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EFFECTS OF β-ADRENOCEPTOR DRUG STIMULATION ON VARIOUS MODELS OF GASTRIC ULCER IN RATS

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1 Experiments were designed to evaluate the effect of the pharmacological activation of β-adrenoceptors on various models of gastric ulcer in the rat.

2 Pretreatment with the β-adrenoceptor stimulant drugs, isoprenaline or salbutamol, significantly inhibited stress-induced gastric ulcers. This anti-ulcer effect was abolished by propranolol but not by atenolol, suggesting that β_2-adrenoceptors mediate this response.

3 In the pylorus-ligation model, salbutamol inhibited lesion formation and reduced the intragastric content of hydrogen ions, histamine and pepsin although the latter was only affected with the higher dose of salbutamol.

4 Salbutamol also prevented the ulcerogenic action on the gastric mucosa of an exogenously perfused artificial gastric juice, showing that the anti-ulcer effect is not necessarily dependent on acid inhibition.

5 Salbutamol also reduced the formation of acute ulcers induced by various iatrogenic means (histamine, polymyxin B, reserpine and indomethacin).

6 Long-term treatment with salbutamol accelerated the healing of experimental chronic gastric ulcer.

7 In anaesthetized rats, salbutamol produced a dose-related increase in mucosal blood flow which may contribute to its mode of action.

8 It is concluded that β-adrenoceptor agonists exert preventive and curative effects on gastric damage induced in the rat. This effect seems specific and mediated through β-adrenoceptor activation.

Introduction

It has been postulated that the adrenergic system has an important function in the gastrointestinal tract. This theory is reinforced by the histochemical studies of Costa & Gabella (1971) demonstrating that the gastric mucosa is richly innervated by adrenergic fibres and by the known influence of sympathetic nerve stimulation in gastric physiology (Sanders, 1976).

However, the role of catecholamines in gastric ulceration has not yet been clearly established. Available evidence indicates that α-adrenoceptor stimulant drugs produce, presumably by virtue of their mucosal vasoconstrictor action, an unfavourable effect on the gastric mucosa. The role played by the β-adrenoceptors in gastric ulceration remains controversial.

β-Adrenoceptor stimulant drugs have been reported to inhibit gastric mucosal lesions induced by immobilization, indomethacin or reserpine in rats (Fielding, Router & Curwain, 1975; Kékes-Szabó, 1976). Furthermore, these agents have been shown to reduce the hydrogen ion back diffusion induced by salicylates in exteriorized segments of canine gastric mucosa (McGreevy & Moody, 1977; Ritchie & Shearburn, 1977). In contrast, Hano, Bugajski & Danak (1977) in rats and Djahanguiri, Sadeghi, Hemati, Pousti & Firouzabadi (1968) in guinea-pigs, found that isoprenaline was ineffective in protecting the animals against the ulcerogenic effects of stress and histamine, respectively.

In the pathogenesis of gastric mucosal erosion it is generally accepted that gastric acid secretion (Alphin, Vocak, Gregory, Bolton & Tawes, 1977), histamine formation (Goldman & Rosoff, 1968), degranulation of mast cells (Guth & Hall, 1966) and reduction of mucosal blood flow (Guth, 1972; Hase & Moss, 1973) along with inhibition in the biosynthesis of prostaglandins (Whittle, 1981) are important factors.

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It has recently been shown that β-adrenoceptor agonists are able to decrease both acid secretion (Misher, Pendleton & Staples, 1959; Bass & Pattersson, 1967; Lundell & Svensson, 1974) and gastric histamine formation (Lundell & Svensson, 1974) in rats. In other experimental animals these agents have been found to increase gastric mucosal blood flow (Curwain & Holton, 1972; Reed & Smy, 1976). Of interest also is the finding that incubation of rat stomach fundus and other tissues with catecholamines *in vitro* increased the production of prostaglandin E (Pace-Asciak, 1972; Collier, McDonald-Gibson & Seed, 1976) which has the property of protecting gastric mucosa against injury (Robert, Nezamis, Lancaster & Hanchar, 1979).

In the present study we have investigated the effect of β-adrenoceptor stimulant drugs on various models of acute gastric ulceration in the rat with reference to their influence on histamine, hydrogen ion and intragastric pepsin concentrations and on gastric mucosal blood flow. We have also determined whether the effect was indeed independent of acid inhibition. The effect on the healing of chronic gastric ulcer was also examined. To avoid potential side effects due to activation of β_1-adrenoceptors, salbutamol, a selective β_2-agonist, has been used in the major part of this study. Some of these results were presented at the 7th International Congress of Pharmacology (Martí-Bonmatí, Aliño, Lloris & Esplugues, 1978).

Methods

Animals

Male Wistar rats, weighing 200–250 g, were deprived of food but allowed free access to water 24 h before the start of the experiments. They were kept in cages provided with a wire net base to avoid coprophagy. During the experiments, the animals, if not otherwise indicated, were kept in a temperature of 22–24°C.

Acute gastric mucosal erosions

Stress-induced gastric lesions These were produced by the method described by Senay & Levine (1967). The animals were restrained in rigid plastic tubes and placed in a cold chamber at a temperature of 3 ± 1°C for a period of 3 h. Thereafter, the rats were killed and the stomachs examined for mucosal lesions.

Pylorus-ligation ulcers Ulcer formation was obtained by pyloric ligation according to the procedure first described by Shay, Komarov, Fels, Meranze, Gruenstein & Siplet (1945). The surgical manipulation was carried out under light ether anaesthesia. The animals were killed 12 h after ligation of the pylorus, the abdomen opened and the stomach removed. The gastric content was carefully collected and its volume measured. Aliquots were analysed for hydrogen ion concentration by electrometric titration to pH 7 with 0.1 N NaOH; the pepsin concentration was estimated by the colorimetric method of Anson (1938) involving haemoglobin digestion (2%, pH 2, 37°C, 15 min), followed by alkaline condensation with Folin-Ciocalteau Reagent, and measurement of the absorption at 660 nm (Unicam SP1800 spectrophotometer); histamine concentration was estimated by the method of Hakanson, Rönnberg & Sjölund (1972) in which alkaline condensation under nitrogen, at 0°C, with *ortho*-phthaldialdehyde is followed by acidification (pH 1.3, 60 min) and measurement of fluorescence (350/450 nm, EEL fluorometer). The lesions in the mucosa were recorded for evaluation.

Gastric distension erosions A modification of the rat preparation described by Alphin *et al.* (1977) was used to produce ulcers. A simulated gastric juice (100 mM H^+, 600 mg pepsin/l) was continuously perfused in anaesthetized rats (urethane 1.6 g/kg i.m.) via the oesophagus through the stomach at a rate of 0.5 ml/min. The intragastric pressure necessary for the development of gastric lesions was adjusted by placing the open end of the outlet duodenal catheter 120 mm above the stomach level. After 3 h the animals were killed and the stomachs examined for mucosal erosions.

Histamine-induced gastric lesions The technique of Okabe, Takeuchi & Takata (1976) was used. The animals received a single intraperitoneal injection of histamine dihydrochloride 300 mg/kg. Four hours later the rats were killed and the stomachs examined for mucosal lesions.

Polymyxin B-induced gastric lesions The lesions were produced by the method of Franco-Browder, Masson & Corcoran (1959). The animals received a single intraperitoneal injection of 1.25 mg/kg of the histamine liberator agent, polymyxin B; 2 h later the rats were killed, the stomachs removed and the glandular erosions induced in the gastric mucosa recorded.

Reserpine-induced gastric lesions The method used to induce gastric erosions by means of reserpine was that described by Gupta, Tangri & Bhargava (1974). A single intramuscular injection of reserpine 5 mg/kg produced marked gastric ulcerations. The rats were killed 9 h later and the stomachs removed and examined for gastric erosions.

Indomethacin-induced gastric lesions The technique of Whittle (1975) was used. The animals were given indomethacin 30 mg/kg subcutaneously and killed 6 h later. The stomach from each animal was removed and gastric mucosal damage assessed.

Chronic gastric ulcer: acetic acid injection model

The experiment was carried out according to the method of Takagi, Okabe & Saziki (1969). The rats were anaesthetized with ether and subjected to a midline laparotomy. Once the stomach was exposed, 0.025 ml of 20% acetic acid was carefully injected under the serosal surface at the junction of the body of the glandular stomach and the antrum. Care was taken to avoid leakage of acid and disturbance of blood vessels. The animals were killed by an overdose of pentobarbitone 21 days after operation. The ulcerated area (mm^2) was measured under a dissecting microscope.

Measurement of gastric mucosal blood flow

Gastric mucosal blood flow was determined by radioactive aniline clearance (Curwain & Holton, 1972). The animal preparation used was similar to that described by Main & Whittle (1973). Briefly, rats anaesthetized with urethane (1.6 g/kg i.m.) were continuously perfused (0.5 ml/min) through a catheter inserted into the oesophagus, with acid saline (0.01 N HCl, pH 2) in order to ensure aniline trapping. The perfusion fluid was collected, at 20 min intervals, from a cannula inserted into the stomach via the proximal duodenum. A stock solution of carrier aniline sulphate (3.5 mg/ml) and [^{3}H]-analine (5 μCi/ml) in sterile saline was prepared. One hour after surgery [^{3}H]-aniline was injected into a jugular vein in a loading dose of 2 μCi/kg followed by a continuous infusion of 0.033 μCi kg^{-1} min^{-1} to maintain a steady plasma concentration. The [^{3}H]-aniline content of arterial blood and gastric perfusate was determined in a Nuclear Chicago liquid scintillation counter. Clearance, which gives an expression for the blood flow to the gastric mucosa, was calculated as the ratio of the gastric output to blood concentration of [^{3}H]-aniline and expressed as percentage of the control value, which is the mean of the three values prior to injection of the drug. Acid content was determined by titration of aliquots with 0.1 N NaOH using phenol red as indicator. Arterial blood pressure was continuously monitored from a cannula in a carotid artery connected to a pressure transducer coupled to a recorder device.

Experimental procedure

The animals were divided into groups comprising a minimum of 10 animals each and receiving the following combination of drugs and dosages: 2 ml/kg physiological saline i.p. (control group); isoprenaline or salbutamol (0.04 and 0.4 mg/kg i.p. for both drugs); propranolol (2 mg/kg i.p.); propranolol plus isoprenaline or salbutamol (0.4 mg/kg i.p.); atenolol (20 mg/kg i.p.); atenolol plus isoprenaline or salbutamol (0.4 mg/kg i.p.).

All drugs, except indomethacin, were dissolved in physiological saline solution (0.9% w/v NaCl solution) and administered in a volume not exceeding 2 ml/kg. Indomethacin was dissolved in saline with the aid of dropwise addition of NaOH 0.1 N and ascorbic acid was added to the isoprenaline solution to prevent oxidation.

The β-adrenoceptor agonists were given to the rats 15 min prior to the experiment. In the case of pylorus ligation and reserpine-induced ulcers, the treatment was repeated 6 h later. The β-blocking drugs were administered 30 min before immobilization. In the chronic gastric ulcer model, salbutamol and saline were given once daily for a period of 20 days starting 24 h after acetic acid injection.

Evaluation of the ulcerogenic index

At the end of the experiments the animals were killed by an overdose of pentobarbitone, the stomach of each removed, cut open along the greater curvature, pinned out on cork and the length of each elongated lesion (mm) was measured individually under a dissecting microscope. The acetic acid-induced ulcers were round or oval in shape so that the area (mm^2) of each lesion was measured. To obtain the ulcer index the length or area of the lesions in each group was summed and the result divided by the total number of rats. The percentage of animals with lesions in each group was also recorded. Student's *t* test was used for statistical evaluation of data. The persons measuring the ulcers were unaware of the treatment administered.

Results

Acute gastric mucosal erosions

Stress-induced gastric lesions The effect of two β-adrenoceptor agonists, isoprenaline and salbutamol, was investigated in stress lesions induced by restraint and exposure to cold. The results are shown in Table 1. Both agonists significantly reduced ulcer formation. Propranolol did not prevent stress ulceration. However, this β-antagonist, when administered in combination with isoprenaline or salbutamol, abolished the protective effect of the β-agonists completely. In contrast, atenolol did not modify either the

Table 1 Effect of the β-adrenoceptor agonists, isoprenaline and salbutamol, on gastric ulcers induced in the rat by 3 h restraint plus cold (3 ± 1°C) and its modification by pretreatment with the β-antagonists propranolol and atenolol

Treatment	*Dose* (mg/kg i.p.)	*Pretreatment*	*Dose* (mg/kg i.p.)	*Number of rats*	*Animals with ulcers (%)*	*Ulcer index* (mm)	P
Control	—	—	—	38	100	12.8 ± 2.8	—
Isoprenaline	0.04	—	—	16	75	6.9 ± 1.7	< 0.05
	0.4	—	—	16	60	5.2 ± 1.3	< 0.05
Salbutamol	0.04	—	—	16	81	5.0 ± 1.4	< 0.05
	0.4	—	—	16	81	3.9 ± 1.5	< 0.01
Propranolol	2	—	—	16	100	13.3 ± 2.7	NS
Isoprenaline	0.4	Propranolol	2	16	87	11.7 ± 2.6	NS
Salbutamol	0.4	Propranolol	2	16	80	12.3 ± 1.2	NS
Atenolol	20	—	—	16	100	12.6 ± 2.7	NS
Isoprenaline	0.4	Atenolol	20	16	86	6.1 ± 1.6	< 0.05
Salbutamol	0.4	Atenolol	20	16	75	4.7 ± 2.1	< 0.05

Treatments were administered 15 min prior to immobilization and pretreatments 30 min before agonist administration. Ulcer index values are mean ± s.e.mean. The comparisons (*P* values) between control and treated groups were made by Student's *t* test. NS is not significant.

ulcer index from the control group or the anti-ulcer effect of the β-agonists used.

Pylorus-ligation ulcers Reduction of the Shay's conventional period of time of pyloric ligation from 18 to 12 h resulted in extensive gastric erosions in 80% of the animals studied. Table 2 shows the effect of salbutamol on this type of gastric ulcer lesions. Salbutamol administered (i.p.) 15 min prior to and 6 h after pyloric occlusion significantly reduced the severity of gastric erosions. This antiulcer effect was accompanied by a moderate although not statistically significant reduction of the volume of the gastric juice collected at the end of the experiment. However, as shown in Table 2, the acid concentration found in the gastric content of animals receiving salbutamol was markedly reduced mainly at the dose of 0.4 mg/kg.

The reduction in the histamine content of the gastric juice was less pronounced than that observed for the acid concentration. With respect to pepsin, salbutamol, significantly reduced its concentration in the group receiving 0.4 mg/kg but the lower dose of the drug failed to affect pepsin production significantly.

Gastric distension erosions In this and previous studies from this laboratory (Martí-Bonmatí, Aliño, Lloris & Esplugues, 1980), acute gastric lesions were induced in the glandular part of the stomach by the combined action of hydrochloric acid (0.1 N), pepsin (600 mg/l) and intragastric distension (120 mmH_2O). The rumenal segment was rarely compromised (incidence less than 5%) and disturbances at this level consisted mainly in petechia and diffuse inflammatory reactions.

In this model, pretreatment with salbutamol produced a significant protection (Table 3) as indicated by the reduction in ulcer index.

Histamine and polymyxin B-induced gastric lesions Acute gastric erosions were induced in rats at 4 and 2 h after administration of histamine and polymyxin B respectively. Both methods produced several haemorrhagic areas distributed over an erythemic

Table 2 Effect of the β_2-adrenoceptor agonist, salbutamol, on the 12 h pylorus-ligated rat

Treatment	*Dose* (mg/kg i.p)	*Number of rats*	*Animals with ulcers (%)*	*Ulcer index* (mm)	*Gastric content parameters* *Volume* (ml)	*Acid* (Eq H^+ /h)	*Pepsin* (mg/h)	*Histamine* (μg/ml)
Control	Untreated	12	83	5.06 ± 0.8	8.5 ± 0.7	44.3 ± 8.6	0.56 ± 0.12	0.29 ± 0.04
Salbutamol	0.04 × 2	12	58	2.97 ± 0.6*	7.1 ± 0.7	22.3 ± 7.4*	0.51 ± 0.09	0.19 ± 0.03*
Salbutamol	0.4 × 2	12	50	1.50 ± 0.5**†	6.8 ± 0.5	3.4 ± 2.9**	0.33 ± 0.04*	0.13 ± 0.01**

Ulcer index and gastric content values are mean ± s.e.mean. *$P < 0.05$ and **$P < 0.01$ compared with control. †$P < 0.05$ with respect to the lower dose.

Table 3 Effect of the β_2-adrenoceptor agonist, salbutamol, on acute and chronic gastric ulcers produced by various procedures in rats

Ulcers induced by	*Dose* (mg/kg i.p)	*Number of rats*	*Experimental period* (h)	*Animals with ulcers* (%)	*Ulcer index* (mm^2)	P
Gastric distension	—	12	3	100	7.9 ± 1.6	—
	0.04	12	3	100	4.1 ± 1.7	< 0.05
	0.4	12	3	100	3.6 ± 1.5	< 0.05
Histamine	—	15	4	80	10.2 ± 2.8	—
	0.04	15	4	46	3.4 ± 1.2	< 0.05
	0.4	15	4	33	1.1 ± 1.3	< 0.05
Polymyxin B	—	14	2	71	2.5 ± 0.7	—
	0.04	14	2	43	0.7 ± 0.3	< 0.05
	0.4	14	2	33	0.3 ± 0.4	< 0.01
Indomethacin	—	12	6	100	5.9 ± 1.6	—
	0.04	12	6	42	1.2 ± 1.7	< 0.05
	0.4	12	6	25	0.8 ± 1.2	< 0.05
Reserpine	—	14	9	86	5.5 ± 1.2	—
	0.04	14	9	78	2.2 ± 1.1	< 0.05
	0.4	14	9	78	1.1 ± 0.7	< 0.005
Acetic acid*	—	10	20	100	38.9 ± 6.4	—
	0.04	10	20	90	24.5 ± 4.3	< 0.05
	0.4	10	20	60	13.8 ± 2.3	< 0.005

Ulcer index values are mean ± s.e.mean. The comparison (*P* values) between control and treated groups were made by Student's *t* test. *In the acetic acid group, the experimental period is expressed in days and the ulcer index in mm^2.

and oedematous mucosa and ulcers mainly located in the body part of the stomach. The incidence and ulcer index were significantly reduced after pretreatment with salbutamol (Table 3).

Indomethacin and reserpine-induced gastric lesions

These methods produced small longitudinal lesions distributed all over the stomach although a higher proportion was found in the lesser curvature. Salbutamol significantly reduced ulcer formation in both models (Table 3). It should be noted that in all the acute ulcer models, with the exception of gastric distension and reserpine, the number of animals with ulcers was reduced by treatment with β-agonists.

Chronic gastric mucosal erosions: acetic acid injection model

The administration of salbutamol for 20 days produced a moderate but significant curative effect (Table 3). This agent at 0.4 mg/kg produced complete healing in 40% of treated rats. With the lower dose complete healing was obtained only in 10% of the rats.

Gastric mucosal blood flow

Clearance of [^{3}H]-aniline and acid secretion was determined during basal conditions and after single intraperitoneal injections of salbutamol at 0.04 or 0.4 mg/kg. Under resting conditions, clearance and acid secretion were stable. The lower dose of salbutamol caused a negligible reduction of the basal acid output (by 5.3 ± 3.6%, $n = 4$) while the higher dose produced a moderate inhibition (by 18.3 ± 6.2%, $n = 4$, $P < 0.05$). In contrast both doses of this drug induced a marked and dose-related increase in mucosal blood flow (by 33.3 ± 8% and 85 ± 11%, respectively) until a steady plateau level was reached. A dose-dependent fall in mean arterial blood pressure (16 ± 7 mmHg and 38 ± 12 mmHg for the lower and higher dose, respectively) accompanied these changes.

Discussion

The results obtained in the present study show the wide protective activity afforded by the pharmacological activation of β-adrenoceptors against ulcer formation produced by various methods in rats.

In the first set of experiments it was found that both β-adrenoceptor stimulants, isoprenaline (β_1 and β_2) and salbutamol (β_2) attenuated the gastric mucosal lesions induced in rats by the concomitant application of cold and restraint. These results are comparable with those obtained by Kékes-Szabó (1976) in rats subjected to simple immobilization for 24 h. By con-

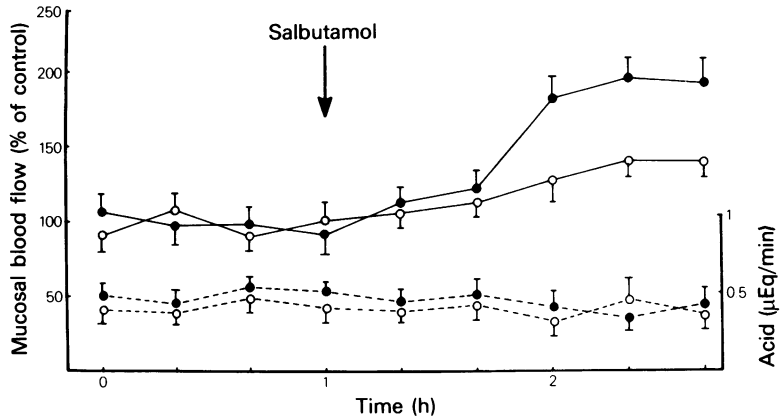

Figure 1 Effect of the β_2-adrenoceptor agonist, salbutamol, (○) 0.04 mg/kg and (●) 0.4 mg/kg i.p., on basal mucosal blood flow (continuous lines) and spontaneous acid secretion (broken lines) in the anaesthetized rat. The results are the means from four individual animals. Vertical lines are s.e.mean.

trast Hano *et al.* (1977) reported that in rats exposed to restraint and cold, isoprenaline failed to prevent the generation of gastric mucosal erosions. However, when the negative results of these authors are considered by confidence intervals in the way suggested by Rothman (1978) a beneficial effect of the amine is shown.

In this part of the study it was also found that the protection afforded either by isoprenaline or salbutamol against stress-ulcer formation was virtually abolished by the β-adrenoceptor antagonist propranolol but remained unmodified after the β_1 selective blocking agent, atenolol. Therefore, the antiulcer effect of these drugs may be attributed to a selective β-adrenoceptor mechanism, probably of the β_2 type.

In the second set of experiments, it was found that salbutamol protected against gastric ulcers induced by pyloric ligation. This effect appears to be produced, at least in part, by the suppression of acid secretion, since the acid concentration of the gastric content in the salbutamol-treated animals was profoundly reduced as compared with the control. However, diminution of the gastric hydrogen ion concentration may be either the result of an antisecretory action or reflect the leaking back of hydrogen ions into the mucosa which will be removed by the increase in mucosal blood flow produced by salbutamol. The antisecretory effect of β-adrenoceptor agonists described in pylorus-occluded rats (Bass & Patterson, 1967; Yamaguchi, Hiroi & Kumada, 1977) as well as in other animal species (Curwain & Holton, 1972; Curwain, Holton, McIsaac & Spencer, 1974; Archibald, Moody & Simons, 1974; Reed & Smy, 1976; Daly, Long & Stables, 1978) is evidence against the hypothesis of hydrogen ion back diffusion although this possibility cannot be ruled out. Indeed, increased back diffusion of acid into the mucosa would rather be associated with increased erosive incidence (Davenport, 1970).

Although pepsin plays a major role in the genesis of gastric erosions, the effect of catecholamines on pepsin secretion has received much less attention than hydrochloric acid. By studying data collected on animal experiments, Holton (1973) concluded that β-agonists had a stimulant effect on pepsin secretion. By contrast, in this study, it was found that salbutamol reduced pepsin secretion in the group of rats receiving the larger dose of the drug while reducing the lesion index for both doses. This suggests that inhibition of pepsin secretion, although it may be of importance, is not essential in the protective effect of β-agonists.

The antiulcer effect elicited by salbutamol in the pylorus-ligation model may also be related to a restrictive activity on histamine formation (Assem & Feigenbaum, 1972; Lundell & Svensson, 1974). In fact, this mechanism has been previously suggested by Curwain *et al.* (1974) to explain the antisecretory effects of β-adrenoceptor agonists. This view is further supported by the present results showing lower histamine levels in the gastric juice from rats receiving salbutamol. This mechanism may also be responsible for the antiulcer effect of salbutamol against polymyxin B-induced gastric ulcers where histamine is known to be released.

In the model of gastric ulcer production by histamine, treatment with salbutamol also elicited a clear anti-ulcer effect that could be related to a direct antagonism of this drug to the histamine-induced increase in gastric acid secretion and microvascular permeability (Green, 1972; Lundell & Svensson, 1974).

The preventive effect produced by salbutamol on

reserpine and indomethacin-induced ulcers are in close agreement with the results obtained by Kékes-Szabó (1976) and Fielding *et al.* (1975) respectively. Although the ulcerogenic mechanism of reserpine is still unclear, the antiulcer effect of the β-agonist could be related to an effect on the same factors allegedly involved in the deleterous action of reserpine, such as increased acid production, mast cell degranulation and vasomotor problems (Räsänen & Taskinen, 1976).

To determine whether a drug prevents gastric damage by some mechanism other than acid inhibition various models have been used. In the present work it has been demonstrated that salbutamol reduced ulcer formation induced by an exogenous acidic-solution. Since prostaglandins exert a similar effect (Whittle, 1975; Martí-Bonmatí *et al.*, 1980), and β-agonists promote the production of these substances in rat stomach (Pace-Asciak, 1972), the possibility that prostaglandins mediate, at least in part, the antiulcer effect of β-agonists should be taken into consideration.

In 1969, Takagi *et al.* introduced the reliable method of injecting acetic acid into the submucosa of the rat stomach wall for producing chronic ulceration. In this study it was found that long-term treatment with salbutamol accelerated the healing of chronic gastric ulcer so produced. Whether this curative action is the direct consequence of increased mucosal regeneration, of enhanced mucosal blood flow or simply of acid inhibition remains to be elucidated.

In the last part of the present work it was found that salbutamol elicited a two fold increase in gastric mucosal blood flow in anaesthetized rats. This result is in agreement with those obtained for isoprenaline in both conscious and anaesthetized animals (Curwain & Holton, 1972; Curwain *et al.*, 1974; Archibald *et al.*, 1974; Reed & Smy, 1976; Ritchie & Shearburn, 1977). By contrast, it has recently been reported that β_2-agonists do not significantly affect mucosal blood flow in Shay rats (Bernardini, Del Tacca, Martinotti & Soldani, 1980) although this may be due to the method used (aminopyrine) which seems unsuitable for small animals (Main & Whittle, 1972).

The results obtained in the anaesthetized rat, apart from illustrating the divergent effects of β-adrenoceptor agonists on gastric acid secretion and mucosal blood flow, suggest that the anti-ulcer effect of salbutamol may be due to its action on mucosal blood flow, a conclusion also reached by other authors (Ritchie & Shearburn, 1977; Johnston & McIsaac, 1980) in studying experimental canine gastritis.

In conclusion, β-adrenoceptor stimulant drugs prevent the development of experimental gastric ulcers induced by surgical, stress-related or iatrogenic means in rats. This action appears to be related to the activation of β-adrenoceptors and does not only rely on acid inhibition. This work may have important clinical implications and supports the concept that β_2-adrenoceptor agonists, as a group, should be investigated further for their possible effectiveness in the treatment of peptic ulcer, at least in cases of resistance to conventional anti-ulcer treatment regimens. Clinical studies are needed to support this assumption.

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