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AGGRAVATING ACTION OF CLONIDINE ON ETHANOL-INDUCED GASTRIC LESIONS: PROBABLE MECHANISM OF ACTION

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Abstract : Large doses of the imidazoline alpha$_2$ adrenoceptor agonist clonidine aggravate ethanol-induced gastric lesions. The alpha$_2$ adrenoceptor antagonist phentolamine, the opioid antagonist naloxone and the H_2 antagonist cimetidine do not prevent this action of clonidine suggesting that it is not mediated by alpha$_2$, opioid or H_2 receptors. Further, like clonidine, high doses of phentolamine and cimetidine aggravate gastric lesions per se, suggesting that all three may be acting at a common 'receptor' site, possibly the imidazoline-preferring receptor (IPR).

Key words : clonidine ethanol lesions imidazoline-preferring receptor

INTRODUCTION

The imidazoline alpha$_2$ adrenoceptor agonist, clonidine, has been reported to potentiate gastric ulcers in high doses (1). However, the model of gastric ulcer used in this study was dimaprit-induced ulcer, which involves increased acid secretion. As clonidine has been reported to enhance gastric acidity in high doses (2), it is possible that such an action may lead to potentiation of dimaprit-induced ulcers.

We observed earlier that high doses of clonidine also aggravate ethanol-induced gastric lesions, a model of gastric ulcer which is acid independent (3). Clonidine is a drug with "many faces" (4). In addition to its effect on alpha$_2$ adrenoceptors, clonidine has been reported to activate H_2 receptors (5) and to interact with opioid receptors (6). Further, the hypotensive action of clonidine has been shown to be mediated, at least in part, by the imidazoline-preferring receptor-IPR (7).

In view of these diverse actions of clonidine, this study was undertaken to investigate the probable mechanism of its gastric lesion aggravating effect.

METHODS

Male Wistar rats (200-250g) were deprived of food but allowed water ad libitum for 24 h prior to the studies. Animals were randomly divided into groups of six and received the following drugs (ip unless specified otherwise) 30 min before the administration of 1 ml of the ulcerogen, 75% ethanol a) 0.9% Nacl W/V (saline) in the same volume as other drugs (1 ml/kg), b) clonidine 0.75, 1.0 and 1.25 mg/kg, c) phentolamine 10 and 20 mg/kg 30 min before saline, d) phentolamine 10 mg/kg 30 min before clonidine 1 mg/kg, e) naloxone 1 mg/kg (SC) 30 min before saline, f) naloxone 1 mg/kg (SC) 30 min before clonidine 1 mg/kg, g) cimetidine 50 and 100 mg/kg 30 min before saline and h) cimetidine 50 mg/kg 30 min before clonidine 1 mg/kg.

Induction of gastric lesions: Rats were administered 1 ml of 75% ethanol orally and killed after 1 hr. The stomach was opened along the greater

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curvature, rinsed with normal saline and the area of red haemorrhagic bands measured in mms and summed up for each stomach. While one of us performed the experiments, the other two assessed each coded stomach independently.

All data are expressed as mean ± SEM and analysed by employing 't' test.

RESULTS AND DISCUSSION

The effects of treatment with various antagonists and of combination of antagonist plus clonidine on ethanol-induced stomach lesions is presented in Table I. This study confirms our finding that in high doses, clonidine aggravates ethanol-induced gastric lesions in rats. The alpha$_2$ adrenoceptor antagonist phentolamine fails to prevent the action of clonidine, suggesting that it is not mediated by alpha$_2$ adrenoceptor (Table Id). In fact phentolamine, by itself, aggravates ethanol-induced lesions (Table Ic). Though phentolamine is known to enhance gastric acid secretion and exacerbate peptic ulcer via a cholinergic mechanism (8), it is unlikeyl that such an action which lead to aggravation of ethanol-induced lesions, which are acid independent.

TABLE I : Effect of some receptor blocking agents and of combinaton of the blockers with clonidine on ethanol-induced gastric lesions in rats.

Treatment group	*Dose (mg/kg)*	*Area of haemorrhagic lesions (mm2) Mean ± SEM*
a) Saline	1 ml/kg	39.2 ± 2.5
b) Clonidine	0.75	41.8 ± 3.5
	1.00	56.2 ± 2.9*
	1.25	68.5 ± 2.2*
c) Phentolamine	10.0	48.5 ± 2.5*
	20.0	59.2 ± 2.2*
d) Phentolamine + Clonidine	10.0 1.0	54.8 ± 3.5
e) Cimetidine	50.0	37.9 ± 3.4
	100.0	50.4 ± 2.9*
f) Cimetidine + Clonidine	50.0 1.0	59.8 ± 2.2
g) Naloxone	1.0	36.5 ± 3.5
h) Naloxone+ Clonidine	1.0 1.0	60.5 ± 4.2

All treatments were given ip naloxone which was given sc 30 min before ethanol (1 ml, 75% solution). There were 6 rats per group.
*P< 0.01

The interaction of clonidine with opiate receptors has been demonstrated by several workers. Naloxone has been reported to block some effects of clonidine like hypotension (9) and changes in ventricular refractoriness (6). However other effects of clonidine like antidiarrhoeal, diuretic and antinoceptive effects (10) are not blocked by narcotic antagonists. In this study, naloxone which did not affect ethanol-induced lesions per se, did not also prevent the gastric lesion aggravating action of clonidine (Table Ih) suggesting that opioid receptors are not involved.

Clonidine has been shown to activate H_2 receptors both in peripheral and cerebral sites (5). H_2 receptor antagonists have been reported to block the stimulant action of clonidine on gastric secretion (2) and also its potentiating effect on dimaprit induced ulcers (1). On the other hand, H_2 receptor antagonists do not protect significantly against ethanol-induced ulcers both in animals (3,11) and humans (12). In our study the H_2 antagonist cimetidine does not prevent the gastric lesion aggravating action of clonidine, suggesting the H_2 receptors have no role to play. Further, we observed that though cimetidine per se does not affect ethanol lesions in the lower dose of 50 mg/kg i.p., it aggravates these lesions if the dose is increased (100 mg/kg i.p.). (Table I).

It has recently been shown that clonidine binds to imidazoline (imidazole) binding sites in addition to aplpha$_2$ adrenoceptors in the ventrolateral medulla of bovine brain (13). Such imidazoline binding sites have been demonstrated in various tissues in several species (14). Ernsberger et al (15) have escribed (^{3}H) para amino clonidine (PAC) binding sites in rat kidney. Such sites are recognized by many imidazoline compounds including the imidazole cimetidine (13, 15). In our study, high doses of the imidazolines clonidine and phen-

tolamine and the imidazole cimetidine aggravate ethanol-induced gastric lesions. Could this effect be mediated by a common receptor such as IPR? In the absence of a specific antagonist at the IPR in the rat, it is perhaps too premature to conclude that the imidazolines used in this tudy act on (^{3}H) PAC - like sites (15) in the gastric mucosa. Further work, including radioligand binding studies, only could clarify this possibility.

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