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Progress report

Prostaglandins and the gastrointestinal tract

Prostaglandins (PGs) are hydroxy-fatty acids widely distributed in animal and human tissues and biologically active in minute amounts. Despite the vast literature[1-8] their physiological role remains unclear. They are present in the gastrointestinal tract and although comparatively little is known about the function of these PGs[9-12], there is some evidence that they may be concerned in some physiological and pathological processes affecting the gut. This review examines the present state of knowledge about PGs in relation to the gastrointestinal tract.

Chemical Structure and Synthesis

The PGs are derived from 'prostanoic acid'. They are unusual amongst biological compounds in that they contain no nitrogen, but consist of a C_{20} molecule with a five-membered ring between C_8 and C_{12} (figs 1 and 2)[1, 13-15]. Many naturally occurring PGs have been isolated, but the gastrointestinal effects of only PGE_1, PGE_2, and $PGF_{2\alpha}$ and to a lesser extent PGA_1 and $PGF_{1\alpha}$ have been studied. Although the F type PGs differ from prostaglandins of the E type solely in having a hydroxyl instead of a ketone group at the C_9 position, their biological properties are markedly different.

Only PGs produced by biosynthetic methods have so far been available for study, but chemical methods are being developed[16-22]. Earlier methods yielded racemic mixtures of PGs and their analogues[20,22,23] which not surprisingly were considerably less active than the natural compounds[24]. An exciting advance has been the development of stereospecific methods of synthesis with early optical resolution and intermediate steps common to several of the prostaglandins[18]. It is likely therefore that larger amounts of these compounds may soon become available for study.

Occurrence and Release

Prostaglandins have been isolated from gastrointestinal mucosa and muscle and from the pancreas of both animals and man[25-37], and they have been detected in animal but not human liver[28,29]. There are species differences in the occurrence of various PGs in the gut. For example, the human tissues studied have yielded mainly PGE_2[33,36,37] but both PGE_2 and $PGF_{2\alpha}$ have been found in animals[27,29,31]. Similarly PGE_1 is the predominant PG in rat gastric mucous membrane[32,38] in contrast to human gastric mucosa which contains mainly PGE_2[33]. The interpretation of data on the distribution and tissue levels of the various prostaglandins is made difficult because of the many pitfalls that can beset the investigator. For example, the type of PG and

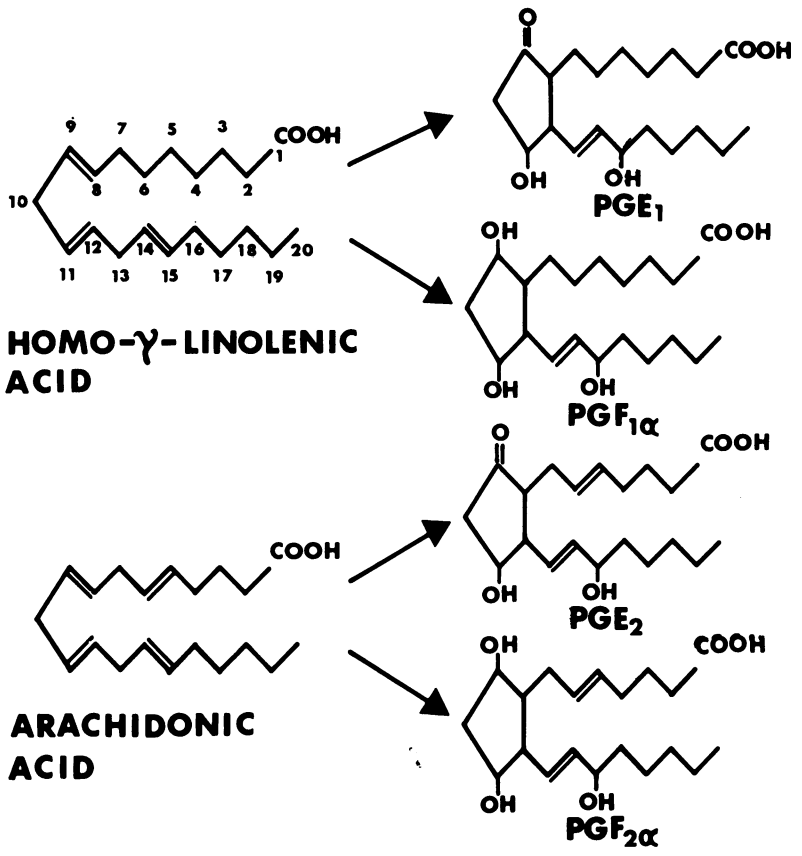

Fig 1 *PGE_1, PGE_2, $PGF_{1\alpha}$, and $PGF_{2\alpha}$ and their precursors. Stereoisomerism at the C_9 position in PGFs, the naturally occurring isomers having the α configuration. The suffix represents the number of double bonds in the molecule.*

its concentration may depend on the method used for its characterization and erroneously high levels may be recorded because non-enzymic formation of PGs (autoxidation) can occur during homogenization, even when this procedure is carried out in the cold[39]. Moreover the isolation of a PG from a tissue does not necessarily imply that the PG is stored in that tissue. It seems more likely that PGs are continuously formed and liberated as required[4] because gut homogenates can synthesize various PGs from appropriate fatty

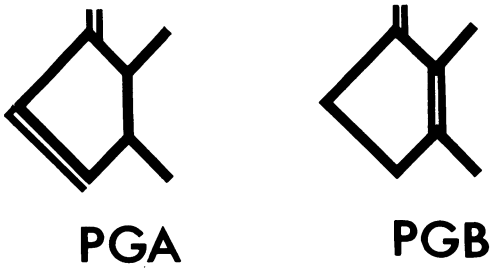

Fig 2 *PGAs and PGBs differ from the E and F type PGs with respect to the presence of double bonds in the five-membered ring.*

acid precursors (fig 1)[31,39–42], and vascular perfusion of frog intestine with labelled precursors leads to the recovery of tagged prostaglandin from the venous effluent[43].

Spontaneous release of PGs from a variety of gastrointestinal preparations both *in vitro*[30,44–50] and *in vivo*[32,37,38,51] have been reported. The type of PG released depends on the species studied, the preparation used, whether collections are made from the serosal[26] or mucosal surface[28,32], and finally by the capability of the assay system to detect them; so far PGE_1, PGE_2, $PGF_{1\alpha}$, and PGA_1 have been identified. The amount released can be greatly altered by various stimuli and also by the availability of the biosynthetic substrate. Stimuli which increase the rate at which PGs are released from intestinal muscle or mucosa include acetylcholine[48], DMPP[48], transmural and vagal electrical stimulation[31,32,38,46,49,51,52], gastrin[38], pentagastrin[51], histamine[51], theophylline and cyclic AMP (cAMP)[38,51], arachidonic acid[47,48], and phospholipase A[45,47,48]. Perfusion of isolated rat liver with glucagon also releases PGA_1[53].

Vane[54] has recently shown that anti-inflammatory drugs, such as aspirin and indomethacin, inhibit synthesis of PGs in lung homogenates, probably by affecting PG synthetase[55], and similar findings have been reported for isolated strips of rabbit jejunum[50]. Corticosteroids were considerably less effective in inhibiting PG synthesis[50]. These observations may possibly be relevant to the known ulcerogenic properties of anti-inflammatory drugs, because PGs have been shown to protect animals from experimentally induced gastroduodenal ulceration[56–58].

Inactivation

Discussion of effects which follow intravenous infusions of PGs into animals should take account of the observation that 90-95% of the E and F types and 60% of the A type are removed from the blood during one circulation through the lungs or liver[59–62]. Intraluminally administered PGE_1 is inactivated in the small intestinal wall of rats[63,64]. This rapid removal of PGs from the circulation is probably effected enzymatically and three enzymes capable of inactivating PGs have been isolated from gut and blood. 15-Hydroxy-PG-dehydrogenase, which is present in pig lung[65], stomach, liver, and small intestine[66,67], is capable of degrading PGE_1 and PGE_2 and less rapidly PGA_1[68] *in vitro*. A reductase is present in the small intestine, liver, stomach, and pancreas of the pig[66,67], whilst the blood of several animals contains an isomerase which can inactivate PGA_1[69,70]. Further, beta-oxidation of PGEs[64,69,71,72] and ω-oxidation of PGA_1[73] have been demonstrated, *in vitro*, using fractions of animal liver and small intestine or isolated perfused rat liver[74].

Little is known about PG metabolism in man, but labelled PGs are rapidly removed from the blood and the label is excreted in urine and faeces[75–77]. Analysis of urinary metabolites indicates that a 15-hydroxy-PG-dehydrogenase, a reductase, beta- and ω-oxidation are all involved in PG degradation[76,78,79]. Human liver can inactivate PGA_1 *in vitro*[79], but no PGA isomerase has been demonstrated in human blood[70].

Since PGs can be synthesized and degraded in the same tissues it seems likely that under physiological conditions they may act as local regulators rather than as circulating hormones. The rapid removal of PGs from venous

blood and the marked cardiovascular effects of minute amounts of PGEs and PGAs lend further support to this concept, although in pathological states they might be carried in the blood stream to act at distant sites[2]. Indeed it has been suggested that PG synthesis and degradation probably occur within the same cell[80]. Such a theory could explain some of the discrepancies between findings *in vitro* and *in vivo*, not only because intravenous PGs are rapidly destroyed, but also because tissues vary in their ability to take up exogenous PGs[38,81]. Similarly stimuli which bring about intracellular formation of PGs are likely to be more effective than exogenous PGs.

Gastrointestinal Motility

The great sensitivity of gastrointestinal smooth muscle to PGs has been exploited for the bioassay and identification of these substances. However, the effects of PGs on the gut examined *in vitro* show considerable variability which depends on the type of PG, the dose, the species, and even the muscle layer studied. It is therefore not possible to make any general statement without defining the variables mentioned.

STUDIES *in vitro*

Human and animal longitudinal muscle from both small and large intestine is contracted by the PGEs and $PGF_{2\alpha}$ (and by arachidonic acid)[82-93], whilst the circular muscle is relaxed by the E type[89,93], but contracted by the F type of PGs[93,96,97]. However, exceptions to this general rule have been reported[82,96,98,99]. Effects of PGs on the stomach have been less studied. Human gastric circular muscle is relaxed by PGE_2, whilst the response of longitudinal muscle is variable[33]; $PGF_{2\alpha}$ contracts both circular and longitudinal gastric muscle[96]. On the other hand both circular and longitudinal strips of rat fundus are contracted by the E and F groups of PGs (and by arachidonic acid)[87,91,100-102]. No studies of the effect of PGs on oesophageal muscle have yet been reported, although it has been shown that they are released from the oesophagus[49]. Gastrointestinal muscle seems relatively insensitive to PGs of the A group, but small contractions of some animal and human longitudinal muscle have been described[60,90,93].

Differences in the effects of PGs applied to the mucosal or serosal surface complicate the picture further. PGE_1 applied serosally to isolated segments of guinea-pig ileum has the expected effects resulting in decreased propulsion of intraluminal contents[103], but the longitudinal layer is unaffected when PGE_1 is placed in the lumen[103], probably because either PGE_1 is metabolized[64] before reaching the longitudinal muscle or because it is not absorbed.

Pharmacological analysis suggests that the contractions or relaxations produced by PGs are mediated by different mechanisms. Relaxations result from direct action of PG on the receptors on or in the smooth muscle cells[89,92,93,97], but excitatory responses may be mediated either via the intrinsic nerves or at non-neural sites[89] (possibly by potentiating intrinsic acetylcholine[104]). The way in which PGs act on smooth muscle cells is uncertain; the process is oxygen dependent and alterations in the amount of intracellular bound Ca^{++}, in permeability to Ca^{++}, or in the mycoplasmic Ca^{++} concentration produced either directly or indirectly through changes in cAMP levels, have all been invoked[100,105,106].

STUDIES *in vivo*

Effects on motility of PG administered *in vivo* are usually in accord with observations recorded *in vitro*, but relatively high doses often accompanied by unpleasant side effects are required to elicit the responses.

In animals E type PGs inhibit contractions of vagally driven canine antral pouches[107], inhibit jejunal motility[108] but increase ileal pressures[103,109]; $PGF_{2\alpha}$ increases both jejunal and ileal pressures[108,109]. The lower oesophageal sphincter of the opossum has a differential response to PGs: it is contracted by $PGF_{2\alpha}$ but relaxed by PGE_1[110,111]. There are no published data on the colonic response to PGs in laboratory animals.

The way human gastrointestinal motility is affected by PGs has not been extensively studied[112]. Intravenous $PGF_{2\alpha}$ increases cardiac sphincter pressures[113] and PGA_1 prevents heartburn caused by intravenous histamine[114], suggesting that PGs might be involved in the control of the lower oesophageal sphincter. It is not yet known whether PGE_1 relaxes the cardiac sphincter or inhibits the motility of the human stomach as it does in animals[107], but this might be expected from the nausea and vomiting which this substance produces. Moreover oral administration of PGE_1 is associated with the reflux of bile into the stomach[115], which could be taken as indirect evidence for inhibition of gastric motility. Abdominal cramps and the passage of clear watery fluid per rectum, with an accelerated transit of markers through the gut and an increased number of progressive pressure waves in the pelvic colon, follow oral PGE_1[116]; but the increased rate of transit may, at least in part, be secondary to the net secretion of fluid into the small intestinal lumen[117]. Intravenous infusions of $PGF_{2\alpha}$ inhibits segmental pressure activity in both the jejunum and ileum. Later in the course of the infusion fluid is secreted into the lumen and abnormal progressive pressure waves, which might have been expected to facilitate propulsion, occur in the ileum. Despite these effects, no clear changes in transit time (measured with a dye technique) could be detected in a 30-cm segment of the small intestine[118]: perhaps because of the limitation of the dye method. Although the speed of transit was unaffected, it seems likely that the volume of fluid entering the right colon was increased, possibly initiating mass movements and causing the subsequent diarrhoea experienced by the subjects. Abdominal colic occurred despite the inhibition of small intestinal motor activity, but at the moment the mechanism of this symptom is uncertain[118]. Abdominal pain may be associated with high intraluminal pressure waves[119], but these were not observed in the colon after oral PGE_1[116], and only very rarely in the small gut during intravenous $PGF_{2\alpha}$[118]. Prostaglandin antagonists, eg, polyphloretin phosphate and SC19220, have recently been introduced and tested mostly against the effects of PGs on gastrointestinal motility *in vitro*[120–122,96]. These substances are ineffective against the inhibitory effects of PGs and their ability to block excitatory effects varies with the tissue and species under study[96]. However, they are said to decrease muscle tone[96]. More recently it has been shown that inhibition of PG synthesis by anti-inflammatory drugs progressively lowers the tone of isolated segments of rabbit jejunum, although the tissue is still responsive to exogenous PGs[50]. On the other hand the tone of untreated jejunal strips increased steadily over the same period of time[50], as did the tone of strips of colonic muscle repeatedly stimulated electrically without changing the organ bath fluid[123]: this increase in tone was accompanied by a continuous release of PGs into organ bath fluid[50,123]. These

observations suggest that PGs may be involved in the local maintenance of gastrointestinal muscle tone, and, if confirmed, would be a very interesting development in the physiology of the gut. Meanwhile it seems likely that PGs are involved in the local regulation of gastrointestinal motility. However, it is not possible at this stage to decide whether diarrhoea following their administration is caused primarily by the effects of PGs on intestinal motility[10] or whether it is secondary to the net secretion of fluid and electrolytes also caused by these substances[117,118].

Gastric Secretion and Ulcer Formation

ANIMAL STUDIES

Evidence is accumulating that PGs of the E and A (but not the F) type and their precursors given parenterally or orally reduce the volume and hence output of acid and of pepsin from innervated and denervated stomachs of both conscious and anaesthetized animals. The available data are summarized in table I. This inhibition is non-selective. It affects basal, as well as submaximal and maximal acid secretion brought about by a variety of stimuli acting by different mechanisms[132] (table I). The degree of inhibition depends not only on the dose of PG but also on the stimulus to acid secretion[132].

Just how PGs inhibit gastric secretion is still unknown. It seems unlikely to be secondary to nausea or vomiting, or to the reflux of bile into the stomach from the duodenum[132]. Prostaglandins of the E and A type are powerful vasoactive agents which dilate gastric blood vessels in the fasting animal[138–140,128,129]. However during inhibition of acid secretion with PGE_1, PGE_2, PGA_1 or PGA_2, gastric blood flow is reduced,[128–130,133,134,141,142] but

Animal	*Route of Administration*	*Prostaglandin Tested*	*Dose*	*Stimulus for Acid Secretion*	*Inhibition Noted*
Rat	Subcutaneous	E_1	50-400 μg/kg[57]	None (pylorus and oesophagus ligated for 4 hr)[56,57,124,125]	+
			0·5-1·0 μg/kg/min[57]		
			0·2-0·8 mg/kg[124,125]	Pentagastrin 1 μg/kg subcutaneously at 20-min intervals × 5	+
		Synthetic PGs	0·4-0·32 mg/kg[56,124,125]		
	Intraluminal perfusion	E_1 E_2	0·5-1·0 μg/min[38,51]	None[38,51]	+
			1-5 μg/kg/min[126]	Pentagastrin iv 4 μg/kg[38,51]	+
				Pentagastrin iv 10 ng/kg/min[126]	+
				Histamine iv 500 μg/kg[38,51]	+
				Vagal stimulation[38,51]	+
		$F_{1\alpha}$ $F_{2\alpha}$	Not given[38]		±
	Intravenous infusion	E_1 E_2	0·2-2·0 μg/min[127]	Pentagastrin iv 0·05-2 μg/min[127]	+
			2·0 μg/kg/min[128,125]	Pentagastrin iv 0·33 μg/kg/min[128,129]	+
		A_1 A_2	4 μg/kg/min[128,129]	Histamine iv 33 μg/kg/min[128,129]	+
Cat	Intravenous infusion	E_2[130]	8 μg/kg/30 min	Pentagastrin 8 μg/kg/hr	+
Dog Pavlov Heidenhain fistula	Intravenous infusion	E_1 E_2	0·5-1·5 μg/kg/min or 200 μg/kg[56,131,132]	Food[56,131,132]	+
				Histamine iv 1-2·5 mg/hr[56,131,132]	+
		A_1	1-2 μg/kg/min[56,131,133,134]	Histamine iv 200 μg/kg/hr[133,134]	+
				Pentagastrin 0·3 μg/kg/min[56,131,132]	+
				2-Deoxyglucose 70-200 mg/kg/min[56,131,132]	+
		Arachidonic acid[135]	10 μg/kg/min	Histamine ED50	+
		$F_{2\alpha}$	1 μg/kg/min	Histamine 1 mg/hr	−
	Intravenous injection	E_2[136]	20 μg/kg	Histamine (no dose given)	+
		$MePGE_2$[136]	2 μg/kg	Pentagastrin (no dose given)	+
Ferret	Subcutaneous	E_1[137]	0·5 mg/kg	Basal	+
				Pentagastrin 10 μg/kg (intraperitoneal)	±

Table I *Effect of prostaglandins on gastric secretion in animals*

the ratio of clearance of amidopyrine or ^{14}C-aniline to acid output rises[140,142,134,128,129]. This observation makes it more likely that the reduction in blood flow is the result rather than the cause of the inhibition of acid secretion[140,142,134,128,129] and not vice versa as other workers believe[134,130]. Using isolated preparations of the bull frog mucosa in which blood flow is not a factor, Way and Durbin[143] showed that PGE_1 inhibited acid secretion stimulated by gastrin and submaximal histamine, but was ineffective against maximal histamine and cAMP. As histamine and gastrin increase adenyl cyclase activity of the isolated frog and guinea-pig mucosa[144,145], PGE_1 might act by inhibiting the formation of cAMP. This hypothesis, however, is not consistent with stimulation of acid output and increased adenyl cyclase activity in isolated gastric mucosae by PGE_1[144,146]. These divergent results could be due to different doses of PGE_1.

Observations *in vivo* are equally conflicting, for whilst the majority of observations suggest that PGs inhibit acid output, cAMP may inhibit or stimulate acid secretion. For example, intraluminal PGE_1 inhibited gastric acid secretion stimulated by cAMP in the anaesthetized rat[51], but both cAMP and PGE_1 given intravenously antagonized histamine stimulated secretion in man and dogs[133]. Clearly much more work is required with careful control of the experimental design before it can be decided whether PGs inhibit gastric secretion by modifying the levels of cAMP.

The importance of PGs in the local regulation of acid secretion[51], perhaps by a negative feedback system[2], is not yet certain. In favour of this idea is the presence of PGs in the gastric mucosa[30–32,38], and in basal and stimulated gastric juice[51], although it is not clear whether the PGs are secreted, or merely derived from exfoliated cells[10]. The finding that infused PGE_1 diminishes the incidence of ulcers induced experimentally in animals is of great interest[51–53], and has led to suggestions that lack of PGs might be a factor in human ulcer diathesis and that PGs might be of value in the treatment of peptic ulcer.

HUMAN STUDIES

The evidence that natural PGs reduce, or act as local regulators of acid secretion in man, is less convincing. The data are summarized in table II. Intravenous PGE_1 and PGA_1 inhibit basal and stimulated acid secretion, but at doses of PGE_1 which often produce unwanted effects[149,150]. These were trivial with PGA_1, but the inhibition was less and became less marked with increasing doses[114]. Oral PGE_1, PGE_2, and intravenous $PGF_{2\alpha}$ do not inhibit pentagastrin-induced acid output[115,151,152]. Histamine or pentagastrin decrease PGE_2 levels in gastric juice, whilst rectal indomethacin fails to augment submaximally stimulated acid output[37]. These latter observations could be taken as evidence against the local role of PGs in human gastric secretion.

The failure of oral PGs to inhibit human gastric secretion in man is interesting[115,147]. It might have been expected that PGE_2 would be more effective, because it is found in gastric tissues[33,37]. However, both intraluminal PGE_1 and PGE_2 inhibit acid output in the rat[38,126] although PGE_1 is present in higher concentrations in the mucosa. More likely alternative explanations are the instability of PGE_1 in an acid environment[115] or the rapid enzymatic degradation of natural PGs to inactive metabolites.

It is difficult to see at this stage how naturally occurring PGs can be used to treat peptic ulcer, because the intravenous route is obviously impracticable,

Route of Administration	*Prostaglandin*	*Dose*	*Stimulus to Acid Secretion*	*No. of Subjects in whom Inhibition of Volume and/or Output Noted*	*Unwanted Effects*
Oral	PGE_1[115]	10-40 μg/kg/30 min	Subcutaneous pentagastrin 6 μg/kg	0/4*	Diarrhoea
	PGE_2[147]	2·5 mg	None	0/1*	None
		4·0 mg		0/3*	
			None	14/14**	
	15(R)15 $MePGE_2$[148]	100-200 μg	Intramuscular pentagastrin 6 μg/kg	8/8**	Nil reported
	PGE_1[149,150]	4 μg/kg/30 min	None	8/8	Cardiovascular
		7 μg/kg/30 min	Intravenous pentagastrin 2 μg/kg/hr	7/8	Desire to defaecate
Intravenous infusion	PGA_1[114]	0·5-0·6 μg/kg/min	None	1/1	
			Intravenous histamine 0·015 mg/kg/hr	9 subjects but no. in whom inhibition noted not given ($P<0·01$)	Pulse rate ↑
			None	0/2	Occasional nausea
		1-1·25 μg/kg/min	Intravenous histamine 0·015 mg/kg/hr	9 subjects but no. in whom inhibition noted not given (P-NS)	
	$PGF_{2\alpha}$[151]	0·5 μg/kg/min for 20 min	Intravenous pentagastrin 0·01 μg/kg/min	0/5	Nil noted
Intravenous injection	15(R)15 $MePGE_2$[148]	100-200 μg	None	0/5	Nil noted

Table II *Effect of prostaglandins on gastric secretion in man*

*There was a tendency for an increase in acid secretion after oral PGE_1 and PGE_2
**A rise in pH was also noted here

the oral route ineffective, and both may be associated with diarrhoea. This gloomy outlook may be radically altered by the introduction of analogues of prostaglandins. As prostaglandins are rapidly inactivated by 15-hydroxy-PG-dehydrogenase, analogues modified at the C_{15} position can be expected to be more stable: one such analogue, 15(S)15-methylprostaglandin E_2 ($MePGE_2$)[21,152], is an effective inhibitor of gastric secretion in animals[136]. This compound is known to have a more prolonged effect on human uterine contractions than natural PGs but is associated with a greater incidence of unwanted effects[153]. However, recently Karim and his colleagues[147,148] examined the effects of the other isomer 15(R)15-methylprostaglandin E_2 (15(R)15$MePGE_2$) on gastric secretion in man. Given orally (100-200 μg), this compound markedly diminished basal and pentagastrin-stimulated gastric acid secretion. The effect was mediated by a reduction in acid concentration and was reflected by a sustained elevation of pH: this was unusual, as after natural PGs most workers have noted an inhibition of volume (and hence output). Intravenous injection of 15(R)15$MePGE_2$ was ineffective against pentagastrin-induced acid secretion[148]. There were no unwanted effects following administration by either route. If confirmed, these new observations now open exciting possibilities for the control of gastric secretion in man.

Intestinal Absorption and Secretion

The main interest in the effects of PGs on intestinal absorptive function is their possible role in the pathogenesis of some diarrhoeal states. Diarrhoea often occurs in women given high doses of oral or intravenous PGE_1, PGE_2, or $PGF_{2\alpha}$ for therapeutic abortion[154-158], but is less frequent with the lower

doses required for induction of labour at term[159,160]. This complication is rarely seen after intravaginal[161] or intraamniotic administration[162], presumably because comparatively little is absorbed. $PGF_{2\alpha}$ tends to cause diarrhoea more often than PGEs. Under experimental conditions diarrhoea is frequently induced by PGEs or $PGF_{2\alpha}$[115,116,118,147,148,155] but rarely by PGA_1[114,163]. Arachidonic acid, a precursor of PGE_2, causes marked diarrhoea in animals[164].

Prostaglandins were known to affect water and electrolyte transport across a variety of biological membranes[165,166], but in the absence of data on gastrointestinal mucosa and because of the potent effects of PGs on gastrointestinal smooth muscle (see above), it was thought that the diarrhoea was caused by stimulation of gastrointestinal motility[10]. However, the presence of clear fluid in the faecal output in man following oral PGE_1 suggested that water and electrolyte transport across the mucous membrane of the gut was altered and that the accelerated intestinal transit was due, at least in part, to the mechanical effect of the increased bulk of intestinal contents[116]. Recent reports support this theory.

In vitro PGE_1, PGE_2, and $PGF_{2\alpha}$ inhibited Na^+ absorption and stimulated Cl^- secretion by isolated rabbit ileal mucosa[167–169], whilst PGE_2 reduced the net absorption of electrolyte and water by everted sacs of hamster terminal ileum[170]. *In vivo* intraarterial infusion of PGE_1, PGA_1, or $PGF_{2\alpha}$ caused a prompt secretion of water and electrolytes into Thiery Vella jejunal loops of anaesthetized dogs. On the other hand intraluminal PGE_1 was less active: it reduced net absorption but there was no secretion of water and electrolytes into the lumen[171]. It seemed unlikely that alterations in blood flow were responsible for changes in electrolyte and water secretion, although the profound hypotension with high arterial doses of PGs probably accounted for the marked changes in the few jejunal biopsies examined: lower doses had little effect on jejunal morphology[171]. A more likely explanation for the alterations in water and electrolyte transport observed is that PGs modify levels of cAMP. PGE_1, PGE_2, and to a lesser extent $PGF_{2\alpha}$, stimulate adenyl cyclase activity of isolated rabbit and guinea-pig small intestinal mucosa[172,173], whilst cAMP and theophylline increase Cl^- secretion and inhibit Na^+ absorption by isolated rabbit and human ileal mucosa[174,175]. *In vivo*, in anaesthetized dogs, subthreshold doses of $PGF_{2\alpha}$ and theophylline had a synergistic effect, suggesting that both may act by increasing cAMP[171]. It thus seems probable that PGs influence electrolyte and water transport by small intestinal mucosa through alterations in cAMP levels.

In man intrajejunal PGE_1 caused secretion of water and electrolytes apparently resulting from increased unidirectional flux from blood to lumen[117,176]. In healthy male volunteers intravenous infusions of $PGE_{2\alpha}$ (0·28-0·81 μg/kg/min) produced net secretion of water and electrolytes into the jejunum and ileum. More $PGF_{2\alpha}$ was needed to stimulate jejunal than ileal secretion and all but one of the 15 subjects passed loose motions at the end of the study regardless of whether secretion was noted or not: many also experienced abdominal cramps[118].

Exogenous PGs are thus associated with diarrhoea. It is possible that some forms of clinical diarrhoea might be caused by excessive or abnormal endogenous synthesis of these substances, but the data available are circumstantial. For example, some patients with medullary carcinoma of the thyroid, neural crest tumours, or phaochromocytomas have diarrhoea and in a few high levels of $PGF_{2\alpha}$ and PGE_2 were found in tumour tissue, and in

peripheral and tumour venous blood[177,178]. It is also possible that $PGF_{2\alpha}$ is responsible for diarrhoea during menstruation, because high levels of $PGF_{2\alpha}$ are present in the menstrual flow[179,180]. A similar mechanism might account for the infantile diarrhoea which sometimes occurs when a lactating mother menstruates[180]. The validity of these suggestions awaits the availability of sensitive methods for the assay of PGs in peripheral blood[181–187] and of specific antagonists which can be used in man. Early reports suggest that pretreatment with the PG antagonist polyphloretin phosphate (PPP) prevents diarrhoea caused by exogenous PGs in mice[109,188]. An alternative approach is to measure the urinary excretion of metabolites as an index of the rate of PG synthesis[189].

In cholera profuse watery diarrhoea with severe dehydration occurs. Cholera exotoxin (CT) inhibits water and Na^+ absorption by isolated animal and human ileal mucosa[167,175], stimulates adenyl cyclase activity *in vitro* and *in vivo*[172,190–192], and increases the cAMP levels *in vitro*[193]: all these effects resemble the actions of PGs. However, intestinal secretion induced in dogs by CT, though slower in onset, was considerably greater than the response to either intraluminal PGE_1 or intraarterial $PGF_{2\alpha}$. Moreover the effect persisted for several hours after the CT had been removed from the loop, whereas the response to PGs did not[171]. Release of PGs within the cells by CT[80] might account for its greater effect as compared with that of exogenous PGs. Aspirin inhibits the synthesis of PGs[54], and it has been proposed that it might be possible to determine whether PGs are involved in cholera by giving this drug to patients with this disease[194]. This idea may be difficult to evaluate clinically, because unless fluid lost is promptly replaced intravenously, cholera is often fatal. Recent studies suggest that animals pretreated with large doses of oral or parenteral antiinflammatory drugs are protected from the effects of CT[195,196]. These observations raise the possibility that such drugs might protect patients from the effects of cholera but give no indication whether the treatment would be effective once the disease is established.

The effect of PGs on electrolyte transport by the colon has not been investigated. A recent report suggests that intraluminal sulphasalazine prevents colonic secretion of water and electrolytes in patients with ulcerative colitis[197], but the rapidity of the effect is difficult to reconcile with the observation that a metabolite of the drug is the active agent[198]. However, PGs are released by damaged tissues[199–201], and as sulphasalazine has antiinflammatory properties, it may inhibit synthesis of PGs by the damaged mucosa. It is conceivable that PGs may be a factor in the pathogenesis of ulcerative colitis.

Exocrine Pancreas

The few published observations regarding PGs and pancreatic function are of uncertain significance. In animals PGEs but not PGFs inhibit secretin-stimulated fluid and electrolyte secretion[202,203], produce hypotension, and decrease pancreatic blood flow[203]. In cats this inhibition was sometimes preceded by a transient stimulation of secretion and of blood flow[203]. The effects of PGs on enzyme output by the pancreas depended on the species studied; whilst neither PGEs nor PGFs influenced enzyme secretion in the cat[203], PGE_1 caused an increase in enzyme output in the dog[202], which

probably did not result from pancreozymin release[204]. *In vitro*, on the other hand, PGEs and PGFs stimulated fluid and electrolyte output by the saline-perfused pancreas and this effect was potentiated by theophylline[203]; the adenyl cyclase was also increased by PGE_1 in guinea-pig pancreas[202]. PGE_1 decreased and $PGF_{2\alpha}$, PGB_1 and PGB_2 increased the vascular resistance of the pancreas *in vitro*[205,206]. It is possible therefore that PGs may stimulate pancreatic secretion, perhaps through adenyl cyclase, but that this effect is masked *in vivo* by diminution of blood flow, or by the release of an anti-secretory agent, or both[203].

Comment

There is thus no lack of evidence for the synthesis, release, and breakdown of PGs in gastrointestinal tissues, nor that under experimental conditions they markedly affect gastrointestinal function. The evidence is less clear that PGs have a role in gastrointestinal physiology, although it seems likely that if they do, they act as local regulators. There is some circumstantial evidence to suggest that they may play a part in pathological conditions. With the arrival of analogues that appear to have specific actions on the gastrointestinal tract yet few unwanted effects, a role for PGs in the treatment of gastrointestinal disorders begins to look promising.

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