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Mechanism of Action of Paracetamol

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Paracetamol (acetaminophen) is generally considered to be a weak inhibitor of the synthesis of prostaglandins (PGs). However, the in vivo effects of paracetamol are similar to those of the selective cyclooxygenase-2 (COX-2) inhibitors. Paracetamol also decreases PG concentrations in vivo, but, unlike the selective COX-2 inhibitors, paracetamol does not suppress the inflammation of rheumatoid arthritis. It does, however, decrease swelling after oral surgery in humans and suppresses inflammation in rats and mice. Paracetamol is a weak inhibitor of PG synthesis of COX-1 and COX-2 in broken cell systems, but, by contrast, therapeutic concentrations of paracetamol inhibit PG synthesis in intact cells in vitro when the levels of the substrate arachidonic acid are low (less than about 5 μmol/L). When the levels of arachidonic acid are low, PGs are synthesized largely by COX-2 in cells that contain both COX-1 and COX-2. Thus, the apparent selectivity of paracetamol may be due to inhibition of COX-2–dependent pathways that are proceeding at low rates. This hypothesis is consistent with the similar pharmacological effects of paracetamol and the selective COX-2 inhibitors. COX-3, a splice variant of COX-1, has been suggested to be the site of action of paracetamol, but genomic and kinetic analysis indicates that this selective interaction is unlikely to be clinically relevant. There is considerable evidence that the analgesic effect of paracetamol is central and is due to activation of descending serotonergic pathways, but its primary site of action may still be inhibition of PG synthesis. The action of paracetamol at a molecular level is unclear but could be related to the production of reactive metabolites by the peroxidase function of COX-2, which could deplete glutathione, a cofactor of enzymes such as PGE synthase.

Keywords: acetaminophen, paracetamol, prostaglandin, COX-1, COX-2

INTRODUCTION

Paracetamol (acetaminophen) has been used for about 50 years, but, surprisingly, its mode of action is unclear. The analgesic and antipyretic actions of paracetamol resemble those of the nonsteroidal antiinflammatory drugs (NSAIDs), but, in contrast to conclusions about the mode of action of the NSAIDs, it is widely stated that paracetamol is not an inhibitor of the synthesis of prostaglandins (PGs). However, there is considerable evidence showing that this common conclusion about the weak effects of paracetamol on PG synthesis is incorrect.

Following the seminal work of Vane,[1] it is now accepted that the older NSAIDs, such as aspirin, indomethacin, and ibuprofen, produce their wide range of therapeutic activities as well as many of their adverse reactions by inhibition of the enzymes cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). These enzymes are central to the production of PGs and related compounds, such as prostacyclin and thromboxane A_2.

A major advance in physiology and pharmacology was the discovery that there were 2 COX isoenzymes. This discovery was followed quickly by the development of selective COX-2 inhibitors, which are now major drugs. In this article, we present evidence of our hypothesis that paracetamol produces its analgesic and antipyretic actions through inhibition of the COX-2

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pathway of PG synthesis, although the details of its actions at a molecular level are still unclear. Several of these ideas have been presented previously[2–4] but are discussed here in more detail, together with new findings that support our hypothesis.

In vivo effects of paracetamol: Similar effects to those of selective COX-2 inhibitors

Paracetamol has never been classified as a selective COX-2 inhibitor, yet its clinical effects are similar to those of the now widely used selective COX-2 inhibitors, such as celecoxib and rofecoxib (Table 1). Thus, paracetamol is an analgesic and antipyretic drug with little or no toxic effect on the gastrointestinal tract and little tendency to produce asthma in aspirin-sensitive asthmatics.[5] Paracetamol also has little antiplatelet activity, although the production of thromboxane A_2 by platelets is inhibited by therapeutic plasma concentrations of paracetamol,[6] and after an oral dose of 2 g (twice the usual single therapeutic dose), paracetamol inhibits the aggregation of platelets.[7] Antiplatelet activity is characteristic of the nonselective NSAIDs due to their inhibition of COX-1 but is shown only by high concentrations of the selective COX-2 inhibitors.

Much has been made of the finding that paracetamol does not suppress the inflammation of rheumatoid arthritis.[8,9] Consistent with this finding, paracetamol does not decrease the concentration of PGE_2 or the metabolites of prostacyclin or thromboxane A_2 in synovial fluid of patients with rheumatoid arthritis.[10] Paracetamol does, however, decrease tissue swelling following oral surgery in humans, with activity very similar to that of ibuprofen.[11,12] It also inhibits a variety of inflammatory models in experimental animals, particularly carrageenan-induced edema.[13–17] High doses of paracetamol are required in the rat (200–1000 mg/kg) but doses of 100 to 300 mg/kg produce spinal concentrations equivalent to therapeutic concentrations in humans.[18] The antiinflammatory effect of paracetamol is at least partially central in rats because a small dose injected into a lateral ventricle suppresses inflammation.[17] It can be concluded, therefore, that paracetamol does have some antiinflammatory activity, although it does not suppress the severe inflammation of rheumatoid arthritis in humans. The common statement that paracetamol has no antiinflammatory activity is incorrect.

Overall, the pharmacological effects of paracetamol are those of a selective COX-2 inhibitor (Table 1). Despite this similarity, paracetamol is widely accepted to be a weak inhibitor of PG synthesis. As is outlined below, this conclusion is based on inadequate examination of its pharmacology.

Inhibition of prostaglandin synthesis in vivo by paracetamol

There is direct evidence that paracetamol inhibits PG synthesis in vivo, particularly in the central nervous system. Thus, paracetamol decreases the concentrations of a PGE-like material in the cerebrospinal fluid of cats simultaneously with an antipyretic response in the cats.[19] Similarly, in an excellent study,[18] paracetamol prevented the rise in PGE_2 in dialysates of the spinal cord after a painful stimulus applied to the hindpaw of the rat. Most important, this effect was produced at levels of paracetamol that are within the therapeutic concentrations in plasma (10–100 μM^2).

Synthesis of prostaglandins: Bifunctional activities of COX-1 and COX-2 and compartmentalization of enzymes

In any examination of the mechanism of action of paracetamol, several aspects of the pathway of PG synthesis should be emphasized. The first is that COX-1 and COX-2 are both bifunctional enzymes. Thus, they have both cyclooxygenase and peroxidase activities (Fig. 1).[20] While the common abbreviation of the titles of these enzymes refers only their cyclooxygenase activities, their peroxidase activities should not be

Table 1. Comparative clinical and toxic effects of therapeutic doses of paracetamol, and selective COX-2 inhibitors.

Action on	Paracetamol	Selective COX-2 inhibitors
Pain	Active	Active
Fever	Active	Active
Inflammation	Inactive in rheumatoid arthritis*	Active
Platelets	Inactive	Inactive
Aspirin-induced asthma	Weakly active[60,61]	Inactive[62]
Intestinal damage	Inactive	Inactive
Decreased renal Na^+ excretion	Inactive	Active

*Paracetamol decreases inflammation after oral surgery and is active in inflammatory tests in rats.[4]
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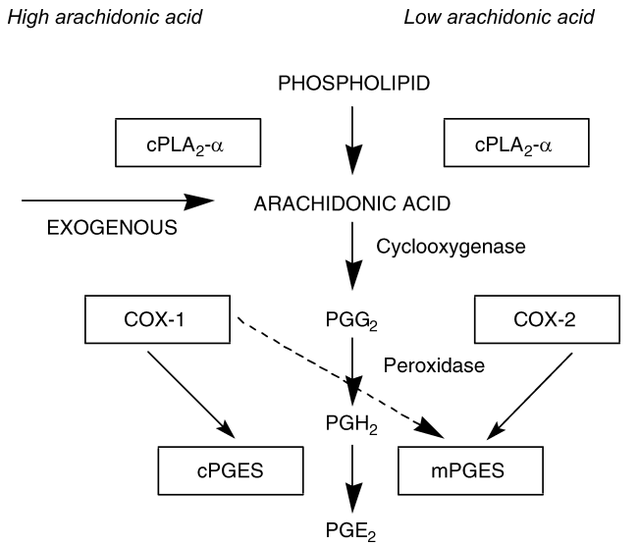

FIGURE 1. Scheme for the synthesis of PGE_2 and compartmentalization of enzymes involved in its synthesis.[23] Both COX-1 and COX-2 have cyclooxygenase and peroxidase functions. PGH_2 synthesized from high concentrations of arachidonic acid is largely converted to PGE_2 by cytosolic PGE synthase (cPGES; as shown by the solid arrow), although membrane-associated PGES (mPGES) is also used (shown by the dashed arrow). Low concentrations of arachidonic acid are converted mainly to PGE_2 by COX-2 and mPGES (solid arrow).

forgotten. The cyclooxygenase activity utilizes oxygen and converts arachidonic acid to PGG_2, which is a hydroperoxide. The peroxidase activity then catalyzes the metabolism of PGG_2 to PGH_2. This second step requires a reductant. The intracellular reductant has not been identified but, in broken cell preparations, a phenol is commonly added as the reductant. Often this is phenol itself. As is discussed below, this addition of a phenol is a major problem in understanding the mechanism of action of paracetamol.

The conversion of PGG_2 to PGs and related products requires specific enzymes. For example, the production of PGE_2 from PGH_2 is catalyzed by PGE synthases (Fig. 1). A membrane-associated PGE synthase has been studied in most detail and requires glutathione as a cofactor.

Another important background factor is the compartmentalization of enzymes involved in PG synthesis. In cells that are synthesizing PGE_2 and contain both COX-1 and COX-2, it appears that COX-2 is linked predominately to membrane-associated PGE synthase. Thus, PGH_2 formed by COX-2 is largely converted to PGE_2 by membrane-associated PGE synthase.[21–24] On the other hand, PGH_2 formed by COX-1 is largely metabolized to PGE_2 by cytosolic PGE synthase.

A further critical observation for understanding the actions of paracetamol is that the availability of arachidonic acid controls to a large extent the activities of the 2 pathways in cells that contain both COX-1 and COX-2. At low concentrations of arachidonic acid, PGE_2 is synthesized mainly by COX-2 and a membrane-associated PGE synthase.[23,25] On the other hand, high concentrations of arachidonic acid are converted to larger amounts of PGE_2 by COX-1 and cytosolic PGE synthase. Thus, stimulation of cells with a cytokine leads to low concentrations of free arachidonic acid (probably less than 1 μmol/L) and the predominant production of PGE_2.[25] Calcium ionophore is often used to stimulate cells to produce PGs. According to Murakami et al,[23] calcium ionophore leads to the availability of high concentrations of arachidonic acid and therefore to its conversion to PGE_2 largely through the COX-1 pathway.

It should be emphasized that these schemes involving compartmentalization of PG synthesis and control by the level of arachidonic acid have been developed mainly from macrophages, and their more general validity in other cell types remains to be determined.

Effects of paracetamol on prostaglandin synthesis in broken cell systems: The reason why paracetamol is stated to be a weak inhibitor of PG synthesis

Although the actions of paracetamol are similar to those of the selective COX-2 inhibitors, paracetamol is not a potent inhibitor of PG synthesis in broken cell preparations. In both COX-1 and COX-2 systems, paracetamol generally shows biphasic activity, stimulating PG synthesis at low concentrations with lesser stimulation or even inhibition at higher concentrations (Fig. 2).[26–28] However, as discussed in more detail below, paracetamol is a phenol and this biphasic activity on PG synthesis is also shown by other phenols[27,29] It is therefore surprising to see the activity of paracetamol tested in the presence of another phenol. The phenol is, of course, added to increase the baseline COX activity, and the response to paracetamol is then determined by its activity in the presence of a fixed concentration of the phenol. It is therefore very difficult to interpret the effects of paracetamol under these conditions when another phenol is present. A further problem is that other phenols are potent inhibitors of PG synthesis in intact cells with IC_{50} values down to micromolar concentrations.[30,31] This is discussed below.

Despite the low potency of paracetamol on isolated COX-1 in the presence of an added phenol, there are still some observations that allow limited correlation with the effects of paracetamol on intact cells. Most important, the addition of the hydroperoxide (HPETE)

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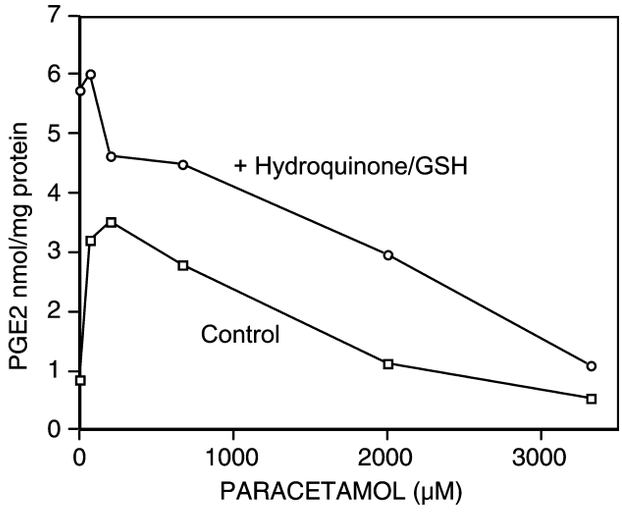

FIGURE 2. Effects of paracetamol on the prostaglandin synthesis by bovine seminal vesicles in the absence (control) and presence of hydroquinone and glutathione. Redrawn from the data of Robak et al.[26]

or the intermediate hydroperoxide PGG_2 attenuated the inhibition produced by very high concentrations of paracetamol (0.5 or 1 mmol/L) on the metabolism of arachidonic acid by isolated COX-1.[32] Similarly, the reduction in peroxides by the addition of glutathione and glutathione peroxidase increased the potency of paracetamol in a COX-1 preparation, although not down to therapeutic levels of the drug.[33]

There has been little study of the effects of paracetamol on the activities on COX-2 in broken cell preparations. However, the general finding is that the effect of paracetamol is weak.[28,32,34] Again, the addition of peroxides and higher concentrations of arachidonic acid attenuated the activity of high concentrations of paracetamol,[32] and, although the presence of phenol in these purified enzyme preparations is problematic, it is of note that there are parallelisms with the effect of paracetamol on intact cells (see next section).

Although supratherapeutic concentrations of paracetamol are generally required to inhibit PG synthesis in broken cell preparations, this is not universally true. Two studies have shown that therapeutic concentrations of paracetamol have inhibited PG synthesis in brain homogenates.[35,36] However, these results have not been confirmed in other studies.[29,37]

Effects of paracetamol on PG synthesis in intact cells: Potent inhibition of PG synthesis at low concentrations of arachidonic acid

Paracetamol has variable effects on PG synthesis by intact cells. However, a pattern can be seen. Paracetamol is a potent inhibitor of PG synthesis when the concentration of added arachidonic acid is low or when the arachidonic acid is released from endogenous phospholipids after the addition of cytokines or lipopolysaccharide (Table 2). Paracetamol is also a weaker inhibitor of PG in cells stimulated by calcium ionophore or a phorbol ester. As discussed above, the addition of a calcium ionophore causes the release of "flooding" amounts of arachidonic acid,[23] and the weak activity of paracetamol in the presence of a calcium ionophore therefore correlates with its weak activity at high concentrations of exogenous arachidonic acid (Table 2).

A good example of the influence of the concentration of arachidonic acid is seen in monocytes (Fig. 3). The sensitivity to paracetamol is higher in the presence of 2 μmol/L arachidonic acid than when 20 μmol/L arachidonic acid is added. This pattern is also seen with platelets in which paracetamol inhibits the production of thromboxane A_2. Platelets contain COX-1, but the sensitivity to paracetamol is still decreased by increasing concentrations of exogenous arachidonic acid.[32] Thus, although paracetamol was less potent on platelets than on endothelial cells, paracetamol showed the same pattern of effects.

Another potentially important aspect of the effect of paracetamol is the attenuation of its effect by increased levels of peroxide. Thus, Boutaud et al[32] found that butyl hydroperoxide completely blocked the inhibitory effect of a supratherapeutic concentration of paracetamol (660 μmol/L) on prostacyclin production by endothelial cells. Peroxides produce similar effects on COX-1 and COX-2 in broken cell preparations, although, as noted above, very high concentrations of paracetamol were used in the presence of phenol and the clinical significance is therefore uncertain.

Intracellular mode of action of paracetamol

Several intracellular mechanisms of action may be suggested for paracetamol. The first is related to metabolic oxidation to reactive compounds. Paracetamol is a substituted phenol (Fig. 4), which is, like many other phenols, oxidizable. It is well known that paracetamol is oxidized by cytochrome P-450 in the liver to *N*-acetyl-*p*-benzoquinoneimine (NAPQI). NAPQI is highly unstable and reacts very rapidly with thiol compounds, particularly the most common low molecular thiol, glutathione, to form the glutathione adduct of paracetamol. At high doses of paracetamol, glutathione levels are depleted through reaction with the large amounts of NAPQI formed. Depletion of glutathione and/or reaction of NAPQI with hepatic proteins then leads to the characteristic centrilobular toxicity of paracetamol overdose.

It is less well known that NAPQI is also produced by the peroxidase function of COX-1 and, because of the

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Table 2. Inhibition of PG synthesis by paracetamol in intact cells (excluding data on platelets and thromoboxane A_2).

Cell type	Stimulant	IC_{50}(μmol/L)	Ref.
Stimulated with low concentrations of arachidonic acid (AA), cytokines, or related factors			
Endothelial cells	AA (2 μmol/L)	4.3 (PGI_2)	Boutaud et al (2002)[32]
Spinal cord slices	Capsaicin	4.4	Malmberg and Yaksh (1994)[63]
Synoviocytes	IL-1β	4.2 ($PGF_{2\alpha}$)	Graham et al (2001)[4]
		7.2	
Microglial cells	LPS	7.5	Fiebich et al (2000)[64]
Microglial cells	LPS	7.6	Greco et al (2003)[65]
Macrophages	LPS	10.7	Cryer and Feldman (1998)[66]
Astrocytoma cells	β-Amyloid	≈10*	Landolfi et al (1998)[67]
	IL-6	≈10*	
	IL-1β	≈40	
Whole blood	LPS	44	Sciulli et al (2003)[68]
	Thrombin	111	
Monocytes	LPS	≈200	
Whole blood	LPS	49	Warner et al (1999)[69]
CHO cells (COX-1)§	AA (0.5 μmol/L)	50	Riendeau et al (1997)[70]
Stimulated with tetradecanoylphorbol acetate (TPA) or calcium ionphore A23187			
Macrophages	TPA	80	Brune et al (1981)[71]
Astrocytes	A23187	135	Lanz et al (1986)[72]
Macrophages	A23187	155	
Macrophages	TPA	190	Brune and Peskar (1980)[73]
Stimulated with AA at concentrations ≥5μmol/L			
Endothelial cells	AA (20 μmol/L)	57	Boutaud et al (2002)[32]
Endothelial cells	AA (20 μmol/L)	72 (PGI_2)	
Macrophages†	AA (30 μmol/L)	100–1000	Simmons et al (1999)[74]
Macrophages	AA (30 μmol/L)‡	>6700 (PGI_2)	Mitchell et al (1994)[75]
Insect cells§			
COX-1	AA (5 μmol/L)	130	Chandrasekharan et al (2002)[41]
COX-1	AA (30 μmol/L)	>1000	
COX-2	AA (5 μmol/L)	5900	
COX-2	AA (30 μmol/L)	>1000	
COX-3	AA (5 μmol/L)	64	
COX-3	AA (30 μmol/L)	460	

PGE_2 was the prostanoid measured except where noted. The therapeutic plasma concentrations of paracetamol are on the order of 10 to 100 μmol/L[2].
*Shallow concentration response relationship from 10 to 1000 μmol/L.
†30% inhibition at much lower concentrations.
‡After induction of variant COX-2 and apoptosis by diclofenac.
Reproduced from Graham and Scott [2] with permission.

strongly conserved structure and function of the 2 COX isoenzymes, it is anticipated that paracetamol should also be oxidized by the peroxidase function of COX-2. The peroxidases also convert paracetamol to a free radical intermediate that dimerizes and is converted to further polymers in vitro (Fig. 4).[38,39] The free radical intermediate formed by the peroxidases also reacts, in part, with glutathione, which is oxidized to the dithiol with the concomitant reduction of the free radical back to paracetamol.

We suggest that there may be 2 important consequences of the metabolism of paracetamol by the peroxidase function of the COX-1 and COX-2. First, the metabolism utilizes reduced glutathione and there may be a local depletion of the glutathione. Reduced glutathione is a cofactor of many enzymes and, in particular, is a cofactor of membrane-associated PGE synthase. Consequently, the local depletion of reduced glutathione may lead to decreased production of PGE_2. The second possible consequence of the metabolism of paracetamol is that the 2 reactive metabolites may combine directly with enzymes involved in PG synthesis and inhibit them. For example, there could be inhibition of enzymes such as a COX isoenzyme or an associated enzyme, such as PGE synthase. In overdose, the formation of NAPQI causes necrosis of

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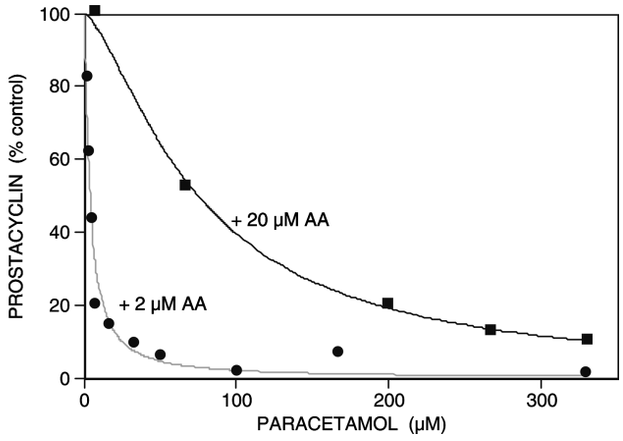

FIGURE 3. Effect of paracetamol on the synthesis of prostacyclin (measured as its metabolite, 6-keto-$PGF_{1\alpha}$) by endothelial cells in the presence of 2 and 20 μmol/L arachidonic acid (AA). The cells were activated by IL-1α. The therapeutic concentrations of paracetamol are on the order of 10 to 100 μmol/L.[2] Redrawn from Boutaud et al.[32]

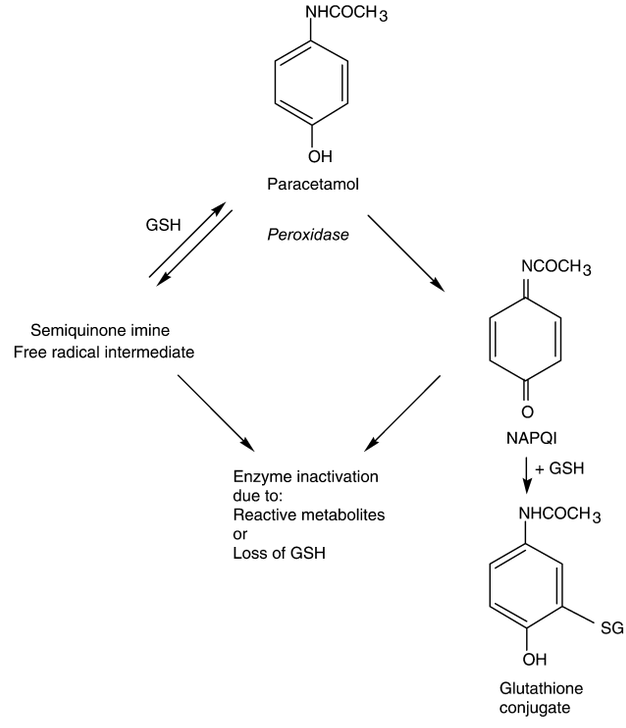

FIGURE 4. Metabolism of paracetamol by the peroxidase function of COX-1.[39,40] It is anticipated that similar metabolism occurs with COX-2. Either the utilization of reduced glutathione (GSH) may inhibit enzymes, such as PGE synthase, for which GSH is a cofactor or the reactive metabolites of paracetamol may inactivate enzymes involved with PG synthesis.

hepatocytes. Obviously, the oxidative metabolism of paracetamol at its site of action cannot produce such a degree of cytotoxicity. However, we are suggesting that the metabolism of paracetamol causes related effects in the immediate environment of the COX isoenzymes.

A second possibility is that paracetamol is a competitive inhibitor of cyclooxygenase. This is indicated by the observation that paracetamol can competitively inhibit the cyclooxygenase function of COX-1 under conditions in which the peroxidase function is inactive.[40] This finding is consistent with the decreased activity of paracetamol in the presence of high concentrations of arachidonic acid but, unfortunately, the potency of paracetamol in this study was not recorded.

Paracetamol and COX-3

In recent years, the effect of paracetamol on a splice variant of COX-1 has received considerable attention. Chandrasekharan et al[41] discovered splice variants of mRNA of COX-1 in dog brain, and COX-1 variants have also been detected in the rat.[42–44] In the studies of Chandrasekharan et al,[41] 2 splice variants of the canine COX-3 were transfected into insect cells. One variant encoded an enzyme that, in the insect cells, produced considerable amounts of PGE_2. This protein was termed COX-3, largely because of its apparent contrasting sensitivity to NSAIDs and, in particular, to paracetamol. Thus, paracetamol was a more potent inhibitor of the production of PGE_2 in insect cells containing COX-3 than in cells containing mouse COX-1 or COX-2 (Table 2).

The greater sensitivity to paracetamol in cells containing COX-3 has been cited widely as indicating that the target of paracetamol is COX-3. However, there are confounding problems that may very well invalidate this conclusion. First, in the absence of paracetamol, insect cells containing COX-1 produced about 5 times as much PGE_2 as cells containing COX-3, while cells containing the COX-2 produced approximately 25 times as much PGE_2 as cells containing COX-3. Thus, there is an inverse relationship between the rate of production of PGE_2 and the sensitivity of the pathway to paracetamol. As discussed above, paracetamol potently inhibits PG synthesis at low concentrations of arachidonic acid and at low rates of PG synthesis. The more potent effects of paracetamol on the cells containing COX-3 may not indicate any specific activity of paracetamol on this isoenzyme but, rather, may have resulted from the low rate of PG production in cells containing COX-3.

A further problem with the COX-3 hypothesis is that paracetamol causes analgesia and antipyresis, which appears to be related to inhibition of COX-2. Thus, paracetamol is, like the selective COX-2 inhibitors, analgesic and antipyretic. Furthermore, lipopolysaccharide

and interleukin-1β do not cause fever in COX-2 knockout mice, but they do produce fever in COX-1 knockout mice.[45,46] If, as appears likely, the primary effect of paracetamol is inhibition of PG synthesis, then it follows that its site of action is COX-2 or a linked enzyme, such as membrane-associated PGE synthase. An effect on COX-1 or a variant, such as COX-3, appears unlikely. Furthermore, recent DNA analysis makes it unlikely that a catalytically active COX-3 could occur in human tissues.[47,48]

Interaction with serotonergic systems in the central nervous system

An effect of paracetamol on the central nervous system is shown by its potent analgesic effect when low doses are injected intrathecally in rats.[49,50] Furthermore, a variety of experiments indicates that central serotonergic pathways are involved in the central action of paracetamol (reviewed by Bonnefont et al[51]). In particular, the central effect of paracetamol is blocked by some serotonin antagonists, although the receptors have not been identified precisely.[49,50,52,53] Correspondingly, the depletion of brain serotonin also blocks the analgesic effect of paracetamol.[54,55] The interaction between paracetamol and serotonin appears to be indirect because no binding of paracetamol has been detected with a variety of serotonergic receptors or on the uptake of serotonin.[50,56] Furthermore, no significant binding or interaction with uptake sites has been found with other neurotransmitters. However, paracetamol may interact with serotonergic pathways through a decrease in PG synthesis. This is indicated from the finding that several monoamine neuron types in the brain contain the EP3 receptor, a major receptor for PGE_2. Thus, almost all serotonergic cells in the medulla oblongata of the rat brain contain the EP3 receptor.[57] This receptor subtype has been implicated in the febrile response to pyrogens.[58] The EP3 receptor was also found in cells in the locus ceruleus, which also contained dopamine β-hydroxylase.

Overall, there is now considerable evidence that the analgesic effect of paracetamol is at least partly produced through a supraspinal activation of descending serotonergic pathways.[59] However, the primary effect may still be inhibition of PG synthesis, although direct evidence of this hypothesis on PG synthesis and serotonergic pathways is required.

CONCLUSIONS

Our analysis indicates that paracetamol inhibits PG synthesis in intact cells when the rate of synthesis is low and the peroxide tone is also low. The pathway involving COX-2 is predominant when the concentration of arachidonic acid is low, and it follows that paracetamol is selective for this pathway. Functionally, paracetamol is acting as a selective COX-2 inhibitor. Paracetamol may have its most potent effects on the central nervous system because peroxide tone and arachidonic acid levels are likely to be lower than at peripheral sites of substantial inflammation, as in rheumatoid arthritis.

It is not uncommon to dismiss any effects of paracetamol on the synthesis of PGs because, if the conditions of the studies are disregarded, the majority of studies indicate that it is a weak inhibitor. However, a consistent pattern of effects of paracetamol on PG synthesis can be seen from published work. The major point is that in intact cells at low concentrations of arachidonic acid, paracetamol does inhibit the synthesis of PGs. If this is so, why is paracetamol not a better antiinflammatory drug? The answer to this question is, first, that paracetamol does have some antiinflammatory activity, as has been discussed. Second, the lack of antiinflammatory activity in rheumatoid arthritis may be due to high extracellular concentrations of arachidonic acid and peroxides, both of which decrease the effect of paracetamol on PG synthesis in intact cells. The activity of paracetamol in rheumatoid arthritis may be greater if higher doses could be administered. Toxicity, however, prevents this.

It should be emphasized that the molecular mechanism by which paracetamol inhibits the synthesis of PGs and related compounds is not known, although inhibition of COX-3 appears to be unlikely.

The effects of paracetamol on PG synthesis appears similar to other phenols. Thus, several other phenols have biphasic effects on PG synthesis in broken cell systems yet are potent inhibitors of PG synthesis by intact cells.[27,29–31,40] The key to the similarity is possibly that many phenols are, like paracetamol, oxidizable.

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