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Paracetamol: New Vistas of an Old Drug

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ABSTRACT

Paracetamol (acetaminophen) is one of the most popular and widely used drugs for the treatment of pain and fever. It occupies a unique position among analgesic drugs. Unlike NSAIDs it is almost unanimously considered to have no antiinflammatory activity and does not produce gastrointestinal damage or untoward cardiorenal effects. Unlike opiates it is almost ineffective in intense pain and has no depressant effect on respiration. Although paracetamol has been used clinically for more than a century, its mode of action has been a mystery until about one year ago, when two independent groups (Zygmunt and colleagues and Bertolini and colleagues) produced experimental data unequivocally demonstrating that the analgesic effect of paracetamol is due to the indirect activation of cannabinoid CB_1 receptors. In brain and spinal cord, paracetamol, following deacetylation to its primary amine (p-aminophenol), is conjugated with arachidonic acid to form N-arachidonoylphenolamine, a compound already known (AM404) as an endogenous cannabinoid. The involved enzyme is fatty acid amide hydrolase. N-arachidonoylphenolamine is an agonist at TRPV1 receptors and an inhibitor of cellular anandamide uptake, which leads to increased levels of endogenous cannabinoids; moreover, it inhibits cyclooxygenases in the brain, albeit at concentrations that are probably not attainable with analgesic doses of paracetamol. CB_1 receptor antagonist, at a dose level that completely prevents the analgesic activity of a selective CB_1 receptor agonist, completely prevents the analgesic ac-

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tivity of paracetamol. Thus, paracetamol acts as a pro-drug, the active one being a cannabinoid. These findings finally explain the mechanism of action of paracetamol and the peculiarity of its effects, including the behavioral ones. Curiously, just when the first CB_1 agonists are being introduced for pain treatment, it comes out that an indirect cannabinomimetic had been extensively used (and sometimes overused) for more than a century.

INTRODUCTION

Paracetamol (recommended international nonproprietary name) (acetaminophen) was synthesized in 1878 by Morse (148) and first used clinically by von Mering in 1887 (220). But it was quickly discarded in favor of phenacetin. The studies of Brodie and Axelrod (36) led to its "rediscovery" and marketing in the 1950s in the United States as an analgesic replacement for phenacetin, which was "condemned" for its nephrotoxicity. Unfounded concerns about paracetamol safety delayed its widespread acceptance until the 1970s. From then on, paracetamol became one of the most popular and widely used drugs in the world for the treatment of pain and fever; probably the most commonly prescribed medicine in children (21,158,179).

Paracetamol occupies a unique position among analgesic drugs, both for the type of pain relieved and for the side effects. So, for example, unlike NSAIDs, paracetamol is almost unanimously considered to be ineffective in inflammatory, as well as in intense pain. Unlike opiates, it is ineffective in pain arising from smooth muscle spasm in hollow viscera and has no depressant effect on respiration. Also, unlike NSAIDs paracetamol does not produce gastrointestinal damage or untoward cardiorenal effects.

The peculiarity of effects and side effects of paracetamol should have suggested a peculiar mechanism of action for this drug. On the contrary, and curiously, surprising efforts have repeatedly been made in order to demonstrate that paracetamol shares the mechanism(s) of action of NSAIDs. So, in the sixties, it was stated that "...the mechanism of obtundation of pain by acetaminophen is similar to that described for the salicylates" (232) (elsewhere in the same chapter, the same Author wrote: "...the salicylates are capable of alleviating certain types of pain by virtue of a selective depressant effect on the CNS, the mechanism of which has not yet been elucidated"). And after the discovery that the main mechanism underlying the therapeutic and toxic effects of NSAIDs is the inhibition of the activity of cyclooxygenases (218), efforts were directed at demonstrating that paracetamol, too, inhibits these enzymes. In fact, it was found that "inhibition of prostaglandin synthetase in brain explains the antipyretic activity of paracetamol" (84). However, despite much research, definitive proof that the analgesic and antipyretic effects of paracetamol are dependent on COXs inhibition is still lacking. Indeed, inhibition of a third form of COX, COX-3, is one of the more recent proposals that have been put forward to explain the unusual effects of paracetamol, but further analysis has suggested that this interaction is unlikely to be clinically relevant.

Thus, after well more than a century of clinical use, and in spite of being one of the most prescribed and consumed drugs in the world, paracetamol's mechanism of action has remained a mystery. Two independent groups (Zygmunt and colleagues; Bertolini and colleagues) have now produced experimental data which demonstrate that the analgesic activity of paracetamol involves a completely unforeseen mechanism, i.e., the potentiation of the cannabinoid/vanilloid tone in the brain and in dorsal root ganglia (102). The

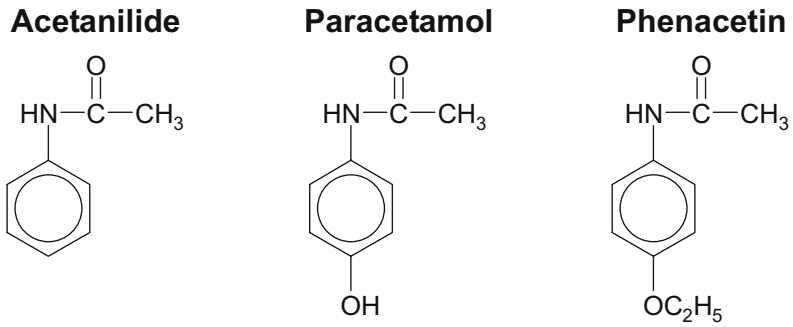

Fig. 1. Chemical structures of "aniline" analgesics.

blockade of cannabinoid CB_1 receptors has been shown to completely prevent the analgesic activity of paracetamol in rats (154). These unexpected and exciting findings place paracetamol into a completely new chapter of the pharmacology and therapy of pain: that of "cannabinoid analgesics." It is worthy of note that just when the first CB_1 agonists are being introduced for the treatment of pain, it comes out that an indirect cannabinomimetic had already been used as an analgesic for more than a century.

HISTORY AND CHEMISTRY

Paracetamol is virtually the sole survivor of the so-called "aniline derivatives" or "aniline analgesics": acetanilide, phenacetin and paracetamol (acetaminophen). Phenacetin and paracetamol are both derivatives of acetanilide (Fig. 1).

Acetanilide was serendipitously found to possess antipyretic activity and quickly introduced into medical practice under the name of antifebrin Cahn and Hepp (47), and was shown to possess analgesic as well as antipyretic activities. But its unacceptable toxic effects, the most alarming being cyanosis due to methemoglobinemia, prompted the search for less toxic aniline derivatives. A number of compounds were tested. The most satisfactory came out to be phenacetin (acetophenetidin) and N-acetyl-p-aminophenol (acetaminophen, paracetamol). Paracetamol had been synthesized by Morse in 1878 (148).

Phenacetin and paracetamol were introduced into clinical use in 1887 by von Mering (220), who soon discarded paracetamol in favor of phenacetin, because he assumed that the latter was less toxic (for reviews see: 33,54,83,91,138,202).

Albeit in part overshadowed by aspirin, introduced into medicine by Dreser in 1899, phenacetin has known for many decades an extraordinary popularity and has been indiscriminately used, especially as an ingredient of proprietary analgesic mixtures (particularly over-the-counter "headache mixtures," usually containing phenacetin, an aminopyrine derivative or aspirin, caffeine, and sometimes a barbiturate) and widely advertised to the public.

The chronic overuse/abuse of such mixtures by the laity, sometimes in prodigious amounts over periods of years, caused many serious chronic intoxications characterized by anemia, methemoglobinemia, and severe renal damage, with a high incidence of papillary necrosis ("analgesic nephropathy," "phenacetin nephropathy") (172).

In 1948, Brodie and Axelrod (36) demonstrated that the major metabolite responsible for the analgesic action of acetanilide and phenacetin is paracetamol, while methemoglobinemia is produced by another metabolite, phenylhydroxylamine.

So, paracetamol was "rediscovered" and marketed since the mid 1950s. It rapidly gained in popularity, and in many countries, including the United Kingdom, paracetamol sales exceeded those of aspirin since about 1980. This was accompanied by the virtual commercial demise of phenacetin, blamed as the cause of "analgesic nephropathy," hematological toxicity, and psychotropic effects which may contribute to its liability for abuse (54).

PHARMACOLOGICAL EFFECTS

It is generally accepted that the two systemic effects of paracetamol of therapeutic significance are analgesia and antipyresis, while its antiinflammatory and antirheumatic activities are negligible (39,54,177). Moreover, it has been repeatedly reported that following paracetamol ingestion, relaxation, slight drowsiness, euphoria, or feeling of tranquillity may be experienced (3,76,149). These effects are shared by the other members of the "aniline analgesics" (acetanilide and phenacetin) (3,76,101,171). It has been repeatedly described that a person may become habituated to these drugs and will continue to take them for a number of years. It has also been reported that withdrawal symptoms, characterized by restlessness and excitement, may be present for 3 or 4 days after medication is stopped (232). In rats, at antinociceptive doses, systemically administered phenacetin and paracetamol produce a conditioned place preference (3).

The lack of antiinflammatory activity by "aniline analgesics" has been questioned by some investigators. Their claims were supported in part by experimental (1,2,133,219, 231) and clinical (126,193,194) data.

The analgesic efficacy of paracetamol is equivalent to that of aspirin, while its plasma levels required for the analgesic activity are higher than those needed for the antipyretic activity (18).

At 1,000 mg paracetamol reaches its ceiling effect in adults. Further increase in the dose does not increase analgesic activity (196,232), but does increase toxicity.

MECHANISM OF ACTION

In spite of the remarkable feature that clearly distinguishes paracetamol from non-steroidal antiinflammatory drugs (NSAIDs) — that is, the absence of antiinflammatory activity (with very few exceptions) — the aim to demonstrate that the mechanism of action of paracetamol and NSAIDs is the same has been steadily and perversely pursued.

The first, almost prophetic, albeit unsubstantiated, hypothesis was that "the CNS is the major site of the analgesic effect" (of both paracetamol and NSAIDs) ["The salicylates are capable of alleviating certain types of pain, by virtue of a selective depressant effect on the CNS, the mechanism of which has not yet been elucidated... The mechanism of central obtundation of pain by phenacetin and acetaminophen is similar to that described for salicylates..." (232)]. After the discovery that the effects of NSAIDs are mainly the result of

the inhibition of the activity of prostaglandin endoperoxide synthase, or cyclooxygenase (COX) (38,218), efforts were directed at demonstrating that paracetamol also inhibits COX. Indeed, it was found that the antipyretic effect of paracetamol is due to the inhibition of COX in the brain (84). It was later confirmed that paracetamol is able to inhibit COX, provided that the ambient concentration of peroxides is kept low (94) (these data have been repeatedly confirmed: 32,155). Such a peroxide-dependent inhibition of COX might explain why paracetamol is not active at sites of inflammation, where peroxides concentration is high, while being active in the brain, where peroxides concentration is very low. It has been observed that the *in vivo* effects of paracetamol are similar to those of the selective COX-2 inhibitors (90). Furthermore, while paracetamol is a weak inhibitor of prostaglandin synthesis in broken cell systems, therapeutic concentrations of paracetamol inhibit prostaglandin synthesis in intact cells *in vitro* when the levels of arachidonic acid are low. Under these conditions prostaglandins are synthesized largely by COX-2. Thus, it has been suggested that the effects of paracetamol may be due to selective inhibition of COX-2 dependent pathways that are proceeding at low rates (90).

Others have hypothesized that paracetamol has no affinity for the active site of COXs, but instead blocks their activity by reducing the conversion of the active oxidized form of the enzymes to an inactive form; this would explain why paracetamol is more effective under reducing conditions of low peroxide concentration (32,127,155).

Some years ago, a splice variant of COX-1, derived from the same gene, was characterized in dog brain which was sensitive to inhibition with paracetamol (48); it was designated COX-3 (48), and subsequent data (31) seemed to support the view that analgesia and hypothermia due to paracetamol are mediated by inhibition of COX-3. But later studies have shown that while COX-3 might be active in canines, its low expression level and the unfavorable kinetics indicate unlikely clinical relevance. In rodents and humans COX-3 encodes proteins with completely different amino acid sequences than COX-1 or COX-2 and without COX activity, so that it is improbable that COX-3 in these species plays a role in prostaglandin-mediated fever and pain (see for a review: 112). A definitive proof that the analgesic and antipyretic effects of paracetamol are dependent on COX is still lacking.

In the nineties, data began to be produced that substantiated the early hypothesis, i.e., that the site of action of paracetamol's antinociceptive effect may be in the CNS (232). It was shown that the intravenous injection of paracetamol produces a dose-dependent depression of nociceptive activity evoked in the rat ventral thalamus by C-fiber stimulation (45). This finding was confirmed in humans by measuring pain-related cerebral potentials in response to intracutaneously applied current pulses (37). Moreover, it was shown that activation of spinal serotoninergic descending projections is involved in the antinociceptive effect of paracetamol (213). Conversely, reduction of serotoninergic neurotransmission in CNS decreased the analgesic effect of paracetamol (164). Furthermore, other findings suggested that spinal and supraspinal antinociception induced by high doses of paracetamol involves brain opioid systems (100). In particular, it was found that paracetamol-induced antinociception in rats is associated with a decrease of dynorphin A levels in the frontal cortex, and is prevented by blockade of k-opioid receptors (186).

Other suggested mechanisms of action of paracetamol have included inhibition of nitric oxide generation (27,41) and of hyperalgesia induced by either N-methyl-D-aspartate or substance P (27,107).

Recently, and using a different approach, Zygmunt and colleagues (102) and Bertolini and colleagues (154) discovered a completely new and unforeseen mechanism of action of paracetamol. Zygmunt and colleagues started from the observation of the striking structural similarity between paracetamol and the fatty acid amide N-arachidonoylphenolamine (AM404). AM404 belongs to the group of bioactive N-acylamines that includes the endogenous lipid anandamide (arachidonoyl-ethanolamide, AEA) (69), N-arachidonoyldopamine (106), and N-arachidonoylglycine (105), the synthetic compounds: olvanil (109), arvanil (136), linvanil (66,136), and others (66,136). These compounds share the ability of cannabinoids to display analgesic activity in a variety of animal tests, and to lower body temperature (25,92,109).

AM404 is a potent activator of vanilloid subtype 1 receptors (TRPV1) (235), and an inhibitor of the cellular anandamide uptake (anandamide membrane transporter, AMT), which leads to increased levels of endogenous cannabinoids (19,66,82,210,235) [evidence for partially overlapping ligand recognition properties of TRPV1 and the AMT has been provided (66,210)]. On the other hand, a direct action of AM404 on cannabinoid CB_1 receptors seems negligible, as suggested by its quite low affinity (K_i values for CB_1 receptors are 78 nM for anandamide and 1760 nM for AM404) (235), and also by the fact that AM404, in contrast to cannabinoid CB_1 receptor agonists, does not inhibit forskolin-induced cyclic AMP accumulation (19). TRPV1 (and also cannabinoid CB_1) receptors are present in pain and thermoregulatory pathways (66,111,165,209,210,216). Zygmunt and colleagues have shown that paracetamol, following deacetylation to its primary amine (p-aminophenol) is conjugated with arachidonic acid in the brain and spinal cord to form AM404. The involved enzyme is fatty acid amide hydrolase (FAAH), which catalyzes the hydrolysis of anandamide and which can also act in the reverse direction and catalyze the synthesis of anandamide from ethanolamine and arachidonic acid. Zygmunt and colleagues have shown that FAAH can indeed synthesize AM404 from p-aminophenol and arachidonic acid *in vitro*, and that, in addition, no formation of AM404 is observed *in vitro* or *in vivo* in brain tissue from FAAH gene knockout mice (102).

Bertolini and colleagues started from the consideration of the peculiarity of the analgesic-antipyretic effect of paracetamol, that does not lead to the inhibition of the inflammatory response, is not accompanied by gastric side effects, and is often characterized by a peculiar sense of well-being, relaxation and tranquillity (effect that is shared by the other members of the "aniline analgesics," in particular by phenacetin, and that has been considered responsible for the liability for abuse of these compounds). Bertolini and colleagues were impressed by similarities of the overall effect of paracetamol and that of cannabinoids. Indeed, cannabinoids produce analgesia either in animal models of pain (both acute pain and tonic pain) or in clinical painful conditions (for reviews see: 161,221), and endogenous cannabinoids are tonically released to participate in the control of basal nociceptive threshold (137). As mentioned above, the antinociceptive effect of paracetamol involves the activation of spinal serotoninergic descending projections (213). Cannabinoids also produce their antinociceptive effect by descending spinal inhibition, CB_1 receptors being almost exclusively involved. Experimental data suggest that paracetamol antinociception involves CNS opioid networks (100), is associated with a decrease of dynorphin levels in the frontal cortex, and is prevented by κ-receptor antagonists (186). The cannabinoid-induced antinociception has been shown to depend to some extent on the release of opioid peptides and their interaction with brain μ and spinal κ receptors (51). Moreover, besides inhibiting nociception, cannabinoids markedly lower body temperature (156)

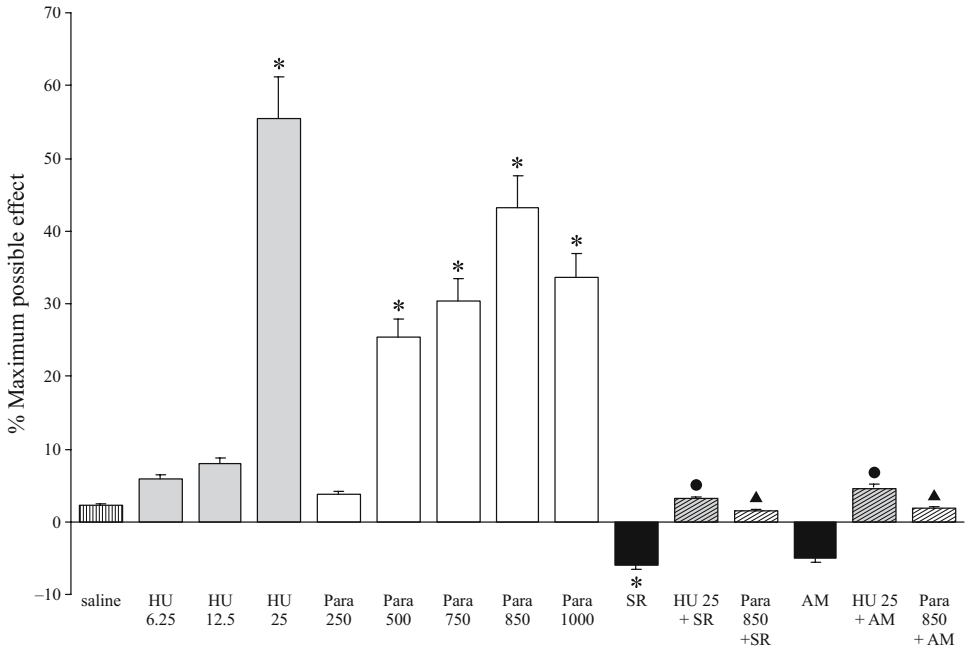

Fig. 2. Effect of CB_1 receptor-blockade on the analgesic activity of paracetamol (Para) and of a specific CB_1 agonist (HU210)(HU). Hot-plate test (temperature of the plate: 54.0 ± 0.4°C); 8–12 rats per group. SR141716A and AM281 were injected i.p. at 30 min before the administration of HU210 or paracetamol; HU210 was. injected i.p. at 60 min before test; paracetamol was given by p.o. at 60 min before test. HU210 was used at 6.25, 12.5, or 25 μg/kg; paracetamol at 250, 500, 750, 850, or 1,000 mg/kg. The antinociceptive activity is expressed as percentage of the maximum possible effect (%MPE). $^*P < 0.05$ vs. saline-treated group; $^\bullet P < 0.05$ vs. HU210 at the dose of 25 μg/kg; $^\blacktriangle P < 0.05$ vs. Para at 850 mg/kg (ANOVA followed by the Student – Newman – Keuls test).

through the activation of CB_1 receptors in the preoptic area. Finally, the well-known subjective effects of acute marijuana consumption (in particular euphoria, relaxation, feeling of tranquillity) are shared by the aniline analgesics (232).

In experiments performed in rats, Bertolini and coworkers have shown that pretreatment with a CB_1 receptor antagonist (either SR141716A or AM281), at a dose level that completely prevents the analgesic activity of a selective CB_1 receptor agonist (HU210), completely prevents the analgesic activity of paracetamol (Fig. 2) (154).

These novel findings explain the mechanism of action of paracetamol and may provide an explanation of the observation that paracetamol inhibits prostaglandin production in the brain (84). Indeed, Zygmunt and colleagues have shown that AM404 concentration-dependently inhibits both COX-1 and COX-2, as well as LPS-induced prostaglandin E_2 formation in macrophages. The formation of AM404 from p-aminophenol may also reduce the production of prostaglandins because of the consumption of arachidonic acid. However, the actual contribution of these activities of AM404 to the analgesic effect of paracetamol seems negligible. Indeed, after administration of paracetamol at 300 mg/kg to rats, the brain concentration of AM404 has been found to be 10.3 ± 1.9 pmol/g tissue wet weight (102). Assuming an even distribution of AM404 in brain, this would corre-

spond to a tissue concentration of about 10 nM. At this concentration AM404 activates both rat (102,235) and human (66) TRPV1 receptors, while significant COX-1 and COX-2 inhibition and prostaglandin E_2 formation reduction are obtained at micromolar concentrations (102). It is of course possible (but not demonstrated) that higher concentrations of AM404 are formed in CNS regions expressing high levels of FAAH, such as neuronal somata and dendrites of mesencephalic trigeminal nucleus, layer V of the somatosensory cortex, Purkinje cells of the cerebellar cortex and olfactory glomeruli (77). This would lead to a local significant inhibition of COX activities, that could contribute to the effect of paracetamol. At the present time this possibility remains speculative.

Thus, paracetamol would act as a pro-drug, with the active metabolite (AM404) being formed in the brain through conjugation of the deacetylated derivative of paracetamol (p-aminophenol) with arachidonic acid, by the action of fatty acid amide hydrolase (FAAH). At analgesic doses of paracetamol, AM404 that is formed in rat brain regions expressing high levels of FAAH, can indirectly activate CB_1 receptors and directly activate TRPV1 receptors (66,102,235). Interestingly, in brain regions with high expression of FAAH, both TRPV1 and CB_1 receptors are also found (mesencephalic trigeminal nucleus, primary sensory neurons) (12,77,140).

PHARMACOKINETICS

The adult oral doses of paracetamol for the treatment of pain or fever are 650–1000 mg every 4 h as needed, up to a recommended maximum daily dose of 4 g. The pediatric oral doses are 10–15 mg/kg/dose every 4–6 h, up to a maximum of 5 doses/day. It is recommended to increase the dosing interval to every 6 h in patients with moderate renal failure (GFR = 10 to 50 mL/min), and every 8 h in patients with severe renal failure (GFR = less than 10 mL/min) (20). The therapeutic concentrations range from 5 to 20 mg/mL. The onset of analgesic activity in fasting subjects after oral administration is about 0.5 h; the duration of the analgesic effect is about 4 h (5).

The time to peak concentration is approximately 45–60 min after oral administration of regular release tablets (71) and there may be large variation in individual plasma paracetamol concentrations measured 60 min after oral administration (174).

Liquid paracetamol (drops, syrup) has a time to peak of about 30 min (54,71). Extended-release paracetamol has a time to peak of 60–120 min, but by 5 h, 95% of the drug is absorbed (73). Peak concentrations of paracetamol after recommended oral doses range from 8 to 32 μg/mL.

The area under the curve of 1,000 mg paracetamol tablets has been found to be 43.5 and 34.6 μg/h/mL in fasted and fed healthy volunteers, respectively (207); food reduced the maximum concentration of oral paracetamol by 49% (207) [when paracetamol is coadministered with food, the absorption rate of the drug is decreased; for rapid relief of pain, paracetamol should not be taken with food or after a meal, especially if high in carbohydrates (71)].

Paracetamol is subjected to a first-pass metabolism, with hepatic extraction ratio of 0.11–0.37 in adults (30); so, the oral bioavailability is 60–89% (178); and the absorption half-life is 4.5 min with no lag time (7) [a lag time of 4.2 min has been reported in children (222)].

The absorption from the rectal route of administration is erratic and unpredictable (8,60), with reported values of bioavailability ranging from 24 to 98% (28,59,146,150, 190) the mean absorption half-life is 35 min with 40 min lag time (7), but is largely dependent on the physical composition of the suppositories, which varies between manufacturers (60,113), so that the time to peak plasma concentration ranges from 107 to 288 min after rectal administration (9,24,123). In children, an initial rectal dose of 40 mg/kg has been recommended in order to achieve therapeutic plasma concentrations (24); a rectal dose of 45 mg/kg has been reported to produce in children a mean peak plasma concentration of 13 μg/mL (146), comparable with that obtained with an oral dose of 10–15 mg/kg (188). It is currently agreed that an initial rectal dose of 40–45 mg/kg followed by regular doses to a maximum of 90 mg/kg/day should provide adequate plasma concentrations of paracetamol (222,234). At plasma concentrations of less than 60 μg/mL, paracetamol does not apparently bind to plasma proteins; at 90 μg/mL protein binding is less than 5%; after toxic doses, with plasma concentrations of up to 250 μg/mL, protein binding varies from 8 to 43% with no correlation between binding and plasma paracetamol concentration (86). Other aniline analgesics have a substantially higher binding to plasma proteins: 10 to 30% (20 to 50% in case of overdosage) (20,87,203). Between 10 and 20% of administered paracetamol is bound to red blood cells (54).

The volume of distribution is 1 to 2 L/kg in adults and 0.7 to 1 L/kg in children (20,163,175). Paracetamol is uniformly distributed throughout most body fluids, freely crosses the placenta (119) and penetrates the blood-brain barrier, reaching liquoral peak concentrations in 2 to 3 h after oral administration. A tissue:plasma concentration ratio of unity is achieved in all tissues, except fat and cerebrospinal fluid (CSF). At equilibration, the CSF to plasma partition coefficient has been estimated as 1.18 (6,13).

Following usual oral doses, approximately 25% of paracetamol is metabolized on the first passage through the liver (53). In adults, the majority (approximately 90%) of paracetamol is conjugated with glucuronide (40–67%) and, to a lesser extent (20–46%), with sulphate, or cysteine (3%) (64,206), inactive and harmless metabolites. In premature infants, newborns, and young infants, the majority of paracetamol is conjugated with sulphate. A fraction usually ranging from 5 to 15% is oxidized by CYP2E1, CYP1A2, CYP3A4, and CYP2A6 subfamilies of the P450 mixed-function oxidase system, resulting in the formation of the highly reactive N-acetyl-p-benzoquinoneimine (NAPQI) (58). Glutathione quickly combines with this intermediate, and the resulting complex is then converted to non-toxic cysteine or mercaptate conjugates, which are eliminated in urine (141) (Fig. 2). As mentioned above (mechanism of action section), it has been shown that in brain, spinal cord, and dorsal root ganglia of rats, paracetamol, following deacetylation (mainly in the liver) to p-aminophenol, is conjugated by enzyme fatty acid amide hydrolase (FAAH) with arachidonic acid to form N-arachidonoyl-phenolamine (AM404) (102).

The formation of AM404 is dose-dependent. 20 min after the intraperitoneal injection of 300 mg/kg of paracetamol, the AM404 levels in the brain were 10.3 ± 1.9 pmol/g (102). This novel metabolic pathway (fatty acid conjugation) is of crucial functional importance because it generates the active metabolite of paracetamol. It is negligible, however, in the overall biotrasformation of the drug.

Some drugs that induce cytochrome P450 enzymes (in particular, sulfinpyrazone, isoniazid, anticonvulsants) may increase paracetamol metabolism (142). Hepatic enzyme in-

duction may increase paracetamol toxicity (e.g., in chronic alcoholism), whereas decreased hepatic metabolism (e.g., in acute ethanol ingestion) may be protective (78).

In the overdose situation, when the sulphate and glucuronide stores are saturated, a large percent of the dose is oxidized to cysteine and mercapturic acid conjugates (64). Only 1 to 4% of paracetamol is excreted unchanged in the urine (10,170). The metabolic products are excreted mainly by the kidney. The urinary clearance of paracetamol is 13.5 L/h (7).

Formation of oxidative metabolites and renal excretion follow first-order kinetics (i.e., elimination rate is concentration-dependent); the conjugation of sulphate and glucuronide metabolites follows Michaelis-Menten kinetics (combined zero- and first-order) (197).

Elimination occurs almost entirely through the kidneys. As a moderately lipid-soluble weak organic acid, paracetamol undergoes glomerular filtration with subsequent extensive tubular reabsorption, whereas the highly polar glucuronide and sulphate conjugates are actively secreted by the tubules (147).

Biliary excretion is not an important elimination pathway in man: in one study on patients with tube drainage of the common bile duct (191) total biliary excretion was 2.6% of the oral dose (1 g) (unchanged paracetamol 0.26%, sulphate conjugate 0.36%, glucuronic acid conjugate 0.36%, and the cysteine conjugate 1.63%).

The elimination half-life is 2 to 4 h in normal individuals (5,20). Some evidence indicates that in geriatric patients there is a significant increase in the mean half-life of paracetamol and that this increase is due to a reduction in paracetamol clearance. However, this finding has not been confirmed by all studies (215) and based on the current kinetic data no specific dosage adjustment is necessary in the elderly (72).

In a study of 12 very elderly patients (mean age 89 years), the average single-dose (1 g) half-life and cumulative-dose (1 g three times daily for 5 days) half-life were 2.77 and 2.74 h, respectively (14).

The mean elimination half-life is increased in premature infants (11 h), while it is 4 to 5 h in newborns (95,217).

Hemodialysis (but not peritoneal dialysis) removes significant amounts of paracetamol and its conjugates from plasma. In patients receiving therapeutic doses, half-life values were reduced by 40 to 50% during hemodialysis (153).

DRUG INTERACTIONS

Paracetamol potentiates the anticoagulant effects of acenocoumarol and warfarin, with increased risk of bleeding. The suggested mechanisms are inhibition of the metabolism of oral anticoagulants or interference with the hepatic synthesis of factors II, VII, IX, and X (29); but more recent data did not confirm these hypotheses (115). Patients receiving oral anticoagulants should be cautioned to limit their intake of paracetamol.

Carbamazepine increases the risk of paracetamol hepatotoxicity by inducing the hepatic metabolism of paracetamol and thus increasing the formation of toxic metabolites (233). In addition, paracetamol has been shown to have lower bioavailability in epilectic patients receiving enzyme inducing anticonvulsants (162), including phenytoin and fosphenytoin. On the other hand, paracetamol enhances the urinary elimination of lamotrigine (67).

Sulfinpyrazone, like carbamazepine, increases the risk of paracetamol toxicity by increasing the formation of hepatotoxic metabolites (142). Coadministration of paracetamol with zidovudine may result in neutropenia or hepatotoxicity (180); these effects were not have been reported consistently (42,187,205).

Of major concern is the interaction with alcohol. Alcohol – paracetamol syndrome is defined as the development of acute toxic hepatic symptoms in long-term alcoholics who take paracetamol, in doses generally considered non-toxic.

Patients wih alcohol-paracetamol syndrome have a worse prognosis than non-alcoholic patients overdosed with paracetamol. Overall mortality in alcohol-paracetamol syndrome is about 20%, and exceeds 75%, if acute liver failure develops (16,75,120,129). Concurrent use of alcohol and paracetamol may increase the CYP2E1-mediated metabolism of paracetamol to the highly hepatotoxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). In non-alcoholics, NAPQI is detoxified by conjugation with glutathione. In alcoholics, the combination of CYP2E1 induction and glutathione depletion results in NAPQI accumulation (75). In these subjects, the highest risk of paracetamol toxicity occurs after a brief (12 h) abstinence of alcohol, since CYP2E1 is still induced, but alcohol is not present to compete for CYP2E1 metabolism (75).

TOXICOLOGY

Paracetamol is a safe drug at appropriate dosage. Amounts of 7.5 g in an adult or 150 mg/kg in a child are widely considered as the lowest acute dose capable of causing toxicity (26). There have been no reports of acute toxicity in healthy adults ingesting a single dose of paracetamol below 125 mg/kg; historical data suggest that toxicity generally occurs only above 150 mg/kg (176) (the therapeutic paracetamol dose is 10–15 mg/kg, therefore the therapeutic index is ~10).

Liver is typically and by far the most involved organ in paracetamol acute toxicity. Once absorbed, approximately 90% of paracetamol normally undergoes hepatic glucuronide (40–67%) and sulphate (20–46%) conjugation to form inactive, harmless metabolites, which are eliminated in urine (in the fetus and early life, sulfation predominates; glucuronidation predominates after age 10). A small fraction of unchanged paracetamol (<5%) and other minor metabolites reach the urine, but are not thought to be clinically relevant. The remaining fraction, usually ranging from 5 to 15%, is oxidized by the CYP2E1, CYP1A2, CYP3A4, and CYP2A6 subfamilies of the P450 mixed-function oxidase system, resulting in the formation of N-acetyl-p-benzoquinoneimine (NAPQI) (50,62,159, 211). Glutathione quickly combines with NAPQI; the resulting complex is then converted to non-toxic cysteine or mercaptate conjugates, which are eliminated in urine. After appropriate paracetamol dosing, glutathione supply far exceeds that which is required to detoxify NAPQI. After overdose, the rate and quantity of NAPQI formation may outstrip glutathione supply and regeneration. When glutathione stores are depleted below a critical value (about 30% of normal stores) free NAPQI rapidly and covalently binds and arylates critical cell proteins, inducing a series of events that may result in cell death (143). Critical, possibly irreversible, events in cell death include oxidation of enzymes, DNA fragmentation, and mitochondrial injury (Fig. 3). A massively increased production of nitrogen/oxygen species may also be important in paracetamol-induced acute toxicity (108)

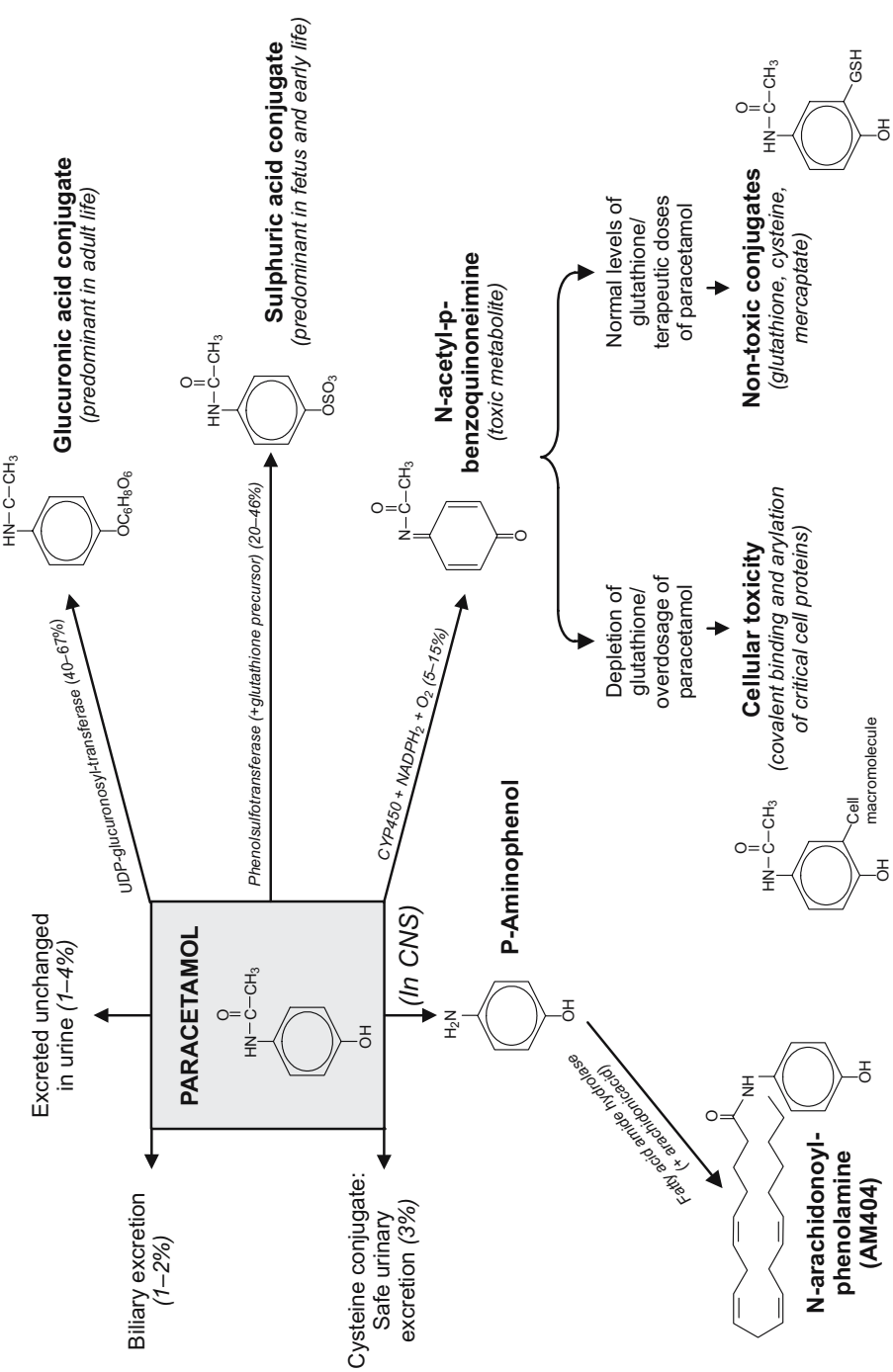

Fig. 3. Metabolism of paracetamol in humans.

as well as several components of liver innate immune system (natural killer cells, natural killer T cells, Kupfer cells/macrophages, neutrophils) (125).

It is now clear that this process can be not only prevented or interrupted, but even reversed after NAPQI binding has occurred.

Factors that may predispose to hepatotoxicity include increased frequency of paracetamol dosing, prolonged duration of excessive dosing, increased capacity for P450 activation to NAPQI (as in patients chronically treated with agents that induce hepatic microsomal enzymes, like anticonvulsants, isoniazid, etc.), decreased glutathione availability, or decreased capacity for glucuronidation and sulfation. Another important factor of increased risk is chronic ethanol abuse (3 or more alcoholic drinks per day). Liver toxicity and acute renal tubular necrosis in alcoholics have been associated with daily doses of 4 to 6 g paracetamol for 3 to 4 days.

While chronic ethanol increases risk from acute paracetamol dosing (121,189,214) on the basis of induced P450 paracetamol metabolism, and consequent increased formation of NAPQI, or decreased glutathione supply or hepatic regeneration power (118), acute ethanol coadministration with paracetamol may be somewhat hepatoprotective (212,214) presumably by competitive inhibition of P450 paracetamol metabolism to NAPQI.

Serious hepatotoxicity or death after acute paracetamol overdose has been reported in children, but is extremely rare (11,122,181), particularly in children under 5 years of age. A likely explanation would be the increased glutathione supply and regenerative capacity of children (117). However, following excessive repeated paracetamol dosing, there is no evidence that children are relatively protected. In fact, infants and children with acute febrile illnesses comprise one of the few groups in which toxicity after repeated excessive dosing has been described (43,49,52,65,74,99,151,201,208). In any child with acute febrile illness and reported dosing that exceeds 75 mg/kg in any 24-h period, or if symptoms or signs of hepatotoxicity are evident, regardless of reported dosing, blood levels of paracetamol and aspartate aminotransferase (AST) must be measured (26).

In the liver, most oxidative drug metabolism is concentrated in the centrilobular zone (zone III), and this zone is first and most profoundly affected by paracetamol toxicity, due to the local formation of NAPQI. In more severe cases, necrosis may extend into zones I and II to destroy the entire liver parenchyma. Fulminant hepatic failure may develop in severely poisoned patients from the third to the sixth day. It is characterized by deepening jaundice, encephalopathy, increased intracranial pressure, grossly disordered hemostasis with disseminated intravascular coagulation and hemorrhage, hyperventilation, acidosis, hypoglycemia and renal failure. These patients are candidates for as early as possible liver transplantation (152). The bioartificial liver is used as supportive care in patients awaiting transplant, and as primary therapy in patients who have contraindication that precludes transplantation (68).

Kidney is the second target organ of paracetamol toxicity: renal dysfunction occurs in about 25% of cases with significant hepatotoxicity (63,172) and in more than 50% of those with hepatic failure (128,230). Overt renal failure necessitating hemodialysis occurs nearly always among patients with marked hepatic injury (44). [Renal abnormalities are more common after sustained repeated excessive dosing (173)]. However, renal impairment after acute paracetamol overdose may also occur in the absence of hepatotoxicity (44,169). Also the pathophysiology of renal dysfunction after acute paracetamol overdose is mainly the result of the local formation of NAPQI, that causes tubular necrosis (34,80, 103). However, several other nephrotoxic mechanisms have been proposed (97,130), also

because acute renal failure has been reported despite adequate treatment with N-acetyl cysteine (63). In addition, volume depletion and hepatorenal syndrome are often cofactors. While the peak disturbance in liver function occurs 2 to 4 days after a paracetamol overdose, renal impairment, if it develops, becomes more evident after 1 week and returns to normal about 2 to 3 weeks after ingestion (55,61). Renal damage is also produced by chronic use of paracetamol; in a case-control study involving 1,077 subjects who frequently took paracetamol, a dose-dependent relationship between heavier paracetamol use and an increased risk of end-stage renal disease was demonstrated (160).

Injury to other organs is rarely reported. The mechanism causing myocardial damage, reported in some patients with paracetamol-induced fulminant hepatic failure, is thought to be part of multisystem organ failure rather than being paracetamol specific (35,124). Pancreatic toxicity is extremely rare (88,145).

Early recognition and treatment of patients with paracetamol poisoning are essential in order to minimize morbidity and mortality. This task is made difficult by the lack of predictive clinical findings early in the course of paracetamol poisoning, and clinicians should not feel reassured by a patient's lack of symptoms soon after ingestion. The first symptoms after paracetamol overdose may be those of hepatic injury, which develops many hours after the ingestion, when antidotal therapy is already less effective (26).

In stage I of toxicity (0.5–24 h after ingestion) clinical signs, when present, are non specific (anorexia, nausea, vomiting, malaise, diaphoresis); but the patient may instead appear normal.

Stage II (24–72 h after ingestion) represents the onset of liver injury, which occurs in only a fraction of patients who overdosed; symptoms mimic those of infectious hepatitis. Aspartate aminotransferase (AST) is the most sensitive measure to detect the onset of hepatotoxicity, and AST elevation always precedes the other laboratory signs of actual liver dysfunction (elevation of transaminases, bilirubine, INR), hypoglycaemia, metabolic acidosis.

Stage III (72–96 h after ingestion) is the time of maximal hepatotoxicity; the clinical manifestations vary from absent to fulminant hepatic failure. Fatalities from fulminant hepatic failure generally occur between 3 and 5 days after overdose. Death results from either single or combined complications of multiorgan failure, including hemorrhage, acute respiratory distress syndrome, sepsis and cerebral edema. Patients who survive stage III usually recover completely (stage IV: 96 h – 2 weeks), without sequelae.

There are no reported cases of chronic hepatic dysfunction solely because of paracetamol poisoning; in most cases, laboratory assays are normal by 5–7 days after overdose.

The risk determination after acute paracetamol overdose is obviously and chiefly based on the determination of paracetamol serum levels. The so-called "paracetamol nomogram" (168,182,183) plots serum paracetamol concentration versus time after ingestion. The line starts at a paracetamol level of 200 (United Kingdom) or 150 (United States) μg/mL at 4 h after ingestion and ends at 6.25 (UK) or 4.7 (U.S.) μg/mL at 24 h after ingestion. Patients whose levels are below such "treatment line" do not require further evaluation or treatment for their acute paracetamol overdose (26). The "treatment line" is one of the most sensitive screening tools used in medicine (26). The incidence of nomogram failures in the United States approaches zero (199).

A specific antidote is available for the treatment of paracetamol poisoning: N-acetylcysteine (NAC). NAC prevents toxicity by serving as a glutathione precursor, leading to increased glutathione availability (116). It can also serve as a glutathione substitute, com-

bining with NAPQI and being converted to cysteine and mercaptate conjugates, just as glutathione (40). NAC can also increase the substrate for non-toxic sulfation, allowing increased metabolism by this route and less metabolism by oxidation to NAPQI (198). In a mouse model, NAC actually reversed NAPQI oxidation (58), but there is no evidence of such a process in humans.

Since time is required to saturate non-toxic metabolism, form excessive NAPQI, and deplete glutathione, there is a window of opportunity after paracetamol overdose during which NAC can be initiated prior to the onset of liver injury, without any loss of efficacy. Based on large clinical trials, it appears that NAC efficacy is nearly complete as long as it is initiated within 8–10 h of paracetamol overdose (200): there have been no deaths in cases so treated (182). Efficacy then decreases in a stepwise fashion with further delays, and there is no benefit if NAC administration is started more than 15 h after the overdose (167). However, several observations suggest that NAC has other mechanisms of action that are effective also after NAPQI formation and binding: enhancement of oxygen delivery and utilization (70,96,204). These effects include non-specific antioxidant effects, preservation of cerebral blood flow and perfusion in cerebral edema after liver failure (224).

Once NAC therapy begins, based on the "paracetamol nomogram," the entire course of NAC should be administered regardless of the location of subsequent levels of paracetamol on this nomogram: subsequent plasma levels of paracetamol that fall below the treatment line are not an indication to stop NAC therapy (79).

A 5% solution of NAC should be given as an oral loading dose of 140 mg/kg; 17 further doses of 70 mg/kg should be given every 4 h; for a total dose of 1,330 mg/kg over 72 h. The intravenous route of administration is used in the following three situations: fulminant hepatic failure, inability to tolerate oral NAC, paracetamol poisoning in pregnancy (26). Finally, it is worth mentioning an increased evidence of asthma in chronic paracetamol users (17,192). In a case-controlled study involving 1,574 young adults, daily or weekly chronic use of paracetamol was strongly associated with asthma and severity of asthma. Depletion of glutathione in airway epithelial lining fluid by paracetamol metabolites has been suggested as the possible cause (192).

THERAPEUTIC USES

The non-opiate analgesics, including paracetamol, aspirin and other COX-1/COX-2 inhibitors, and COX-2-specific inhibitors (coxibs), are among the most widely used medications in the world. In 2004, individuals in the United States spent >$2.5 billion on over-the-counter (OTC) non-opiate analgesics, and filled >100 million prescriptions. Among non-opiate analgesics paracetamol was one of the most commonly used. In most countries, paracetamol is the most used analgesic-antipyretic drug in children (21,158, 179).

It is worth remembering that paracetamol has a ceiling effect at the oral dose of 1,000 mg in adults. Further increases in dosage do not produce further increases in the analgesic activity (196). The analgesic-antipyretic effect of a dose of paracetamol lasts 3–4 h.

Paracetamol is indicated for mild-to-moderate pain, such as that caused by headaches, cold, flu, muscle aches, sprains, backache (including low back pain) (4), dysmenorrhea, minor arthritis pain, toothaches. Paracetamol is the drug of choice for treating minor-moderate, non-inflammatory conditions in patients who are prone to gastric damage, and is preferable to aspirin in patients receiving anticoagulants or in patients with coagulation disorders.

Paracetamol, alone or in combination, may be a useful adjunct in pain during menstruation; however NSAIDs are usually more effective, due to their mechanism of action (inhibition of cyclooxygenases).

Paracetamol, at oral doses of 15–20 mg/kg up to every 4 h, is the mainstay of treatment in childhood headache; since rectal absorption is variable, doses up to 45 mg/kg may be required for this route of administration (89,131,223).

Paracetamol has been shown to be effective in the treatment of moderate pain associated with minor surgical procedures (195). A recent meta-analysis (15) concluded that single dose oral paracetamol is effective for the treatment of moderate to severe, acute postoperative pain. In a total of 47 double-blinded, randomized, placebo-controlled trials involving 4,186 patients (paracetamol $n = 2,561$, placebo $n = 1,625$) there were no significant differences between the doses of paracetamol (325, 500, 600, 650, 1000, and 1500 mg), whereas all doses of paracetamol were statistically superior to placebo. Pain relief was assessed using visual analog scales and/or categorical scales. The mean proportion of patients experiencing at least 50% reduction in pain ranged from 38 to 69% in paracetamol-treated groups, and from 16 to 46% in placebo-treated groups.

In a double-blind, placebo-controlled study ($n = 120$), high rectal doses of paracetamol (40 or 60 mg/kg) significantly reduced pain and morphine requirements in pediatric patients undergoing elective day surgery (114).

Several clinical studies and large meta-analyses have shown that paracetamol — at oral doses between 500 and 1,000 mg — provides rapid pain relief superior to that of placebo for treatment of pain associated with third-molar extraction or other dental treatments (57,132,134). The dose of 1,000 mg was effective for up to 5 h after oral surgery (134), although pain relief was maximal at 1 to 2 h after administration (22), and was shown to be an effective treatment for extraction of impacted third molars and for various other oral surgeries, including difficult extractions, alveolectomy, multiple extractions, apicoectomy, biopsy, and deep gingival curettage (135,196).

Paracetamol must be considered as a safe alternative to NSAIDs for the relief of mild-to-moderate pain in elderly patients, in patients with kidney disease (144), hypertension (56,93,104,110,166,184,185,225), congestive heart failure (81,85,98,139,157). In such patients, NSAIDs, for their mechanism of action, may worsen the renal and cardiovascular function, besides causing gastrointestinal damage (23,85,227,228,229). Moreover, the concomitant use of NSAIDs in individuals with hypertension taking β-blockers, ACE-inhibitors, and/or loop diuretics has been shown to adversely destabilize blood pressure control (93,110,166,225,226). It can also antagonize the platelet inhibition induced by low dose aspirin and lessens its cardioprotective effect (46).

CONCLUSIONS

For well more than a century the mechanism of action of paracetamol (acetaminophen), one of the most commonly used drugs in the world, has been one of the mysteries of pharmacology. This does not represent an exception, however, since the mechanism of action of aspirin has been discovered 72 years after its introduction into therapy and the mechanisms of action of opium and cannabis have been discovered after many thousands of years of use and abuse by mankind; and so on.

The recent discovery that paracetamol acts as a prodrug (a donor of a moiety of an endogenous cannabinomimetic) by triggering the CB_1-mediated effects of the cannabinoid system provided explanation of the peculiar effects of this drug. It also raised a series of questions, since cannabinoids, in addition to nociception are involved in short- and long-term forms of synaptic plasticity, including depolarization-induced suppression of both excitatory and inhibitory neurotransmission, long-term potentiation and depression, and long-term depression of inhibition. The obvious implications are that cannabinoids and similarly acting drugs may regulate cognitive functions, modulate food intake, affect both female and male reproduction, provide neuroprotection and be involved in neurodegenerative diseases; pathophysiology of shock; inhibition of fertilized oocyte implantation; inhibition of cancer growth, angiogenesis and metastasis (for a review see ref. 71).

A final remark: by an odd coincidence, just when the first CB_1 agonists are being introduced for pain treatment (with some concern) — it turns out that for well more than a century an indirect cannabinomimetic has been used for the treatment of pain, and it is one of the safest drugs.

ADDENDUM

The abbreviations used are:

ACE, angiotensin-converting enzyme;

AM281, *N*-(morpholin-4-yl)-5-(4-iodophenyl)-1-(2,4-dichlorphenyl)-4-methyl-1H-pyrazole-3-carboxamide;

AM404, *N*-(4-hydroxyphenyl)arachidonylamide;

AST, Aspartate Aminotransferase;

CNS, central nervous system;

COX, cyclooxygenase;

CSF, cerebrospinal fluid;

FAAH, fatty acid amide hydrolase;

GFR, glomerular filtration rate;

HU210, (6aR)-*trans*-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,dimethyl-6*H*-dibenzo[b,d]pyran-9-methanol;

INR, International Normalized Ratio;

LPS, lipopolysaccharide;

NAC, N-acetylcysteine;

NAPQI, N-acetyl-p-benzoquinoneimine;

NSAIDs, Non-Steroidal Anti-Inflammatory Agents;

SR141716A, N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride;

TRPV1, transient receptor potential cation channel, subfamily V, member 1 protein.

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