Role of ATP-Sensitive Potassium Channels in Prostaglandin-Mediated Gastroprotection in the Rat

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ABSTRACT

This study compares the involvement of ATP-sensitive potassium (KATP) channels and prostaglandins in various forms of gastroprotection in the rat. Instillation of 1 ml of 70% ethanol induced severe gastric mucosal damage (lesion index 39 ± 0.8), which was substantially but not maximally reduced by oral pretreatment with 16,16-dimethyl-prostaglandin (PG) E2 (75 ng/kg), 20% ethanol (1 ml), sodium salicylate (15 mg/kg), the metal salt lithium chloride (7 mg/kg), the sulphydryl-blocking agent diethylmaleate (5 mg/kg), and the thiol dimercaprol (10 mg/kg). Administration of indomethacin (20 mg/kg) increased gastric mucosal damage induced by 70% ethanol (lesion index 45 ± 0.8) and significantly reduced the protective effect of 20% ethanol, sodium salicylate, lithium chloride, diethylmaleate, and dimercaprol. The blocker of KATP channels glibenclamide (5–10 mg/kg) significantly antagonized the protective effect of 16,16-dimethyl-PGE2, 20% ethanol, sodium salicylate, lithium chloride, diethylmaleate, and dimercaprol. The inhibition of protection induced by glibenclamide was reversed by pretreatment with the KATP Channel activator cromakalim (0.3–0.5 mg/kg). In conclusion, our results indicate a role of KATP channels in the gastroprotective effect of 16,16-dimethyl-PGE2 and of the other agents tested. Since the protection afforded by these agents is additionally indomethacin-sensitive, it is suggested that under these conditions endogenous prostaglandins act as activators of KATP Channels, and this mechanism, at least in part, mediates gastroprotection.

Various natural and synthetic prostaglandins (PGs) have been shown to be protective against tissue injury in animal models of myocardial infarction (Thiemermann and Zacharowski, 2000). This effect is, at least in part, caused by activation of ATP-sensitive potassium (KATP) channels (Thiemermann and Zacharowski, 2000). Exogenous and endogenous prostaglandins are potent protective agents in the stomach that are effective against a variety of noxious stimuli (Hawkey and Rampton, 1985). The importance of endogenous prostaglandins for gastric mucosal integrity is underlined by the observation that cyclooxygenase inhibitors such as indomethacin can damage the gastric mucosa directly. In addition, cyclooxygenase inhibitors can inhibit the protection exerted by various exogenous agents, e.g., 20% ethanol (Robert et al., 1983). The direct damaging effect of indomethacin in rat gastric mucosa has been shown to be aggravated by the blocker of KATP channels, glibenclamide, and induced by activators of these channels such as cromakalim or diazoxide (Akar et al., 1999; Toroudi et al., 1999). Intragastric instillation of concentrated ethanol induces macroscopic and histologic mucosal injury within seconds, associated with vascular stasis, increased vascular permeability, subepithelial hemorrhages, cellular exfoliation, and enhanced leukocyte-endothelial cell interaction (Guth et al., 1984; Szabo, 1987; Kviety et al., 1990; Peskar, 1991). Rat gastric mucosal damage induced by high concentrations of ethanol has been widely used to investigate gastroprotective phenomena (Robert et al., 1984; Hawkey and Rampton, 1985; Peskar et al., 1988; Peskar, 1991; Stroff et al., 1996; Gretzer et al., 1998; Araki et al., 2000). Numerous agents in addition to prostaglandins, including sodium salicylate, metals, thiols, and sulphydryl blockers, protect the gastric mucosa against damage induced by ethanol. The effect of modulators of KATP channels on these gastroprotective phenomena has so far not been investigated. We have now compared the effects of indomethacin with those of glibenclamide on the gastroprotective activity of such agents. These investigations should elucidate the contribution of endogenous prostaglandins to the activity of the protective agents as well as the importance of KATP Channels. Finally, it is already known that gastroprotection afforded by pretreatment with 20% ethanol (adaptive gastroprotection) is inhibited by selective cyclooxygenase-2 inhibitors (Gretzer et al., 1998) as well as by nonspecific inhibitors like indomethacin (Robert et al., 1983; Gretzer et al., 1998). We have now investigated the effect of glibenclamide and its modification by cromakalim on adaptive gastroprotection induced by 20% ethanol.

ABBREVIATIONS: PG, prostaglandin; CGRP, calcitonin gene-related peptide; KATP, channels, ATP-sensitive potassium channels.
Materials and Methods

Drugs. The prostaglandin analog 16,16-dimethyl-PGE₂ was obtained from Paesel & Lorei (Frankfurt, Germany). Indomethacin, sodium salicylate, lithium chloride, diethylmaleate, dimercuracol, glibenclamide, cromakalim, and all other compounds were purchased from Sigma-Aldrich (St. Louis, MO).

Animals. Male Wistar rats (weighing 180–220 g) were purchased from Harlan-Winkelmann (Paderborn, Germany). They were deprived of food for 24 h with free access to tap water. Rats were kept on a 12-h light/dark cycle and under conditions of controlled temperature (22 ± 1°C). The studies reported in this article have been carried out in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the U.S. National Institutes of Health. All experimental protocols were approved by the Animal Care Committee of the Ruhr-University of Bochum.

Assessment of Gastric Mucosal Damage. Rats received 1 ml of 70% ethanol by oral intubation. After a further 5 min, rats were killed by cervical dislocation. The stomach was removed and gross mucosal damage was assessed in a blinded manner by calculation of a lesion index by use of a 0–3 scoring system based on the number and severity factor of lesions as described previously (Stroff et al., 1996). The severity factor was defined according to the length of the lesions. Severity factor 0 = no lesions; I = lesions < 1 mm; II = lesions 2–4 mm; III = lesions > 4 mm. The lesion index was calculated as the total number of lesions multiplied by their respective severity factor.

Assessment of Gastric Mucosal 6-Keto-PGF₁α Formation. Groups of six rats were treated with glibenclamide (10 mg/kg, p.o.) or vehicle. Mucosal fragments were excised from the glandular part of the stomach 60 min later, and 2 aliquots (40 mg) were incubated in oxygenated Tyrode’s solution at 37°C for 10 min. In addition, glibenclamide (final concentration 10 μM) was added in vitro to the incubation medium of a third aliquot of mucosal tissue obtained from vehicle-treated control rats. It has been shown previously that under identical experimental conditions, indomethacin causes dose-dependent inhibition of prostaglandin formation (Peskar et al., 1988; Gretzer et al., 1998). The medium was analyzed for the content of 6-keto-PGF₁α by radioimmunoassay (Peskar et al., 1988; Gretzer et al., 1998). The radioimmunoassay used is highly specific for 6-keto-PGF₁α with less than 0.1% cross-reaction by other eicosanoids or related compounds.

Administration of Protective Agents. Groups of six to eight rats were treated orally with the following protective agents: 16,16-dimethyl-PGE₂ (0.25% methylcellulose for the protective agents) or 1 ml of distilled water (diluent for the protective agents) or 1 ml of 70% ethanol (diluent for 20% ethanol). The dose of indomethacin used has been shown previously to inhibit rat gastric mucosal prostaglandin formation under identical experimental conditions by more than 90% (Peskar et al., 1988; Gretzer et al., 1998). All rats were challenged with 1 ml of 70% ethanol 30 min after administration of the protective agent or vehicle and were killed 5 min later.

Pretreatment with Glibenclamide and Cromakalim. Groups of six to eight rats were treated with glibenclamide (5–10 mg/kg, p.o.) 30 min before administration of the protective agents. Glibenclamide was administered in 2.5 ml/kg 0.02 N NaOH containing 4% glucose to minimize hypoglycemia. Glibenclamide exhibited protective activity against 70% ethanol when the dose was increased above 5 to 10 mg/kg or the pretreatment period was prolonged over 60 min. Therefore, for each set of experiments a threshold dose of glibenclamide without protective activity when given alone was determined, and the doses finally used differed between 5 and 10 mg/kg. Additional groups of six rats received cromakalim (0.3–0.5 mg/kg, p.o.). Cromakalim was dissolved in 30% ethanol and further diluted with distilled water. Cromakalim was administered in a volume of 2.5 ml/kg 30 min before glibenclamide, and the final concentration of ethanol was 6%. All rats received either active agents or the corresponding vehicle so that the background of volumes and solvents was identical in all groups. All rats were challenged with 70% ethanol 30 min after administration of the protective agent. Vehicles for all drugs and their combinations were tested in groups of four to six rats for a possible interference with the damaging effect of 70% ethanol.

In an additional set of experiments, rats (n = 6) received cromakalim (0.5 mg/kg, p.o.) 90 min and indomethacin (5 mg/kg, p.o.) 60 min before 70% ethanol. A control group (n = 6) received cromakalim (0.5 mg/kg, p.o.) followed by methylcellulose (0.25%, 2.5 ml/kg, p.o.) instead of indomethacin.

Statistical Analysis. All data are expressed as mean ± S.E.M. of n values. Comparisons between groups were made by use of the Wilcoxon rank test for nonparametric data. A p value of < 0.05 was considered significant.

Results

Oral instillation of 1 ml of 70% ethanol induced severe gastric mucosal damage (lesion index 39 ± 0.8). Pretreatment with indomethacin (20 mg/kg, p.o., 60 min) augmented the injurious effect of 70% ethanol (lesion index 45 ± 0.8, p < 0.001).

Neither the solvent for glibenclamide (lesion index 39 ± 0.9), the solvent for cromakalim (lesion index 39 ± 1.8), nor the solvent for indomethacin and the protective agents (lesion index 38 ± 2) interfered with the damaging effect of 70% ethanol. Furthermore, neither pretreatment with cromakalim (0.3 mg/kg and 0.5 mg/kg, p.o., 90 min before 70% ethanol; lesion index 38 ± 3.8 and 36 ± 2.8, respectively) nor the dose of glibenclamide used in a specific set of experiments (5–10 mg/kg, p.o., 60 min before 70% ethanol) modified the injury caused by 70% ethanol. However, cromakalim (0.5 mg/kg, p.o., 90 min before 70% ethanol) induced significant (p < 0.001) gastroprotection (lesion index 16 ± 3) in rats treated additionally with indomethacin (5 mg/kg, p.o., 60 min before ethanol) as compared with controls treated with cromakalim only (lesion index 39 ± 2).

Gastric mucosal fragments obtained from vehicle-treated rats released 425 ± 45 pg/mg/10 min 6-keto-PGF₁α during incubation in vitro. Release of 6-keto-PGF₁α was not significantly different when glibenclamide (final concentration 10 μM) was added to the incubation medium (379 ± 68 pg/mg/10
Furthermore, oral treatment with glibenclamide (10 mg/kg) did not inhibit gastric mucosal release of 6-keto-PGF₁α ex vivo (411 ± 48 pg/mg/10 min) as compared with controls.

**Effect of 16,16-Dimethyl-PGE₂.** Ethanol-induced gastric mucosal damage was significantly (by 74%) reduced by pretreatment with 16,16-dimethyl-PGE₂ (75 ng/kg). The protective effect of the prostaglandin was attenuated by pretreatment with glibenclamide (10 mg/kg, p < 0.001 versus 16,16-dimethyl-PGE₂ alone). Administration of cromakalim (0.3 mg/kg) 30 min before glibenclamide (10 mg/kg) fully restored the protective effect of 16,16-dimethyl-PGE₂. Results are shown in Fig. 1.

**Adaptive Gastroprotection.** Oral instillation of 1 ml of the mild irritant 20% ethanol reduced gastric mucosal damage induced by a subsequent instillation of 1 ml of 70% ethanol by 83% (p < 0.001). Pretreatment with indomethacin (20 mg/kg, 30 min) abolished the protective effect of 20% ethanol. Pretreatment with glibenclamide (10 mg/kg) 30 min before instillation of 20% ethanol near-maximally inhibited the protection induced by the mild irritant (p < 0.001 versus 20% ethanol alone). Cromakalim (0.3 mg/kg) counteracted the effect of glibenclamide and restored the protective activity of the mild irritant (p < 0.001 versus glibenclamide before 20% ethanol). Results are shown in Fig. 2.

**Effect of Sodium Salicylate.** Sodium salicylate (15 mg/kg) reduced the injurious effect of 70% ethanol by 80% (p < 0.001 versus controls treated with vehicle instead of sodium salicylate). The protective effect of sodium salicylate was significantly diminished by pretreatment with glibenclamide (7.5 mg/kg, p < 0.001 versus sodium salicylate alone) and was restored after combined treatment with cromakalim (0.3 mg/kg) and glibenclamide (p < 0.001 versus sodium salicylate and glibenclamide). Indomethacin (20 mg/kg) abolished the protection conferred by sodium salicylate. Results are shown in Fig. 3.

**Effect of Lithium Chloride.** Administration of lithium chloride (7 mg/kg) reduced gastric mucosal damage induced by 70% ethanol by 67%. The protective effect was significantly inhibited by pretreatment with lithium chloride (7 mg/kg, p < 0.001). Pretreatment with lithium chloride (7.5 mg/kg, p < 0.001 versus sodium salicylate alone) and was restored after combined treatment with cromakalim (0.3 mg/kg) and lithium chloride (p < 0.001 versus sodium salicylate and lithium chloride). Indomethacin (20 mg/kg) abolished the protection conferred by lithium chloride. Results are shown in Fig. 3.

**Effect of Diethylmaleate.** The sulfhydryl-blocking compound diethylmaleate (15 mg/kg) inhibited gastric mucosal injury induced by 70% ethanol by 66%. Pretreatment with diethylmaleate (5 mg/kg) reduced the protective effect of diethylmaleate (p < 0.001 versus diethylmaleate alone). Pretreatment with lithium chloride (7 mg/kg, p < 0.001 versus sodium salicylate alone) and was restored after combined treatment with cromakalim (0.3 mg/kg) and lithium chloride (p < 0.001 versus sodium salicylate and lithium chloride). Indomethacin (20 mg/kg) abolished the protection conferred by lithium chloride. Results are shown in Fig. 4.
versus glibenclamide before lithium chloride.

Rats treated with lithium chloride alone (Veh) were pretreated with the vehicles for cromakalim and glibenclamide. Pretreatment with indomethacin (Indo, 20 mg/kg, p.o.) increased damage induced by 70% ethanol and inhibited the protective effect of lithium chloride. Values are the mean ± S.E.M. of 5–7 rats. ***, p < 0.001 versus controls (Co); ●●●, p < 0.001 versus lithium chloride alone; ###, p < 0.001 versus lithium chloride before lithium chloride.

**Discussion**

The main new findings of the present work are: 1) the gastroprotection of various agents of different chemical classes in submaximal doses depends on an intact prostaglandin system; and 2) the prostaglandins mediating the protective effect act, at least in part, by opening K<sub>ATP</sub> channels. A scheme summarizing the proposed mechanism of gastroprotection and the targets of drug actions is shown in Fig. 7. The conclusion that the gastroprotection conferred by submaximally effective doses of 16,16-dimethyl-PGE<sub>2</sub> as well as of sodium salicylate, 20% ethanol, lithium chloride, diethylmaleate, and dimercaprol is, at least partially, mediated by activation of K<sub>ATP</sub> channels is supported by the inhibition of protection by glibenclamide, a blocker of K<sub>ATP</sub> channels.

Fig. 5. Gastroprotection by the sulfhydryl-blocking compound diethylmaleate and effect of glibenclamide, cromakalim, and indomethacin. Administration of diethylmaleate (15 mg/kg, p.o.) reduced gastric damage induced by 70% ethanol. Pretreatment with glibenclamide (Gibl, 10 mg/kg, p.o.) inhibited the protection conferred by diethylmaleate; administration of cromakalim (Crom, 0.3 mg/kg, p.o.) before glibenclamide restored the protective effect of lithium chloride. Values are the mean ± S.E.M. of 5–6 rats. ***, p < 0.001 versus controls (Co); ●●●, p < 0.001 versus diethylmaleate alone; ###, p < 0.001 versus glibenclamide before diethylmaleate.

Fig. 6. Gastroprotection by the sulfhydryl-containing agent dimercaprol and effect of glibenclamide and indomethacin. Administration of dimercaprol (10 mg/kg, p.o.) inhibited gastric damage induced by 70% ethanol. Pretreatment with glibenclamide (Gibl, 10 mg/kg, p.o.) inhibited the protection conferred by dimercaprol; administration of cromakalim (Crom, 0.4 mg/kg, p.o.) before glibenclamide restored the protective effect of dimercaprol. Rats treated with dimercaprol alone (Veh) were pretreated with the vehicles for cromakalim and glibenclamide. Pretreatment with indomethacin (Indo, 20 mg/kg, p.o.) increased damage induced by 70% ethanol and attenuated the protective effect of diethylmaleate. Values are the mean ± S.E.M. of 5–6 rats. ***, p < 0.001 versus controls (Co); ●●●, p < 0.001 versus dimercaprol alone; ###, p < 0.001 versus glibenclamide before dimercaprol.

Fig. 4. Gastroprotection by lithium chloride and effect of glibenclamide, cromakalim, and indomethacin. Administration of lithium chloride (7 mg/kg, p.o.) reduced gastric damage induced by 70% ethanol. Pretreatment with glibenclamide (Gibl, 10 mg/kg, p.o.) inhibited the protection conferred by lithium chloride; administration of cromakalim (Crom, 0.3 mg/kg, p.o.) before glibenclamide restored the protective effect of lithium chloride. Rats treated with lithium chloride alone (Veh) were pretreated with the vehicles for cromakalim and glibenclamide. Pretreatment with indomethacin (Indo, 20 mg/kg, p.o.) increased damage induced by 70% ethanol and inhibited the protective effect of lithium chloride. Values are the mean ± S.E.M. of 5–7 rats. ***, p < 0.001 versus controls (Co); ●●●, p < 0.001 versus lithium chloride alone; ###, p < 0.001 versus lithium chloride before lithium chloride.

Fig. 3. In addition, gastroprotection by submaximally effective doses of sodium salicylate, 20% ethanol, lithium chloride, and indomethacin. Administration of sodium salicylate, 20% ethanol, lithium chloride, and indomethacin increased damage induced by 70% ethanol. Pretreatment with glibenclamide (Gibl, 10 mg/kg, p.o.) reduced gastric damage induced by 70% ethanol. Pretreatment with glibenclamide (Gibl, 10 mg/kg, p.o.) inhibited the protection conferred by lithium chloride; administration of cromakalim (Crom, 0.3 mg/kg, p.o.) before glibenclamide restored the protective effect of lithium chloride. Rats treated with lithium chloride alone (Veh) were pretreated with the vehicles for cromakalim and glibenclamide. Pretreatment with indomethacin (Indo, 20 mg/kg, p.o.) increased damage induced by 70% ethanol and attenuated the protective effect of diethylmaleate. Values are the mean ± S.E.M. of 5–7 rats. ***, p < 0.001 versus lithium chloride alone; ###, p < 0.001 versus glibenclamide before lithium chloride.

The sulfhydryl-containing agent dimercaprol (10 mg/kg) exerted 67% protection against gastric damage induced by 70% ethanol. Pretreatment with glibenclamide (Gibl, 0.4 mg/kg, p.o.) before dimercaprol restored the protective effect of dimercaprol (p < 0.01 versus dimercaprol pretreatment). Likewise, pretreatment with indomethacin (20 mg/kg) attenuated the protective effect of diethylmaleate (p < 0.001 versus diethylmaleate alone). Results are shown in Fig. 5.

**Effect of Dimercaprol.** The sulfhydryl-containing agent dimercaprol (10 mg/kg) exerted 67% protection against gastric damage induced by 70% ethanol. Pretreatment with glibenclamide (10 mg/kg) reduced the protective effect of dimercaprol (p < 0.01 versus dimercaprol alone). Cromakalim (0.4 mg/kg) reversed the effect of glibenclamide (p < 0.001 versus pretreatment with glibenclamide). Similarly, pretreatment with indomethacin (20 mg/kg) attenuated the protective effect of dimercaprol (p < 0.01 versus dimercaprol alone). Results are shown in Fig. 6.

The main new findings of the present work are: 1) the gastroprotection of various agents of different chemical classes in submaximal doses depends on an intact prostaglandin system; and 2) the prostaglandins mediating the protective effect act, at least in part, by opening K<sub>ATP</sub> channels. A scheme summarizing the proposed mechanism of gastroprotection and the targets of drug actions is shown in Fig. 7. The conclusion that the gastroprotection conferred by submaximally effective doses of 16,16-dimethyl-PGE<sub>2</sub> as well as of sodium salicylate, 20% ethanol, lithium chloride, diethylmaleate, and dimercaprol is, at least partially, mediated by activation of K<sub>ATP</sub> channels is supported by the inhibition of protection by glibenclamide, a blocker of K<sub>ATP</sub> channels (Sturgess et al., 1985; Quast, 1993). Furthermore, cromakalim, an opener of such channels (Quast and Cook, 1989; Quast 1993; Quayle et al., 1995) prevents the glibenclamide effect. Antagonistic interaction of glibenclamide and cromakalim has generally been accepted as evidence for the involvement of K<sub>ATP</sub> channels (Standen et al., 1989; Quayle et al., 1995). Cromakalim has been shown previously (Akbar et al., 1999) to prevent indomethacin-induced injury. Our results demonstrate that cromakalim not only reverses the glibenclamide-induced inhibition of gastroprotection, but can also directly antagonize ethanol-induced gastric mucosal damage. In the dosage used, this effect is, however, observed only after additional treatment with indomethacin. This result is in agreement with data of Armstead (2001) showing that cyclooxygenase-dependent superoxide generation impairs the vasodilatory effect of cromakalim and that the potency of cromakalim is increased after inhibition of cyclooxygenase by indomethacin.

In addition, gastroprotection by submaximally effective doses of sodium salicylate, 20% ethanol, lithium chloride,
The EP receptor subtype responsible for cardioprotection has been identified as EP3 using subtype-specific receptor agonists, concluded that gastroprotection against 0.15 N HCl in 60% ethanol is mediated by EP1 receptors. Their results were strongly supported by data obtained in knock-out mice. Although both EP1 and EP3 knock-out mice reacted with gastric mucosal damage to HCl/ethanol, only EP1 knock-out mice could not be protected by exogenous PGE2, whereas EP3 knock-out mice did not differ from wild-type mice. Neither EP1 nor EP3 receptors are involved in increased blood flow (Araki et al., 2000; Thiemermann and Zacharowski, 2000). Further experiments are necessary to clarify exactly the prostaglandin receptor subtypes involved in various types of organ protection.

Whereas in our study gastric mucosal damage induced by 70% ethanol was not affected by oral glibenclamide at the doses used, glibenclamide administered intravenously aggravated mucosal injury induced by gastric perfusion with 15% ethanol/0.15 N HCl (Iwata et al., 1997; Doi et al., 1998). Mucosal hyperemia induced by acidified ethanol or capsaicin was attenuated by glibenclamide, suggesting that under these experimental conditions, the KATP channel blocker most likely acts at the arteriolar level to attenuate the vasodilatory effect of endogenous calcitonin gene-related peptide (CGRP) released from afferent nerve terminals in the gastric mucosa (Iwata et al., 1997). This interpretation is supported by data showing that the increase in gastric mucosal blood flow induced by exogenous CGRP was also attenuated by glibenclamide (Doi et al., 1998). Mucosal lesions produced by intragastric superfusion with 15% ethanol/0.15 N HCl were exacerbated by glibenclamide but ameliorated by exogenous CGRP. The authors concluded that CGRP protects the gastric mucosa, at least in part, through the activation of KATP channels (Doi et al., 1998). It should be pointed out, however, that gastroprotective effects are not necessarily associated with mucosal hyperemia but can occur when gastric mucosal blood flow remains unchanged or is even substantially decreased. Examples are PGE2 (Whittle et al., 1985), 16,16-dimethyl-PGE2 (Arakawa et al., 1989), and tachykinin neurokinin-2 receptor agonists (Stroff et al., 1996). It is not known which structures, such as vasculature, epithelium, etc., of the gastric mucosa contain the KATP channels activated by prostaglandins.

In conclusion, our results indicate an essential contribution of KATP channels to gastroprotection afforded by submaximally effective doses of 16,16-dimethyl-PGE2 as well as of other agents such as 20% ethanol, sodium salicylate, lithium chloride, diethylmaleate and dimercaprol. The protection conferred by these compounds in the dosage used was additionally found to be indomethacin-sensitive and thus depends on an intact prostaglandin system. The results suggest that under these conditions endogenous prostaglandins act as activators of KATP channels and this mechanism, at least in part, mediates gastroprotection.

References


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