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Progress report

Prostaglandins and ulcerative colitis

The prostaglandins are a family of hydroxy fatty acids derived from 20-carbon polyunsaturated precursors found in the cell membranes of all mammalian tissues. In man, the predominant prostaglandin precursor is arachidonic acid, released from membrane phospholipids by one or more lipases (Figure).[1 2] Arachidonic acid can be enzymatically metabolised to two main groups of compounds with diverse biological effects. As well as being metabolised along the familiar cyclo-oxygenase pathway to prostaglandins and thromboxanes, arachidonic acid can be converted by the more recently recognised lipoxygenase enzymes to hydroperoxy acids, hydroxy acids and leukotrienes (Figure), which have pronounced effects on leucocyte locomotion.

Since Gould first reported raised prostaglandin excretion in the stool of patients with active ulcerative colitis,[3] attention has focused on the possibility that arachidonic acid and its metabolites (henceforward referred to collectively as 'eicosanoids') may play a role in the pathogenesis of the

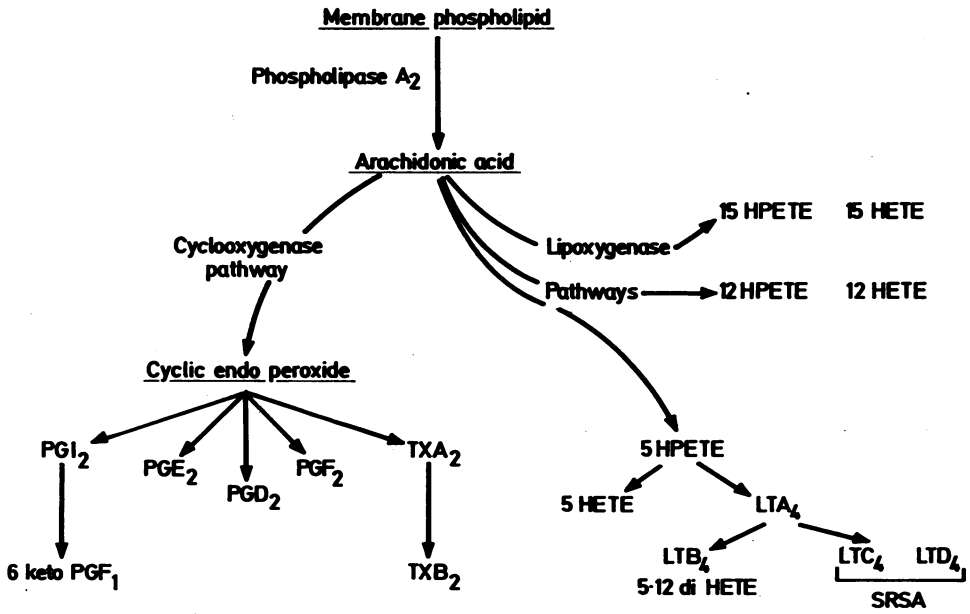

Figure *Arachidonic acid metabolism. (Phospholipase A_2 is probably only one of several lipases catalysing release of arachidonic acid from membrane phospholipid[1 2]). (PG-prostaglandin; TX-thromboxane; LT-leukotriene; HPETE-hydroperoxyeicosatetraenoic acid; HETE-hydroxyeicosatetraenoic acid; SRSA-slow releasing substance of anaphylaxis).*

disease. In this progess report, after describing the occurrence and effects of eicosanoids in the large intestine, we shall discuss their role in active and quiescent ulcerative colitis and in particular whether this is predominantly harmful or beneficial, and whether pharmacological manipulation of colorectal eicosanoid metabolism might be of therapeutic value. We shall then consider the related proposal that changes in eicosanoid metabolism may explain the beneficial effects of sulphasalazine and corticosteroids before turning, lastly, to the possible association between enhanced colorectal cyclo-oxygenase activity and the increased risk of cancer in patients with ulcerative colitis. From the outset it should be made clear that unequivocal answers to many of the questions which we shall raise have yet to be achieved.

Production of eicosanoids in the normal large intestine

In 1949 Vogt isolated from frog intestine a substance which contracted smooth muscle,[4] and this was subsequently shown to contain a mixture of prostaglandins.[5] Since then there have been many reports about the occurrence of eicosanoids in the gastrointestinal tract.[6–9] *In vitro* studies have shown that normal human colon contains arachidonic acid and can synthesise PGI_2, PGE_2, PGD_2, $PGF_{2\alpha}$, TXB_2 and 12 HETE,[10–18] the pattern of results varying widely with assay methods and experimental conditions. Normal colonic smooth muscle appears to synthesise more bioassayable prostaglandin during homogenisation than the mucosa,[10] while in more recent *in vitro* studies of cultures of cells harvested from the mucosa, mononuclear cells synthesised at least as much PGE_2, PGI_2, and TXB_2 as epithelial cells.[18]

Because all *in vitro* techniques may alter eicosanoid synthesis and release rates as a result of mechanical and biochemical disruption of tissue,[10] eicosanoid synthesis by undisturbed large bowel mucosa has been estimated by measurement of the rate of release of prostaglandins into dialysis bags placed in the rectal lumen,[19 20] and this approach has confirmed that normal colorectal mucosa also synthesises PGE_2 *in vivo*.

Production of eicosanoids in the large intestine of patients with ulcerative colitis

There is general agreement that in active ulcerative colitis, large intestinal mucosa produces increased quantities of eicosanoids, whether assessed *in vitro*,[11 12 14 16 17 21–23] or *in vivo* by assay of faeces,[3 24 25] rectal dialysate,[19 20 26 27] venous blood [25 28] or urine;[25 29] this applies to stable prostaglandins, PGI_2, TXB_2, and, according to preliminary reports, 12-HETE, 5-HETE, 15-HETE and LTB_4.[17 23] The increase in eicosanoid production bears a direct relationship with disease activity, results in patients in remission approaching those of control subjects.[11 14 16 19–21 24 25]

The cell types responsible for the net increases in eicosanoid production in active ulcerative colitis are uncertain. Whether the increases are due to increased synthesis, to reduced degradation of eicosanoids, or, as in carrageenan-induced colitis in guinea pigs, to both,[30] is also unresolved. Of more clinical relevance is whether the observed alterations in eicosanoid

metabolism in active ulcerative colitis are in any way related to the pathophysiology of the disease, and to answer this question it is first necessary to review the effects of eicosanoids on colorectal function.

Effects of eicosanoids on large intestinal function

WATER AND ELECTROLYTE TRANSPORT

Early reports showed that oral PGE_1,[31 32] and intravenous $PGF_{2\alpha}$[33] evoked watery diarrhoea in humans. While this effect was initially attributed to changes in gut motility,[6] subsequent work has indicated that mucosal secretion of water and electrolytes is likely to be the dominant factor in prostaglandin-induced diarrhoea.[9 34–38] Although there is little doubt, however, that physiological as well as pharmacological doses of several prostaglandins can produce secretion in the small intestine,[39] their effect in the human colon is more equivocal.

Although initial *in vivo* experiments in man[40] led to the conclusion that $PGF_{2\alpha}$ and PGE_2 had no effect on colonic mucosal water and electrolyte transport, the difficulties inherent in the perfusion technique allowed the successful study of very few subjects.[40] Subsequent experiments using various *in vivo* and *in vitro* models in the rat and rabbit showed that high concentrations of PGE_1, PGE_2, and PGA_1 (but not PGI_2) impaired colonic fluid transport,[41–47] while very recently 5-HPETE and 5-HETE (but not other HPETEs, LTB_4, or LTC_4) have been shown to stimulate short-circuit current and active chloride secretion in rabbit colon.[48] Neither physiological nor pharmacological concentrations of any of these compounds, however, have yet been proved to affect human colonic mucosal water and electrolyte absorption.

The mechanisms by which eicosanoids affect colonic mucosal secretory function in animals are unclear but may include stimulation of adenyl cyclase activity,[34 35 45 46 49–53] increased calcium gating,[53] inhibition of Na-K-ATPase activity[54] and alterations in mucosal blood flow or motility (*vide infra*), although the latter could not explain the effects of prostaglandins on ion transport in short-circuit preparations *in vitro*.

Clearly more work is required in this area. We also need information about the effects on fluid transport of thromboxanes and leukotrienes, and about the sites of action of eicosanoids. In addition, we need to know whether the acute effects of prostaglandins on fluid transport occur in mucosa exposed to them for longer periods, because limited experimental evidence suggests that an adaptive loss of sensitivity rapidly occurs.[38]

MUCUS

Prostaglandins stimulate mucus release in the stomach[55] and small intestine,[56] and in the colon, too, perfusion with PGE_2 released mucus and protein into the lumen.[47] Cyclic AMP stimulated glycoprotein synthesis in organ cultures of rat colonic mucosa[57] and could theoretically mediate any effect of prostaglandins on large intestinal mucus production. In view of the possible contribution of mucus to protection of the mucosal surface (*vide infra*), this field merits further study.

BLOOD FLOW

The effects of eicosanoids on the splanchnic vasculature have been

reviewed elsewhere,[9 58 59] but there are little data specifically related to large intestinal blood flow. F-series prostaglandins and TXA_2 generally produce mesenteric vasoconstriction, while E-series prostaglandins and PGI_2 evoke vasodilation, but the changes reported vary with the experimental model. More information is required about the effects of eicosanoids on colorectal blood flow: elucidation of their influence upon the mucosal microvasculature would be particularly interesting.

MOTILITY

Much work has been published on the effects of eicosanoids on intestinal smooth muscle.[6–10 60] In general, longitudinal muscle is contracted by PGE, PGF, and leukotrienes, while circular muscle relaxes to PGE and contracts to PGF; again, however, the effects recorded depend on species and experimental conditions.

The abdominal cramps produced by administration of prostaglandins[31–33 60] suggest that, at least in pharmacological doses, these compounds affect intestinal motility in man. As with other aspects of gut function, more is known about motility changes produced by prostaglandins in the small than in the large intestine.[9] Oral PGE_1 enhanced progressive pressure waves in the human left colon,[32] while intravenous PGE_2 inhibited segmental contractions in the sigmoid colon[60] (a change which may predispose to diarrhoea)[61] and $PGF_{2\alpha}$ had no effect.[60] The effects of other eicosanoids on human colonic smooth muscle activity *in vivo* are unknown.

INFLAMMATION

There is much experimental evidence, mainly obtained from animal studies, that prostaglandins are involved in the mediation of inflammation.[62 63] Often acting synergistically with other inflammatory mediators – for example histamine and bradykinin, they produce increased vascular permeability, vasodilatation, oedema, pain, fever, and alterations of lymphocyte function, and their enhanced synthesis may lead to the generation of toxic free radicals.[64] Leukotrienes may also contribute to the cellular content of inflamed tissue by promoting leucocyte egress from the vasculature.[63 65] Although eicosanoids are likely to have at least some of these effects in human tissues *in vivo,* there is no direct evidence as yet that they produce such changes in the intact human colon. It should be added that under certain conditions, some prostaglandins, albeit at very high concentrations, have been shown to exert an anti-inflammatory effect.[63]

CYTOPROTECTION BY EXOGENOUS PROSTAGLANDINS

Indomethacin and other non-steroidal anti-inflammatory drugs cause gastric erosions and gastric and small intestinal ulceration in animals. Exogenous prostaglandins can prevent these changes as well as some manifestations of the gastric damage caused by other noxious agents. This apparent protective influence has been described as 'cytoprotection'.[66–68] It has been proposed that prostaglandins may be 'cytoprotective' to the colonic mucosa also, but evidence for this proposition is more limited. 16,16-dimethyl PGE_2 appears to reduce the morbidity and mortality of clindamycin-induced colitis in the hamster[69] and PGE_2 may abrogate ethanol-mediated colonic damage in the rat.[70] The only direct study of

possible cytoprotection of the human colon by exogenous prostaglandins, undertaken in patients with ulcerative colitis, however, failed to support such a role, perhaps because of difficulties with experimental design (*vide infra*).[71]

EFFECT OF PROSTAGLANDIN SYNTHESIS INHIBITORS

There is some evidence, albeit indirect and mainly anecdotal, that depletion of endogenous prostaglandins may be harmful to the large bowel.

In rats and dogs indomethacin can cause colonic ulceration but does so less readily than in the small intestine, and it is not known whether the changes can be prevented by exogenous prostaglandins.[72 73] Local side effects such as irritation, bleeding, and tenesmus occur in 10–30% of patients given indomethacin suppositories for treatment of rheumatic conditions,[74 75] but frank indomethacin-induced proctitis, while widely believed in, has been adequately documented only rarely.[76] Recently two patients have been described in whom a reversible acute colitis was produced by mefenamic acid;[77] this may be a consequence of cyclo-oxygenase inhibition, but fenamates also appear to have prostaglandin-independent laxative and cytolytic properties.[78] Patients have also been described in whom colonic perforation was associated with the administration of indomethacin in its standard[79] and osmotically activated slow release formulation (Osmosin).[80] More recently, an uncontrolled study showed that eight patients with rheumatic disorders had abnormal sigmoidoscopic mucosal appearances, potential differences and potassium transport, while treated with indomethacin suppositories. When treatment was withdrawn these reverted towards normal at the same time as rectal mucosal PGE_2 release, measured by *in vivo* rectal dialysis, doubled.[81]

Although these findings are compatible with a 'cytoprotective' role for prostaglandins in the human large intestine, there is as yet no evidence which unequivocally supports this proposition. The mechanism of any such effect also remains uncertain; by analogy with the stomach, possibilities include stimulation by prostaglandins of vasodilatation, mucus secretion, mucosal hyperplasia, membrane (including lysosomal) stabilisation, adenyl cyclase activity, and cellular extrusion of sodium and/or chloride.[63 66–68 82–85]

Abnormalities of large intestinal function in active ulcerative colitis

Active ulcerative colitis is characterised clinically by diarrhoea with blood, mucus and pus, and, on sigmoidoscopy and biopsy, features of acute and chronic inflammation.[86] Cramping abdominal pain occurs in some patients, and in many the affected colon is radiologically inert. Experimental studies *in vitro* and *in vivo* show impairment of water and electrolyte transport,[19 20 87–93] and alterations in blood flow.[94] From the preceding section it is clear that, at least in acute experiments, eicosanoids mimic many of the features of active ulcerative colitis, and it is for this reason that the pathophysiology of relapse has been widely attributed to enhanced local eicosanoid production.[3 7 11 12 14 16 21 24 25 28 29 37 38 46 48 93 95–97]

Before considering the evidence for this hypothesis two general points deserve mention. Firstly, it is possible that some of the features of active

ulcerative colitis are, in a teleological sense, of protective value. Diarrhoea, for example, may facilitate expulsion of putative luminal toxins from the bowel, and mucus could limit their access to the mucosal surface; blood flow and inflammatory changes may serve to increase their clearance from the mucosa itself. If such speculation is true, and if eicosanoids do mediate any of these changes, then their enhanced production in active disease could be beneficial rather than harmful to the host.

Secondly, it is possible that increased mucosal eicosanoid production in relapse is a consequence rather than the cause of local inflammation: it may be a measurable epiphenomenon of no clinical significance.

Do eicosanoids cause the abnormalities of large intestinal function in active ulcerative colitis?

If enhanced synthesis of eicosanoids is critical in the pathophysiology of active ulcerative colitis, eicosanoid receptor antagonists or synthesis inhibitors should be effective treatment. In the case of cyclo-oxygenase products, however, selective receptor antagonists for use in man do not exist, and presently available drugs which inhibit prostaglandin synthesis are not totally specific. Interpretation of the results obtained in trials of their use is therefore not straightforward. Furthermore, the assessment of indomethacin in active ulcerative colitis rests on only three small uncontrolled studies which have failed to show any benefit from giving the drug either orally (three patients)[25] or rectally (24 patients).[98 99] Although these trials were not large enough to prove unequivocally that indomethacin is ineffective in active ulcerative colitis, the treated patients did not show the dramatic improvement which might have been expected if increased prostaglandin synthesis was of central importance. Indeed, in some patients indomethacin appeared to produce deterioration.[25 99] Oral flurbiprofen,[26 27] another potent prostaglandin synthesis inhibitor, also had a detrimental effect in patients with active ulcerative colitis assessed clinically, sigmoidoscopically, and by measurement of rectal mucosal potential difference as an index of epithelial integrity.[19 90 91]

At face value these findings suggest that increased mucosal prostaglandin production is unlikely to be of major pathogenetic importance in active ulcerative colitis and indeed provide some support for the suggestion that prostaglandins could have a protective role in ulcerative colitis. The results cannot be explained by a failure of the drugs used to inhibit colonic prostaglandin synthesis, as both *in vivo* and *in vitro* [15–17 21 30 100 101] studies show them to be highly potent cyclo-oxygenase inhibitors in the human as well as animal large intestine.

An alternative explanation for the deleterious effects of cyclo-oxygenase inhibitors in active ulcerative colitis is that they divert arachidonic acid metabolism down lipoxygenase pathways (Figure) (an effect which has been shown in several tissues but not yet in intestinal mucosa).[102 103] To test the possibility that excessive leukotriene production in active ulcerative colitis[17 23] might be harmful, benoxaprofen, a lipoxygenase inhibitor, was given orally for 18 days to 10 patients with active ulcerative colitis:[104] no symptomatic, sigmoidoscopic or histological improvement occurred. Further evaluation of lipoxygenase inhibitors would seem worthwhile, however, despite these negative results, as benoxaprofen's

potency as a lipoxygenase inhibitor is limited and it also inhibits cyclo-oxygenase, albeit weakly.[105]

Water and electrolyte transport is the only colorectal function the response of which to cyclo-oxygenase inhibition has been studied in detail in patients with active ulcerative colitis.[26 27] In untreated colitics investigated with *in vivo* rectal dialysis, rectal mucosal PGE_2 release varied inversely with sodium transport and directly with potassium transport and potential difference as well as with disease activity assessed sigmoidoscopically;[19 20 27] these findings were compatible with the hypothesis that prostaglandins are responsible for the abnormal transport function.[19 37 93] Flurbiprofen, however, given to 10 patients in relapse produced significant deterioration in mucosal potential difference and transport of sodium and potassium at the same time as it reduced PGE_2 release.[27] Although an effect of flurbiprofen on leukotriene synthesis could not be excluded, the dissociation between the effects of the cyclo-oxygenase inhibitor on mucosal PGE_2 release and transport function suggested that increased prostaglandin production was unlikely to be a major determinant of the abnormalities of electrolyte transport found in ulcerative colitis. The correlations between PGE_2 release and electrolyte transport in untreated patients were probably because of the dependence of each of these variables upon some other consequence of tissue damage.

In summary, present evidence does not support the view that prostaglandins are responsible for the pathological features and abnormal electrolyte transport of patients with active ulcerative colitis. Indeed clinical experience with cyclo-oxygenase inhibitors in such patients suggests that reduction of mucosal prostaglandin concentrations may do more harm than good, a possibility which has received more attention in relation to quiescent disease.

What is the role of eicosanoids in inactive ulcerative colitis?

Although there are no systematic data on the effects of cyclo-oxygenase inhibitors deliberately prescribed to patients with inactive ulcerative colitis, two recent reports support the view[100] that transient mucosal prostaglandin deficiency may predispose them to relapse.

In the first, four patients were described in whom prescription of cyclo-oxygenase inhibitors for coincident painful disorders appeared to precipitate relapse of their previously quiescent disease.[106] In a subsequent survey to compare the events preceding the clinic attendance of 62 outpatients in remission with those occurring before the onset of relapse in 21 attending with active ulcerative colitis, ingestion of paracetamol and other analgesics was noted significantly more frequently in patients attending in relapse (76% *vs* 39% remission).[107] The interpretation of both these pieces of data is complicated by the possibility that the events leading to the ingestion of the analgesics, rather than the drugs themselves, may have induced relapse, and by the fact that paracetamol, although not yet tested in human colonic mucosa, has not generally been found to inhibit prostaglandin synthesis outside the brain.

While these results require confirmation, they could be explained in part by enhanced mucosal leukotriene synthesis[102 103] as well as by a reduction in mucosal functional integrity as a result of cyclo-oxygenase inhibition.

To test the possibility that exogenous prostaglandins might be cytoprotective in quiescent ulcerative colitis, Goldin and Rachmilewitz gave 15 (R), 15-methyl PGE_2 orally to 12 patients previously maintained in remission with sulphasalazine.[71] Not surprisingly, seven of the patients developed watery diarrhoea on this treatment, and in four of these recrudescence of their ulcerative colitis became apparent sigmoidoscopically and histologically. Unfortunately interpretation of this trial is compromised by the use of a diarrhoeagenic prostaglandin. Studies using either a stable (non-diarrhoeagenic) PGI_2 analogue or alternatively a drug such as carbenoxolone, which in the stomach, at least, inhibits prostaglandin inactivation,[108] are needed to assess further the role of mucosal prostaglandin deficiency in the genesis of relapse in patients with previously quiescent ulcerative colitis.

Do sulphasalazine and steroids act by changing eicosanoid metabolism?

Elucidation of the role of eicosanoids in ulcerative colitis has been of interest in relation not only to possible therapeutic innovations with either inhibitors of their synthesis or with eicosanoids themselves, but also in order to elucidate the mechanism of action of conventional treatment with sulphasalazine and corticosteroids.

SULPHASALAZINE

A number of *in vitro* studies have shown that sulphasalazine and 5-aminosalicylic acid (5-ASA, sulphasalazine's active breakdown product),[109] but not sulphapyridine (SP, the apparently inactive breakdown moiety),[109] can reduce prostaglandin synthesis, probably by inhibition of the microsomal prostaglandin synthetase system.[3 12 16 21 25 95 101 110] These effects were seen only at high concentrations, and sulphasalazine and 5-ASA were much less potent inhibitors of prostaglandin synthesis than, for example, indomethacin and flurbiprofen.[15–17 21 30 100 101]

In direct contrast, Hoult has reported that, in lower concentrations, sulphasalazine, but not 5-ASA or sulphapyridine, inhibited degradation of prostaglandins *in vitro* in colonic mucosa and other tissues.[30 100 111] Prostaglandin degradation is an important determinant of net prostaglandin concentrations in the stomach *in vivo*,[112] where activities of catabolic enzymes are high, but it is not clear whether the same is true of the colon. Recently, Hoult has also reported that 5-ASA could act as a cofactor for prostaglandin biosynthesis in human rectal mucosa.[15] At higher concentrations he too found that sulphasalazine and 5-ASA inhibited prostaglandin synthesis, but it remains uncertain as to which (if any) of these actions predominates in the human colon *in vivo*. Nonetheless, Hoult's findings relating to prostaglandin degradation have led to the hypothesis that sulphasalazine may act by enhancing net colonic prostaglandin concentrations and thereby preventing loss of mucosal integrity in patients in remission.

A third hypothesis proposes that lipoxygenase products, because of their potent chemotactic and chemokinetic properties,[65] may mediate the recruitment of inflammatory cells in active ulcerative colitis.[17] The recent demonstration that sulphasalazine can inhibit synthesis of lipoxygenase

products in human colonic mucosa and other tissues,[113–115] provides a further possible explanation of how it works.

Whether these *in vitro* effects on eicosanoid metabolism bear any relation to the clinical efficacy of sulphasalazine or 5-ASA is unknown. Although serial studies have shown colonic mucosal prostaglandin production to vary directly with disease activity in conventionally treated patients,[11 14 16 19–21 24 25] this does not prove that sulphasalazine acts by inhibiting prostaglandin synthesis, as, however mediated, a reduction in tissue inflammation will lead to a fall in local prostaglandin concentrations. There are in fact no data to suggest that sulphasalazine modifies colonic prostaglandin production in patients whose disease activity is unaltered by the treatment. In the only relevant study, withdrawal of sulphasalazine from patients with inactive ulcerative colitis produced no change in either disease activity or rectal mucosal PGE_2 release, a measure of the net result of any alterations in mucosal PGE_2 synthesis or degradation.[116] In the same study, sulphasalazine withdrawal led to a deterioration in mucosal water and electrolyte transport, confirming an earlier report that the drug had a beneficial effect on fluid transport.[117] That this effect was unassociated with any change in PGE_2 release argued against a prostaglandin-mediated effect of sulphasalazine on fluid transport. As yet unexplored is the possibility that sulphasalazine improves absorption *in vivo* by reducing synthesis of lipoxygenase products.[48 113–115]

Despite, therefore, the several effects of sulphasalazine and 5-ASA on colonic eicosanoid metabolism *in vitro*, these data suggest that sulphasalazine and 5-ASA do not exert their favourable influence on the course of ulcerative colitis through a global effect on prostaglandin synthesis or breakdown. It remains possible that they exploit some differential effect on individual eicosanoids. Indeed, sulphasalazine has recently been shown to inhibit thromboxane synthesis in human colonic mucosa[115] (and platelets)[118] at concentrations which may not affect other arachidonic acid derivatives. Such a modulation of eicosanoid metabolism could alter immune function[119] or render the mucosa more resistant to damage. On present evidence, however, it is quite conceivable that sulphasalazine acts through mechanisms (for example alterations in leucocyte mobility, immunoregulation or bacterial flora)[86] totally unrelated to changes in arachidonic acid metabolism.

CORTICOSTEROIDS

Prednisolone can reduce colonic mucosal prostaglandin synthesis *in vitro*.[14 16 22] As well as inhibiting release of arachidonic acid from cell membranes by induction of the inhibitory protein macrocortin,[1] prednisolone has been shown to inhibit human colonic mucosal cyclo-oxygenase activity in living cells, perhaps by an analogous mechanism.[22] Through their effect on arachidonic acid release, corticosteroids can also inhibit synthesis of lipoxygenase products. As with sulphasalazine, however, it is not yet clear whether these effects occur *in vivo* or have any relevance to the clinical efficacy of steroid therapy in patients with active ulcerative colitis.

Cyclo-oxygenase activity and cancer in ulcerative colitis

Two lines of evidence point to a possible link between enhanced

cyclo-oxygenase activity and the increased risk of large intestinal carcinoma associated with long-standing extensive ulcerative colitis.[86]

Firstly, colonic cancers, like many other tumours, show increased prostaglandin synthesis,[120] an abnormality which it has been suggested may contribute to loss of normal growth restraints, bony metastasis and hypercalcaemia.[121 122] Secondly, studies with purified cyclo-oxygenase preparations show that during prostaglandin synthesis part of the enzyme can act as a co-oxygenase of substrates other than unsaturated fatty acids.[123] These include polycyclic aromatic hydrocarbons such as benzo(a)pyrene, oxidation products of which are potentially carcinogenic. Very recently, colonic mucosa from patients with ulcerative colitis has been reported to have an increased capacity for benzo(a)pyrene oxidation.[124] It is not yet known whether this reaction is catalysed by cyclo-oxygenase itself or another oxidase enzyme, nor whether the unstable reaction product is in fact carcinogenic to human colonic mucosa, but this area is worthy of further study.

A specific instance of a possible link between prostaglandins and colonic neoplasia is provided by a case report describing a patient with a villous adenoma which secreted large amounts of PGE_2; the copious rectal effluent, as well as its PGE_2 content, were reduced by treatment with indomethacin.[125]

Conclusions

Despite the intense attention paid to the subject of eicosanoids and ulcerative colitis over the last decade, it remains possible that they are simply measurable epiphenomena of the colorectal inflammatory process. Our tools for dissecting out which pathways of arachidonic acid metabolism might be responsible for the various pathological characteristics of the disease are at present too coarse. Specific enzyme inhibitors or receptor antagonists for use in man, as well as more refined ways of assessing the pathological features of the disease itself, are badly needed. Unfortunately, there is as yet no adequate experimental animal model of human ulcerative colitis.

It is not yet possible to say whether prostaglandin deficiency, prostaglandin excess, or leukotriene excess is the more important pathogenetic factor in ulcerative colitis, or if none of them are, and it is likely that the answers will depend in part on disease activity at the time of study. It will clearly be a long and difficult task to unravel the biological complexities produced by the large and interacting family of eicosanoids, each with differing effects, in the human colon.

Lessons learned from the study of ulcerative colitis should be useful in the evaluation of other inflammatory bowel disorders, including particularly Crohn's disease, in which increased and possibly unbalanced eicosanoid production by colorectal mucosa[126] and peripheral blood monocytes[127] has been shown. The carrot leading us on in the study of all these diseases is a new and specific therapy acting at a defined point on one of the metabolic pathways of arachidonic acid.

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