J. Pub. Health &Tox. Res., 1(1): 42-46 (2023)
https://jphtr.com/index.php/journal

Caffeine as a Psychoactive Drug: The Genetic Basis for Differences in Response by Caffeine Sensitive and Caffeine Tolerant Individuals- A Mini Review

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Article History
Received: 09 Aug 2023
Accepted: 21 Sept 2023
Published: 11 Oct 2023

Keywords:
Caffeine,
Psychoactive,
Central Nervous System

Abstract

Background: Caffeine (1,3,7 – trimethylxanthine) is a chemical compound that has a psychoactive effect on the central nervous system of the brain. It is obtained from the fruits, leaves and seeds of different plant species.

Objectives: It is widely consumed by millions of people. In addition to other sources, consumption of coffee and energy drink are the major means through which caffeine enters the body.

Methods: While caffeine is well tolerated by some individuals, it also causes some serious pharmacological health issues such as, difficulty in breathing, cardiac conduction anomaly, insomnia, headaches, anxiety, gut dysfunction, diuresis, increased heart rate, increased mental alertness and motor activity.

Results: It was discovered that there is a genetic basis for these different responses or reactions to caffeine.

Conclusions: This paper, therefore, reviews the genetic basis for the different reactions to caffeine and suggested recommendations for proper administration of caffeine to consumers as well as an area for further scientific research.

How to cite this paper: Dibie, D. C., Njideaka, T. O., & Onyeukwu, O. B. (2023). Caffeine as a Psychoactive Drug: The Genetic Basis for Differences in Response by Caffeine Sensitive and Caffeine Tolerant Individuals- A Mini Review. *Journal of Public Health and Toxicological Research, 1*(1), 42–46. Retrieved from https://jphtr.com/index.php/journal/article/view/20.

Introduction

Caffeine, which is also known by its IUPAC name 1,3,7-Trimethylpurine-2,6-dione is an alkaloid that acts as a chemical stimulant. It is also categorized under a group of compounds referred to as "'trimethyl-xanthine" and can be found in different parts of various plant species (Chaugule et al., 2019). In the leaves, fruits and seeds it is found naturally, its chemical characteristics enables protective functions against plant pathogens and help attract agents during pollination (dePaula and Farah, 2019; wright *et al*., 2013). Caffeine is obtained from different sources such as kola-nuts (Cola acuminata), tea (Thea sinensis), coffee (Caffea arabica) and chocolate (Cocoa bean).

The structure of caffeine is heterocyclic just like the structure of purine. Therefore, it is like adenine and guanine structurally. Caffeine (1,3,7-Trimethylpurine-2,6-dione) is the most widely used psychoactive stimulant in the world. Caffeine is always consumed in the form of coffee and energy drinks (Mitchell *et al*., 2015, Richards and Smith, 2016) by millions of people to effect wakefulness, reduce fatigue, and cause an overall improvement in concentration and focus. However, increased heart rate, mental alertness diuresis and motor activity are some pharmacological effects associated with caffeine.

Food and food nutrients are very important for human survival and maintenance/sustenance of health. The nutrients obtained from foods are vital requirements needed by the body. These food nutrients are important for the various organs and cells in the body to carry out their functions effectively (Chen *et al.*, 2018). Thus, the body needs to get the right information from these food nutrients for it to function well. In other words, the nutrients we take in give our bodies information and instruction on how to function (Chen *et al.*, 2018). According to the US Food and Drug Administration, consumption of caffeine is safe provided it does not exceed 200ppm in cola-type beverages (Nehlig, 2018). Also, it's been generally assumed that caffeine consumption is mostly safe, as such it is consumed at levels above the recommended amount. The effects of caffeine when consumed at low doses could be mild. However, when caffeine is consumed excessively, it could lead to serious health issues such as anxiety, insomnia and

cause an increase in heart rate (Eskelinen and Kivipelto, 2010).

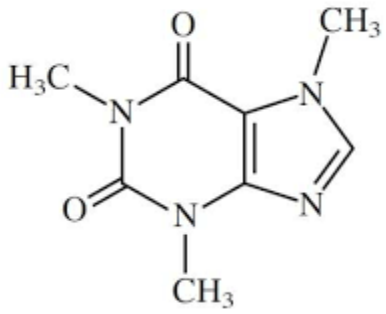

Figure 1: Chemical representation of caffeine (Source: Abebe, 2011)

Caffeine metabolism in the liver

Caffeine is circulated in the system almost immediately after oral consumption. During circulation, caffeine goes through the liver where it reacts with the enzyme (cytochrome P450 enzyme) which converts or transforms it to a form by which it can be eliminated the kidneys (Cornelis *et al*., 2006). The group of enzymes known as cytochrome p450 enzymes are majorly responsible for the clearance of most of the absorbed caffeine. Usually, complete absorption of caffeine takes place within 45 minutes after oral intake.

According to research, it takes about four hours for half of the amount of caffeine consumed to be completely metabolised, but this may vary in certain individuals like people with impaired liver function and pregnant women (Nehlig, 2018; Yang *et al*., 2010) and possibly also in people with caffeine sensitivity. Hence the effect of caffeine can last for several hours. The genetic code of the enzyme which breakdown caffeine is CYP1A2. CYP1A2 is highly expressed in the human liver and is equivalent to about 13% of cytochrome P450 enzymes in total (Wang & Zhou, 2009). The enzyme's activity, however, is influenced by such factors like race, pre-existing disease, exposure to inducers and genetic polymorphisms (Nehlig, 2018; Yang *et al*. 2010; Arnaud, 2011). In this review however, the focus with regards to caffeine metabolism, will be on exposure to CYP1A2 inducers and genetic polymorphisms.

Cytochrome P450 enzyme (CYP1A2)

The activity of cytochrome P450 enzyme (CYP1A2) is very important in the overall metabolism of caffeine, certain drugs and aromatic/heterocyclic amines (Gunes and Dahl, 2008). It belongs to the CYP1 family. The gene that codes for CYP1A2 enzyme is located on chromosome 15 and its expression is controlled by the aryl hydrocarbon receptor (AhR) pathway. CYP1A2 is induced by the transactivation of the aromatic hydrocarbon receptor by ligand binding and nuclear translocation (Zhou *et al*., 2009). Caffeine is a common substrate of CYP1A2 gene expression/activity, and it can be used as a substrate; to probe for CYP1A2 activity (Kot and Daniel, 2008a). In the human liver, CYP1A2 gene expression and activity occurs with about 40-fold variations inter individually. In addition to environmental factors, genetic factors have also been reported to affect CYP1A2 activity. Therefore, genetic variation among individuals, influences the responses to CYP1A2 metabolism of caffeine. Hence, CYP1A2 enzyme activity may vary from individual to individual.

Caffeine catabolism reactions

The CYP enzymes functions to catalyse reactions on its substrates either through oxidation/reduction, dehalogenation, dealkylation or through hydroxylation. (Heller, 2013; Lin *et al*., 2012). Caffeine being a psychoactive drug, is mainly (about 70–80%) metabolised or broken down in the human liver. This happens through the demethylation of the nitrogen atom at position "3" thus giving rise to another compound known as paraxanthine (1,7-dimethylxanthine or 17X) (Kot and Daniel, 2008b; Begas *et al*., 2007) (see figure 3 below). This reaction occurs through the action of CYP1A2 enzyme on caffeine, in the liver (Begas *et al*. 2007). According to past experiments with the microsomes from human liver, it has been shown that demethylation of the nitrogen atom also occurs at position "1" and "7"; which then gives rise to theobromine (7-8% of caffeine breakdown) and theophylline (also 7-8% of caffeine breakdown) respectively. (Kot and Daniel, 2008b). Paraxanthine, which is the main product of caffeine breakdown; further undergoes demethylation of the nitrogen atom at position "7" and hydroxylation at of the carbon atom position "8" to form 1-methylxanthine and 1,7-dimethyluric acid, respectively. Also, theobromine is acted upon by xanthine oxidase to form 3,7-dimethyluric acid. The action on theophylline by CYP1A2 and CYP1A1 cytochrome P450 enzymes gives rise to both 1-methylxanthine and 3-methylxanthine.

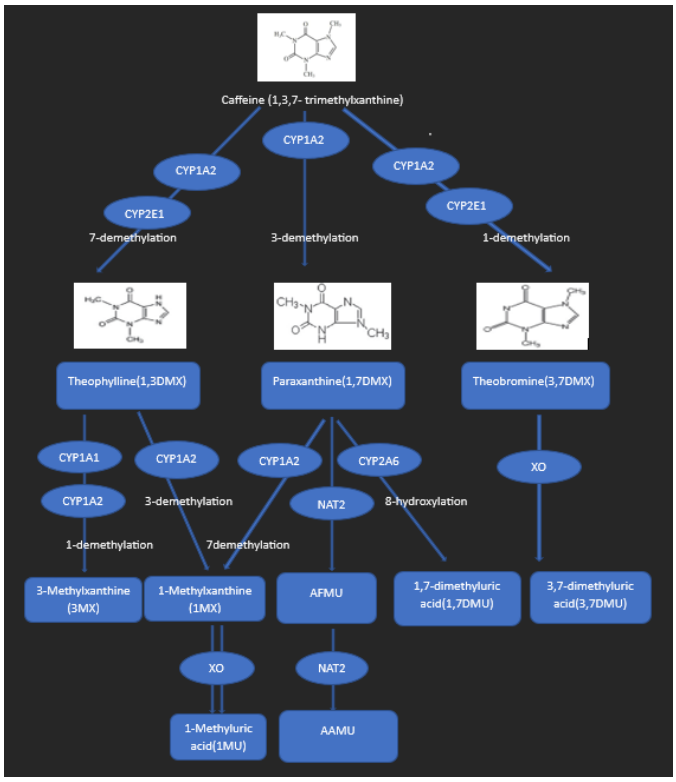

Figure 2: Metabolism of caffeine pathway. (CYP, cytochrome P450; NAT2, N-acetyltransferase-2; XO, xanthine oxidase; AFMU,5-acetylamino-6-formylamino-3-methyluracil; AAMU, 5-acetylamino-6-amino-3-methyluracil). (Source: Nehlig, 2018).

Mechanism of action of caffeine in the brain.

The absorption of caffeine takes place within one hour after intake and gets distributed all around the body water. It goes through the cell membranes including the brain. Caffeine has been categorized as a drug that affects the central nervous system. There are three major modes by which caffeine affects the central nervous system.

First caffeine can act as an antagonist in such a way that it antagonizes adenosine by binding to adenosine receptors in the brain. Caffeine, therefore, acts by antagonizing the various receptors of adenosine such as A1, A2A, A3 and A2B. When adenosine is created in the brain; it binds to adenosine receptors. This binding regulates or slows down the activity of nerve cells, thus this regulates the release of neurotransmitters which control sleep, arousal, memory, learning and cognition (Sebastião et al., 2009). Due to its antagonistic effect, caffeine binds to adenosine receptors. This occurrence in turn affects the release of neurotransmitters that control mood, learning, memory, cognition sleep and mental alertness (IOM, 2014). The binding of caffeine to adenosine receptors causes increased nerve cell activity. The pituitary gland in the brain senses this occurrence and then it releases hormones which then tells the adrenal glands to produce adrenaline. Adrenaline is the "flight or fight" hormone; the production of this hormone therefore results in different effects on the body such as elevated blood pressure, heart rate, increased energy, motor activity, and mental alertness.

Another mode of action for caffeine can be described; thus, caffeine enhances the influx of calcium via the plasma membrane and the sarcoplasmic reticulum. Calcium then gets released through synaptic transmission into the peripheral and central nervous systems; and these systems also rely on a controlled release of neurotransmitters. These neurotransmitters again also depend on the calcium influx that travels into the nerve endings. Thus, at very low concentrations of caffeine (1,3,7- trimethyl xanthine), the uptake of calcium as well as its release via the endoplasmic reticulum is enhanced. In contrast also, at high doses of 1,3,7-methylxanthine, the uptake of calcium and its release as well through the endoplasmic reticulum becomes inhibited (Osz et al., 2022; Chirasani et al., 2021; Fredholm et al., 2017).

In actual sense, the reactions associated with caffeine intake are not linked directly to the suppression of adenosine, gamma-aminobutyric acid (GABA) or noradrenaline. In the body, there are three different intracellular pools of calcium and at low concentration of caffeine, pools two and three become sensitive to the normal intracellular release of calcium via the sarcoplasmic reticulum. However, this mode of action is unlikely to occur except if the caffeine concentration is very high, then it can be considered as a possible cause of 1,3,7-methylxanthine's antagonistic effect.

The third mode of action for caffeine is as follows. Caffeine inhibits phosphodiesterase enzymes. These enzymes breakdown cyclic adenosine monophosphate (cAMP). Therefore, the inhibition of phosphodiesterase enzymes in turn causes cAMP to accumulate. When cAMP accumulates, it enhances the release of neurotransmitters such as dopamine, epinephrine, and norepinephrine. This in turn leads to an alteration in memory, cognition, mood and alertness (IOM, 2014). However, this third mechanism through which caffeine acts may not really be the likely occurrence when compared to the way caffeine antagonises adenosine receptors in the brain. The reason is that for this mechanism to occur, the concentration of caffeine consumed should have been very high and therefore toxic to the body. With reference to caffeine's mechanism of action, the focus however will be on "caffeine" as an antagonist on adenosine receptor.

Genetic polymorphisms/variability in caffeine receptors and in the gene coding for CYP1A2.

Receptors known as adenosine A2 receptors are important in enhancing the reactions associated with caffeine. Caffeine blocks adenosine A2A receptors (A2Ars) in the brain and as such it antagonises these receptors. Caffeine binds with adenosine A1 (A1Rs) and A2A (A2ARs) receptors, therefore the actions of adenosine at both receptors are antagonized. According to Huang *et al.* (2011) adenosine is an inhibitory neuromodulator which controls the sleep-wake cycle.

There are differences in the expression levels of the adenosine A2A receptor gene (ADORA2A) between self-rated caffeine-sensitive individuals and caffeine-insensitive individuals (Retey *et al*., 2007). Therefore, the intake of the same quantity and concentration of caffeine by different individuals can affect these individuals differently, depending on their genetic make-up.

Also, a study on caffeine considered the differences in blood pressure (BP) associated with caffeine intake and suggested that the differences in the blood pressure may be caused by genetic polymorphisms in the receptors of adenosine A2A and α2-adrenergic receptors (Rendal *et al*., 2012).

Research suggests that there is a decreased likelihood of having the ADORA2A genotype due to excessive caffeine consumption. Thus; people with this genotype may be less reactive to caffeine and its effects (Nehlig, 2018; Yang *et al*., 2010; Retey *et al*., 2007).

With regards to the response to caffeine, the population may be divided into 'fast' and 'slow' caffeine metabolizers, and this could be due to variations in gene which codes for CYP1A2 enzyme that is involved the metabolism of caffeine (Nehlig 2018; Yang *et al*., 2010).

In another research also, they investigated the relationship between increased intake of coffee and CYP1A2 polymorphism. Thus, the population was divided into fast caffeine metabolizers and slow caffeine metabolizers (Denden *et al*., 2016).

Discussion

After the intake of caffeine, absorption takes place around 45 minutes. It takes about four hours for half of the amount of caffeine consumed to be completely metabolised. This means that; the higher the concentration and amount consumed, the longer it takes for it to be completely metabolised and eventually, eliminated from the body. Thus, it can be said that the reactions associated with caffeine intake as discovered from previous works is time dependent and this time value

varies also depending on how fast or slow the individual metabolises caffeine. Therefore, these different reactions caused by the effect of caffeine can last for several hours, and this varies for different individuals.

Again, directing the focus to CYPIA2 (cytochrome P450 enzyme); it is an enzyme that is very crucial to the breakdown of caffeine into simpler products that can be eliminated by the kidneys. Even in caffeine sensitive individuals, caffeine being a substrate for the expression/activity of CYPIA2, such enzyme activity/expression could exist, but not at an adequate speed that it should occur. According to Koonrungsesomboon *et al. (*2018), they investigated 'the impact of genetic polymorphisms on CYP1A2 activity in humans' and discovered an increased enzyme activity in a certain type of CYP1A2 polymorphism. However, in the other CYP1A2 polymorphisms, no increased or altered enzyme activity was observed. Thus, the difference in the enzyme activity among individuals could also be the reason behind having such categories as fast caffeine metabolizers and slow caffeine metabolizers. Caffeine is a psychostimulant drug that can cross the barrier between the blood and the brain and exert its effects. Now, with reference to genetic polymorphisms of adenosine receptors, differences in the gene that code for these adenosine receptors could probably be responsible for this occurrence.
This statement agrees with the findings of Banks *et al. (2019)* who discovered that genetic polymorphisms in ADORA2A and CYP1A2 influence caffeine's effect on postprandial glycaemia. Thus, if really there are genetic differences, this explains why the reactions associated with caffeine intake are pleasant in some individuals and adverse in others. Therefore, this supports the outcome of different reactions to caffeine intake by different individuals (Fulton *et al*., 2018). Thus, if adenosine A2A receptor genes are less expressed in an individual, it is possible that the reactions associated with caffeine intake are favourable or pleasant because 1,3,7-trimethyl xanthine does not bind to the receptors of adenosine in the brain to cause unpleasant effects. Instead, they are metabolized in the liver and eliminated. Therefore, it can be said that caffeine sensitive individuals have highly expressed adenosine receptor genes and the presence of this psychostimulant drug in these group of individuals has a high antagonistic effect on the receptors of adenosine in the brain. However according to research, a decrease in adenosine receptor gene (ADAORA2A genotype) expression correlates with increased caffeine consumption. Hence, the reason for the tolerance of caffeine (Nehlig 2018).

Conclusion

Caffeine is a psychoactive drug, known to be consumed widely by millions of people to cause wakefulness, reduce fatigue, and cause an overall improvement in concentration and focus. Although caffeine is assumed to be generally safe, individuals react differently to this psychoactive stimulant when consumed. Intake of caffeine in excessive amount causes headache, difficulty in breathing, alteration of cardiac conduction, anxiety, restlessness, sleeplessness and dysfunction of the gut. Genetic variability in the receptors of adenosine in the brain and in the gene which codes for CYP1A2 (the enzyme responsible for the breakdown of caffeine) are possible reasons or factors responsible for the different reactions to caffeine. Therefore, caffeine should be avoided by caffeine sensitive individuals and caffeine tolerant individuals should also avoid consuming caffeine in excess, to prevent the adverse effects associated with it. Also, adequate information such as the adverse effects of this psychoactive drug (especially when consumed in excess) should be published where necessary, so that its consumers are well informed. Further scientific research can be done to find out specifically how caffeine exerts its pleasant or favourable effects in caffeine tolerant people.

Declaration of Interest

This manuscript's authors claim no conflicts of interest. No financial, personal, or professional relationships might bias this research or its presentation. This manuscript's findings are based exclusively on data analysis and the authors' professional judgment.

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