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Review

Non-steroidal anti-inflammatory drugs and apoptosis in the gastrointestinal tract: potential role of the pentose phosphate pathways

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed drugs, primarily for treatment of arthritis. NSAIDs can have two effects independent of their anti-inflammatory action. In the stomach and small bowel long term NSAID consumption can lead to ulceration, whereas in the colon NSAID use can regress existing tumours. In this review, we hypothesise that NSAID-induced damage occurs predominantly by promoting apoptosis, involving a number of mechanisms depending on the type and the redox state of the cell. In addition to inhibiting cyclooxygenase (COX) activity, this includes interfering with glucose metabolism through both arms of the pentose phosphate pathways and energy production via glycolysis and oxidative phosphorylation. Shifting the cellular balance from proliferation to apoptosis is probably the most important outcome by which NSAIDs exhibit their differing actions. Understanding how these different pathways can be reconciled and their contribution to the balance between cell birth and cell death is the challenge for the future. The pentose phosphate pathways may provide a pivotal point for understanding links between factors which alter proliferative activity (e.g. COXs), provide energy metabolism (particularly aerobic and anaerobic metabolism of glucose), and change the redox state of the cell leading to apoptosis. © 2000 Elsevier Science B.V. All rights reserved.

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1. Overview

The human gastrointestinal tract comprises four individual components: the mouth and oesophagus, the stomach, the small intestine (consisting of the duodenum, jejunum, and ileum), and the large intestine (colon and rectum) (Guyton, 1994). Each component plays a distinct functional role that together comprises digestion and absorption of food and fluid. However, the gastrointestinal tract is also extremely susceptible to disease conditions, including those induced by certain enterally-administered drugs.

Non-steroidal anti-inflammatory drugs (NSAIDs) are one example of such drugs, with an action on the intestine at odds with their prescribed treatment modality. They have great clinical utility in the treatment and control of inflammatory conditions (Laurence and Bennett, 1987) but chronic administration can result in inflammation and ulceration of the stomach and small intestine (Spangler, 1996). Ulcers have been defined by Larkai et al. (1987) as ''three-dimensional, circumscribed mucosal defects, associated with an exudate, and having a diameter of 5 mm or more''. NSAID-induced ulcers usually occur in the stomach (gastric ulcer) or proximal small intestine (duodenal ulcer).

NSAIDs have another interesting effect which is also seemingly unrelated to their anti-inflammatory action. Administration of some NSAIDs to patients and animals suffering from colonic polyps and colon cancer causes regression of the aberrant growth, while epidemiological

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studies have shown that long-term consumption of NSAIDs, particularly aspirin, greatly reduces the risk of developing colon cancer (Thun, 1997).

The role of programmed cell death, or apoptosis, in the observed intestinal activities of NSAIDs is under continuing investigation. Apoptosis is likely to play an extremely important part in the pathogenesis of NSAID-induced ulcerogenesis, and is also likely to be involved in regression of colon cancer and other neoplasms. We hypothesise that apoptosis in the gastrointestinal tract may be linked to the pentose phosphate pathways of glucose metabolism, since these pathways provide reducing potential to the cell in the form of NADPH and ribose-5-phosphate for DNA and RNA synthesis. Potentially, any blockade of such a pathway could lead to apoptosis, since the cell cannot protect itself from oxidant damage if NADPH production is diminished.

This review will examine NSAIDs, apoptosis, and the pentose phosphate pathways in more detail, focussing on how these three factors may be linked in the pathogenesis of NSAID-induced enteropathy and cancer regression.

2. Non-steroidal anti-inflammatory drugs

NSAIDs are among the most widely prescribed drugs, with over 100 million prescriptions filled annually in the USA alone (Mahmud et al., 1996). Approximately, 65% of all patients regularly consuming NSAIDs will develop small intestinal inflammation, whilst between 10% and 30% will develop peptic ulceration (Langman, 1989).

NSAIDs encompass many structurally unrelated compounds, with varying degrees of toxicity and anti-inflammatory activity. The first synthesised NSAID was acetylsalicylic acid, or aspirin, which has extensive analgesic, anti-pyretic and anti-inflammatory actions (Laurence and Bennett, 1987). Several other distinct classes of NSAIDs have subsequently been developed, notably the propionic acids, of which naproxen and ibuprofen are the classical examples; the acetic acids, such as indomethacin and sulindac; and the oxicams, typified by piroxicam. There are also several other classes possessing strong anti-inflammatory action but which exhibit a high degree of gastrointestinal toxicity, such as the fenamates and pyrazolones. Paracetomol (acetominophen) is also termed an NSAID, although it is primarily analgesic and exhibits little if any anti-inflammatory action (Rang and Dale, 1991).

2.1. Inhibition of cyclooxygenase (COX) by NSAIDs

Vane (1971) first identified that aspirin was capable of blocking prostaglandin production. Prostaglandins are critical to the defence and integrity of the gastric and intestinal wall since they regulate mucosal blood flow, mucus and bicarbonate secretion and epithelial cell proliferation and repair (Wallace and Tigley, 1995). Prostaglandins are produced by the COX enzymes, of which there are two isoforms. COX-1 is the constitutively expressed tissue isoform, responsible for catalysis of prostaglandin formation from arachidonic acid, whereas COX-2 is the inducible enzymatic isoform expressed during inflammatory episodes (Subbaramaiah et al., 1997).

Traditionally, it has been suggested that the effects of COX in promoting inflammation are due to differential expression of COX-1 and -2. Current dogma suggests that the anti-inflammatory actions of NSAIDs are due to their inhibition of COX-2 at inflammatory sites, whereas the gastrotoxic side effects are due to the concomitant inhibition of COX-1. Several lines of evidence support this theory in both inflammatory situations and cancer. The selectivity of NSAIDs for COX-2 in preference to COX-1 appears to correlate with their toxic effect on the intestine in vivo (Mitchell and Warner, 1999). For example, indomethacin is highly gastrotoxic and is more selective for COX-1, while diclofenac is minimally gastrotoxic and is much more selective for COX-2. For this reason, researchers have recently developed selective COX-2 inhibitors in an attempt to prevent gastrointestinal side effects of NSAID use while maintaining their anti-inflammatory and anti-neoplastic profiles.

2.2. Selective COX-2 inhibitors

In an attempt to minimise the enteropathy associated with NSAID usage, several selective COX-2 inhibitors have been developed, for example meloxicam and celecoxib (Schachna and Ryan, 1999). Simon et al. (1999) examined over 1000 rheumatoid arthritis patients treated with celecoxib, naproxen, or placebo twice daily for 12 weeks. Both drugs significantly improved arthritis symptoms, but naproxen induced gastrointestinal side effects in 31% of patients, while celecoxib induced adverse gastrointestinal effects in up to 28% of patients depending on dose. Ulcers accounted for 6% of these effects in the celecoxib group and 26% in patients consuming naproxen. Indeed, Wallace et al. (1998), using several different selective COX-2 inhibitors, discovered that significant anti-inflammatory effects of these drugs are only evident at doses that also inhibit COX-1, and at these concentrations mucosal erosions are evident. This result suggests that both COX-1 and COX-2 have roles in NSAID-induced gastrointestinal inflammation.

3. Apoptosis

Apoptosis, or programmed cell death, is the dominant manner in which cells die in vivo. Its primary function is to balance cell proliferation, removing redundant cells in a manner which does not induce an inflammatory reaction of potential harm to the host (Pritchard and Watson, 1996).

Three morphological stages have been identified in cells undergoing apoptosis (Arends and Wyllie, 1991): an initial stage in which the cell shrinks in size, cellular chromatin condenses and organelles, including the cytoskeleton, begin to aggregate. The second stage is characterised by membrane blebbing, whereby small portions of plasma membrane form vesicles containing various cellular components, which bud off from the main body of the cell. In the final stage, nuclear material and cellular structures within these apoptotic bodies undergo degeneration. It is important to note that apoptosis is quite distinct from necrosis, whereby a cell is damaged and lyses, releasing cellular contents and inducing inflammation (Pritchard and Watson, 1996).

Cell death by apoptosis is characterised by the need for new gene expression. Several genes have been identified that control the regulation of apoptosis, namely *Bcl-2*, *p53* and *c-myc*. In the gastrointestinal tract, *Bcl-2* null mice exhibit increased loss of small intestinal cells by exfoliation and a significant reduction in mitotic progenitor cells (Kamada et al., 1995), indicative of an important functional role for *Bcl-2* in the regulation of cellular turnover in the intestine. There are numerous other *Bcl-2*-related genes that are also important in apoptosis. All display some degree of homology to *bcl-2*, including *bcl-x*, which can be spliced to the cell death inhibitor *bcl-*x_L or the apoptosis promoter *bcl-*x_S (Boise et al., 1993); *bax*, which appears critical to small intestinal crypt cell death (Krajewski et al., 1994); *bad*, which promotes cell death (Yang et al., 1995); and *bak*, another inducer of apoptosis (Farrow et al., 1995).

The *p53* gene produces a 53 kDa cellular protein that binds to specific DNA sequences (Pritchard and Watson, 1996) and affects cell cycle progression. The resulting expression of *p53* protein causes cell cycle arrest at the G1 stage, allowing time for damaged DNA to repair itself (Lin et al., 1992). Potentially *p53* can initiate apoptosis, which occurs if DNA repair fails (Zunino et al., 1997). The *p53* gene is located on the short arm of chromosome 17, which is deleted in 75% of colorectal cancers (Baker et al., 1989). Loss of *p53* in cancer, with subsequent lack of DNA repair and apoptosis promotion mechanisms, is proposed to be one of the most important events in the differentiation of normal colonic epithelium into adenomas and carcinomas (Watson, 1995).

The *c-myc* proto-oncogene encodes a small DNA-binding protein which acts as a transcription factor (Thompson, 1998). The c-myc protein has two seemingly mutually exclusive functions: it can induce rapid proliferation which proceeds uncontrolled and prevents the cell leaving the cell cycle (Evan and Littlewood, 1993), and it can induce apoptosis (Evan et al., 1992). It has been proposed that c-myc has a role in increasing glycolysis in cancer cells (Dang et al., 1997), which may provide a link between provision of energy for apoptosis and NSAID-induced cellular damage.

3.1. Caspases and endonucleases

The cysteine-rich aspartate-specific protease (caspase) cascade now appears to be the main pathway by which cellular death is mediated. All caspases require cleaving preferentially after an Asp residue (Stennicke and Salvesen, 1998), leading to formation of the active enzyme from an inactive pro-form. The caspases are proposed to cause cellular death by cleavage or degradation of several important proteins, including poly(adenosine diphosphate-ribose) polymerase, which is associated with DNA repair (Lincz, 1998; Hetts, 1998). Caspase-3, which is the only caspase so far identified in gastrointestinal tissue (Krajewska et al., 1997), also acts to degrade the nuclear membrane by lamin proteolysis (Villa et al., 1997).

While the caspases are responsible for destroying proteins within the apoptotic cell, the degradation of DNA is due to the action of endonucleases. At least one of these, termed caspase-activated deoxyribonuclease (CAD), can be activated by caspase-3 (Enari et al., 1998; Sakahira et al., 1998). This protein also has an inhibitor that can prevent cell death by binding to CAD and preventing its DNase activity (Enari et al., 1998). Other endonucleases have also been implicated in apoptosis, including the Ca^{2+}/Mg^{2+}-dependent enzymes and the acidic endonucleases (for review, see Walker and Sikorska, 1997).

3.2. NSAID-induced apoptosis in gastrointestinal cancers

Apoptosis can be induced in the gastrointestinal tract by a variety of stimuli, including NSAIDs (Pritchard and Watson, 1996). Traditionally, cancer has been examined from the viewpoint of increased proliferation. Now, however, it appears that decreased apoptosis is also extremely important, and in reality cancer is likely to result from an imbalance between cell birth (proliferation) and cell death (apoptosis). NSAIDs induce apoptosis both during ulcerogenesis and in colonic polyps and carcinomas, leading to a decrease in neoplastic tissue.

Aspirin induces apoptosis in HT29 colon cancer cells in vitro at concentrations up to 3 mM, while also arresting cells in the G0/G1 phase of the cell cycle (Qiao et al., 1998). The aspirin metabolite salicylate also induces apoptosis in colonic carcinoma and adenocarcinoma cell lines, but interestingly, adenoma lines exhibited a markedly reduced sensitivity to apoptosis (Elder et al., 1996). Accumulation of cells in G0/G1 phase was also observed in this study.

Moreover, Castaño et al. (1999) have shown that aspirin induces apoptosis in HT29 colon cancer cells in a caspase-dependent manner by increasing phosphatidylserine externalisation, a hallmark of apoptosis that allows circulating macrophages to recognise and destroy apoptotic cells. However, aspirin did not activate endonuclease-dependent cleavage of the cell death substrate poly(ADP ribose) polymerase, which in itself is dependent on cas-

pase-3, suggesting that this particular caspase is not utilised in the apoptotic cascade induced by aspirin in colon cancer cells.

Interestingly, sulindac has been demonstrated by several research groups to induce apoptosis in a COX-independent manner. In HCT-15 colon cancer cells, which do not produce prostaglandins when stimulated, Hanif et al. (1996) demonstrated that sulindac and piroxicam induced apoptosis and altered cell cycle phase distribution, and that this effect could not be reversed by the provision of exogenous prostaglandins. Similarly, Piazza et al. (1997) demonstrated that sulindac induces apoptosis in colonic adenocarcinoma cells independent of COX, and again exogenous prostaglandins could not alter this effect.

In vivo, mesalazine, a derivative of salicylic acid, caused a significant increase in apoptosis when administered topically to patients with colorectal carcinoma (Bus et al., 1999). Despite increased apoptosis within the tumour, no effect was observed on normal mucosa within 5 cm of the tumour. This suggests that mesalazine selectively targets tumour cells, with these authors further suggesting this is due to higher COX-2 levels in tumour cells compared to normal cells.

Gastric carcinomas are also susceptible to NSAID-induced apoptosis. Zhu et al. (1999) have demonstrated in gastric cancer cells with both wild-type and mutant *p53* that indomethacin induced greater apoptosis in cells with wild-type *p53* and that this occurred in parallel with an increase in c-myc protein expression. Cells with mutant *p53* upregulated their *p53* gene expression without changing either c-myc expression or cell cycle.

3.3. NSAID-induced apoptosis in gastroduodenal ulcers

The role of apoptosis in NSAID-induced ulcer disease is unclear. Little work has investigated apoptosis in or near ulcers induced by NSAIDs, preferring to concentrate on aspects of mucosal defence. There is some evidence to suggest that NSAIDs can induce apoptosis in normal intestinal cells in vitro and in vivo. In vitro, Kusuhara et al. (1998) has shown that aspirin can induce apoptosis in rat gastric mucosal cells. Both diclofenac and indomethacin induced apoptotic DNA fragmentation in RGM1 cells in a time- and dose-dependent manner, with concomitant upregulation of cellular caspases.

In vivo, administration of 60 mg/kg indomethacin to rats for 2 h induced apoptosis at the site of haemorrhagic lesions and was significantly increased in those animals receiving indomethacin compared to control (Piotrowski et al., 1999). Caspase-3 activity was also upregulated at these sites, and there was a strong correlation between the degree of apoptosis and caspase-3 expression.

3.4. NSAIDs and colon cancer risk

Apart from decreasing the size and number of polyps and carcinomas, numerous epidemiological studies suggest that regular use of aspirin can decrease the risk of developing colon cancer by up to 50% (reviewed by Thun, 1997). The balance between proliferation and apoptosis is likely to play an important role in both of these observed effects.

In the largest population-based study to date, Smalley et al. (1999) analysed data from almost 105,000 patients taking prescription NSAIDs daily for 4 of the previous 5 years. All NSAIDs exhibited a decreased risk of developing colon cancer, with the pooled data suggesting a relative risk of 0.49, although the risk increased if no NSAIDs had been consumed in the last year of the study. The observed decrease in risk of developing cancer was independent of dose, with low doses equally as effective as higher doses.

3.5. NSAIDs and cellular metabolic pathways

Until recently, NSAIDs have been thought to induce apoptosis through inhibition of the COX enzymes in vitro and in vivo. This view is now being reassessed, since several other cellular systems can be inhibited by NSAIDs, possibly leading to apoptosis, and in fact NSAIDs may inhibit many cellular pathways leaving the cell with no option but to apoptose.

It has long been recognised that NSAIDs can affect mitochondrial energy metabolism, particularly oxidative phosphorylation (Adams and Cobb, 1958; Whitehouse, 1964). It appears from recent work that all classes of NSAIDs containing a carboxyl group can uncouple oxidative phsophorylation, since the double bonded oxygen acts as a proton translocator (Fosslien, 1998). Using isolated coupled rat liver mitochondria, Mahmud et al. (1996) demonstrated that a wide variety of NSAIDs could stimulate uncoupling in a pK_a-dependent manner. Drugs with poor gastrointestinal tolerability, such as indomethacin and piroxicam, caused uncoupling at significantly lower concentrations than drugs with a lower gastrointestinal side-effect profile, such as NO-flurbiprofen, and non-acidic COX-2 selective inhibitors. A similar profile has been established in vivo, with mitochondrial damage assessed by electron microscopy after NSAID administration being indistinguishable from that induced by the known uncoupler dinitrophenol (Somasundaram et al., 1997). Similarly, Moreno-Sánchez et al. (1999), investigating a wide variety of NSAIDs, concluded that most uncouple mitochochondrial energy metabolism, although in a pK_a-independent manner.

The role that other pathways of ATP generation may play during NSAID-induced apoptosis is also of interest. Given that NSAIDs inhibit oxidative phosphorylation and that apoptosis is an energy-dependent process requiring new gene expression, it may be expected that other pathways such as glycolysis are upregulated during NSAID-induced apoptosis. Recent work in isolated perfused livers from rats treated with aspirin has suggested that glycolysis was strongly stimulated while oxidative phosphorylation was inhibited (Petrescu and Tarba, 1997). Mefenamic acid,

at low concentrations, appears to have similar effects but is inhibitory at high concentrations (Kemmelmeier and Bracht, 1989).

The pentose phosphate pathways of glucose metabolism, which provide ribose-5-phosphate and reducing equivalents in the form of NADPH to the cell (Butler et al., 1990), are further cellular metabolic pathway which may be affected by NSAIDs.

4. The pentose phosphate pathways

The pentose phosphate pathways of glucose metabolism provide the only de novo source of ribose-5-phosphate, the essential precursor of RNA and DNA, in addition to providing reducing equivalents in the form of NADPH (Butler et al., 1990). The pathway consists of two separate arms (Fig. 1): the irreversible oxidative pentose pathway, with the rate limiting enzyme being glucose-6-phosphate dehydrogenase (G6PDH; EC 1.1.1.49), and the reversible non-oxidative pentose pathway, in which the two key enzymes are transketolase (EC 2.2.1.1) and transaldolase (EC 2.2.1.2) (Stryer, 1988).

4.1. The oxidative pentose pathway

The oxidative pentose pathway, and in particular its rate limiting enzyme G6PDH, has been well studied in a variety of both normal tissues and cancers. For each glucose 6-phosphate molecule metabolised through the oxidative pathway, one molecule of ribose 5-phosphate and two NADPH molecules are produced (Stryer, 1988). The ribose 5-phosphate is utilised in DNA and RNA synthesis while the NADPH is essential in many cellular pathways, including fatty acid biosynthesis and as a cofactor for antioxidant enzyme formation.

The enzyme G6PDH has been extensively studied since it is the rate-limiting step of the oxidative pentose pathway and deficiency in humans can cause haemolytic disorders (Martini and Ursini, 1996). G6PDH catalyses the formation of gluconolactone-6-phosphate from glucose-6-phosphate via a dehydrogenation reaction, with concomitant production of NADPH. However its most important role in humans does not appear to be production of ribose 5-phosphate but rather NADPH, a critical component of one of the pathways for detoxifying oxygen free radicals (Tian et al., 1998).

Interestingly, aspirin can inhibit G6PDH in yeast (Han et al., 1980) and human tissue (Sengupta et al., 1987). Using isolated *Saccharomyces cerevisiae* G6PDH, Han et al. (1980) demonstrated that at aspirin concentrations of 1.25–10 mM, inhibition of the enzyme was rapid and both dose- and pH-dependent. Furthermore, the authors calculated that it was necessary for one molecule of aspirin to react with one G6PDH protein for inactivation, and that such inactivation was irreversible even after extensive dialysis. In human fetal tissue, Sengupta et al. (1987) have

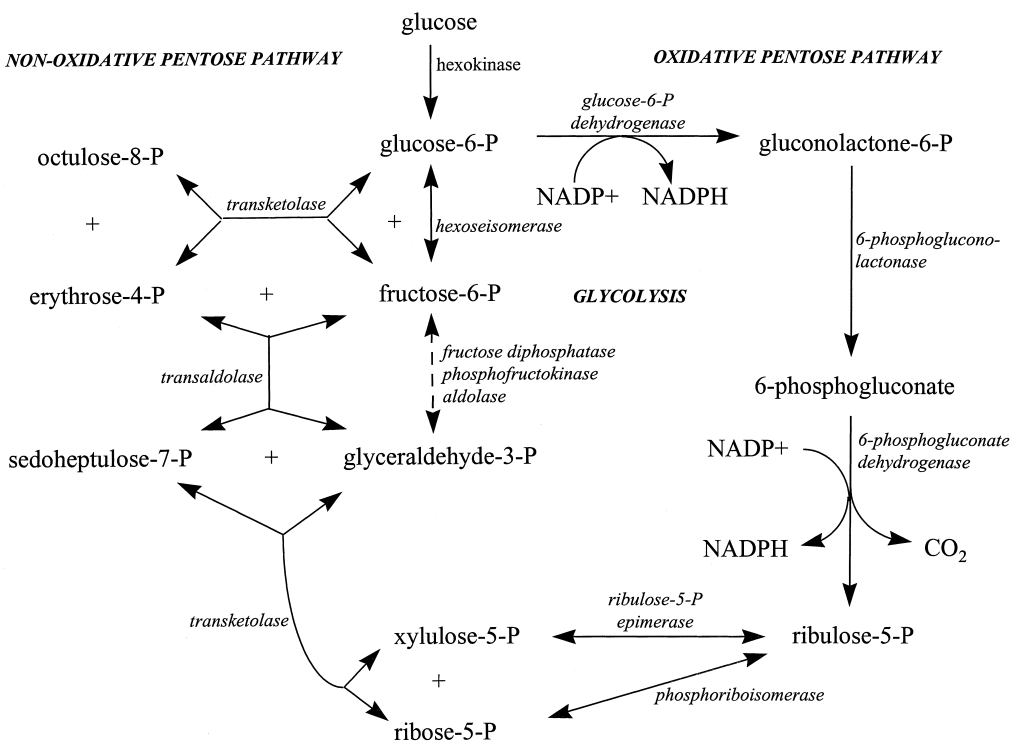

Fig. 1. The pentose phosphate pathways of glucose metabolism. Glucose-6-phosphate can be metabolised either through the reversible non-oxidative pentose pathway or the irreversible oxidative pentose pathway. The non-oxidatve pathway can also recycle ribose 5-phosphate to glucose-6-phosphate. The rate-limiting enzyme of the oxidative pentose pathway is G6PDH, while both transaldolase and transketolase have been proposed as rate limiting in the NOPP. Several steps of the non-oxidative pentose pathway have products common to glycolysis.

shown that aspirin inhibits both G6PDH and the other NADPH-producing enzyme of the oxidative pentose pathway, 6-phosphogluconate dehydrogenase (EC 1.1.1.44), in the brain, heart, and testis. An aspirin dose of 50 or 100 nmol/mg protein in this study inhibited both enzymes by up to 72% (our calculations). Some controversy exists however, since Stockman et al. (1978) were unable to show G6PDH or pentose pathway inactivation in human erythrocytes challenged with aspirin.

Blockade of the oxidative arm of the pathway can be examined experimentally with the steroid dehydroepiandrosterone, a competitive inhibitor of G6PDH (Butler et al., 1993). This compound has been demonstrated to decrease both tumour incidence and burden when administered to mice carrying Ehrlich's ascites tumour cells in vivo (Boros et al., 1997).

In fibroblasts, Tian et al. (1999) have shown that inhibition of G6PDH potentiates apoptosis induced by both the pro-oxidant hydrogen peroxide and by serum deprivation, and that upregulation of G6PDH protects against apoptosis induced by these two factors. Addition of the G6PDH substrates G6P and NADP abrogated the apoptosis induced by serum deprivation.

4.2. The oxidative pentose pathway and oxidative stress

The oxidative pentose pathway is critical for every cell, not just for ribose 5-phosphate provision but because it provides reducing power to the cell in the form of NADPH. As mentioned above, one molecule is produced from the dehydrogenation of glucose 6-phosphate, while another is produced later in the pathway after 6-phosphogluconate is converted to ribulose-5-phosphate and CO_2 by 6-phosphogluconate dehydrogenase. Critically, NADPH allows the cell to reduce GSSG, the oxidised form of glutathione (GSH) generated after that molecule detoxifies a pro-oxidant or free radical (Fig. 2).

Several studies have suggested that the primary function of the oxidative pentose pathway is production of NADPH rather than ribose 5-phosphate. Using mouse embryonic stem cells and recombinant clones of G6PDH with differing functions, it has been shown that the enzyme is essential to protect against even mild oxidative stress induced by hydrogen peroxide and the sulfhydryl oxidiser diamide, but by altering oxygen tension function can be restored (Pandolfi et al., 1995). These authors suggested that G6PDH is dispensable for ribose 5-phosphate synthesis but essential for protection against oxidative stress. Similarly, blocking G6PDH with dehydroepiandrosterone in a canine kidney cell line and providing exogenous ribose 5-phosphate cannot restore growth factor induced cell proliferation (Tian et al., 1999), suggesting that ribose 5-phosphate is not the most important product of the oxidative pentose pathway.

Similarly, in regions of neocortex derived postmortem from Alzheimer's disease patients, the activity of the NADPH-producing enzymes G6PDH and 6PGDH is elevated in the face of increased prooxidant load. This sug-

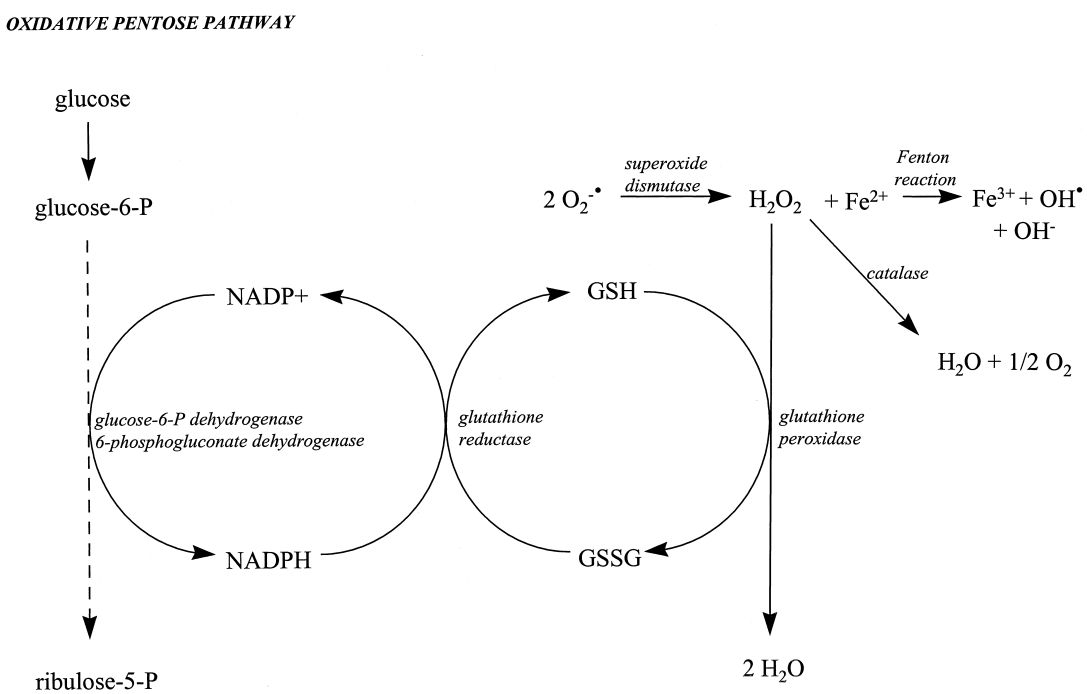

Fig. 2. The oxidative pentose pathway provides NADPH essential for antioxidant functions. An NADPH molecule is formed at both G6PDH and 6-phosphogluconate dehydrogenase, which is necessary to reduce oxidised glutathione (GSSG) to glutathione (GSH). Glutatione is an important pathway by which the dominant pro-oxidant molecule, hydrogen peroxide (H_2O_2), is detoxified. The formation of the hydroxyl radical (OH^-) and peroxynitrite ($ONOO^-$), both of which are implicated in tissue injury, is also shown.

gests that in response to oxidative stress, the pentose phosphate pathway is upregulated to produce NADPH in preference to ribose-5-phosphate (Palmer, 1999).

4.3. The non-oxidative pentose pathway

Regulation of the non-oxidative pentose pathway is less well understood, although the two most important enzymes are thought to be transketolase and transaldolase. In cancer cells, the non-oxidative pentose pathway appears to be upregulated, producing up to 85% of ribose 5-phosphate in a pancreatic cell line (Boros et al., 1997). The non-oxidative pentose pathway also provides a link with glycolysis, as glyceraldehyde-3-phosphate is a common metabolite of both routes of glucose metabolism (Stryer, 1988). Work by Banki et al. (1996) in T cells has shown that the non-oxidative pentose pathway may regulate the oxidative pathway and thus exert significant control on the redox state of the cell, which may be important should NSAIDs affect the OPP.

5. Conclusions

In summary, NSAIDs appear to affect many more cellular systems than the COX enzymes, including mitochondrial energy metabolism, glycolysis and the pentose phosphate pathways. Understanding how these different pathways can be reconciled and their contribution to the balance between cell birth and cell death is the challenge for the future. Undoubtedly, the pentose pathway may provide a pivotal point for understanding links between factors which alter proliferative activity (e.g. COXs), provision of energy metabolism (particularly aerobic and anaerobic metabolism of glucose), the redox state of the cell and apoptosis. Cellular death by apoptosis is induced by NSAIDs, and while induction of apoptosis has important potential in chemoprevention of colonic neoplasms, it may well represent a mechanism by which NSAIDs exhibit toxic side effects in the stomach and small intestine independent of COX inhibition. The pentose phosphate pathways are cellular metabolic pathways that have potential for manipulation in peptic ulcer disease and colon cancer. NSAIDs and apoptosis appear intrinsically linked in both ulcer disease and colonic cancer, and the pentose phosphate pathways represent potential cellular sites for manipulation warranting further investigation. One of the keys to the differential effects of NSAIDs is the redox state of the cells or tissue under investigation. Cancer cells exhibit a highly reduced intracellular environment whereas normal cells have a metabolism that is oxidatively driven. In both settings, manipulation of this state can affect the outcome or balance of cell birth versus cell death.

In conclusion, NSAIDs encompass a vast variety of drugs with anti-inflammatory actions, most of which also induce apoptosis in the gastrointestinal tract, leading to ulcers and regression of cancers. Understanding how NSAIDs interact with cellular metabolic pathways is likely to further explain differential effects.

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