ORIGINAL RESEARCH PAPER

Pharmaceutical Science

REVIEW ON RECENT TRENDS IN DISCOVERIES RELATED TO CAFFEINE

KEY WORDS: Caffeine, Central nervous system stimulant, Coffee.

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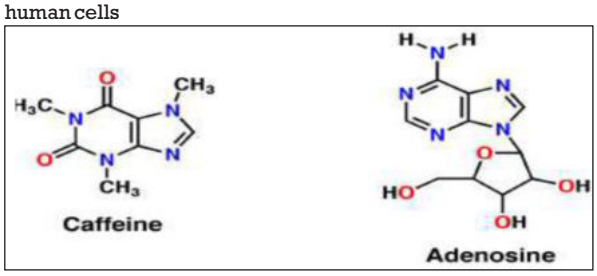
ABSTRACT

BACKGROUND-Caffeine is the most widely consumed behaviorally active substance in the world. Caffeine produces its behavioral effects through adenosine receptor antagonism and subsequent changes in many neurotransmitter systems. This results in increased alertness, and caffeine may be especially beneficial in low arousal situations (e.g., working at night, prolonged work, or sleep deprivation). It improves performance on tasks that are impaired when alertness is low (vigilance and sustained response). Coffee and tea is the major sources of caffeine, which has been shown to have a number of behavioral effects. The beneficial effects often increase with dose (within the limits consumed by the majority of the population). **MAIN BODY**-Caffeine has less effect on memory but has recently been shown to improve retrieval from general knowledge and the ability to think logically. Improvements following ingestion of caffeinated coffee are most easily observed when alertness is low (e.g. after sleep deprivation; in the early morning; after lunch; when performing at night; after prolonged work; when the person has a minor illness such as the common cold). It has been suggested that the positive effects of caffeine merely reflect removal of negative effects of withdrawal. **CONCLUSION-**The beneficial effects of caffeine can be demonstrated using realistic consumption patterns. Caffeine acts as a central nervous system stimulant in humans. Generally, CNS stimulants speed up physical and mental processes.

BACKGROUND

Caffeine acts as a central nervous system (CNS) stimulant in humans. Generally, CNS stimulants speed up physical and mental processes. The caffeine molecule has several aspects that make it a perfect molecule to act as a CNS stimulant. **First**, it is able to easily cross the brain's blood barrier, similarly to other drugs such as alcohol, nicotine, and antidepressants. The brain blood barrier serves to protect the CNS by preventing viruses and other molecules from crossing into the brain. This barrier is so effective that many drugs cannot pass through it, and those that can pass through typically enter it slower than other membranes. However, caffeine passes through the blood barrier incredibly easily. The exact reason for this is not yet clear, but there are a few possible reasons(7).

Caffeine is both water and fat-soluble, which allows it to pass through nearly all membranes easily. Also, caffeine could be helped across the barrier by attaching to a transporter that is usually associated with adenosine, a molecule created in all human cells



Fig,1. Caffeine and adenosine have similar structures, which allows it to affect the brain.

The **second** way caffeine is able to affect the brain so strongly is because of its structural similarity to adenosine(fig.1.). Adenosine is a molecule produced by all humans, and has various functions throughout the body. In the brain, adenosine acts as an inhibitory neurotransmitter, or CNS depressant. It bonds to neurotransmitters in the brain, and this binding creates a pathway that slows the activity of nerve cells and causes brain blood vessels to dilate, leading to a feeling of drowsiness. Since adenosine is being continually made by the body, the amount of adenosine increases throughout the day. As a result, as the day goes on and adenosine continues to build up, drowsiness increases (2).

Physicochemical properties of caffeine

- Caffeine is odorless and has characteristic bitter taste.
- It is a colorless powder, moderately soluble in water and organic solvents.
- At higher temperature, the solubility of caffeine in water is considerably increased.Its melting point is 236° C and the temperature of sublimation at atmospheric pressure is 178° C.
- Caffeine is relatively stable in dilute acids and alkalis, forming unstable salts with acids. Being a very weak base, it reacts with acids giving readily hydrolyzed salts.
- The pH of a 1 % solution is 6.9, with an estimated pKa of
- approximately 14 and pKb of 14.2(4)
- Caffeine exhibits an ultraviolet absorption spectrum with a max of 274 nm, and E = 9700 in the aqueous phase has been used to deter- mine caffeine concentrations at 272 nm.(5)

Mechanism of action:

caffeine has multiple pharmacological effects, including adenosine receptor antagonism, presynaptic α1 receptor antagonism and phosphodiesterase inhibition, which results in increased catecholamine release, and A-adrenergic receptor stimulation.

Caffeine stimulates the central nervous system and, in general, increases cyclic AMP. Caffeine acts through different molecular pathways, resulting in a wide range of biological effects. (1)

a) Adenosine receptors

The action and effect of adenosine on the body's different physiological systems are generally the opposite of the action and effect of caffeine. Caffeine is a methylxanthine which, being similar to purine, binds to the A1 and A2a adenosine receptors. The majority of caffeine's pharmacological effects seem to depend on the antagonistic action of adenosine in cell surface receptors. At the plasma concentrations found following mean caffeine intake in an adult diet, caffeine is the non-selective antagonist of the A1 and A2a adenosine receptors. Caffeine acts by inhibiting the A1, A2a and A2b adenosine receptors and has a low affinity for A3 receptors.

b) Phosphodiesterases

Caffeine is a weak competitive inhibitor of phosphodiesterase, increasing the effect and duration of intracellular cAMP. The result is a strengthening of the effects of catecholamines.

c) Calcium channels.

Caffeine activates the ryanodine-sensitive calcium channels found in the endoplasmic and sarcoplasmic reticula, triggering the release of intracellular calcium and affecting

calcium homeostasis. Doses much higher than the therapeutic concentration of caffeine are required to trigger these effects, which become particularly acute in the event of overdose.

d) GABAa receptors

Caffeine acts as an antagonist in the binding sites of benzodiazepine, which blocks the GABAa receptors. Nevertheless, the concentration of caffeine required to produce this effect is much greater than that commonly reached as part of a normal adult diet.

e) Others

Other areas in which caffeine acts include various ion channels, with the release of neurotransmitters, and a number of different enzymes. In general, this effect is inhibitory in nature. Effects on calcium entry and potassium and calcium channels have also been described. Caffeine also seems to increase the sensitivity of Mg- ATPase to the stimulating effects of calcium in the cardiac myofibrils. (11)

Therapeutic uses:

Fig.2. Tea and coffee the most commonly used source of caffeine.

Adverse effects:

The most common adverse effects are –

- palpitation
- tachycardia
- gastric disturbances
- tremor
- nervousness and
- insomnia
- High doses can cause intense anxiety, fear and panic attacks.
- Jaundice, liver synthetic dysfunction and cholestatic hepatitis are also seen. (5)

MAIN TEXT

Global Caffeine Consumption Through Coffee

Currently, approximately 80% of the world's population consumes a caffeinated product every day, mainly for its stimulating effects, which makes it the most widely consumed psychoactive substance in the world. So where does coffee consumption stand in relation to other caffeine sources? Over the last 50 years, world coffee consumption increased at a mean annual growth rate of 1.9%, to almost 9.7 million tons in 2019.The highest coffee consumption occurs especially in the Americas, Europe and Japan(fig.). The European Union is responsible for the largest consumption volume (about 28% of the total world consumption), but breaking up into individual countries, the USA are the first consumer country (about 16% of the total world consumption), followed by Brazil (the largest producer, with 13% of world consumption), European Union countries, and Japan. Philippines, Russia, Ethiopia, Canada and Mexico contribute about 2.8%, 2.5%, 2.4%, 2.3% and 1.5% of total world consumption, respectively Considering these data, it is not difficult to accept that coffee is the major contributor to caffeine intake in most countries worldwide. Exceptions occur in specific areas, such as regions of South America, Ireland and the United Kingdom, China, India and other Asian countries, where other beverages, such as maté leaves, natural guaraná beverage, and black/green *Camelia sinensis teas*, are typically consumed as a source of caffeine. (8)

Recent Discoveries Of Caffeine

Year	Studies done on caffeine	Implication/effecticity
2021	The study was done to analyze the impact of caffeine on the physical and mental health of people. The data for the study has been collected from case studies enunciated and highlighted in the previous research studies in this subject area and using that data, the analysis was conducted to analyze the impact of caffeine in the context of the target population.	The recent studies implies that mainstream of people consume caffeine on an everyday basis. It was also found that coffee is the chief product of consumed caffeine amongst the people of United Kingdom. The mean consumption was 268 mg/day that is 2 to 3 cups, with people taking more caffeine than adults. Greater caffeine consumption by the local populace carries with it a greater likelihood of headache, anxiety, and psychological suffering. At the same time, caffeine consumption is related to nervousness in people at the multivariate level. (18)
2020	The study was done based on the effects of coffee and caffeine consumption and its health-linked effects. Based on the increased popularity of the cold-brew coffee, the study has provided a comprehensive overview of the effects of cold-brew coffee on health and exercise performance.	The recent studies implies that consumption of 3 to 4 cups of coffee (300–400 mg/day) was associated with decreased risk factors of cancers, cardiovascular diseases, diabetes and Alzheimer disease. It is noteworthy that caffeine intake in specific groups, particularly in women, needs special consideration(17)
2019	The study was done to identify the main effects of caffeine on the body, a substance found in various food products like coffee and chocolate, consumed worldwide and used by athletes as food supplement as well. Caffeine is known to increase energetic metabolism throughout the brain, but it also decreases cerebral blood flow, inducing relative cerebral hypoperfusion	The recent studies implies that According to the literature, it can be confirmed that caffeine directly interferes with the central nervous system. It can be affirmed that the moderate consumption of coffee does not represent a risk to health, presenting a protective effect in several pathologies. The proven benefits of coffee justify its inclusion in the functional foods group, not only for caffeine but also for other compounds present in coffee. Current evidence has shown moderate consumption of caffeine is a therapeutic resource as it promotes physical and mental performance. (16)
2018	The study was done on The Acute Effects of Caffeinated Black Coffee on Cognition and Mood in Healthy Young and Older Adults	The recent studies implies that Regular coffee produced the expected effects of decreased reaction time and increased alertness when compared to placebo(12)

CONCLUSIONS

Caffeine is now thought to be the most widely used psychoactive drug in the world. Coffee and tea is the major sources of caffeine, which has been shown to have a number of behavioral effects. The beneficial effects often increase with dose. Caffeine acts as a central nervous system stimulant in humans. Generally, CNS stimulants speed up physical and

mental processes. Caffeine is generally used to restore mental alertness or wakefulness during fatigue or drowsiness. It's having multiple health benefits such as, it boosts energy level, improve physical performance, reduce depression etc. Along with it caffeine has multiple adverse effects like palpitation, tachycardia, gastric disturbances etc.

Caffeine is rapidly and essentially completely absorbed from the gastrointestinal tract into the bloodstream. After absorption, Caffeine is distributed throughout the body fluid and tissues. The liver is the primary site of caffeine metabolism. The elimination half-life of caffeine ranges between 3 and 7 h and can be influenced by many factors, including sex, age etc.

List of abbreviations-
Central nervous system –CNS

Declaration
Ethics approval and consent to participate- not applicable
Consent for publication- not applicable

Availability of data and material- All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Competing interests- The author declare that they have no conflict of interest

Funding- T*he author received no financial support for the research, authorship, and/or publication of this article.*

Authors' contributions- The author has collected data and information from various articles and complied it.

Acknowledgements- I want to thank anonymous referees for their useful data

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