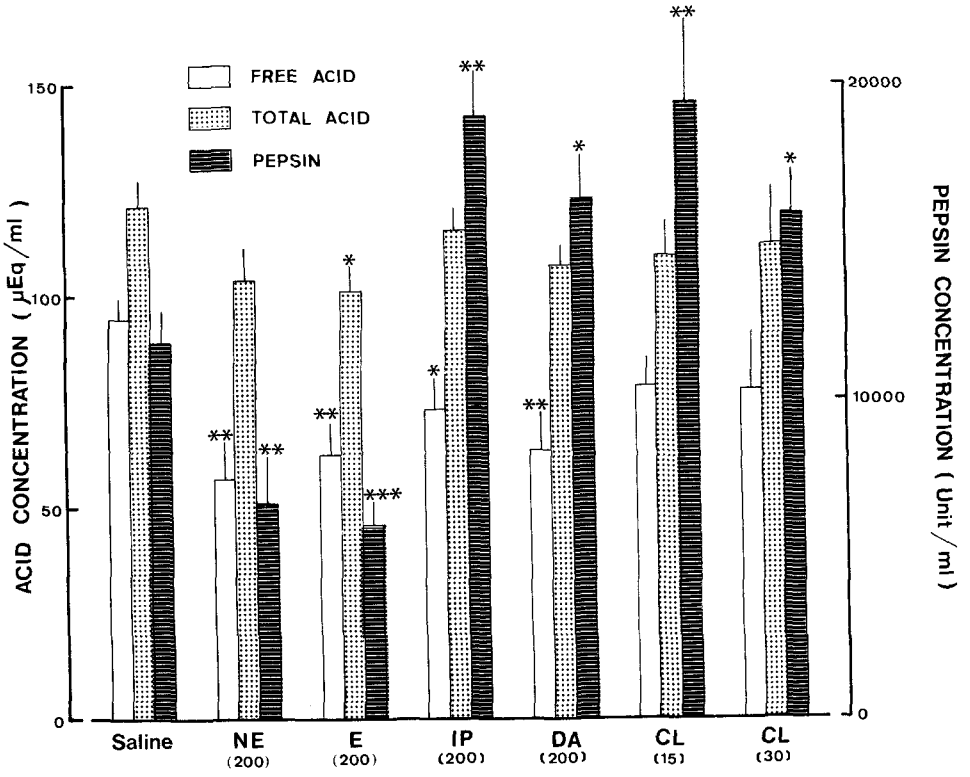

Fig. 3. Effects of i.c.v. injection of adrenergic drugs on the gastric acid and pepsin concentration in 4 hour-cold-restraint rats. Parentheses are doses in μg/kg. NE = norepinephrine ; E = epinephrine ; IP = isoproterenol ; DA = dopamine ; CL = clonidine. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ (Difference from saline-treated group).

of cold-restraint were analysed to measure volume, free acidity, total acidity and peptic activity (Table 2).

In the saline-treated group, an average volume of 0.67 ± 0.06 ml/100 g/hr was collected from the pylorus-ligated rats after 4 hours of cold-restraint. The volume of gastric juices was decreased by i.c.v. injections of the adrenergic drugs used in this study. This effect was most notable in the dopamine-treated group. The effects of norepinephrine, isoproterenol, a low dose of clonidine and epinephrine on the volume of gastric juice were similar to that of dopamine. Treatment with a large dose of clonidine was the least effective (Table 2, Fig. 1).

Treatment of rats with norepinephrine or epinephrine markedly suppressed the output of free acid, total acid and pepsin in the same manner as with the volume of gastric juice. But in the case of the concentrations, only that of free acid and pepsin were markedly decreased (Table 2, Fig. 2, Fig. 3).

Similarly, the output of free and total acid and the concentration of free acid were decreased by isoproterenol, dopamine or a low dose of clonidine. In contrast to the acidity, pepsin output was not significantly changed in these groups (Table 2, Fig. 2, Fig. 3). Although these three groups showed similar changes in volume, acidity and peptic activity, the resulting gastric ulcerogeneses were quite different. Gastric ulcerogenesis was high in the isoproterenol-treated group, but low in the dopamine-or low dose of clonidine-treated groups (Table 1).

The effects of a high dose (30 μg/kg, i.c.v.) of clonidine were quite different from those of a low

dose (15 μg/kg, i.c.v.). Treatment of rats with large dose of clonidine caused no changes in the acidity and output of pepsin and a small increase in the concentration of pepsin (Table 2, Fig. 2, Fig. 3).

DISCUSSION

Restraint with exposure to a temperature of 4℃ has been commonly employed to induce stress ulcers in rat stomach. In comparison with simple physical restraint, this technique elicits more consistent lesions not only in the frequency of occurrence, but also in type and location (Senay and Levine, 1967). Djahanguiri *et al.* (1973) reported that cold (4℃)-restraint for 2 hours produced ulcers in 96.8% of the rats and that these ulcers occurred only in the glandular portion of the stomach. In the present study, combined immobilization and cold (4℃) exposure produced ulcers in 100% of rats after 4 hours. Almost all of the ulcers produced by this technique were located in the glandular portion of the stomach. These data are consistent with the reports of Senay and Levine (1967) and Djahanguiri *et al.* (1973).

In stress-induced ulcers, an increase in acidity was observed in rats subjected to restraint stress (Brodie *et al.*, 1962) or to water immersion stress (Murakami *et al.*, 1985). On the other hand, intense stress induces depletion of several brain biogenic amines including norepinephrine and dopamine (Corrodi *et al.*, 1968; Palkovits *et al.*, 1975; Benedict *et al.*, 1979). Thus, in the present study, we attempted to investigate the relationship between stress ulceration with increased acidity and adrenergic activity in the brain.

It has been suggested that intact brain noradrenergic function is essential for coping with stress, and that when noradrenergic function is decreased, the effects of stress may be exacerbated. Glavin (1985) observed that selective depletion of norepinephrine in the brain markedly exacerbated ulcerogenesis in cold-restraint rats. In the present study, an i.c.v. injection of norepinephrine markedly suppressed stress-induced gastric ulcerogenesis. In addition, the i.c.v. injection of clonidine, an α_2-adrenergic receptor agonist, showed a similar effect. However, an i.c.v. injection of isoproterenol did not change the stressinduced ulcerogenesis. Thus, it is strongly suggested that central α-receptor activation, but not β-receptor, is essential for coping with stress-induced ulcerogenesis. Furthermore, central α_2-receptor is involved in this antiulcerogenic effect mediated by central α-receptor activation.

The antiulcerogenic effect of norepinephrine, epinephrine and clonidine was accompanied by a decrease in the volume of gastric juice and gastric acidity. The decreased concentration of the free acid mainly contributed to this decrease in gastric acidity. These data are consistent with the report of Brodie *et al.* (1962) who proposed that an increase in acid concentration is an important change produced by the restraint stress. However, i.c.v. injection of isoproterenol, which had no antiulcerogenic effect, also caused a decrease in the volume of gastric juice and gastric acidity. Pepsin secretion, another parameter of gastric function, was decreased by an i.c.v. injection of norepinephrine or epinephrine, but not by that of isoproterenol or clonidine. Thus, it is suggested that the decreased volume of gastric juice and gastric acidity are concerned with the antiulcerogenic effect which is mediated by central α-adrenergic receptor, and also it is suggested that decreased pepsin secretion may not be the main causative factor of this antiulcerogenic effect. Furthermore, there is the possibility that other factors, such as gastric defense mechanisms, may contribute to a central α-receptor mediated antiulcerogenic effect.

Osumi *et al.* (1977) showed that an injection of norepinephrine into the lateral ventricle decreased basal gastric acid secretion. Moreover, central administration of norepinephrine completely blocked an increase in gastric acid output secondary to lateral hypothalamic electrical stimulation. Yamaguchi *et al.* (1977) found that the central administration of nafazoline, a sympathomimetic agent, reduced gastric acid secretion. This antisecretory effect was antagonized by the α-antagonist, phentolamine, but not by the β-antagonist, propranolol. However, the effect of clonidine, an α-adrenergic agonist, on gastric acid secretion varies considerably. Although clonidine inhibits gastric acid secretion in conscious rats (Pascaud and Roger, 1976; Jennewein, 1977), it stimulates acid secretion in anesthetized rats (Walz and Van Zwieten, 1970; Karppanen and Westermann, 1973). Concerning this dual effect of clonidine, Cheng *et al.* (1981) reported that clonidine reduced gastric acid secretion by both central and peripheral mechanisms, but as the dose increased, clonidine also stimulated gastric acid secretion which appeared to be mediated by

histamin H_2-receptor stimulation. The central and peripheral inhibitory effect was proposed to be due to its effect on the α_2-adrenergic receptors (Pascaud *et al.*, 1983). In the present study, a high dose of clonidine (30 μg/kg, i.c.v.) caused no changes in gastric ulcerogenesis and gastric secretory function. These effects may be mediated central and/or peripheral histamine H_2-receptor activation by clonidine. Overall these results support the concept that stimulation of α-adrenergic mechanisms in the central nervous system inhibits gastric acid secretion. The present experiment also clearly demonstrated the role of central α-adrenergic mechanisms in regulating gastric secretion in cold-restraint rats. However, gastric acid secretion was decreased by activation of central β-adrenergic receptors as well as α-adrenergic receptors in the cold-restraint rats. This discrepancy of the role of the central β-adrenergic receptors on the gastric acid secretion may be due to differences in the experimental models or the high dose of isoproterenol used in the present study.

Intracerebroventicular injection of dopamine in cold-restraint rats markedly suppressed ulcerogenesis and depressed gastric secretory function similar to a low dose of clonidine. These results are consistent with the report of Nemeroff *et al.* (1982) who observed that a blockade of the central dopamine receptor with haloperidol aggravated the effect of cold-restraint stress. Additional neurochemical studies revealed that the protective effect of dopamine depends on an increased dopamine neurotransmission at extrahypothalamic sites (Hernandez *et al.*, 1984; Claustre *et al.*, 1986). On the basis of our data, dopamine suppressed stress-incued ulcerogenesis, and this effect of dopamine was concerned with a decrease in the volume of gastric juice and acid secretion. However the effect of activation of α-adrenergic receptor by dopamine could not be ruled out.

In conclusion, cold-restraint induced ulcerogenesis was suppressed by activation of central α-adrenergic and dopamine receptors, and this effect may be mediated by a decrease in gastric acid secretion. It is also suggested that other factors can be involved in this antiulcerogenic effect mediated by central α-adrenergic or dopamine receptors.

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═국문초록═

스트레스성 궤양발생에 대한 중추 아드레날린성 활성도의 역할

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스트레스로 인한 위궤양형성에 중추성 교감신경의 영향 여부를 추구하기 위하여 norepinephrine, epinephrine, dopamine, isoproterenol 및 clonidine을 흰쥐의 뇌실내로 투여하고 한냉환경(4℃)에서 4시간 구속방치하여 위 분비기능의 변동과 궤양 발생 정도를 검색하여 다음과 같은 결과를 얻었다.

1. Norepinephrine, epinephrine, dopamine 및 소량의 clonidine 처치로 궤양 발생이 현저하게 감소하였다.
2. Norepinephrine 또는 epinephrine 처치군에서는 위액분비, 산분비 및 펩신 분비의 감소와 궤양 발생 감소가 초래되었다.
3. Dopamine 혹은 소량의 clonidine 처치군에서는 궤양 발생의 감소와 위액분비 및 산분비 감소가 초래되었으나 펩신 분비는 변동 없었다.
4. Isoproterenol 처치군에서는 궤양 발생과 펩신 분비는 대조군과 차이 없고, 위액분비 및 산분비의 감소만 나타났다.
5. 대량의 clonidine 투여군에서는 궤양발생, 산분비 및 펩신분비 모두 변동없이 약간의 위액분비 감소가 나타났다

이상의 결과로 보아 중추성 교감신경자극은 궤양 형성을 억압하는 작용이 있고, 이에는 교감신경성 α-수용체 및 도파민성 수용체가 관여된다고 믿어지며, 이 효과는 위액분비 감소 및 산분비 감소작용과 아울러 또다른 요인이 관여한다고 추측된다.