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Caffeine Addiction

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SUMMARY

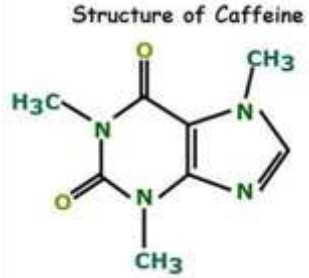
Caffeine is rapidly and completely absorbed within an hour following ingestion. It is distributed throughout body water and readily crosses cell membranes including the brain. Its primary mechanisms for stimulatory activity appear to be the blocking of adenosine receptors and inhibition of phosphodiesterase. Caffeine is metabolized and excreted in humans primarily as paraxanthine, which also has pharmacologic activity. With repeated caffeine dosing, paraxanthine may contribute to development of tolerance and withdrawal symptoms. Caffeine clearance rates are affected by both environmental and physiological factors, such as use of oral contraceptives, smoking, and pregnancy. Tolerance to some of caffeine's physiological affects develops with continued use.

INTRODUCTION

Caffeine (1, 3, 7-trimethylxanthine) is a plant alkaloid with a chemical structure of $C_8H_{10}N_4O_2$. It is a bitter, white crystalline purine, a methylxanthine alkaloid, and is chemically related to the adenine and guanine bases of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). It is found in the seeds, fruits, nuts, or leaves of a number of plants native to Africa, East Asia and South America and helps to protect them against herbivores and from competition by preventing the germination of nearby seeds, as well as encouraging consumption by select animals such as honey bees. The best-known source of caffeine is the coffee bean, the seed of the *Coffea* plant. It is a central nervous system (CNS) stimulant of the methylxanthine class and is the most commonly consumed psychoactive substance globally. It is mainly used for its eugeroic (wakefulness promoter), ergogenic (physical performance enhancing), or nootropic (cognition improving) properties. Caffeine acts by blocking binding of adenosine at a number of adenosine receptor types, inhibiting the centrally depressant effects of adenosine and enhancing the release of acetylcholine (Ribeiro and Sebastio 2010).

Global Consumption rate

People may drink beverages containing caffeine to relieve or prevent drowsiness and to improve cognitive performance. Caffeine-containing drinks, such as coffee, tea, and cola, are consumed globally in high volumes. In 2020, almost 10 million tonnes of coffee beans were consumed globally. Caffeine is the world's most widely consumed psychoactive drug. Unlike most other psychoactive substances, caffeine remains largely unregulated and legal in nearly all parts of the world. Caffeine has both positive and negative health effects. It can treat and prevent the premature infant breathing disorders bronchopulmonary dysplasia of prematurity and apnea of prematurity. Caffeine citrate is on the WHO Model List of Essential Medicines (WHO Report 2023). It may confer a modest protective effect against some diseases, including Parkinson's disease (Callaghan *et al.*, 2018). Some people experience sleep disruption or anxiety if they consume caffeine, but others show little disturbance. Evidence of a risk during pregnancy is equivocal; some authorities recommend that pregnant women limit caffeine to the equivalent of two cups of coffee per day or less (Jahanfar and Jaafar 2015). Caffeine can produce a mild form of drug dependence, associated with withdrawal symptoms such as sleepiness, headache, and irritability, when an individual stops using caffeine after repeated daily intake (Juliano and Griffiths (2004)).



Structure

Caffeine is similar in structure to purines, adenine, and guanine. The nitrogen atoms in the first, third, and ninth positions of the purine ring are bound to methyl groups, and the carbon atoms in the second and sixth positions are doubly bonded to oxygen atoms. Caffeine has a three-dimensional structure similar to that of adenosine, which allows it to bind and block its receptors (Hillis et al., 2015).

Function

Caffeine is a central nervous system (CNS) stimulant that acts as an adenosine receptor antagonist. It binds to adenosine receptors in the CNS, which inhibits adenosine binding. This stimulates the activity of the medullary, vagal, vasomotor, and respiratory centers in the brain.

Effects

Low doses of caffeine can increase alertness and elevate mood, while high doses can cause dizziness and headache.

Absorption

Caffeine is rapidly absorbed by the small intestine after oral administration, and its peak value occurs at around 30 minutes.

Toxicity

A single dose of 200 mg of caffeine or less is usually not associated with toxic effects in healthy people.

Addiction

People can develop a dependence on coffee and other caffeinated beverages quite quickly. This is due to the chemical changes that sustained consumption produces in the brain. If someone drinks caffeine on a daily basis, they will develop a tolerance just as they would to other drugs or alcohol. After a while, the user requires more and more caffeine to produce the same effects of alertness. Regular caffeine drinkers become acclimated to the wake-up effect that the substance produces and gradually require higher amounts to achieve the same "caffeine fix." Similar to other drugs, people who abruptly stop drinking caffeine after prolonged use will start to suffer from withdrawal symptoms and experience cravings. This causes many individuals to relapse when attempting to quit and resume drinking caffeine, regardless of the health problems associated with chronic caffeine use.

Compulsive caffeine consumption under any circumstances has not been observed, and caffeine is therefore not generally considered addictive. However, some diagnostic models, such as the ICDM-9 and ICD-10 (International Classification of Diseases, Tenth Revision), include a classification of caffeine addiction under a broader diagnostic model. Some state that certain users can become addicted and therefore unable to decrease use even though they know there are negative health effects (Meredith *et al.*, 2013).

Overdose

Consumption of 1–1.5 grams (1,000–1,500 mg) per day is associated with a condition known as **caffeinism** (Winston *et al.,* 2005). Caffeinism usually combines caffeine dependency with a wide range of unpleasant symptoms including nervousness, irritability, restlessness, insomnia, headaches, and palpitations after caffeine use (Iancu *et al.,* 2007). Caffeine overdose can result in a state of central nervous system overstimulation known as caffeine intoxication, a clinically significant temporary condition that develops during, or shortly after, the consumption of caffeine. This syndrome typically occurs only after ingestion of large amounts of caffeine, well over the amounts found in typical caffeinated beverages and caffeine tablets (*e.g.,* more than 400–500 mg at a time). The Diagnostic and Statistical Manual of Mental Disorders (DSM) lists caffeine-related syndromes, including caffeine intoxication, caffeine-induced anxiety disorder, and caffeine withdrawal syndrome.

According to the DSM-5, caffeine intoxication may be diagnosed more than five of the following symptoms develop after recent consumption of caffeine: restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal disturbance, muscle twitching, rambling flow of thought and speech, tachycardia or cardiac arrhythmia, periods of inexhaustibility, and psychomotor agitation. According to the International Classification of Diseases (ICD-11), cases of very high caffeine intake (e.g. more than 5 g) may result in caffeine intoxication with symptoms including mania, depression, lapses in judgment, disorientation, disinhibition, delusions, hallucinations or psychosis, and rhabdomyolysis (Mortality and Morbidity Statistics 2019)

Severe intoxication

As of 2007 there is no known antidote or reversal agent for caffeine intoxication. Treatment of mild caffeine intoxication is directed toward symptom relief; severe intoxication may require peritoneal dialysis, haemodialysis, or hemofiltration. Intralipid infusion therapy is indicated in cases of imminent risk of cardiac arrest in order to scavenge the free serum caffeine.

Caffeine metabolism

Caffeine is metabolized in the liver by the *cytochrome P450* oxidase enzyme system (particularly by the CYP1A2 isozyme) into three dimethylxanthines, each of which has its own effects on the body:

- Paraxanthine (84%): Increases lipolysis, leading to elevated glycerol and free fatty acid levels in blood plasma.
- Theobromine (12%): Dilates blood vessels and increases urine volume.
- Theobromine is also the principal alkaloid in the cocoa bean (chocolate).
- Theophylline (4%): Relaxes smooth muscles of the bronchi, and is used to treat asthma.

The therapeutic dose of theophylline, however, is many times greater than the levels attained from caffeine metabolism. 1,3,7-Trimethyluric acid is a minor caffeine metabolite. 7-Methylxanthine is also a metabolite of caffeine (Singh *et al.,* 2022). Each of the above metabolites is further metabolized and then excreted in the urine. Caffeine can accumulate in individuals with severe liver disease, increasing its half-life.

A 2011 review found that increased caffeine intake was associated with a variation in two genes that increase the rate of caffeine catabolism. Subjects who had this mutation on both chromosomes consumed 40 mg more caffeine per day than others. This is presumably due to the need for a higher intake to achieve a comparable desired effect, not that the gene led to a disposition for greater incentive of habituation.

Decaffeination

Germany, the birthplace of decaffeinated coffee, is home to several decaffeination plants, including the world's largest, Caffein Compagnie (Charles 2016). Over half of the decaf coffee sold in the U.S. first travels from the tropics to Germany for caffeine removal before making its way to American consumers.

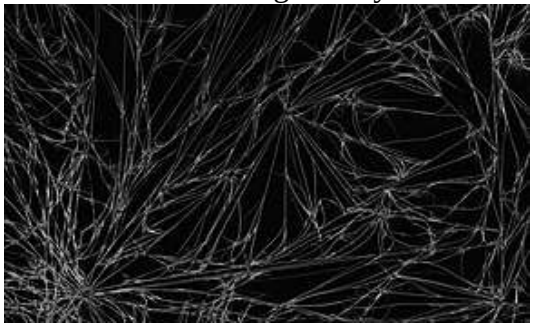


Fig 1. Fibrous crystals of purified caffeine. Dark-field microscopy image, about 7 mm × 11 mm.

Extraction of caffeine from coffee, to produce caffeine and decaffeinated coffee, can be performed using a number of solvents.

Following are main methods (Senese 2005):

Water extraction: Coffee beans are soaked in water. The water, which contains many other compounds in addition to caffeine and contributes to the flavor of coffee, is then passed through activated charcoal, which removes the caffeine. The water can then be put back with the beans and evaporated dry, leaving decaffeinated coffee with its original flavor. Coffee manufacturers recover the caffeine and resell it for use in soft drinks and over-the-counter caffeine tablets.

Supercritical carbon dioxide extraction: Supercritical carbon dioxide is an excellent nonpolar solvent for caffeine, and is safer than the organic solvents that are otherwise used. The extraction process is simple: CO_2 is forced through the green coffee beans at temperatures above 31.1 °C and pressures above 73 atm. Under these conditions, CO_2 is in a "supercritical" state: It has gas like properties that allow it to penetrate deep into the beans but also liquid-like properties that dissolve 97–99 % of the caffeine. The caffeine-laden CO_2 is then sprayed with high-pressure water to remove the caffeine. The caffeine can then be isolated by charcoal adsorption (as above) or by distillation, recrystallization, or reverse osmosis.

Extraction by organic solvents: Certain organic solvents such as ethyl acetate present much less health and environmental hazard than chlorinated and aromatic organic solvents used formerly. Another method is to use triglyceride oils obtained from spent coffee grounds.

CONCLUSION

Decaffeinated coffees do in fact contain caffeine in many cases – some commercially available decaffeinated coffee products contain considerable levels. One study found that decaffeinated coffee contained 10 mg of caffeine per cup, compared to approximately 85 mg of caffeine per cup for regular coffee. Decaffeinated tea can be a good alternative for people who want to limit their caffeine intake, but it may not have as many health benefits as regular tea.

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