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SHORT COMMUNICATION

AGGRAVATING ACTION OF HYDRALAZINE ON ETHANOL-INDUCED GASTRIC LESIONS

P. N. BHANDARE, P. V. RATABOLI, R. S. DINIZ, D'SOUZA AND V. G. DHUME

Department of Pharmacology,
Goa Medical College,
P.O. Bombolim Complex,
Tiswadi, GOA - 403 202

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Abstract : Endogenous nitric oxide has been proposed as one of the mediators of gastric cytoprotection. We studied the effect of the vasodilator hydralizine which acts via nitric oxide and thus is expected to have a gastroprotective action. However, hydralazine aggravates ethanol-induced gastric lesions. This effect is not influenced by pretreatment with the selective α_1 adrenergic antagonist prazosin but is abolished by the angiotensin converting enzyme inhibitor, captopril suggesting the involvement of the renin-angiotensin system.

Key words : hydralazine ethanol lesions nitric oxide prazosin captopril

INTRODUCTION

Recent studies have demonstrated the vasodilator role of endogenous nitric oxide (NO) in rat gastric microcirculation (1) and its importance in the regulation of gastric mucosal integrity (2). The nitrovasodilator, nitroprusside, which acts by releasing NO (3), has been reported to inhibit mucosal damage following intravenous administration (4). NO has also been implicated in the mechanism of action of the vasodilator hydralazine. NO can be generated from hydrazaline *in vitro* (5) and part of the vascular relaxation caused by hydrazaline is dependent on the presence of the endothelium (6). Thus the mechanism of action of hydralazine is similar to the mechanism of action of EDRF, organic nitrates and sodium nitroprusside (7). In view of the above, this study was undertaken to investigate the effect of hydralazine on ethanol-induced gastric lesions.

METHODS

Male Wistar rats (200-250 gm) were deprived of food but not water for 24 h prior to drug administration. The animals were randomly divided into groups of six and received the following drugs i.p., 30 min before the administration of the ulcerogen 100% ethanol a) 0.9% Nacl (W/V, saline) in the same volume as other drugs (1 ml/kg), b) Hydralazine sulphate 5, 10 and 15 mg/kg, c) Prazosin 1 mg/kg, 30 minutes before saline, d) Prazosin 1 mg/kg, 30 min before hydralazine 10 mg/kg, e) Captopril 2.5 mg/kg, 30 min before saline, f) Captopril 2.5 mg/kg, 30 min before hydralazine 10 mg/kg.

Induction of ethanol-induced gastric lesions : Animals were administered 1 ml of 100% ethanol orally and sacrificed after one hour. The stomachs were then opened along the greater curvature, rinsed with normal saline and pinned on a flat surface. The length and width of each red haemorrhagic band was then transposed on a cardboard with the help of callipers and measured with a scale to find out its area. The total area of haemorrhagic bands was then summed up for each stomach. While one of us per-

*Corresponding Author

formed the experiments, the other two assessed each coded stomach separately.

Statistical analysis : All data are expressed as mean ± S.E.M. and analysed using student's t test.

RESULTS AND DISCUSSION

Table I shows the effect of three doses of hydralazine on ethanol-induced gastric lesions and of pretreatment with prazosin and captopril. It can be seen that hydralazine produces a significant dose-dependent aggravation of ethanol-induced gastric haemorrhagic lesions. Several studies have highlighted the role of gastric mucosal blood flow in experimental gastric injury. Incarasing mucosal blood flow by treatment with a prostaglandin analogue (8), isoproterenol (9) or nitroprusside (4) protects against gastric injury. Endogenous nitric oxide has been proposed as one of the mediators of gastric mucosal defense (2). Thus hydralazine which is a vasodilator capable of generating NO *in vitro* (5) should have definitely protected against ethanol-induced lesions. However, responses to vasodilator drugs are not uniform in all vascular beds. Further, the contribution of reflexly mediated vasoconstrictor responses to the haemodynamic profile of a drug should not be overlooked. Hydralazine has been reported to reduce blood flow to the stomach and small intestine probably due to reflex vasoconstrictor responses mediated via the autonomic and renin-angiotensin systems (10). To determine the influence of these two reflex mechanisms in the action of hydralazine, we used the selective α_1 receptor antagonist prazosin and the angiotensin converting enzyme (ACE) inhibitor, captopril. Prazosin failed to modify the aggravating action of hydralazine suggesting that the reflex sympathetic vasoconstriction is probably not involved. On the other hand, pretreatment with captopril prevented the aggravating action of hydralazine showing that reflex increase in the activity of renin-angiotensin system may play a role. However, captopril only abolished the aggravating action of hydralazine and did not unmask any protective action. Thus, hydralazine, inspite of being a vasodilator acting via NO, does not have intrinsic protective activity against ethanol-induced gastric lesions. Thus it appears that NO may not play a major role in the gastric action of hydralazine. At this juncture, cognizance should also be taken of a recent study showing that the administration of the L-arginine analogue NG-monomethyl L-arginine (L-NMMA), an inhibitor of NO synthesis does not produce gastric damage when administered alone (2) though it produces a reduction in gastric blood flow (1).

TABLE I : Effect of hydralazine *per se* and of combination of hydralazine with prazosin and captopril on ethanol-induced gastric lesions in rats.

Treatment group		Dose *mg/kg, i.p.*	Area of haemorrhagic *lesions (mm^2) Mean ± SEM*
a)	Saline	1 ml/kg	38.4±3.5
b)	Hydralazine	5.0	49.1±2.8*
		10.0	61.7±4.2*
		15.0	75.9±3.0*
c)	Prazosin	1.0	41.1±3.5
d)	Prazosin + Hydralazine	1.0 10.0	59.9±4.6
e)	Captopril	2.5	34.8±4.2
f)	Captopril + Hydralazine	2.5 10.0	36.4±3.2**

n = 6 ; *P < 0.05; **P < 0.01 as compared to hydralazine.

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