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Research Article

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Acetaminophen: for Its Mechanism of Analgesic Action in Vivo Using Molecular Docking

Haider Sami Alaskiry*

Department of Pharmacy, Al-Zahrawi University in Iraq

***Corresponding Author**
Haider Sami Alaskiry, Department of Pharmacy, Al-Zahrawi University in Iraq

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Abstract

Paracetamol is the most widely used over-the-counter drug in world. The mechanism of action of its analgesic and antipyretic effect by relying on the association of activation of dopamine D2 receptors through two mechanisms of action. A new metabolic pathway involving the generation of an active metabolite p-aminophenol By being metabolized in the liver by acylamidase/N-deacetylase, and Metabolism of paracetamol to C_6 H_7 NO_2 by its hepatic metabolism CYP2A6. This paper describes the experimental Data that showed the involvement of these two metabolic pathways in analgesic and antipyretic action of paracetamol and its relationship with dopamine D2 receptors "It also explains how new targets and systems play an important role in the action of paracetamol" Finally, treatment strategies for pain and Antipyretic.

Keywords: Para-Aminophenol, Dopamine D2 Receptors, Paracetamol, Pain, Molecular Docking.

1. Introduction

The word acetaminophen and paracetamol both come from chemical names for the compound para-acetylamino phenol [1,2]. In some contexts, it is simply abbreviated as APAP, for N-acetyl- para- aminophenol. Paracetamol is widely used over-the counter analgesic (pain reducer) and antipyretic fever reducer [3-5]. It is commonly used for the relief from fever, headaches and other minor aches and pains and is a major ingredient in numerous cold and flu remedies in combination with non-steroidal anti-inflammatory drugs and opioid analgesics [6]. Paracetamol is used also in the management of more severe pain such as cancer of postoperative pain [7]. Although it is safe for humans within recommended doses, excessive doses are likely to cause hepatotoxicity. Paracetamol poisoning is the number one cause of liver failure in the West, and it is behind most cases of overdose in the United States, United Kingdom, Australia and New Zealand and the risk increases with drinking alcoholic beverages [8-11]. In the short term, paracetamol is safe and effective when used correctly Short-term adverse effects are uncommon and similar to ibuprofen, but paracetamol is usually safer than NSAIDs for long-term use [12-14].

2. Method of Mechanism of Paracetamol Metabolism

Studies have shown that paracetamol, following its hepatic deacetylation to p-aminophenol Fig. 1, is metabolized in the brain by the fatty acid amide hydrolase (FAAH) enzyme to form AM404 (N-(4-Hydroxyphenyl) -5Z, 8Z, 11Z, 14Z-eicosatetraenamide). After administration of deuterium-labeled paracetamol in rats, they detected deuterium labeled AM404 and p-aminophenol in the brain. They further showed that formation of p-aminophenol was present in all tissues, with highest levels in the liver and that AM404 was mainly found in the brain. The latter results were confirmed in a recent study [15]. Incubation of brain homogenate with p-aminophenol in vitro but not with paracetamol (except at high doses) leads to the formation of AM404 [16].

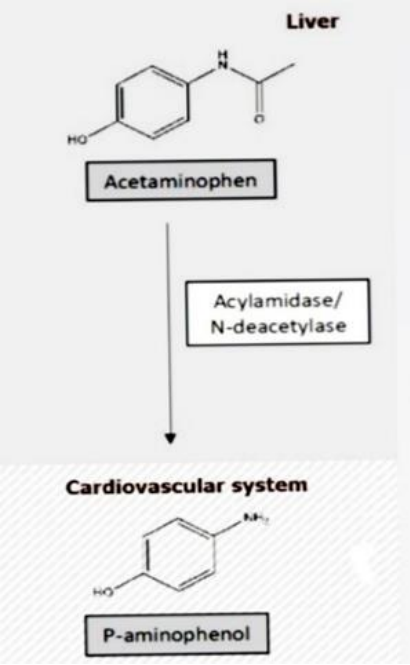

Figure 1: Metabolization of paracetamol into p-aminophenol

acetaminophen undergoes deacetylation in the liver by acylamides and N-deacetylases to produce p-aminophenol. P-aminophenols are Distribution through the cardiovascular system to the central nervous system (CNS) and present in all tissues, and as a result We took the p-aminophenol compound with the dopamine D2 receptor and performed a binding test on the molecular docking program. It was bound at the site of the 7DFP dopamine receptors used in the docking program, as shown in Fig. 2 . Where there was a link between them and the activation of dopamine, the binding activity was in The original binder is good. But Paracetamol may have an active site other than the active site of the original binder.

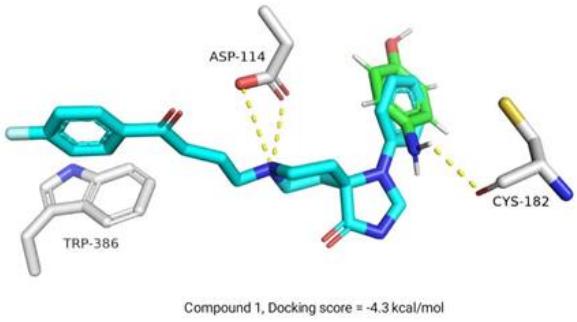

Figure 2: docking score :D2 and p-aminophenol

We also found that when paracetamol is metabolized to 3_ hydroxyparacetamol via CYP2A6 in the liver, whereby 3_ hydroxyparacetamol reaches the brain and it is possible for the N-deacetylase process to occur, and thus the next compound becomes C_6 H_7 NO_2 as shown in the following Fig. 3 , as the resulting compound binds to dopamine receptors And by identifying D2 receptors, as this was proven by experiment in the molecular docking program using the 7DFP receptors, and when using the compound resulting from the analysis of paracetamol to the C6H7NO2 compound, we found its association with the dopamine D2 receptor, and the association was very clear, as shown in Fig. 4,5

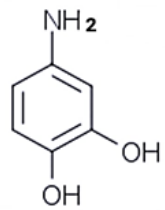

Figure 3: C_6 H_7 NO_2

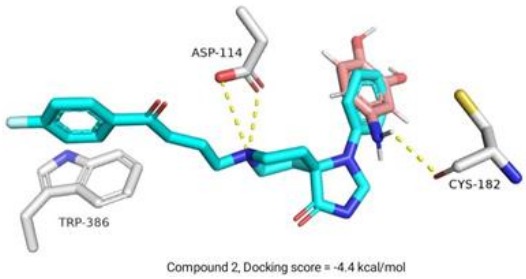

Figure 4: Docking score:D2 and 3-Hydroxy paracetamol

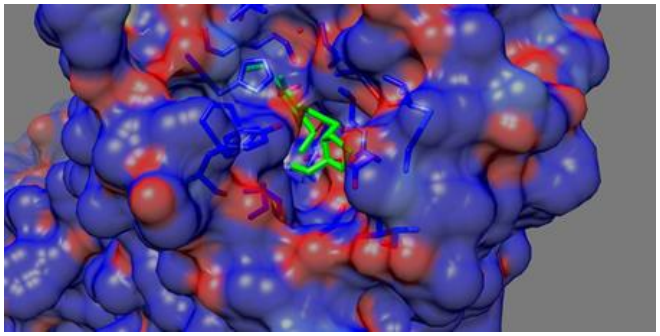

Figure 5: Docking score:D2 and 3-Hydroxy paracetamol

3. Dopamine Receptor Subtypes and Their Function

Semi-family D1 justice Activation of D1-family-like receptors is associated with Gαs, which then activate adenylate cyclase, and an increase in the intracellular concentration of the second messenger system of cAMP. D1 is encoded by the dopamine D1 receptor gene. D5 is encoded by the dopamine D5 receptor gene. Semi -D2 family justice Activation of D2-like family receptors is coupled with Gαi, which directly inhibits the formation of cAMP by inhibiting adenylate cyclase [17].

D1 is encoded by the dopamine D1 receptor gene, of which there are two types: D2Sh (short) and D2Lh (long): The D2Sh motif is pre-synaptic located, and has modulatory functions (meaning that autoreceptors, which regulate neurotransmitters by feedback mechanisms, influence the assembly, storage, and release of dopamine in the synaptic cleft). The D2Lh form may function as a conventional post-synaptic receptor, ie to transmit information (either in an excitatory or inhibitory manner) unless it is blocked by receptor antagonists or partial synthetic inducers.

D3 is encoded by the dopamine D3 receptor gene. Higher signaling of D3 dopamine receptors is observed in the islets of Calleja and the nucleus accumbens. D4 is encoded by the dopamine D4 receptor gene [18]. D4 receptor genes display polymorphisms that differ in the number of variants and tandem repeats within the exon 3 coding sequence. Some of these alleles are associated with an increased prevalence of certain diseases. For example, the D4.7 alleles have been associated with ADHD [19-21].

4. Results and Research

As a result, what we have achieved when paracetamol binds to dopamine receptors will act by inhibiting cAMP, such as the action of dopamine on human cells, and this is considered the secondary signal to the cells, and thus the signal does not reach the phosphodiesterase enzyme, and thus the phosphodiesterase is not converted to arachidonic acid, and thus inhibition of prostaglandins and as a result of that The body temperature will decrease, as well as the D2 cells inhibit the lymphocytes, thus reducing the body temperature as well. As the cyclic nucleotide phosphodiesterase includes a group of enzymes that analyze the phosphodiester bond in the second messenger molecules cAMP and cGMP. They regulate the localization, duration and amplitude of cyclic nucleotide signals within subcellular

domains. PDEs are therefore important regulators of signal transduction mediated by second reporter molecules.

Dopamine effects depend on the dose taken, so that its effects include increased excretion of sodium by the kidneys, an increase in the amount of urine, an increase in heart rate, and an increase in blood pressure, and at low doses it works through the sympathetic nervous system to increase the force of contraction. heart muscle and heart rate, thus increasing cardiac output and blood pressure. High doses cause narrowing of blood vessels and thus an increase in blood pressure, while some of the effects of stimulating dopamine receptors are produced [22,23]. Therefore, paracetamol also depends on the dose used and the duration of treatment use, and because it binds to dopain receptors and specifically D2, it may lead to a mechanism of action that increases blood pumping in blood vessels, and thus increases the access of oxygen to the brain and increases blood production to the brain. The pressure in the brain decreases and the headaches resulting from the expansion of the venous sinuses in the brain decrease and the lack of oxygen in it, as the work of the venous sinuses in the brain is long cavities located in the vicinity of the brain. to the heart via the superior vena cava. In addition, D2 receptors also dilate the pulmonary arteries, thus helping to increase deoxygenated blood in the lungs. In the short term, paracetamol is considered safe and effective when used correctly [12]. Short-term adverse effects are uncommon and similar to ibuprofen, but paracetamol is usually safer than NSAIDs for long-term use [13,14].

Paracetamol is also used frequently in patients who cannot tolerate NSAIDs. Some epidemiological studies have linked paracetamol to cardiovascular, renal, and gastrointestinal disease, but these are largely due to confounding biases and are not relevant to paracetamol in the short term [24,25]. Paracetamol may slightly increase systolic blood pressure in hypertensive patients at a dose of 4 grams per day [26,27]. An increased incidence of asthma and growth disorders has been observed in women using paracetamol during pregnancy, although it is not clear whether or not paracetamol is the real cause of this increase. Some studies suggest that there is evidence of a relationship between paracetamol during pregnancy and autism spectrum disorder and attention deficit hyperactivity disorder.

Some experiments and studies have also shown that the daily use of paracetamol leads to an increase in pressure for people with heart disease and atherosclerosis, as well as an increase in heart rate, as well as an increase in the risk of a heart attack or stroke by 20%, for those suffering from high blood pressure, stressing that doctors should They give the lowest possible dose for the shortest time, to control pain if the patient needs it A team of American scientists at the University of Michigan found that dopamine levels in the brain decreased during migraine attacks, as the scientists resorted to conducting a brain scan to measure the activity and levels of dopamine among 8 migraine patients during its attacks, along with 8 migraine patients. Healthy subjects. The research team analyzed the swabs of the participants and compared the smears of migraine patients and healthy subjects.

The scientists found that migraine patients had stable levels of dopamine between headaches similar to healthy subjects, however, it was noted that with migraine attacks, dopamine levels decreased significantly. Noticeable. This indicates that dopamine deficiency is associated with migraines, as well as normal headaches Kenneth Casey, a professor of neuroscience at the University of Michigan, USA, said that dopamine is one of the main neurotransmitters that control sensitivity, so a decrease in dopamine can lead to an increase in sensitivity so that sensory signals are usually painless on the surface of the skin, except It may be painful between muscles and blood vessels.

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