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Review Article

CAFFEINE AND NEUROLOGICAL DISORDERS

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A R T I C L E I N F O

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A B S T R A C T

Caffeine serves as a double-edged sword, possessing both advantageous and detrimental impacts on human health. Caffeine is one of the world's oldest beverages and it continues to be a subject of active research for its potential benefits. Whether through coffee, tea, cocoa, and chocolate we regularly introduce various forms of caffeine into our bodies. When consumed moderately, caffeine exhibits several positive effects on our health, but caution is warranted as higher dosages can have harmful consequences. Numerous studies in the literature explore the consumption of caffeine and its potential benefits, predominantly relying on animal models for testing. However, the transition to human studies is essential, especially in utilizing caffeine as a therapeutic drug for managing disease where effective therapy is still elusive. Caffeine's impact extends to various aspects, including the brain, heart, liver, kidney, and psychological as well. In this context, we have outlined the effects of caffeine, particularly in the realm of neurological disorders.

INTRODUCTION

Caffeine holds the title of being the most widely consumed psychoactive substance globally. Its consumption mainly occurs through coffee, tea, soft drinks, cocoa, chocolate, guarana berries, and even some medicines (1). It acts as a stimulant, anti-oxidant, and anti-inflammatory as well (2).The effects of caffeine on human health are two-sided offering both advantages and drawbacks. The health-promoting effects of caffeine are not only limited to neurology but caffeine is cardio protective, hepatoprotective, and nephroprotective as well (3).

Caffeine exerts diverse biological effects that influence physiological and psychological performance. It has been associated with benefits such as enhancing long-term memory and reduced risk of degenerative diseases. However, it is important to note that in higher doses, caffeine may elevate the risk of certain conditions including headache and stroke. Caffeine also sensitizes malignant cells like glioma and neuroblastoma for chemotherapeutic agents (4).Continuous therapeutic investigations are underway to discover remedies for neurological and various disorders. Within the medical community, caffeine consumption is a daily ritual, observed among both overworked residents and understaffed nursing personnel. Many individuals kick off their mornings with a comforting cup of coffee often without delving into the intricacies of their potential health advantages. Ongoing research endeavors aim to uncover and harness the beneficial components within these globally cherished drinks, coffee.

Mechanism of action of caffeine

Caffeine stimulates the central nervous system by acting as an antagonist of A1 and A2 adenosine receptors. Adenosine acts as an inhibitory modulator of the central nervous system via these receptors. Additionally, caffeine enhances the level of various neurotransmitters, including dopamine, adrenaline, nor adrenaline, and glutamate (5).At higher doses, caffeine inhibits phosphodiesterase enzymes to increase the concentration of cAMP. It also mobilizes intracellular calcium stores, interacts with GABA-A receptors inhibiting the production of prostaglandins, and inhibits ATM Kinase, a crucial DNA damage response (4) (6). This inhibition of ATM kinase contributes to heightened efficacy in certain chemotherapeutic drug applications (4).

Pharmacokinetics

Caffeine is absorbed rapidly and gets distributed in all human tissues, reaching a maximum plasma level within 30-120 min after oral intake (7). Caffeine has a half-life of 3-7 hours in healthy adults and is primarily metabolized in the liver by the cytochrome P450 oxidase enzyme system into paraxanthine, bromine, and theophylline which are finally excreted in urine (8).

Adequate Dosage Recommendation

According to the FDA, a daily caffeine intake of up to 400 mg per day, roughly equivalent to four to five cups of coffee, is generally considered safe for adults. However, individual sensitivity and metabolic rates can vary. For pregnant or breastfeeding individuals, a limit of 200 mg per day is considered safe (9). Various beverages contain different

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amounts of caffeine, with a 12-ounce caffeinated soft drink containing 30-40 milligrams, an 8-ounce cup of green or black tea containing 30-50milligrams, and an 8-ounce cup of coffee containing 80-100 milligrams. Even a decaffeinated coffee still contains 2-15 milligrams of caffeine per 8-ounce cup. Rapid consumption of up to 1200 mg of caffeine can lead to toxic effects, including seizures. While the FDA has not established a specific caffeine limit for children, the American Academy of Pediatrics advises against the consumption of caffeine and other stimulants by children and adolescents.

Caffeine and Nervous system effects

1 **Headache-** Caffeine can both relieve and trigger headaches. Caffeine, at regular consumption levels, blocks A2A receptors on peripheral nerve endings, leading to antinociception and contributing to its analgesic effects in humans. Additionally, the release of dopamine induced by caffeine further contributes to its analgesic properties (10). Not only migraine but caffeine has therapeutic use in treating hypnic headaches, post-dural puncture headaches, and spontaneous intracranial hypotension headaches (11). However long-term consumption of caffeine can worsen the original headache and can cause caffeine withdrawal headaches (11).

The symptoms of caffeine withdrawal share similarities with the prodromal phase of migraine albeit without sensory hypersensitivity. Interestingly, caffeine withdrawal, particularly noticeable on weekends, can trigger migraine attacks (12).A US study revealed a correlation between higher caffeine intake and the onset of Chronic daily headache(CDH)(OR 1.5, p=0.05)compared to episodic headaches (13). The Nord Trondelag Health Study from Norway was an 11-year longitudinal study on risk factors for medication overuse headaches. It found that consumption of 540 mg caffeine daily vs 240 mg per day was associated with a 1.4 times increase in the risk of medication overuse headache (14).Prolonged and elevated caffeine intake has been linked to potential issues like sleep disorders dehydration, and hypomagnesaemia due to diuresis at higher doses, potentially acting as a trigger for migraine.

Therefore, it is advisable for individuals experiencing headaches to continue consuming caffeinated beverages as long as they adhere to low to moderate amounts of caffeine intake levels(<200 mg/day). To prevent caffeine withdrawal it is recommended to maintain no more than 24 hours between caffeine-containing beverages (15).

2 **CVD and Stroke**- Research findings indicate that excessive caffeine consumption (>6 cups/day coffee) is associated with an elevated risk of cardiovascular disease whereas moderate consumption (3 cups/day) decreases the risk of cardiovascular events (16, 17). Giornio *et al* discovered an inverse correlation between coffee consumption and arterial stiffness and blood pressure (18). According to the American Heart Association, moderate coffee consumption reduces the stroke risk. A meta-analysis of 11 studies showed a nonlinear relation between stroke and coffee consumption. The relative risk of total stroke was 0.87 for 2, 0.84 for 3-4, 0.88 for 6, and 0.94 for 8 cups per day of coffee (19). High coffee consumption increases CVD risk by increasing the levels of low-density lipoprotein cholesterol, total cholesterol, and apolipoprotein B (16).

3 **Neurodegenerative disease**- Regular coffee consumption is linked with a lower risk of neurodegenerative disease. Caffeine intake is associated with a low risk of cognitive disorders, especially Alzheimer's disease with a relative risk of 0.73(95% CI 0.55 to 0.97) (20). Caffeine, capable of crossing the blood-brain barrier not only antagonizes adenosine receptors but also inhibits phosphodiesterase enzyme and hinders calcium release. In addition, caffeine modulates the excessive activity of glial cells, preventing uncontrolled neuroinflammation in neurodegenerative disorders.

Furthermore, caffeine offers protection against alpha-synuclein-induced neurotoxicity, as demonstrated in a mice model where exposure to caffeine in drinking water reduced apoptotic neuronal cell death in the striatum and suppressed microglial and astrocyte activation that could otherwise lead to synucleinopathies (21). In an animal model of Parkinson's disease (PD), caffeine demonstrates neuroprotection by reducing levels of NO thereby safeguarding dopaminergic neurons. Within a murine microglial cell line caffeine inhibits the production of proinflammatory cytokines like NO, Prostaglandins, and TNF alpha (22). Additionally in a mice model caffeine has been shown to reduce striatal pathology in Machado Joesph disease through the inactivation of adenosine receptors (23).

4 **Encephalopathy in preterm infants-** Caffeine is emerging as a valuable neuroprotective drug, particularly in shielding premature infants from hypoxia-induced brain damage. Its therapeutic application extends to addressing apnea of prematurity (24). Early administration of caffeine specifically within 2 hours at a dose of 20 mg/kg in premature infants has demonstrated greater circulatory improvement coupled with a lower incidence of cerebral palsy and hearing damage compared to the conventional approach of caffeine administration within 12 hours at the same dosage. (25). Research by Lodha A *et al* suggests that premature infants with a birth weight below 1.25 kg should receive caffeine treatment within the first week of birth, and should be discontinued at 33-35 weeks corrected gestational age (26) (27).

5 **Anti-tumor activity**- Extensive research has delved into anticancer properties of caffeine, revealing its ability to promote apoptosis through various pathways like p53 dependent and independent mechanism, as well as the phosphatase and tensin homolog, PI3K/ protein kinase B, and mammalian target of rapamycin pathways(mTOR)(28).Within neurological cancers, caffeine exerts anticancer activity against glioblastoma. Maougeri *et al* found that caffeine significantly reduces HIF- 1 alpha and VEGF expression in Glioblastoma (GBM) cells exposed to hypoxia by inhibiting the PI3K/Akt and

MAPK/ERK signaling pathway(29). Furthermore, caffeine has been shown to enhance the chemotherapeutic effect of temozolamide in glioma patients (4).Its potential to increase glioma cell death is attributed to the reduction of histone deacetylase activity and augmentation of histone acetyltransferase p300 activity in vitro (30).

6 **Anti-Inflammatory**–Caffeine has been shown to reduce inflammation, degree of demyelination, and microglia activation in animal models of multiple sclerosis(31).A study by Wang *et al* highlighted the anti-inflammatory effect of caffeine on experimental autoimmune encephalomyelitis(EAE) showcasing a reduction in the infiltration of inflammatory cells, demyelination, and activation of microglia in EAE mice. However, the translation of these findings to human applications awaits further research through human studies.

7 **Traumatic brain injury**- In the animal model of TBI, caffeine administration reduced the influx of inflammatory cells and also suppressed the production of inflammatory mediators (32).These findings underscore the possible advantages of consistent caffeine consumption in averting traumatic brain injury(TBI). They also lay the groundwork for exploring the relationship between TBI and human caffeine intake through epidemiological studies.

8 **Effect on sleep**- In a study by Landolt *et al*, participants were administered 200mg of caffeine at 7 am and although the concentration of caffeine in saliva dropped to one-fifth at 16 hours, it was observed that this dosage resulted in reduced sleep efficiency and total sleep time (TST) compared to a placebo (33). Additionally, daytime caffeine intake was associated with a decrease in the primary metabolite of melatonin during the subsequent night, leading to sleep interruption (34). Furthermore, caffeine has been found to influence the distribution of sleep stages, shifting rapid eye movement (REM) to the early part of the night and stages 3 and 4 to the latter end of the shortened sleep period (35).

9 **Memory**- Jarvis *et al* conducted a study on British adults, utilizing four tests- simple reaction time, choice reaction time, incidental verbal memory, and visuospatial reasoning. The result indicated that participants with higher levels of coffee consumption had better performance in all four tests ($p<0.001$) (36). In another study employing the scopolamine model of amnesia, 16 healthy individuals were administered 250 mg of caffeine. The findings revealed that caffeine mitigated scopolamine-induced impairment of free recall from both short and long-term memory. Additionally, it improved the quality and speed of retrieval from long-term memory in a word-learning task along with enhancing various cognitive and non-cognitive measures. The study concluded that caffeine's antagonism of adenosine results in cholinergic stimulation, contributing to cognitive enhancement observed with caffeine (37).

10 **Better Performance-**Studies have shown that even a modest intake of 32 mg of caffeine can lead to improved performance on psychological tasks. Caffeine intake results in increased vigilance, arousal, activation, alertness, psychomotor speed, and positive mood. (38). Adenosine has sleep-promoting activity, and inhibits the release of excitatory neurotransmitters, leading to reduced cortical excitability. However, even a single cup of coffee containing caffeine antagonizes A1 and A2A adenosine receptors, resulting in increased alertness through an elevation in cortical excitability (39).

Adverse effect at higher dosage- Caffeine at high doses can cause agitation, tremors, tinnitus, headache, and sleeplessness. More than 500mg of caffeine creates more adverse effects with tachycardia, agitated behavior, and stress(40).

CONCLUSION

Caffeine stands out as the most consumed alkaloid in beverages, with almost every adult around the world incorporating it into their daily routines. Within the realm of neurology, caffeine exhibits numerous effects both beneficial and harmful, although some are well established while others warrant further research.

SUMMARY

Caffeine indeed stands as one of the most cherished gifts from ancient civilizations to humanity. Whether enjoyed through coffee or tea. Caffeine consumption in moderate doses has multiple beneficial effects on human health. Amidst the ongoing quest for cures and prevention for various neurological disorders in the age of artificial intelligence, caffeine has become a subject of significant interest for medical researchers.

Numerous animal trials have shed light on the potential therapeutic benefits of caffeine. The anticipation now rests on forthcoming human studies that may not only reinforce its role as a beverage but also explore its potential applications as a therapeutic agent. The journey continues, as researchers delve deeper into the multifaceted aspects of caffeine's impact on neurological health and therapeutics as well.

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