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STUDY OF CENTRAL NEUROTRANSMITTERS IN STRESS-INDUCED GASTRIC ULCERATION IN ALBINO RATS

K.P. BHARGAVA, M. DAAS, G.P. GUPTA & M.B. GUPTA

Neuropharmacology Unit (C.S.I.R.), Department of Pharmacology & Therapeutics, King George's Medical College, Lucknow—226003, INDIA

1 Restraint when combined with cold (4°C) consistently induces gastric ulceration in rats at 2 h. The cold-restraint ulcer (CRU) technique provides a suitable model for acute studies.

2 The peripheral mechanisms in CRU seem to be increased sympathetic and parasympathetic outflow since CRU was significantly reduced by prior spinal transection or vagotomy or by appropriate blocking agents. Since metiamide significantly reduced CRU, H_2-histamine receptors are also involved.

3 Central catecholaminergic as well as cholinergic mechanisms seem to be responsible for the activation of peripheral sympathetic and parasympathetic outflow in CRU, since central administration of dibenamine, propranolol, 6-hydroxydopamine and atropine prevented the CRU.

4 Exogenous administration of putative neurotransmitters (adrenaline, noradrenaline and acetylcholine) into the cerebroventricular system produced gastric ulceration similar to CRU. However, dopamine, histamine and 5-hydroxytryptamine failed to induce gastric ulceration.

5 The results with intracerebroventricular adrenaline and acetylcholine indicate a central cholinergic link distal to adrenergic activation in the ulcerogenesis.

6 Intracerebroventricular adrenaline-induced gastric ulceration appears to be most akin to CRU. However, other central neurotransmitter mechanisms may also be involved.

Introduction

There is no unanimity regarding the mechanism of stress-induced ulcerogenesis. Both central and peripheral mechanisms seem to be involved in ulceration. Brodie & Hanson (1960) and Dai & Ogle (1974) showed that cholinergic outflow along the vagus plays a contributory role in restraint ulcerogenesis. Djahanguiri, Taubin & Landsburg (1973) suggested that peripheral sympathetic activation plays an important role in the induction of ulcers by restraint. Singh, Sharma & Kar (1967) and Hayden, Thomas & West (1978) implicated peripheral histamine in restraint ulcerogenesis. Similarly, Moore & Lariviere (1964); Gordon, Spector, Sjoerdsma & Udenfriend (1966) and Corrodi, Fuxe & Hokfelt (1968) have found central sympathetic activation during stress. However, the exact mechanisms involved in the pathogenesis of stress ulcers are not yet clear. In the present investigation the central and peripheral neurohumoral mechanisms in the pathogenesis of restraint ulcers have been investigated. In addition, the mechanism of gastric ulceration induced by exogenous administration (intracerebroventricular) of putative neurotransmitters in albino rats has been studied to elucidate the neurotransmitter mechanisms in restraint ulcerogenesis. A preliminary account of this work was given at the VIIth International Congress of Pharmacology (Bhargava, Daas, Gupta & Gupta, 1978).

Methods

Adult albino rats of either sex weighing between 120 and 150 g were divided into groups. Since pregnancy and prior feeding have been shown to prevent the ulcerogenic activity of certain drugs (Kelly & Robert, 1969; Robert & Dale, 1971), in the present study pregnancy was excluded and animals were deprived of food for 24 h before the start of experiments. Water was allowed *ad libitum* to the animals.

Intracerebroventricular cannulation in albino rats

Preparation of cannula A polythene tube (diameter 0.5 mm) was passed through the centre of a nichrome wire loop (diameter 5.0 mm). The wire loop was heated to redness by passing an electric current. Within a few seconds the polythene tube inside the loop swelled up into a bulb and the electric current was switched off. The polythene tube was cut at a

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distance of 3.5 to 4.0 mm from the bulb on one side and 4.0 cm from the bulb on the other side. The shorter end up to the bulb was inserted into the skull and drugs were injected through the other end.

Implantation of cannula Parameters for implantation of a cannula into the lateral cerebral ventricle of the rat anaesthetized with pentobarbitone (40 mg/kg i.p.) were the same as those used by Noble, Wurtman & Axelrod (1967). After fixing the head of the rat in a horizontal position, the bregma was exposed through a mid-sagital incision. A no. 2 dental burr was used to make two holes in the skull bone 1.5 to 2 mm lateral to the sagital suture, one 1.5 to 2 mm anterior and other 1.5 to 2 mm posterior to the coronal suture. A screw (diameter 0.5 mm) was tightened only bone deep into the anterior hole 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 by heating. The skin flaps were sutured. The cannulated rats were placed in separate cages and were used for study after two days.

Stress-induced gastric ulceration

The rats were restrained according to the method of Selye (1936) by tying the fore and hindlimbs together by metallic wire for periods of 6, 8, 18 or 24 h. In another series of experiments the rats were restrained by tying the fore and hindlimbs together and kept at 4°C for 2 h according to the method of Senay & Levine (1967). The animals were killed and the stomach was removed and examined under a dissecting microscope for gastric lesions. The following arbitrary scoring system was used to grade the incidence and severity of the lesions: (i) shedding of epithelium = 10; (ii) petechial and frank haemorrhages = 20; (iii) one or two ulcers = 30; (iv) many ulcers = 40; (v) perforated ulcers = 50. The presence of any of these lesions was considered to be a positive ulcerogenic response. The ulcer index was the mean score of all the rats in each group.

Gastric ulceration induced by central administration of putative transmitters

Adrenaline, noradrenaline, dopamine, acetylcholine, histamine and 5-hydroxytryptamine (5-HT) were injected into the lateral cerebral ventricle through an indwelling polythene cannula implanted two days earlier. The volume of drug solution injected into the lateral ventricle did not exceed 20 µl. The rats were killed 24 h after drug administration and the stomach was examined for the incidence and severity of ulceration and/or lesions as described earlier.

In order to elucidate the mechanism underlying ulcerogenesis induced by restraint and centrally administered putative neurotransmitters, the animals were pretreated i.c.v. or i.p. with the drugs known to influence adrenergic, cholinergic, histaminergic and tryptaminergic function, 30 min before restraint or i.c.v. injection of putative neurotransmitters. Rats were killed 24 h later and their stomachs were examined for the lesions.

All surgical procedures were carried out under light ether anaesthesia. Bilateral total extirpation of adrenals was done (48 h before administration of drug or exposure to restraint) by the method of Schultzer (1935). Spinal transection was at C7 – T1 (2 h before drug administration) after exposing the spinal cord by laminectomy. To ensure complete transection of the cord an aneurysm needle was passed to lift any possible fragments of the intact cord and then plasticine was filled in the laminectomy gap. Finally the skin was sutured. Vagotomy was performed (24 h earlier) by the method employed by Kennedy (1974).

The drugs used were: adrenaline bitartrate, noradrenaline bitartrate, dopamine hydrochloride, acetylcholine chloride, physostigmine sulphate (eserine), histamine diphosphate, 5-hydroxytryptamine creatinine sulphate, dibenamine, yohimbine, propranolol hydrochloride, β-phenylisopropyl hydrazine hydrochloride (JB-516), 6-hydroxydopamine, hexamethonium chloride, atropine sulphate, atropine methylnitrate, mepyramine maleate, metiamide and cyproheptadine hydrochloride. All the drugs were dissolved in 0.9% w/v NaCl solution (saline).

The results were analysed statistically by the Chi-squared test.

Results

Time course of gastric ulceration induced by restraint

The time course of gastric ulceration induced by restraining the rats is shown in Figure 1. The rats subjected to restraint for 6, 8, 18 or 24 h showed gastric ulceration in 27, 80, 100 and 100% of the animals respectively. Simultaneous exposure to cold (4°C) and restraint for 2 h, produced gastric ulcers in 90% animals. The cold restraint ulcer technique (CRU) has been employed in the present study. It is apparent that exposure to cold greatly enhanced the ulcerogenic effect of restraint, the incidence of ulcers observed after 2 h at 4°C was comparable to the incidence observed after 8, 18 or 24 h of restraint in the absence of cold.

Effect of adrenalectomy, spinal transection and vagotomy on cold restraint ulcers (CRU)

Table 1 shows the effect of bilateral adrenalectomy, spinal transection and vagotomy on the incidence of

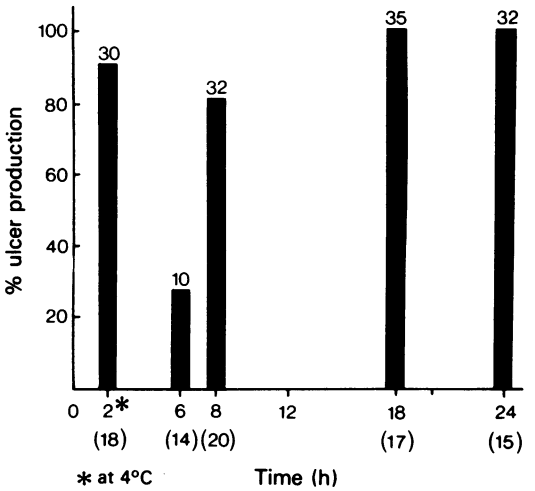

Figure 1 Histogram showing the time course of gastric ulceration induced by 2 h restraint at 4°C and 6, 8, 18 and 24 h restraint at room temperature. Numbers in parentheses indicate the number of animals used. Number on the top of each column indicates ulcer index.

restraint ulcers. The surgical procedures *per se* did not produce gastric ulcers. Spinal transection and vagotomy significantly ($P < 0.02$ in each case) reduced the restraint ulcers whereas bilateral adrenalectomy had no effect.

Effect of intraperitoneal pretreatment with antagonists of biogenic amines on CRU

Table 2 shows the effect of intraperitoneal pretreatment with receptor antagonists of biogenic amines on the incidence of gastric ulceration induced by 2 h restraint at 4°C. The α-adrenoceptor antagonist (dibenamine), cholinoceptor antagonist (atropine) and H_2-receptor blocking agent (metiamide) significantly reduced the incidence of cold restraint ulcers, whereas the β-adrenoceptor blocking agent (propranolol in a dose of 1.0 mg/kg i.p.), H_1-receptor blocking agent (mepyramine) and anti-5-HT agent (cyproheptadine) were ineffective. However, a higher dose of propranolol (5 mg/kg i.p.) significantly reduced the incidence of cold restraint ulcer ($P < 0.001$).

Table 1 Effect of bilateral adrenalectomy, spinal transection and vagotomy on cold-restraint ulcers in rats

Condition of rats exposed to restraint at 4°C	*No. of rats with ulcer / No. of rats studied*	*% ulcer*	*Ulcer index*	P *value*
Normal	18/20	90	30	—
Bilateral adrenalectomized	16/20	80	29	>0.05
Spinal cord transected	5/14	36	11	<0.02
Vagotomized	5/13	38	12	<0.02

Table 2 Effect of intraperitoneal injection of antagonists of biogenic amines on cold-restraint ulcers in rats

Pretreatment (30 min before restraint)	*Dose (mg/kg)*	*No. of rats with ulcer / No. of rats studied*	*% ulcer*	*Ulcer index*	P *value*
Normal saline (control)	0.2 ml	18/20	90	30	—
Dibenamine	10	3/10	30	9	<0.01
Propranolol	1	6/10	60	20	>0.05
	5	2/10	20	8	<0.001
Atropine	1	3/10	30	11	<0.01
Mepyramine	10	8/10	80	28	>0.05
Metiamide	5	3/10	30	10	<0.01
Cyproheptadine	5	7/10	70	27	>0.05

Effect of intracerebroventricular (i.c.v.) administration of adrenoceptor antagonists, 6-hydroxydopamine and atropine on cold restraint ulcers

The effect of i.c.v. injection of adrenoceptor antagonists, 6-hydroxydopamine or atropine was investigated on restraint ulcers and the results are shown in Table 3. I.c.v. pretreatment with dibenamine, propranolol, 6-hydroxydopamine and atropine significantly reduced the incidence of restraint ulcers. JB-516 (500 μg i.c.v. for 2 days), a monoamine oxidase inhibitor, significantly enhanced the incidence of ulcers induced by 6 h restraint ($P < 0.01$).

Ulcerogenic effect of i.c.v. administered putative neurotransmitters in unrestrained rats

Ulcerogenic effects of i.c.v. injection of putative neurotransmitters and drugs in normal rats are shown in Figure 2. Adrenaline, noradrenaline, isoprenaline, acetylcholine and physostigmine given i.c.v. led to dose-dependent gastric ulceration. However, dopamine, histamine and 5-HT up to doses of 200, 20 and 20 μg i.c.v. respectively did not produce gastric ulceration.

Effect of i.c.v. pretreatment with antagonists of biogenic amines on gastric ulceration induced by adrenaline, noradrenaline, acetylcholine and physostigmine

Table 4 shows the effect of i.c.v. pretreatment with adrenoceptor blockers and atropine on gastric ulceration induced by i.c.v. adrenaline, noradrenaline, acetylcholine and physostigmine in rats. I.c.v. pretreatment with α- and β-adrenoceptor blockers (yohimbine, dibenamine and propranolol) significantly reduced the incidence of gastric ulceration induced by i.c.v. adrenaline. Dibenamine also protected the animals against noradrenaline (i.c.v.)-induced ulceration. However, dibenamine and propranolol given i.c.v. failed to protect against ulceration induced by i.c.v. acetylcholine and physostigmine. Ulceration induced by adrenaline (i.c.v.), acetylcholine (i.c.v.) and physostigmine (i.c.v.) was blocked by i.c.v. pretreatment with atropine.

Effect of intraperitoneal pretreatment with adrenoceptor and cholinoceptor antagonists on gastric ulceration induced by i.c.v. adrenaline and acetylcholine

The results obtained following intraperitoneal pretreatment with dibenamine, atropine methylnitrate and hexamethonium on i.c.v. adrenaline- and acetylcholine-induced gastric ulceration are shown in Table 5. Intraperitoneal injection of dibenamine blocked the ulcerogenic response to i.c.v. adrenaline but was ineffective against i.c.v. acetylcholine-induced ulceration. Intraperitoneal administration of atropine methylnitrate and hexamethonium significantly reduced the incidence of gastric ulceration induced by i.c.v. adrenaline and acetylcholine.

Effect of bilateral adrenalectomy and vagotomy on gastric ulceration induced by i.c.v. adrenaline and acetylcholine

Table 6 shows the effect of bilateral adrenalectomy and vagotomy on gastric ulceration caused by i.c.v. adrenaline and acetylcholine in normal albino rats. Bilateral adrenalectomy significantly reduced the inci-

Table 3 Effect of intracerebroventricular (i.c.v.) injection of adrenoceptor antagonists, 6-hydroxydopamine, atropine and JB-516 on the incidence of gastric ulceration induced by 2 h restraint at 4°C and 6 h restraint at room temperature

Pretreatment 30 min before restraint (2h at 4°C)	*Dose (μg) (total)*	*No. of rats with ulcer / No. of rats studied*	*% ulcer*	*Ulcer index*	P *value*
Normal saline (control)	20 μl	18/20	90	30	—
Atropine	100	2/10	20	7	<0.001
Dibenamine	200	2/10	20	8	<0.02
Propranolol	150	5/10	50	14	<0.05
6-OHDA*	250	1/10	10	5	<0.001
Normal saline†	0.03 ml	4/14	27	10	—
JB-516†	500	8/10	80	22	<0.01

* Administered once daily for two days.
† Restraint for 6 h at room temperature.

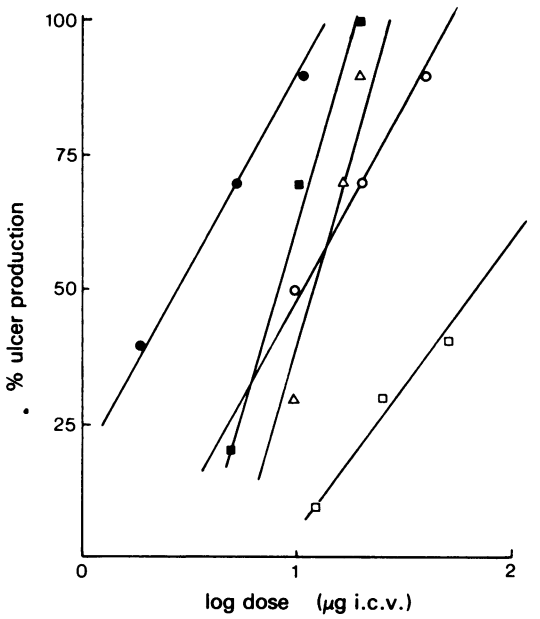

Figure 2 Regression lines showing the gastric ulceration induced by intracerebroventricular administration of adrenaline (●), noradrenaline (○), isoprenaline (□), acetylcholine (△) and physostigmine (■).

dence of gastric ulceration induced by i.c.v. adrenaline but not that induced by acetylcholine. Vagotomy significantly reduced the incidence of gastric ulceration induced by both i.c.v. adrenaline and acetylcholine.

Discussion

That the central nervous system is intimately concerned in the genesis of gastric ulceration is now well known. Electrical stimulation of specific areas of the brain can induce increased gastric acidity and ulceration in animals (Sen & Anand, 1957; Feldman, Bernhaum & Behar, 1961). Stress is believed to be important in the causation of hyperacidity and ulceration (Selye, 1936; Brodie, Marshall & Moreno, 1962). Obviously, there is involvement of the CNS in stress-induced ulceration. Central sympathetic activation is invariably associated with stress (Gordon *et al.*, 1966; Corrodi *et al.*, 1968). The technique of restraint in albino rats provides a model for the study of stress-induced gastric ulceration (Brodie, 1968). If the restraint is combined with cold (4°C) the ulcerogenesis is hastened and the gastric ulceration observed at 2 h is comparable to that observed after 8 h without cold (see Figure 1). Thus, the cold restraint ulcer (CRU) technique provides a suitable model for acute studies on ulcerogenesis (Senay & Levine, 1967; Djahanguiri *et al.*, 1973).

Since vagotomy or spinal transection (at C7) very significantly prevented the cold-restraint ulcer, the peripheral pathways in the production of stress-induced ulceration must be the vagus and the sympathetic outflow. Furthermore, pretreatment with atropine, dibenamine or propranolol successfully prevented the CRU (Table 1 and 2). Bilateral adrenalectomy, however, failed to prevent the cold-restraint ulcer. Other workers have also reported the failure of

Table 4 Effect of i.c.v. pretreatment with adrenoceptor antagonists and atropine on gastric ulceration induced by i.c.v. injection of adrenaline, noradrenaline, acetylcholine and physostigmine

Ulcerogenic agents	*Dose (μg) i.c.v.*	*Pretreatment*	*Dose (μg) i.c.v.*	*No. of rats with ulcer / No. of rats studied*	*% ulcer*	*Ulcer index*	*P value*
Adrenaline	10	—	—	18/20	90	29	—
	10	Yohimbine	100	3/10	30	8	<0.01
	10	Dibenamine	200	2/15	13	4	<0.001
	10	Propranolol	150	5/10	50	13	<0.02
	10	Atropine	100	3/10	30	9	<0.01
Noradrenaline	40	—	—	9/10	90	22	—
	40	Dibenamine	200	3/10	30	9	<0.01
Acetylcholine	20	—	—	9/10	90	32	—
	20	Atropine	100	2/10	20	9	<0.001
	20	Dibenamine	200	8/10	80	28	>0.05
	20	Propranolol	150	8/10	80	27	>0.05
Physostigmine	10	—	—	7/10	70	22	—
	10	Atropine	100	1/10	10	7	<0.001
	10	Dibenamine	200	6/10	60	19	>0.05
	10	Propranolol	150	5/10	50	20	>0.05

The antagonists were administered 30 min prior to the ulcerogenic agents and the ulceration was observed after 24 h.

bilateral adrenalectomy to prevent restraint ulcers (Brodie and Hanson, 1960; Djahanguiri *et al.*, 1973). Increased plasma histamine levels have been observed during stress (Singh *et al.*, 1967). Hayden *et al.* (1978) have reported that metiamide and mepyramine inhibit stress-induced gastric lesions. However, in our study mepyramine and cyproheptadine pretreatment did not afford protection against cold-restraint ulcer. Metiamide, a selective H_2-receptor blocker was, on the other hand, found to antagonize effectively the cold-restraint ulcer.

Drugs which modify the adrenergic and cholinergic mechanisms were injected into the ventricular system of the brain with a view to elucidating the central mechanisms involved in the activation of peripheral sympathetic and parasympathetic outflows, which characterize the CRU. Pretreatment with an i.c.v. injection of dibenamine, propranolol, 6-hydroxydopamine or atropine sulphate significantly reduced the incidence of CRU. A monoamine oxidase inhibitor, JB-516, enhanced the incidence of ulcers. These findings show that both adrenergic and cholinergic mechanisms in the CNS and both central α- and β-adrenoceptors and muscarinic receptors are involved in the genesis of the CRU. In this connection it is interesting to note that Corrodi *et al.* (1968) and Gordon *et al.* (1966) reported an increase in central catecholamines biosynthesis and turnover rate during stress.

In view of the above findings we explored the possibility of inducing gastric ulcers by exogenous admin-

Table 5 Effect of intraperitoneal pretreatment with dibenamine, atropine methylnitrate and hexamethonium on gastric ulceration induced by i.c.v. adrenaline and acetylcholine

Ulcerogenic agents	*Dose (μg) i.c.v.*	*Pretreatment*	*Dose (mg/kg) i.p.*	*No. of rats with ulcer / No. of rats studied*	*% ulcer*	*Ulcer index*	*P value*
Adrenaline	10	—	—	18/20	90	29	—
	10	Dibenamine	10	1/10	10	3	<0.001
	10	Atropine methylnitrate	1	2/10	20	10	<0.001
	10	Hexamethonium*	20	1/10	10	3	<0.001
Acetylcholine	20	—	—	9/10	90	32	—
	20	Dibenamine	10	8/10	80	23	>0.05
	20	Atropine methylnitrate	1	3/10	30	10	<0.01
	20	Hexamethonium*	20	1/10	10	5	<0.001

The antagonists were administered 30 min prior to the neurohumors and the ulceration was observed after 24 h.
* Administered (20 mg/kg i.p.) once daily for two days.

Table 6 Effect of bilateral adrenalectomy and vagotomy on gastric ulceration induced by i.c.v. adrenaline and acetylcholine

Ulcerogenic agents	*Dose (μg) i.c.v.*	*Condition of rats*	*No. of rats with ulcer / No. of rats studied*	*% ulcer*	*Ulcer index*	*P value*
Adrenaline	10	Normal	18/20	90	29	—
	10	Bilaterally adrenalectomized	8/18	39	13	<0.02
	10	Vagotomized	3/10	30	9	<0.01
Acetylcholine	20	Normal	9/10	90	32	—
	20	Bilaterally adrenalectomized	8/10	80	25	>0.05
	20	Vagotomized	2/10	20	9	<0.001

istration of putative neurotransmitters into the cerebral ventricle of rats. It was observed that i.c.v. injection of adrenaline, noradrenaline, isoprenaline, acetylcholine and physostigmine induced dose-dependent gastric ulceration in normal albino rats (see Figure 2). I.c.v. injection of dopamine, histamine and 5-HT failed to induce gastric ulceration. While the 20 µl volume of injection of these putative neurotransmitters is quite large, it cannot be stated with certainty whether the agents reached the central receptor sites for ulcerogenesis. Increased gastric secretion has been observed with intrahypothalamic injection of noradrenaline in rats by Carmona & Slangen (1973). Similarly, Light, Bishop & Kendall (1932) have reported that i.c.v. injection of pilocarpine increases gastric secretion and causes gastric ulceration in rabbits. The ulcerogenic effect of adrenaline (i.c.v.) was significantly reduced by i.c.v. pretreatment with α- and β-adrenoceptor blockers (yohimbine, dibenamine and propranolol). Dibenamine (i.c.v.) also protected the animals from i.c.v. noradrenaline-induced gastric ulceration. Isoprenaline was much less effective than noradrenaline in inducing gastric ulceration (see Figure 2). Furthermore, dibenamine was more effective than propranolol in reducing the incidence of i.c.v. adrenaline-induced gastric ulceration (Table 4). It seems that α-adrenoceptors are more important than β-adrenoceptors in the central nervous system in the pathogenesis of adrenaline (i.c.v.)-induced gastric ulceration. Pretreatment with i.c.v. atropine sulphate significantly prevented the adrenaline (i.c.v.), acetylcholine (i.c.v.) and physostigmine (i.c.v.)-induced gastric ulceration suggesting that muscarinic receptors in the CNS are involved in gastric ulceration induced not only by acetylcholine and physostigmine but also by adrenaline. Blockade of i.c.v. adrenaline-induced ulceration by i.c.v. atropine supports a cholinergic link subsequent to central sympathetic activation. However, central sympathetic activation in acetylcholine and physostigmine-induced ulceration seems unlikely since i.c.v. dibenamine and propranolol failed to likely since i.c.v. dibenamine and propranolol failed to reduce gastric ulceration by these two agents (Table 4).

It was considered interesting to elucidate the peripheral mechanism concerned in the mediation of centrally induced ulcerogenic response of adrenaline and acetylcholine. There are four possible mechanisms through which the centrally initiated stimuli may cause gastric ulceration: (1) increased outflow of impulses through sympathetic nerves; (2) increased parasympathetic outflow along vagus; (3) increased discharge of catecholamines from adrenal medulla; (4) activation of the pituitary-adrenal axis leading to a discharge of adrenal cortical steroids. Adrenaline (i.c.v.)-induced gastric ulceration was blocked by intraperitoneal pretreatment with dibenamine, atropine methylnitrate, hexamethonium and prior bilateral adrenalectomy and vagotomy (Tables 5 and 6) indicating that sympathetic and parasympathetic outflow as well as adrenal cortical steroid and/or catecholamine released from adrenals are involved in this adrenaline-induced ulcerogenesis. The corticoids probably do not play a major role since corticoid-induced gastric ulceration develops in 4 days in rats (Kowalenski, 1959; Robert & Nezamis, 1963). In the present study, on the other hand, adrenaline (i.c.v.) induced gastric ulceration within 24 h. Moreover, inhibition of adrenaline-induced ulceration by dibenamine does not favour the participation of adrenal corticoids, although the possibility that they have an additional contributory role cannot be completely ruled out. These observations suggest an involvement of catecholamines released from the adrenal medulla in the production of gastric ulcers by adrenaline. Furthermore, parenteral catecholamines have been shown to produce gastric ulceration (Brown, Rice & Szakacs, 1959; Sethbhakdi, Pfeiffer & Roth, 1970). Acetylcholine (i.c.v.)-induced gastric ulceration was blocked by intraperitoneal pretreatment with atropine methylnitrate, hexamethonium and vagotomy but not by dibenamine and bilateral adrenalectomy. These observations suggest that increased cholinergic outflow along the vagus is concerned in acetylcholine-induced gastric ulceration. Thus, it may be concluded that both adrenergic and cholinergic mechanisms are operating in the CNS and at the periphery in the pathogenesis of stress-induced gastric ulceration.

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