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PAF and the Digestive Tract. A Review

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In 1972 it was shown that a soluble polar lipid originating from immunoglobulin IGE-sensitized basophils caused platelet aggregation: hence the name platelet-activating factor (PAF) (Benveniste et al 1972). This name has gained the greatest acceptance, despite the varied biological action of the lipid. PAF is, in fact, a potent vasodilator (Blank et al 1979); it increases vascular permeability (McManus et al 1981), stimulates polymorphonuclear leucocytes to aggregate (Lin et al 1982), reduces renal blood flow, glomerular filtration rate and urine volume (Schlondorff & Neuwirth 1986), increases airway resistance (Cuss et al 1986) and causes contraction of smooth muscles (Stimler & O'Flaherty 1983).

The structure of PAF has been identified as 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine (Benveniste et al 1979; Demopoulos et al 1979). In contrast with the two long-chain acyl groups that are present in phosphatidylcholine, PAF contains a long-chain alkyl group joined to the glycerol backbone in an ether linkage at position 1 and an acetyl group at position 2. PAF actually represents a family of phospholipids, because the alkyl group at position 1 can vary in length from 12 to 18 carbon atoms (mainly 16–18) (Benveniste 1988). Like eicosanoids, PAF is not stored in cells but is synthesized in response to stimulation (Benveniste 1988). A notable exception is the blood in which pre-formed circulating PAF (named lipopaf) is bound to blood lipoprotein (Stafforini et al 1987; Benveniste et al 1988; Lombard et al 1996). After appropriate stimulation PAF is rapidly synthesized by a wide variety of inflammatory cell types, including monocytes, macrophages, neutrophils, eosinophils, platelets, basophils and vascular endothelial cells. Cells not classically classified as pro-inflammatory, such as fibroblasts, keratinocytes, intestinal cells and bacteria also, however, produce PAF (Michel et al 1988, 1990; Denizot et al 1989, 1990).

Two metabolic steps are involved in PAF biosynthesis (Fig. 1): after appropriate stimulation, phospholipase A_2 cleaves the fatty acid from the 2′ position of the choline-containing membrane alkyl-ether phospholipids resulting in the production of the relatively inactive precursor for PAF, lysoPAF (Billah et al 1985). Interestingly, in some cells the fatty acid usually released in this reaction is arachidonic acid, the precursor of the major prostaglandins and leukotrienes, substances which can mediate an inflammatory process, intestinal secretion and motility (Bennett 1992). In the second step, lysoPAF is acetylated by acetyl coenzyme A in a reaction catalysed by lysoPAF acetyltransferase, yielding the biologically active molecule (Gomez-Cambronero et al 1984). This is the rate-limiting step. Both the phospholipase and acetyltransferase are calcium-dependent enzymes and PAF synthesis is regulated by the availability of calcium (Hanahan 1986; Snyder 1989).

The inactivation of PAF also occurs in two steps. Initially, the acetyl group of PAF is removed by PAF acetylhydrolase, an enzyme present both in cells and in plasma, to form lyso-PAF (Chilton et al 1984). LysoPAF is then converted to a 1-*O*-alkyl-2-acyl-*sn*-glycero-3-phosphocholine by an acyltransferase. This second step is inhibited by calcium. There are, however, two pathways whereby PAF can be generated, because de-novo synthesis (Fig. 2) from 1-alkyl-2-lyso-*sn*-glycero-3-phosphate can be achieved by acetylation, dephosphorylation and transfer of phosphorylcholine (Snider 1990). This de-novo pathway is not involved in the generation of PAF in inflammatory cells (Morley 1984). Recognition that two distinct pathways exist for PAF formation is important, for this might enable selective inhibition of PAF generation during an inflammatory reaction, without influencing the physiological formation of PAF.

Motility

Stomach

PAF induces contraction of the fundus of the stomach (Findlay et al 1981). The response is long-lasting, resistant to washing and displays complete agonist-specific desensitization. The observed desensitization is apparently PAF-specific, because pre-treatment of the tissue with lysoPAF (which causes no contraction) does not desensitize the tissue to subsequent PAF-induced contraction (Levy 1987). The exact mechanism of desensitization is not known, but it might involve direct phosphorylation of receptors (Sibley et al 1987), inactivation of the receptor-phospholipase link (Smith et al 1987), direct interference with calcium channels or activation of protein kinase C (Kamata et al 1993a). PAF-induced contractile response in the rat stomach fundus is the result of an influx of calcium through voltage-dependent calcium channels and receptor-operated calcium channels (Kamata et al 1993b). PAF also stimulates the turnover of phosphatidylinositol, but this is not responsible for the PAF-induced contractile response (Gallizzi et al 1987).

PAF causes dose-dependent increases in the force of gastric contractions that are highly correlated with phasic changes in vascular resistance (Yan et al 1992), supporting the hypothesis that hypercontractility might contribute to the development of mucosal ischaemia during ulceration. The contraction of the stomach could, on the other hand, give rise to regions along the base or rugal folds which, because of compression, result in reduced mucosal blow flow. It is in these regions that necrosis is most often observed (Mersereau & Hinchey 1982). Local intra-arterial infusion of PAF (but not lyso-PAF) causes an initial, well-maintained and dose-related contraction of the rat

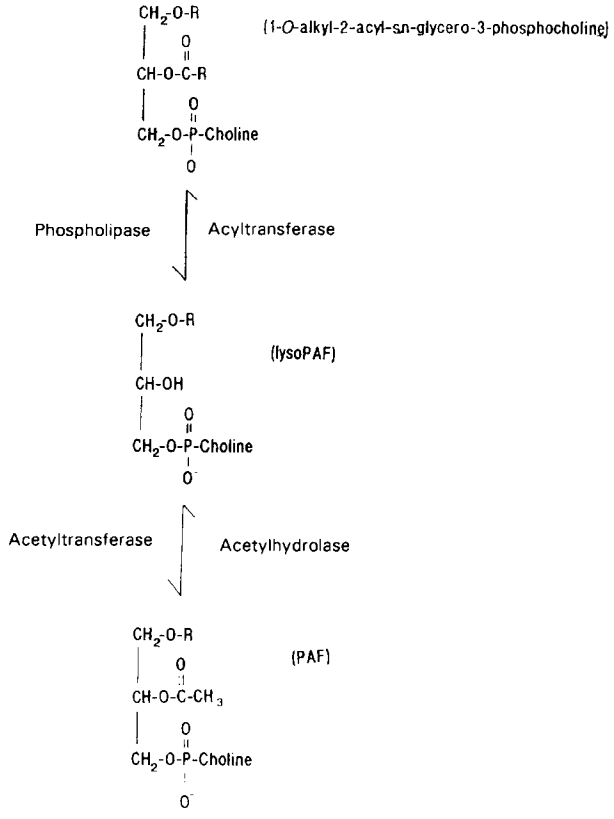

FIG. 1. Synthesis and degradation of PAF.

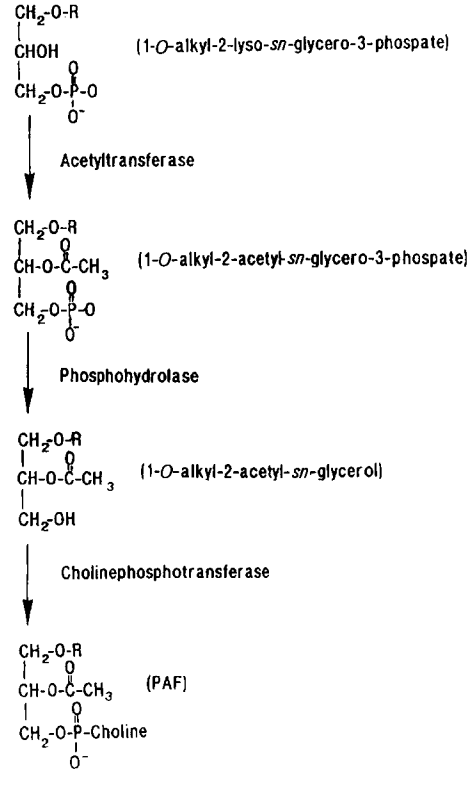

FIG. 2. PAF synthesis by de-novo pathway.

stomach (Esplugues & Whittle 1989). This is followed by a secondary, greater gastric contraction which begins after termination of the PAF infusion and is maintained for up to 60 min. This effect does not appear to reflect changes in systemic arterial blood pressure, because lower doses of PAF that cause these motility changes induce only minimal hypotension. The H_2 receptor antagonist cimetidine and the 5-HT receptor antagonist methysergide both partially inhibit this effect of PAF. Because both these spasmogenic amines can be released from mast cells, it is possible that the initial response to PAF reflects, in part, an action on mucosal mast cells or possibly on circulating basophils; such an effect would have to be extremely rapid in onset. By contrast, the second phase of the contraction is not affected by 5-HT or histamine antagonists, but it is abolished by tetrodotoxin, suggesting that stimulation of local neuronal activity underlies the motility response. Tetrodotoxin reduces the duration of the initial contraction and abolishes the secondary phase, yet greatly augments mucosal damage, suggesting the role of local neuronal activity in the regulation of mucosal integrity. The mechanism underlying the activation of such a neuronal process by PAF is obscure, because this secondary contraction has been observed only after termination of PAF administration, irrespective of the duration of the infusion. It is possible that a component of this secondary increase in intragastric pressure is a consequence of tissue microvascular reperfusion after a period of ischaemia, with the local release of oxygen free radicals or other metabolites (Parks & Granger 1983). PAF is able to potentiate the response of rat stomach strips to prostaglandin E_2 (PGE_2; Izzo et al 1993a) This synergism is not a result of sensitization of smooth muscle myofilaments because the potentiation is specific for PGE_2, nor is it a result of liberation of endogenous prostaglandins. It is probable that PAF accelerates the penetration or the exposure of PGE_2 to its receptor because a shortening of the latent period for the response to PGE_2 is observed.

As with the gastrointestinal damage, hypotension and plasma leakage, the endogenous release of PAF appears to contribute to the motility changes after endotoxin administration in rodent (Esplugues & Whittle 1989) and non-rodent (King & Gerring 1990) species. The temporal profile of endotoxin-induced changes was not, however, identical with those obtained by local infusion of PAF; this might reflect the time-course of the release of PAF from gastric tissue (Wu et al 1986).

Intestine

The contractile effects of PAF have been examined on various regions of isolated rat intestine. The duodenum, jejunum and ileum show only the tonic component of contraction at low doses (< 10 nM), whereas high doses (100 nM) induced biphasic contractions consisting of a phasic followed by a tonic component (Tokumura et al 1984). In the colon, however, low doses of PAF cause a slow, sustained contraction, and at high doses the phasic and tonic components are not dissociated. The different profiles of motility effects in the colon compared with those of the small intestine is interesting in the light of the observation that PAF infusion results in severe injury to the duodenum, jejunum, and ileum, but not to the colon (Wallace & Whittle 1986b), supporting a role for motility in the pathogenesis of PAF-induced gastrointestinal damage. PAF-

induced contractions are not mediated by the cholinergic nervous system by bioamine or eicosanoid release (Tokumura et al 1988). The ascending colon was found to be most responsive compared with the transverse or distal colon (Tokumura et al 1991). The contractions are dependent on external calcium and persist even when the tissue is washed several times. Addition of bovine serum albumin to the washing solution leads, however, to rapid relaxation to the basal level, probably by removing PAF tightly bound to the tissue. Also, the inhibitory effect of CV-3988, a structural analogue of PAF (but not FR-900452, which is structurally unrelated to PAF) is irreversible and did not disappear after washing (Tokumura et al 1991). This suggests that PAF and related homologous antagonists penetrate slowly into the outer half of the lipid bilayer of plasma membranes of cells and then rapidly diffuse laterally to associate firmly with specific binding sites.

PAF induces contraction of isolated smooth muscle cells from the circular layer of guinea-pig ileum (Jeanneton et al 1993). This action is myogenic, because it occurs in isolated cells devoid of any neural connection and because tetrodotoxin did not modify the effect of PAF. The PAF-induced contraction is probably a result of interaction of PAF with a specific receptor linked to a pertussis toxin-sensitive G protein, which triggers an influx of extracellular calcium into the cell.

The contraction of gastrointestinal tissue by PAF has been proposed as a method of bioassay. It could be an alternative to platelet aggregation or 5-HT release in existing bioassays, using rat descending colon in an organ bath (overcoming the frequently observed tachyphylaxis by washing the tissue with bovine serum albumin) (Tokumura et al 1988) or superfusion bioassays that use various tissues (Cirino & Wallace 1988). The superfusion bioassay is more advantageous because it is faster, provides the opportunity to measure PAF in samples with negligible dilution and offers the possibility of direct measurement of PAF release by an organ. Using this in-vitro system Wallace et al (1989) have shown that the colon excised from control rats is contracted by PAF whereas the colon of rat with two-week colitis is unresponsive. This emphasizes the importance of PAF in the prolongation of inflammation and ulceration, showing again that the contractility changes might occur as a consequence of inflammation.

Intraperitoneal injection of PAF markedly alters the (interdigestive) motility pattern in rats, indicating a possible role for PAF in the digestive motor function changes observed during gastrointestinal or general inflammatory and allergic states (Bardon & Deragnaucourt 1985). PAF can induce disruption of the migrating myoelectric complex, which is replaced by clustered contractions (Pons et al 1991a, b). The functional significance of such activity is unknown, although it is classically associated with the transport of watery stools, especially when there is excess fluid in the small intestine (Read et al 1980). These clustered contractions are supposed to be associated with accelerated intestinal transit (Bueno et al 1975).

PAF-induced alterations in intestinal motility mimic the intestinal alteration obtained after endotoxin administration and PAF antagonists reduce endotoxin-induced changes in the migrating myoelectric complex pattern, suggesting a role of PAF in the endotoxin-induced motility changes (Pons et al 1991a, b). Prostaglandins and free radicals are involved both in PAF- and endotoxin-induced pathophysiology. A combination of indomethacin and BN 52021, a PAF receptor antagonist, abolishes the effects of endotoxin.

Secretion

Stomach

Few and controversial data are available on the role of PAF on gastric acid secretion. PAF, but not lysoPAF, increases acid secretion (assessed by uptake of [^{14}C]aminopyrine) by isolated pig parietal cells, which is inhibited by the PAF antagonist CV-6209. This increase is dependent on extracellular Ca^{2+} and is not the cause of gastric erosion (Nogami et al 1990). In contrast, PAF has been shown to be involved in endotoxin-induced acute inhibition of the acid response to pentagastrin (Martinez-Cuesta et al 1992). The inhibitory effect of the endotoxin involves nitric oxide production, because it was reversed by the combined administration of N^G-nitro-L-arginine methyl ester hydrochloride (L-NAME, an inhibitor of nitric oxide synthesis) and WEB 2086, a PAF receptor antagonist. The exact relationship between nitric oxide and PAF has not, however, been established.

Because PAF and PAF-metabolizing enzymes are present in the brain, Cucala et al (1989) have studied rat gastric acid secretion and gross mucosal integrity in response to intracerebroventricular PAF and have compared its effect with that of thyrotropin-releasing hormone (TRH), a centrally-active gastric secretagogue. PAF acts within the brain to inhibit gastric acid output stimulated peripherally by pentagastrin, whereas central TRH increases acid output. Because TRH and PAF induced different morphological changes in the stomach, a central gastric secretion modulatory system might exist, through which PAF initiates gastroprotective effects.

Intestine

There are few reports on the effect of PAF on intestinal water and electrolyte secretion. Most of these studies were performed in-vitro and concern electrolyte movement monitored using muscle-stripped sheets of the tissue mounted in Ussing chambers.

PAF has a potent chloride secretory effect on the rat descending colon (Buckley & Hoult 1989); this effect is independent of specific PAF receptors, probably because PAF is a very small lipid molecule and might have direct effects on cell membranes independent of receptors. PAF produces in the rat colon an increase in transepithelial potential difference, together with an increase in short-circuit current when the epithelium is voltage-clamped. These electrical changes are not accompanied by marked changes in conductivity and are, therefore, similar to those changes which occur in response to other colonic secretagogues, such as carbachol, kinins, prostaglandins and vasoactive intestinal peptide (VIP; Buckley & Hoult 1989). The action of lysoPAF is similar to that of PAF, although much less striking, suggesting the possibility that colonic epithelium contains an acetyltransferase capable of rapidly forming PAF from its precursor. In contrast, MacNaughton & Grant Gall (1991) showed that the secretory effect of PAF on rat jejunal ion transport was receptor-specific. Differences in the response to PAF could be because of differences between the regions of the gut studied. In the rabbit colon, PAF inhibits neutral NaCl absorption and causes a sustained biphasic increase in the short-circuit current, the

effect being inhibited by hexamethonium, tetrodotoxin and atropine (Hanglow et al 1989). Similar results have been observed in the rat jejunum; an early rise in short-circuit current within 2–3 min then drops to a new elevated baseline by 15 min. PAF antagonists abolish only the early phase of the response; the late phase is unaffected. This could accord with the involvement of different PAF receptors in the response to PAF. The response of PAF is histamine-, 5-HT- and leukotriene-independent, although it is reduced by doxantrozone, a mast cell-stabilizing drug; the PAF response also is reduced by tetrodotoxin, indicating an involvement of enteric nerves (Bern et al 1989; Buckley & Hoult 1989).

The effect of PAF on ion transport in the small and large intestines is prostaglandin-dependent because the effect of PAF is associated with PGE_2 (but not prostacyclin) production and it is reduced by cyclo-oxygenase inhibitors (Bern et al 1989; Hanglow et al 1989). In addition, the response to PAF is calcium-dependent and this is consistent with a role for PGE_2. Intestinal transport can also be altered by changes in membrane fluidity (Meddings et al 1990), and because PAF can alter membrane fluidity (Fink & Gross 1984), a direct effect on the enterocyte membrane is possible.

PAF increases after administration of laxatives (Pinto et al 1989, 1992; Capasso et al 1993; Izzo et al 1993b), although this enhancement seems more related to intestinal injury than to intraluminal fluid accumulation, because: there is a correlation between PAF production and acid release of phosphatase (an indicator of intestinal injury); damaging laxatives (castor oil, magnesium sulphate, bisacodyl, phenolphthalein) produce PAF, whereas less toxic laxatives (senna, sulphosuccinate, mannitol) do not; and PAF antagonists do not affect laxative-induced diarrhoea and intraluminal fluid accumulation but reduce gross damage and acid phosphatase release. However, it has been recently shown that PAF could be one of the mediators of cholera toxin-induced secretion in rabbits (Guerrant et al 1994).

Damage

Stomach

The effect of PAF on the gastrointestinal tract has been evaluated in the rat after intravenous or intra-arterial infusion. There is, at present, no information about the pathological effect of PAF administered via the digestive tract lumen.

On a molar basis, PAF is the most potent ulcerogen known (Rosam et al 1986; Benveniste et al 1992). When given intravenously, it causes haemorrhagic erosion of the gastric and small-intestinal mucosa that extend into the submucosa (Wallace & Whittle 1986b). This effect is not mediated by histamine or adrenergic receptors, nor by cyclo-oxygenase products or platelet activation, although it is possible that platelet aggregation might stimulate thromboxane A_2, a potent ulcerogen. PAF causes aggregation of neutrophils, which might restrict the drainage of blood from the mucosa and thereby predispose it to damage induced by topical irritants (Valone & Goetzi 1983). Neutrophil-derived free radicals, which have been shown to have potent damaging action on various tissues (Droy-Lefaix et al 1991), and increased vascular permeability (Hatakeyama et al 1991) could contribute to PAF-induced gastrointestinal damage. PAF-induced increases in vascular permeability result in accumulation of plasma in the lamina propria which could result in 'stretching' of the epithelium with loss of plasma from the intravascular space. This loss of plasma gives rise to haemoconcentration, another factor implicated in PAF-induced ulceration.

Microcirculation plays an important role in the maintenance of the functional integrity of the gastrointestinal mucosa (Whittle 1993). PAF induces changes in microvascular circulation with stasis, which might contribute to the ulcerogenic action (Whittle et al 1986).

PAF might be involved in gastric mucosal damage in rats treated with ethanol, indeed gastric PAF levels increase after ethanol administration (Izzo et al 1994) and PAF antagonists reduce gastric lesions caused by alcohol (Braquet et al 1988). PAF might also play an important role in water-immersion, restraint stress or ischaemia-reperfusion-induced gastric mucosal injury (Nogami et al 1991; Yoshikawa et al 1992). In this type of damage, PAF antagonists exert their beneficial effect mainly by inhibiting neutrophil superoxide production induced by PAF. PAF might play an important role in mediating the adhesive interaction between circulating leucocytes and the microvascular endothelium during ischaemia/reperfusion and might promote the leucocyte extravasation associated with ischaemia/reperfusion (Kubes et al 1990). Microvascular PAF-induced mucosal ischaemia is primarily a result of vasoconstriction and might involve oedema formation owing to increased filtration (Wood et al 1992).

PAF is a likely endogenous mediator of glucocorticoid-induced gastric mucosal damage (Filep et al 1991a,b, 1992), because a PAF antagonist reduced the damage caused by administration of dexamethasone. In contrast, PAF does not appear to be involved in pylorus-ligated rats, or in aspirin- or phenylbutazone-induced gastric damage (Braquet et al 1988).

Intestine

PAF is a mediator of the gastrointestinal damage associated with septic or endotoxic shock (Terashita et al 1985; Wallace & Whittle 1986c; Wallace et al 1987a, b; Whittle et al 1987). Administration of endotoxin results in the stimulation of PAF, and PAF-induced ulcerations mimic the gastrointestinal impairment obtained after endotoxin administration, and the gastrointestinal effects of endotoxin administration can be abrogated by pre-treatment with PAF receptor antagonists. PAF is the major mediator of immunocomplex-induced enteropathy (Bloch et al 1991) and PAF, released from an undetermined source in nematode-sensitized rats, produces altered blood flow in the stomach and proximal small intestine (Mathison et al 1990). PAF has been shown to be involved in various diseases of the large intestine although intravenous administration of PAF, at doses producing increased vascular permeability and injury in the small intestine, do not affect the distal colon (Rosam et al 1986). The reason for this resistance of the distal colon is not clear.

PAF biosynthesis is significantly elevated in animal models of colitis (Eliakim et al 1988; Wallace 1988; Mascolo et al 1995). Interestingly, in trinitrobenzene-induced colitis, PAF increases during the chronic, but not the acute phase of the inflammation. A role for PAF in chronic colitis is further supported by the demonstration that treatment with the PAF antagonist BN 52021 reduces colonic inflammation and ulceration. PAF plays a central role in mediating hypoxia-

induced intestinal necrosis (Caplan et al 1990, 1991); acidosis might enhance the effect of hypoxia on PAF production.

PAF and other mediators

PAF production and its effect in inflammatory bowel diseases could result from interaction with other inflammatory mediators, particularly eicosanoids. Lipoxygenase metabolites, but not those of cyclo-oxygenase, mediate the ulcerogenic actions of intravenous infusions of PAF (Hsueh et al 1986; Wallace & Whittle 1986a; Wallace & MacNaughton 1988). Leukotrienes and PAF arise from similar membrane phospholipids. Both might regulate the biosynthesis of each other in the damaged mucosa and could act in concert in acute mucosal injury caused by topical irritants such as ethanol, bile salts and stress (Konturec & Brzozowski 1991). Leukotriene C_4 is released by perfused rat intestine in response to PAF (Hsueh et al 1986). PAF production in rats fed for three months with an essential fatty acid diet is significantly reduced in the intestine of rats treated with acetic acid (Mascolo et al 1995) or lipopolysaccharide (LPS; Autore et al 1994). PAF is also involved in endothelin 1-induced small intestinal tissue damage (Filep et al 1991b); PAF might be involved in the process of regional fibrinolytic activation induced by endothelin 1 (Kurose et al 1992). PAF and endothelin can act in concert to increase vascular permeability in the rat gastrointestinal tract (Filep et al 1991b).

There is also evidence supporting a role for PAF as an intermediate of some of the action of tumour necrosis factor (TNF; Sun & Hsueh 1988). PAF and TNF, in fact, induce identical morphological bowel lesions, TNF stimulates PAF release and PAF antagonists provide a protective effect against TNF-induced bowel injury. The effect of TNF and endotoxin on PAF release are, furthermore, synergistic for inducing bowel necrosis.

More recently, nitric oxide has been claimed to modulate PAF damage. Indeed the ulcerogenic effect of PAF could be attenuated by endogenous nitric oxide, because L-NAME, an inhibitor of nitric oxide synthesis, worsens gastrointestinal damage induced by PAF (MacKendrick et al 1993). In addition, a nitric oxide-donating compound inhibits PAF-induced gastrointestinal plasma leakage, a measure of the initiation of vascular damage (Boughton-Smith et al 1992). Endogenous nitric oxide protects the intestine from hypoxia-induced injury and the balance between local PAF and nitric oxide modulates the outcome of hypoxia-stressed intestine (Caplan et al 1994). Endogenous nitric oxide is also able to (down-) regulate PAF synthesis in the duodenum of rats treated with castor oil (Mascolo et al 1996).

Clinical Studies

Three experimental procedures have been used to investigate PAF during inflammatory digestive diseases. One technique is to measure PAF in gastrointestinal biopsy specimens (Acherman et al 1990; Kald et al 1990). Measurements might, however, be misleading because: PAF is not stored but rather produced in response to tissue trauma; a slight variation in the place of biopsy sampling with regard to the site of inflammation might give incorrect information about PAF levels and the acetylhydrolase activity in the biopsy specimen might lead to an underestimation of the level of PAF. Biopsies can also be cultured and stimulated in an appropriate medium (Rachmilewitz et al 1990), but PAF production cannot be easily extrapolated to in-vivo production rates from these in-vitro studies.

Another procedure is to measure PAF in the stool. PAF stool concentrations are strikingly increased in patients with active inflammatory bowel disease and the assessment of faecal PAF could be helpful in the investigation of disease activity (Chaussade et al 1992). Faecal PAF levels are, however, inappropriate for estimation of local PAF release and for location of the source of PAF production. A useful sample-collection technique has recently been developed for study of in-vivo PAF production in inflammatory colonic disease (Guimbaud et al 1994, 1995). This method involves measuring the rate of PAF accumulation in a dialysis bag placed in the empty rectum. This atraumatic approach reduces artefactual mediator formation and is a good index of the balance between production and degradation in-vivo. PAF can be easily recovered from human saliva (Cooney et al 1991), gastric juice (Sobhani et al 1993) or blood (Caramelo et al 1987).

PAF in gastric juice

PAF is not normally detected in the gastric juice of normal subjects, although high concentrations of PAF precursors are found. These levels increase fivefold during pentagastrin infusion and there is a positive correlation between PAF precursor and acid or pepsin output, indicating a possible role for PAF in the gastric acid secretion (Sobhani et al 1993). Elevated PAF levels are present in the gastric juice of patients with erosive gastritis and oesophagitis, but not those with Zollinger–Ellison syndrome and duodenal ulcer (Sobhani et al 1992).

PAF in gastrointestinal biopsy specimens

In contrast with gastric juice, PAF is increased in fundic, antral and duodenal mucosa from patients with duodenal ulcer as compared with normal subjects; there is a decrease after ulcer healing, suggesting a role for PAF in the pathogenesis of duodenal ulcer (Acherman et al 1990). The opposite results for patients with duodenal ulcer might be explained by the use of biopsy specimens rather than gastric juice for measurement of PAF.

Mucosal PAF is considerably increased both in the ileum and in the colon in patients with acute Crohn's disease, reduced by glucocorticoid therapy and might return to normal in quiescent Crohn's disease (Olaison et al 1989; Kald et al 1990; Sobhani et al 1992). This increase is related neither to the severity, nor to the type of inflammatory cell infiltration, suggesting the possibility that PAF could originate from non-inflammatory cells. The lack of increase in PAF precursor might suggest that increased PAF levels are related to increased acetyltransferase rather that to PLA_2 activity, although PLA_2 has been shown to increase in Crohn's disease patients (Olaison et al 1989).

PAF increases upon ionophore stimulation, in-vitro, in ulcerative colitis colonic mucosa (Rachmilewitz et al 1990); PAF production is inhibited by sulphasalazine and prednisolone, two therapeutic agents used in the treatment of ulcerative colitis. Human isolated gastrointestinal mucosa/submucosa incubated with ricinoleic acid (Capasso et al 1992) and other stimulant laxatives (Capasso and Bennett, unpub-

lished data) releases PAF, suggesting a role for PAF both in the laxation and in the mucosal injury caused by laxatives.

PAF in the blood

PAF and TNF are increased in the plasma of patients with neonatal enterocolitis (Caplan et al 1989); there is, however, no correlation between individual TNF and PAF levels. PAF release could result from hypoxia, an important risk factor for enterocolitis. The role of PAF as a mediator in enterocolitis damage is supported by the observation that PAF infection of rat splanchic circulation develops into an experimental model of enterocolitis (Gonzales-Crussi & Hsueh 1983). PAF is also elevated in the blood from patients with cirrhosis of the liver (Caramelo et al 1987).

PAF in the stools

PAF is present in the stools of patients with ileoanal reservoir and severe pouchitis, and low amounts of PAF are observed in stools of patients with mild or terminal ileostomy (Chaussade et al 1991); no PAF is detected in ileal secretions of normal volunteers. The lyso-PAF resulting from degradation of most eukaryotic cell membranes is abundant in the pouch after phospholipase A_2-activation or cell damage, or both, thus providing the 'raw material' to be acetylated into PAF. As PAF production by rectal mucosa has been shown to be increased in patients with ulcerative colitis, this could indicate that pouchitis and ulcerative colitis share the same aetiology or initiating events. PAF is detected in the stools of patients with Crohn's disease and ulcerative colitis, but it is absent in those of patients with irritable bowel syndrome and malabsorption with diarrhoea (Denizot et al 1992a, b). The aetiologic differences between these diseases (i.e. inflammatory or non-inflammatory state) could explain this difference, supporting the hypothesis that PAF production is related to the inflammatory state, rather than to the initiating event triggering the inflammatory response. PAF is present in high concentrations in the faecal fluids of patients with bacterial disease, but absent after eradication of the disease, suggesting a role for PAF in infectious diarrhoea (Denizot et al 1991, 1992a, b). In contrast, PAF was undetectable in the stools of children with rotavirus, corona-like virus or adenovirus infection. The absence of faecal PAF during rotavirus infection might be explained by the site of mucosal inflammation (e.g. the proximal small intestine) and by gradual degradation of PAF after transit of the luminal contents through the inflammatory site to the colon. PAF is also absent in AIDS patients infected by cytosporidium (a non-invasive protozoan) and in immunocompetent patients with parasitic diarrhoea. This is not a consequence of elevated acetylhydrolase activity and might be a result of the absence of intestinal inflammatory lesions in AIDS patients or of direct inhibition of PAF biosynthesis by viruses and parasites.

PAF in colonic perfusion

More recently, PAF has been estimated in-vivo by rectal dialysis (Guimbaud et al 1994, 1995). The perfusion liquid must, however, contain human serum albumin (HSA, 0·1%) to bind PAF while lyso-PAF is detected also without HSA. With this new technique, no PAF is detected in normal volunteers whereas patients suffering from ulcerative colitis release large amounts of PAF. Lyso-PAF and levels of acetylhydrolase are also increased (approximately 50-fold), indicating rapid degradation and consequently synthesis of new PAF. It is of interest to note that corticosteroid-resistant patients release more PAF that responsive patients, although this finding needs confirmation. The possible source of PAF are the polymorphonuclear cells, because there is also an intraluminal release of myeloperoxidase in colitis patients.

Origin of PAF in the gastrointestinal tract

The origin of PAF in the healthy digestive tract is unknown. One candidate might be the cellular infiltrate at the site of inflammation (mast cells, platelets, monocytes, macrophages, eosinophils, neutrophils and basophils) which can produce PAF under several experimental conditions. A second possible origin might be intestinal epithelial cells. Phospholipase C stimulates the release of PAF in cultured intestinal cells (Gustafson et al 1991; Sobhani et al 1991) A third possible origin, besides host eukaryotic cells, might be infectious bacteria present in the digestive tract. Indeed, various strains of bacteria (*E. coli*, *Salmonella typhimurium*, *Helicobacter pylori*) produce PAF using exogenous PAF precursors in-vitro (Denizot et al 1989; Michel et al 1990). No data have shown PAF production in-vivo, however. This origin of PAF could be of importance both in physiological interactions between bacteria and the intestinal wall and in the pathology of infectious disease and gastric colonization by *Helicobacter pylori*.

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