Inflammopharmacol (2013) 21:201–232
DOI 10.1007/s10787-013-0172-x

Inflammopharmacology

REVIEW

The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings

Garry G. Graham · Michael J. Davies · Richard O. Day · Anthoulla Mohamudally · Kieran F. Scott

Received: 4 February 2013 / Accepted: 18 April 2013 / Published online: 30 May 2013

Abstract Paracetamol is used worldwide for its analgesic and antipyretic actions. It has a spectrum of action similar to that of NSAIDs and resembles particularly the COX-2 selective inhibitors. Paracetamol is, on average, a weaker analgesic than NSAIDs or COX-2 selective inhibitors but is often preferred because of its better tolerance. Despite the similarities to NSAIDs, the mode of action of paracetamol has been uncertain, but it is now generally accepted that it inhibits COX-1 and COX-2 through metabolism by the peroxidase function of these isoenzymes. This results in inhibition of phenoxyl radical formation from a critical tyrosine residue essential for the cyclooxygenase activity of COX-1 and COX-2 and prostaglandin (PG) synthesis. Paracetamol shows selectivity for inhibition of the synthesis of PGs and related factors when low levels of arachidonic acid and peroxides are available but conversely, it has little activity at substantial levels of arachidonic acid and peroxides. The result is that paracetamol does not suppress the severe inflammation of rheumatoid arthritis and acute gout but does inhibit the lesser inflammation resulting from extraction of teeth and is also active in a variety of inflammatory tests in experimental animals. Paracetamol often appears to have COX-2 selectivity. The apparent COX-2 selectivity of action of paracetamol is shown by its poor anti-platelet activity and good gastrointestinal tolerance. Unlike both non-selective NSAIDs and selective COX-2 inhibitors, paracetamol inhibits other peroxidase enzymes including myeloperoxidase. Inhibition of myeloperoxidase involves paracetamol oxidation and concomitant decreased formation of halogenating oxidants (e.g. hypochlorous acid, hypobromous acid) that may be associated with multiple inflammatory pathologies including atherosclerosis and rheumatic diseases. Paracetamol may, therefore, slow the development of these diseases. Paracetamol, NSAIDs and selective COX-2 inhibitors all have central and peripheral effects. As is the case with the NSAIDs, including the selective COX-2 inhibitors, the analgesic effects of paracetamol are reduced by inhibitors of many endogenous neurotransmitter systems including serotonergic, opioid and cannabinoid systems. There is considerable debate about the hepatotoxicity of therapeutic doses of paracetamol. Much of the toxicity may result from overuse of combinations of paracetamol with opioids which are widely used, particularly in USA.

Keywords Paracetamol · Acetaminophen · Pain · Analgesia · Inflammation · Prostaglandin · Thromboxane · Prostacyclin · Cyclooxygenase, COX-1 · COX-2 · COX-3 · Myeloperoxidase · Atherosclerosis · Peroxidase · MIF · Diabetes, rhabdomyolysis · Resveratrol

G. G. Graham (✉) · R. O. Day
Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, University of New South Wales, Sydney, Australia
e-mail: g.graham@unsw.edu.au

G. G. Graham · R. O. Day
Department of Pharmacology, University of New South Wales, Sydney, Australia

M. J. Davies
Faculty of Medicine, University of Sydney, Sydney, Australia

M. J. Davies
The Heart Research Institute, Sydney, Australia

A. Mohamudally
Territory Palliative Care, Royal Darwin Hospital, Darwin, Australia

K. F. Scott
School of Medicine, University of Western Sydney, Sydney, Australia

Introduction

Paracetamol (acetaminophen) is one of the world's most widely used non-prescription medicines from cradle to grave. It is readily available and inexpensive. As an analgesic, paracetamol is better tolerated than the non-steroidal anti-inflammatory drugs (NSAIDs) although it may be somewhat less efficacious. During the 1980s a decline in the use of aspirin due to its association with Reye's syndrome allowed paracetamol to become the antipyretic and analgesic of choice in children (Belay et al. 1999) and it is now the standard antipyretic and analgesic in all age groups. Although a useful and important drug, the dose of paracetamol is inconveniently large and a full dose of 4 g daily requires a large number of tablets to be taken.

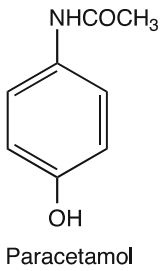
In his Nobel Prize-winning work on the mechanism of action of aspirin and other NSAIDs, Vane (1971) demonstrated that these drugs inhibit the formation of prostaglandins (PGs), local factors that are associated with pain, fever and inflammation. However, paracetamol did not appear to inhibit PG synthesis, despite its actions similar to those of the NSAIDs. The mechanism of the basic pharmacological effects of paracetamol is only now becoming clear and it is now recognised to be an inhibitor of PG synthesis in cellular systems under specific conditions and has an apparent selectivity for one of the cyclooxygenase (COX) enzymes, namely COX-2.

This article is a review of the pharmacology of paracetamol, particularly on its mechanism of action and therapeutic effects, with an emphasis on discoveries that have been made in the past 10 years. Some aspects of the clinical pharmacology of paracetamol, such as its pharmacokinetics, metabolism and adverse effects are not covered in detail although its metabolism by peroxidases and the claimed hepatotoxicity of therapeutic doses are reviewed. New pharmacological actions of paracetamol have been identified in recent years, particularly its interaction with haem peroxidases, such as myeloperoxidase, that is discussed in this review. These recently discovered actions have largely been detected in vitro but may lead to new clinical uses of this old drug.

Chemistry and distribution

Paracetamol is a low-molecular-mass compound (Fig. 1). It is an extremely weak acid (pK_a 9.7) and is, therefore, essentially unionised at physiological pH values (Craig 1990). Its partition coefficient between octanol and water is 3.2 and in the range where passive diffusion through cell membranes is likely. The binding of paracetamol to plasma proteins is negligible Gazzard et al. (1973) and with a volume of distribution of about 50 L after intravenous dosage (Prescott et al. 1989), it is concluded that paracetamol distributes throughout the body without binding to tissues. This lack of binding indicates that the concentrations of paracetamol in experiments in vitro can be correlated directly with its concentrations in vivo without corrections for tissue uptake or protein binding. The peak plasma concentrations of paracetamol after a therapeutic dose (1 g) are approximately 20 mg/L (130 μM) up to 30 mg/L (200 μM) after intravenous injection or rapid oral absorption, and concentrations of up to 30 mg/L can be considered as therapeutic. At a dosage of 1 g four times daily, the trough concentrations are of the order of 2 mg/L (13 μM).

Fig. 1 Structure of paracetamol



Chemically, paracetamol is a phenol and, like many phenols, it is easily oxidised. This oxidation is central to its postulated mechanism of action as a substrate and an inhibitor of the peroxidase function of COX-1 and COX-2. Paracetamol is also oxidised by and inhibits other haem peroxidases, including myeloperoxidase.

Therapeutic and toxic actions: similarities and differences from NSAIDs

Much of the pharmacology and toxicology of paracetamol are similar to those of the non-selective NSAIDs, such as ibuprofen, ketoprofen and naproxen, and it shows particular similarity to the selective COX-2 inhibitors, such as celecoxib and etoricoxib (Table 1). On average, however, paracetamol has weaker analgesic activity than both groups of NSAIDs (see "Clinical analgesic efficacy of paracetamol" section). A major difference is that paracetamol, unlike both groups of NSAIDs, has only weak anti-inflammatory activity (Table 1; see Anti-inflammatory effect).

Much of the toxicity of therapeutic doses of NSAIDs, particularly that arising from the older non-selective NSAIDs, is not seen with paracetamol. In particular, paracetamol does not cause significant gastrointestinal toxicity at therapeutic doses (Zhang et al. 2004). Paracetamol is also a weak precipitant of asthma in aspirin-sensitive asthmatics although it may increase the incidence of asthma (see "Bronchoconstriction and asthma" section). Paracetamol does, however, have specific and dangerous

Table 1 Summary of pharmacological and clinical activities of paracetamol, selective COX-2 inhibitors and non-selective NSAIDs

Pharmacological activity	Paracetamol	Selective COX-2 inhibitor	Non-selective NSAID
Analgesia	Active	Active	Active
Antipyresis	Active	Active	Active
Anti-inflammatory	Active in mild inflammation	Active	Active
Anti-platelet	Low activity	Inactive	Active
Damage to stomach and small intestine	Low activity	Low activity	Active
Aspirin-induced asthma	Weakly active	Inactive	Active
Blood pressure	Variable data	Increase	Increase
Renal	Lesser effects than both NSAID classes	Impaired function in stressed kidneys	Impaired function in stressed kidneys
Increased risk of thrombosis	Inactive	Active	Active

hepatotoxicity of a type that is not seen with the NSAIDs (see "Adverse effects" section). By contrast, apart from aspirin and salicylate, both types of NSAIDs overdoses do not produce life-threatening reactions.

Both classes of NSAIDs have been associated with increase in blood pressure (Laine et al. 2008), more so in patients treated for hypertension than normotensive individuals (Snowden and Nelson 2011). The effect of paracetamol has been studied to a lesser extent with inconsistent results (Sudano et al. 2012; Turtle et al. 2012). A notable result is that paracetamol increased the risk of hypertension in women although bias due to taking paracetamol for painful conditions is possible (Curhan et al. 2002). In studies on patients treated with antihypertensives, paracetamol has little effect on blood pressure and a lesser effect than NSAIDs (Radack et al. 1987; Pavlicevic et al. 2008; Aljadhey et al. 2012). It is possible that blood pressure increases in some patient groups and an important recent finding is that paracetamol increases blood pressure by about 3 mmHg in patients with coronary artery disease (Sudano et al. 2010). In clinical practice, it is reasonable to check for hypertension in patients taking regular paracetamol. Conversely, a temporary decrease in blood pressure has been noted after intravenous injection of paracetamol in acutely ill patients (Hersch et al. 2008; de Maat et al. 2010; den Hertog et al. 2012).

Renal prostaglandins and prostacyclin are synthesised by both COX-1 and COX-2. It is now apparent that NSAIDs have little or no effect on renal function in patients with good renal function but may cause renal impairment in patients with risk factors. These risk factors include already impaired kidney function (particularly in elderly patients) (Murray et al. 1995; Whelton et al. 2000), dehydration, sodium depletion (Colletti et al. 1999; Farquhar et al. 1999) heart failure, diabetes, liver disease or taking the combination of a diuretic together with inhibitors of angiotensin converting enzyme (ACE) or angiotensin receptor (Bouvy et al. 2003; Loboz and Shenfield 2005). In patients with these risk factors, the function of PGs is important in maintaining renal function and significant inhibition of their synthesis leads to renal impairment.

Although paracetamol has apparent COX-2 inhibitory activity (see "Reasons for the apparent COX-2 selectivity of paracetamol" section), it is widely regarded as being safe in patients with risk factors for renal impairment in contrast to patients taking NSAIDs. Experimental proof of this concept is scanty but NSAIDs decreased GFR to a greater extent than placebo or paracetamol in a trial involving stressed kidneys (low sodium diet, dehydration and exercise) (Farquhar et al. 1999), and immediately after surgery in elderly patients (Koppert et al. 2006). Similarly, ibuprofen depressed renal function to a greater extent than paracetamol during surgery on sodium-depleted, anaesthetised dogs (Colletti et al. 1999). Peripheral oedema was also less common in a clinical trial comparing paracetamol and naproxen (Temple et al. 2006). The renal safety of paracetamol is also indicated by two studies finding no increase in the risk of hospitalisation for heart failure (Merlo et al. 2001) and no worsening of renal function in patients with grades 4–5 kidney disease (Evans et al. 2009). Both are conditions in which NSAIDs are expected to worsen renal function. Conversely, in an epidemiological study, Fored et al. (2001) reported that paracetamol exacerbated the development of chronic renal failure, although bias could not be excluded in this population study.

The effect of paracetamol on infarction is of considerable interest because of its widespread use. The highly selective COX-2 inhibitor, rofecoxib, was associated with increased myocardial infarction and its availability was consequently stopped. There is a small tendency for low doses of the presently available COX-2 selective inhibitors and the non-selective NSAIDs to lead to myocardial infarction while paracetamol appears safe (Latimer et al. 2009).

Clinical analgesic efficacy of paracetamol

Acute pain

The results of some recent reviews and meta-analyses of the analgesic activity of paracetamol and combinations with other analgesics are summarised in Table 2. Single doses of paracetamol show analgesic activity in a variety of acute pain syndromes; however, a common finding is that paracetamol is somewhat less effective than NSAIDs. Furthermore, paracetamol has, like the NSAIDs and selective COX-2 inhibitors, better analgesic activity in acute post-surgical pain than in the long-term pain of osteoarthritis (Table 2). However, paracetamol is used extensively and increasingly given intravenously post-operatively as part of multi-modal analgesia regimens.

Treatment of chronic pain, low back pain, osteoarthritis

Chronic pain is a major and common problem with significant associated disability and health care burden. Paracetamol provides pain relief in chronic osteoarthritic pain although the effect size is small (Table 2). As in the treatment of acute pain, the NSAIDs provide better pain relief but the effect size of NSAIDs is still small (Table 2). Like NSAIDs, paracetamol may decrease the synovitis of osteoarthritis (Brandt et al. 2006), although, as determined by serial X-rays, treatment with paracetamol still resulted in a slight deterioration of knee osteoarthritic manifestations in many patients after treatment for 2 years (Williams et al. 1993).

There are, however, some important limitations in many clinical trials. The short duration, often only up to 6 weeks, is a clear limitation for a drug which may be used for very long periods but continued clinical trial of an inactive placebo is unethical.

Despite its lower efficacy than NSAIDs, paracetamol is widely recommended as the preferred initial analgesic in osteoarthritis and low back pain because of its superior tolerance (Day and Graham 2005; Nikles et al. 2005). In terms of cost-benefit, paracetamol is favoured over both the non-selective NSAIDs and the selective COX-2 inhibitors even when these drugs are used with proton pump inhibitors to reduce their adverse gastrointestinal effects (Latimer et al. 2009). This is because the better control of the symptoms by both classes of NSAIDs is outweighed by the cost of treatment of their adverse effects (Latimer et al. 2009). The NSAIDs are of course considered if the response to paracetamol is inadequate.

Several international guidelines including those of the American Geriatric Society (American Geriatrics Society Panel on Chronic Pain in Older Persons 1998) and the European League of Associations of Rheumatology (Jordan et al. 2003; Zhang et al. 2005) recommend paracetamol as the first-line analgesic of choice for mild to moderate pain in osteoarthritis. Recent recommendations by the American College of Rheumatology for the treatment of osteoarthritis in the hip and knee are not entirely clear cut but still appear to place treatment with full-dose paracetamol before NSAIDs (Hochberg et al. 2012). If initial treatment with paracetamol is positive, it is recommended for continued long-term use for osteoarthritis and low back pain (Nikles et al. 2005).

The treatment of the pain of osteoarthritis and other chronic non-cancer pain is still very difficult and requires an understanding of the cause of the pain, patient education, realistic expectations, good communication and regular review and support (Zhang et al. 2005; Milder et al. 2010). The programme needs to encompass physical, psychological and social elements. Weight loss and exercise may be very beneficial. Opioid analgesics have previously been avoided due to misunderstandings about addiction, tolerance and dependence, but "Opioid analgesics, with or without paracetamol, are useful alternatives in patients in whom NSAIDs including COX-2 selective inhibitors (coxibs), are contraindicated, ineffective, and/or poorly tolerated" (Zhang et al. 2005).

Cancer pain

Paracetamol is widely administered with opioids for the treatment of pain due to cancer. It is listed as an essential drug for hospice use (IAHPC 2007). The WHO Pain Relief Ladder lists prompt oral administration of drugs in the following order: non-opioids such as NSAIDs or paracetamol; then combination products for moderate pain containing opioids such as codeine, hydrocodone or oxycodone; then, as necessary, strong opioids such as morphine or transdermal fentanyl, as necessary until the patient is pain free. This three-step approach is inexpensive and stated to be 70–90 % effective (Jadad and Browman 1995). In Europe and Australia paracetamol is routinely prescribed at step 1 and continued at steps 2 and 3, whereas in North America paracetamol is often confined to steps 1 and 2. Patients in severe cancer pain should be treated immediately with opioids. A variety of other drugs and treatments, including corticosteroids, anti-depressants, epidural dosage of analgesics and neurolytical techniques may be useful depending upon the cancer and its treatment (Christo and Mazloomdoost 2008).

Despite the recommendations in the WHO Pain Relief Ladder, the value of paracetamol in the treatment of cancer pain is still contentious and poorly studied. Stockler et al. (2004) showed small, though statistically significant benefits in pain and wellbeing and concluded that the addition of paracetamol is worth considering in all patients with

Table 2 Clinical analgesic activity of paracetamol (P) compared with placebo, NSAIDs and combinations of paracetamol and opioids

Pain	Comparison	Number of clinical trials, number of patients in first group, number of patients in comparator group	Result	References
Osteoarthritis (pain)	P vs. placebo	2, 193,198	ES[a] = 0.21	Zhang et al. (2004)
	NSAIDs vs. P	11, 824, 814	ES = 0.20	
Osteoarthritis (pain)	P vs. NSAIDs	3	ES = 0.33	Wegman et al. (2004)
Postoperative	P 500 mg vs. placebo	6, 290, 271	50 % pain relief NNT[b] = 3.5, RB[c] = 1.9	Toms et al. (2008)
	P 600–650 mg vs. placebo	19, 954, 932	50 % pain relief NNT = 4.6, RB = 2.4	
	P 975–1,000 mg vs. placebo	29, 1,903, 1329	50 % pain relief NNT = 3.6, RB = 2.7	
Oral surgery Pain relief at 6 h	P (<1,000 mg) vs. placebo	9, 190, 188	50 % pain relief NNT = 6, RB = 1.9	Weil et al. (2007)
	P (1,000 mg) vs. placebo	6, 487,690	50 % pain relief NNT = 3, RB = 4.2	
Post partum pain	P (500–650 mg) vs. placebo	5, 275, 207	Adequate relief NNT = 4, RB = 1.9	Chou et al. (2010)
	P (1,000 mg) vs. placebo	6, 425, 372	Adequate relief NNT = 3, RB = 2.4	
Postoperative including dental	P (800–1,000 mg) + codeine (60 mg) vs. P (800–1,000 mg)	4, 153, 151	50 % pain relief NNT = 6.1, RB = 1.3	Toms et al. (2009)
Over 4–6 h	P (600–650 mg) + codeine (60 mg) vs. P (600–650 mg)	10, 309, 313	50 % pain relief NNT = 8.2, RB = 1.3	
	P (800–1,000 mg + codeine (60 mg) vs. placebo	3, 121, 71	50 % pain relief NNT = 2.2, RB = 6.3	
	P (600–650 mg) + codeine (60 mg) vs. placebo	17, 857, 556	50 % pain relief NNT = 3.9, RB = 2.6	
Postoperative including dental over 4–6 h	P (1,000 mg) + oxycodone (10 mg) vs. placebo	3, 147, 142	50 % pain relief NNT = 1.8, RB = 4.9	Gaskell et al. (2009)
	P (650 mg) + oxycodone (10 mg) vs. placebo	10, 680, 363	50 % pain relief NNT = 2.7, RB = 3.9	

Data from meta-analyses and reviews

[a] ES = Difference between treated and control groups divided by the standard deviation of the groups; ES of 0.2 is considered small, ES = 0.5 moderate and ES >0.8 large

[b] NNT = number of patients needed to be treated with paracetamol or combination to obtain one more patient with pain relief than in the control (placebo or paracetamol alone)

[c] RB = relative benefit = Relative proportions of patients with pain relief in treatment and control (placebo) groups

cancer-related pain. However, others have not found paracetamol to offer additional relief of cancer pain over opioids although non-blinded comparisons of treatments are difficult to compare because of selection bias and small numbers of patients (Tasmacioglu et al. 2009; Zernikow et al. 2006). If paracetamol is being used in combination

with an opioid for cancer pain, one clinical approach with well-controlled pain is to ask "the patient to try going without paracetamol for a couple of days —. Those who do feel a difference go back on their regular dose of paracetamol." (Axelsson et al. 2008).

Analgesic effects of combinations with NSAIDs, opioids and caffeine in non-cancer pain

Paracetamol plus NSAIDs

Generally, the combination of NSAIDs and paracetamol provides greater analgesia than paracetamol alone for the acute pain after orthopaedic, gynaecological and dental surgery (Ong et al. 2010). The contrast between the combination and NSAIDs alone is less clear although 64 % of studies show that the combination has greater acute analgesic activity than NSAIDs alone (Ong et al. 2010). More recently, greater activity has been noted for combinations of paracetamol (1,000 mg) and ibuprofen (400 mg) than that produced by combinations of paracetamol (1,000 mg) or ibuprofen (400 mg) with codeine 30 mg (Daniels et al. 2011).

In experimental animals, the combination of paracetamol and an NSAID produces synergistic effects (Miranda et al. 2006, 2008) or additive actions (Fletcher et al. 1997; Kumar et al. 2010) in tests of anti-nociceptive activity.

There have been few studies on the efficacy of the combination of paracetamol and an NSAID in the treatment of osteoarthritis. However, a recent large-scale trial showed that the combination of paracetamol (3 g daily) and ibuprofen (1.2 g daily) generally produced a slightly greater effect than the same dose of paracetamol alone, but there was no significant contrast with ibuprofen alone (Doherty et al. 2011).

Although paracetamol does not suppress the inflammation of rheumatoid arthritis, combinations with NSAIDs show greater analgesic and anti-rheumatic activity than the NSAIDs alone (Seideman 1993; Seideman and Melander 1988). The combination of indomethacin and paracetamol is of particular note as indomethacin (50 mg daily) and paracetamol (4 g daily) has very similar efficacy to a much larger dose of indomethacin (150 mg daily) alone (Seideman and Melander 1988). Further clinical trials of this type (i.e. a small dose of a NSAID and a full dose of paracetamol versus a larger dose of an NSAID alone) should be conducted.

Alternating dosage of paracetamol and ibuprofen has been used as an antipyretic treatment in children but is only used if the child does not respond to one drug alone (Nabulsi 2009).

Paracetamol plus opioids

The addition of paracetamol to opioids can increase efficacy and provide an 'opioid-sparing' effect. Thus, intravenous paracetamol often lowers the required opioid dosage in acute pain (Macario and Royal 2011; Tsang et al. 2013) but the adverse effects of opioid treatment may not be decreased (Maund et al. 2011). Systematic reviews examining paracetamol combined with various opioids for acute postoperative pain have shown increased efficacy when combined with codeine and oxycodone (Table 2).

Combinations of paracetamol and codeine are used widely but the use of codeine in these preparations has received particular criticism. Codeine is a prodrug, its metabolism to morphine being responsible for its analgesic efficacy. Ultrafast metabolism to morphine by some patients may lead to greater relief of pain but an increased likelihood of adverse effects. Conversely, codeine is not converted to morphine in about 8 % of patients with a variant cytochrome P450 2D6, the result being a greatly reduced effect.

Hydrocodone and oxycodone are widely used in combination with paracetamol, particularly in USA. While these combinations have greater efficacy than paracetamol alone, the two directly acting opioids present greater abuse potential than codeine and the high incidence of unintentional overdose in USA is probably due, at least in part, to the widespread use of these combinations (see "Unintentional versus intentional overdose" section). A further difficulty is that hydrocodone and oxycodone are also subject to metabolic interactions with other drugs. For example, the metabolism of oxycodone is inhibited by ketoconazole and induced by rifampicin (Kummer et al. 2011).

Paracetamol plus caffeine

The clinical analgesic activity of single doses of paracetamol is increased to a small, but statistically significant extent, by caffeine (Palmer et al. 2010; Renner et al. 2007). The mechanism may be the increased rate of absorption of paracetamol after dosage with caffeine (Renner et al. 2007). Conflicting interactions between caffeine have been reported in the mouse with caffeine both producing both lesser analgesia and a greater depression of the synthesis of nitric oxide (NO·) in the spinal cord (Godfrey et al. 2006, Godfrey et al. 2007; see below). One group has reported that PG synthesis is inhibited by caffeine alone (Fiebich et al. 2000) but confirmation of this observation is required.

In recent years, a considerable number of papers have claimed that caffeine potentiates the hepatotoxicity of paracetamol. However, a critical review of the data has indicated that there is no significant evidence for such toxicity at therapeutic levels, and some studies indicate the opposite effect (i.e. decreased hepatotoxicity). Furthermore, the studies showing greater toxicity have all been conducted at supratherapeutic concentrations (Palmer et al. 2010).

Inhibition of the synthesis of PGs and related factors

For many years, the mechanism of action of paracetamol was uncertain. The pharmacological and toxicological properties of paracetamol are consistent with inhibition of the synthesis of PGs from arachidonic acid, the similar actions being particularly noticeable with the selective COX-2 inhibitors (Table 1). However, in broken cell preparations and partially purified COX isoenzymes, only supratherapeutic concentrations of paracetamol inhibit the synthesis of PGs; low concentrations often increase PG synthesis (Robak et al. 1978; Bambai and Kulmacz 2000; Swierkosz et al. 2002). These findings led to the conclusion that paracetamol does not produce its therapeutic actions by inhibition of the synthesis of PGs and related factors. This conclusion is incorrect. Paracetamol inhibits the production of PGs from arachidonic acid under specific conditions, namely when the peroxide tone of isolated cells is low (see "Reasons for the apparent COX-2 selectivity of paracetamol" section).

A recent finding is that there are two source enzymes of arachidonic acid, the precursors of the intermediate PGs, PGG_2 and PGH_2 (Nomura et al. 2011). Cytosolic phospholipase A_2 hydrolyses phospholipids to liberate arachidonic acid in many tissues but, in brain, liver and lung, the hydrolysis of the endocannabinoid, 2-arachidonoylglycerol by monoacylglycerol lipase yields arachidonic acid and may even be the rate-limiting source of arachidonic acid in these tissues (Fig. 2; Nomura et al. 2011).

Bifunctional enzymatic activities of COX-1 and COX-2

In order to understand the mechanism of action of paracetamol, it is necessary to outline the enzymology of COX-1 and COX-2. Both enzymes are bifunctional, each enzyme possessing two activities: cyclooxygenase and peroxidase (Fig. 2). The first function of both enzymes is cyclooxygenase activity with the oxidation of arachidonic acid to PGG_2. It is of note that PGG_2 is a *hydroperoxide,* with this species being metabolised subsequently by the *peroxidase* activities of COX-1 and COX-2 to PGH_2 which, in turn, is converted by specific enzymes to prostanoids (Fig. 2). The activity of COX-1 and COX-2 is dependent on the peroxidase function, but this can operate independently, i.e. the peroxidase function can oxidise a variety of organic substances in the presence of hydrogen peroxide or other peroxides. Paracetamol is one of the oxidisable substrates of COX-1 (Potter and Hinson 1987; Harvison et al. 1988) and it is assumed that the peroxidase function of COX-2 can also oxidise paracetamol.

Separation of COX-1 and COX-2 pathways

In cells containing both COX-1 and COX-2, there appears to be a compartmentalisation of pathways that synthesise PGs (Fig. 2). Thus, when both COX-1 and COX-2 are present in cells, COX-2 is the major COX isoenzyme involved in PG synthesis when the concentrations of arachidonic acid are low (Murakami et al. 2000). At high concentrations of arachidonic acid, PG synthesis is mediated largely by COX-1 if both enzymes are present. A further separation of COX-1 and COX-2 is that "COX-1 is expressed constitutively and generally produces PGs to modulate physiological processes, whereas COX-2 is inducible and typically produces proinflammatory PGs in response to physiological stresses such as infection and inflammation" (Lee et al. 2007). However, in some cells in the central nervous system and kidney, COX-2 is present constitutively (Yaksh et al. 2001).

Until recently, all work on the interaction between paracetamol considered arachidonic acid as the substrate for the COX isoenzymes. However, a recently discovered complexity is that selective COX-2 inhibitors and non-selective NSAIDs (through their COX-2 inhibitory activity) inhibit the COX-2 selective oxygenation of the endocannabinoids, 2-arachidonoylglycerol and anandamide (arachidonoylethanolamide) (Fig. 2; Duggan et al. 2011). The products of the oxidation are PG conjugates that are pharmacologically active (Fig. 2; Woodward et al. 2008). Although not yet documented, it is likely that paracetamol, as well as COX-2 selective inhibitors, decrease the oxidation of endocannabinoids. The inhibited metabolism of the endocannabinoids may be responsible in part for the interactions between endocannabinoids with paracetamol and the NSAIDs (see "Endogenous cannabinoids" section). Interestingly, the COX-2 mediated oxidation of endocannabinoids is also blocked by the R isomers of ibuprofen and related drugs which do not inhibit the oxidation of free arachidonic acid by COX-2 (Duggan et al. 2011).

Reasons for the apparent COX-2 selectivity of paracetamol

Hanel and Lands (1982) reported that paracetamol was a more potent inhibitor of COX-1 when the levels of peroxides are low. The concentrations of paracetamol were still supratherapeutic but indicated a point of separation from the non-selective NSAIDs. In contrast, the potency of the NSAIDs is not increased by decreasing the concentrations of lipid peroxides (Hanel and Lands 1982).

This finding has now been extended to intact cells where paracetamol-induced blockade of PG synthesis is markedly reduced by *t*-butylperoxide (Boutaud et al. 2002; Lucas et al. 2005). It now evident that therapeutic concentrations of paracetamol inhibit PG synthesis in *intact* cells when the concentration of added arachidonic acid is low or the cells are stimulated with cytokines, such as interleukin 1β,

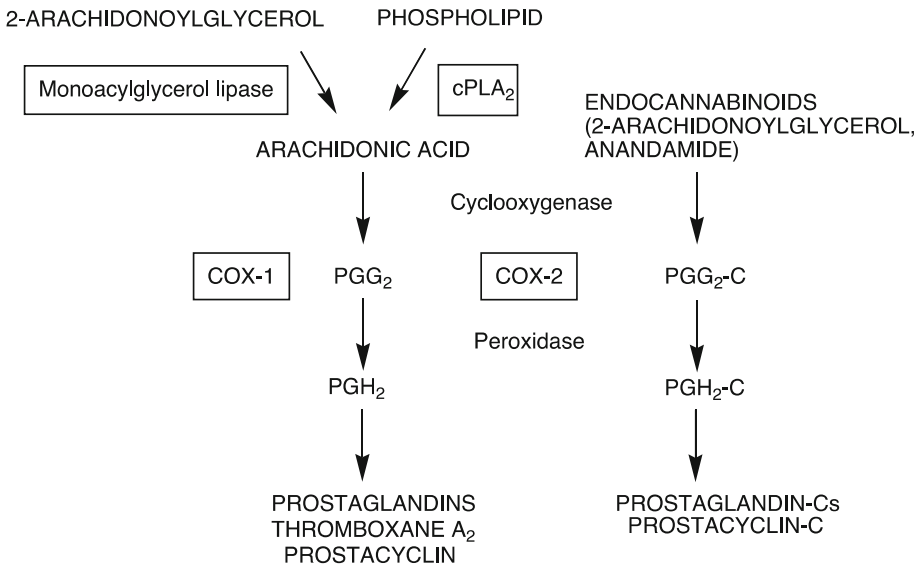


Fig. 2 Prostaglandin (PG) synthesis from precursors, phospholipid (the principal source in many tissues) and the endocannabinoid, 2-arachidonoyl glycerol (present in the brain, liver and lung; Nomura et al. 2011). Both COX-1 and COX-2 both have cyclooxygenase and peroxidase functions. The endocannabinoids, 2-arachidonoyl glycerol and anandamide (arachidonoylethanolamide) are both substrates for COX-2 forming glycerol or ethanolamide conjugates with the intermediate prostaglandins (PGG_2-C and PGH_2-C), final prostaglandins (prostaglandin-Cs), thromboxane A_2 (thromboxane A_2-C) and prostacyclin (prostacyclin-C) (Duggan et al. 2011; Woodward et al. 2008)

which cause the release of low levels of arachidonic acid (Fig. 3, Boutaud et al. 2002; Graham and Scott 2005). High concentrations of arachidonic acid markedly reduce the inhibitory action of paracetamol. It is suggested that low levels of arachidonic acid lead to low intracellular levels of PGG_2, which is a hydroperoxide and a potent effect of paracetamol on PG synthesis results.

When concentrations of arachidonic acid are low, the COX-2 pathway is activated in preference to the COX-1 pathway (Murakami et al. 2000) and, therefore, paracetamol generally *appears* to be a selective COX-2 inhibitor in vitro with IC_{50} values often below 10 μM, well within the therapeutic plasma concentration range (Boutaud et al. 2002; Graham and Scott 2005; Kis et al. 2004). This explains why paracetamol has anti-nociceptive or antipyretic actions involving COX-2 (Li et al. 2008). In contrast, paracetamol does not have anti-inflammatory agent in rheumatoid arthritis or acute gout where the peroxide levels are likely to be high. By comparison, the classical COX-2 selective inhibitors, such as celecoxib, are active anti-inflammatory agents in the treatment of rheumatoid arthritis because their effect on COX-2 is not peroxide dependent.

Paracetamol does not possess significant antiplatelet activity, a COX-1 dependent action, because of the high concentrations of arachidonic acid and peroxides, including PGG_2, that are released (Boutaud et al. 2002). This lack of significant antiplatelet activity is a major factor which makes paracetamol *appear* COX-2 selective.

Paracetamol may also inhibit COX-1 dependent PG synthesis if the peroxide tone is low. For example, paracetamol inhibits acetic acid-induced writhing in mice. The writhing (or abdominal constriction) produced by the intraperitoneal injection of acetic acid is still inhibited by paracetamol in COX-2 knockout mice but is lost in COX-1

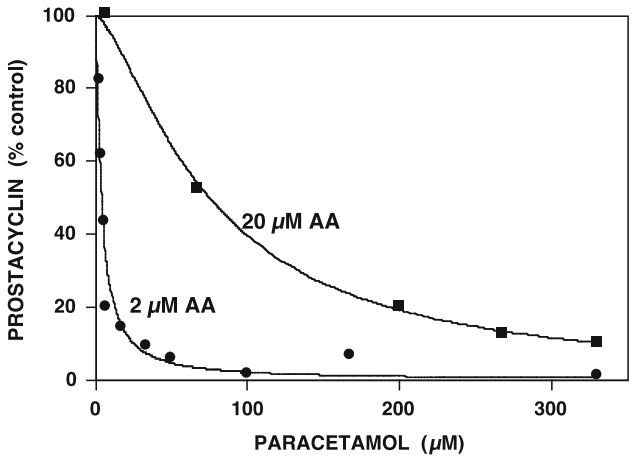


Fig. 3 Effect of paracetamol on prostacyclin synthesis showing the greater inhibition of paracetamol at lower concentrations of paracetamol (Redrawn from Boutaud et al. 2002)

knockout mice (Ayoub et al. 2006). This activity of paracetamol could be due, therefore, to inhibition of COX-1 under conditions of low peroxide tone within the central nervous system. (See "Inhibition of COX-3" section).

Overall, the selectivity of paracetamol appears to be based on peroxide tone. It should not be termed a selective COX-2 inhibitor although it often *appears* to be so.

A finding of potential clinical interest is an association between the levels of a polyunsaturated fatty acid, eicosapentaenoic acid, in plasma and inhibition of the synthesis of PGs and related factors by paracetamol. The plasma concentrations of eicosapentaenoic acid are increased by the long-term intake of fish oil, and the synthesis of PGs in blood of rheumatoid patients is inhibited to a greater extent in patients with higher levels of the fatty acid than in patients with lower levels of the same (Caughey et al. 2010).

Molecular mechanisms of action of paracetamol on COX 1/2 and other haem enzymes

It is now well established that paracetamol inhibits the production of PGs by acting as a substrate of the peroxidase cycles of COX-1 and COX-2 (Fig. 4) although, as discussed above, the major effect is often on COX-2 (Boutaud et al. 2002; Graham and Scott 2005; Aronoff et al. 2006).

The initial species generated on oxidation of paracetamol by COX-1 and COX-2 is the paracetamol phenoxyl free radical. In vitro, this radical undergoes either rapid dimerization with another paracetamol radical to yield dimers, or reduction by glutathione back to paracetamol with consequent formation of glutathione disulphide (Fig. 5; Potter and Hinson 1987; Harvison et al. 1988). Higher polymers may also be produced by additional radical reactions (Fig. 5). The extent of the formation of these dimers and higher polymers in vivo and their clinical relevance are unknown.

In addition to its direct interaction with the peroxidase cycles of COX-1 and COX-2, paracetamol may also scavenge peroxynitrite, which is an activator of COX enzymes (Schildknecht et al. 2008).

Paracetamol is also metabolised by other haem peroxidises in addition to the peroxidase function of COX-1 COX-2, the most important of which may be the leukocyte-derived species myeloperoxidase (Fig. 5). This enzyme is released by activated neutrophils, monocytes and some tissue macrophages at sites of inflammation in response to inflammatory stimuli. Although this occurs primarily in response to invading pathogens, inappropriate or excessive cell stimulation can result in release of myeloperoxidase at the wrong time or place. The subsequent reaction of the released peroxidase with H_2O_2 in the presence of halide, or pseudohalide, ions results in the generation of the powerful oxidants HOCl (hypochlorous acid, from chloride ions), HOBr (hypobromous acid from bromide ions) and HOSCN (hypothiocyanous acid from thiocyanate ions). These oxidants are cytotoxic/cytostatic to bacteria, but can also induce severe host tissue damage. The result of the oxidation of paracetamol is decreased synthesis of HOCl, HOBr and HOSCN. Such inhibition has been detected with both the isolated myeloperoxidase, stimulated neutrophils (Koelsch et al. 2010) and with the related enzyme, eosinophil peroxidase and also with stimulated neutrophils (Kajer et al. unpublished) (see "Inhibition of myeloperoxidase" section).

Inhibition of COX-3

A major advance in the mechanism of action of paracetamol was proposed when Chandrasekharan et al. (2002)

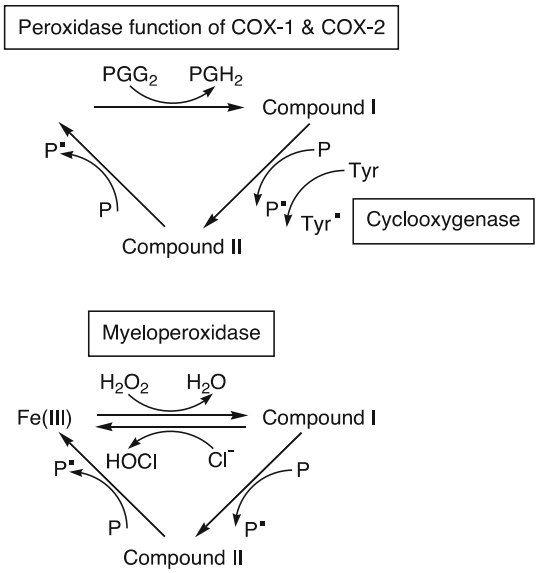


Fig. 4 Parallel effects of paracetamol on the peroxidase functions of the COX isoenzymes (COX-1 and COX-2) and on myeloperoxidase. *COX-1 and COX-2* Oxidation of paracetamol by the peroxidase function to the paracetamol free radical (P·) occurs in competition with oxidation of a tyrosine residue on the enzyme to a tyrosine phenoxyl radical which is essential for the cyclooxygenase function of COX-1 and COX-2 (Boutaud et al. 2002; Graham and Scott 2005; Aronoff et al. 2006). As a result, paracetamol inhibits the cyclooxygenase function of COX-1 and COX-2 and hence the production of PGG_2. Concomitant with the oxidation of paracetamol (Fig. 5), the high oxidation state haem species formed on the enzyme as a result of the initial reaction with peroxide is reduced. The overall result is that the oxidation of paracetamol by compound I decreases the cyclooxygenase activities of COX-1 and COX-2. *Myeloperoxidase* The oxidation of paracetamol by compound I decreases the formation of hypochlorous acid (HOCl) from chloride. Thus, the chlorination cycle is reduced while the peroxidase is increased with the resulting oxidation of paracetamol to free radical species. The free radical species are then mainly converted to the dimer (Koelsch et al. 2010; Fig. 5)

found that insect cells transfected with a splice variant of COX-1 from mice were more sensitive to paracetamol than cells containing either COX-1 or COX-2. Because of its apparent high sensitivity to paracetamol, the splice variant of COX-1 was termed COX-3. Despite the greater sensitivity of insect cells expressing COX-3, it should be noted that the IC_{50} in the insect cells was 450 μM, still well above therapeutic plasma concentrations of paracetamol. As COX-3 is a splice variant of COX-1, COX-1 and COX-3 are formed from a common gene.

There has been considerable discussion about this hypothesis. First, there is considerable argument about the detection of COX-3 in man and its enzymatic activity with vigorous attack (Kis et al. 2005a, b) and defence of the methodology (Simmons et al. 2005). Three splice variants of COX-1 are present in man. It is unlikely that the major splice variant (COX-1b_1) is enzymatically active as it is truncated protein but at least one of the remaining two

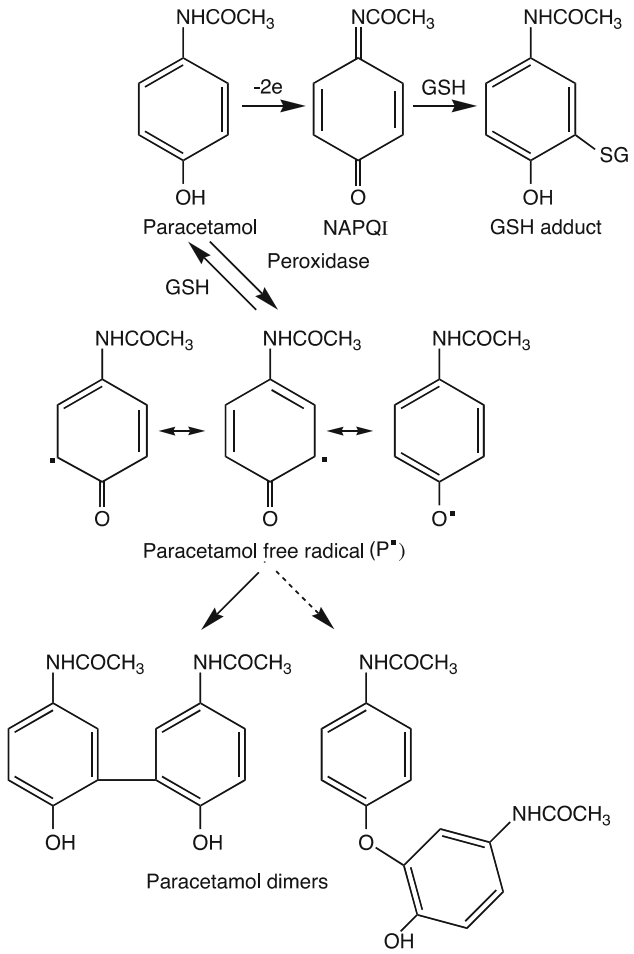


Fig. 5 Metabolism of paracetamol by the peroxidase function of COX isoenzymes and by myeloperoxidase. Three of the five canonical forms of the free radical of paracetamol (P·) are shown. The radical–radical interaction yields at least two dimers of paracetamol, the major being 3,3′diparacetamol. Two-electron oxidation by cytochrome P450 produces the hepatotoxic metabolite *N*-acetyl-*p*-quinone imine (NAPQI) which is deactivated by reaction with glutathione (GSH). Some NAPQI is also formed by the peroxidase function of the COX isoenzymes

minor splice variants (COX-1b$_2$) does have enzymatic activity (Qin et al. 2005). However, paracetamol shows no preferential inhibition of this isoform in a cell free system and, as expected, the IC_{50} is very high (>2 mmol/L) (see "Reasons for the apparent COX-2 selectivity of paracetamol" section).

A second problem has not been considered widely but may very well invalidate the COX-3 hypothesis as the major molecular site of action of paracetamol. This comes from consideration of the kinetic details of the original finding (Graham and Scott 2005). In the absence of paracetamol, insect cells containing COX-1 produced about five 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. As discussed above, paracetamol potently inhibits PG synthesis at low concentrations of arachidonic acid and at low rates of PG synthesis. Therefore, 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 COX-3 expressing cells.

A further problem for the acceptance of the COX-3 hypothesis is that only one study has compared the sensitivity to paracetamol of cells expressing COX-1, COX-2 and COX-3. Independent verification of this finding is required.

Action of paracetamol on diclofenac-induced COX-2

Supratherapeutic concentrations of diclofenac induce the formation of COX-2 in a macrophage cell line (Ayoub et al. 2011). In contrast to the loss of activity of paracetamol when high levels of peroxides are present in other cellular incubations (see "Reasons for the apparent COX-2 selectivity of paracetamol" section), a therapeutic concentration of paracetamol (10 μM) inhibits PG production by the macrophage cell line even when *t*-butyl hydroperoxide is added (Ayoub et al. 2011). However, an unusual result in these experiments was the absence of a concentration–response relationship with similar levels of inhibition at 10, 100 and 1,000 μM paracetamol. A problem in the interpretation of these results is that very high concentrations of diclofenac were removed from the cells by a single wash of the medium. Residual diclofenac may have reduced the cyclooxygenase activity sufficiently to allow paracetamol to inhibit PG production. Nevertheless, the results of Ayoub et al. (2011) should be studied further. The first is a more general examination of the induction of COX-2 by NSAIDs. The effect of paracetamol on this induced COX-2 has potential clinical significance and should also be examined.

Time-dependent pathways of PG synthesis and paracetamol action

As noted above, COX-1 is constitutive while COX-2 is often up-regulated by infection and inflammation. In the spinal cord, however, COX-2 is constitutive although still up-regulated by peripheral inflammation (Beiche et al. 1996). COX-1 is actually down-regulated in oral mucosa after oral surgery, and it has been suggested that paracetamol may inhibit COX-1 in the early stages of inflammation but with continuing inflammation, COX-2 is induced (Khan et al. 2007; Lee et al. 2007) and is then subject to inhibition by paracetamol.

Genetically mediated expression of COX-1 and COX-2

While the expression of COX-1 typically decreases after oral surgery and COX-2 is generally induced, there are wide inter-subject variations in the altered expression of the two enzymes. Such inter-patient variation has been associated with changes in the analgesic actions of ibuprofen and rofecoxib (Lee et al. 2006) and could also contribute to the variable response to paracetamol.

In summary, paracetamol often appears to show COX-2 selectivity but may inhibit COX-1 dependent PG synthesis in the presence of low levels of arachidonic acid. However, paracetamol is not entirely analogous to the selective COX-2 inhibitors because paracetamol also inhibits myeloperoxidase and other peroxidases (see "Inhibition of myeloperoxidase" section).

Relationship of COX-2 inhibition to the therapeutic and adverse actions of paracetamol

As outlined above, the pharmacological and toxicological effects of paracetamol are similar to those of the NSAIDs, particularly the COX-2 selective inhibitors, such as celecoxib and etoricoxib (Table 1). The ability of paracetamol to inhibit PG synthesis in cellular systems and in vivo provides good evidence for its primary action being inhibition of the synthesis of PGs and related factors.

Analgesia

There is considerable evidence that the analgesic effect of paracetamol is related to its inhibition of the synthesis of PGs and related factors. First, PGs potentiate the pain produced by pain mediators such as bradykinin and paracetamol inhibits bradykinin-induced pain in animal models (Botha et al. 1969). Second, paracetamol not only inhibits of PG synthesis but also decreases PGE_2 concentrations of in vivo simultaneously with it anti-nociceptive effects in experimental animals (Muth-Selbach et al. 1999; Lee et al. 2007; Crawley et al. 2008). Inhibition of the synthesis of PGs and related factors triggers changes in several neural systems (see "Linkages to other neuronal systems" section) but, taken together, the data suggest that the primary effect of paracetamol is its inhibition of the synthesis of PGs and related factors with changes in other neural pathways being secondary to this.

Antipyretic effect

Pyrogens increase the concentrations of PGE_2 in cerebrospinal fluid and mediates pyresis (Ivanov and Romanovsky 2004). This increase is blocked by paracetamol (Feldberg et al. 1973; Dey et al. 1974; Li et al. 2008). As is the case with the analgesic activity of paracetamol, the antipyretic activity appears to be due to COX-2 blockade, as no effect of paracetamol is seen in COX-2 knockout mice. Furthermore, lipopolysaccharide and interleukin-1β do not cause fever in COX-2 knockout mice but they do produce fever in COX-1 knockout mice. As COX-3 is a spice variant of COX-1, the antipyretic action of paracetamol cannot be due to inhibition of COX-3 (Li et al. 2008). Also, selective COX-2 inhibitors are antipyretic in man.

Anti-inflammatory effect

The major pharmacological difference between paracetamol and COX-2 inhibitors is the widely cited lack of effect of paracetamol on the inflammation of rheumatoid arthritis. Paracetamol is not acutely anti-inflammatory in rheumatoid arthritis (Boardman and Hart 1967; Ring et al. 1974; Table 3). Correspondingly, paracetamol does not suppress PGE_2 concentrations in synovial fluid in rheumatoid patients whereas the NSAIDs do (Seppala et al. 1985). However, paracetamol does suppress inflammation under conditions of lesser inflammation: after dental extraction (Bjørnsson et al. 2003), possibly in osteoarthritis and in a variety of inflammatory tests in experimental animals (Table 3). The suppression of low-grade inflammation by paracetamol may be due to low levels of arachidonic acid and/or peroxides; conditions where paracetamol is a potent inhibitor of PG synthesis (Fig. 3). Anti-inflammatory activity may be possible in rheumatoid arthritis with high doses but toxicity prevents this use.

Safety in the gastrointestinal tract

PGs are cytoprotective in the stomach and are synthesised by the combination of COX-1 and COX-2 activities and inhibition of both pathways is established as the major cause of the gastrointestinal toxicity of the non-selective NSAIDs. A great attribute of paracetamol is that it has no significant toxicity on the upper gastrointestinal tract (Graham et al. 2001). In this regard, paracetamol resembles the selective COX-2 inhibitors (Table 1) and is the major reason for the superior tolerance of paracetamol over the non-selective NSAIDs. As it has excellent gastrointestinal tolerance, paracetamol is a suitable mild analgesic for patients with a history of peptic ulcer (Nielsen et al. 2006). However, a loss $\geq$10 g/L haemoglobin has been reported in 7 % of patients treated with 3 g paracetamol daily (Doherty et al. 2011). This result may indicate gastrointestinal blood loss in some patients even though, on average, there is no significant decline in haemoglobin levels. Possibly, paracetamol produces some damage to the small intestine, as has been noted with celecoxib and etoricoxib.

Table 3 The variable anti-inflammatory effects of paracetamol

Method	Result in presence of paracetamol	Comments	References
No anti-inflammatory effect			
Circumference of fingers and thumbs (jewellers' rings)	No effect vs placebo	High dose of paracetamol (6 g daily)	Boardman and Hart (1967)
Thermography	No effect	Moderate dose of paracetamol (3 g daily)	Ring et al. (1974)
Positive anti-inflammatory effect			
Carrageenan induced pleurisy and adjuvant arthritis in rats	Both reduced by paracetamol		Vinegar et al. (1976)
Carrageenan inflammation of rat paws	Inflammation reduced		Glenn et al. (1977)
Adjuvant arthritis in rats	Inflammation and bone degeneration reduced	Synergistic activity of paracetamol and tolmetin	Wong and Gardocki (1983)
Carrageenan-induced inflammation of rat paws	Inflammation reduced.	Inflammation enhanced by arachidonic acid but enhanced inflammation was not inhibited by paracetamol	Lewis et al. (1975)
Carrageenan-induced inflammation of rat paws	Inflammation reduced	Concurrently decreased Fos in dorsal horn	Honore et al. (1995)
Local swelling after oral surgery in man	Swelling reduced by 30 % compared to placebo.		Løkken and Skjelbred (1980)
Local swelling after oral surgery in man	Swelling reduced by paracetamol (total 4 g daily)	Similar effect to ibuprofen (2,400 mg daily)	Bjørnsson et al. (2003)
Swelling after orthopaedic surgery in dogs.	Swelling reduced to very similar extent by paracetamol (33 %) compared to aspirin (24 %)		Mburu et al. (1988)
Synovial volume in osteoarthritis	Volume decreased to similar extent as ibuprofen	No placebo	Brandt et al. (2006)

Bronchoconstriction and asthma

Paracetamol precipitates asthma in about 7 % of aspirin-sensitive asthmatics although the syndrome is shorter and more easily treated than if caused by aspirin (Jenkins et al. 2004; Szczeklik et al. 2002; Table 1). The selective COX-2 inhibitors do not induce asthma in aspirin-sensitive asthmatics (Stevenson 2004) whereas the non-selective NSAIDs all cross-react with aspirin. The weak effect of paracetamol is consistent with its predominant selectivity for COX-2.

Despite the weak induction of acute asthma by paracetamol, several epidemiological studies indicate that paracetamol increases risk of asthma in children and adults (Etminan et al. 2009; Beasley et al. 2011). Exposure of children to asthma could occur by long-term changes in the expression of inflammatory mediators, but this mechanism does not explain the association between asthma and prenatal exposure to paracetamol (Shaheen et al. 2010; Eyers et al. 2011). The influence of prenatal dosage raises the possibility of an epigenetic phenomenon, i.e. an heritable change without changes in the DNA sequences.

There are suggestions that the association between paracetamol use in children and the development of asthma is confounded. Confounders may include the use of paracetamol in children with asthma leading to a greater risk of respiratory and ear infections and, consequently, more common treatment with paracetamol (Chang et al. 2011; Lowe et al. 2012). Most reviewers of this topic have stated that randomised prospective trials are required to determine if there is a causal relationship between paracetamol and asthma. This would, however, be a very difficult task. Nevertheless, it is rational to check respiratory function in children taking regular paracetamol.

The mechanism of any paracetamol-induced risk of asthma is unclear, but recent work in mice indicates that paracetamol produces localised inflammation and increases the expression of myeloperoxidase in the trachea (Nassini et al. 2010). These effects appear to be due to activation of transient receptor potential ankyrin-1 (TRPA1) cation

channel by NAPQI, the hepatotoxic metabolite of paracetamol, as these effects are produced by the intratracheal application of NAPQI and are not produced in TRPA1 knockout mice. As outlined in this review, inhibition of myeloperoxidase by paracetamol is considered as an anti-inflammatory effect but this effect on the trachea appears to be an inflammatory response to the drug. This up-regulation of myeloperoxidase requires careful examination in human studies.

Anti-platelet effect

Paracetamol has little anti-platelet activity, another point of similarity with the selective COX-2 inhibitors. Paracetamol does, however, inhibit the production of thromboxane A_2 and platelet aggregation at peak concentrations when used at high doses, particularly those achieved after intravenous dosage (Lages and Weiss 1989; Niemi et al. 2000; Munsterhjelm et al. 2003; Munsterhjelm et al. 2005); this activity is, however, lost rapidly because of the short half-life of paracetamol.

An advantage of paracetamol over the non-selective NSAIDs, such as ibuprofen and naproxen, is that paracetamol does not interfere with the antiplatelet activity of aspirin (Catella-Lawson et al. 2001; Gladding et al. 2008). Thus, paracetamol can be used with low-dose aspirin which is now widely used for the prevention of cardiac re-infarction. The selective COX-2 inhibitors also do not block the antiplatelet activity of aspirin. The lack of effect of both the paracetamol and selective COX-2 inhibitors is a factor adding to the apparent COX-2 selectivity of paracetamol.

Sites of action

Paracetamol is widely stated to have only a central site of action as opposed to peripheral sites of action of the NSAIDs and selective COX-2 inhibitors. This is incorrect. The theory of a preferential site of action of paracetamol in the central nervous system arose primarily from the widely cited work of Flower and Vane (1972) who found that paracetamol produced more potent inhibition of the synthesis of PGs and related factors in the microsomal fraction of rabbit brain than dog spleen. With the aid of hindsight, one can see that the experimental method was faulty in that the activity of the paracetamol was measured when the "cofactor" was hydroquinone, an oxidisable cofactor. The utility of using one phenol, hydroquinone, to measure the activity of another phenol, paracetamol, is unsound.

The peripheral site of action of NSAIDs came originally from the studies of Lim et al. (1964). By cross-perfusion experiments in dogs, Lim et al. (1964) concluded that the analgesic activity of aspirin was purely peripheral. However, many studies have now shown that NSAIDs, like paracetamol, have both central and peripheral actions (see below).

Central and peripheral sites of action of paracetamol

A significant site of action of paracetamol is the central nervous system where systemic administration inhibits the rise in central PGE_2 produced by peripheral application of pyrogens or painful stimuli (Feldberg et al. 1973; Muth-Selbach et al. 1999). Paracetamol also decreases PGE_2 production in the central nervous system after the intraperitoneal injection of acetic acid in mice (writhing test) (Ayoub et al. 2006).

A further indication of the central effect of paracetamol is the effect of injection of small doses of paracetamol directly into the central nervous system intrathecally (i.t.) or intracerebroventricularly (i.c.v.) (Table 4) (Malmberg and Yaksh (1992a); Alloui et al. (1996)). Paracetamol blocks the nociceptive behaviour produced by the i.t. administration of central neurotransmitters, including substance P (Crawley et al. 2008; Choi et al. 2001; Bjorkman et al. 1994), glutamate (Choi et al. 2001) and the 5-HT-3 receptor antagonist, tropisetron (Pelissier et al. 1996). All these observations indicate a central site of action of paracetamol.

There is also evidence for peripheral effects of paracetamol. For example, the local (intraplantar) injection of very small doses of paracetamol decreases neuropathic pain in rats (Dani et al. 2007) Low doses (approximately 30 mg) applied as a gel to the tooth socket also decrease pain after molar extraction, an indicator of a direct peripheral effect (Moore et al. 1992). Correspondingly, the systemic administration of paracetamol decreases pain and PGE_2 concentrations in surgical sites following removal of molar teeth (Lee et al. 2007). The same effect on PGE_2 occurs with rofecoxib. In vitro, paracetamol inhibits PG synthesis by a variety of peripheral cells as well as cells derived from the central nervous system (Graham and Scott 2005).

Overall, both central and peripheral actions of paracetamol are indicated.

Central and peripheral sites of action of NSAIDs and selective COX-2 inhibitors

The inhibition of the synthesis of PGs and related factors in peripheral systems has been widely observed with NSAIDs and selective COX-2 inhibitors. However, i.t. injections of classical NSAIDs and selective COX-2 inhibitors also have anti-nociceptive activity (Bannwarth et al. 1995; Nishiyama 2006). Furthermore, as discussed below, non-selective NSAIDs block the effects of i.t. injections of glutamate or substance P (Table 4), again indicating a central site of action of NSAIDs.

In summary, paracetamol, NSAIDs and selective COX-2 inhibitors all have both central and peripheral effects.

Table 4 Interactions of paracetamol, NSAIDs and selective COX-2 inhibitors with other neural systems and neurotransmitters

Interacting neurotransmitter and system	Principal results	References
Serotonin (5-hydroxytryptamine, 5-HT)	Antinociceptive effect of paracetamol is inhibited by:	
	5-HT-3 antagonists in mice	Alloui et al. (1996, 2002)
	5-HT-2 antagonist in rats	Ruggieri et al. (2008), Pelissier et al. (1996)
	5-HT-3 antagonist in humans	Pickering et al. (2006, 2008), Bandschapp et al. (2011)
	Destruction of descending 5-HT pathways by 5,7-dihydroxytryptamine in mice	Mallet et al. (2008)
	Depletion of brain content of 5-HT by *p*-chlorophenylalanine	Miranda et al. 2003
	Antinociceptive effect of aspirin is inhibited by 5-HT blockers and by *p*-chlorophenylalanine	Sandrini et al. (2002); Vitale et al. (1998)
	Anti-nociceptive effect of several NSAIDs and selective COX-2 inhibitors inhibited by blockade of 5-HT synthesis by depletion of brain 5-HT by *p*-chlorophenylalanine	Miranda et al. (2003)
Opioid	Anti-nociceptive effect of paracetamol inhibited by μ and κ opioid receptor antagonists in rats	Pini et al. (1997)
		Sandrini et al. (2001)
		Ruggieri et al. (2008)
	Analgesic effect of COX-2 inhibitors blocked by naltrexone	Franca et al. (2006)
	Analgesic effect of ketorolac in mice is reduced by naloxone	Domer (1990)
Cannabinoid	Anti-nociceptive effect of paracetamol blocked:	
	By CRB_1 antagonist	Ottani et al. (2006)
	In CRB_1 knockout mice	Mallet et al. (2008)
	By chronic exposure of mice to tetrahydrocannabinol	Anikwue et al. (2002)
	Cannabinoid receptor antagonists block the effects of local (intraplantar) injections of paracetamol	Dani et al. (2007)
	Anti-nociceptive effect of an i.c.v. cannabinoid agonist is enhanced by i.c.v. paracetamol	Ahn et al. (2007)
	Subeffective dose of paracetamol potentiates the anxiolytic effect of an endocannabinoid	Umathe et al. (2009)
	Anti-nociceptive effect of several NSAIDs and celecoxib is blocked by chronic exposure of mice to tetrahydrocannabinol	Anikwue et al. (2002)
	Anti-inflammatory effect of indomethacin is blocked by CB_2 antagonist in mice	Holt et al. (2005)
	Anti-nociceptive effect of indomethacin is blocked by CB_1 antagonist and in CB_1 knockout mice	Gühring et al. (2002), Ates et al. (2003)
Noradrenaline	Synergistic interaction with clonidine, an α_2 agonist which decreases sympathetic outflow from central nervous system	Miranda and Pinardi (2004)
	Synergistic interaction with phentolamine in abdominal constriction test in mice. Both drugs dosed i.t.	Raffa et al. (2001)
Acetylcholine	Synergistic interaction with acetylcholinesterase inhibitor (neostigmine) in abdominal constriction test in mice	Miranda et al. (2002)
Glutamate, *N*-methylaspartate and substance P	Paracetamol inhibits nociceptive behaviour of rats and mice after i.t. NMDA, glutamate or substance P	Bjorkman et al. (1994)
		Choi et al. (2001)
	NSAIDs decrease the excessive sensitivity to pain (hyperalgesia) induced by the activation of spinal glutamate and substance P receptors	Malmberg and Yaksh (1992b)
Nitric oxide (NO·)	Anti-nociceptive action of paracetamol after i.t. NMDA or substance P is reversed by precursor of NO·, L-arginine	Bjorkman et al. (1994)
	Inhibitors of NO· synthase potentiate anti-nociceptive effect of paracetamol.	Bujalska (2004)
	Paracetamol may inhibit NO· synthesis in the spinal cord.	Godfrey et al. (2007)
	Anti-nociceptive activity of i.t. indomethacin not shown in mice lacking inducible NO synthase (iNOS knockout mice)	Gühring et al. (2000)

Linkages to other neuronal systems

The anti-nociceptive actions of paracetamol are substantially linked to other neuronal systems. There are two general types of linkage to other systems. One type of linkage is essential to the activity of paracetamol and may even be activated by paracetamol. The analgesic activity of paracetamol is blocked by inhibitors of these systems. Most notably, the anti-nociceptive effects of paracetamol are decreased by inhibitors of serotonin (5-hydroxytryptamine, 5-HT), endogenous opioids, endogenous cannabinoids and possibly acetylcholine (Table 4).

A second general mechanism of interaction is provided by neurotransmitters or factors whose effects are inhibited by paracetamol. Blockers of systems involving these factors are expected to potentiate the anti-nociceptive action of paracetamol. Examples include the nociceptive effects of substance P, glutamate, fos and, possibly, noradrenaline (Table 4).

Both classes of anti-nociceptive effects can be related to inhibition of the synthesis of PGs and related factors by paracetamol as they are generally also shown by non-selective NSAIDs and selective COX-2 inhibitors (Table 4).

A significant problem in relating the therapeutic effect of paracetamol to neuronal systems is that experimental data are often inconsistent, with only some investigators observing positive results. Bannwarth et al. (1995) suggested that these inconsistencies were related to the bell-shaped dose–response relationships seen with the hyperalgesic effects of PGs (Uda et al. 1990). However, the full reasons for the inconsistencies remain to be resolved.

5-Hydroxytryptamine (5-HT, serotonin)

The maintenance or activation of some serotonergic systems is essential for the analgesic effect of paracetamol. This has been demonstrated convincingly in experimental animals (Table 4). The clinical involvement of 5-HT systems is indicated by the recent findings that the analgesic activity of paracetamol is decreased by the 5-HT3 receptor antagonists, tropisetron and granisetron, in human volunteers although ondansetron and tropisetron did not decrease the analgesic effect of paracetamol after surgery in man (Jokela et al. 2010; Pickering et al. 2011).

In rats, the analgesia produced by paracetamol is blocked by a 5-HT_{1A} receptor antagonist, but the analgesic activity of the NSAID, diclofenac, is not (Bonnefont et al. 2007). This result provides an argument for the analgesic activity of paracetamol being unrelated to inhibition of the COX enzymes. However, although the interaction of 5-HT mechanisms has been studied to a much lesser degree with NSAIDs or selective COX-2 inhibitors than with paracetamol, there are several studies indicating that the analgesic activity of the NSAIDs and COX-2 inhibitors appears to be dependent on intact central 5-HT systems (Table 4).

Opioids

The analgesic activity of paracetamol is reversed in experimental animals by opioid antagonists (Table 4), indicating that this action of paracetamol involves endogenous opioids. An indication of linkage between paracetamol and opioids and the further association with serotonergic systems is the observation that naloxone inhibits the paracetamol-induced increase in 5-HT and decreased 5-HT_2 receptors in the cerebral cortex (Pini et al. 1997). An interaction of COX-2 inhibitors with opioid systems is also evident as the opioid antagonist, naltrexone, can also block the analgesic effects of COX-2 inhibitors in rats (Table 4).

Possible effects of paracetamol on opioid systems in human have not been examined well. However, the analgesic effect of paracetamol has been reported to correlate with a decrease in the plasma concentrations of beta-endorphin in osteoarthritis (Shen et al. 2006).

Endogenous cannabinoids

Endocannabinoids are involved in spinal pathways of pain and the involvement of endocannabinoids in the analgesic action of paracetamol is indicated by its reduced activity under conditions of decreased activity of the endocannabinoid system (Table 4). As with interactions with 5-HT and endogenous opioids, an interaction with endocannabinoids is also shown by non-selective NSAIDs (Gühring et al. 2002; Ates et al. 2003; Fowler, 2004). Also, like a non-selective NSAID and a selective COX-2 inhibitor, paracetamol enhances the anti-nociceptive activity of a cannabinoid agonist in rats (Ahn et al. 2007).

Overall, it appears that maintenance of the endocannabinoid system contributes to the analgesic activity of paracetamol. Several mechanisms may contribute to the involvement of endocannabinoids in the analgesic actions of paracetamol and NSAIDs. First, COX inhibitors block the conversion of arachidonic acids to PGs and, consequently, the central metabolism of arachidonic acid may be diverted to endocannabinoids (Fowler 2004). A second mechanism may be direct inhibition of the COX-2 mediated oxygenation of endocannabinoids (see "Inhibition of the synthesis of PGs and related factors" section). Colocalisation of serotonergic and cannabinoid receptors within the central nervous system may also lead to crosstalk between the two systems (Hermann et al. 2002). As has been discussed above, the involvement of serotonergic

pathways in the analgesic activity of paracetamol could lead, in turn, to an interaction of paracetamol with cannabinoid systems.

Cholinergic systems

The anti-nociceptive activity of paracetamol shows synergistic activity with the well-known anticholinesterase, neostigmine, when the drugs are administered intraperitoneally or intrathecally (Table 4). Similar interactions are known with several non-selective NSAIDs and selective COX-2 inhibitors (Miranda et al. 2002). These results indicate that the maintenance of central cholinergic systems may be important in the actions of paracetamol.

Central noradrenergic systems

The anti-nociceptive activity of paracetamol is increased by clonidine, an α_2 agonist which decreases sympathetic tone (Table 4). As with other anti-nociceptive tests, the interaction with clonidine is produced with non-selective NSAIDs and selective COX-2 inhibitors. (Table 4; Miranda and Pinardi 2004) There are conflicting results with the non-selective α blocker, phentolamine, which has been associated with both potentiation (Raffa et al. 2001) and antagonism (Hu et al. 1994) of paracetamol-induced anti-nociception. The contrast may be related to the very different tests: abdominal irritation (Raffa et al. 2001) and stimulation of splanchnic nerve (Hu et al. 1994).

Glutamate and substance P

Paracetamol blocks the apparent nociceptive behaviour produced by the i.t. injection of both the excitatory amino acid, glutamate, and substance P (Table 4). Aspirin similarly inhibits the glutamate-induced nociceptive behaviour but appears inactive against substance P-induced nociception (Choi et al. 2001) while several NSAIDs inhibit the hyperalgesia produced by glutamate and substance P (Table 4).

Nitric oxide ($NO^{\cdot}$)

Although the data are sometimes conflicting, $NO^{\cdot}$ is generally considered to potentiate pain responses in the central nervous system (Hamza and Dionne 2009). It appears that the analgesic effect of paracetamol may involve $NO\cdot$ but the mechanism is unclear (Table 4).

Fos

Fos is an early response protein which is up-regulated in many cells following noxious stimuli and, in the spinal cord, is an indicator of neurone activation. Simultaneously with blockade of the inflammatory effect of intraplantar carrageenan, paracetamol decreases the number of neurones expressing Fos in the dorsal horn after the intraplantar injection in the rat (Honore et al. 1995; Abbadie and Besson 1994). Again, this effect is also shown by the non-selective NSAIDs, aspirin (Honore et al. 1995; Abbadie and Besson 1994), diclofenac (Buritova et al. 1995) and both intrathecal ketorolac and celecoxib (Lee and Seo 2008).

Spinal fos is down-regulated by the intrathecal injection of a NSAID and a selective COX-2 inhibitor indicating a local effect of these drugs on fos expression.

Action through the formation of N-arachidonylphenolamine (AM404)

A novel mechanism of action was indicated in 2005 when a bioactive paracetamol metabolite, N-arachidonylphenolamine, was found in mouse brain after dosage with paracetamol. (Högestätt et al. 2005) AM404 is a conjugate of arachidonic acid and *p*-aminophenol (*p*-hydroxyaniline) (Fig. 6). This metabolite inhibits endocannabinoid uptake (Beltramo et al. 2000) and has been considered an important mediator in the analgesic properties of paracetamol but, as far as we are aware, only one research paper

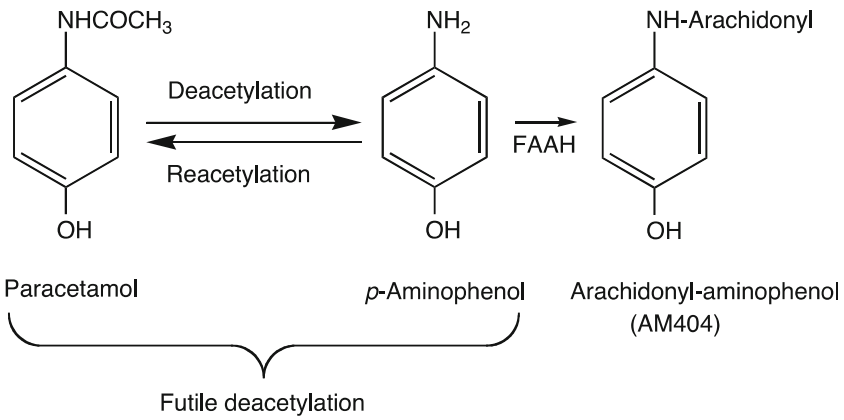


Fig. 6 Suggested metabolism of paracetamol to AM404 (arachidonyl conjugate of *p*-aminophenol) and the futile cycling of paracetamol by consecutive deacetylation and reacetylation. The main function of FAAH (fatty acid amide hydrolase) is to hydrolyse endocannabinoids, anandamide, but it may act in the reverse direction to synthesise AM404

Table 5 Experimental results in favour and against the hypothesis AM404 that is synthesised from paracetamol and mediates the pharmacological effects of paracetamol

In favour	Against
AM404 is present in mouse brain after dosage with paracetamol. The presumed intermediate *p*-aminophenol is also present (Fig. 6; Högestätt et al. 2005)	Deuterium labelled AM404 and *p*-aminophenol were detected in rat brain after the administration of deuterium-labelled paracetamol but no unlabelled AM404 or *p*-aminophenol was detected (see text) (Högestätt et al. 2005)
Inhibitors of fatty acid amide hydrolase (FAAH; Fig. 6) block the formation of AM404 (Högestätt et al. 2005) and analgesic effect (Mallet et al. 2008) of paracetamol	Inhibitor of FAAH does not block the action of paracetamol in the writhing test in mice (Soukupova et al. 2010)
AM404 has anti-nociceptive activity. AM404 inhibits allodynia in rats, an activity which is blocked by CB1 antagonist (Ruggieri et al. 2008)	Ketanserin blocks the anti-nociceptive action of paracetamol but not that of AM404 (Mitchell et al. 2007)
AM404 ($\geq$0.1 μM) inhibits the production of PGs which are mediators of pain, fever and inflammation (Högestätt et al. 2005)	Low concentrations of AM404 ($\sim$0.01 μM) present in rat brain do not appear sufficient to block COX-1 or COX-2 (Bertolini et al. 2006)

documents the synthesis of AM404 and the presence of *p*-aminophenol in vivo after the administration of paracetamol. Confirmation of the results of Högestätt et al. (2005) is required for support of the AM404 hypothesis.

Several findings question the AM404 hypothesis (Table 5). Not only are there problems in correlating the actions of paracetamol and AM404 but also, as noted above, the actions of paracetamol on peroxidases and the peroxidase function of COX isoenzymes are consistent with a direct inhibitory action of paracetamol on PG production without metabolism to AM404. It seems likely that paracetamol, as well as NSAIDs and selective COX-2 inhibitors, interact with endocannabinoid systems though their inhibition of the synthesis of PGs and related factors. These interactions are consistent with a COX-2 inhibitory role of paracetamol and do not require metabolism to AM404.

Metabolism of paracetamol through the intermediate, *p*-aminophenol, is however, supported by the futile deacetylation of paracetamol (Fig. 6; Nicholls et al. 1997). In this metabolic pathway, the acetyl group of 1–2 % of an oral dose is removed to form *p*-aminophenol which is then reacetylated to form paracetamol again. Further experimental evidence of this pathway of futile deacetylation is, however, required.

Genetic interactions and future possibilities

There are few reports of genetic interactions of paracetamol or NSAIDs. With the production of inflammation and pain in the formalin test in rats, paracetamol changes the expression of several spinal systems including increased expression of receptor for insulin-like growth factor-1. The insulin-like growth factor appears significant in paracetamol action because its analgesic activity is blocked by an antagonist of the receptor for the growth factor (Bonnefont et al. 2007). Up-regulation of phosphorylated (i.e. activated) ERK1/2 also occurs and has been also linked to paracetamol-induced analgesia. Unfortunately, the effects of NSAIDs and selective COX-2 inhibitors on these pathways have not been studied and it is not known if the upregulation seen with paracetamol is definitely related to inhibition of COX-1 or COX-2.

The upregulation of COX-2 is common in several inflammatory states. Paracetamol and rofecoxib further upregulate COX-2 gene expression after oral surgery in man although their influence is small compared with the change produced by the surgically induced inflammation and pain themselves (Lee et al. 2007). The expression of COX-2 in this peripheral system is very variable and may be partly responsible for the considerable inter-patient variation in the response to paracetamol and other selective COX-2 inhibitors (Lee et al. 2006). Interleukin 1β up-regulates the expression of COX-2 and, not surprisingly, there is up-regulation of the gene for interleukin 1β in this model, but neither paracetamol nor rofecoxib altered its expression (Lee et al. 2007).

Another feature of the oral surgical model is the approximately 20-fold increase in the gene expression for type IIA secretory phospholipase A_2 (Lee et al. 2006). This enzyme hydrolyses phospholipids to release arachidonic acid but also has an enzyme independent signalling function to up-regulate cytosolic phospholipase A_2 ($cPLA_2$) and COX-2 leading to greater PG synthesis (Bryant et al. 2011). The influence of paracetamol on the expression of this gene has not been recorded although ibuprofen and rofecoxib had no significant effect on its expression (Lee et al. 2006). Type IIA $sPLA_2$ is also present in other sites associated with pain and inflammation (e.g. rheumatoid synovium). Inhibitors of this enzyme have been developed and tested in rheumatoid arthritis, but although there was an initial effect, efficacy was not maintained over 1–2 months (Bradley et al. 2005). Interestingly, an inhibitor of $sPLA_2$ shows centrally mediated analgesic actions (Svensson et al. 2005).

It would be of interest to test the actions of inhibitors of $sPLA_2$, $cPLA_2$ or monoacylglycerol lipase (see "Inhibition

of the synthesis of PGs and related factors" section) with paracetamol to determine if decreased release of arachidonic acid potentiates the analgesic actions or even the anti-inflammatory effect of paracetamol. Sequential blockade could lead to marked reduction in PG synthesis although gastrointestinal damage could result from the generalised inhibition of the synthesis of PGs and related factors.

In the trachea of mice, paracetamol increases the expression of myeloperoxidase, an effect which, if also produced in humans, may increase the bronchoconstriction and asthma (see "Inhibition of myeloperoxidase" and bronchoconstriction and asthma sections).

Cardiovascular effects of paracetamol: adverse or beneficial?

Vascular effects

A major concern with the selective COX-2 inhibitors has been the increased tendency to thrombosis which has been correlated with their lack of anti-platelet effects and decreased synthesis of prostacyclin. This toxicity led to the withdrawal of the selective COX-2 inhibitor, rofecoxib. As discussed above, paracetamol appears to be a selective COX-2 inhibitor and it has been suggested that paracetamol may also show a similar pattern of adverse effects on the vascular system (Hinz et al. 2008; Hinz and Brune 2012). The effect of paracetamol on blood pressure is unclear (Table 1; see "Therapeutic and toxic actions—similarities and differences from NSAIDs" section). Major cardiovascular events may be increased by paracetamol although the effect was only seen in smokers (Chan et al. 2006). Of more concern is the finding from a large epidemiological study that paracetamol increases the risk of preeclampsia (Rebordosa et al. 2010). Again, this was suggested to be due to the imbalance in the prostacyclin and thromboxane A_2 caused by the COX-2 selectivity of paracetamol. Confirmation of this finding on pregnancy is, however, required.

Inhibition of myeloperoxidase and other peroxidases may largely overcome or reverse the effects of paracetamol on blood pressure and thrombosis due to selective inhibition of COX-2.

Inhibition of myeloperoxidase

As well as being an inhibitor of COX-1 and COX-2 through an action on its associated peroxidase function, paracetamol is also a substrate and inhibitor of myeloperoxidase, an enzyme in neutrophils and to a lesser extent in monocytes (Figs. 4, 5). Myeloperoxidase catalyses the formation of hypochlorous acid (HOCl) from hydrogen peroxide and chloride ions and the inappropriate production of HOCl is widely considered to be involved in the oxidative damage to tissues that are subject to acute or chronic inflammation (Davies 2011; Davies et al. 2008; van der Veen et al. 2009).

Paracetamol decreases the production of hypochlorite by myeloperoxidase with an IC_{50} value of about 80 μmol/L (Graham et al. 1999; Koelsch et al. 2010). Paracetamol also inhibits the activity of myeloperoxidase in intact neutrophils. As is the case with the peroxidase function of COX-1, inhibition of myeloperoxidase results from the oxidation of paracetamol to fluorescent polymers, mainly diparacetamol (Figs. 4, 5). Interestingly, the IC_{50} of the major dimer is approximately 38 μM and thus is approximately twice as potent as paracetamol itself (Kajer et al. unpublished).

As well as inhibiting the production of HOCl, paracetamol may inhibit the generation of other powerful oxidants by myeloperoxidase, including hypobromous acid, HOBr (from bromide ions; though this appears to be a relatively minor product) (Chapman et al. 2009; Morgan et al. 2011) and hypothiocyanous acid, HOSCN, from thiocyanate ions. The latter is potentially of major importance as markedly elevated levels of the precursor ion, thiocyanate (SCN^-), are present in some subjects, particularly smokers and those on particular diets, and this ion is the preferred substrate for the enzyme. Unlike HOCl and HOBr, which are relatively promiscuous oxidants that damage multiple targets, HOSCN is a highly selective oxidant of thiol groups and has been shown to have marked effects of cellular redox balance, cell signalling processes and apoptosis (Lloyd et al. 2008; Lane et al. 2010).

Nitrite is an anion which, like chloride, bromide and thiocyanate, may be involved in inflammatory processes. Nitrite is readily oxidised by compound I of myeloperoxidase (Burner et al. 2000; Fig. 4) and converts tyrosine residues of proteins to nitro tyrosine residues (Van der Vliet et al. 1997). As outlined below, paracetamol inhibits the oxidation of low-density lipoproteins by myeloperoxidase in the presence of nitrite. This effect of paracetamol may also be a significant aspect of its effects on inflammatory processes.

The production of HOCl is a mechanism of the antibacterial and anti-fungal actions of neutrophils, but other pathways are also important and inhibition of myeloperoxidase is unlikely to increase the likelihood of infections (Rosen and Michel 1997). This suggestion is supported by findings in people with naturally occurring MPO deficiency that show no effect on MPO deficiency on bacterial infection rates. However, the IC_{50} for paracetamol-induced inhibition of MPO is approximately 80 μM compared with

plasma concentrations fluctuating from about 13 to 200 μM (see "Chemistry and distribution" section). Consequently, inhibition of MPO by paracetamol appears only partial and it is unlikely that infections will be increased by paracetamol. There has been concern that antipyretics decrease immunological function but paracetamol does not appear to change the course of severe gram-negative sepsis (Mohr et al. 2012). Furthermore, paracetamol does not interfere significantly with bacterial killing by amoxycillin or cephalosporins in serum (Carsenti-Etesse et al. 1998).

Potential effects of paracetamol on factors involved in atherogenesis

Inhibition of myeloperoxidase by paracetamol may be of particular importance in decreasing the oxidation of both low- and high-density lipoproteins by HOCl. Oxidation of low-density lipoproteins is considered to be pro-atherogenic while damage to high-density lipoproteins may diminish their anti-atherogenic actions (Malle et al. 2006a, b). Compelling evidence has also been presented for the presence of myeloperoxidase in the subendothelial matrix of blood vessels (Baldus et al. 2001) in advanced atherosclerotic lesions that are liable to rupture (Daugherty et al. 1994; Sugiyama et al. 2001) and may be a mediator of pathological formation of neointima in atherosclerosis (Yang et al. 2006). More directly, low doses of paracetamol reduce the thickness and amount of oxidised protein in rat aorta (Rice et al. 2012) and have also been reported to decrease fatty streaks in the aortas of rabbits fed 1 % cholesterol although only abstracts of this latter work have been presented (Taylor et al. 1999).

Paracetamol inhibits the myeloperoxidase-induced chlorination of the amino groups of heparan sulphate and extracellular matrix (Koelsch et al. 2010). Heparan sulphate is a major component of the basement membrane of blood vessels and its chlorination and degradation may be important in the development of atherosclerosis and kidney disease (Nicholls and Hazen 2005; Malle et al. 2003). Therapeutic concentrations of paracetamol also decrease the nitrite-induced oxidation of low-density lipoproteins by myeloperoxidase (Chou and Greenspan 2002) and monocytes in vitro (Nenseter et al. 1995) and in vivo in experimental animals (Ozsoy and Pabuccuoglu 2007).

Overall, the cardiovascular effects of myeloperoxidase appear significant in the development of atherosclerotic lesions and, consequently, inhibition of myeloperoxidase by paracetamol could slow the development of atherosclerosis. There is sufficient evidence to indicate that paracetamol should be evaluated carefully in clinical trials on atherosclerosis.

Potential novel clinical effects of paracetamol

Effects of paracetamol on osteoarthritis and rheumatoid arthritis

Myeloperoxidase may be associated with the development of osteoarthritis. In early, although not in late osteoarthritis, there are elevated levels of myeloperoxidase and chlorinated proteins in synovial fluid (Steinbeck et al. 2007). Paracetamol has been linked to decreased volumes of synovial fluid in osteoarthritis, an indication of an anti-inflammatory effect, but more detailed clinical evaluation is required (Table 3). Very large numbers of neutrophils are present in the synovial fluid of patients with rheumatoid arthritis with the possibility of inflammatory effects from the myeloperoxidase in these cells.

It has been suggested that inhibition of myeloperoxidase could be a site of the action of thiol drugs, such as penicillamine, in the treatment of rheumatoid arthritis (Cuperus et al. 1985). Although penicillamine is not widely used now for the treatment of rheumatoid arthritis, inhibition of myeloperoxidase by paracetamol could provide long-term benefit in rheumatoid arthritis. This should be tested.

Inflammation is a feature common to both rheumatoid arthritis and atherosclerosis, and inhibition of both by paracetamol may have clinical potential.

Inhibition of ischaemia–reperfusion injury

An exciting new aspect of the pharmacology of paracetamol is that it may decrease ischaemia/reperfusion injury. Reperfusion of ischaemic tissues results in increased formation of oxidising free radicals that lead to tissue damage. Several studies have shown that paracetamol decreases tissue damage after reperfusion in experimental animals. The tissue damage that is decreased by paracetamol includes cerebral mitochondrial dysfunction (Baliga et al. 2010, 2011), arrhythmias (Merrill et al. 2007) and myocardial damage (Merrill et al. 2004; Zhu et al. 2006) after reperfusion. However, experimental studies are still inconsistent and no cardioprotective effect was found by Leshnower et al. (2006) in sheep and rabbits.

A novel effect of paracetamol is its inhibition of the up-regulation of osteopontin in the right cortex following ischaemia–reperfusion of the brain (Baliga et al. 2011). Osteopontin is a factor associated with several inflammatory responses including reperfusion injury. It is significant that these effects were produced at therapeutic doses (5–15 mg/kg). The data are, however, conflicting with an absence of activity of paracetamol in some ischaemia/reperfusion studies (Rork et al. 2006).

An activity of paracetamol analogous to its actions on ischaemia–reperfusion injury may be its attenuation of

neuronal cell death induced by menadione which is described as a "superoxide releasing oxidant stressor" (Tripathy and Grammas 2009). Pretreatment of neuronal cultures with paracetamol (25–300 μM) increases the survival of neurones and decreases the secretion of several inflammatory cytokines in cortical cultures exposed to menadione.

The mechanism of these positive actions of paracetamol is uncertain but a possibility is inhibition of myeloperoxidase. Despite the conflicting results, there are sufficient positive results for paracetamol to be evaluated in limiting stroke and myocardial infarction.

Attenuation of rhabdomyolysis

Rhabdomyolysis is due to muscle injury which releases myoglobin into the circulation resulting in acute renal impairment which can be very severe. The mechanism of the renal damage is thought to be redox cycling of the heme group in myoglobin resulting in the oxidation of lipoproteins and vasoconstriction. A recent study showed that the renal damage in a rat model of rhabdomyolysis is decreased by paracetamol (Boutaud et al. 2010). The mode of action of paracetamol in this situation appears to be similar to its inhibition of myeloperoxidase and the peroxide functions of COX-1 and COX-2, involving the oxidation of paracetamol to free radicals and dimers (Fig. 4; Boutaud and Roberts 2011). In view of the safety of paracetamol and the danger of rhabdomyolysis, it would seem advantageous to test the usefulness of paracetamol in this condition.

Inhibition of macrophage migration inhibitory factor (MIF)

MIF is considered to be an important cytokine in the development of rheumatoid arthritis and atherosclerosis and possibly also in diabetes and cancer. This cytokine also has enzymatic activities of keto–enol isomerism (tautomerase) (Fig. 7; Rosengren et al. 1997) and, possibly also, thiol-protein oxidoreductase activities (Kleemann et al. 1998). The significance of the tautomerase activity is unclear but this enzymatic action may be required for protein–protein interactions (Conroy et al. 2010). Paracetamol is an inhibitor of the tautomerase activity but the reported potency is very variable with IC_{50} values: from very low therapeutic levels of 1–3 μM (Molnar and Garai 2005) to grossly supratherapeutic concentrations of 10 mM (Senter et al. 2002). The hepatotoxic metabolite of paracetamol, NAPQI, is an inhibitor of the tautomerase with a quite a high IC_{50} of 46 μM (Senter et al. 2002). NAPQI does, however, decrease the immunoreactivity and cellular binding of MIF (Senter et al. 2002). Interestingly, when MIF is cocrystallized with NAPQI, the NAPQI is converted to a paracetamol dimer (Fig. 5) which binds reversibly to MIF (Crichlow et al. 2009).

The interactions between paracetamol and MIF are unclear but a significant interaction at therapeutic concentrations could lead to clinically important effects on rheumatoid arthritis, atherosclerosis and diabetes.

Antidiabetic actions

Paracetamol has antidiabetic actions in diabetes in mice produced by streptozotocin and high-fat diets (Shertzer et al. 2008; Kendig et al. 2008). Paracetamol also decreases the increase in body fat produced by the high-fat diet or olanzapine in mice (Kendig et al. 2008; Shertzer et al. 2010). The non-selective NSAIDs produce the same effects, indicating that these effects are produced by inhibition of the synthesis of PGs and related factors (Kendig et al. 2008; Shertzer et al. 2008). Salicylate also has some antidiabetic effects in man and is a further indication that COX inhibition causes the reduction in blood glucose (Desouza 2010).

It is significant that the antidiabetic actions of paracetamol are produced at relatively low doses (20–30 mg/kg daily) in mice, an indication of potential clinical effects in man.

Adaptations of muscle and tendon

Recent studies have shown surprising effects of paracetamol on muscle and tendon when its dosage was concurrent with resistance training of the quadriceps femoris muscle in adults aged more than 60 years. Treatment with paracetamol (4 g daily) together with resistance training of the quadriceps produced greater increases in muscle volume and strength than training alone (Trappe et al. 2011). The diameter of the patellar tendon also increased and there

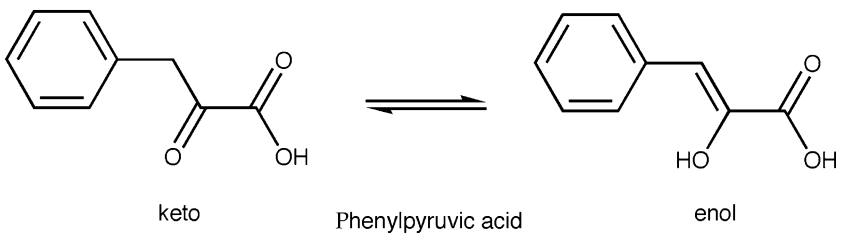


Fig. 7 Keto–enol tautomerism of phenylpyruvic acid catalysed by macrophage migration inhibitory factor (MIF)

were also changes in the mechanical properties of the tendon (Carroll et al. 2011). Ibuprofen produced similar changes to paracetamol in the muscle but not in the patellar tendon. The clinical significance of these changes is unclear but requires further study, particularly considering the wide use of paracetamol and the value of exercise in the treatment of osteoarthritis.

Cancer

Unlike the considerable amount of work showing that aspirin and the selective COX-2 inhibitors have potential value in the prevention and treatment of colon and other cancers, there has been little corresponding work on paracetamol. However, paracetamol may decrease the incidence of prostate cancer (Jacobs et al. 2011) although it may increase the rate of acute leukaemia and multiple myeloma (Robak et al. 2008). Conflicting influences of paracetamol on ovarian cancer have been reported with a decreased rate (Bonovas et al. 2006; Deffieux et al. 2007) whereas two studies have found no significant association with ovarian or endometrial cancer (Setiawan et al. 2012; Neill et al. 2012). Experimentally, paracetamol protected against induced colon cancer in rats (Williams et al. 2002).

Formulations of paracetamol

Several formulations of paracetamol are available including plain, effervescent and sustained release tablets, drops for children, suppositories and intravenous preparations. An injectable glycine ester of paracetamol, propacetamol, was used but has been replaced with a simple solution of paracetamol. The paracetamol in the presently available formulation contains 1 g paracetamol in 100 mL and can only be used by short intravenous infusion as the volume is too large to be administered intramuscularly or subcutaneously.

Levy (1980), a notable pioneer in pharmacokinetic research, contends that rapid absorption leads to a greater continuing analgesia of non-narcotic analgesics. According to this hypothesis, greater initial analgesia due to faster absorption leads to increased analgesia for several hours. Consistent with this hypothesis, greater continuing analgesia has been produced by intravenous paracetamol than oral paracetamol in at least one study (Jarde and Boccard 1997) although no such contrast was observed in another study (Moller et al. 2005).

There are conflicting data on the time course of analgesic activities of oral formulations of paracetamol. In agreement with Levy's hypothesis, no significant analgesia was seen after 2 g of sustained-release paracetamol although 0.5 and 1 g doses of immediate-release paracetamol showed analgesic activity in tests of experimental pain (Nielsen et al. 1992). The faster absorption of paracetamol when administered with caffeine is associated with greater overall analgesic activity of paracetamol (Renner et al. 2007). On the other hand, slower absorption has been associated with lesser initial analgesic effects, but more prolonged analgesia in other studies (Møller et al. 2000; Strom et al. 1990).

Concerns about the rate of absorption of paracetamol are significant for the formulation of sustained-release paracetamol. Presently marketed sustained-release tablets of paracetamol contain both immediate and sustained release layers. Although the data on the effect of rate of absorption are conflicting, it still seems optimal to combine fast and slow absorption components in the one tablet.

Adverse effects

The excellent tolerance, particularly the gastrointestinal tolerance of therapeutic doses of paracetamol, is a major reason for its recommendation and widespread acceptance as an analgesic.

Gastrointestinal tolerance

Paracetamol is generally tolerated well by the gastrointestinal tract (Latimer et al. 2009) This is in contrast to the well-known adverse effects of the non-selective NSAIDs. The introduction of the selective COX-2 inhibitors improved gastrointestinal tolerance but some adverse effects on the upper gastrointestinal tract remain (see "Therapeutic and toxic actions: similarities and differences from NSAIDs" section; Latimer et al. 2009).

The gastrointestinal tolerance of combinations of paracetamol and NSAIDs is more questionable. Large-scale clinical and epidemiological studies on paracetamol and non-selective NSAIDs indicate that the combination of paracetamol and a non-selective NSAID may produce greater gastrointestinal toxicity than either drug alone (Doherty et al. 2011; Rahme et al. 2008). In experimental animals, paracetamol (100 mg/kg) produces no significant gastric damage but the combination of paracetamol with meloxicam (0.9 mg/kg) or ibuprofen (100 mg/kg) produces greater gastric damage than meloxicam or ibuprofen alone (Kumar et al. 2010). Further work on the possible adverse gastrointestinal effects of combinations of paracetamol and NSAIDs is required.

Hepatotoxicity

Overdoses of paracetamol are well known to cause major hepatotoxicity which may progress to death if the dose is

sufficient and the patients are not treated adequately with *N*-acetylcysteine. Paracetamol poisoning is now the most common cause of acute liver failure in the United States and the United Kingdom.

The hepatotoxicity of paracetamol overdoses is due to the formation of the oxidised metabolite of paracetamol and its reaction with glutathione (Fig. 5). Glutathione, in its reduced form, maintains the appropriate redox balance in cells and prevents cell death. Centrilobular necrosis occurs because of depletion of glutathione and also because, after depletion of hepatocellular glutathione, the oxidised paracetamol metabolite reacts with essential cellular proteins. A variety of factors affect the hepatotoxicity of paracetamol but, apart from the contentious area of hepatotoxicity of therapeutic doses of paracetamol, are not reviewed in this communication.

Hepatotoxicity from therapeutic doses of paracetamol

Occasional hepatotoxicity is claimed widely but critical examination of cases shows that most patients whose toxicity is claimed from therapeutic doses have probably taken overdoses (Prescott 2000a; Graham et al. 2005). A background presentation to a FDA conference on paracetamol and hepatotoxicity contained the statement that "rare cases of acute liver injury have been linked to amounts lower than 2.5 g/day" but there was no comment on the difficulty in assigning hepatotoxicity to therapeutic doses of paracetamol (FDA Background 2009), as has been noted from a large USA survey (Larson et al. 2005).

Re-challenge of patients with hepatotoxicity from claimed therapeutic dosage is extremely uncommon. However, three patients with hepatotoxicity have been re-challenged with a rapid rise in transaminase concentrations in plasma detected (Graham and Scott 2005). Elevated plasma transaminases are also noted in some young patients during treatment with therapeutic doses of paracetamol (Watkins et al. 2006), but the high transaminase levels have declined or reverted to normal over time despite continuing dosage (Kuffner et al. 2006). An important recent observation is the comparative levels of alanine aminotransferase in hospitalised patients taking paracetamol. The levels of alanine aminotransferase were similar in older and younger patients despite higher plasma concentrations of paracetamol in the older patients (Mitchell et al. 2011). A further indication of the safety of therapeutic doses of paracetamol is that serious hepatotoxicity has never been recorded in prospective clinical trials on 30,865 patients (Dart and Bailey 2007). Admittedly, prospective trials are conducted in controlled conditions and patients with complex medical histories are often excluded. Nevertheless, the absence of any serious hepatotoxicity in clinical trials is a strong indicator of the safety of paracetamol.

Overall, the risk of severe hepatotoxicity from therapeutic doses appears extremely low.

FDA decision on dosage

The United States FDA recently limited the paracetamol content of prescription tablets to 325 mg, making the total daily dose of paracetamol 2,600 mg if eight tablets are taken daily.

Unintentional versus intentional overdose

In the UK, a great majority of overdoses are intentional (Makin and Williams 2000; Craig et al. 2011). There is conflicting data on the causes of hepatotoxicity in USA. In one survey of severe overdose from USA, 48 % reported unintentional overdosage with 44 % overdoses taken with suicidal intent (Larson et al. 2005). However, in two other surveys, approximately 70 % of overdoses were reported as intentional (Schiodt et al. 1997; Yarema et al. 2010). The numbers of unintentional overdoses have increased at a greater rate than intentional overdoses (Yarema et al. 2010).

The reasons for the high rate of unintentional overdose in USA are uncertain but, almost certainly, a contributing factor is the very high usage of combination tablets of paracetamol (presently 500 mg, to be reduced to 325 mg) with the potent opiates, hydrocodone or oxycodone. A recent survey in the USA indicates that even the prescribed dose of combination tablets yields more than the maximum paracetamol dose of 4 g daily in 8 % of all prescriptions (Mort et al. 2011). Further, most patients (63 %) with unintentional overdose were taking the combination of paracetamol and an opioid (Larson et al. 2005). Excessive dosage may be due not only to high prescribed doses but also to worsening pain leading to increased self-administration of both plain and combination tablets of paracetamol and opioids (Larson et al. 2005). Continued dosage of the opioids may increase the development of tolerance to the opioid with the subsequent increase in the dosage of the opioid and a greater subsequent dose of paracetamol.

The FDA requirement for a lower dose of paracetamol in the combination tablets is designed largely to reduce the problem of unintentional overdose although intentional overdosage may also be reduced. A more long-term improvement may be to restrict greatly the use of the full opioid/paracetamol combinations or to separate hydrocodone and oxycodone from the paracetamol (Larson et al. 2005).

The over-the-counter (OTC) sales of paracetamol are now restricted to small numbers of paracetamol tablets in blister packs in UK and many other countries. Surveys in England and Wales found that there were 765 fewer deaths

(43 % reduction) in the 11 years since the introduction of the small blister packs (Hawton et al. 2013). The causes of this reduced severe poisoning from paracetamol are still unclear but the uncontrolled availability of packs containing large numbers of plain paracetamol (up to 1,000) in USA is a clear danger for overdoses, particularly for children (Graham et al. 2010).

Alcohol and the risk of hepatotoxicity

The role of alcohol in the hepatotoxicity of paracetamol is contentious. Chronic alcohol abuse is recorded in about 50 % patients who have taken overdoses of paracetamol, whether these are unintentional or intentional (Makin and Williams 2000; Larson et al. 2005; Craig et al. 2011). Many alcoholics claim that they have taken only therapeutic doses of paracetamol, but obtaining reliable histories from these patients is notoriously difficult and the ingestion of no more than therapeutic doses in alcoholic subjects is almost certainly grossly overstated (Prescott 2000b; Dart et al. 2000). A recent prospective trial indicated that the hepatotoxicity of therapeutic doses of paracetamol is not increased in newly abstinent alcoholic patients who should have been most sensitive to the hepatotoxicity of paracetamol due to up-regulation of oxidising cytochrome P450 systems (Dart et al. 2010).

Although evidence for a causal relationship between alcohol and paracetamol-induced hepatotoxicity is weak (Graham et al. 2005), the FDA has required all formulations containing paracetamol to be labelled with an alcohol warning, namely that the patient should ask their doctor if they should take paracetamol if they consume three or more alcoholic drinks per day. As far as we are aware, this labelling is not required in other countries.

Hepatotoxicity and malnutrition

Several case studies of hepatotoxicity have included statements that patients have developed hepatotoxicity from therapeutic doses of paracetamol when they have not been eating well or fasting. Causal relationships are, however, difficult to establish (Lauterburg 2002). More directly, the metabolism of paracetamol is not changed in obese patients during food restriction (Schenker et al. 2001).

Interactions

A feature of the clinical use of paracetamol is its small number of interactions with other drugs although, not surprisingly, opioids and NSAIDs, potentiate the analgesic actions of paracetamol (see "Clinical analgesic efficacy of paracetamol" section).

Apart from the mutual potentiation with other analgesics, paracetamol also can potentiate the anticoagulant effects of warfarin, and clotting tests should be conducted if paracetamol treatment is added or removed from the treatment of patients taking warfarin. Paracetamol does not have sufficient anti-platelet effect to potentiate the anticoagulant effect of warfarin and the interaction is due to paracetamol decreasing the synthesis of vitamin K-dependent clotting factors (Mahe et al. 2006).

There has been much concern about the potential effects of other drugs, including alcohol, on the oxidative metabolism and hepatotoxicity of paracetamol. Substantial hepatotoxicity from therapeutic doses of paracetamol appears unlikely (see "Hepatotoxicity from therapeutic doses of paracetamol" section), but a proven interaction is the extended half-life of paracetamol when taken with probenecid (Abernethy et al. 1985). The dosage of paracetamol should then be decreased to a maximum of 3 g daily.

Comparative activities of paracetamol and other phenols

The literature now contains many studies on plant phenolics with similar overall pharmacology to paracetamol. An example is the well-known complex phenol and potential anti-cancer agent, resveratrol (Fig. 8), which has similar pharmacological activities to paracetamol (Table 6). Further work is, however, required to compare resveratrol and

Table 6 Some pharmacological properties of resveratrol which are also shown by paracetamol

Pharmacological action	References
Centrally mediated analgesia in rats	Falchi et al. (2010)
Antipyresis	Sebai et al. (2009)
Oxidation by myeloperoxidase and inhibition of HOCl production	Kohnen et al. (2007)
Inhibition of prostaglandin synthesis in vitro	Wendeburg et al. (2009)
Inhibition of up-regulation of osteopontin	Sutra et al. (2008)
Inhibition of tautomerism activity of MIF	Molnar and Garai (2005)

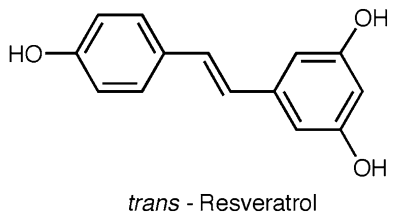


Fig. 8 Structure of resveratrol

paracetamol in the same studies to determine if the two phenols have similar molecular mechanisms. In particular, the literature does not appear to answer one crucial question: are resveratrol or other plant phenols selective inhibitors of cellular PG synthesis at low rates of peroxide tone, in a similar fashion to paracetamol?

The pharmacokinetics of paracetamol differs from that of other phenols, particularly the more complex phenols. The distinctive features of the clinical pharmacology of paracetamol are that it is well absorbed and attains very high plasma concentrations (up to about 30 μg/mL; see "Chemistry and distribution" section). After a large dose of resveratrol (5 g), the peak plasma concentrations of resveratrol are much lower at about 2 μg/mL and are very variable (Howells et al. 2011). Further work to optimise the absorption of resveratrol and other complex phenols is required. Possibly, more lipid soluble prodrugs may be useful.

As outlined above, paracetamol inhibits COX-1, COX-2, myeloperoxidase and rhabdomyolysis through the formation of free radicals. Similarly, resveratrol is converted to free radicals and dimerised by reactions with oxymyoglobin and peroxynitrite (Brito et al. 2002). The conversion of both paracetamol and resveratrol to free radicals raises the possibility of interactions between the radicals of paracetamol and resveratrol or other plant phenols although no data are available as yet.

Conclusions

Paracetamol is a familiar drug with widespread prescription and non-prescription use and there is little doubt that paracetamol will continue to be a useful analgesic in acute and chronic settings, both alone and in combination with NSAIDs and opioids. It has a remarkable safety record and minimal interactions with other drugs. Hepatotoxicity at excessive doses is a clear problem but the evidence for toxicity at doses up to 4 g/day is questionable. Paracetamol has a superior side-effect profile to other analgesics. The debate regarding the balance between recognising the efficacy and regulation to limit adverse effects of paracetamol continues.

The mechanism of action of paracetamol is clearly linked to PG pathways and the consequent interaction with other pain pathways. New indications for its use as an antioxidant are being investigated, particularly effects related to inhibition of myeloperoxidase.

References

Abbadie C, Besson JM (1994) Chronic treatments with aspirin or acetaminophen reduce both the development of polyarthritis and Fos-like immunoreactivity in rat lumbar spinal cord. Pain 57:45–54

Abernethy DR, Greenblatt DJ, Ameer B, Shader RI (1985) Probenecid impairment of acetaminophen and lorazepam clearance: direct inhibition of ether glucuronide formation. J Pharmacol Exp Ther 234:345–349

Ahn DK, Choi HS, Yeo SP et al (2007) Blockade of central cyclooxygenase (COX) pathways enhances the cannabinoid-induced antinociceptive effects on inflammatory temporomandibular joint (TMJ) nociception. Pain 132:23–32

Aljadhey H, Tu W, Hansen RA, Blalock SJ, Brater DC, Murray MD (2012) Comparative effects of non-steroidal anti-inflammatory drugs (NSAIDs) on blood pressure in patients with hypertension. BMC Cardiovasc Disord 12:93. doi:10.1186/1471-2261-12-93

Alloui A, Pelissier T, Dubray C, Lavarenne J, Eschalier A (1996) Tropisetron inhibits the antinociceptive effect of intrathecally administered paracetamol and serotonin. Fundam Clin Pharmacol 10:406–407

Alloui A, Chassaing C, Schmidt J et al (2002) Paracetamol exerts a spinal, tropisetron-reversible, antinociceptive effect in an inflammatory pain model in rats. Eur J Pharmacol 443:71–77

American Geriatrics Society Panel on Chronic Pain in Older Persons (1998) The management of chronic pain in older persons. J Am Geriatr Soc 46:635–651

Anikwue R, Huffman JW, Martin ZL, Welch SP (2002) Decrease in efficacy and potency of nonsteroidal anti-inflammatory drugs by chronic Δ^9-tetracannabinol administration. J Pharmacol Exp Ther 303:340–346

Aronoff DM, Oates JA, Boutaud O (2006) New insights into the mechanism of action of acetaminophen: its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H_2 synthases. Clin Pharmacol Ther 79:9–19

Ates M, Hamza M, Seidel K, Kotalla CE, Ledent C, Guhring H (2003) Intrathecally applied flurbiprofen produces an endocannabinoid-dependent antinociception in the rat formalin test. Eur J Neurosci 17:597–604

Axelsson B, Stellborn P, Strom G (2008) Analgesic effect of paracetamol on cancer related pain in concurrent strong opioid therapy. A prospective clinical study. Acta Oncol 47:891–895

Ayoub SS, Colville-Nash PR, Willoughby DA, Botting RM (2006) The involvement of a cyclooxygenase 1 gene-derived protein in the anti-nociceptive action of paracetamol. Eur J Pharmacol 538:57–65

Ayoub SS, Joshi A, Chol M, Gilroy DW, Seed MP (2011) Inhibition of the diclofenac-induced cyclooxygenase-2 activity by paracetamol in cultured macrophages is not related to the intracellular lipid hydroperoxide tone. Fundam Clin Pharmacol 25:186–190

FDA Background (2009) http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM164897.pdf. Last Accessed 22 January 2011

Baldus S, Eiserich JP, Mani A et al (2001) Endothelial transcytosis of myeloperoxidase confers specificity to vascular ECM proteins as targets of tyrosine nitration. J Clin Invest 108:1759–1770

Baliga SS, Jaques-Robinson KM, Hadzimichalis NM, Golfetti R, Merrill GF (2010) Acetaminophen reduces mitochondrial dysfunction during early cerebral postischemic reperfusion in rats. Brain Res 1319:142–154

Baliga SS, Merrill GF, Shinohara ML, Denhardt DT (2011) Osteopontin expression during early cerebral ischemia-reperfusion in rats: enhanced expression in the right cortex is suppressed by acetaminophen. PLoS ONE 6:e14568

Bambai B, Kulmacz RJ (2000) Prostaglandin H synthase. Effects of peroxidase cosubstrates on cyclooxygenase velocity. J Biol Chem 275:27608–27614

Bandschapp O, Filitz J, Urwyler A, Koppert W, Ruppen W (2011) Tropisetron blocks analgesic action of acetaminophen: a human pain model study. Pain 152:1304–1310

Bannwarth B, Demotes-Mainard F, Schaeverbeke T, Labat L, Dehais J (1995) Central analgesic effects of aspirin-like drugs. Fundam Clin Pharmacol 9:1–7

Beasley RW, Clayton TO, Crane J et al (2011) Acetaminophen use and risk of asthma, rhinoconjunctivitis, and eczema in adolescents: International Study of Asthma and Allergies in Childhood Phase Three. Am J Respir Crit Care Med 183:171–178

Beiche F, Scheuerer S, Brune K, Geisslinger G, Goppelt-Struebe M (1996) Up-regulation of cyclooxygenase-2 mRNA in the rat spinal cord following peripheral inflammation. FEBS Lett 390:165–169

Belay ED, Bresee JS, Holman RC, Khan AS, Shahriari A, Schonberger LB (1999) Reye's syndrome in the United States from 1981 through 1997. N Engl J Med 340:1377–1382

Beltramo M, de Fonseca FR, Navarro M et al (2000) Reversal of dopamine D2 receptor responses by an anandamide transport inhibitor. J Neurosci 20:3401–3407

Bertolini A, Ferrari A, Ottani A, Guerzoni S, Tacchi R, Sheila Leone S (2006) Paracetamol: new vistas of an old drug. CNS Drug Rev 12:250–275

Bjorkman R, Hallman KM, Hedner J, Hedner T, Henning M (1994) Acetaminophen blocks spinal hyperalgesia induced by NMDA and substance P. Pain 57:259–264

Bjørnsson GA, Haanaes HR, Skoglund LA (2003) A randomized double-blind crossover trial of paracetamol 1000 mg four times daily vs ibuprofen 600 mg: effect on swelling and other postoperative events after third molar surgery. Br J Clin Pharmacol 55:405–412

Boardman PL, Hart FD (1967) Clinical measurement of the anti-inflammatory effects of salicylates in rheumatoid arthritis. Med J Aust 4:264–268

Bonnefont J, Daulhac L, Etienne M et al (2007) Acetaminophen recruits spinal p42/p44 MAPKs and GH/IGF-1 receptors to produce analgesia via the serotoninergic system. Mol Pharmacol 71:407–415

Bonovas S, Filioussi K, Sitaras NM (2006) Paracetamol use and risk of ovarian cancer: a meta-analysis. Br J Clin Pharmacol 62:113–121

Botha B, Müller FO, Krueger FGM, Melnitzky H, Vermaak L, Louw L (1969) Quantitative assessment of analgesia conferred by various analgesics, as determined by blocking the intra-arterial bradykinin-evoked pain-response in the rat. Eur J Pharmacol 6:312–321

Boutaud OL, Roberts LJ (2011) Mechanism-based therapeutic approaches to rhabdomyolysis-induced renal failure. Free Rad Biol Med 51:1062–1067

Boutaud O, Aronoff DM, Richardson JH, Marnett LJ, Oates JA (2002) Determinants of the cellular specificity of acetaminophen as an inhibitor of prostaglandin H_2 synthases. Proc Natl Acad Sci USA 99:7130–7135

Boutaud O, Moore KP, Reeder BJ et al (2010) Acetaminophen inhibits hemoprotein-catalyzed lipid peroxidation and attenuates rhabdomyolysis-induced renal failure. Proc Natl Acad Sci USA 107:2699–2704

Bouvy ML, Heerdink ER, Hoes AW, Leufkens HG (2003) Effects of NSAIDs on the incidence of hospitalisations for renal dysfunction in users of ACE inhibitors. Drug Saf 26:983–989

Bradley JD, Dmitrienko AA, Kivitz AJ et al (2005) A randomized, double-blinded, placebo-controlled clinical trial of LY333013, a selective inhibitor of group II secretory phospholipase A2, in the treatment of rheumatoid arthritis. J Rheumatol 32:417–423

Brandt KD, Mazzuca SA, Buckwalter KA (2006) Acetaminophen, like conventional NSAIDs, may reduce synovitis in osteoarthritic knees. Rheumatology (Oxford) 45:1389–1394

Brito P, Almeida LM, Dinis TC (2002) The interaction of resveratrol with ferrylmyoglobin and peroxynitrite; protection against LDL oxidation. Free Rad Res 36:621–631

Bryant KJ, Bidgood MJ, Lei PW et al (2011) A bifunctional role for group IIa secreted phospholipase A_2 in human rheumatoid fibroblast-like synoviocyte arachidonic acid metabolism. J Biol Chem 286:2492–2503

Bujalska M (2004) Effect of nitric oxide synthase inhibition on antinociceptive action of different doses of acetaminophen. Pol J Pharmacol 56:605–610

Buritova J, Honore P, Chapman V, Besson JM (1995) Concurrent reduction of inflammation and spinal Fos-LI neurons by systemic diclofenac in the rat. Neurosci Lett 188:175–178

Burner U, Furtmuller PG, Kettle AJ, Koppenol WH, Obinger C (2000) Mechanism of reaction of myeloperoxidase with nitrite. J Bol Chem 275:20597–20601

Carroll CC, Dickinson JM, LeMoine JK et al (2011) Influence of acetaminophen and ibuprofen on in vivo patellar tendon adaptations to knee extensor resistance exercise in older adults. J Appl Physiol 111:508–515

Carsenti-Etesse H, Farinotti R, Durant J et al (1998) Pharmacokinetic parameters and killing rates in serum of volunteers receiving amoxicillin, cefadroxil or cefixime alone or associated with niflumic acid or paracetamol. Eur J Drug Metab Pharmacokinet 23:357–366

Catella-Lawson F, Reilly MP, Kapoor SC et al (2001) Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. N Engl J Med 345:1809–1817

Caughey GE, James MJ, Proudman SM, Cleland LG (2010) Fish oil supplementation increases the cyclooxygenase inhibitory activity of paracetamol in rheumatoid arthritis patients. Complement Ther Med 18:171–174

Chan AT, Manson JE, Albert CM et al (2006) Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. Circulation 113:1578–1587

Chandrasekharan NV, Dai H, Roos KL et al (2002) COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. Proc Natl Acad Sci USA 99:13926–13931

Chang KC, Leung CC, Tam CM, Kong FY (2011) Acetaminophen and asthma: spurious association? Am J Respir Crit Care Med 183:1570

Chapman AL, Skaff O, Senthilmohan R, Kettle AJ, Davies MJ (2009) Hypobromous acid and bromamine production by neutrophils and modulation by superoxide. Biochem J 417:773–781

Choi SS, Lee JK, Suh HW (2001) Antinociceptive profiles of aspirin and acetaminophen in formalin, substance P and glutamate pain models. Brain Res 921:233–239

Chou TM, Greenspan P (2002) Effect of acetaminophen on the myeloperoxidase-hydrogen peroxide-nitrite mediated oxidation of LDL. Biochim Biophys Acta 1581:57–63

Chou D, Abalos E, Gyte GM, Gülmezoglu AM (2010) Paracetamol/acetaminophen (single administration) for perineal pain in the early postpartum period. Cochrane Database Syst Rev 3:CD008407

Christo PJ, Mazloomdoost D (2008) Interventional pain treatments for cancer pain. Source Ann NY Acad Sci 1138:299–328

Colletti AE, Vogl HW, Rahe T, Zambraski EJ (1999) Effects of acetaminophen and ibuprofen on renal function in anesthetized normal and sodium-depleted dogs. J Appl Physiol 86:592–597

Conroy H, Mawhinney L, Donnelly SC (2010) Inflammation and cancer: macrophage migration inhibitory factor (MIF)—the potential missing link. Q J Med 103:831–836

Craig PN (1990) Drug compendium. In: Hansch C, Sammes PG, Taylor JB (eds) Comprehensive medicinal chemistry. Pergamon, Oxford, p 245

Craig DG, Bates CM, Davidson JS, Martin KG, Hayes PC, Simpson KJ (2011) Overdose pattern and outcome in paracetamol-induced acute severe hepatotoxicity. Br J Clin Pharmacol 71:273–282

Crawley B, Saito O, Malkmus S et al (2008) Acetaminophen prevents hyperalgesia in central pain cascade. Neurosci Lett 442:50–53

Crichlow GV, Lubetsky JB, Leng L, Bucala R, Lolis EJ (2009) Structural and kinetic analyses of macrophage migration inhibitory factor active site interactions. Biochemistry 48:132–139

Cuperus RA, Muijsers, Wever R (1985) Antiarthritic drugs containing thiol groups scavenge hypochlorite and inhibit its formation by myeloperoxidase from human leukocytes. A therapeutic mechanism of these drugs in rheumatoid arthritis? Arthritis Rheum 28:1228–1233

Curhan GC, Willett WC, Rosner B, Stampfer MJ (2002) Frequency of analgesic use and risk of hypertension in younger women. Arch Intern Med 162:2204–2208

Dani M, Guindon J, Lambert C, Beaulieu P (2007) The local antinociceptive effects of paracetamol in neuropathic pain are mediated by cannabinoid receptors. Eur J Pharmacol 573:214–215

Daniels SE, Goulder MA, Aspley S, Reader S (2011) A randomised, five-parallel-group, placebo-controlled trial comparing the efficacy and tolerability of analgesic combinations including a novel single-tablet combination of ibuprofen/paracetamol for postoperative dental pain. Pain 152:632–642

Dart RC, Bailey E (2007) Does therapeutic use of acetaminophen cause acute liver failure? Pharmacotherapy 27:1219–1230

Dart RC, Kuffner EK, Rumack BH (2000) Treatment of pain or fever with paracetamol (acetaminophen) in the alcoholic patient: a systematic review. Am J Ther 7:123–134

Dart RC, Green JL, Kuffner EK, Heard K, Sproule B, Brands B (2010) The effects of paracetamol (acetaminophen) on hepatic tests in patients who chronically abuse alcohol—a randomized study. Aliment Pharmacol Ther 32:478–486

Daugherty A, Dunn JL, Rateri DL, Heinecke JW (1994) Myeloperoxidase, a catalyst for lipoprotein oxidation, is expressed in human atherosclerotic lesions. J Clin Invest 94:437–444

Davies MJ (2011) Myeloperoxidase-derived oxidation: mechanisms of biological damage and its prevention. J Clin Biochem Nutr 48:8–19

Davies MJ, Hawkins CL, Pattison DI, Rees MD (2008) Mammalian heme peroxidases: from molecular mechanisms to health implications. Antioxid Redox Signal 10:1199–1234

Day RO, Graham GG (2005) Paracetamol should be first-line treatment in osteoarthritis. Med J Aust 182:198–199

de Maat MM, Tijssen TA, Bruggemann RJ, Ponssen HH (2010) Paracetamol for intravenous use in medium- and intensive care patients: pharmacokinetics and tolerance. Eur J Clin Pharmacol 66:713–719

Deffieux X, Touboul C, Uzan C et al (2007) Chemoprevention and prophylactic surgery in ovarian carcinoma. J Gynecol Obstet Biol Reprod 36:756–763

den Hertog HM, van der Worp HB, van Gemert HM, van Gijn J, Koudstaal PJ, Dippel DW (2012) Effects of high-dose paracetamol on blood pressure in acute stroke. Acta Neurol Scand 125:265–271

Desouza CV (2010) An overview of salsalate as a potential antidiabetic therapy. Drugs Today 46:847–853

Dey PK, Feldberg W, Gupta KP, Milton AS, Wendlandt S (1974) Further studies on the role of prostaglandin in fever. J Physiol 241:629–646

Doherty M, Hawkey C, Goulder M et al (2011) A randomised controlled trial of ibuprofen, paracetamol or a combination tablet of ibuprofen/paracetamol in community-derived people with knee pain. Ann Rheum Dis 70:1534–1541

Domer F (1990) Characterization of the analgesic activity of ketorolac in mice. Eur J Pharmacol 177:127–135

Duggan KC, Hermanson DJ, Musee J et al (2011) (R)-Profens are substrate-selective inhibitors of endocannabinoid oxygenation by COX-2. Nat Chem Biol 7:803–809

Etminan M, Sadatsafavi M, Jafari S, Doyle-Waters M, Aminzadeh K, Fitzgerald JM (2009) Acetaminophen use and the risk of asthma in children and adults: a systematic review and metaanalysis. Chest 136:1316–1323

Evans M, Fored CM, Bellocco R et al (2009) Acetaminophen, aspirin and progression of advanced chronic kidney disease. Nephrol Dial Transpl 24:1908–1918

Eyers S, Weatherall M, Jefferies S, Beasley R (2011) Paracetamol in pregnancy and the risk of wheezing in offspring: a systemic review and meta-analysis. Clin Exp Allergy 41:482–489

Falchi M, Bertelli A, Galazzo R, Vigano P, Dib B (2010) Central antalgic activity of resveratrol. Arch Ital Biol 148:389–396

Farquhar WB, Morgan AL, Zambraski EJ, Kenney WL (1999) Effects of acetaminophen and ibuprofen on renal function in the stressed kidney. J Appl Physiol 86:598–604

Feldberg W, Gupta KP, Milton AS, Wendlandt S (1973) Effect of pyrogen and antipyretics on prostaglandin activity in cisternal c.s.f. of unanaesthetized cats. J Physiol 234(2):279–303

Fiebich BL, Lieb K, Hull M et al (2000) Effects of caffeine and paracetamol alone or in combination with acetylsalicylic acid on prostaglandin E(2) synthesis in rat microglial cells. Neuropharmacology 39:2205–2213

Fletcher D, Benoist JM, Gautron M, Guilbaud G (1997) Isobolographic analysis of interactions between intravenous morphine, propacetamol, and diclofenac in carrageenin-injected rats. Anesthesiology 87:317–326

Flower RJ, Vane JR (1972) Inhibition of prostaglandin synthase in brain explains the antipyretic activity of paracetamol (4-acetamidophenol). Nature 240:410–411

Fored CM, Ejerblad E, Lindblad P et al (2001) Acetaminophen, aspirin, and chronic renal failure. N Engl J Med 345:1801–1808

Fowler CJ (2004) Possible involvement of the endocannabinoid system in the actions of three clinically used drugs. TIPS 25:59–61

Franca DS, Ferreira-Alves DL, Duarte IDG et al (2006) Endogenous opioids mediate the hypoalgesia induced by selective inhibitors of cyclo-oxygenase 2 in rat paws treated with carrageenan. Neuropharmacology 21:37–43

Gaskell H, Derry S, Moore RA, McQuay HJ (2009) Single dose oral oxycodone and oxycodone plus paracetamol (acetaminophen) for acute postoperative pain in adults. Cochrane Database Syst Rev 3:CD002763

Gazzard BG, Ford-Hutchinson AW, Smith MJ, Williams R (1973) The binding of paracetamol to plasma proteins of man and pig. J Pharm Pharmacol 25:964–967

Gladding P, Webster M, Farrell H, Zeng I, Park R, Ruijne N (2008) The Antiplatelet effect of six non-steroidal anti-inflammatory drugs and their pharmacodynamic interaction with aspirin in healthy volunteers. Am J Cardiol 101:1060–1063

Glenn EM, Bowman BJ, Rohloff NA (1977) Anti-inflammatory and PG inhibitory effects of phenacetin and acetaminophen. Agents Actions 7:513–516

Godfrey L, Yan L, Clarke GD, Ledent C, Kitchen I, Hourani SM (2006) Modulation of paracetamol antinociception by caffeine and by selective adenosine A2 receptor antagonists in mice. Eur J Pharmacol 531:80–86

Godfrey L, Bailey I, Toms NJ, Clarke GD, Kitchen I, Hourani SM (2007) Paracetamol inhibits nitric oxide synthesis in murine spinal cord slices. Eur J Pharmacol 562:68–71

Graham GG, Scott KF (2005) Mechanism of action of paracetamol. Am J Ther 12:46–55

Graham GG, Day RO, Milligan MK, Ziegler JB, Kettle AJ (1999) Current concepts of the actions of paracetamol (acetaminophen) and NSAIDs. Inflammopharmacology 7:255–263

Graham GG, Robins S-A, Bryant KJ, Scott KF (2001) Inhibition of prostaglandin synthesis in intact cells by paracetamol (acetaminophen). Inflammopharmacology 9:131–142

Graham GG, Scott KF, Day RO (2005) Tolerability of paracetamol. Drug Saf 28:227–240

Graham GG, Day RO, Graudins A, Mohamudally A (2010) FDA proposals to limit the hepatotoxicity of paracetamol (acetaminophen): are they reasonable? Inflammopharmacology 18:47–55

Gühring H, Görig M, Ates M et al (2000) Suppressed injury-induced rise in spinal prostaglandin E2 production and reduced early thermal hyperalgesia in iNOS-deficient mice. J Neurosci 20:6714–6720

Gühring H, Hamza M, Sergejeva M et al (2002) A role for endocannabinoids in indomethacin-induced spinal antinociception. Eur J Pharmacol 454:153–163

Hamza M, Dionne RA (2009) Mechanisms of non-opioid analgesics beyond cyclooxygenase enzyme inhibition. Curr Mol Pharmacol 2:1–14

Hanel AM, Lands WEM (1982) Modification of anti-inflammatory drug effectiveness by ambient lipid peroxides. Biochem Pharmacol 31:3307–3311

Harvison PJ, Egan RW, Gale PH, Christian GD, Hill BS, Nelson SD (1988) Acetaminophen and analogs as cosubstrates and inhibitors of prostaglandin H synthase. Chem Biol Interact 64:251–266

Hawton K, Bergen H, Simkin S et al (2013) Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: interrupted time series analyses. Br Med J 346. doi: 10.1136/bmj.f403

Hermann H, Marsicano G, Lutz B (2002) Coexpression of the cannabinoid receptor type 1 with dopamine and serotonin receptors in distinct neuronal subpopulations of the adult mouse forebrain. Neuroscience 109:451–460

Hersch M, Raveh D, Izbicki G (2008) Effect of intravenous propacetamol on blood pressure in febrile critically ill patients. Pharmacotherapy 28:1205–1210

Hinz B, Brune K (2012) Paracetamol and cyclooxygenase inhibition: is there a cause for concern? Ann Rheum Dis 71:20–25

Hinz B, Cheremina O, Brune K (2008) Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. FASEB J 22(2):383–390

Hochberg MC, Altman RD, April KT et al (2012) American College of Rheumatology 2012 Recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip and knee. Arthritis Care Res 64:465–474

Högestätt ED, Jönsson BA, Ermund A et al (2005) Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system. J Biol Chem 280:31405–31412

Holt S, Comelli F, Costa B, Fowler CJ (2005) Inhibitors of fatty acid amide hydrolase reduce carrageenan-induced hind paw inflammation in pentobarbital-treated mice: comparison with indomethacin and possible involvement of cannabinoid receptors. Br J Pharmacol 146:467–476

Honore P, Buritova J, Besson JM (1995) Aspirin and acetaminophen reduced both Fos expression in rat lumbar spinal cord and inflammatory signs produced by carrageenin inflammation. Pain 63:365–375

Howells LM, Berry DP, Elliott PJ et al (2011) Phase I randomized, double-blind pilot study of micronized resveratrol (srt501) in patients with hepatic metastases—safety, pharmacokinetics, and pharmacodynamics. Cancer Prev Res 4:1419–1425

Hu XH, Tang HW, Li QS, Huang XF (1994) Central mechanism of indomethacin analgesia. Eur J Pharmacol 263:53–57

IAHPC (2007) List of essential medicines for palliative care. http://www.hospicecare.com/resources/emedicine.htm

Ivanov AI, Romanovsky AA (2004) Prostaglandin E2 as a mediator of fever: synthesis and catabolism. Front Biosci 9:1977–1993

Jacobs EJ, Newton CC, Stevens VL, Gapstur SM (2011) A large cohort study of long-term acetaminophen use and prostate cancer incidence. Cancer Epidemiol Biomark Prev 20:1322–1328

Jadad AR, Browman GP (1995) The WHO analgesic ladder for cancer pain management. Stepping up the quality of its evaluation. JAMA 174:1870–1873

Jarde O, Boccard E (1997) Parenteral versus oral route increases paracetamol efficacy. Clin Drug Investig 14:474–481

Jenkins C, Costello J, Hodge L (2004) Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. Br Med J 328:434–437

Jokela R, Ahonen J, Seitsonen E, Marjakangas P, Korttila K (2010) The influence of ondansetron on the analgesic effect of acetaminophen after laparoscopic hysterectomy. Clin Pharmacol Ther 87:672–678

Jordan KM, Arden NK, Doherty M et al (2003) EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 62:1145–1155

Kendig EL, Schneider SN, Clegg DJ, Genter MB, Shertzer HG (2008) Over-the-counter analgesics normalize blood glucose and body composition in mice fed a high fat diet. Biochem Pharmacol 76:216–224

Khan AA, Iadarola M, Yang HY, Dionne RA (2007) Expression of COX-1 and COX-2 in a clinical model of acute inflammation. J Pain 8:349–354

Kis B, Snipes JA, Busija DW (2005a) Acetaminophen and the cyclooxygenase-3 puzzle: sorting out facts, fictions, and uncertainties. J Pharmacol Exp Ther 315:1–7

Kis B, Snipes JA, Busija DW (2005b) Response to comments on "Acetaminophen and the cyclooxygenase-3 puzzle: sorting out facts, fictions, and uncertainties". J Pharmacol Exp Ther 315:1415–1417

Kis B, Snipes JA, Simandle SA, Busija DW (2004) Acetaminophen-sensitive prostaglandin production in rat cerebral endothelial cells. Am J Physiol Regul Integr Comp Physiol 288:R897–R902

Kleemann R, Kapurniotu A, Frank RW et al (1998) Disulfide analysis reveals a role for macrophage migration inhibitory factor (MIF) as a thiol-protein oxidoreductase. J Mol Biol 280:85–102

Koelsch M, Mallak R, Graham GG et al (2010) Acetaminophen (paracetamol) inhibits myeloperoxidase-catalyzed oxidant production and biological damage at therapeutically achievable concentrations. Biochem Pharmacol 79:1156–1164

Kohnen S, Franck T, van Antwerpen P et al (2007) Resveratrol inhibits the activity of equine neutrophil myeloperoxidase by a direct interaction with the enzyme. J Agric Food Chem 55:8080–8087

Koppert W, Frotsch K, Huzurudin N et al (2006) The effects of paracetamol and parecoxib on kidney function in elderly patients undergoing orthopedic surgery. Anesth Analg 103:1170–1176

Kuffner EK, Temple AR, Cooper KM, Baggish JS, Parenti DL (2006) Retrospective analysis of transient elevations in alanine aminotransferase during long-term treatment with acetaminophen in osteoarthritis clinical trials. Curr Med Res Opin 22:2137–2148

Kumar G, Hota D, Saikia UN, Pandhi P (2010) Evaluation of analgesic efficacy, gastrotoxicity and nephrotoxicity of fixed-dose combinations of nonselective, preferential and selective cyclooxygenase inhibitors with paracetamol in rats. Exp Toxicol Pathol 62:653–662

Kummer O, Hammann F, Moser C, Schaller O, Drewe J, Krahenbuhl S (2011) Effect of the inhibition of CYP3A4 or CYP2D6 on the pharmacokinetics and pharmacodynamics of oxycodone. Eur J Pharmacol 67:67–71

Lages B, Weiss HJ (1989) Inhibition of human platelet function in vitro and ex vivo by acetaminophen. Thromb Res 53:603–613

Laine L, White W, Rostom A, Hochberg M (2008) COX-2 selective inhibitors in the treatment of osteoarthritis. Semin Arthritis Rheum 38:165–187

Lane AE, Tan JT, Hawkins CL, Heather AK, Davies MJ (2010) The myeloperoxidase-derived oxidant HOSCN inhibits protein tyrosine phosphatases and modulates cell signalling via the mitogen-activated protein kinase (MAPK) pathway in macrophages. Biochem J 430:161–169

Larson AM, Polson J, Fontana RJ et al (2005) Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 42:1364–1372

Latimer N, Lord J, Grant RL, O'Mahony R, Dickson J, Conaghan PG (2009) Cost effectiveness of COX 2 selective inhibitors and traditional NSAIDs alone or in combination with a proton pump inhibitor for people with osteoarthritis. Br Med J 339:b2538

Lauterburg BH (2002) Analgesics and glutathione. Am J Ther 9:225–233

Lee IO, Seo Y (2008) The effects of intrathecal cyclooxygenase-1, cyclooxygenase-2, or nonselective inhibitors on pain behavior and spinal Fos-like immunoreactivity. Anesth Analg 106:972–977

Lee YS, Kim H, Wu TX, Wang XM, Dionne RA (2006) Genetically mediated interindividual variation in analgesic responses to cyclooxygenase inhibitory drugs. Clin Pharmacol Ther 79:407–418

Lee YS, Kim H, Brahim JS, Rowan J, Lee G, Donne RA (2007) Acetaminophen selectively suppresses peripheral prostaglandin E2 release and increases COX-2 gene expression in a clinical model of acute inflammation. Pain 129:279–286

Leshnower BG, Sakamoto H, Zeeshan A et al (2006) Role of acetaminophen in acute myocardial infarction. Am J Physiol Heart Circul Physiol 290:H2424–H2431

Levy G (1980) Clinical pharmacokinetics of salicylates: a re-assessment. Br J Clin Pharmacol 10(Suppl 2):285S–290S

Lewis AJ, Nelson DJ, Sugrue MF (1975) On the ability of prostaglandin E1 and arachidonic acid to modulate experimentally induced oedema in the rat paw. Br J Pharmacol 55:51–56

Li S, Dou W, Tang Y, Goorha S, Balou LR, Blatteis CM (2008) Acetaminophen: antipyretic or hypothermic in mice? In either case, PGHs-1b is irrelevant. Prostaglandins Lipid Mediat 85:89–99

Lim RK, Guzman F, Rodgers DW et al (1964) Site of action of narcotic and non-narcotic analgesics determined by blocking bradykinin-evoked visceral pain. Arch Int Pharmacodyn Ther 152:25–58

Lloyd MM, van Reyk DM, Davies MJ, Hawkins CL (2008) Hypothiocyanous acid is a more potent inducer of apoptosis and protein thiol depletion in murine macrophage cells than hypochlorous acid or hypobromous acid. Biochem J 414:271–280

Loboz KK, Shenfield GM (2005) Drug combinations and impaired renal function—the 'triple whammy'. Br J Clin Pharmacol 59:239–243

Løkken P, Skjelbred P (1980) Analgesic and anti-inflammatory effects of paracetamol evaluated by bilateral oral surgery. Br J Clin Pharmacol 10:253S–260S

Lowe AJ, Dharmage SC, Lodge CJ, Abramson MJ, Allen KJ (2012) Does the evidence really indicate that acetaminophen causes asthma? http://pediatrics.aappublications.org/content/128/6/1181. Accessed 25 Apr 2013

Lucas R, Warner TD, Vojnovic I, Mitchell JA (2005) Cellular mechanisms of acetaminophen; role of cyclo-oxygenase. FASEB J 19:635–637

Macario A, Royal MA (2011) A literature review of randomized clinical trials of intravenous acetaminophen (paracetamol) for acute postoperative pain. Pain Practice 11:290–296

Mahe I, Bertrand N, Drouet L et al (2006) Interaction between paracetamol and warfarin in patients: a double-blind, placebo-controlled, randomized study. Haematologia 91:1621–1627

Makin A, Williams R (2000) Paracetamol hepatotoxicity and alcohol consumption in deliberate and accidental overdose. Q J Med 93:341–349

Malle E, Buch T, Grone HJ (2003) Myeloperoxidase in kidney disease. Kidney Int 64:1956–1957

Malle E, Marsche G, Arnhold J, Davies MJ (2006a) Modification of low-density lipoprotein by myeloperoxidase-derived oxidants and reagent hypochlorous acid. Biochim Biophys Acta 1761:392–415

Malle E, Marsche G, Panzenboeck U, Sattler W (2006b) Myeloperoxidase-mediated oxidation of high-density lipoproteins: fingerprints of newly recognized potential proatherogenic lipoproteins. Arch Biochem Biophys 445:245–255

Mallet C, Daulhac L, Bonnefont J et al (2008) Endocannabinoid and serotonergic systems are needed for acetaminophen-induced analgesia. Pain 139:190–200

Malmberg AB, Yaksh TL (1992a) Antinociceptive actions of spinal nonsteroidal anti-inflammatory agents on the formalin test in the rat. J Pharmacol Exp Ther 263:136–146

Malmberg AB, Yaksh TL (1992b) Hyperalgesia mediated by spinal glutamate or substance P receptor blocked by spinal cyclooxygenase inhibition. Science 257:1276–1279

Maund E, McDaid C, Rice S et al (2011) Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction of morphine-related side-effects after major surgery: a systematic review. Br J Anaesth 106:292–297

Mburu DN, Mbugua SW, Skoglund LA, Lokken P (1988) Effects of paracetamol and acetylsalicylic acid on the post-operative course after experimental orthopaedic surgery in dogs. J Vet Pharmacol Ther 11:163–171

Merlo J, Broms K, Lindblad U et al (2001) Association of outpatient utilisation of non-steroidal anti-inflammatory drugs and hospitalised heart failure in the entire Swedish population. Eur J Clin Pharmacol 57:71–75

Merrill GF, Merrill JH, Golfetti R et al (2007) Antiarrhythmic properties of acetaminophen in the dog. Exp Biol Med 232:1245–1252

Merrill GF, Rork TH, Spiler NM, Golfetti R (2004) Acetaminophen and myocardial infarction in dogs. Am J Physiol - Heart Circul Physiol 287(5):H1913–H1920

Milder TY, Williams KM, Richie JE, Lipworth WL, Day RO (2010) Use of NSAIDs for osteoarthritis amongst older-aged primary care patients: engagement with information and perceptions of risk. Age Ageing 43:254–259

Miranda HF, Pinardi G (2004) Isobolographic analysis of the antinociceptive interactions of clonidine with nonsteroidal anti-inflammatory drugs. Pharmacol Res 50:273–278

Miranda HF, Sierralta F, Pinardi G (2002) Neostigmine interactions with non steroidal anti-inflammatory drugs. Br J Pharmacol 135:1591–1597

Miranda HF, Lemus I, Pinardi G (2003) Effect of the inhibition of serotonin biosynthesis on the noceception induced by nonsteroidal anti-inflammatory drugs. Brain Res Bull 61:417–425

Miranda HF, Puig MM, Prieto JC, Pinardi G (2006) Synergism between paracetamol and nonsteroidal anti-inflammatory drugs in experimental acute pain. Pain 121:22–28

Miranda HF, Prieto JC, Puig MM, Pinardi G (2008) Isobolographic analysis of multimodal analgesia in an animal model of visceral acute pain. Pharmacol Biochem Behav 88:481–486

Mitchell VA, Greenwood R, Jayamanne A, Vaughan CW (2007) Actions of the endocannabinoid transport inhibitor AM404 in neuropathic and inflammatory pain models. Clin Exp Pharmacol Physiol 34:1186–1190

Mitchell SJ, Hilmer SN, Murnion BP, Matthews S (2011) Hepatotoxicity of therapeutic short-course paracetamol in hospital inpatients: impact of ageing and frailty. J Clin Pharm Ther 36:327–335

Mohr N, Skrupky L, Fuller B et al (2012) Early antipyretic exposure does not increase mortality in patients with gram-negative severe sepsis: a retrospective cohort study. Int Emerg Med 7:463–470

Moller PL, Sindet-Pedersen S, Petersen CT, Juhl GI, Dillenschneider A, Skoglund LA (2005) Onset of acetaminophen analgesia: comparison of oral and intravenous routes after third molar surgery. Br J Anaes 94:642–648

Møller PL, Nørholt SE, Ganry HE et al (2000) Time to onset of analgesia and analgesic efficacy of effervescent acetaminophen 1000 mg compared to tablet acetaminophen 1000 mg in postoperative dental pain: a single-dose, double-blind, randomized, placebo-controlled study. J Clin Pharmacol 40:370–378

Molnar V, Garai J (2005) Plant-derived anti-inflammatory compounds affect MIF tautomerase activity. Int Immunopharmacol 5:849–856

Moore UJ, Seymour RA, Rawlins MD (1992) The efficacy of locally applied aspirin and acetaminophen in postoperative pain after third molar surgery. Clin Pharmacol Ther 52:292–296

Morgan PE, Pattison D, Talib J et al (2011) High plasma thiocyanate levels in smokers are a key determinant of thiol oxidation induced by myeloperoxidase. Free Rad Biol Med 51:1815–1822

Mort JR, Shiyanbola OO, Ndehi LN, Xu Y, Stacy JN (2011) Opioid-paracetamol prescription patterns and liver dysfunction: a retrospective cohort study in a population served by a US health benefits organization. Drug Saf 34:1079–1088

Munsterhjelm E, Niemi TT, Syrjälä MT, Ylikorkala O, Rosenberg PH (2003) Propacetamol augments inhibition of platelet function by diclofenac in volunteers. Br J Anaes 91:357–362

Munsterhjelm E, Niemi TT, Ylikorkala O, Silvanto M, Rosenberg PH (2005) Characterization of inhibition of platelet function by paracetamol and its interaction with diclofenac in vitro. Acta Anaesthesiol Scand 49:840–846

Murakami M, Naraba H, Tanioka T et al (2000) Regulation of prostaglandin E2 biosynthesis by membrane-associated prostaglandin E2 synthase that acts in concert with cyclooxygenase-2. J Biol Chem 276:32783–32792

Murray MD, Black PK, Kuzmik DD et al (1995) Acute and chronic effects of nonsteroidal antiinflammatory drugs on glomerular filtration rate in elderly patients. Am J Med Sci 310:188–197

Muth-Selbach US, Tegeder I, Brune K, Geisslinger G (1999) Acetaminophen inhibits spinal prostaglandin E2 release after peripheral noxious stimulation. Anesthesiology 91:231–239

Nabulsi M (2009) Is combining or alternating antipyretic therapy more beneficial than monotherapy for febrile children? Br Med J 339:b3540

Nassini R, Materazzi S, Andre E et al (2010) Acetaminophen, via its reactive metabolite *N*-acetyl-*p*-benzo-quinoneimine and transient receptor potential ankyrin-1 stimulation, causes neurogenic inflammation in the airways and other tissues in rodents. FASEB J 24:4904–4916

Neill AS, Nagle CM, Protani MM et al (2012) Aspirin, nonsteroidal anti-inflammatory drugs, paracetamol and risk of endometrial cancer: a case-control, systematic review and meta-analysis. Int J Cancer

Nenseter MS, Halvorsen BN, Rosvold Ø, Rustan AC, Devon CA (1995) Paracetamol inhibits copper ion-induced, azo compound-initiated, and mononuclear cell-mediated oxidative modification of LDL. Arterioscler Thromb Vasc Biol 15:1338–1344

Nicholls SJ, Hazen SL (2005) Myeloperoxidase and cardiovascular disease. Arterioscler Thromb Vasc Biol 25:1102–1111

Nicholls AW, Farrant RD, Shockcor JP et al (1997) NMR and HPLC-NMR spectroscopic studies of futile deacetylation in paracetamol metabolites in rat and man. J Pharm Biomed Anal 15:901–910

Nielsen JC, Bjerring P, Arendt-Nielsen L, Petterson KJ (1992) Analgesic efficacy of immediate and sustained release paracetamol and plasma concentration of paracetamol. Double blind, placebo-controlled evaluation using painful laser stimulation. Eur J Clin Pharmacol 42:261–264

Nielsen OH, Ainsworth M, Csillag C, Rask-Madsen J (2006) Systematic review: coxibs, non-steroidal anti-inflammatory drugs or no cyclooxygenase inhibitors in gastroenterological high-risk patients? Aliment Pharmacol Ther 23:27–33

Niemi TT, Backman JT, Syrjälä MT, Viinikka LU, Rosenberg PH (2000) Platelet dysfunction after intravenous ketorolac or propacetamol. Acta Anaesthesiol Scand 44:69–74

Nikles JC, Yelland M, Del Mar C, Wilkinson D (2005) The role of paracetamol in chronic pain: an evidence-based approach. Am J Ther 12:80–91

Nishiyama T (2006) Analgesic effects of intrathecally administered celecoxib, a cyclooxygenase-2 inhibitor, in the tail flick test and the formalin test in rats. Acta Anaesthesiol Scand 50:228–233

Nomura DK, Morrison BE, Blankman JL et al (2011) Endocannabinoid hydrolysis generates brain prostaglandins that promote neuroinflammation. Science 2011:809–813

Ong CK, Seymour RA, Lirk P, Merry AF (2010) Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesth Analg 110:1170–1179

Ottani A, Leone S, Sandrini M, Ferrari A, Bertolini A (2006) The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. Eur J Pharmacol 531:280–281

Ozsoy MB, Pabuccuoglu A (2007) The effect of acetaminophen on oxidative modification of low-density lipoproteins in hypercholesterolemic rabbits. J Clin Biochem Nutr 41:27–31

Palmer H, Graham G, Williams K, Day R (2010) A risk-benefit assessment of paracetamol (acetaminophen) combined with caffeine. Pain Med 11:951–965

Pavlicevic I, Kuzmanic M, Rumboldt M, Rumboldt Z (2008) Interaction between antihypertensives and NSAIDs in primary care: a controlled trial. Can J Clin Pharmacol 15(3):e372–e382

Pelissier T, Alloui A, Caussade F et al (1996) Paracetamol exerts a spinal antinociceptive effect involving an indirect interaction with 5-hydroxytryptamine3 receptors: in vivo and in vitro evidence. J Pharmacol Exp Ther 278:8–14

Pickering G, Loriot MA, Libert F, Eschalier A, Beaune P, Dubray C (2006) Analgesic effect of acetaminophen in humans: first evidence of a central serotonergic mechanism. Clin Pharmacol Ther 79:371–378

Pickering G, Esteve V, Loriot MA, Eschalier A, Dubray C (2008) Acetaminophen reinforces descending inhibitory pain pathways. Clin Pharmacol Ther 84:47–51

Pickering G, Faure M, Commun F et al (2011) Tropisetron and paracetamol association in post-operative patients. Fundam Clin Pharmacol 26:432–437

Pini LA, Vitale G, Ottani A, Sandrini M (1997) Naloxone-reversible antinociception by paracetamol in the rat. J Pharmacol Exp Ther 280:934–940

Podrez EA, Schmitt D, Hoff HF, Hazen SL (1999) Myeloperoxidase-generated reactive nitrogen species convert LDL into an atherogenic form in vitro. J Clin Invest 103:1547–1560

Potter DW, Hinson JA (1987) The 1- and 2-electron oxidation of acetaminophen catalyzed by prostaglandin H synthase. J Biol Chem 262:974–980

Prescott LF (2000a) Therapeutic misadventure with paracetamol: fact or fiction. Am J Ther 7:99–114

Prescott LF (2000b) Paracetamol, alcohol and the liver. Br J Clin Pharmacol 49:291–301

Prescott LF, Speirs GC, Critchley JA, Temple RM, Winney RJ (1989) Paracetamol disposition and metabolite kinetics in patients with chronic renal failure. Eur J Clin Pharmacol 36:291–297

Qin N, Zhang SP, Reitz TL, Mei JM, Flores CM (2005) Cloning, expression, and functional characterization of human cyclooxygenase-1 splicing variants: evidence for intron 1 retention. J Pharmacol Exp Ther 315:1298–1305

Radack KL, Deck CC, Bloomfield SS (1987) Ibuprofen interferes with the efficacy of antihypertensive drugs. A randomized, double-blind, placebo-controlled trial of ibuprofen compared with acetaminophen. Ann Intern Med 107:628–635

Raffa RB, Codd EE (1996) Lack of binding of acetaminophen to 5-HT receptor or uptake sites (or eleven other binding/uptake assays). Life Sci 59:37–40

Raffa RB, Stone DJ, Tallarida RJ (2001) Unexpected and pronounced antinociceptive synergy between spinal acetaminophen (paracetamol) and phentolamine. Eur J Pharmacol 412:R1–R2

Raffa RB, Walker EA, Sterious SN (2004) Opioid receptors and acetaminophen (paracetamol). Eur J Pharmacol 503:209–210

Rahme E, Barkun A, Nedjar H, Gaugris S, Watson D (2008) Hospitalizations for upper and lower GI events associated with traditional NSAIDs and acetaminophen among the elderly in Quebec, Canada. Am J Gastroenterol 103:872–882

Rawlins MD, Henderson DB, Hijab AR (1977) Pharmacokinetics of paracetamol (acetaminophen) after intravenous and oral administration. Eur J Clin Pharmacol 11:283–286

Rebordosa C, Zelop CM, Kogevinas M, Sørensen HT, Olsen J (2010) Use of acetaminophen during pregnancy and risk of preeclampsia, hypertensive and vascular disorders: a birth cohort study. J Matern Fetal Neonat Med 23:371–378

Remy C, Marret E, Bonnet F (2005) Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. Br J Anaesth 94:505–513

Renner B, Clarke G, Grattan T et al (2007) Caffeine accelerates absorption and enhances the analgesic effect of acetaminophen. J Clin Pharmacol 47:715–726

Rice KM, Meduru S, Kakarla SK et al (2012) Chronic paracetamol treatment influences indices of reactive oxygen species accumulation in the aging Fischer 344 X Brown Norway rat aorta. Ann Clin Lab Sci 42:152–161

Ring EFJ, Collins AJ, Bacon PA, Cosh J (1974) Quantitation of thermography in arthritis using multi-isothermal analysis. II. Effect of nonsteroidal anti-inflammatory therapy on the thermographic index. Ann Rheum Dis 33:353–356

Robak J, Wieckowski A, Gryglewski R (1978) The effect of 4-acetamidophenol on prostaglandin synthetase activity in bovine and ram seminal vesicle microsomes. Biochem Pharmacol 27:393–396

Robak P, Smolewski P, Robak T (2008) The role of non-steroidal anti-inflammatory drugs in the risk of development and treatment of hematologic malignancies. Leuk Lymphoma 49:1452–1462

Rork TH, Hadzimichalis M, Baliga SS, Golfetti R, Merrill GF (2006) New perspectives on acetaminophen. Curr Cardiol Rev 2:131–146

Rosen H, Michel BR (1997) Redundant contribution of myeloperoxidase-dependent systems to neutrophil-mediated killing of *Escherichia coli*. Infect Immun 65:4173–4178

Rosengren E, Åman P, Thelin S et al (1997) The macrophage migration inhibitory factor (MIF) is a phenylpyruvate tautomerase. FEBS Lett 417:85–88

Ruggieri V, Vitale G, Pini LA, Sandrini M (2008) Differential involvement of opioidergic and serotonergic systems in the antinociceptive activity of *N*-arachidonoyl-phenolamine (AM404) in the rat: comparison with paracetamol. Naunyn Schmiedebergs Arch Pharmacol 377:219–229

Rumack BH (1978) Aspirin versus acetaminophen: a comparative view. Pediatrics 62(5 Pt 2 Suppl):943–946

Sandrini M, Romualdi P, Capobianco A et al (2001) The effect of paracetamol on nociception and dynorphin A levels in the rat brain. Neuropeptides 35:110–116

Sandrini M, Vitale G, Pini LA (2002) Central antinociceptive activity of acetylsalicylic acid is modulated by brain serotonin receptor subtypes. Pharmacology 65:193–197

Schenker S, Speeg KV, Perez A, Finch J (2001) The effects of food restriction in man on hepatic metabolism of acetaminophen. Clin Nutr 20:145–150

Schildknecht S, Daiber A, Ghisla S, Cohen RA, Bachschmid MM (2008) Acetaminophen inhibits prostanoid synthesis by scavenging the PGHS-activator peroxynitrite. FASEB J 22:215–224

Schiodt FV, Rochling FA, Casey DL, Lee WM (1997) Acetaminophen toxicity in an urban county hospital. N Engl J Med 337:1112–1117

Schwab JM, Beiter T, Linder JU et al (2003) COX-3: a virtual pain target in humans? FASEB J 17:2174–2175

Sebai H, Ben-Attia M, Sani M, Aouani E, Ghanem-Boughanmi N (2009) Protective effect of resveratrol in endotoxemia-induced acute phase response in rats. Arch Toxicol 83:335–340

Seideman P (1993) Addiitive effect of combined naproxen and paracetamol in rheumatoid arthritis. Br J Rheumatol 32:1077–1082

Seideman P, Melander A (1988) Equianalgesic effects of paracetamol and indomethacin in rheumatoid arthritis. Br J Rheumatol 27:117–122

Senter PD, Al-Abed Y, Metz CN et al (2002) Inhibition of macrophage migration inhibitory factor (MIF) tautomerase and biological activities by acetaminophen metabolites. Proc Natl Acad Sci USA 99:144–149

Seo YJ, Kwon MS, Choi HW et al (2008) The differential effects of acetaminophen on lipopolysaccharide induced hyperalgesia in various mouse pain models. Pharmacol Biochem Behav 91:121–127

Seppala E, Nissila M, Isomaki H et al (1985) Comparison of the effects of different anti-inflammatory drugs on synovial fluid prostanoid concentrations in patients with rheumatoid arthritis. Clin Rheumatol 4:315–320

Setiawan VW, Matsuno RK, Lurie G, Wilkens LR, Carney ME, Henderson B et al (2012) Use of nonsteroidal anti-inflammatory

drugs and risk of ovarian and endometrial cancer: the Multiethnic Cohort. Cancer Epidem Biomark Prev 21:1441–1449
Shaheen SO, Newson RB, Ring SM, Rose-Zerilli MJ, Holloway JW, Henderson AJ (2010) Prenatal and infant acetaminophen exposure, antioxidant gene polymorphisms, and childhood asthma. J Allergy Clin Immunol 126(1141):1148.e7
Shen H, Sprott H, Aeschlimann A et al (2006) Analgesic action of acetaminophen in symptomatic osteoarthritis of the knee. Rheumatology 45:765–770
Shertzer HG, Schneider SN, Kendig EL, Clegg DJ, D'Alessio DA, Genter MB (2008) Acetaminophen normalizes glucose homeostasis in mouse models for diabetes. Biochem Pharmacol 75:1402–1410
Shertzer HG, Kendig EL, Nasrallah HA, Johansson E, Genter MB (2010) Protection from olanzapine-induced metabolic toxicity in mice by acetaminophen andtetrahydroindenoindole. Int J Obes 34:970–979
Simmons DL, Chandrasekharan NV, Hu D, Roos KL, Tomsik J (2005) Comments on acetaminophen and the cyclooxygenase-3 puzzle: sorting out facts, fictions, and uncertainties. J Pharmacol Exp Ther 315:1412–1414
Snowden S, Nelson R (2011) The effects of nonsteroidal anti-inflammatory drugs on blood pressure in hypertensive patients. Cardiol Rev 19:184–191
Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S (2010) The comparative safety of analgesics in older adults with arthritis. Arch Int Med 170:1968–1976
Soukupova M, Palazzo E, De Chiaro M et al (2010) Effects of URB597, an inhibitor of fatty acid amide hydrolase (FAAH), on analgesic activity of paracetamol. Neuroendocrinol Lett 31:507–511
Steinbeck MJ, Nesti LJ, Sharkey PF, Parvizi J (2007) Myeloperoxidase and chlorinated peptides in osteoarthritis: potential biomarkers of the disease. J Orthopaed Res 25:1128–1135
Stevenson DD (2004) Aspirin and NSAID sensitivity. Immunol Allergy Clin N Am 24:495–505
Stjernsward J (1988) WHO cancer pain relief programme. Cancer Surv 7:195–208
Stockler M, Vardy J, Pillai A, Warr D (2004) Acetaminophen (paracetamol) improves pain and well-being in people with advanced cancer already receiving a strong opioid regimen: a randomized, double-blind, placebo-controlled cross-over trial. J Clin Oncol 22:3389–3394
Strom C, Forsberg O, Quiding H, Engevall S, Larsson O (1990) Analgesic efficacy of acetaminophen sustained release. J Clin Pharmacol 30:654–659
Sudano I, Flammer AJ, Periat D et al (2010) Acetaminophen increases blood pressure in patients with coronary artery disease. Circulation 122:1789–1796
Sudano I, Flammer AJ, Roas S, Enseleit F, Noll G, Ruschitzka F (2012) Nonsteroidal antiinflammatory drugs, acetaminophen, and hypertension. Curr Hypertens Rep 14:304–309
Sugiyama S, Okada Y, Sukhova GK, Virmani R, Heinecke JW, Libby P (2001) Macrophage myeloperoxidase regulation by macrophage colony-stimulating factor in human atherosclerosis and implications in acute coronary syndromes. Am J Pathol 158:399–403
Sutra T, Oiry C, Azay-Milhau J (2008) Preventive effects of nutritional doses of polyphenolic molecules on cardiac fibrosis associated with metabolic syndrome: involvement of osteopontin and stress. J Agric Food Chem 56:11683–11687
Svensson CI, Lucas KK, Hua XY, Powell HC, Dennis EA, Yaksh TL (2005) Spinal phospholipase A2 in inflammatory hyperalgesia: role of the small, secretory phosphlipase A2. Neuroscience 133:543–553
Swierkosz TA, Jordan L, McBride M, McGough K, Devlin J, Botting RM (2002) Actions of paracetamol on cyclooxygenases in tissue and cell homogenates of mouse and rabbit. Med Sci Monit 8:BR496–BR503
Szczeklik A, Nizankowska E, Mastalerz L, Szabo Z (2002) Analgesics and asthma. Am J Ther 9:233–243
Tasmacioglu B, Aydinli I, Keskinbora K et al (2009) Effect of intravenous administration of paracetamol on morphine consumption in cancer pain control. Support Care Cancer 17:1475–1481
Taylor AA, Raya JL, Rogers LK, Smith CV (1999) Acetaminophen inhibits fatty streak formation and LDL oxysterols in hypercholesterolemic rabbits. Circulation 100:1–697 (abstract 3677)
Temple AR, Benson GD, Zinsenheim JR, Schweinle JE (2006) Multicenter, randomized, double-blind, active-controlled, parallel-group trial of the long-term (6–12 months) safety of acetaminophen in adult patients with osteoarthritis. Clin Ther 28:222–235
Tjolsen A, Lund A, Hole K (1991) Antinociceptive effect of paracetamol in rats is partly dependent on spinal serotonergic systems. Eur J Pharmacol 193:193–201
Toms L, McQuay HJ, Derry S, Moore RA (2008) Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. Cochrane Database Syst Rev 4:CD004602
Toms L, Derry S, Moore RA, McQuay HJ (2009) Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. Cochrane Database Syst Rev 1:CD001547
Trappe TA, Carroll CC, Dickinson JM et al (2011) Influence of acetaminophen and ibuprofen on skeletal muscle adaptations to resistance exercise in older adults. Am J Physiol Reg Integr Comp Physiol 300:R655–R662
Tripathy D, Grammas P (2009) Acetaminophen inhibits neuronal inflammation and protects neurons from oxidative stress. J Neuroinflam 6:10
Tsang KS, Page J, Mackenney P (2013) Can intravenous paracetamol reduce opioid use in preoperative hip fracture patients? Orthopedics 36:20–24
Turtle EJK, Dear JW, Webb DJ (2012) A systematic review of the effects of paracetamol on blood pressure in hypertensive and non-hypertensive subjects. Br J Clin Pharmacol. doi: 10.1111/bcp.12032
Uda R, Horiguchi S, Ito S et al (1990) Nociceptive effects induced by intrathecal administration of prostaglandin D2, E2 or F2α to conscious mice. Brain Res 510:26–32
Umathe SN, Manna SS, Utturwar KS, Jain NS (2009) Endocannabinoids mediate anxiolytic-like effect of acetaminophen via CB1 receptors. Progr Neuro Psychopharmacol Biol Psychiatry 33:1191–1199
van der Veen BS, de Winther MP, Heeringa P (2009) Myeloperoxidase: molecular mechanisms of action and their relevance to human health and disease. Antioxid Redox Signal 11:2899–2937
Van der Vliet A, Eiserich JP, Halliwell B, Cross CE (1997) Formation of reactive nitrogen species during peroxidase-catalyzed oxidation of nitrite. A potential additional mechanism of nitric oxide-dependent toxicity. J Biol Chem 272:7617–7625
Vane JR (1971) Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol 231:232–235
Vinegar R, Truax JF, Selph JL (1976) Quantitative comparison of the analgesic and anti-inflammatory activities of aspirin, phenacetin and acetaminophen in rodents. Eur J Pharamacol 37:23–30
Vitale G, Pini LA, Ottani A, Sandrini M (1998) Effect of acetylsalicylic acid on formalin test and on serotonin system in the rat brain. Gen Pharmacol 31:753–758
Watkins PB, Kaplowitz N, Slattery JT et al (2006) Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized, controlled trial. JAMA 296:87–93
Wegman A, van der Windt D, van Tulder M et al (2004) Nonsteroidal antiinflammatory drugs or acetaminophen for osteoarthritis of

the hip or knee? A systematic review of evidence and guidelines. J Rheumatol 31:344–354
Weil K, Hooper L, Afzal Z et al (2007) Paracetamol for pain relief after surgical removal of lower wisdom teeth. Cochrane Database Syst Rev 3:CD004487
Wendeburg L, de Oliveira ACP, Bhatia HS, Candelario-Jalil E, Fiebich BL (2009) Resveratrol inhibits prostaglandin formation in IL-1β-stimulated SK-N-SH neuronal cells. J Neuroinflamm 6:26
Whelton A, Schulman G, Wallemark C et al (2000) Effects of celecoxib and naproxen on renal function in the elderly. Arch Intern Med 160:1465–1470
Williams HJ, Ward JR, Egger MJ et al (1993) Comparison of naproxen and acetaminophen in a two-year study of treatment of osteoarthritis of the knee. Arthritis Rheum 36:1196–1206
Williams GM, Iatropoulos MJ, Jeffrey AM (2002) Anticarcinogenicity of monocyclic phenolic compounds. Eur J Cancer Prev 11(Suppl 2):S101–S107
Winnike JH, Li Z, Wright FA, Macdonald JM, O'Connell TM, Watkins PB (2010) Use of pharmaco-metabonomics for early prediction of acetaminophen-induced hepatotoxicity in humans. Clin Pharmacol Ther 88:45–51
Wong S, Gardocki JF (1985) Anti-inflammatory and antiarthritic evaluation of acetaminophen and its potentiation of tolmetin. J Pharmacol Exp Ther 226:625–632
Woodward DF, Carling RWC, Cornell CL et al (2008) The pharmacology and therapeutic relevance of endocannabinoid derived cyclo-oxygenase (COX)-2 products. Pharmacol Ther 120:71–80
Ximenes VF, Maghzal GJ, Turner R, Kato Y, Winterbourn CC, Kettle AJ (2010) Serotonin as a physiological substrate for myeloperoxidase and its superoxide-dependent oxidation to cytotoxic tryptamine-4,5-dione. Biochem J 425:285–293
WHO. http://www.who.int/cancer/palliative/painladder/en
Yaksh TL, Dirig DM, Conway CM, Svensson C, Luo ZD, Isakson PC (2001) The acute antihyperalgesic action of nonsteroidal, anti-inflammatory drugs and release of spinal prostaglandin E2 is mediated by the inhibition of constitutive spinal cyclooxygenase-2 (COX-2) but not COX-1. J Neurosci 21:5847–5853
Yamamoto T, Nozaki-Taguchi N (2002) The role of cyclooxygenase-1 and -2 in the rat formalin test. Anesth Analg 94:962–967
Yang J, Chen Y, Ji R, Zhang C (2006) Novel model of inflammatory neointima formation reveals a potential role of myeloperoxidase. Am J Physiol Heart Circ Physiol 291:H3087–H3093
Yarema ALC, Shaheen AAM, Myers RP (2010) Trends in the epidemiology of acetaminophen overdose in the United States: a population-based study. Can J Emerg Med 12:248
Zernikow B, Smale H, Michel E, Hasan C, Jorch N, Andler W (2006) Paediatric cancer pain management using the WHO analgesic ladder—results of a prospective analysis from 2265 treatment days during a quality improvement study. Eur J Pain 10:587–595
Zhang W, Jones A, Doherty M (2004) Does paracetamol (acetaminophen) reduce the pain of osteoarthritis? a meta-analysis of randomised clinical trials. Ann Rheum Dis 63:901–907
Zhang W, Doherty M, Arden N et al (2005) EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 64:669–681
Zhu YZ, Chong CL, Chuah SC et al (2006) Cardioprotective effects of nitroparacetamol and paracetamol in acute phase of myocardial infarction in experimental rats. Am J Physiol Heart Circ Physiol 290:H517–H524