Enantiomers of flurbiprofen can distinguish key pathophysiological steps of NSAID enteropathy in the rat

T Mahmud, S Somasundaram, G Sigthorsson, R J Simpson, S Rafi, R Foster, I A Tavares, A Roseth, A J Hutt, M Jacob, J Pacy, D L Scott, J M Wrigglesworth, I Bjarnason

Abstract

Background—Non-steroidal anti-inflammatory drugs (NSAIDs) cause gastrointestinal damage by a non-prostaglandin (PG) dependent “topical” action and by inhibiting cyclooxygenase.

Aims—To discriminate between these two effects by studying some key pathophysiological steps in NSAID enteropathy following administration of (R)- and (S)-flurbiprofen, the racemic, and an uncoupler, dinitrophenol.

Methods—The effects of dinitrophenol, racemic, (R)-, and (S)-flurbiprofen on mitochondria were assessed in vitro and on key pathophysiological features of small intestinal damage in vivo (ultrastructure by electron microscopy, mucosal prostanooid concentrations, intestinal permeability, inflammation, and ulcer count) in rats.

Results—All the drugs uncoupled mitochondrial oxidative phosphorylation in vitro, caused mitochondrial damage in vivo, and increased intestinal permeability. Dinitrophenol and (R)-flurbiprofen caused no significant decreases in mucosal prostanooid concentrations (apart from a decrease in thromboxane (TX) B concentrations following (R)-flurbiprofen) while racemic and (S)-flurbiprofen reduced mucosal prostanooids significantly (PGE, TXB2, and 6-keto-PGF1α concentrations by 73–95%). Intestinal inflammation was significantly greater following administration of (S)-flurbiprofen and racemate than with dinitrophenol and (R)-flurbiprofen. No small intestinal ulcers were found following dinitrophenol or (R)-flurbiprofen while both racemic and (S)-flurbiprofen caused numerous ulcers.

Conclusions—Dinitrophenol and (R)-flurbiprofen show similarities in their actions to uncouple mitochondrial oxidative phosphorylation in vitro, alter mitochondrial morphology in vivo, increase intestinal permeability, and cause mild inflammation without ulcers. Concurrent severe decreases in mucosal prostanooids seem to be the driving force for the development of severe inflammation and ulcers.

(Gut 1998;43:775–782)

Keywords: non-steroidal anti-inflammatory drug; enteropathy; flurbiprofen

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for symptomatic relief of pain and inflammation, but there is concern over their gastrointestinal side effects which affect both the gastroduodenal and the small intestinal mucosa.1 2 It is widely believed that this toxicity is a consequence of inhibition of cyclooxygenase 1 (COX-1) while the analgesic and anti-inflammatory therapeutic effects are due to COX-2 inhibition.3 Selective COX-2 inhibition is therefore thought to be desirable therapeutically. However most conventional NSAIDs have equal or greater, depending on the assay system, in vitro inhibitor activity for COX-1 than COX-2.4 5 and when given at full therapeutic doses, inhibit both enzymes.

There is, however, circumstantial evidence that COX-1 inhibition by itself may not be the only factor in the development of the gastrointestinal damage.6 7 Firstly, much larger doses of aspirin (aspirin doses of 1024 mg/kg produce small bowel lesions in about 30% of fasted animals9) are required to cause consistent small bowel damage than the dose required for effective COX inhibition in the rat.10 11 Also, despite comparable and effective inhibition of gastric COX activities induced by rectal administration of a variety of NSAIDs in rats some fail to cause gastric damage.12 Secondly, there is no clear correlation between inhibition of COX and intestinal damage, unlike the anti-inflammatory actions of NSAIDs.13 14 Thirdly, COX-1 knockout mice have less than 1% of normal mucosal prostanooid concentrations yet do not spontaneously develop gastrointestinal lesions.15

Another aspect of the gastrointestinal damage by NSAIDs relates to the “topical” effect(s) of this drugs. This term is used for the non-prostaglandin mediated effect of NSAIDs which occurs when high concentrations of the drugs are in contact with the mucosa, following ingestion or via biliary excretion, or during drug absorption. The topical effect can be documented in man by endoscopy where short term tolerability to NSAIDs can be enhanced by changing the drug formulation or route of administration (enteric coating, NSAID-phospholipid formulation, rectal administration, etc.)16 17 18 abolishing gastric acid secretion,19 and by rendering some NSAIDs non-acidic by forming an ester linkage to a moiety that contains20 21 or does not contain22 nitric oxide.

The “ion trapping hypothesis” provides a basis for the “topical” action of NSAIDs but...
not the mechanism.\textsuperscript{24, 25} One suggestion is that uncoupling of oxidative phosphorylation may be the biochemical mechanism underlying the “topical” toxicity of NSAIDs.\textsuperscript{26–28} Most conventional NSAIDs and acidic pro-NSAIDs (fenbufen and sulindac) uncouple mitochondrial oxidative phosphorylation.\textsuperscript{29–30} Furthermore, there are some indications that non-acidic NSAIDs (such as nitric oxide containing NSAIDs and nabumetone), which do not uncouple mitochondrial oxidative phosphorylation,\textsuperscript{31} are associated with enhanced gastrointestinal tolerability.\textsuperscript{12, 20–22, 31}

In this context it has been suggested that NSAID damage is a sequential multistage pathogenic process\textsuperscript{32} which can be summarised as:

**Biochemical effects**—These include uncoupling of oxidative phosphorylation\textsuperscript{26–29} (topical action) and COX inhibition (local and systemic action leading to a decrease in mucosal prostaglandin production).

**Transitional stage**—Characterised by increased intestinal permeability which could be the consequence of either uncoupling of oxidative phosphorylation or decreased mucosal prostaglandins.

**Tissue reaction**—Inflammation (including neutrophil chemotaxis, chemokinesis, intercellular adhesion molecule upregulation, neutrophil adhesiveness and margination, etc.) and ulcers that are proposed to be the consequences of increased intestinal permeability\textsuperscript{32–33} and the effects of decreased prostaglandins on the microvasculature.\textsuperscript{34, 35}

The relative contribution and effect of uncoupling and COX inhibition in the pathogenesis of stages (2) and (3) is however unknown.

Commercially available flurbiprofen is marketed as a racemate, an equal parts mixture of the (R) and (S) enantiomers. The (S) enantiomer accounts for most of the COX inhibition while the (R) enantiomer is relatively inactive in this respect in vitro.\textsuperscript{39} The (R) enantiomer might therefore be used to study selectively the topical action in isolation from the effect on prostaglandin production.

We aimed to assess the role and consequences of uncoupling of mitochondrial oxidative phosphorylation, in isolation from COX inhibition, in the pathogenesis of NSAID enteropathy by comparing the effects of the two enantiomers and racemic flurbiprofen on key pathophysiological features of the damage in rats where chiral inversion of (R)- to (S)-flurbiprofen is limited to about 10%\textsuperscript{37} or less.\textsuperscript{37} As a possible “positive” control we studied the effect of dinitrophenol (DNP), an uncoupler of oxidative phosphorylation: if the “topical toxicity” hypothesis is correct it should cause changes similar to those of (R)-flurbiprofen.

**Materials and methods**

**ANIMALS AND DRUG DOSES**

Separate groups of male Sprague-Dawley rats, weighing 200–250 g, were used to determine: (a) the effect of the drugs on mitochondria in vitro (six experiments at each concentration) and in vivo (n=4); (b) mucosal prostaglandin (PG) and thromboxane (TX) concentrations (n=8); (c) intestinal permeability (n=8); (d) inflammation (n=8); and (e) 25 hour and seven day ulcer count (n=8).

For the in vivo experiments animals received single doses of 0.5 ml of 3.0 mM DNP (higher doses were associated with appreciable mortality), racemic, (R)-, or (S)-flurbiprofen by gavage (10 mg/kg each: 1 ml of 12 mM solution, with a final concentration of dimethylsulphoxide (DMSO) less than 5%, to a 250 mg rat). The enantiomers were obtained from Boots Pharmaceutical Company (Nottingham, UK) and DNP and racemic flurbiprofen from Sigma Chemical Company (Dorset, UK). The same dose of racemic, (R)-, and (S)-flurbiprofen was given (mg/kg) as we sought to achieve a similar topical effect with all drug forms.

The (R)- and (S)-flurbiprofen were 99.7% and 99.6% enantiomerically pure, respectively, and the racemate was a 1:1 mixture of each. Animals given the vehicle (1 ml of a 5% solution of DMSO) acted as controls.

**MITOCHONDRIAL EXPERIMENTS**

**In vitro**

**Preparation of mitochondria**—Coupled mitochondria were obtained as previously described.\textsuperscript{40} The validity of using rat liver mitochondria as surrogate for monitoring chemiosmotic uncoupling in the intestine is consistent with the accepted universality of the chemiosmotic coupling mechanism between electron transfer and oxidative phosphorylation.\textsuperscript{40}

The animals were killed by cervical dislocation and the liver rapidly dissected and placed in ice cold homogenising solution (75 mM sucrose, 225 mM mannitol, 10 mM 4-morpholine-propanesulfonic acid (MOPS), 1 mM EDTA, and 5 mg/ml bovine serum albumin (BSA) at pH 7.4), cut finely into approximately 1 cm$^3$ pieces with scissors, and washed twice with homogenising solution to remove excess blood. The liver was then suspended in 50 ml of the same solution and homogenised in a Potter-Elvjehm homogeniser by six strokes of a rotating Teflon pestle. The homogenate was then centrifuged at 500 g for 10 minutes to remove excess blood, nuclei, and cell debris. The supernatant was centrifuged at 11 000 g for another 10 minutes, after which the mitochondrial pellet was removed and resuspended in 40 ml homogenising solution. The last centrifugation step was repeated and the mitochondrial pellet resuspended in 1–2 ml of homogenising buffer. The isolation procedure takes some 45 minutes with the homogenate being kept between 0 and 4°C. The mitochondrial protein concentration was determined using Pierce’s BCA protein assay kit (Pierce, Illinois, USA), with BSA as the standard protein.

**Measurement of oxygen consumption**—Oxygen consumption, phosphate to oxygen utilisation ratio (P/O ratio) and respiratory control ratios were measured using a Clarke type oxygen electrode (Rank Brothers, Cambridge) as described by Chance and Williams.\textsuperscript{41} The elec-
Pathogenesis of NSAID enteropathy

or more severe evidence of uncoupling,12 42 drial changes. Mitochondria may show subtle
from each animal with reference to mitochon-
tive enterocytes for analysis were examined.
microscope in transmission mode. Regions of
electron microscopy. Samples were cut ul-
ligament of Trietz) was then placed in glutaral-
0.1 M sodium phosphate bu
er, pH 7.3–7.4. A
V
the prostanoids.
Radioimmunoassay

Eicosanoids were determined in duplicate by
radioimmunoassay using suitable dilutions of
prostaglandin (PG) E, thromboxane (TX) B, or
6-keto-PGF antiserum: TXB 100%; PGF 2
PGB2 0.3%.

PGE antiserum: PGE 2 100%; PGE1 100%;
PGF1 á
PGF antiserum: 6-keto-PGF 1
antiserum (Sigma Chemical
antiserum standard (Amersham
Assay sensitivi-
ties were 10 pg, and the intra-assay and
interassay coefficients of variation ranged from
2 to 5% depending on the prostanoid
measured. As the PGE antiserum did not distin-
guish between PGE1 or PGE2, the results are
expressed as PGE.
The immunological cross-reaction specifici-
ties of the antiseras were:
- PGE antiserum: PGE, 100%; PGE, 100%;
PGE, 0.35%; PGE, 0.3%; PGA, 0.4%;
PGA, 0.3%.
- TXB antiserum: TXB , 100%; PGF, <0.1%;
PGE, <0.01%; 6-keto-PGF, <0.01%;
6-keto-PGF, <0.01%; PGA, <0.1%; PGB, <0.1%.
- 6-keto-PGF antiserum: 6-keto-PGF, 100%;
PGE, 4.0%; PGE, 23.0%; PGB, 7.0%;
PGA, 0.2%; PGB, 0.6%; TXB, 0.6%.
Scintillation counts were measured using a
Packard 2200 CA fitted with a Securia

PROSTANOID DETERMINATION

Extraction
Animals were fasted overnight and throughout,
but had access to water. At 8:00 am they
received the drugs; five hours later they were
sniffed by a blow to the back of the head
and killed. A part of the small bowel, approxi-
mately 20 cm distal to the ligament of Treitz, was
snap frozen and removed for prostanoid ex-
traction and quantification. This time point had
been decided on from previous studies using
indomethacin and other NSAIDs and prelimi-
nary studies with the isoforms of flurbiprofen
where intestinal prostanoids were measured
one, five, and 24 hours after drug administra-
tion. The one and five hour results show compa-
rable decreases in mucosal prostanoid concen-
trations, but the five hour data give more
consistent results. There is variable, but substan-
tial recovery at 24 hours (data not shown).

Pieces were shaved (kept at 0°C) and
individual segments homogenised with a cold
Silverson homogeniser in 2 ml ice cold
acidified methanol/water (1:1 vol/vol adjusted
to pH 3 with formic acid) for 30 seconds. The
homogenate was transferred to an extraction
tube and the homogenate head was washed
with a further 2 ml of acidified cold methanol/
water which was added to the extraction tube.
The homogenate was extracted with chlo-
form (8 ml) and the mixture centrifuged at
2700 g for 20 minutes at room temperature.
The separated lower chloroform layer was
evaporated to dryness using a Gyrator at 37°C
and stored at −20°C until analysis when the
extract was reconstituted in 2 ml of ethanol/
phosphate buffer saline (1:9 vol/vol) at the time
of radioimmunoassay. The extraction efficacy
of this procedure is in excess of 90% for each of
the prostanoids.

INTESTINAL PERMEABILITY

After an overnight fast and 20 hours after
receiving the drugs, 10 µCi (approximately 50
nmol) of chromium-51 labelled EDTA (Amers-
ham International) in a volume of 0.5 ml in
water was administered by gavage (without anaesthesia), followed by 1 ml of water. The animals were placed in individual metabolic cages for five hours for collection of urine and had access to water. Laparotomy was then performed under anaesthesia and the bladder emptied by puncture. The total five hour radioactivity excreted in the urine was determined, together with that of standards, in a Wallac 1284 gamma counter for five minutes; this gives a minimal detectable activity of less than 0.01% of the administered dose.

GRANULOCYTE MARKER PROTEIN
Granulocyte marker protein (GMP)\textsuperscript{20 47 48} was determined from daily faecal samples. Collections were made for three days prior to gavage with the drugs. Faecal collection was continued for a further seven days after drug administration. The stools were stored at $-20^\circ$C and thawed at the time of assay. Aliquots (1 g) were suspended in 4 ml of faecal extraction buffer which was homogenised, then centrifuged at 45 000 g for 20 minutes at 4°C. The supernatant was used to determine the granulocyte marker protein concentrations by enzyme linked immunosorbent assay (ELISA) as described previously.\textsuperscript{20} Microtitre plates were coated by adding 200 µl of an IgG fraction of rabbit anti-GMP diluted 1/1000 in phosphate buffered saline (PBS) to each well. The plates were then covered with Mylar foil and stored at 4°C until required. Granulocyte marker standards, ranging from 2.34 to 75 ng/ml, were prepared by diluting purified granulocyte marker in the assay buffer. The intra-assay and interassay coefficients of variation are 13% and 10%, respectively.\textsuperscript{48} The granulocyte marker protein is stable and not significantly degraded by bacteria for at least a week at room temperature.\textsuperscript{47 48}

MACROSCOPIC DAMAGE
At 25 hours the anaesthetised animals underwent laparotomy and the intestinal mucosa was exposed by a cut through the antimesenteric side of the intestine. The number and size of ulcers (pointed if less than 5 mm or longitudinal if more than 5 mm) were recorded for each animal. The assessor was not aware of the treatments.

STATISTICAL ANALYSIS
The SYSTAT statistical package was used for calculations. Results are expressed as mean (SE). Statistical differences between groups were assessed by the non-parametric Mann-Whitney test and differences in sequential studies (GMP excretion) by the paired Student’s $t$ test using Bonferroni’s correction.

Results
MITOCHONDRIAL FUNCTION
Figure 1 shows that DNP was an effective uncoupler of oxidative phosphorylation in vitro. Individual enantiomers and racemic flurbiprofen increased mitochondrial respiration by two- to threefold from the baseline concentration ($p<0.01$) at concentrations between 0.25 and 1.0 mM, but at no concentration was there a significant difference between racemic, (R)-, and (S)-flurbiprofen. Stimulation of respiration was followed by a progressive decrease in oxygen consumption with further increases in drug concentration; this is indicative of inhibition of electron transport along the

![Figure 1](http://gut.bmj.com/)  
**Figure 1** Effect of DNP, racemic, (R)-, and (S)-flurbiprofen on coupled mitochondrial respiration. The rate of oxygen utilisation is expressed as percentage of baseline respiration (horizontal dashed line). Results are expressed as mean (SEM) of six experiments.

![Figure 2](http://gut.bmj.com/)  
**Figure 2** Changes in mucosal prostanoid concentrations after administration of DNP, racemic, (R)-, and (S)-flurbiprofen. *$p<0.05$, **$p<0.01$ (differences from control; Mann-Whitney).
respiratory chain. This pattern of respiratory response to increasing concentrations of an agent is characteristic of the group of drugs known as respiratory uncouplers.49

No electron microscopy abnormalities were detected in the control animals and their quantitative mitochondrial score was 0–5%. By comparison the quantitative mitochondrial damage score was 30, 30, 30, and 40% for DNP; 40, 60, 60, and 90% for (R)-flurbiprofen; 50, 50, 50, and 60% for (S)-flurbiprofen; and 20, 60, 60, and 60% for the racemate. All differed significantly (p<0.01) from control, but there was no significant difference (p>0.05) among the flurbiprofen treated groups.

INTESTINAL PROSTANOID CONCENTRATIONS

Figure 2 shows the mucosal concentrations of PGE, TXB₂, and 6-keto-PGF₁α from the different groups of animals and the percentage change from control concentrations five hours after their administration. DNP and (R)-flurbiprofen did not alter prostanoid concentrations significantly (p>0.1) apart from TXB₂ concentrations following (R)-flurbiprofen which were significantly (p<0.05) decreased from control concentrations. There were no significant differences between (S)-flurbiprofen and the racemate; both significantly (p<0.01) decreased mucosal PGE by 90–95%, TXB₂ by 78–82%, and 6-keto-PGF₁α by 73%–79% from controls. Prostanoid concentrations following (R)-flurbiprofen were significantly higher (p<0.05) than those following (S)-flurbiprofen and the racemate.

INTESTINAL PERMEABILITY

Figure 3 shows that intestinal permeability to ⁵¹Cr-EDTA was significantly (p<0.01) increased at 1–6 and 20–25 hours after administration of DNP. Similarly the individual enantiomers and racemic flurbiprofen increased intestinal permeability significantly (p<0.01) at both time points. There was no significant (p>0.05) difference in the urinary excretion of ⁵¹Cr-EDTA between the groups 1–6 hours after administration of the drugs or at 20–25 hours.

Permeability returned towards the predose values by day 7 following the drugs, reaching control concentrations in the case of DNP and racemic flurbiprofen.
INTESTINAL INFLAMMATION

Figure 4 shows that the faecal excretion of the granulocyte marker protein remained low after administration of solvent and increased significantly (p<0.01) on the first and/or second day following DNP, racemic, (R)-, and (S)-flurbiprofen administration. In all cases the increased excretion was transient with a return towards control values within two days.

The intensity of the inflammation was significantly (p<0.01) greater following the administration of racemic and (S)-flurbiprofen than DNP or (R)-flurbiprofen as assessed by the cumulative excretion of the granulocyte marker protein (less than the mean baseline excretion on days 1 and 2 after administration of the drug.

INTESTINAL ULCERATION

No ulcers were seen at 24 hours or at seven days after vehicle, DNP, or (R)-flurbiprofen. By contrast the groups gavaged with racemic or (S)-flurbiprofen developed both pointed (mean 12 (2) and 12 (1), respectively) and longitudinal (mean 10 (1) and 10 (3), respectively) small intestinal ulcers at 24 hours. Seven days post-dose there were on average 9 (2) and 12 (1), respectively) and longitudinal ulcers in the (S)-flurbiprofen and racemate groups, respectively, but no pointed ulcers.

Discussion

Previous in vitro studies indicated that increasing concentrations of acidic NSAIDs unouple mitochondrial oxidative phosphorylation and then inhibit mitochondrial respiration, a response characteristic of the so called inhibitory uncoupplers. The lack of stereoselectivity in mitochondrial damage in the present study, which has also been shown with other chiral compounds, suggests the independence of uncoupling of mitochondrial oxidative phosphorylation from COX inhibition.

Although DNP increased mitochondrial respiration to the greatest extent and at a lower concentration than racemic, (R)-, or (S)-flurbiprofen in vitro, it was associated with significantly less in vivo changes to mitochondria. There are a number of possible reasons for this apparent discrepancy. The drugs were given in different quantities (0.5 ml of 3 mM DNP and 1 ml of 12 mM flurbiprofen) and there may be differences in pharmacokinetic factors (rate and site of absorption) between DNP and flurbiprofen due to their different physicochemical properties. The in vivo electron microscopy changes of mitochondria following DNP and flurbiprofen were nevertheless almost identical to those reported to be caused by aspirin in mouse and canine stomach, and alcohol and bile acids, both of which are potent uncoupplers of oxidative phosphorylation, in mouse stomach. Whether the concentrations required for uncoupling to occur in vitro (0.03–1.0 mmol) are achieved in vivo within the intestinal mucosa following therapeutic oral administration of NSAIDs has not been determined directly, but a mechanism for NSAID accumulation within epithelial cells during absorption has been proposed previously by the “ion trapping” hypothesis. DNP and (R)-flurbiprofen did not alter mucosal prostaglandins appreciably from control concentrations, apart from the decrease in TXB2 concentrations following the latter. The stereoselective inhibition of COX by (R)-flurbiprofen in vivo is somewhat less impressive than that observed in vitro, but is nevertheless in agreement with some ex vivo rat and human data. The reason for the difference between the in vitro and in vivo stereoselectivity of (R)-flurbiprofen may be due to the slight chiral inversion of the (R)- to the (S)-enantiomer in vivo or indeed the minute quantities of (S)-flurbiprofen (0.3%) in the (R)-flurbiprofen preparation. In contrast racemic and (S)-flurbiprofen decreased prostaglandin concentrations significantly and equally despite the fact that the latter only contained half as much of the drug active for COX inhibition. The explanation for this may be our use of the high doses of flurbiprofen in these experiments, conventionally used for producing consistent small intestinal damage in the rat, that are many times higher than that required for effective COX inhibition.

The five hour urinary excretion of 51Cr-EDTA following gavage is widely used as a marker of the integrity of the gastrointestinal mucosa from the stomach to caecum. It seems likely that it is the small intestine which is the main determinant of the five hour urine excretion of 51Cr-EDTA in healthy and diseased rats. It racemic, (R)-, and (S)-flurbiprofen all increased intestinal permeability to a similar degree, in agreement with that previously described with enantiomers of etodolac, flurbiprofen, ketoprofen, and ibuprofen, but had differential effects on mucosal prostaglandins. Furthermore, the effect of DNP on intestinal permeability conforms to the findings of increased paracellular permeability in human epithelial monolayers after application of agents that similarly interfere with ATP production. Collectively this suggests that the increase in intestinal permeability following flurbiprofen is a consequence of uncoupling (topical effect) rather than the consequence of a decrease in mucosal prostaglandins, as suggested directly and indirectly by a number of studies.

The immediate consequence of increased intestinal permeability is uncertain, but we have suggested that it may be a central mechanism in the development of intestinal inflammation in man, including NSAID enteropathy. The faecal excretion of the granulocyte marker protein has previously been validated as a marker of intestinal inflammation. The intensity of the inflammation following DNP and (R)-flurbiprofen was comparable and significantly less than that associated with the (S)-enantiomer and racemate. If the inflammation is a response to the increase in intestinal permeability, this implies that a concomitant decrease in physiological
mucosal prostaglandin concentrations may be associated with an increased intensity of the inflammatory response. Furthermore, as DNP and \((R)-\)flurbiprofen did not cause ulcers, while increasing intestinal permeability to a similar extent to that caused by \((S)-\)flurbiprofen and racemate, it seems that a significant decrease in mucosal prostaglandins may be the driving force in the development of ulcers; this observation may relate to the known effects of prostaglandins on the microcirculation.\(^8\) 75-79

In summary, our main aim was to exploit the different properties of the \((R)-\) and \((S)-\) enantiomers of flurbiprofen to dissociate their uncoupling topical effect from their effect on COX and to compare the effect of the \((R)-\)enantiomer with that of the uncoupler DNP. The results show that racemic and \((S)-\)flurbiprofen caused similar pathophysiological changes to other conventional NSAIDs in respect of uncoupling in vitro and in vivo, and intestinal permeability, prostanoid, inflammatory, and ulcerative changes.\(^2\) 34 42 \((R)-\)flurbiprofen had a similar effect on mitochondria and intestinal permeability, but a significantly smaller effect on mucosal prostanoids and intestinal inflammation; it was not associated with small bowel ulcers. By comparison there was a close similarity between the changes induced by \((R)-\)flurbiprofen and those of DNP, except that the latter had no significant effect on mucosal prostanoids. These findings conform to the suggestion that the mitochondrial effects of NSAIDs may lead to increased intestinal permeability and low grade inflammation. Profound decreases in mucosal prostanoids seem to be instrumental in increasing the severity of the intestinal inflammation and in the development of ulcers. The implications are that both actions (uncoupling and inhibition of COX) are important in the pathogenesis of flurbiprofen induced intestinal injury.

Dr Mahmud was supported by an NHS Executive R&D Grant, Dr Sigthorsson by the Helga Jonsdottir & Sigurlidi Kristjansson Memorial Fund, Iceland, and Dr Jacob was the recipient of the BSG 1997 (Sigthorsson G, Mahmud T, Somasundaram S, Hayllar J. Early pathogenic events in NSAID-induced gastrointestinal injury. Gastroenterology 1996;110:253–60).

Dr Sigthorsson by the Helga Jonsdottir & Sigurlidi Kristjansson Memorial Fund, Iceland, and Dr Jacob was the recipient of the BSG 1997 (Sigthorsson G, Mahmud T, Somasundaram S, Hayllar J. Early pathogenic events in NSAID-induced gastrointestinal injury. Gastroenterology 1996;110:253–60).

References