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Effects of Selective β-Adrenoceptor Antagonists on Gastric Ulceration in the Rat

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Abstract

Metoprolol and butoxamine, β-adrenoceptor antagonists which act selectively at the β_1- and β_2-adrenoceptors, respectively, have been investigated for their actions on the ethanol, indomethacin and cold-restraint stress ulcer models.

Oral administration of butoxamine but not metoprolol significantly attenuated gastric mucosal damage in the three types of ulcer model. Intraperitoneal injection of butoxamine reduced indomethacin ulceration but not that of the other two models. The stimulatory effect of butoxamine on the gastric mucosal potential difference and intramucosal mucus level correlated positively with its anti-ulcer action. Only oral administration of butoxamine significantly increased the mucosal prostaglandin E_2 (PGE_2) level but not after intraperitoneal injection. Oral administration of butoxamine also significantly increased the mucosal PGE_2 level in the three types of ulcer model but this drug was only effective in the indomethacin ulcer model after intraperitoneal injection. Gastric acid and pepsin output were not affected by either drug. Metoprolol significantly reduced systemic blood pressure; this could be attributed to a reduction in gastric mucosal blood flow.

These results imply that β_2-adrenoceptors play a significant role in the pathogenesis of gastric ulceration. We suggest that the anti-ulcer effect of butoxamine was in part a result of strengthening of the mucosal barrier but that this was not effected by modification of acid or pepsin secretions in the stomach. Stimulation of PGE_2 in the gastric mucosa could contribute in part to the anti-ulcer action of the drug, especially when given by the oral route.

The non-selective β-adrenoceptor antagonist propranolol has been reported to inhibit gastric mucosal necrosis induced by noxious agents and stress in mice (Bhandare et al 1990) and in portal hypertensive rats (Woo & Cho 1994). The type of β-adrenoceptor involved in this action is not, however, clear.

Previous results showed that propranolol elevated the gastric potential difference and intramucosal mucus level (Kaan & Cho 1996). In fact, preservations of gastric mucus level, potential difference and mucosal blood flow are major factors that contribute significantly to the enhancement of the gastric mucosal barrier (Menguy 1969; McGreevy 1984; Jacobson 1985). Improvement of these parameters increases the resistance of the vulnerable epithelium against the damaging action of gastric acid and other ulcerogenic substances (Menguy 1969). Prostaglandin E_2 (PGE_2) also protects against mucosal barrier disruption (Bommelaer & Guth 1979). Alternatively, reduction of gastric acid (Cho & Ogle 1990b) and pepsin (Sonnenberg 1988) secretions is in part responsible for protection against ulceration. It has been shown that β-adrenoceptor agonists stimulate acid output in isolated rat stomach and that these actions can be antagonized by β-blockers (Canfield et al 1981). These observations suggest that blocking the β-adrenoceptors not only strengthens the mucosal barrier but also could alleviate the aggressive action of acid and perhaps pepsin on the gastric mucosa. Clarification of the type of β-adrenoceptors involved in these actions is also of great interest.

We have, therefore, used metoprolol and butoxamine, selective for β_1- and β_2-adrenoceptors respectively, to investigate the role of the β-adrenergic system in the three types of ulceration including ethanol, indomethacin and stress, with reference to their actions on the gastric mucosal barrier and on acid and pepsin secretions.

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Materials and Methods

General

Male Sprague–Dawley rats, 220–240 g, were housed in a temperature- and humidity-controlled room (22°C, 65–70% relative humidity) and fed with a standard diet of laboratory chow (Ralston, Purina) and tap water. Animals were fasted 24 h before drug administration, but allowed free access to water.

Induction of gastric mucosal damage in conscious animals

Animals were given either saline (0·9% NaCl, w/v), (±)-metoprolol (Sigma; 5 or 10 mg kg^{-1}) or butoxamine (Sigma; 2·5 or 5 mg kg^{-1}) intraperitoneally or orally. These doses, expressed in moles, were similar for the two drugs. The ulcerogenic challenge was given 30 min after drug administration. Three types of ulcer model were employed: ethanol, indomethacin and stress. In the ethanol-treated animals, a single oral dose (10 mL kg^{-1}) of 60% v/v ethanol was given to the animals via a gastric tube for 30 min. In the indomethacin model, 30 mg kg^{-1} indomethacin (Sigma), prepared in 1% methylcellulose (Sigma), was administered orally to the animals for 4 h. Cold-restraint stress was also used (Senay & Levine 1967). Animals were immobilized individually in restraint cages at 4 ± 1°C for 2 h.

Measurements of lesion index and intramucosal mucus level
All rats were killed by a blow on the head followed by cervical dislocation. The stomachs were removed and dissected along the greater curvature, under an illuminated magnifier, to expose the glandular mucosa. Using a single-blind method, lesion areas in the ethanol-induced mucosal necrosis were measured as previously described (Woo & Cho 1994). In the indomethacin and stress models, mucosal damage was directly measured along the ulcer length (Cho & Ogle 1990a).

To determine the intramucosal mucus level, gastric glandular mucosa was fixed in a 10% buffered formalin solution and processed for paraffin embedding. Sections (6 μm) were cut and stained with periodic acid-Schiff reagent. The amount of mucus within the mucosa was assessed by measuring the relative thickness of the mucus-containing cells (Luk et al 1994). This method was based on the determination of the length of the gastric pit and isthmus over the total mucosal thickness (× 100). For each section, four sets of measurement were taken and the results were averaged.

Preparation of ex-vivo chamber in anaesthetized animals
Animals were anaesthetized with pentobarbitone sodium (Abbott; 60 mg kg^{-1}, i.p.) and kept warm with a heating lamp. The trachea was cannulated and the ex-vivo chamber was prepared as described previously (Wong et al 1986). The experiment consisted of two sequential periods of 15 and 30 min. In the first period, the chamber was filled with deionized water (1·5 mL), which was replaced by the same solution at the beginning of the second period. Saline (2 mL kg^{-1}), metoprolol (5 or 10 mg kg^{-1}) or butoxamine (2·5 or 5 mg kg^{-1}) were given to the animals by intraperitoneal injection. The chamber solution was kept in the chamber until the end of the second period. In a separate experiment, the deionized water was replaced by the same solution or by a β-blocker (metoprolol, 5 or 10 mg kg^{-1} or butoxamine, 2·5 or 5 mg kg^{-1}) in deionized water at the beginning of the second period. This incubated solution remained in the chamber until the end of the experiment. All the chamber solutions were collected for determination of gastric pepsin and hydrogen ion (acid) output. The gastric mucosal blood flow and potential difference were also examined in this study. The left carotid artery of each rat was cannulated for blood-pressure and heart-rate measurements throughout the experiment.

Measurements of gastric mucosal blood flow, systemic blood pressure and heart rate
The gastric mucosal blood flow was measured (Shepherd & Riedel 1982) before drug administration and at the end of each experiment by means of a laser Doppler flow-meter (Periflux, Sweden). The blood flow was recorded in arbitrary units. Blood pressure and heart rate were recorded on a physiograph (Narco MK-IV, USA). Arterial blood pressure (mmHg) was expressed as the mean blood pressure, derived as diastolic plus 1/3 of the pulse pressure. Heart rate was calculated as beats min^{-1}.

Determination of acid and pepsin secretion
The chamber luminal solution was collected at 15 and 45 min, and was stored at −70 ± 2°C until measurement of acid and pepsin secretion. All samples were titrated with 0·01 M NaOH to pH 7·4 with an autotitrator (Radiometer, TTT 80, Denmark). The luminal pepsin activity was determined by the method developed by Berstad (1975) in which bovine haemoglobin (2·5%, Sigma; 2 mL) is used as substrate. After these had been mixed with HCl (0·3 M; 0·5 mL) the solution was immediately incubated at 25°C for 10 min; 0·3 M trichloroacetic acid was added to terminate the reaction and the precipitate was filtered. Optical density at 280 nm was measured with a Beckman DU 650 spectrophotometer. The result was calculated using a pepsin standard (from porcine stomach mucosa; Sigma) and the standard curve ranged from 0 to 15 μg.

Determination of PGE_2 in the gastric mucosa
Mucosal PGE_2 was measured after the administration of the antagonists and also after lesion-inducing treatment. After the rats were killed, their stomachs were quickly removed. The glandular mucosa was removed by scraping with a glass slide at 0°C and the mucosal samples were frozen in liquid nitrogen and then stored at −70°C until assay.

When tissue PGE_2 was determined, the mucosal sample was placed in ice-cold Kreb's solution. The sample was then homogenized and centrifuged at 15 000 *g* for 20 min at 4°C. PGE_2 was measured using a [^{125}I] radioimmunoassay kit (Amersham). The protein level was measured by Coomassie blue G dye-binding assay (Read & Northcote 1981).

Measurement of potential difference and statistical analysis
Potential difference was measured by the method of Morimoto et al (1994). One of the KCl-agar electrodes was placed in the ex-vivo chamber, the other was inserted into the peritoneal cavity. The potential difference was recorded at 15 and 45 min.

All data were expressed as means ± s.e.m. Statistical significance between groups was analysed by unpaired Student's *t*-test and analysis of variance.

Results

The effects of butoxamine on the three types of ulcer model are shown in Table 1. Butoxamine, especially when given orally, significantly ($P < 0·05$) reduced gastric mucosal damage in the three types of ulcer model. Metoprolol, irrespective of dose and route of administration, had no effect on the three types of ulcer model.

The intramucosal mucus ratio in the gastric mucosa of untreated animals was 28 ± 4. This ratio was significantly higher than those of animals which were challenged with the three ulcerogenic stimuli ($P < 0·05$). Butoxamine also successfully preserved the integrity of the intramucosal mucus (Table 2).

Table 3 shows the effects of butoxamine and metoprolol on gastric mucosal blood flow and potential difference. Butoxamine at both doses did not affect the gastric mucosal blood flow, irrespective of the route of administration, but significantly increased the potential difference ($P < 0·05$). Metoprolol, on the other hand, reduced the gastric mucosal blood flow ($P < 0·05$) but did not affect the potential difference.

Table 4 shows the effects of β-blockers on systemic blood pressure and heart rate. Butoxamine did not affect these parameters. Metoprolol, after either route of administration, dose-dependently reduced the blood pressure ($P < 0·05$) and heart rate ($P < 0·05$).

Table 1. Effects of β-blockers on ethanol (60%)-, indomethacin (30 mg kg^{-1})- or cold-restraint stress-induced gastric mucosal damage.

Pretreatment	Dose (mg kg^{-1})	Ethanol (mm^2)	Indomethacin (mm)	Stress (mm)
Intraperitoneal route				
Saline, 2 mL kg^{-1}		35 ± 5·3	9 ± 1·7	2·7 ± 0·4
Butoxamine	2·5	35 ± 9·2	4 ± 1·3*	3·3 ± 0·9
	5·0	37 ± 10·6	3 ± 1·2**	1·1 ± 0·5
Metoprolol	5·0	47 ± 6·5	5 ± 1·3	1·3 ± 0·5
	10·0	51 ± 10·7	6 ± 2·0	2·9 ± 1·2
Oral route				
Water, 2 mL kg^{-1}		41 ± 5·0	7 ± 1·3	3·1 ± 0·7
Butoxamine	2·5	14 ± 3·0***	4 ± 0·7*	3·5 ± 1·2
	5·0	25 ± 5·1*	4 ± 0·6*	0·8 ± 0·4**
Metoprolol	5·0	23 ± 7·8	10 ± 1·2	3·8 ± 1·1
	10·0	25 ± 6·2	11 ± 2·2	2·5 ± 1·1

The β-blockers were given 30 min before treatment to induce mucosal damage. Values are the means ± s.e.m. from 8–12 rats. *$P < 0.05$, **$P < 0.02$ and ***$P < 0.001$ compared with its own vehicle control.

Table 2. Effects of β-blockers on the relative length of intramucosal mucus-secreting units (ratio × 10^2) after challenge with ethanol (60%), indomethacin (30 mg kg^{-1}) or cold-restraint stress.

Pretreatment	Dose (mg kg^{-1})	Ethanol (mm^2)	Indomethacin (mm)	Stress (mm)
Intraperitoneal route				
Saline, 2 mL kg^{-1}		7 ± 2·1	11 ± 1·6	11 ± 1·1
Butoxamine	2·5	9 ± 1·2	20 ± 1·3*	13 ± 4·3
	5·0	9 ± 2·0	19 ± 1·6**	14 ± 1·9
Metoprolol	5·0	12 ± 2·5	15 ± 2·2	13 ± 2·5
	10·0	10 ± 2·5	15 ± 2·1	12 ± 2·5
Oral route				
Water, 2 mL kg^{-1}		11 ± 0·8	11 ± 1·0	11 ± 1·9
Butoxamine	2·5	21 ± 1·5***	20 ± 2·8**	13 ± 1·2
	5·0	26 ± 3·0**	24 ± 1·9***	22 ± 2·5*
Metoprolol	5·0	12 ± 0·6	11 ± 1·1	11 ± 2·7
	10·0	12 ± 3·6	15 ± 1·1	12 ± 1·3

The β-blockers were given 30 min before challenge. Values are the means ± s.e.m. of 4–6 rats. *$P < 0.02$, **$P < 0.01$ and ***$P < 0.001$ compared with its vehicle control.

Table 3. Effects of β-blockers on gastric mucosal blood flow and gastric mucosal potential difference in anaesthetized rats.

Pretreatment	Dose (mg kg^{-1})	Gastric mucosal blood flow (arbitrary units)		Potential difference (−mV)	
		15 min	45 min	15 min	45 min
Intraperitoneal route					
Saline, 2 mL kg^{-1}		32 ± 1·4	31 ± 1·4	26 ± 1·9	29 ± 1·9
Butoxamine	2·5	33 ± 1·3	31 ± 1·5	26 ± 1·8	37 ± 1·6§,††
	5·0	32 ± 1·8	26 ± 2·9	25 ± 2·0	30 ± 1·6*
Metoprolol	5·0	30 ± 1·2	24 ± 1·1‡,‡‡	26 ± 2·1	28 ± 2·6
	10·0	31 ± 1·3	22 ± 1·9†,‡‡	23 ± 1·4	29 ± 2·1
Intragastric route					
Water, 1·5 mL		32 ± 1·3	23 ± 1·7	28 ± 2·1	
Butoxamine	2·5	33 ± 1·2	29 ± 2·6	26 ± 2·2	29 ± 3·4
	5·0	32 ± 1·2	31 ± 1·6	25 ± 2·3	33 ± 3·9*
Metoprolol	5·0	33 ± 2·4	29 ± 1·9	25 ± 2·2	29 ± 3·0
	10·0	31 ± 1·4	26 ± 2·1*·**	24 ± 0·8	28 ± 2·3

β-Blockers were given at 15 min. Values are the means ± s.e.m. of results from 7–12 rats. *$P < 0.05$, $^{†}P < 0.02$, $^{‡}P < 0.01$ and $^{§}P < 0.001$ compared with its own group at 15 min; **$P < 0.05$, $^{††}P < 0.02$ and $^{‡‡}P < 0.01$ compared with its corresponding vehicle control.

Table 4. Effects of β-blockers on systemic mean blood pressure and heart rate in anaesthetized rats.

Pretreatment	Dose (mg kg^{-1})	Blood pressure (mmHg)		Heart rate (beats min^{-1})	
		15 min	45 min	15 min	45 min
Intraperitoneal route					
Saline, 2 mL kg^{-1}		113 ± 5·5	110 ± 4·6	423 ± 11	438 ± 11
Butoxamine	2·5	119 ± 3·5	114 ± 3·9	435 ± 19	432 ± 18
	5·0	117 ± 4·3	110 ± 5·3	412 ± 19	407 ± 17
Metoprolol	5·0	118 ± 3·4	106 ± 4·1	418 ± 9	333 ± 6‡,‡‡
	10·0	104 ± 4·3	87 ± 5·5†,††	411 ± 17	319 ± 13‡,‡‡
Intragastric route					
Water, 1·5 mL		117 ± 3·1	114 ± 4·1	441 ± 5	443 ± 6
Butoxamine	2·5	121 ± 7·8	121 ± 7·5	416 ± 13	434 ± 12
	5·0	122 ± 2·7	120 ± 3·5	441 ± 14	450 ± 16
Metoprolol	5·0	104 ± 6·3	94 ± 6·9**	448 ± 15	424 ± 14
	10·0	107 ± 3·5	99 ± 4·1§	419 ± 22	381 ± 26*,**

β-Blockers were given at 15 min. Values are the means ± s.e.m. of results from 7–12 rats. *$P < 0·05$, $^{\dagger}P < 0·01$ and $^{\ddagger}P < 0·001$ compared with its own group at 15 min, $^{\S}P < 0·05$, **$P < 0·02$, $^{\dagger\dagger}P < 0·01$ and $^{\ddagger\ddagger}P < 0·001$ compared with its corresponding vehicle control.

Table 5. Effects of β-blockers on gastric acid and pepsin output in anaesthetized rats.

Pretreatment	Dose (mg kg^{-1})	Gastric acid output (μmol/15 min)		Pepsin output (μg/15 min)	
		15 min	45 min	15 min	45 min
Intraperitoneal route					
Saline, 2 mL kg^{-1}		12·6 ± 2·2	17·1 ± 3·2	34·4 ± 4·4	36·6 ± 4·9
Butoxamine	2·5	19·4 ± 4·8	25·1 ± 7·0	27·9 ± 4·4	34·7 ± 9·8
	5·0	19·9 ± 6·0	25·8 ± 7·4	24·2 ± 7·5	29·9 ± 9·9
Metoprolol	5·0	12·6 ± 2·2	19·2 ± 4·3	45·5 ± 9·8	37·3 ± 6·2
	10·0	14·0 ± 3·1	12·8 ± 3·6	24·5 ± 4·9	26·2 ± 6·1
Intragastric route					
Water, 1·5 mL		16·5 ± 3·2	17·5 ± 4·0	39·4 ± 6·4	45·6 ± 7·4
Butoxamine	2·5	13·8 ± 1·8	13·3 ± 4·3	29·1 ± 4·9	38·4 ± 7·1
	5·0	14·5 ± 4·0	19·2 ± 8·5	29·8 ± 9·7	52·2 ± 13·1
Metoprolol	5·0	22·9 ± 5·4	20·7 ± 4·7	29·6 ± 7·1	19·0 ± 5·0
	10·0	18·1 ± 2·0	8·6 ± 2·4	32·7 ± 9·9	33·0 ± 14·9

β-Blockers were given at 15 min. Values are means ± s.e.m. of results from 7–12 rats.

Table 6. Effects of β-blockers on gastric mucosal prostaglandin E_2 in rats.

Treatment	Dose (mg kg^{-1})	Intraperitoneal route	Oral route
Water/saline 2 mL kg^{-1}		456 ± 48	484 ± 60
Butoxamine	2·5	432 ± 130	1220 ± 166**
	5·0	566 ± 98	756 ± 98*
Metoprolol	5·0	604 ± 90	718 ± 94
	10·0	710 ± 110	378 ± 56

Values (pg (mg protein)$^{-1}$) are means ± s.e.m. of results from 6–9 rats. *$P < 0·05$ and **$P < 0·001$ when compared with its corresponding vehicle control.

There was no significant difference in basal gastric acid output among different drug treatments and routes of administration (Table 5). Similar findings were observed for pepsin secretion.

The results of mucosal PGE_2 level are shown in Tables 6 and 7. Oral administration of butoxamine increased basal PGE_2 level ($P < 0·01$). Metoprolol did not affect the mucosal PGE_2 level, irrespective of the route of administration. Indomethacin but not the other types of ulceration reduced the PGE_2 level. Oral administration of butoxamine dose-dependently preserved the mucosal PGE_2 level in the three types of ulcer model. In the intraperitoneal groups, butoxamine was only effective in the indomethacin model.

Discussion

Although the anti-ulcer effect of the non-selective β-adrenoceptor antagonist, propranolol, has been reported (Bhandare et al 1990; Woo & Cho 1994), the type and role of β-adrenoceptor antagonists in this protection are still undefined. The present study showed that butoxamine but not metoprolol had an anti-ulcer effect in ethanol, indomethacin and stress ulcer models (Table 1), suggesting that the anti-ulcer action might be attributed to a selective β_2-adrenoceptor mechanism. Recent

Table 7. Effects of butoxamine on prostaglandin E_2 in ethanol (60%)-, indomethacin ($30\,mg\,kg^{-1}$)- or cold-restraint stress (4°C) ulcer models.

Pretreatment	Dose ($mg\,kg^{-1}$)	Ethanol	Indomethacin	Stress
Intraperitoneal route				
Saline, $2\,mL\,kg^{-1}$		650 ± 132	40 ± 6	571 ± 183
Butoxamine	2·5	523 ± 73	64 ± 10*	196 ± 51
	5·0	904 ± 240	90 ± 24*	195 ± 41
Oral route				
Water, $2\,mL\,kg^{-1}$		407 ± 78	34 ± 5	534 ± 58
Butoxamine	2·5	670 ± 78*	57 ± 5**	590 ± 141
	5·0	823 ± 175*	89 ± 20*	1072 ± 224*

Butoxamine was given 30 min before ulcer-inducing treatment. Values (pg (mg protein)$^{-1}$) are means ± s.e.m. of results from 6 or 7 rats. $*P < 0.05$ and $**P < 0.01$ when compared with its corresponding vehicle control.

reports have shown that a β_3-adrenoceptor agonist has a protective action on the gastric mucosa when treated with indomethacin subcutaneously (Kuratani et al 1994). The involvement of β_3-adrenoceptors in ulceration is, however, still not clear because of the lack of a specific β_3-adrenoceptor antagonist.

Oral administration of butoxamine seemed to be more effective in its anti-ulcer action than that given by intraperitoneal injection (Table 1). Doses as low as $2.5\,mg\,kg^{-1}$ still had a significant effect in the ethanol and indomethacin ulcer models. Bhandare et al (1990) suggested that the anti-ulcer action resulting from oral administration of propranolol might be related to endogenous prostaglandin release. A similar effect was observed after oral administration of butoxamine-the mucosal PGE_2 level was significantly increased but this effect was not observed in the intraperitoneal group (Table 6). The same effects were found when butoxamine was administered after the lesion-inducing treatments. These findings indicated that butoxamine could have the local action on the gastric mucosa of stimulating endogenous PGE_2 release. It is plausible that oral butoxamine has an additional effect through the prostaglandin pathway which is not shared by intraperitoneal butoxamine. Although 60% ethanol and cold-restraint stress for 2 h did not reduce the mucosal PGE_2 level in our study, enhancement of endogenous PGE_2 release would be beneficial to the gastric mucosa in preventing lesion formation. Indeed, prostaglandins protect the gastric mucosa against lesions (Robert et al 1977). It is interesting that intraperitoneal injection of butoxamine was effective at reducing mucosal damage in the indomethacin ulcer model only. It is also noted that butoxamine only partially preserved both mucosal PGE_2 level and mucosa from ulceration. It is expected that other ulcerogenic mechanisms, in addition to depletion of prostaglandins in the gastric mucosa, could be part of the damaging action of indomethacin (Alican et al 1995).

It has been claimed that a decrease in potential difference might result from a deterioration of mucosal integrity and function (Takeuchi et al 1986). Our results showed that butoxamine not only increased the basal potential difference level but also elevated the intramucosal mucus level. Improvement of these two parameters, which can be achieved by β_2-adrenoceptor blockade (Tables 2 and 3), would strengthen the mucosal barrier (Menguy 1969; McGreevy 1984).

Metoprolol is currently one of the β_1-adrenoceptor blockers used to relieve hypertension. It significantly reduced the systemic blood pressure and heart rate (Table 4), actions which seemed to occur in parallel with a reduction of gastric mucosal blood flow (Table 3). These findings further confirm that the state of gastric mucosal blood flow correlates positively with the systemic blood pressure (Cho et al 1994). Metoprolol, however, did not significantly affect the ulcerogenesis of the three types of ulcer model (Table 1), suggesting that the drug by itself could have anti-ulcer action which could counteract the detrimental effects provoked by gastric mucosal blood flow reduction. This action did not, furthermore, alter the transmucosal potential difference (Table 3), implying that both gastric mucosal blood flow and systemic blood pressure might not be the only factors which control the level of mucosal potential difference (Takeuchi et al 1986).

The integrity of the gastric mucosa partly depends on the amount of acid and other aggressive factors acting on it (Flemström & Turnberg 1984). Although in-vitro studies showed that β-adrenoceptor antagonists significantly attenuated gastric acid output (Canfield et al 1981), their effect in intact animals was not confirmed (Table 5). Pepsin secretion was not, furthermore, affected by either type of β-adrenoceptor antagonist, suggesting that the anti-ulcer action of butoxamine is unrelated to gastric acid and pepsin secretion. Our study also substantiates the proposal that secretion of both acid and pepsin are independent of the state of gastric mucosal blood flow (Cho 1992) because metoprolol reduces gastric mucosal blood flow without affecting secretory function of the stomach.

It is concluded that β_2-adrenoceptors play a significant role in the pathogenesis of gastric ulceration. Blocking these receptors by butoxamine would prevent ulcer formation by strengthening the mucosal barrier, presumably through preservation of intramucosal mucus and enhancement of mucosal tight junction in the stomach. In addition, stimulation of PGE_2 in the gastric mucosa could contribute in part to the anti-ulcer action of the drug, especially when it was given by the oral route.

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