Paracetamol

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Paracetamol (acetaminophen) is one of the most commonly prescribed drugs worldwide. Synthetized over 150 years ago, paracetamol is highly efficient as analgesic and antipyretic and is on the list of the World Health Organization's essential medicines. Paracetamol is also a hypothermic agent.

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1. Introduction

Paracetamol (acetaminophen) is one of the most commonly prescribed drugs worldwide. Synthetized over 150 years ago, paracetamol is highly efficient as analgesic and antipyretic and is on the list of the World Health Organization's essential medicines. However, the drug is considered to be devoid of anti-inflammatory properties [1].

High doses of paracetamol pose a serious risk for hepatotoxicity due to the lack of neutralisation of the oxidation metabolite N-acetyl-p-benzoquinone imine (NAPQI), secondary to the depletion of glutathione [2].

Aside from the analgesic and antipyretic effects, paracetamol also presents hypothermic effects. Hypothermia induced by paracetamol was firstly described in the 1960s in rats treated with high doses of the drug in the presence of hepatic failure. A decade later, paracetamol was shown to produce profound hypothermia when administered intracerebroventricularly [3]. In 1982, Massey et al. demonstrated its hypothermic effects in mice treated with non-toxic doses [4].

The serendipitous discovery of the hypothermic effect, together with the clinical implications of the therapeutic induced hypothermia, led to new pharmacodynamic studies to understand the mechanism behind paracetamol's effect of lowering body temperature.

2. Short History of the Research Regarding the Mechanisms of Paracetamol-Induced Analgesic and Antipyretic Effects

For a long time, the analgesic and antipyretic activities of paracetamol were believed to be explained mainly by the inhibition of cyclooxygenase (COX) at the central nervous system (CNS) level [5].

Moreover, an argument for this theory was the fact that paracetamol acts especially in sites with low amounts of peroxides —like those found in the brain tissues—because of the interference of the drug with the peroxidase site of COX (POX-), which leads to paracetamol inactivation [6]. The high amounts of peroxides at the sites of inflammation can also be an explanation of the fact that paracetamol does not present anti-inflammatory properties [7].

More specifically, the analgesic and antipyretic effects of paracetamol were suggested to be produced by inhibition of the COX-1 and COX-2 subtypes [8]. However, data showed that COX-2 inhibition is less involved in the analgesic effects, as Ayoub et al., 2006, demonstrated that paracetamol also has an analgesic effect in COX-2 knockout (K.O.) mice [9].

Chandrasekaran et al., 2002, revealed that the COX-3 subtype (with one intron-retaining gene of COX-1) was the target molecule for paracetamol's central analgesic mechanism [10], but this mechanism is probably irrelevant in humans and rodents, according to Graham G.G. and Scott K.F., 2005 [11].

In more recent years, the lack of proof that the analgesic effects of paracetamol are dependent only on COX's central inhibition has made researchers discover and describe other peripheral and non-COX effects [12].

Pini et al., 1996, demonstrated that paracetamol's analgesic effects also depend on the serotoninergic system, showing that the depletion of serotonin in mice brains (with D,L p-chlorophenylalanine) prevents the antinociceptive effect of

paracetamol [13]. Moreover, the opioid and NMDA glutamatergic mechanisms of action were also researched for explaining paracetamol-induced analgesia [14][15][16].

3. Recent Developments on Paracetamol's Analgesic and Antipyretic Effects

In the last 15 years, there have been numerous studies focused on the role of the cannabinoid system in explaining the analgesic effect of paracetamol. Högestätt E.D. et al. (2005) showed that paracetamol is metabolised in two steps: firstly, to p-aminophenol, and secondly, to N-arachidonoyl-phenol amine (AM404), a derivative of the arachidonic acid [17].

AM404 acts as a TRPV1 agonist (transient receptor potential cation channel subfamily V member 1) and an anandamide reuptake inhibitor, which causes an increase in endogenous cannabinoids. Cannabinoids produce anti-nociceptive effects that are primarily mediated by CB1 receptors [17][18][19]. Recent studies have also shown that AM404 may have an additional anti-inflammatory role, inhibiting COX activity and prostaglandin synthesis in the CNS [20].

Another line of research that expanded in recent years is the investigation of serotoninergic involvement in paracetamol's analgesic effect. Paracetamol increases serotonin levels, especially in the pons and frontal cortex of rats, further involving both 5-HT_2 receptors and opioid receptors (μ_1 and κ) [21][22]. Moreover, 5-HT_2 and 5-HT_3 receptors seem to play an important role in the analgesic effect of paracetamol, while the implications of 5-HT_1 receptors are still unclear [23][24]. However, it should be noted that there does not seem to be any direct binding of paracetamol with either the 5-HT_2 receptors or with the 5-HT_1 or 5-HT_3 receptors, and the mechanism is likely to be indirect [24][25][26].

The latest developments on paracetamol's analgesic effect are those that involve blocking the CNS T-type Cav3.2 calcium channels and stimulating the Kv7 potassium channels found in the dorsal root ganglion and spinal dorsal horn neurons. These discoveries may represent new targets in analgesia. The latest data is best summarised in a recent review of Przybyła G.W. et al., 2020 [27].

4. The Role of Paracetamol in Inducing Hypothermia as a Therapeutic Option

The hypothermic effect of different substances, including paracetamol, became of clinical interest in the early 2000s when two prospective randomized trials indicated that inducing hypothermia may be beneficial for some cardiac arrest patients [28].

Nowadays, inducing a state of mild hypothermia (34–35 °C) named "targeted temperature management" represents an efficacious therapeutic option for neuroprotection in different neurological injuries secondary to ischemic stroke, post-cardiac arrest, post-traumatic brain injury with high intracranial pressure, or to perinatal asphyxia-related cardiac arrest in newborns [29][30][31][32][33].

However, paracetamol alone did not show any significant benefits when investigated in two trials that studied targeted temperature management. High doses of paracetamol induced small decreases in core body temperature (CBT) in normothermic or subfebrile patients with ischaemic acute stroke. Studies that investigate paracetamol in addition to other methods that induce hypothermia are scarce [34][35].

It is thus certain that paracetamol is not efficacious in producing or maintaining the targeted temperature in therapeutic hypothermia, but its hypothermic mechanism of action could be of high interest in developing new pharmacological tools for lowering the body temperature.

A comprehensive review on the role of prostaglandins and nonsteroidal anti-inflammatory drugs in the hypothermic response in animals was published by Aronoff D.M. and Romanovsky A.A. in a volume of Sharma H., 2007 [36].

The article published by Coman L et al., 2022 tried to make a review of the last 15 years data from animal (rodents) studies regarding the mechanisms involved in the efects of paracetamol on body temperature. These studies were performed in vivo and in vitro, using various methods.

Paracetamol's mechanism of lowering the normal central body temperature is still a subject of debate for researchers. Many of these data are disparate, and some are not confirmed in the further (from a chronological point of view) articles.

- Paracetamol's hypothermic action is due to the inhibition of a COX-1 variant (probably constitutive), and its antipyretic action is due to the inhibition of COX-2;
- Mitochondrial-related functions are involved in paracetamol's hypothermic effect;
- Endothelin receptor antagonists potentiate the hypothermic effect of paracetamol;
- Opioid receptor (μ, κ, or δ) antagonists or nociceptin (NOP) receptor antagonists have no effect on paracetamol-induced hypothermia;
- Cannabinoid CB1 receptor antagonists do not influence paracetamol-induced hypothermia;
- Paracetamol has no involvement on the serotoninergic system concerning hypothermia (as opposed to its analgesic effect);
- Paracetamol's hypothermic effect is mediated somehow through $GABA_A$ receptors;
- TRPV1 has no effect on paracetamol-induced hypothermia; and
- TRPA1 is involved in the hypothermic response to paracetamol, possibly via NAPQI, a paracetamol metabolite produced in CNS.

The hypothermic mechanism of paracetamol is different from its antipyretic mechanism. More data is needed, but TRPA1 agonists have the potential to be used in clinical practice to induce hypothermia (for targeted temperature management).

Human studies confirm the in vivo and in vitro experiments in rodents regarding the presence of a hypothermic mechanism after high, non-toxic doses of paracetamol (in sub-neutral ambient temperature and humidity conditions).

Taking into account all these statements, it can be observed that paracetamol's hypothermic effect can be regarded in a dual perspective:

- A favorable one, regarding its protective cellular action against brain ischaemia; and
- An unfavorable one, regarding its toxicity on mitochondrial function and the inhibition of lipolysis.

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