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The Role of Nitric Oxide and Sulphydryls in Gastric Mucosal Protection Induced by Sodium Cromoglycate in Rats

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Abstract

The role of endogenous nitric oxide and sulphydryls in gastric protection afforded by sodium cromoglycate against ethanol-induced gastric lesions was studied in rats. Drugs were administered either intraperitoneally (i.p.) or subcutaneously (s.c.) 30, 45 or 60 min before oral administration of ethanol.

Administration of cromoglycate before ethanol dose-dependently inhibited ethanol-induced gastric lesions. Pretreatment with N^G-nitro-L-arginine methyl ester (L-NAME), an inhibitor of nitric oxide biosynthesis, dose-dependently aggravated gastric lesions and reduced cromoglycate-induced gastric protection. The attenuating effect of L-NAME on gastric protection elicited by cromoglycate was reversible by pretreatment with L-arginine but not by D-arginine. On the other hand, ethanol-induced gastric lesions were found to be associated with a reduction of nonprotein sulphydryl content of glandular stomachs. Pretreatment with cromoglycate prevented non protein sulphydryl depletion and afforded protection. Pretreatment with *N*-ethylmaleimide, a sulphydryl blocker, caused dose-dependent enhancement of ethanol-induced gastric lesions and further depletion of non protein-sulphydryl. Treatment with *N*-ethylmaleimide before cromoglycate reduced the gastric protection that was associated with depletion of nonprotein sulphydryls. Furthermore, combined *N*-ethylmaleimide and L-NAME pretreatment caused a greater aggravation of ethanol-induced gastric lesions and significantly produced a higher reduction of the protective effects of cromoglycate. However, pretreatment with L-arginine only partially restored the protective effects of cromoglycate.

These results suggest that the protective effects of cromoglycate may be dependent on the maintenance of a critical level of both endogenous nitric oxide and nonprotein sulphydryls in the gastric mucosa.

Sodium cromoglycate is widely used as a prophylactic agent in the treatment of bronchial asthma. In addition to its anti-asthmatic properties, cromoglycate has been reported to possess gastric protection effects. The mechanisms of its anti-asthmatic and gastric protection effects have been attributed to the stabilization of mast cell membranes (Brogden et al 1974; Ogle & Lau 1979; Goossens et al 1987; Beck et al 1988) and thus preventing the release of bronchoconstrictor and pro-ulcerogenic substances such as histamine, 5-hydroxytryptamine (5-HT), leukotrienes and other agents.

Recently, the gastric protection effects of certain compounds has been shown to be mediated through sulphydryl-sensitive processes (Szelenyi & Brune 1986; Szabo & Brown 1987; Gutierrez-Cabano 1989; Ali 1991) indicating the importance of sulphydryls in maintaining gastric mucosal integrity. More recently, nitric oxide (NO) which is biosynthesized from L-arginine in various cells (Moncada et al 1991) has been implicated in the gastric protective effects of aluminium-containing antacids (Konturek et al 1992), sucralfate (Konturek et al 1994) and morphine (Gyires 1994). Moreover, NO has been shown to have a regulatory role in gastric mucosal blood flow (Pique et al 1989, 1992; Lippe & Holzer 1992) and in mast cell reactivity (Salvemini et al 1994). This study was undertaken to investigate the possible role of endogenous sulphydryl and NO in the protective mechanisms of cromoglycate. For this purpose, *N*-ethylmaleimide, a sulphydryl blocker (Szabo et al 1981), N^G-nitro-L-arginine methyl ester (L-NAME), a NO-synthase inhibitor (Ishii et al 1990) and the substrate for NO synthase, L-arginine were used.

Materials and Methods

Animals and drug preparation

Male Wistar rats, 220–250 g, were obtained from the Animal House, College of Medicine, King Saud University. The rats were housed individually in single cages which had wire-net floor to prevent coprophagy. The animals were fasted for 24 h before the experiments but had free access to water.

Absolute ethanol (BDH, UK), sodium cromoglycate Fison Ltd, from Spincap cartridges, *N*-ethylmaleimide N^G-nitro-L-arginine methyl ester (L-NAME), L-arginine and D-arginine were purchased from Sigma Chemical Co, UK. Drugs were dissolved in distilled water (water) and were administered intraperitoneally (i.p.) except *N*-ethylmaleimide which was given subcutaneously (s.c.) in a volume of 1 mL kg^{-1}. Absolute ethanol (ethanol) or water (1 mL per animal) was given orally as inducing agents.

Experimental design and drug treatment

Following 24-h fasting, the rats were randomly allocated to groups of 6–8 animals and water was withdrawn. The

groups were then subjected to various treatment schedules as detailed below.

In the initial studies, control groups received water (1 mL per animal, i.p.) and test groups were given cromoglycate (2·5–40 mg kg^{-1}, i.p.) 30 min before oral administration of 1 mL ethanol. In subsequent experiments, cromoglycate (20 mg kg^{-1}, i.p.), L-NAME (12·5–50 mg kg^{-1}. i.p.), L-arginine (200 mg kg^{-1}, i.p.), D-arginine (200 mg kg^{-1}, i.p.) or *N*-methylmaleimide (12·5–50 mg kg^{-1}, s.c.) were administered 30, 45 or 60 min before oral administration of 1 mL ethanol.

Evaluation of lesions

In all studies, rats were killed 1 h after ethanol by cervical dislocation and stomachs were dissected out, opened along the greater curvature and randomized so that the examiner had no knowledge of the treatment given. The severity of the gastric mucosal lesions was scored by a modification of the method of Schiantarelli et al (1984) according to the following arbitrary scale: 0, normal mucosa; 1, hyperaemic mucosa or up to 3 small patches; 2, from 4 to 10 small patches; 4, more than 10 small patches; 6, up to 6 medium patches; 8, more than 6 medium or up to 3 large patches; 10, from 4 to 6 large patches; 12, from 7 to 10 large patches; 14, more than 10 large patches; 16–20 extensive covering of the whole mucosa with haemorrhages. Small was defined as up to 2 mm; medium as between 2 and 4 mm and large as more than 4 mm across. The sum of the scores in each group of rats was divided by the number of animals and expressed as mean lesion score. The percentage decrease or increase of lesions was calculated by comparison with the appropriate control values.

Determination of nonprotein sulphydryls

In separate experiments, following the same drug treatment schedules as described above, gastric glandular nonprotein sulphydryl was measured according to the method of Sedlak & Lindsay (1968). The glandular part of the stomachs was cut, weighed, and homogenized in ice-cold 0·02 M ethylenediaminetetraacetic acid (EDTA). Aliquots (5 mL) of the homogenates were mixed in a 15-mL test tube with 4 mL distilled water and 1 mL 50% trichloroacetic acid. The tubes were shaken intermittently for 15 min and centrifuged at 3000 *g* for 10 min. Two millilitres of supernatant were mixed with 4 mL Tris-buffer (pH 8·9) and 0·1 mL 5,5-dithio-bis-(2-nitrobenzoic acid) (DTNB) was added and the sample was shaken. The absorbance was read within 5 min of addition of DTNB, at 412 nm against a reagent blank with no homogenates in a spectrophotometer (Perkin-Elmer, Lamba 5). The final sulphydryl concentration per gram of tissue was calculated from a previously constructed standard curve and the percentage changes produced by different treatments were calculated by comparison with the group that had received water alone.

Table 1. Effect of intraperitoneal cromoglycate given 30 min before oral administration of ethanol-induced gastric lesions in rats.

Dose (mg kg^{-1})	Lesion score
Control	8·6 ± 0·5
2·5	7·8 ± 0·9
5	6·7 ± 1·0
10	5·2 ± 1·1*
20	2·2 ± 0·9*
40	0·83 ± 0·3*

Mean ± s.e.m. (n = 6). *$P < 0·05$ compared with control.

Statistical analysis

The results are expressed as mean ± s.e.m. The significance of difference between means was calculated by Student's *t*-test for unpaired data when comparing two groups and analysis of variance followed by the Kruskal-Wallis test for multiple comparisons; $P < 0·05$ was considered significant.

Results

The protective effects of cromoglycate on ethanol-induced gastric lesions is shown in Table 1. When ethanol was administered to control animals, marked gross gastric mucosal lesions were induced. These lesions were characterized by multiple haemorrhagic red bands (patches) of different sizes along the long axis of the glandular stomach. Pretreatment of rats with cromoglycate dose-dependently

Table 2. Effect of intraperitoneal administration of L-NAME and cromoglycate (20 mg kg^{-1}, 30 min before ethanol) in ethanol-induced gastric lesions in rats with or without L-arginine and D-arginine (200 mg kg^{-1}).

Treatment before ethanol administration		Lesion score	
60 min	45 min	Without cromoglycate	With cromoglycate
–	–	9·1 ± 0·6	2·7 ± 0·4†
–	L-NAME (mg kg^{-1})		
–	12·5	10·3 ± 0·9	4·2 ± 0·6†
–	25	12·1 ± 1·2*	9·3 ± 1·1
–	50	13·2 ± 0·7*	10·8 ± 0·9
L-Arginine	–	7·5 ± 1·3	–
D-Arginine	–	9·2 ± 1·2	–
L-Arginine	25	–	2·6 ± 0·9†
D-Arginine	25	–	11·4 ± 1·6

Mean ± s.e.m. (n = 6–8). *$P < 0·05$ compared with control; †$P < 0·05$ compared with corresponding experiment without cromoglycate or L-arginine.

Table 3. Effect of subcutaneous administration of *N*-ethylmaleimide and intraperitoneal cromoglycate (20 mg kg^{-1}, 30 min before ethanol) on ethanol-induced gastric lesions and on nonprotein sulphydryls in rats.

Treatment with *N*-ethylmaleimide (mg kg^{-1}), 60 min before ethanol	Lesion score		Nonprotein sulphydryls (μmol (g tissue)$^{-1}$)	
	Cromoglycate		Cromoglycate	
	without	with	without	with
Control	9·4 ± 0·7	3·2 ± 0·2†	3·2 ± 0·3‡	5·2 ± 0·3
12·5	12·2 ± 0·8*	8·9 ± 0·4†	3·4 ± 0·4‡	4·2 ± 0·4‡
25	13·5 ± 0·8*	11·3 ± 1·0	2·9 ± 0·6‡	3·7 ± 0·8‡
50	14·6 ± 0·6*	12·8 ± 1·1	2·5 ± 0·5‡	3·0 ± 0·6‡

Mean ± s.e.m. (n = 6). *$P < 0·05$ compared with control; †$P < 0·05$ compared with corresponding experiment without cromoglycate. ‡$P < 0·05$ compared with nonprotein sulphydryl levels (5·9 ± 0·5 μmol (g tissue)$^{-1}$) in control animals induced with water instead of ethanol.

prevented formation of these lesions. Thus, there was 90% protection against gastric damage with the highest dose of cromoglycate used in this study.

Table 2 shows the effect of pretreatment with L-NAME, L-arginine or D-arginine, individually or in combination, on ethanol-induced gastric lesions and on the gastric protection afforded by cromoglycate. Administration of graded doses of L-NAME (12·5, 25 and 50 mg kg^{-1}) dose-dependently aggravated ethanol-induced lesions. Thus, a dose of 50 mg kg^{-1} caused a rise of about 45% above that achieved with ethanol alone. However, a lower dose (12·5 mg kg^{-1}) produced an increment that was not significantly different from that of the ethanol-treated group. On the other hand, pretreatment with L-arginine or D-arginine (200 mg kg^{-1}) had no significant effect on the development of ethanol-induced lesions. Pretreatment with a submaximal protective dose of cromoglycate (20 mg kg^{-1}) afforded 70% protection against ethanol-induced gastric lesions. This protective effect of cromoglycate was reduced to 59, 27 and 18% by prior administration of 12·5, 25 and 50 mg kg^{-1} of L-NAME, respectively. In contrast, when L-arginine or D-arginine (200 mg kg^{-1}) was given before L-NAME (25 mg kg^{-1}), the blocking effect of L-NAME was reversed and cromoglycate-induced gastric protection was restored to 72% by L-arginine while D-arginine was ineffective.

The effects of different doses of *N*-ethylmaleimide (12·5, 25 and 50 mg kg^{-1}) or cromoglycate (20 mg kg^{-1}) on ethanol-induced gastric lesions and on glandular nonprotein sulphydryls in rats are presented in Table 3. Administration of ethanol alone resulted in gastric haemorrhagic lesions that were associated with a depletion of glandular sulphydryl by 46%. On the other hand, pretreatment with graded doses of *N*-ethylmaleimide dose-dependently aggravated ethanol-induced gastric damage and caused further depletion of sulphydryls. Thus, *N*-ethylmaleimide (50 mg kg^{-1}) produced 55% enhancement of lesions with a corresponding reduction of sulphydryls by 58%. In contrast, pretreatment with a submaximal protective dose of cromoglycate (20 mg kg^{-1}) afforded 66% protection against ethanol-induced gastric lesions and reduced ethanol-induced depletion of sulphydryl to a value of 12% only. The protective effect of cromoglycate was reduced to 27, 16 and 12% with a corresponding depletion of sulphydryl of 29, 37 and 49% by prior administration of 12·5, 25 and 50 mg kg^{-1} *N*-ethylmaleimide, respectively.

Table 4 shows the effect of treatment with *N*-ethylmaleimide and L-NAME individually or in combination on the protective actions of cromoglycate. Administration of cromoglycate (20 mg kg^{-1}) produced 65% protection against ethanol-induced gastric lesions. Pretreatment with *N*-ethylmaleimide (25 mg kg^{-1}) or L-NAME (25 mg kg^{-1}) significantly aggravated ethanol-induced gastric damages by 43 and 32%, respectively. Pretreatment of rats with either *N*-ethylmaleimide or L-NAME before administration of cromoglycate significantly reduced the protective effects of cromoglycate and brought them down to 13 and 20% respectively. Combined treatment with *N*-ethylmaleimide plus L-NAME caused greater aggravation of ethanol-induced lesions with an increase of 76% and nearly complete inhibition of gastric protection afforded by cromoglycate with a protection value of only 9%. Although administration of L-arginine partially reversed the blocking

Table 4. Effect of subcutaneous administration of *N*-ethylmaleimide (25 mg kg^{-1}) alone or in combination with intraperitoneal L-NAME (25 mg kg^{-1}) on the gastroprotective effects of intraperitoneal cromoglycate (20 mg kg^{-1}, 30 min before ethanol) on ethanol-induced gastric lesions in rats.

Treatment before ethanol administration		Lesion score	
60 min	45 min	Without cromoglycate	With cromoglycate
–	–	9·5 ± 0·9	3·3 ± 0·4*
N-Ethylmaleimide	–	13·6 ± 1·2*	11·8 ± 1·1
–	L-NAME	12·6 ± 0·9*	10·1 ± 1·1
N-Ethylmaleimide	L-NAME	16·7 ± 1·0*	15·2 ± 0·7
N-Ethylmaleimide + L-arginine	L-NAME	–	12·6 ± 1·2

Mean ± s.e.m. ($n = 6–8$). *$P < 0·05$ compared with value obtained with no pretreatment.

effect of combined *N*-methylmaleimide and L-NAME pretreatment with a protection value of 25% for cromoglycate but it was not significantly different from the value that was obtained within the group treated with *N*-ethylmaleimide, L-NAME and cromoglycate.

Discussion

Ethanol-induced gastric damage has been shown to be associated with labilization of cell membranes (Chiu et al 1983), degranulation of stomach mast cells (Oates & Hakkinen 1988), depletion of sulphydryl compounds (Szabo et al 1981; Miller et al 1985; Loguercio et al 1993) and microvascular changes (Guth et al 1984; Szabo et al 1985; Takeuchi et al 1989). Thus, it might be anticipated that any agent which may interfere with the pathogenic process should afford protection against ethanol-induced gastric lesions.

Previous studies with cromoglycate have indicated that the gastric protection is due to inhibition of degranulation of mast cells and prevention of subsequent release of proulcerogenic substances (Ogle & Lau 1979; Goossens et al 1987; Beck et al 1988). In the present study, cromoglycate dose-dependently afforded protection after intraperitoneal administration; we also found cromoglycate to be about 50% less effective orally than intraperitoneally with the highest dose used in this study (data not shown). This is consistent with the pharmacokinetic properties of cromoglycate (Brogden et al 1974) and with the observation of Goossens et al (1987). The protection afforded by cromoglycate may indeed be due to stabilization of mast cells since acute administration of ethanol has been reported to cause labilization of cell membranes (Chiu et al 1983). However, possible mechanisms involved in the prevention of ethanol-induced lesions by cromoglycate have further been analysed in the present study.

Pretreatment with either a NO synthase inhibitor, L-NAME or a sulphydryl-blocker, *N*-ethylmaleimide aggravates ethanol-induced lesions, consistent with previous reports (Szabo et al 1981; Takeuchi et al 1989; Endoh et al 1992; Lambrecht et al 1993; Gyires 1994; Konturek et al 1994). This aggravation of lesions by these two different types of blockers may suggest the possible endogenous regulatory roles of both NO and sulphydryls in the induction of ethanol-induced gastric lesions.

Pretreatment with L-arginine or D-arginine itself did not cause any significant change in ethanol-induced lesions. This may suggest that L-arginine, although a substrate for NO synthase in the biosynthesis of NO, possibly fails to show its effects against combinations of factors that are involved in ethanol-induced lesions. On the other hand, pretreatment with L-NAME dose-dependently reduces the protective effects of cromoglycate and prior administration of L-arginine but not D-arginine restores the protective effects of cromoglycate indicating the role of NO in the protective mechanism of cromoglycate. Furthermore, the specificity of the blocking effect of L-NAME is evidenced by the observation that a dose of L-NAME (12·5 mg kg^{-1}) which does not cause significant enhancement of ethanol-induced lesions also reduces the protective effects of cromoglycate. In this context, a similar conclusion regarding the involvement of NO in the protective mechanisms of aluminium-containing antacids, sucralfate and morphine have been drawn by previous workers (Konturek et al 1992, 1994; Gyires 1994).

The maintenance of a critical level of gastric endogenous sulphydryls has been suggested to be important for the gastric mucosa to resist damage when challenged with noxious agents. Thus, ethanol-induced gastric mucosal lesions have been shown to be associated with a depletion of nonprotein sulphydryl concentrations in the gastric mucosa of experimental animals and in man (Szabo et al 1981; Miller et al 1985; Loguercio et al 1993). Exogenous administration of sulphydryl-containing substances has been shown to protect gastric mucosa from ethanol-induced damage, while pretreatment with sulphydryl-blockers prevented the protection (Szelenyi & Brune 1986; Szabo & Brown 1987; Roger et al 1988; Gutierrez-Cabano 1989; Ali 1991). In the present study, there is a significant reduction in the nonprotein sulphydryl content of the gastric mucosa after ethanol administration and *N*-ethylmaleimide pretreatment dose-dependently caused aggravation of ethanol-induced lesions. Moreover, the severity of lesions corresponds to the degree of depletion of glandular sulphydryl content. Pretreatment with cromoglycate affords protection and prevents the depletion of sulphydryls against ethanol-induced damage. In contrast, treatment with *N*-ethylmaleimide (12·5, 25 and 50 mg kg^{-1}) before cromoglycate dose-dependently reduces the protective effects of cromoglycate that are associated with corresponding depletion of sulphydryls. However, it is conceivable that the depletion of sulphydryls may be the consequences of gastric mucosal damage through luminal loss due to the exfoliation of injured mucosal cells, and that the preservation of gastric sulphydryls after pretreatment with cromoglycate is due to the fact that cromoglycate decreases the amount of damage induced by ethanol. Thus, it appears from the data that the severity of lesions is inversely proportional to the changes in glandular sulphydryls. These findings suggest that nonprotein sulphydryls may be involved in the protective mechanisms of cromoglycate against ethanol-induced gastric damage.

Combined *N*-ethylmaleimide and L-NAME pretreatment caused a greater aggravation of ethanol-induced lesions and a greater reduction of protective effects of cromoglycate. However, pretreatment with L-arginine only partially restores the protective effects of cromoglycate. These findings may suggest that L-arginine is specifically able to reverse the blocking effect of L-NAME but not of those due to *N*-ethylmaleimide. Thus, it appears that NO and sulphydryls are two independent systems and depletion of both may result in aggravation of ethanol-induced lesions and restoration of their critical levels are associated with general protective effects.

The mechanism by which cromoglycate is able to activate NO and sulphydryl systems is not known. However, cromoglycate is a mast cell stabilizer (Marshall 1972; Brogden et al 1974; Tasaka 1985). Moreover, both sulphydryl and NO may cause stabilization of mast cell membranes (Guslandi 1987; Salvemini et al 1994) and increase in mucosal blood flow (Szabo et al 1985; Pihan et al 1986; Pique et al 1989, 1992; Moncada et al 1991; Tepperman & Whittle 1992) which would maintain mucosal integrity.

Thus, the gastric protection effect of cromoglycate against ethanol-induced gastric lesions appears to be due to a combination of multiple factors such as stabilization of mast cell membranes, prevention of depletion of glandular nonprotein sulphydryls, maintenance of NO levels and gastric mucosal blood flow.

In conclusion, this study demonstrates that cromoglycate can protect gastric mucosa against ethanol-induced damage and the protective mechanisms seem to be due to the maintenance of a critical level of endogenous NO and nonprotein sulphydryls by modulating both NO and sulphydryl-sensitive systems in the gastric mucosa. Further biochemical, histopathological and clinical studies are warranted to establish the exact mechanisms of its action and possible therapeutic efficacy in peptic ulcer diseases.

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