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Neurologic Effects of Caffeine

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Overview

Caffeine is the most widely used psychoactive substance and has sometimes been considered a drug of abuse. This article summarizes the available data on its neurologic effects.

Classic drugs of abuse lead to specific increases in cerebral functional activity and dopamine release in the shell of the nucleus accumbens (the key neural structure for reward, motivation, and addiction). In contrast, caffeine at doses reflecting daily human consumption does not induce a release of dopamine in the shell of the nucleus accumbens but leads to a release of dopamine in the prefrontal cortex, which is consistent with its reinforcing properties.

Furthermore, caffeine increases glucose utilization in the shell of the nucleus accumbens only at high concentrations; this, in turn, nonspecifically stimulates most brain structures and thus likely reflects the side effects linked to high caffeine ingestion alone. Moreover, this dose is 5-10 times higher than the dose necessary to stimulate the caudate nucleus (extrapyramidal motor system) and the neural structures regulating the sleep-wake cycle, the 2 functions that are most sensitive to caffeine.

Thus, although caffeine fulfills some of the criteria for drug dependence and shares with amphetamine and cocaine a certain specificity of action on the cerebral dopaminergic system, it does not act on the dopaminergic structures related to reward, motivation, and addiction.

Tolerance to caffeine-induced stimulation of locomotor activity has been shown in animals. In humans, tolerance to some subjective effects of caffeine may occur, but most of the time, complete tolerance to many effects of caffeine on the central nervous system (CNS) does not occur. In animals, caffeine can act as a reinforcer, but only in a more limited range of conditions than classic drugs of dependence do. In humans, the reinforcing stimulus functions of caffeine are limited to low or moderate doses, while high doses usually are avoided.

Dietary sources include coffee, tea, cola drinks, and chocolate, as well as energy drinks.[1] The most notable behavioral effects of caffeine occur after consumption of low-to-moderate doses (50-300 mg) and include increased alertness, energy, and ability to concentrate. Whereas moderate consumption rarely leads to health risks, higher doses induce negative effects such as anxiety, restlessness, insomnia, and tachycardia. After sudden caffeine cessation, withdrawal symptoms develop in a modest number of cases but are typically moderate and transient.

The negative effects of high-dose caffeine consumption are seen primarily in a small group of individuals who are caffeine-sensitive. On the other hand, caffeine was considered in one study as a potential drug of abuse and has even been described as a model drug of abuse. On the basis of a review of science and clinical data, the possibility of adding caffeine withdrawal, but not abuse and dependence, to diagnostic manuals is being considered in the United States.

For patient education resources, see the Substance Abuse Center, as well as Drug Dependence and Abuse and Substance Abuse.

Consumption of Caffeine

Caffeine is present in a number of dietary sources including tea, coffee, cocoa beverages, candy bars, and soft drinks. The caffeine content of these food items varies, as follows:

- Coffee – 71-220 mg/150 mL

- Tea – 32-42 mg/150 mL
- Cola drinks – 32-70 mg/330 mL
- Cocoa beverages – 4 mg/150 mL

The 2 major coffee types are arabica (*Coffea arabica*) and robusta (*Coffea canephora*). In a standard 150 mL cup, the content of caffeine ranges from 71 to 120 mg per cup for arabica coffee and from 131 to 220 mg per cup for robusta.

Average caffeine consumption from all sources is approximately 76 mg/person/day but reaches 210-238 mg/person/day in the United States and Canada and exceeds 400 mg/person/day in Sweden and Finland, where 80-100% of the caffeine intake is from coffee alone. In the United Kingdom, the consumption of caffeine is similar to that in Sweden and Finland, but 72% is from tea.

In the United States, the daily intake of caffeine from all sources is estimated to be 3 mg/kg/person, with two thirds of it coming from coffee consumed by subjects older than 10 years. If only caffeine consumers are evaluated, the daily caffeine consumption is 2.4-4.0 mg/kg (170-300 mg) in individuals weighing 60-70 kg. In children, soft drinks represent 55% of the total caffeine intake, chocolate foods and beverages represent 35-40%, and tea represents 6-10%.

Because caffeine is contained in some of the most widely consumed foods and beverages, both in the United States and internationally, it has been extensively investigated in both animal models and human studies. Although caffeine shares some characteristics with other chemicals of abuse with regard to both psychological and physiologic dependence, important differences exist, especially pertaining to the action of caffeine in central nervous system (CNS) neurotransmitter systems.

Clearly, further studies are required to better define the short- and long-term roles of caffeine in the neurologic and cardiovascular systems. The combined results of these future studies will be of keen interest to all those who enjoy a warm cup (or multiple cups) of coffee to start the morning.

Physiologic Effects of Caffeine

Caffeine, or 1,3,7-trimethylxanthine, is related structurally to uric acid. It is metabolized by demethylation and oxidation. The major human pathway results in paraxanthine (1,7-dimethylxanthine), leading to the principal urinary metabolites, L-methylxanthine, 1-methyluric acid, and an acetylated uracil derivative. Minor degradation pathways involve the formation and metabolism of theophylline and theobromine. No evidence exists to suggest that methylxanthines are converted to uric acid or that their ingestion can exacerbate gout.

The rate of elimination of methylxanthines varies from one individual to another, depending on both genetic and environmental factors, and 4-fold differences are not uncommon. In most cases, metabolism obeys first-order elimination kinetics within the therapeutic range. At higher concentrations, however, zero-order kinetics occur with the saturation of metabolic enzymes. This prolongs the decline of caffeine concentrations.

The metabolism of methylxanthines is also influenced by the presence of other agents or specific diseases. For example, cigarette smoking and oral contraceptives produce a small but appreciable increase in methylxanthine clearance. The half-life of theophylline can be prolonged significantly in patients with hepatic cirrhosis, congestive heart failure, or acute pulmonary congestion; values exceeding 60 hours have been reported.

Caffeine has a half-life in plasma of 3-7 hours; this increases approximately 2-fold in women who are in the later stages of pregnancy or are long-term users of oral contraceptive steroids.

Cellular basis of action

The diverse effects of methylxanthines are probably attributable to the following 3 basic cellular actions, listed in order of increasing importance:

- Translocations of intracellular calcium
- Increasing accumulation of cyclic nucleotides
- Adenosine receptor blockade

The ability of methylxanthines to inhibit cyclic nucleotide phosphodiesterases is often cited to explain their therapeutic effects; however, strong evidence for this theory is lacking. Plasma caffeine concentrations that raise blood pressure are below the threshold for phosphodiesterase inhibition. Thus, phosphodiesterase inhibition is probably not important to the therapeutic effects of methylxanthines.

At high concentrations (0.5-1 mmol/L), caffeine interferes with the uptake and storage of calcium by the sarcoplasmic reticulum in striated muscles. This action

can account for the observations that such concentrations of caffeine increase the strength and duration of contractions in both skeletal and cardiac muscles. Similar actions can enhance secretion in certain tissues. However, they are unlikely to play an important role at therapeutic concentrations.

In vitro, methylxanthines (at concentrations of approximately 0.2 mmol/L or higher) generally cause relaxation of vascular smooth muscles in the presence of various stimulators of contraction (eg, norepinephrine and angiotensin). Although this relaxation probably results from a reduction of the cytosolic calcium concentration, it is unclear to what extent methylxanthines can alter calcium binding and transport, either directly or indirectly, by altering cyclic nucleotide metabolism.

Thus, adenosine receptor blockade appears to be the predominant mode of action. Methylxanthines act as competitive antagonists at adenosine receptors at concentrations well within the therapeutic range. The effects of exogenous adenosine frequently oppose those of methylxanthines, and in some experimental settings, removing ambient adenosine (by adding adenosine deaminase) can reproduce the actions of methylxanthines. Plasma concentrations of caffeine that raise blood pressure are within the range for antagonism of adenosine receptors.

Several other caffeine actions that have received relatively little attention to date might prove to be important for certain methylxanthine effects. These include their potentiation of inhibitors of prostaglandin synthesis and the possibility that methylxanthines reduce the uptake or metabolism of catecholamines in nonneuronal tissues.

Effects on central nervous system

Most of the pharmacologic effects of adenosine in the animal brain can be suppressed by relatively low concentrations of circulating caffeine (less than 100 µmol/L, the equivalent of 1-3 cups of coffee). Adenosine decreases the neuronal firing rate and inhibits both synaptic transmission and the release of most neurotransmitters. Caffeine also increases the turnover of many neurotransmitters, including monoamines and acetylcholine.

The A1 and A2a adenosine receptors are the subtypes primarily involved in the caffeine effect, with A2b and A3 receptors playing only a minor role. The A1 receptors are linked negatively to adenyl cyclase, whereas the A2a receptors are linked positively to this enzyme. Adenosine A1 receptors are distributed widely throughout the brain, with high levels in the hippocampus, cerebral and cerebellar cortex, and thalamus.

Conversely, A2a receptors are located almost exclusively in the striatum, nucleus accumbens, and olfactory tubercle. In the latter regions, A2a receptors are coexpressed with enkephalin and dopamine D2 receptors in striatal neurons. Direct evidence exists for a central functional interaction between adenosine A2a and dopamine D2 receptors. Indeed, administration of adenosine A2a receptor agonists decreases the affinity of dopamine for D2 receptors in striatal membranes.

Interaction between adenosine A2a receptors and dopamine D2 receptors in the striatum might underlie some of the behavioral effects of methylxanthines. By antagonizing the negative modulatory effects of adenosine receptors on dopamine receptors, caffeine leads to inhibition and blockade of adenosine A2 receptors, causing potentiation of dopaminergic neurotransmission. The latter interaction might explain the adenosine receptor antagonist–induced increase in behaviors related to dopamine (eg, caffeine-induced rotational behavior).

Clinical studies of central nervous system arousal

In a Dutch study, 11 patients who received either caffeine (250 mg) or placebo were asked to attend selectively to stimuli of a specified color (red or blue) and to react to the presence of a target in the attended category.[2] Reactions were faster in the caffeine group, but no intergroup differences in strategy were observed. Caffeine thus appeared to be associated with a higher overall arousal level, better processing of attended and unattended information, and more rapid motor processes. In addition, there is a growing body of evidence that caffeine has a significant effect on the sleep-wake cycle and on circadian rhythm.[3, 4]

Quinlan et al reported 2 studies evaluating different caffeine levels and different caffeine sources.[5] In study 1, tea and coffee were prepared at different strengths, and control subjects received water or no drinks. Both tea and coffee yielded mild autonomic stimulation and mood elevation. Neither the source (tea or coffee) nor the dose significantly influenced the effects of the caffeine, despite a 4-fold variation in the dose. Greater beverage strength was correlated with greater increases in diastolic blood pressure (DBP) and significant arousal.

In study 2, only the caffeine level was manipulated, with varying amounts of

caffeine added to water or decaffeinated tea.[5] Systolic blood pressure (SBP), DBP, and skin conductance were increased in the caffeine group, and heart rate and skin temperature were reduced in those who received water. A significant dose-response relation to caffeine was documented only for SBP, heart rate, and skin temperature. Although caffeine significantly affected arousal, no dose-response effects could be consistently demonstrated.

In a double-blind controlled study of younger experienced drivers, Reyner and Horn found that 200 mg caffeine (delivered via coffee) reduced early morning driver sleepiness for about 30 minutes after sleep deprivation and for about 2 hours after sleep restriction.[6] In the caffeine group, sleep incidents were significantly reduced for the first 30 minutes, and subjective sleepiness was reduced for 1 hour.

In a placebo-controlled study of the effects of caffeine on learning and retrieval sessions, Herz et al found that whereas caffeine 5 mg/kg reliably increased arousal, it did not affect any emotional characteristics related to pleasure, nor did it have any effect on memory.[7]

Overusing paracetamol-caffeine-aspirin (PCA) powders affects regional brain glucose metabolism in persons with chronic migraine. Increased metabolism in the right insula may be associated with recurrently overusing of PCA powders.[8]

Role of Caffeine in Headaches

A retrospective study found that for both menstruation-associated migraine and migraine not associated with menses, the percentage of responders (ie, those whose pain intensity was decreased to mild or none) was significantly higher among those receiving an acetaminophen-aspirin-caffeine (AAC) regimen than among those receiving placebo at all time points from 0.5 to 6 hours after administration.[9] Treatment effect was essentially equivalent at all time points for menstruation-associated migraine and migraine not associated with menses.

In both menstruating and nonmenstruating women, AAC treatment yielded improvements in migraine characteristics (eg, photophobia, phonophobia, and functional disability) at all time points from 1 to 6 hours.[9] Both menstruating and nonmenstruating women experienced significant relief from nausea with AAC, but relief appeared earlier in the latter.

Beginning at 3 hours after treatment, both groups of AAC-treated women (menstruating and nonmenstruating) were significantly less likely to require rescue medications than their placebo-treated counterparts were.[9] In both groups, the most commonly used rescue medications were the following:

- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Prescription combination analgesics-narcotics
- Prescription migraine preparations

AAC was well tolerated both in women with menstruation-associated migraine and in women with migraine not associated with menses. In general, adverse experiences were similar in the 2 groups. In both menstruating and nonmenstruating women, the percentage of patients who had 1 or more adverse experiences was significantly higher among those receiving AAC than among those receiving placebo. Adverse experiences were similar in type and severity to those previously associated with a single dose of acetaminophen, aspirin, or caffeine.

For related information, see Migraine Headache, as well as the Headache Resource Center.

Post−lumbar puncture headache

The characteristics of headaches associated with low cerebrospinal fluid pressure are very distinct, with typically orthostatic symptoms, but the exact pathophysiology remains poorly understood. Caffeine may lead to vasoconstriction by blocking the adenosine receptors.

There is no standardized protocol for administering caffeine sodium benzoate (CSB), but in previously reported cases, 500 mg of CSB is mixed in 1 L of normal saline or lactated Ringer solution and infused intravenously over 1-2 hours. Most experts recommend an epidural patch or saline infusion if the headaches persist after administration of 1 g of CSB.

Hypnic headache

Hypnic headache is predominantly seen in the elderly patients. However, younger patients and even children might also suffer from hypnic headache. Headache

attacks usually last between 15 and 180 minutes, but some patients report headache attacks up to 10 hours. Almost all patients report motor activity during headache attacks. Cerebral MRI and 24-hour blood pressure monitoring should be performed in the diagnostic workup of these headaches. Other primary headache disorders such as migraine and cluster headache may also be present with sleep-related headache attacks and should be considered first. Caffeine taken as a cup of strong coffee seems to be the best acute and prophylactic treatment option.[10]

Role of Caffeine in Other Neurologic Conditions

Sleep alterations

Every exposure to caffeine can produce cerebral stimulant effects. This is especially true in the areas that control locomotor activity (eg, caudate nucleus) and structures involved in the sleep-wake cycle (eg, locus ceruleus, raphe nuclei, and reticular formation). In humans, sleep seems to be the physiologic function most sensitive to the effects of caffeine. Generally, more than 200 mg of caffeine is required to affect sleep significantly. Caffeine has been shown to prolong sleep latency and shorten total sleep duration while preserving the dream phases.

Whether observed differences in sensitivity to the effects of coffee on sleep can be attributed to tolerance has not been positively established. Some studies suggest that these differences might reflect varying individual sensitivity to caffeine, possibly related to differing rates of caffeine metabolism. Indeed, poor sleepers are reported to metabolize caffeine at a lower rate. The variability in response from one night to the next also should be taken into account.

Nevertheless, there is some evidence that tolerance to caffeine-related sleep disturbances may develop, in that heavy coffee drinkers appear to be less sensitive to such disturbances than light coffee drinkers are. In addition, tolerance to sleep latency and quality of caffeine has been shown to develop over a period of days; however, the tolerance is not complete, and the sleep efficiency remains below 90% of the baseline value after 7 days of caffeine treatment.

The evidence for development of tolerance to some of the effects linked to regular consumption of coffee comes primary from animal data. The data from human studies are less conclusive. This may be the result of individual differences in susceptibility and tolerance to caffeine-induced effects. Moreover, mechanisms of tolerance may be overwhelmed by the nonlinear accumulation of caffeine and its primary metabolites in the human body when caffeine metabolism is saturated under multiple-dosing conditions.

Tremors

It is well recognized that caffeine and beta-adrenergic drugs are capable of both causing tremors and worsening existing tremors. The severity of the effect may vary according to the amount of caffeine consumed. Prompt recognition of drugs that cause or exacerbate tremors can facilitate diagnosis and management and help avoid unnecessary testing.

Parkinson disease

The causes of Parkinson disease remain largely unknown. Several studies have assessed the risk of Parkinson disease with coffee consumption. A meta-analysis carried out by de Lau et al found coffee drinkers to have a significantly reduced risk of Parkinson disease.[11] Caffeine is an inhibitor of the adenosine A2 receptor and was shown to improves motor deficits in a mouse model of Parkinson disease. Because estrogen inhibits the caffeine metabolism by competitive mechanisms, its effect in women may vary with the use of estrogen replacement.

Kitagawa et al, in a study examining the effects of freezing of gait with 100 mg of caffeine, determined that caffeine improved "total akinesia" type of freezing of gait but that, at the same time, tolerance to the beneficial effect of caffeine developed within a few months.[12] However, the effect of caffeine could be restored by a 2-week caffeine withdrawal period.

In addition caffeine neuroprotection may be enhanced in those patitents with a genetic predisposition to Parkinson disease.[13]

Seizures

As mentioned earlier, caffeine acts as a central nervous stimulant by blocking A1 and A2A adenosine receptors. Its effect on seizures is complex. Animal studies and case reports indicate that acute caffeine exposure may induce seizures, whereas chronic exposure might have an opposite effect. In a recent study by Samsonsen et al, no difference was found between the intake of caffeine 24 hours prior to the seizure and the habitual consumption or the consumption on a seizure-

free day. In essence, caffeine does not appear to be a common seizure precipitant.
[14]

Hemorrhagic stroke

The use of caffeine-containing medicines is associated with increased risk of hemorrhagic stroke, both subarachnoid hemorrhage and intracerebral hemorrhage.
[15]

Caffeine Dependence, Withdrawal, and Tolerance

Dependence

Drug dependence is defined as a pattern of behavior focused on the repetitive and compulsive seeking and taking of a psychoactive drug.

Withdrawal

Characteristic symptoms in humans

Caffeine withdrawal results in typical symptoms, of which the most commonly reported are the following:

- Headaches
- Fatigue
- Weakness
- Drowsiness
- Impaired concentration
- Work difficulty
- Depression
- Anxiety
- Irritability
- Increased muscle tension
- Tremor, nausea, and vomiting (occasionally)

Withdrawal symptoms generally begin 12-24 hours after sudden cessation of caffeine consumption and reach a peak after 20-48 hours. In some individuals, however, these symptoms can appear within only 3-6 hours and can last for 1 week.

Withdrawal symptoms do not relate to the quantity of caffeine ingested daily. For example, Strain et al showed that withdrawal symptoms occur in individuals consuming 129-2548 mg/day of caffeine.[16] Some investigators have suggested that caffeine withdrawal symptoms (but not caffeine abuse or dependence) should be added to the list of diagnoses recognized by the American Health System. The *Diagnostic and Statistical Manual of Mental Disorders,Fifth Edition* (*DSM-5*) does include caffeine-related disorders in the substance-related and addictive disorders chapter.[17]

Caffeine consumption, fasting, and preoperative and postoperative headaches are strongly correlated. For every 100-mg increase in the usual daily consumption of caffeine (equivalent to about 1 more cup of coffee), the risk of headache immediately before and after surgery is increased by 12% and 16%, respectively.
[18] The risk can be reduced by drinking caffeine or taking caffeine tablets on the day of the procedure. Thus, permitting caffeine users who are undergoing minor surgical procedures to ingest caffeine preoperatively may be advisable.

Relief of withdrawal symptoms

Caffeine withdrawal symptoms disappear shortly after ingestion of caffeine. This effect is linked strongly to the psychological satisfaction related to the ingestion of caffeine, especially for the first cup of the day. The occurrence of headaches after substitution of decaffeinated coffee predicts subsequent caffeine self-administration. Caffeine content influences coffee consumption, and the beneficial effects of caffeine consumption on mood or alertness seem to encourage consumption of coffee or caffeine-containing beverages.

Heavy consumers of coffee show a preference for caffeine-containing coffee, whereas those who typically drink decaffeinated coffee generally choose either decaffeinated or caffeine-containing coffee. When subjects are categorized as caffeine choosers or nonchoosers, caffeine the former tend to report both positive subjective effects of caffeine (stimulant and positive effects on mood and vigilance) and negative subjective effects of placebo (headache and fatigue), whereas the latter tend to report negative effects of caffeine (anxiety and dysphoria).

Tolerance

In reference to a drug, the term tolerance denotes an acquired change in responsiveness after repeated exposure to the drug. Tolerance can be considered in 2 ways, as follows:

- Tolerance might indicate that the dose necessary to achieve the desired euphoric or reinforcing effects increases with time, thus encouraging increased consumption of the drug
- Tolerance to the aversive effects of high doses of the drug may occur, also leading to increased consumption of the drug over time

Tolerance to many behavioral effects of caffeine has been observed in mice, cats, and squirrel monkeys treated regularly with methylxanthine. Tolerance to caffeine-induced locomotor stimulation, cerebral electrical activity, reinforcement thresholds for electrical brain stimulation, schedule-controlled response maintained by presentation of food, and electric shock and thresholds for seizures induced by caffeine or N-methyl D-aspartate (NMDA) has been described.

In animals, development of tolerance to caffeine is rapid, is usually insurmountable, and shows cross-tolerance with the other methylxanthines, though not with other psychomotor stimulants such as amphetamines and methylphenidate. On the first 2 days after caffeine discontinuance, depression of locomotor activity is noted, with a return to baseline values on day 3 (consistent with a withdrawal syndrome).

Although the exact mechanism underlying the development of tolerance to caffeine remains unclear, tolerance to behavioral effects of caffeine in animals does not seem to involve adaptive changes in adenosine receptors but may result from compensatory changes in the dopaminergic system as a result of chronic adenosine receptor blockade.

In humans, tolerance to some physiologic actions of caffeine can occur. This is the case for the effects of caffeine on blood pressure, heart rate, diuresis, plasma adrenaline and noradrenaline levels, and renin activity. Tolerance usually develops within a few days. Tolerance to some subjective effects of caffeine, such as tension-anxiety, jitteriness, nervousness, and the strength of drug effect, has been shown.

Conversely, although tolerance to the enhancement of arithmetic skills by caffeine has been documented, evidence of tolerance to caffeine-induced alertness and wakefulness is limited. These effects are paralleled by the lack of tolerance of cerebral energy metabolism to caffeine; in one animal study, in that acute administration of 10 mg/kg caffeine induced the same metabolic increase whether the rats were exposed to previous daily treatment with caffeine or with saline for 15 days.

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