Caffeine

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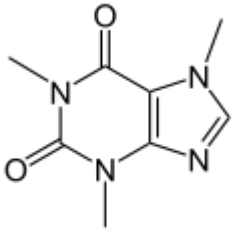
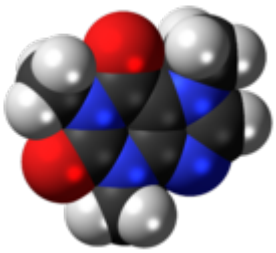
Caffeine is a bitter, white crystalline xanthine alkaloid and a stimulant drug. Caffeine is found in varying quantities in the seeds, leaves, and fruit of some plants, where it acts as a natural pesticide that paralyzes and kills certain insects feeding on the plants, as well as enhancing the reward memory of pollinators. It is most commonly consumed by humans in infusions extracted from the seed of the coffee plant and the leaves of the tea bush, as well as from various foods and drinks containing products derived from the kola nut. Other sources include yerba maté, guarana berries, guayusa, and the yaupon holly.

In humans, caffeine acts as a central nervous system stimulant, temporarily warding off drowsiness and restoring alertness. It is the world's most widely consumed psychoactive drug, but unlike many other psychoactive substances, it is legal and unregulated in nearly all parts of the world. Beverages containing caffeine, such as coffee, tea, soft drinks, and energy drinks, enjoy great popularity. In North America, 90% of adults consume caffeine daily.[1]

Part of the reason caffeine is classified by the Food and Drug Administration as generally

Caffeine





Systematic (IUPAC) name

1,3,7-Trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione

3,7-Dihydro-1,3,7-trimethyl-1*H*-purine-2,6-dione

Clinical data

AHFS/Drugs.com	monograph
Pregnancy cat.	C (US)
Legal status	Unscheduled (AU) GSL (UK) OTC (US)
Dependence liability	Moderate
Routes	Oral, insufflation, enema

Pharmacokinetic data

Bioavailability	99%
Protein binding	17% to 36%
Metabolism	demethylation by CYP1A2
Half-life	5 hours
Excretion	urine (100%)

Identifiers

ATC code	N06BC01
PubChem	CID 2519

recognized as safe is that toxic doses (over 10 grams for an average adult) are much higher than typically used doses (less than 500 milligrams). Ordinary consumption has low health risks, even when carried on for years – there may be a modest protective effect against some diseases, including Parkinson's disease,[2][3] heart disease,[4] and certain types of cancer. Some people experience sleep disruption if they consume caffeine, especially during the evening hours, but others show little disturbance and the effect of caffeine on sleep is highly variable.

DrugBank	DB00201
ChemSpider	2424 ✓
UNII	3G6A5W338E ✓
KEGG	D00528 ✓
ChEBI	CHEBI:27732 ✓
ChEMBL	CHEMBL113 ✓
PDB ligand ID	CFF (PDBe, RCSB PDB)
Chemical data	
Formula	$C_8H_{10}N_4O_2$
Mol. mass	194.19 g/mol
SMILES	
InChI	

Evidence of a risk to pregnancy is equivocal, with some authorities concluding that it is wise for pregnant women to limit consumption to the equivalent of two cups of coffee per day or less.[5][6] Caffeine has pressor and mild diuretic effects when administered to people who are not used to it, but regular users develop a tolerance to this effect, and studies have generally failed to support the common notion that ordinary consumption contributes significantly to dehydration. With heavy use, tolerance develops rapidly to autonomic effects such as elevated heart rate and muscle twitching, but not to the cognitive or arousal effects of caffeine. The degree to which caffeine can produce significant dependency and caffeine addiction remains a subject of controversy in the medical literature.

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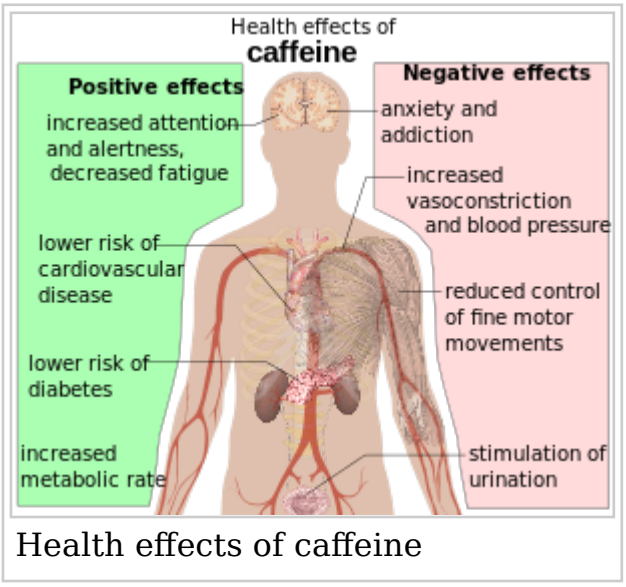


Health effects of caffeine

Caffeine is a central nervous system and metabolic stimulant,[7] and is used both recreationally and medically to reduce physical fatigue and to restore alertness when drowsiness occurs. It produces increased wakefulness, faster and clearer flow of thought, increased focus, and better general body coordination.[8] The amount of caffeine needed to produce effects varies from person to person, depending on body size and degree of tolerance. Effects begin less than an hour after consumption, and a moderate dose usually wears off in about five hours.[8]

Caffeine has a number of effects on sleep, but does not affect all people in the same way. It improves performance during sleep deprivation but may lead to subsequent insomnia.[9] In shift workers it leads to fewer mistakes caused by tiredness.[10] In athletics, moderate

doses of caffeine can improve sprint,[11] endurance,[12] and team sports performance,[13] but the improvements are usually not very large. Interestingly, some evidence suggests that coffee does not produce the ergogenic effects observed in other caffeine sources.[14] High doses of caffeine, however, can impair athletic performance by interfering with coordination.[15] Evidence shows that, contrary to common advice, caffeine may be helpful at high altitude.[16]

Physical effects

Consumption of 1000–1500 mg per day is associated with a condition known as *caffeinism.*[17] Caffeinism usually combines caffeine dependency with a wide range of unpleasant physical and mental conditions including nervousness, irritability, restlessness, insomnia, headaches, and heart palpitations after caffeine use.[18]

Coffee consumption is associated with a lower overall risk of cancer.[19] This is primarily due to a decrease in the risks of hepatocellular and endometrial cancer, but it may also have a modest effect on colorectal cancer.[20] There does not appear to be a significant protective effect against other types of cancers, and heavy coffee consumption may increase the risk of bladder cancer.[20] Moderate coffee consumption may decrease the risk of cardiovascular disease,[4] and it may somewhat reduce the risk of type 2 diabetes.[21] Drinking four or more cups of coffee per day does not affect the risk of hypertension compared to drinking little or no coffee. However those who drink 1–3 cups per day may be at a slightly increased risk.[22] Caffeine increases intraocular pressure in those with glaucoma but does not appear to affect normal individuals.[23] It may protect people from liver cirrhosis.[24] There is no evidence that coffee stunts a child's growth.[25] Caffeine may increase the effectiveness of some medications including ones used to treat headaches.[26] Similarly, intravenous caffeine is often used in hospitals to provide temporary pain relief for headaches caused by low cerebrospinal fluid pressure.

Caffeine consumption during pregnancy does not appear to increase the risk of congenital malformations, miscarriage or growth retardation even when consumed in moderate to high amounts.[27] However as the data supporting this conclusion is of poor quality some suggest limiting caffeine consumption during pregnancy.[28][29] For example the UK Food Standards Agency has recommended that

pregnant women should limit their caffeine intake, out of prudence, to less than 200 mg of caffeine a day – the equivalent of two cups of instant coffee, or one and a half to two cups of fresh coffee.[30] The American Congress of Obstetricians and Gynecologists (ACOG) concluded in 2010 that caffeine consumption is safe up to 200 mg per day in pregnant women.[6] Although the evidence that caffeine may be harmful during pregnancy is equivocal, there is some evidence that the hormonal changes associated with pregnancy slow the metabolic clearance of caffeine from the system, causing a given dose to have longer-lasting effects (as long as 15 hours in the third trimester).[31]

Caffeine is a weak bronchodilator. In clinical tests on adults with athsma, at fairly low doses (5mg/kg of body weight), caffeine has been shown to provide a small improvement in lung function, such that it needs to be controlled for in diagnostic tests.[32] Caffeine is the primary treatment of the breathing disorders apnea of prematurity[33] and may also be effective in preventing bronchopulmonary dysplasia in premature infants.[34] The only short-term risk associated with caffeine citrate treatment is a temporary reduction in weight gain during the therapy,[35] and longer term studies (18 to 21 months) have shown lasting benefits of treatment of premature infants with caffeine.[36] While some authors have raised the possibility of subtle long-term problems,[37] follow-up neurological data at 18 months and at five years after neonatal caffeine treatment revealed the opposite; treatment appears to be neuroprotective, as caffeine-treated children were significantly less likely to have cerebral palsy and had reduced rates of language and cognitive delay.[38][39]

When doses of caffeine equivalent to 2–3 cups of coffee are administered to people who have not consumed caffeine during prior days, they produce a mild increase in urinary output.[40] Because of this diuretic effect, some authorities have recommended that athletes or airline passengers avoid caffeine to reduce the risk of dehydration.[40] Most people who consume caffeine, however, ingest it daily. Regular users of caffeine have been shown to develop a strong tolerance to the diuretic effect,[40] and studies have generally failed to support the notion that ordinary consumption of caffeinated beverages contributes significantly to dehydration, even in athletes.[41][42]

Psychological effects

The US National Institutes of Health states: "[Too] much caffeine can make you restless, anxious, and irritable. It may also keep you from sleeping well and cause headaches, abnormal heart rhythms, or other problems. If you stop using caffeine, you could get withdrawal symptoms. Some people are more sensitive to the effects of caffeine than others. They should limit their use of caffeine. So should pregnant and nursing women.[43]„

Four caffeine-induced disorders are recognized by the American Psychiatric Association (APA) including: caffeine intoxication, caffeine-induced sleep disorder, caffeine-induced anxiety disorder and caffeine-related disorder not otherwise specified (NOS).[44] The DSM-IV defines a person with caffeine-induced sleep disorder as an individual who regularly ingests high doses of caffeine sufficient to induce a significant disturbance in his or her sleep, sufficiently severe to warrant clinical attention.[44] As of 2010 the effect of caffeine on people with ADHD is not known.[45] Some studies have however found a modest protective effect against Alzheimer disease, but the evidence is inconclusive.[46][47][48]

Caffeine can have negative effects on anxiety disorders.[49] A number of clinical studies have shown a positive association between caffeine and anxiogenic effects and/or panic disorder.[50][51] At high doses, typically greater than 300 mg, caffeine can both cause and worsen anxiety[52] or, rarely, trigger mania or psychosis. In moderate doses caffeine may reduce symptoms of depression and lower suicide risk.[45] In moderate doses caffeine typically does not affect learning or memory,[53] and can improve cognitive functions, especially in people who are fatigued, possibly due to its effect on alertness.[54] For some people, anxiety can be very much reduced by discontinuing caffeine use.[55]

Caffeine toxicity

Caffeine overdose can result in a state of central nervous system over-stimulation called *caffeine intoxication* (DSM-IV 305.90).[44] 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 symptoms of caffeine intoxication are comparable to the symptoms of overdoses of other stimulants: they may include restlessness, fidgeting, anxiety, excitement, insomnia, flushing of the face, increased urination, gastrointestinal disturbance, muscle twitching, a

rambling flow of thought and speech, irritability, irregular or rapid heart beat, and psychomotor agitation.[56] In cases of much larger overdoses, mania, depression, lapses in judgment, disorientation, disinhibition, delusions, hallucinations, or psychosis may occur, and rhabdomyolysis (breakdown of skeletal muscle tissue) can be provoked.[57][58]

Primary symptoms of caffeine intoxication[56]

Extreme overdose can result in death.[59][60] The median lethal dose (LD_{50}) given orally is 192 milligrams per kilogram in rats. The LD_{50} of caffeine in humans is dependent on individual sensitivity, but is estimated to be about 150 to 200 milligrams per kilogram of body mass or roughly 80 to 100 cups of coffee for an average adult.[61] Though achieving lethal dose of caffeine would be difficult with regular coffee, it is easier to reach high doses with caffeine pills, and the lethal dose can be lower in individuals whose ability to metabolize caffeine is impaired. Chronic liver disease is one factor that can slow the metabolism of caffeine.[62] There has been a reported death of a man who had liver cirrhosis overdosing on caffeinated mints.[63][64][65] Drugs such as fluvoxamine or levofloxacin can have a similar effect by blocking the liver enzyme responsible for the metabolism of caffeine, thus increasing the central effects and blood concentrations of caffeine five-fold.[58][59][60][66] The exact cause of death in such cases is uncertain, but may result from cardiac arrhythmia leading to cardiac arrest.

Treatment of severe caffeine intoxication is generally supportive, providing treatment of the immediate symptoms, but if the patient has very high serum levels of caffeine then peritoneal dialysis, hemodialysis, or hemofiltration may be required.[56]

Addiction and tolerance

Main article: Caffeine addiction

With repetitive use, physical dependence or addiction may occur. Also, some effects of caffeine, particularly the autonomic effects, decrease over time, a phenomenon known as a tolerance. Tolerance develops quickly to some (but not all) effects of caffeine, especially among

heavy coffee and energy drink consumers.[67] Some coffee drinkers develop tolerance to its sleep-disrupting effects, but others apparently do not.[31]

Withdrawal

Withdrawal symptoms – including headaches, irritability, inability to concentrate, drowsiness, insomnia, and pain in the stomach, upper body, and joints – may appear within 12 to 24 hours after discontinuation of caffeine intake, peak at roughly 48 hours, and usually last from 2 to 9 days.[68] Withdrawal headaches are experienced by 52% of people who stopped consuming caffeine for two days after an average of 235 mg caffeine per day prior to that.[69] In prolonged caffeine drinkers, symptoms such as increased depression and anxiety, nausea, vomiting, physical pains and intense desire for caffeine containing beverages are also reported. Peer knowledge, support and interaction may aid withdrawal.

Caffeine withdrawal is categorized as a mental disorder in the DSM-5 (the 5th edition of the Diagnostic and Statistical Manual published by the American Psychiatric Association).[70] Previous versions of the manual included "caffeine intoxication" but not caffeine withdrawal.

Other animals

> *See also: Effect of psychoactive drugs on animals*

Caffeine has a significant effect on spiders, which is illustrated here in the erratic construction of their webs.

While safe in humans, caffeine is considerably more toxic to various animals, such as dogs and birds.[71][72] The increased toxicity of caffeine in some animals is at least partly due to a poorer ability to metabolize the compound.[73] Caffeine also has a pronounced effect on mollusks, various insects, and spiders.[74]

Microbial remediation

Pseudomonas putida CBB5 can live on pure caffeine and has been observed to break caffeine down into carbon dioxide and ammonia.[75]

Sources and consumption

See also: Caffeinated drink

Global

Caffeine Content in Select Food and Drugs[76][77][78][79][80]

Product	Serving size	Caffeine per serving (mg)	Caffeine (mg/L)
Caffeine tablet (regular-strength)	1 tablet	100	—
Caffeine tablet (extra-strength)	1 tablet	200	—
Excedrin tablet	1 tablet	65	—
Hershey's Special Dark (45% cacao content)	1 bar (43 g or 1.5 oz)	31	—
Hershey's Milk Chocolate (11% cacao content)	1 bar (43 g or 1.5 oz)	10	—
Percolated coffee	207 mL (7.0 US fl oz)	80–135	386–652
Drip coffee	207 mL (7.0 US fl oz)	115–175	555–845
Coffee, decaffeinated	207 mL (7.0 US fl oz)	5–15	24–72
Coffee, espresso	44–60 mL (1.5–2.0 US fl oz)	100	1,691–2,254
Tea – black, green, and other types, – steeped for 3 min.	177 millilitres (6.0 US fl oz)	22–74[79][80]	124–416
Guayakí yerba mate (loose leaf)	6 g (0.21 oz)	85[81]	approx. 358
Coca-Cola Classic	355 mL (12.0 US fl oz)	34	96
Mountain Dew	355 mL (12.0 US fl oz)	54	154
Pepsi Max	355 mL (12.0 US fl oz)	69	194
Guaraná Antarctica	350 mL (12 US fl oz)	30	100
Jolt Cola	695 mL (23.5 US fl oz)	280	403
Red Bull	250 mL (8.5 US fl oz)	80	320

consumption of caffeine has been estimated at 120,000 tonnes per year, making it the world's most popular psychoactive substance. This amounts to one serving of a caffeinated beverage for every person every day.[82]

Caffeine is found in many plant species, where it acts as a natural pesticide, with high caffeine levels being observed in seedlings still developing foliage but lacking mechanical protection;[83] caffeine paralyzes and kills certain insects feeding on the plant.[84] High caffeine levels have also been found in the surrounding soil of coffee

bean seedlings. Therefore, caffeine is understood to have a natural function as both a natural pesticide and an inhibitor of seed germination of other nearby coffee seedlings, thus giving it a better chance of survival.[85] Caffeine has also been found to enhance the reward memory of honeybees, improving the reproductive success of the plant.[86]

Common sources of caffeine are coffee, tea, soft drinks and energy drinks, caffeine supplements, and (to a lesser extent) chocolate derived from cocoa beans.[87] Less commonly used sources of caffeine include the yerba maté, guarana and ilex guayusa plants,[88] which are sometimes used in the preparation of teas and energy drinks. Two of caffeine's alternative names, *mateine* and *guaranine*, are derived from the names of these plants.[89]

The disparity in experience and effects between the various natural caffeine sources could be because plant sources of caffeine also contain widely varying mixtures of other xanthine alkaloids, including the cardiac stimulants theophylline and theobromine, and other substances such as polyphenols that can form insoluble complexes with caffeine.[90]

One of the world's primary sources of caffeine is the coffee "bean" (which is the seed of the coffee plant), from which coffee is brewed. Caffeine content in coffee varies widely depending on the type of coffee bean and the method of preparation used;[91] even beans within a given bush can show variations in concentration. In general, one serving of coffee ranges from 80 to 100 milligrams, for a single shot (30 milliliters) of arabica-variety espresso, to approximately 100–125 milligrams for a cup (120 milliliters) of drip coffee.[92][93] *Arabica* coffee typically contains half the caffeine of the *robusta* variety.[91]

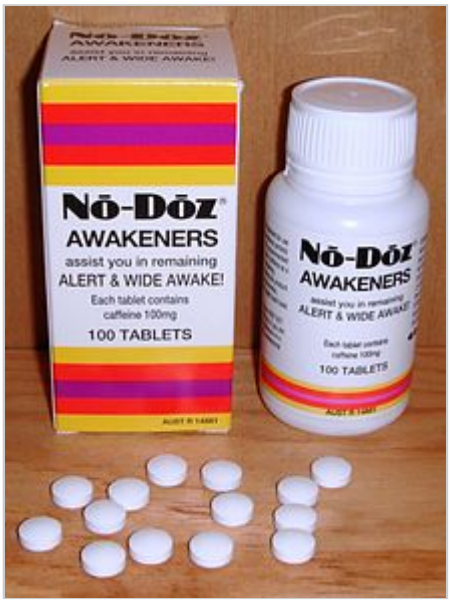
In general, dark-roast coffee has very slightly less caffeine than lighter roasts because the roasting process reduces a small amount of the bean's caffeine content.[92][93]

Tea contains more caffeine than coffee by dry weight. A typical serving, however, contains much less, since tea is normally brewed much weaker. Also contributing to caffeine content are growing conditions, processing techniques, and other variables. Thus, certain types of tea may contain somewhat more caffeine than other teas.[94]

Tea contains small amounts of theobromine and slightly higher levels

of theophylline than coffee. Preparation and many other factors have a significant impact on tea, and color is a very poor indicator of caffeine content. Teas like the pale Japanese green tea, *gyokuro*, for example, contain far more caffeine than much darker teas like *lapsang souchong*, which has very little.[94]

Caffeine is also a common ingredient of soft drinks, such as cola, originally prepared from kola nuts. Soft drinks typically contain about 10 to 50 milligrams of caffeine per serving. By contrast, energy drinks, such as Red Bull, can start at 80 milligrams of caffeine per serving. The caffeine in these drinks either originates from the ingredients used or is an additive derived from the product of decaffeination or from chemical synthesis. Guarana, a prime ingredient of energy drinks, contains large amounts of caffeine with small amounts of theobromine and theophylline in a naturally occurring slow-release excipient.[95]



No-Doz 100 mg caffeine tablets

Chocolate derived from cocoa beans contains a small amount of caffeine. The weak stimulant effect of chocolate may be due to a combination of theobromine and theophylline, as well as caffeine.[96] A typical 28-gram serving of a milk chocolate bar has about as much caffeine as a cup of decaffeinated coffee, although dark chocolate has about the same caffeine as coffee by weight. Some dark chocolate currently in production contains as much as 160 mg per 100 g[77] – which is double the caffeine content of the highest caffeinated drip coffee by weight.

Various manufacturers market caffeine tablets, claiming that using caffeine of pharmaceutical quality improves mental alertness. These effects have been borne out by research that shows caffeine use (whether in tablet form or not) results in decreased fatigue and increased attentiveness.[8]

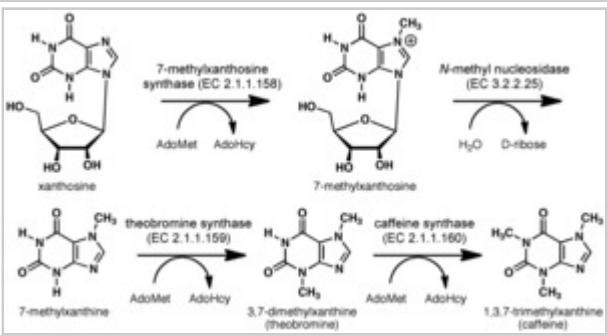
These tablets are commonly used by students studying for their exams and by people who work or drive for long hours.[97] One U.S. company is also marketing dissolving caffeine strips as an alternative to energy drinks.[98] Another unusual intake route is SpazzStick, a caffeinated

lip balm.[99] As of 2013, a number of innovative caffeinated products such as Alert Energy Caffeine Gum, a Wrigley product, had been introduced in the United States, but were under scrutiny; after announcement of an investigation by the FDA of the health effects of added caffeine in foods, Alert Energy Caffeine Gum was voluntarily withdrawn from sale.[100]

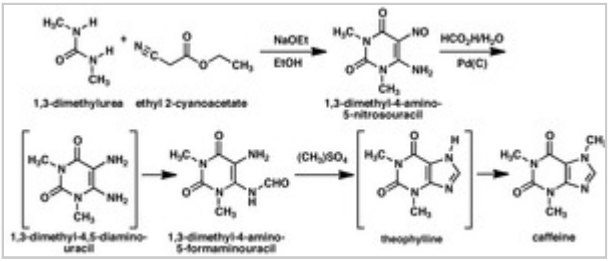
As of 2011, inhaled caffeine is a distribution method under scrutiny by some U.S. lawmakers.[101]

Chemical properties and biosynthesis

Pure anhydrous caffeine is a white colorless powder with a melting point of 227–228 °C. Caffeine is moderately soluble in water at room temperature (2 g/100 mL), but very soluble in boiling water (66 g/100 mL).[105] It is also moderately soluble in ethanol (1.5 g/100 mL).[105] It is weakly basic (pK_a = ~0.6) requiring strong acid to protonate it.[106]



Caffeine biosynthesis[102]



Caffeine laboratory synthesis[103][104]

Caffeine does not contain any stereogenic centers[107] and hence is classified as an achiral molecule.[108]

The xanthine core of caffeine contains two fused rings, a pyrimidinedione and imidazole. The pyrimidinedione in turn contains two amide functional groups that exist predominately in a zwitterionic resonance form where the nitrogen atoms are double bonded to their adjacent amide carbons atoms. Hence all six of the atoms within the pyrimidinedione ring system are sp^2 hybridized and planar. Therefore the fused 5,6 ring core of caffeine contains a total of ten pi electrons and hence according to Hückel's rule is aromatic.[109]

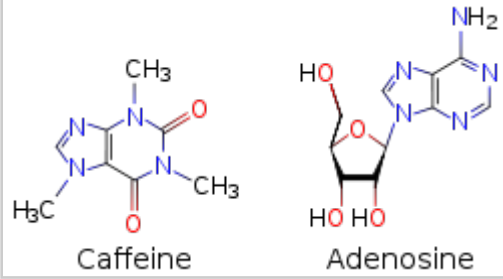
Caffeine is synthesized in plants from the purine nucleotides AMP, GMP, and IMP. These in turn are transformed into xanthosine and then theobromine, the latter being the penultimate precursor of

caffeine.[110] Being readily available as a byproduct of decaffeination, caffeine is not usually synthesized chemically.[111] If desired, it may be synthesized from dimethylurea and malonic acid.[103][104][112]

Pharmacology

Inside the body caffeine acts through several mechanisms, but its most important effect is to counteract a substance called adenosine that naturally circulates at high levels throughout the body, and especially in the nervous system. In the brain, adenosine plays a generally protective role, part of which is to reduce neural activity levels – for example, there is some evidence that adenosine helps to induce torpor in animals that seasonally hibernate.[113]

Mechanism of action



Caffeine's primary mechanism of action is as an antagonist of adenosine receptors in the brain

Adenosine acts as an inhibitory neurotransmitter that suppresses activity in the central nervous system. "Largely as a consequence of its blockade of adenosine receptors, caffeine also has profound effects on most of the other major neurotransmitters, including dopamine, acetylcholine, serotonin, and, in high doses, on norepinephrine",[114] and to a small extent epinephrine, glutamate, and cortisol.[*citation needed*] At high doses, exceeding 500 milligrams, caffeine inhibits GABA neurotransmission. GABA reduction explains why caffeine increases anxiety, insomnia, rapid heart and respiration rate.[*citation needed*]

Because caffeine is both water- and lipid-soluble, it readily crosses the blood–brain barrier that separates the bloodstream from the interior of the brain. Once in the brain, the principal mode of action is as a nonselective antagonist of adenosine receptors (in other words, an agent that reduces the effects of adenosine). The caffeine molecule is structurally similar to adenosine, and is capable of binding to adenosine receptors on the surface of cells without activating them, thereby acting as a competitive inhibitor.[115]

Adenosine is found in every part of the body, because it plays a role in the fundamental adenosine triphosphate (ATP) related energy

producing mechanism and is also needed for RNA synthesis, but it has additional functions in the brain. The evidence indicates that brain adenosine acts to protect the brain by suppressing neural activity and by increasing blood flow via receptors located on vascular smooth muscle.[116] Brain adenosine levels are increased by various types of metabolic stress, including lack of oxygen and interruption of blood flow. There is evidence that adenosine functions as a synaptically released neurotransmitter in some parts of the brain; however, stress-related adenosine increases appear to be produced mainly by extracellular metabolism of ATP. Unlike most neurotransmitters, adenosine does not seem to be packaged into vesicles that are released in a voltage-controlled manner, but the possibility of such a mechanism has not been fully ruled out.[116]

Several classes of adenosine receptors have been described, with different anatomical distributions. A_1 receptors are widely distributed, and act to inhibit calcium uptake. A_{2A} receptors are heavily concentrated in the basal ganglia, an area that plays a critical role in behavior control, but can be found in other parts of the brain as well, in lower densities. There is evidence that A_{2A} receptors interact with the dopamine system, which is involved in reward and arousal. (A_{2A} receptors can also be found on arterial walls and blood cell membranes.)[117]

Beyond its general neuroprotective effects, there are reasons to believe that adenosine may be more specifically involved in control of the sleep–wake cycle. Robert McCarley and his colleagues have argued that accumulation of adenosine may be a primary cause of the sensation of sleepiness that follows prolonged mental activity, and that the effects may be mediated both by inhibition of wake-promoting neurons via A_1 receptors, and activation of sleep-promoting neurons via indirect effects on A_{2A} receptors.[117] More recent studies have provided additional evidence for the importance of A_{2A}, but not A_1, receptors.[118]

Caffeine, like other xanthines, also acts as a phosphodiesterase inhibitor.[119] As a competitive nonselective phosphodiesterase inhibitor,[120] caffeine raises intracellular cAMP, activates protein kinase A, inhibits TNF-alpha[121][122] and leukotriene[123] synthesis, and reduces inflammation and innate immunity.[123]

A number of potential mechanisms have been proposed for the athletic performance-enhancing effects of caffeine.[124] In the classic,

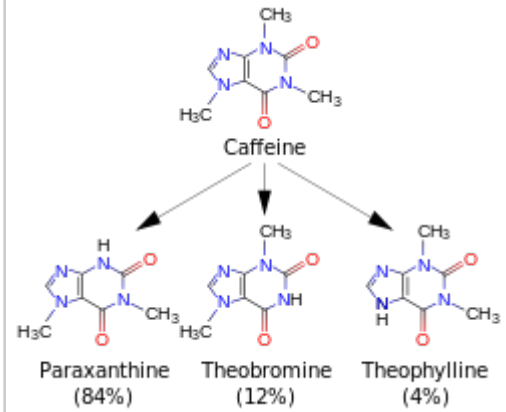
or metabolic theory, caffeine may increase fat utilization and decrease glycogen utilization. Caffeine mobilizes free fatty acids from fat and/or intramuscular triglycerides by increasing circulating epinephrine levels. The increased availability of free fatty acids increases fat oxidation and spares muscle glycogen, thereby enhancing endurance performance. In the nervous system, caffeine may reduce the perception of effort by lowering the neuron activation threshold, making it easier to recruit the muscles for exercise.[125]

Caffeine metabolites

Metabolites of caffeine also contribute to caffeine's effects. Paraxanthine is responsible for an increase in the lipolysis process, which releases glycerol and fatty acids into the blood to be used as a source of fuel by the muscles. Theobromine is a vasodilator that increases the amount of oxygen and nutrient flow to the brain and muscles. Theophylline acts as a smooth muscle relaxant that chiefly affects bronchioles and acts as a chronotrope and inotrope that increases heart rate and force of contraction.[126]

Metabolism

Caffeine from coffee or other beverages is absorbed by the small intestine within 45 minutes of ingestion and then distributed throughout all tissues of the body.[127] Peak blood concentration is reached within 1–2 hours.[128] It is eliminated by first-order kinetics.[129] Caffeine can also be absorbed rectally, evidenced by the formulation of suppositories of ergotamine tartrate and caffeine (for the relief of migraine)[130] and chlorobutanol and caffeine (for the treatment of hyperemesis).[131]



Caffeine is metabolized in the liver into three primary metabolites: paraxanthine (84%), theobromine (12%), and theophylline (4%)

The biological half-life of caffeine – the time required for the body to eliminate one-half of the total amount of caffeine – varies widely among individuals according to such factors as age, liver function, pregnancy, some concurrent medications, and the level of enzymes in the liver needed for caffeine metabolism. It can also be significantly altered by drugs or hormonal states. In healthy adults, caffeine's half-life has been measured with a range of results. Some measures get 4.9

hours,[132] and others are at around 6 hours.[133] Heavy cigarette smokers show a decrease in half-life of 30–50%,[31] oral contraceptives can double it,[31] and pregnancy can raise it even more, to as much as 15 hours during the last trimester.[31] In newborn infants the half-life can be 80 hours or more; however it drops very rapidly with age, possibly to less than the adult value by the age of 6 months.[31] The antidepressant fluvoxamine (Luvox) reduces the clearance of caffeine by more than 90%, and prolongs its elimination half-life more than tenfold; from 4.9 hours to 56 hours.[132]

Caffeine is metabolized in the liver by the cytochrome P450 oxidase enzyme system, in particular, by the CYP1A2 isozyme, into three dimethylxanthines,[134] each of which has its own effects on the body:

- Paraxanthine (84%): Increases lipolysis, leading to elevated glycerol and free fatty acid levels in the blood plasma.
- Theobromine (12%): Dilates blood vessels and increases urine volume. Theobromine is also the principal alkaloid in the cocoa bean, and therefore 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.[*citation needed*]

Each of these metabolites is further metabolized and then excreted in the urine. Caffeine can accumulate in individuals with severe liver disease, increasing its half-life.[135]

Some quinolone antibiotics exert an inhibitory effect on CYP1A2, thereby reducing clearance of caffeine and thus increasing blood levels.[136]

A 2011 analysis published by *PLoS Genetics* reviewed five studies covering more than 47,000 subjects of European descent. Researchers determined that habitual caffeine intake is associated with variations in two genes that regulate how quickly the body processes caffeine. Subjects who had a high-intake mutation of either gene on both chromosomes consumed 40 mg more caffeine per day (equivalent to a can of cola) than people who did not.[137]

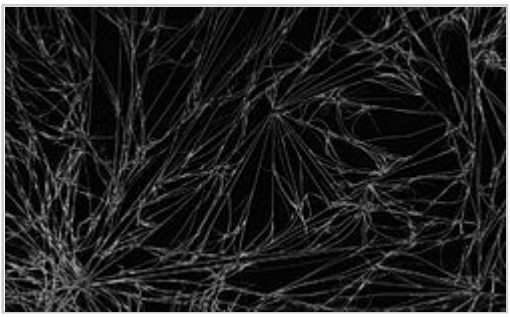
Detection in biological fluids

Caffeine can be quantified in blood, plasma, or serum to monitor

therapy in neonates, confirm a diagnosis of poisoning, or facilitate a medicolegal death investigation. Plasma caffeine levels are usually in the range of 2–10 mg/L in coffee drinkers, 12–36 mg/L in neonates receiving treatment for apnea, and 40–400 mg/L in victims of acute overdosage. Urinary caffeine concentration is frequently measured in competitive sports programs, for which a level in excess of 15 mg/L is usually considered to represent abuse.[138]

Decaffeination

Main article: Decaffeination



Fibrous crystals of purified caffeine. Dark field light microscope image, the image covers an area of approx. 11 by 7 mm.

Extraction of caffeine from coffee, to produce decaffeinated coffee and caffeine, is an important industrial process and can be performed using a number of solvents. Benzene, chloroform, trichloroethylene, and dichloromethane have all been used over the years but for reasons of safety, environmental impact, cost, and flavor, they have been superseded by the following main methods:

- **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.[139]
- **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 gaslike 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.[139]

- **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.[139]

"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.[140]

History

Main articles: History of chocolate, History of coffee, History of tea, and History of yerba mate


Coffeehouse in Palestine, circa 1900

According to Chinese legend, the Chinese emperor Shennong, reputed to have reigned in about 3000 BCE, accidentally discovered tea when he noted that when certain leaves fell into boiling water, a fragrant and restorative drink resulted.[141] Shennong is also mentioned in Lu Yu's *Cha Jing*, a famous early work on the subject of tea.[142]

The earliest credible evidence of either coffee drinking or knowledge of the coffee tree appears in the middle of the fifteenth century, in the Sufi monasteries of the Yemenin southern Arabia.[143] From Mocha, coffee spread to Egypt and North Africa, and by the 16th century, it had reached the rest of the Middle East, Persia and Turkey. From the Middle East, coffee drinking spread to Italy, then to the rest of Europe, and coffee plants were transported by the Dutch to the East Indies and to the Americas.[144]

Use of the kola nut, like the coffee berry and tea leaf, appears to have ancient origins. It is chewed in many West African cultures, individually or in a social setting, to restore vitality and ease hunger pangs. In 1911, kola became the focus of one of the earliest documented health scares, when the US government seized 40 barrels and 20 kegs of Coca-Cola syrup in Chattanooga, Tennessee, alleging

the caffeine in its drink was "injurious to health".[145] Although the judge ruled in favor of Coca-Cola, two bills were introduced to the U.S. House of Representatives in 1912 to amend the Pure Food and Drug Act, adding caffeine to the list of "habit-forming" and "deleterious" substances, which must be listed on a product's label.[146]

The earliest evidence of cocoa bean use comes from residue found in an ancient Mayan pot dated to 600 BCE. In the New World, chocolate was consumed in a bitter and spicy drink called *xocolatl*, often seasoned with vanilla, chile pepper, and achiote. *Xocolatl* was believed to fight fatigue, a belief probably attributable to the theobromine and caffeine content. Chocolate was an important luxury good throughout pre-Columbian Mesoamerica, and cocoa beans were often used as currency.[*citation needed*]

Xocolatl was introduced to Europe by the Spaniards, and became a popular beverage by 1700. The Spaniards also introduced the cacao tree into the West Indies and the Philippines. It was used in alchemical processes, where it was known as "black bean".
[*citation needed*]

The leaves and stems of the yaupon holly (*Ilex vomitoria*) were used by Native Americans to brew a tea called *asi* or the "black drink".[147] Archaeologists have found evidence of this use stretch back far into antiquity,[148] possibly dating to Late Archaic times.[147]

Discovery


Pierre Joseph Pelletier

In 1819, the German chemist Friedlieb Ferdinand Runge isolated relatively pure caffeine for the first time; he called it "*Kaffebase*" (i.e. a base that exists in coffee).[149] According to Runge, he did this at the behest of Johann Wolfgang von Goethe.[150][151] In 1821, caffeine was isolated both by the French chemist Pierre Jean Robiquet and by another pair of French chemists, Pierre-Joseph Pelletier and Joseph Bienaimé Caventou, according to Swedish chemist Jöns Jacob Berzelius in his yearly journal. Furthermore, Berzelius stated that the French chemists had made their discoveries independently of any knowledge of Runge's or each other's work.[152] However, Berzelius later acknowledged Runge's priority in the extraction of caffeine, stating:[153] "However, at this

point, it should not remain unmentioned that Runge (in his *Phytochemical Discoveries*, 1820, pages 146–147) specified the same method and described caffeine under the name *Caffeebase* a year earlier than Robiquet, to whom the discovery of this substance is usually attributed, having made the first oral announcement about it at a meeting of the Pharmacy Society in Paris."

Pelletier's article on caffeine was the first to use the term in print (in the French form *Caféine* from the French word for coffee: *café*).[154] It corroborates Berzelius's account:

> Caffeine, noun (feminine). Crystallizable substance discovered in coffee in 1821 by Mr. Robiquet. During the same period – while they were searching for quinine in coffee because coffee is considered by several doctors to be a medicine that reduces fevers and because coffee belongs to the same family as the cinchona [quinine] tree – on their part, Messrs. Pelletier and Caventou obtained caffeine; but because their research had a different goal and because their research had not been finished, they left priority on this subject to Mr. Robiquet. We do not know why Mr. Robiquet has not published the analysis of coffee which he read to the Pharmacy Society. Its publication would have allowed us to make caffeine better known and give us accurate ideas of coffee's composition ...

Robiquet was one of the first to isolate and describe the properties of pure caffeine,[155] whereas Pelletier was the first to perform an elemental analysis.[156]

In 1827, M. Oudry isolated "théine" from tea,[157] but it was later proved by Mulder[158] and by Carl Jobst[159] that theine was actually caffeine.[151]

In 1895, German chemist Hermann Emil Fischer (1852–1919) first synthesized caffeine from raw materials (i.e. a "total synthesis"), and two years later, he also derived the structural formula of the compound.[160] This was part of the work for which Fischer was awarded the Nobel Prize in 1902.[161]

Legality

Because caffeine is a psychoactive drug, it is often regulated. In the United States the Food and Drug Administration (FDA) restricts

beverages to containing less than 0.02% caffeine.[162]

Historically, coffee and thus caffeine was illegal for some classes in Mecca in parts of the 16th century,[163] and in the Ottoman empire.[164][165] Charles II of England tried to ban it in 1676,[166][167] Frederick II of Prussia banned it in 1777,[168][169] and coffee was banned in Sweden in the years 1756–1769, 1794–1796, 1799–1802, and 1817–1823. The bans on coffee have often had religious, economic, or political reasons rather than being based on concerns for the well-being of the population.[*citation needed*]

Religion

Some Seventh-day Adventists, Church of God (Restoration) adherents, and Christian Scientists do not consume caffeine.[*citation needed*] Some from these religions believe that one is not supposed to consume a non-medical, psychoactive substance, or believe that one is not supposed to consume a substance that is addictive. The Church of Jesus Christ of Latter-day Saints has said the following with regard to caffeinated beverages: "With reference to cola drinks, the Church has never officially taken a position on this matter, but the leaders of the Church have advised, and we do now specifically advise, against the use of any drink containing harmful habit-forming drugs under circumstances that would result in acquiring the habit. Any beverage that contains ingredients harmful to the body should be avoided."[170]

Gaudiya Vaishnavas generally also abstain from caffeine, as it is alleged to cloud the mind and over-stimulate the senses. To be initiated under a guru, one must have had no caffeine, alcohol, nicotine or other drugs, for at least a year.[*citation needed*]

People who refrain from consuming caffeine, for religious or other reasons, may instead use a substitute that performs a culturally similar role to coffee.[*citation needed*]

Caffeinated beverages are widely consumed by Muslims today; in the 16th century, some Muslim authorities made unsuccessful attempts to ban them as forbidden "intoxicating beverages" under Islamic dietary laws.[171][172]

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150. ^ In 1819, Runge was invited to show Goethe how belladonna caused dilation of the pupil, which Runge did, using a cat as an experimental subject. Goethe was so impressed with the demonstration that: "*Nachdem Goethe mir seine größte Zufriedenheit sowol über die Erzählung des durch scheinbaren schwarzen Staar Geretteten, wie auch über das andere ausgesprochen, übergab er mir noch eine Schachtel mit Kaffeebohnen, die ein Grieche ihm als etwas Vorzügliches gesandt. "Auch diese können Sie zu Ihren Untersuchungen brauchen," sagte Goethe. Er hatte recht; denn bald darauf entdeckte ich darin das, wegen seines großen Stickstoffgehaltes so berühmt gewordene Coffein.*" (After Goethe had expressed to me his greatest satisfaction regarding the account of the man [whom I'd] rescued [from serving in Napoleon's army] by apparent "black star" [i.e., amaurosis, blindness] as well as the other, he handed me a carton of coffee beans, which a Greek had sent him as a delicacy. "You can also use these in your investigations," said Goethe. He was right; for soon thereafter I discovered therein caffeine, which became so famous on account of its high nitrogen content.)
This account appeared in Runge's book *Hauswirtschaftlichen Briefen* (Domestic Letters [i.e., personal correspondence]) of 1866. It was reprinted in: Johann Wolfgang von Goethe with F.W. von Biedermann, ed., *Goethes Gespräche*, vol. 10: *Nachträge, 1755–1832* (Leipzig, (Germany): F.W. v. Biedermann, 1896), pages 89–96; see especially page 95 (http://books.google.com/books?id=MacwAAAAYAAJ&pg=PA95).
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External links

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- The Consumers Union Report on Licit and Illicit Drugs, Caffeine-Part 1 (http://www.druglibrary.org/schaffer/Library/studies/cu/CU21.html) Part 2 (http://www.druglibrary.org/schaffer/Library/studies/cu/CU22.html)
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