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Progress report

Gastrointestinal cytoprotection by prostaglandins

Prostaglandins (PGs) are widely distributed throughout the gastrointestinal tract and affect a variety of gastrointestinal functions. The observation that PGs of the E and A series are potent inhibitors of gastric acid secretion and that PGs, especially the E compounds, are released into the gastric lumen during vagal or gastrin stimulation suggests a possible physiological role for these agents as negative feedback inhibitors of gastric secretion[1-8]. Further, Robert's finding that prostaglandins prevent experimental ulceration from numerous causes in different laboratory animals implies a therapeutic use of PGs as anti-ulcer drugs apart from their antisecretory effects[9-11]. This ability of PGs to protect the cells of the gastrointestinal epithelium against a variety of potentially noxious agents which otherwise have the capability of producing cellular damage and necrosis is termed 'cytoprotection'[10-12] and has been observed with all PGs tested, whether or not they possess gastric antisecretory properties. Furthermore, the dose of PG needed for cytoprotection has been shown to be much less than the antisecretory dose for several PGs possessing this latter property. These findings suggest that the cytoprotective action of PGs may be more fundamental than other gastrointestinal actions. If this is true, the potential clinical implications of cytoprotection are far-reaching.

Are prostaglandins indeed cytoprotective? Available evidence suggests that they are. The purpose of this discussion is to review the evidence, examine possible mechanisms for this proposed cytoprotective action of PGs, and suggest clinical situations in which such protection might prove beneficial. Other gastrointestinal actions of PGs, reviewed extensively elsewhere,[10,12-14] will be discussed only as they relate to cytoprotection.

Evidence for cytoprotection

INTESTINAL PROTECTION

In recent years a number of nonsteroidal drugs with anti-inflammatory properties have found increasing use in the treatment of clinical disorders ranging from headache to severe arthritis. Among these drugs are such medications as indomethacin and ibuprofen which share the pharmacological properties of the older drugs, aspirin and phenylbutazone. A small but consistent percentage of patients receiving these agents develop gastrointestinal intolerance which may be manifest merely as nausea and upper abdominal discomfort or result in gastritis, duodenitis, or frank ulcerations associated with bleeding[15-17].

This intolerance to nonsteroidal anti-inflammatory compounds (NOSAC) occurs not only in man but also in a variety of animals in which frank

gastrointestinal ulcerations may be induced[11,18–22]. In the rat, Kent and associates first reported that the administration of indomethacin intragastrically or intramuscularly produced a syndrome characterised by multiple ulcerative lesions of the small intestine involving both the jejunum and ileum[18]. These lesions appeared within 12 to 24 hours after treatment, and subsequently perforated resulting in fatal peritonitis within three to four days. At necropsy, the small intestine presented as a solid mass of adhesions bathed in a thick pool of exudate with hundreds of perforations throughout the gut. Others have confirmed these findings and, in addition to indomethacin, it is now well established that other agents in the NOSAC class, such as flufenamic acid, flurbiprofen, ibuprofen, carbazole, phenylbutazone, and naproxen, also cause small intestinal ulcerations in rats [12,19,20,23].

The explanation for these intestinal lesions remains uncertain. Indomethacin has been reported to possess vasoconstrictive actions[24], but the intestinal lesions produced by this agent do not appear to be ischaemic in origin. Fang *et al.* ligated a major branch of the superior mesenteric artery in the rat and contrasted the microscopic appearance of the resulting ischaemic lesion of the intestine with that of the inflammatory lesion induced by indomethacin[23]. They also were unable to provoke intestinal ulceration with a vasoconstrictor drug.

The observation that aspirin and indomethacin block the activity of the prostaglandin synthetase system both *in vitro* and *in vivo* led Vane[25] to suggest that the gastrointestinal intolerance occasionally encountered in humans treated with NOSAC-type drugs may be due to a deficiency of endogenous prostaglandins. Prostaglandin synthetase is essential for the biosynthesis of PG from arachidonic acid. In studies by Takeguchi and Sih, several other NOSAC were also found to block the activity of prostaglandin synthetase[26].

In testing the hypothesis that NOSAC-induced intestinal lesions may be due to a PG deficiency, Robert found that various natural (PGA_1, PGA_2, PGB_2, PGC_2, PGD_2, $PGF_{2\alpha}$, $PGF_{2\beta}$) and synthetic PGs (methyl analogues of PGA_2, PGE_2, $PGF_{2\alpha}$, $PGF_{2\beta}$) inhibited intestinal ulceration with indomethacin in rats[11]. The inhibition was dose-dependent, and PG A and E compounds were generally most effective. Of interest is the finding that in other respects the PGs tested show different properties. For example, PGE_2 potently inhibits gastric acid output, whereas $PGF_{2\beta}$ is ineffective; nevertheless, both PGs confer full protection against the NOSAC-induced intestinal lesions[10].

Both prostaglandins and antibiotics prevent the inflammatory stimulation of DNA, RNA, and protein synthesis which occurs in the intestinal wall with indomethacin[23]. Both antibiotics and the germ-free state also protect rats against the peritonitis which accompanies the intestinal response to large doses of indomethacin, but do not entirely prevent the development of superficial mucosal ulcerations induced by the drug[18,27]. This may mean that NOSAC lesions alter intestinal mucosal integrity sufficiently to permit bacterial penetration. The flow of bile also seems important since prior ligation of the rat common bile duct prevents the development of the fatal NOSAC lesion[19].

However, as pretreatment with prostaglandins forestalls even superficial mucosal NOSAC lesions in rats, this syndrome seems related primarily

to an alteration in PG biosynthesis. Identification of endogenous PGs in the small bowel mucosa[28], coupled with the observation that agents which precipitate mucosal lesions are inhibitors of PG synthesis, supports this hypothesis. Formation of PG may be necessary for normal cellular integrity, and the administration of NOSAC may be producing the syndrome of acute PG deficiency. Presumably this deficiency allows disruption of the intestinal mucosa with ulceration, penetration of bacteria and bile salts, inflammation and necrosis of the entire gut wall, perforation, and peritonitis. Pretreatment with PG may re-establish a normal tissue level of the substance, thereby obviating the initial stages of this deficiency-type damage to the lining of the intestine.

In support of this, Robert observed that a single oral administration of 16,16 dimethyl PGE_2 30 minutes before, at the same time as or within one hour after indomethacin protected the intestine against ulceration[11]. When this PG was given four hours after indomethacin administration, the incidence of lesions was about the same as in rats given indomethacin alone[11]. These results suggest that the lesions produced by NOSAC progress in an irreversible fashion unless the prostaglandin deficiency is corrected early in the course of the disorder. By six hours after indomethacin alone there are few histological signs of mucosal inflammation and DNA synthesis has not yet begun to rise[23], but at this time irreversible damage has occurred.

The protective effect of the prostaglandins is not limited to prevention of ulcers induced by NOSAC alone. A dose-dependent cytoprotection by 16,16 dimethyl PGE_2 has also been demonstrated against lesions produced in the rat by prednisolone[12,29a]. Although the full thickness of the intestinal wall eventually became necrotic with extensive polymorphonuclear infiltration, the initial lesion was confined to the intestinal mucosa. Steroidal ulcers of the gut are usually limited to the terminal ileum and appear to be infected since microabscesses are seen throughout the thickness of the ileal wall and antibiotics prevent these lesions. The mechanism underlying steroid-induced ulceration may also involve PGs, since steroids inhibit PG formation[29b] or release[29c].

GASTRIC PROTECTION

NOSAC are also ulcerogenic to the gastric mucosa. Aspirin, indomethacin, flufenamic acid, flurbiprofen, ibuprofen, carbazole, mefenamic acid, naproxen and phenylbutazone are all capable of producing acute gastric ulcers in a variety of experimental animals[10,21,22,30–32]. Aspirin, indomethacin and phenylbutazone also appear to be ulcerogenic in the human stomach[33–35].

In the rat, gastric ulcerations consistently develop within three to six hours following either the oral or intraperitoneal administration of NOSAC to fasted animals[10,36–38]. These lesions are characterised by diffuse haemorrhagic ulcerations of the glandular mucosa with sparing of the non-acid secreting forestomach and antrum. Gastric ulcerations have also been produced in guinea pigs,[31] dogs[21,22,30,39] and cats[32] by NOSAC given orally, parenterally or topically to a gastric pouch. The ulcerogenic propensity of these agents may vary considerably depending upon the dose employed, but can affect both the antral and oxyntic glandular mucosae. In high doses both haemorrhage[39] and perforation[21] may occur.

The mechanism underlying these gastric ulcerations remains uncertain. The possibility that these damaging effects may be mediated through changes

in gastric mucosal blood flow has been proposed[8,40,41], but evidence supporting this hypothesis is at present inconsistent and inconclusive. In the rat, Main and Whittle[40] observed that both resting and stimulated gastric mucosal blood flow were significantly diminished following parenteral administration of indomethacin in doses previously shown to be ulcerogenic. A similar reduction in mucosal blood flow was noted by O'Brien and Silen[41] during bathing of the canine gastric mucosa of vagally denervated fundic pouches with aspirin. Augur[42], on the other hand, and Bennett and Curwain[43] were unable to produce substantial changes in blood flow during instillation of 20 mmol aspirin into the nonsecreting Heidenhain pouch. No effect on mucosal blood flow was also noted by these latter investigators[43] when 20 mmol aspirin was administered into the pouch during pentagastrin stimulation, whereas Lin and Warrick[44], using 28 mmol aspirin, found a significant increase in blood flow.

The role of acid in the production of these lesions is likewise unclear. Although indomethacin has been reported to stimulate gastric acid secretion [45,46], most experimental data indicate that NOSAC actually depress acid output (apparently through disruption of the gastric mucosal barrier with resulting back diffusion of hydrogen ion)[22,39,41,43,44], so that acid production *per se* is probably not important in the aetiology of these ulcers. Nevertheless, some acid seems necessary for ulcerogenesis[10,36,39,47] since anticholinergic agents and antacids completely protect the gastric mucosa against the damaging effects of these drugs[10,36,38,45,48]. Furthermore, 0·1 mol hydrochloric acid infused orally abolishes the protective effect of an anticholinergic agent against aspirin[36]. With ulcerations induced in rats by other damaging agents such as ethanol[48,49], acid seems less important, and the ulceration is not ameliorated by antisecretory doses of the anticholinergic methscopolamine bromide[48,49].

Several PGs given orally or parenterally inhibit NOSAC-induced gastric ulceration in the rat[10,48,50]. Since PGs are present in the gastric mucosa[1,2,51, 52] and NOSAC block their synthesis, the ulceration may result from a deficiency in endogenous prostaglandins. The protective effect of PGs does not seem to be mediated through inhibition of gastric acid secretion, since PGs both with and without antisecretory action provided equal protection[10].

Using antrectomised dogs with previously prepared Heidenhain pouches, Cohen found that gastric mucosal damage (as measured by increased back diffusion of hydrogen ions) induced by aspirin and indomethacin could be prevented by the topical administration of 15-(S)-15-methyl PGE_2 methyl ester into the pouch[53]. Similarly, using a canine *ex vivo* fundic flap preparation, we have found that pretreatment with intravenous 16,16 dimethyl PGE_2 (in doses 1 to 10% of the ED_{50} for inhibition of maximally stimulated acid secretion) prevented back diffusion of hydrogen ions induced by topical aspirin[54].

The effect of PGs on NOSAC-induced ulceration in the human stomach has not been studied. Cohen and Pollett[55], using healthy adult males, observed that the usual fall in gastric transmucosal potential difference induced by topical aspirin and indomethacin could be prevented with concomitant administration of PGE_2. While it was concluded that PGE_2 protected the gastric mucosa against the ulcerogenic effects of these agents, the significance of this finding is unclear since changes in potential difference *per se*[56] do not

necessarily indicate the presence of frank gastric mucosal ulcerations. Further studies are needed, therefore, to clarify the effect of PGs on drug-induced ulceration in man.

Gastric mucosal damage induced by bile, 5-hydroxytryptamine (5-HT), alcohol, steroids or restraint is also prevented by PGs[48,49,57–61]. Acute erosive gastritis produced in rats by the intragastric administration of bile was prevented by the concomitant administration of PGE_2 but only partly inhibited by cholestyramine or the antacid Maalox[57].

In the rat, 80% ethanol given orally produced multiple, deep, bleeding ulcers throughout the gastric corpus which were prevented by various PGs including those without antisecretory properties such as 16,16 dimethyl PGA_2 and 15-methyl $PGE_{2\beta}$ but not by the anticholinergic agent, methscopolamine bromide[48]. In other studies[49], gastric ulceration was produced in rats by oral administration of absolute ethanol, 0·75 M HCl, 0·2 M NaOH, 30% NaCl or boiling water. The resulting lesions consisted of severe necrosis of 70-80% of the glandular gastric corpus. Again, various PGs, many of which possessed no antisecretory properties, completely protected the gastric mucosa against damage. The antisecretory PGs protected the gastric mucosa in doses less than 1% of the threshold antisecretory dose. These findings, coupled with the absence of cytoprotection by the antisecretory histamine H_2-receptor antagonists[62,63], strongly suggest that cytoprotection is independent of the inhibition of acid secretion[48,49].

In the rat, PGE_1 significantly reduced the number of 5-HT-induced gastric ulcers and prevented the release of the lysosomal enzyme cathepsin D from the gastric mucosa[58]. Further, PGE_1 directly stabilised lysosomal membranes in the gastric mucosa both *in vivo* and *in vitro*[58]. Since 5-HT may cause gastric ulceration through tissue hypoxia leading to release of lysosomal enzymes[64], PGs may prevent this cellular disruption by stabilisation of lysosomal membranes.

In rats, PGE_1 subcutaneously, and PGE_2 or 16,16 dimethyl PGE_2 orally or subcutaneously strongly inhibit the incidence, severity and number of gastric ulcerations induced by prednisolone[59,60]. Lee *et al.*, on the other hand, could not prevent the formation of steroid-induced ulcers in rats by oral administration of PGE_2[65]. The explanation for this failure is unclear but may be related to a difference in treatment schedule between their study and that of Robert[59,60]. The exact spacing in time between each dose of PGE_2 was not specified by Lee[65], but the three oral administrations of this PG in Robert's study[59] were evenly spaced throughout the day. Such spacing may be necessary to compensate for PG degradation.

Evidence against cytoprotection

Although the preceding information suggests a cytoprotective property of PGs, several observations challenge this concept. Recent work by O'Brien and Carter in Heidenhain pouch dogs indicates that the synthetic PG analogue, 16,16 dimethyl PGE_2, may actually damage the gastric mucosa[63]. Back-diffusion of hydrogen ion significantly increased when 16,16 dimethyl PGE_2 was instilled into the pouch lumen in a concentration of 300 μg/20 ml. Intravenous administration of 7·5 μg and 30 μg altered neither the barrier nor the gastric mucosal response to sodium taurocholate instilled into the pouch. Similarly, Bolton and Cohen reported that in dogs PGE_2, (10, 100, 1000 μg/ml) or 16,16 dimethyl PGE_2 (1, 5 and 10 μg/ml) instilled into a

Heidenhain pouch caused a progressive and highly significant increase in back diffusion of hydrogen ions and a fall in transmucosal potential difference. Furthermore, intravenous 16,16 dimethyl PGE_2 (0·3, 0·6 and 1·2 $\mu g\ kg^{-1}\ hr^{-1}$) also significantly increased gastric mucosal permeability and reduced the potential difference.

The main criticism of both studies is the large amount of PG employed. Thus, are these agents likely to be damaging at antisecretory doses in patients? Robert has shown[59,67] that the ED_{50} (the dose reducing gastric acid secretion by 50%) of topically applied 16,16 dimethyl PGE_2 into a Heidenhain pouch is 5 μg/20 ml, a concentration less than 2% of that used by O'Brien and Carter and only 2·5-25% of that employed by Bolton and Cohen. It is unlikely that the antisecretory effects of 16,16 dimethyl PGE_2 occur because it disrupts the gastric mucosal barrier and so increases back-diffusion of hydrogen ions, since the analogue infused intravenously in a dose 20 times higher than the ED_{50} for secretory inhibition failed to disrupt the barrier[63]. Thus, the damaging effects of topical 16,16 dimethyl PGE_2 appear to be due to irritation from the high concentrations of this agent (or its vehicle) in prolonged contact with the gastric mucosa. A systematic dose-response study of protective versus damaging effects of these PGs seems warranted.

The finding by Bolton and Cohen[66] that intravenous 16,16 dimethyl PGE_2 increases mucosal permeability and lowers potential difference cannot yet be explained. Miller and Tepperman[54] observed that 16,16 dimethyl PGE_2 10 μg/kg and 50 μg/kg intravenously lowered the potential difference. However, neither dose nor the 2 μg/kg used by O'Brien and Carter[63] altered the permeability of the gastric mucosa to hydrogen ions. These doses are considerably higher than those employed by Bolton and Cohen[66]. Furthermore, Miller and Tepperman[54] noted that 16,16 dimethly PGE_2 in doses 1 to 10% of the ED_{50} for antisecretion protect the canine gastric mucosa against the permeability changes induced by aspirin. These findings agree with the observations of Robert that this analogue protects the rat stomach against the ulcerative lesions induced by 80-100% ethanol, 0·75 M HCl, 0·2 M NaOH, 30% NaCl or boiling water, in doses less than 1% of the threshold antisecretory dose[48,49].

The permeability change induced by PGE_2 when given topically into a Heidenhain pouch[66] is surprising since this natural PG effectively inhibits canine acid secretion only when given parenterally[59]. The observation by Bolton and Cohen[66] that intravenous PGE_2 actually decreased gastric mucosal permeability suggests that the findings on topical administration were due to local irritation by high concentrations.

Appraisal of the data

Review of the available literature still leaves unanswered the question: 'Are PGs cytoprotective?' We propose that they are and base this assessment on two major critical observations. First, all PGs tested to date can protect against ulceration, although in other actions PGs differ dramatically. For example, $PGF_{2\alpha}$ potently constricts the bronchi, lower oesophageal sphincter and arteriolar smooth muscle, whereas PGE_2 relaxes these tissues. In addition, the PGs have been shown to protect the gastrointestinal mucosae of a variety of mammalian species, and to offer this protection against all ulcerogenic stimuli tested.

The second critical consideration is the independence of the protective property of PGs from their antisecretory effects, as noted by the fact that PGs both with and without antisecretory properties are cytoprotective and that PGs protect areas of the gastrointestinal tract such as the jejunum and ileum not exposed to acidic gastric juice. While a reduction in gastric acid secretion may contribute to the gastric protection conferred by PGs possessing antisecretory activity, this seems unimportant, since the cytoprotective dose of many PGs is 1% or less of the antisecretory dose. Further, alcohol-induced gastric ulceration is prevented by various PGs but unaffected by the antisecretory anticholinergic agent methscopolamine bromide.

Mechanism of cytoprotection

Robert has suggested that PGs may act as trophic hormones for the gastrointestinal mucosa in much the same way as gastrin has been shown to be trophic for the gastric fundus[10,11]. PGs have been extracted from both the stomach and intestine where they are endogenously synthesised[1,2,28,51,52]. Further, the finding that NOSAC inhibit PG synthesis[25,26] suggests that the gastrointestinal ulcerations induced by these agents may be due to a PG deficiency and that intracellular PGs serve to maintain gastrointestinal epithelial integrity.

The PGs may mediate their anti-ulcer effects through changes in gastric mucosal blood flow[40]. In the rat, using a ^{14}C-aniline clearance technique to measure blood flow, Main and Whittle[40,68] observed that indomethacin, in doses sufficient to inhibit PG formation, significantly reduced gastric mucosal blood flow. They further noted that the incidence and severity of gastric mucosal erosions induced by this agent reached a steady level at a time when gastric mucosal PG levels were much reduced[40]. Having previously found that PGs of the E and A series increased resting mucosal blood flow when perfused locally or administered systemically[69,70], they suggested that these drug-induced lesions may be due to the increased sensitivity of the parietal cells to secretory stimuli coupled with the reduction in mucosal blood flow and accompanying ischaemia resulting from depletion of endogenous PGs[40]. In other rat studies[71], taurocholate alone increased mucosal blood flow and had minimal ulcerogenic effect, but when administered with indomethacin blood flow significantly decreased and the number of erosions correspondingly increased. The effects were reversed by 15-S-methyl-PGE$_2$,[71]. These findings suggest that damage by indomethacin and taurocholate, and protection by the PG analogue may be directly linked to changes in gastric circulation.

Although changes in blood flow may play a role in mediating the protective effects of PGs against some forms of gastrointestinal ulceration, additional experimental observations suggest that other mechanisms must be involved. Not all NOSAC reduce gastric mucosal blood flow. Aspirin, and the non-NOSAC damaging agents, ethanol and bile salts, actually increase gastric mucosal blood flow despite obvious mucosal damage by these agents[72–74]. In addition, Chaudhury and Jacobson[75] observed that indomethacin was equally damaging to the gastric mucosa *in vitro* even though the blood supply was no longer intact, and PG also offered protection in this *in vitro* preparation. Furthermore, ligation of the mesenteric blood supply or administration of the potent vasoconstrictor vasopressin does not produce the intestinal

lesion evoked by indomethacin. Finally, the haemorrhagic necrosis of the gut observed at necropsy in human subjects with lethal intestinal ischaemia is quite unlike the intestinal lesions noted with indomethacin[23,76].

Pierce *et al.*[77] found that PGE_2 and $PGF_{2\alpha}$ cause accumulation of water and electrolytes in the canine small intestine by inhibiting water and electrolyte absorption and stimulating secretion. Using $PGF_{2\alpha}$ and PGE_1, Cummings *et al.*[78] and Matuchansky and Bernier[79,80] noted similar effects on glucose, water and electrolyte absorption in the human small intestine. These observations led Robert to propose that in rats the PG deficiency induced by NOSAC might cause excessive water and electrolyte absorption from the gut leading to disruption of cellular integrity and absorption of noxious substances (including toxins, chemicals and bacteria). These substances might further disrupt the damaged mucosal wall, leading to extensive ulceration and necrosis with eventual perforation[10,11].

Although inhibition of PG synthesis may account for the gastrointestinal ulcerations produced by NOSAC and corticosteroids, the effect of other ulcerogens on PG formation has yet to be established. Ethanol stimulates PG biosynthesis *in vitro*[83], but the effects of this agent *in vivo*, to our knowledge, have not been defined. Similarly, we are unaware of any published information regarding the effects of bile salts or 5-HT on PG formation.

Recently, Shanbour and associates proposed that the initial action of damaging agents on the gastric mucosa was inhibition of active ion transport [84–87]. Using the isolated non-stimulated dog gastric mucosa, these workers found that active transport of sodium was inhibited by ethanol, aspirin and bile salts, although passive transport was unaffected until the mucosa had been exposed to these agents for a long time[84,86,87]. The same agents inhibited histamine-stimulated acid secretion in *in vivo* chambered dog stomach[85,87]. Their findings were interpreted to indicate that the initial damaging effect of ulcerogens was related to inhibition of active transport of sodium and that the gastric sodium pump is essential for the integrity of the gastric epithelium.

Chaudhury and Jacobson found that an early effect of indomethacin on isolated canine gastric mucosa was also inhibition of active transport of sodium[75]. Increased permeability to sodium occurred only after prolonged contact or with high concentrations of indomethacin. Previously, Bowen *et al.* had shown that PG stimulates active sodium transport[88]. Chaudhury and Jacobson found that 16,16 dimethyl PGE_2, dibutyryl cyclic AMP and theophylline completely reversed the action of indomethacin on gastric mucosal sodium transport[75]. This PG also increased mucosal cyclic AMP content. Their hypothesis was that 16, 16 dimethyl PGE_2 stimulates the sodium pump by activating adenylyl cyclase and increasing intracellular cyclic AMP content. Of interest, other work has shown that PGE_1 stimulates sodium transport in the isolated frog skin[89,90] and toad bladder[91], most probably by increasing the intracellular cyclic AMP level, and PGs stimulated adenylyl cyclase activity in the gastric mucosae of several mammalian species.[92].

Although further research is needed to determine whether PGs work in a similar manner in the intestinal epithelium, the finding that indomethacin, alcohol, aspirin and bile salts all inhibit active ion transport before inducing permeability changes in the gastric mucosa suggests a common mechanism underlying damage to the stomach. PGs might therefore protect the mucosa against these agents by stimulating the sodium pump[75]. 5-HT-induced gastric ulcerations in the rat resulted in the release of lysosomal enzymes,

but pretreatment with PGE_1 reduced the number of ulcers and stabilised the lysosomal membranes[58]. Thus 5-HT may inhibit active ion transport leading to an intracellular accumulation of sodium, anions and water. The resultant osmotic swelling of epithelial cells could produce severe damage, altered permeability and disruption of lysosomes. PGs, by activating the gastric sodium pump, may protect the epithelium against these intracellular changes.

Clinical significance of cytoprotection

The data currently supporting a cytoprotective property of PGs are derived from animal experimentation, and extrapolation to man should be cautious. Nevertheless, if the potent antisecretory effect of PGs on human gastric acid secretion[5,93,94], originally derived from animal work[3,4,10,12,13,48,59], applies as well to their anti-ulcer properties, the potential clinical significance of PG cytoprotection in man is considerable.

The widespread use of NOSAC in the treatment of arthritic and other inflammatory disorders carries a small risk of serious morbidity and mortality due to the associated gastrointestinal intolerance. Low doses of PG given in combination with a drug like aspirin or indomethacin might protect the gastrointestinal epithelium against potential drug-induced damage. Although we are unaware of any evidence that PGs have this effect in man, it is of interest that PGE_2 analogues have been shown experimentally to accelerate the healing of human gastric and duodenal ulcers[95,96] suggesting that these agents may prove useful clinically in the management of peptic ulceration. The mechanism underlying this healing is not known, but may be independent of the antisecretory property of the PGs since gastric ulcers are generally associated with either normal or depressed rates of gastric acid output.

The aetiology of the various inflammatory bowel diseases remains a mystery, but the loss of mucosal integrity characteristic of disorders like idiopathic ulcerative colitis, granulomatous enterocolitis and pseudomembranous enterocolitis resembles the syndrome of multiple small bowel ulcerations induced by NOSAC in the rat. The observation that these human disorders are associated with varying degrees of intestinal ulceration suggests that mucosal metabolism is altered. This may include alterations in PG synthesis, but the hypothesis is unsubstantiated, and man does not seem susceptible to the NOSAC-induced intestinal ulcerations which occur in the rat. Nevertheless, studies with PGs may prove to be a fruitful area for future research—for example, in toxic megacolon, a severe complication of ulcerative colitis which shares certain pathological features with the full thickness mucosal ulceration, as occurs in the rat small intestine with drugs like indomethacin.

Although PG cytoprotection has been demonstrated only for the gastrointestinal mucosa, the recent finding that PGs activate sodium transport in the skin[90] and urinary bladder[91] too, suggests that PGs may be cytoprotective for other epithelial tissues as well. Various poorly understood dermatological and urological disorders may ultimately prove to be due to alterations in PG metabolism. PGs occur in human and guinea-pig epidermis[97,98], and recent work suggests that a reduction in PG synthesis may be involved in the pathophysiology of psoriasis[97,98]. Whether other dermatological disorders are also related to alterations in PG metabolism remains unknown.

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