CHAPTER THREE

Molecular targets of caffeine in the central nervous system

Ishita Bhardwaj, Atifa Haseeb Ansari, Swayam Prabha Rai, Sippy Singh, and Durgesh Singh*

Department of Zoology, S.S. Khanna Girls' Degree College, Prayagraj (A Constituent College of University of Allahabad), Prayagraj, Uttar Pradesh, India
*Corresponding author: e-mail address: ddurgesh12@gmail.com

Abstract

Caffeine is an alkaloid obtained from plants and is one of the most consumptive drug in the form of chocolate, coffee and beverages. The potential impact of caffeine within CNS can be easily understood by mechanism of action-antagonism of adenosine receptor, calcium influx, inhibits phosphodiesterases. Adenosine a neuromodulator for adenosine receptors, which are abundantly expressed within the central nervous system. Caffeine antagonized the adenosine receptor, hence stimulate expression of dopamine. It plays pivotal role in many metabolic pathways within the brain and nervous system, it reduced the amyloid-β-peptide (Aβ) accumulation, downregulation of tau protein phosphorylation, stimulate cholinergic neurons and inhibits the acetylcholinestrase (AChE). It also possess antioxidant and antiapoptotic activity. Caffeine act as nutraceutical product, improves mental health. It contains antioxidants, vitamins, minerals and dietary supplements, by reducing the risk factor of several neurodegenerations including Alzheimer's disease, migraine, gallstone, cancer, Huntington's disease and sclerosis. This act as a stimulant and have capability to increase the effectiveness of certain pain killer. Beside positive affects, over-consumption of caffeine leads to negative impact: change in sleep pattern, hallucinations, high blood pressure, mineral loss and even heartburn. This chapter highlights pros and cons of caffeine consumption.

Keywords: Caffeine, Adenosine, Neurodegenerative diseases, Antagonism, Neuromodulator, Nutraceutical

1. Introduction

Caffeine is an organic molecule found in plant constituents such as cocoa beans, chocolate and coffee and is added to variety of food in baked pastries, soft drinks and ice creams. It is also present in food supplements for weight loss and even in medicine and cosmetics as well. It has been observed that this can be taken orally as it is rapidly absorbed by the human body. Historically Caffeine being used as medical nutrient because of easily

Progress in Brain Research, Volume 288
ISSN 0079-6123
https://doi.org/10.1016/bs.pbr.2024.06.012

absorption. In the 10th century, Avicenna, a Persian physician, introduced coffee as a medicinal remedy in his work "The Canon of Medicine". Initially, coffee was utilized for cleansing the skin, reducing underlying humidities, and enhancing body odor. By the 15th century, coffee gained popularity among Muslim dervishes as an energy booster, leading to its widespread diffusion and the establishment of numerous coffee houses in Arabia. With the expansion of sea shipping in the late 17th and 18th centuries, coffee became increasingly prevalent in Europe.

It is the main psychoactive constituent of coffee and was isolated from coffee beans in 1820. It has been reported that several non-prescriptive drugs and analgesics contain drugs. It act as stimulant for the central nervous system by reducing sleep and improving mental alertness. One of the most widely enjoyed and beneficial drinks globally is coffee (Frary et al., 2005). Caffeine is one of the consumptive drug can occur in various forms such as coffee, soda and chocolate and act as stimulant for the central nervous system (CNS). It has great potential in energy metabolism and also activates the noradrenaline neurons. The main effects of caffeine involve various type of stimulant act upon the brain. Coffee being the most healthiest beverages and natural metabolites which provide beneficial affects on health including neuroprotective and cardioprotective whereas heavy consumption leads anxiety, headache and high blood pressure. Coffee improves the memory through cerebral action. It has been reported that parasympathetic and sympathetic acts upon the autonomic system. The blood–brain barrier (BBB) & the blood–cerebrospinal fluid barrier (BCSFB) are the major site for stimulants and are necessary for chemical kinetics for drugs. Within the CNS, adenosine receptor are responsible for regulation of neurotransmitter and also control the sleep pattern, cognitive learning and memory. Caffeine binds to that specific receptor which leads to blockage of receptors in terms of influx of neurotransmitters including dopamine, norepinephrine, glutamate, and gamma-aminobutyric acid (GABA) leads to mood alterations.

2. Origin

The coffee plant, classified under the family Rubiaceae as Coffea, originates from northern region of Africa and is predominantly found in many countries across America, Africa, and Asia. Within the genus Coffea there are four groups consisting of 66 species. These include *C. liberica*, *C. robusta*, *C. arabica*, and *excelsa* species, denoted by *C. excelsa* within the Eucoffea subgroup. Overall, the Coffea genus encompasses about

more than 120 species occurring in Africa, Asia and Australia, as well as in regions like the Madagascar (Clifford et al., 1991; Saud and Salamatullah, 2021; Socała et al., 2020). The chemistry of coffee beans is intricate, with carbohydrates being the predominant component. Alongside carbohydrates, coffee beans contain proteins, fats, tannin, caffeine, minerals, and various elements. The composition of these ingredients is influenced by factors such as the variety of the beans, their origin, and the time of harvest. However, the distinctive aroma and flavor associated with coffee emerge during the roasting process. More than 800 different aroma components have been identified in coffee, originating from molecular derivatives formed as a result of the breakdown of bonds and chemical reactions during roasting. These reactions involve various components in the beans and give rise to a plethora of flavor compounds, including oxygen, nitrogen, or sulfur containing ring compounds such as furan. Ultimately, it's these volatile components that define the rich and complex taste of coffee (Herbst et al., 2010).

3. Caffeine: Central nervous system stimulant

Caffeine has great potential in coordination, (CNS) stands as one of the primary systems in the body, involving of the brain and spinal cord, it is responsible for integrating and processing information (Ansari et al., 2024). In the brain regions caffeine is responsible for hyperexcitability of the CNS, inducing mood and memory tasks. Caffeine, belonging to the methylxanthine class, is a naturally occurring central nervous system stimulant, widely recognized as the most consumed psychoactive stimulant worldwide. While commonly obtained from coffee beans, it also occurs naturally in specific teas and cacao beans, and is additionally incorporated into soda and energy drinks. The primary aim of consuming caffeine is to alleviate fatigue and drowsiness (Evans et al., 2023). The modulation of sleep and vigilance within the central nervous system is influenced by adenosine, which promotes neurotransmitter release via A2A receptors and inhibits it via A1 receptors. It has been observed that the methylxanthine is related to effect of caffeine, thus it stimulates the locomotion in organisms. Caffeine's central stimulating effects stem from its antagonistic action on adenosine receptors. Additionally, A2A agonists have been observed to induce pro-nociceptive effects, with the intensity of pain correlating with increased cAMP levels. Furthermore, the activation of these receptors in vessels results in vasodilation, potentially contributing to the onset of headaches and migraines (Fried et al., 2017; Marchi et al., 2002; Vidyasagar et al., 2013).

Caffeine is present in over 60 plant species, indicating its widespread occurrence in nature. It has been suggested that caffeine initially served as non-essential nutrient for plants but evolved into a highly beneficial pesticide. It exhibit toxicity towards various insects and animals, particularly herbivores. This suggests that plants utilize caffeine as a defense mechanism, enhancing their chances to survive. From such perspective, caffeine could be view as a "co-evolutionary protective factor" aiding plant in their defense against potential threats (Cappelletti et al., 2015). In humans following oral ingestion, caffeine is swiftly absorbed into the bloodstreams with an estimated bio-availability of around 99%. It permeates various regions, before undergoing metabolic pathways in the hepatic tissues. Subsequently, it is primarily eliminated through the kidneys, predominantly in the form of metabolites (dePaula and Farah, 2019).

4. Caffeine and brain structure

Brain is the dynamic complex structure, to understand the brain fluctuation, anatomical studies are necessary. Caffeine has neuronal and vascular effects as well. Previous study suggested that it increases the brain entropy (BEN) indicating high learning capacity in the cortex and lateral region. Result indicates the caffeine effect on cognitive learning and memory. Gray matter is the part of the CNS consists of mainly cell body neurons whereas white matter include long neuronal extensions. It has been observed that the consumption of caffeine is responsible to reduce the volume of gray matter including temporal lobe and hippocampal region. It induces production of acetylcholine, serotonin and dopamine, which will further stabilizes the brain and blood barrier.

5. Biochemistry and metabolic pathway of caffeine

Caffeine, having chemical structure as 1,3,7-trimethylxanthine and serves as the primary alkaloid in coffee berries, contributing to the bitter taste commonly associated with coffee. Methylxanthine show structural similarities with purines and xanthine. The natural compound found in cherries, nuts and coffee beans, it is presumed for protection. Generally, it is easily absorbed rapidly by the gastrointestinal cells and shows complete bio-availability. Coffee involves faster absorption rate for caffeine as compare to the soft drinks. It has capability to disperse and enter into the bio-membranes including BBB and placenta. Caffeine is converted into chemical compound including

dimethylxanthine and dimethyl uric acids within the liver cells and about 2–3% unchanged remaining is excreted out from body. The primary metabolite of caffeine has been found in blood plasma namely: theobromine and paraxanthine. There are about five major metabolic pathway in caffeine metabolism involving demethylization of N-3 into paraxanthine, N-1 into theophylline. Cytochrome P-450 (CYP) an enzyme present in the liver metabolized more than 90% of caffeine. Another pathway involves formation of uracil metabolites and renal elimination. This compound is not only prevalent in coffee but is also found in tea and cocoa, making it one of the most widely consumed psychotropic substances. Research indicates that caffeine exhibits potential benefits, such as alleviating memory loss-induced amnesia in the elderly and reducing the susceptibility to neurodegenerative disorders. Chlorogenic acids, caffeine, cafestol, kahweol, and trigonelline are among the significant bioactive compounds found in coffee (Fig. 1). These compounds are recognized for their potential physiological effects and are considered important contributors to the health benefits associated with coffee consumption. Additionally, coffee leaves contain compounds such as 1,3,7,9-tetramethyluric acid (known as "theacrine"), liberine, and methyllibetine. Furthermore, coffee includes theobromine, theophylline, and nicotinic acid (Xue et al., 2019). It has been observed that caffeine induces positive regulation of catecholamines and increases the systolic and diastolic blood pressures.

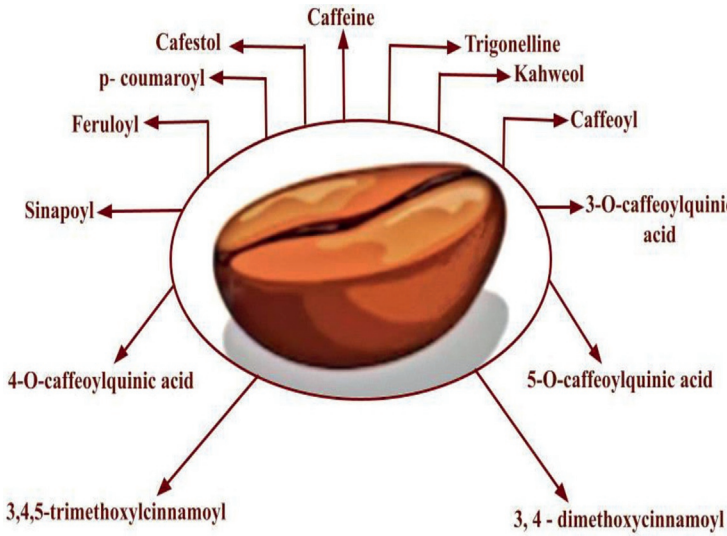

Fig. 1 Name of Bioactive compound found in Coffee.

5.1 Adenosine receptor

Activation of adenosine A1 receptors across different brain regions dampens glutamate release, thereby reducing the strength of postsynaptic currents. The accumulation of adenosine along with other substances that promote sleep, could inhibit the activity of brain regions responsible for wakefulness, consequently facilitating the activation of sleep-promoting regions (Alasmari, 2020). In addition to A1 receptors, the A2A receptor also emerges as a key player in orchestrating sleep-wake cycles among the four subclass of adenosine receptors (Lazarus et al., 2019). At low concentrations, caffeine act as a nonspecific antagonist for adenosine receptors (A1, A2a), it antagonized the endogenous effect. Adenosine's role in regulating sleep-wake cycles is enacted through its interaction with G-protein coupled adenosine receptors: A1, A2A, A2B, and A3 receptors. Laboratory studies indicated that natural levels of adenosine can activate A1, A2A, and A3 receptors.

5.2 Calcium mobilization

Caffeine stimulate calcium ions (Ca^{2+}) discharge from sarcoplasmic reticulum and myofilament activity towards the (Ca^{2+}) whereas decrease the concentration of both sodium potassium pump and adenosine triphosphate (ATP) molecules. This action induces the lipid degradation by lipases and releases fatty acid. Fatty acid acts as fuel for skeletal muscles.

5.3 Caffeine and cyclic adenosine monophosphate (cAMP)

It has been reported that caffeine increases concentration of cyclic adenosine monophosphate (cAMP) through inhibiting phosphodiesterase enzyme within the muscles and adipose tissues. This accumulation of cAMP activates the phosphorylation activity of kinases especially in actin and myosin. Another important function of cAMP is to increase catecholamines in the blood vessels. In energy metabolism, it is considered as potent inhibitor of cAMP and phosphodiesterase in the tissues.

5.4 Mechanism of action of caffeine

Its primary role is to block adenosine receptors and inhibition of phosphodiesterases. Adenosine receptors modulate neuronal and synaptic function, impacting brain ischemic damage and degenerative disorders. A1 receptors suppress neural activity, while A2A receptors promote transmitter release and depolarization. They interact with neurotransmitters like glutamate, NMDA, nitric oxide, and P2 purine receptors. These receptors regulate

inflammatory processes by modulating cytokine release. It has been reported that our brain contain enormous amount of adenosine receptors I, inactivated form it releases certain number of neurotransmitters. While when the adenosine receptors are activated, the nerve cells secrete low concentration of neurotransmitters hence adenosine act as an activator leads to cause fatigue. Influx of calcium ion also responsible to release neurotransmitter. Caffeine bind and block that receptor and improve mental alertness and relief (Fig. 2). Methylxanthine are capable of to act as an antagonist against the adenosine effects. Agonists and antagonists of A1, A2A, and A3 receptors can protect against insults, with outcomes varying based on treatment duration and adaptational changes. Adenosine, a byproduct of ATP depletion in the brain, emerges as sleep ensues. During natural sleep, there is an increase in ATP levels within brain regions associated with wakefulness, whereas sleep deprivation leads to a decline. Prolonged neuronal activity results in ATP accumulation in the extracellular space, where it undergoes conversion to adenosine via the enzyme 5'-EN.

The extracellular concentration of adenosine is believed to elevate during extended periods of wakefulness, signaling the body's need for sleep. This phenomenon is particularly crucial in the basal forebrain, which is implicated in the regulation of sleep-wake cycles. It has been noted that

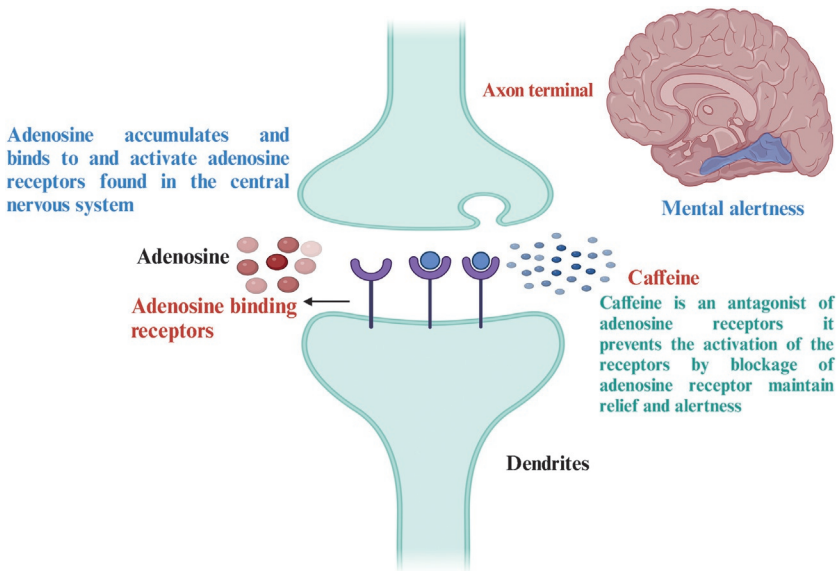

Fig. 2 Mechanism of caffeine at synapses.

caffeine increases the metabolic rate of energy within the CNS but decreases the cerebral blood flow at same time. Caffeine has capability to activates the dopamine and noradrenaline releasing neurons, although its action is also associated with cation of methylxanthine on serotonin releasing nerve cells. Methylxanthine is responsible to increase the locomotor activity in brain. In the CNS and brain adenosine and its receptor is responsible to control and regulate neurotransmission has significant role in cognitive learning. Caffeine binds to that specific receptors by inhibiting binding of adenosine to the receptor. The blockage leads to affect the release of neurotransmitter such as GABA, acetylcholine, dopamine, norepinephrine and serotonin. This leads to cause alteration in mood and memory by improving mental alertness. It has property to stimulate the calcium ion influx through the sarcoplasmic reticulum. Calcium ion is dependent on the neurotransmitter and are released into the central nervous system through synaptic transmission and finally reaches upto nerve cells. At low concentration caffeine induced the calcium influx by endoplasmic reticulum, whereas at higher concentration calcium influx is inhibited. The main mechanism of action does not involve suppression of neurotransmission, it is due to calcium pool. The another mechanism involves by inhibition of phosphodiesterases by preventing degradation of cyclic adenosine monophsphate (cAMP). It leads to vasodilation by reflecting vasoconstriction to central nervous system. The concentrations of adenosine within cells and in the extracellular space are meticulously regulated through complex processes influenced by the metabolic state of both neurons and astrocytes. Enzymes and transporters play key roles in converting adenosine to from ATP via adenosine diphosphate and adenosine monophosphate and S-adenosylhomocysteine, as well as in controlling its release and uptake. Extracellular adenosine primarily arises from the degradation of adenine nucleotides by 5′-ecto-nucleotidases (5'-ENs), which are released alongside glutamate during astrocytic activation, a phenomenon referred to as "gliotransmission." Adenosine kinase (AdK) regulates adenosine levels by phosphorylating it to AMP, while adenosine deaminase (ADA) irreversibly converts adenosine to inosine, particularly following periods of elevated adenosine concentrations such as after sleep deprivation. In addition to ADA, bi-directional equilibrative nucleoside transporters (ENTs) also contribute to extracellular adenosine regulation. Under conditions of heightened adenosine levels, ENTs help maintain balance in extracellular adenosine. As a result, the availability of adenosine at its receptors on cell surfaces is intricately governed by these elaborate biological processes of adenosine formation and removal. For example, local

administration of a selective A2A receptor agonist, CGS21680, near the basal forebrain and lateral preoptic area induces c-fos expression in the ventro-lateral preoptic area and promotes non-rapid eye movement (NREM) sleep. This implies that direct activation of sleep-promoting neurons in the ventro-lateral preoptic region via A2A receptors may underlie this effect. Interestingly, preliminary evidence suggests that mice lacking functional A2A receptors exhibit reduced sleep and a diminished sleep rebound after sleep deprivation, indicating their role in regulating sleep homeostasis in mammals.

6. Pros of caffeine consumption on central nervous system

Caffeine, recognized chemically organic compound and is classified as a purine due to its molecular structure (Higdon and Frei, 2006). Moderate caffeine intake is 3–5 cups/24 h that has been connected to downregulate the anxiety, stress and fatigue, thereby improves mental alertness and memory responses. A cup of coffee consists about 180 mg of caffeine and the amount also varies depending upon the species (Smith, 2002). Caffeine stands as the predominant alkaloid in coffee and in a variety of soft beverages. This methylxanthine is widely acknowledged as one of the most widely used psychostimulants across the globe (Butt and Sultan, 2011). Furthermore, studies have indicated that caffeine possesses neuroprotective, anti-inflammatory (Dórea and da Costa, 2005), antioxidant (Horrigan et al., 2006) and anti-cancer properties (Gökcen and Şanlier, 2019). The previous study suggested that caffeine has the potential to protect against cognitive decline and improve memory retention. Its protective effects extended to preserving memory, learning, and mental abilities (Chee and Oh, 2013). Arendash et al. (2006) conducted an experiment in which he incorporated the caffeine dose 1.5 mg/day for 5 months in mice he finds out restored PKA levels, which are typically decreased in these mice. This restoration of PKA levels helps inactivating c-Raf-1, a protein involved in activating the NF-κB pathway, which ultimately leads to formation of β-secretase-1 (BACE-1) and another proteins associated to Alzheimer's disease (AD).

Thus, caffeine intake of about 500 mg reduces the levels of c-Raf-1, activation of the NF-κB pathway, and production of BACE-1 in APPsw mice. Moreover, caffeine decreases the levels of GSK-3, a protein known to regulate Aβ production, as well as the activity of presenilin (PS)-1 and γ-secretase, and the hyperphosphorylation of tau. Additionally, caffeine

restores PS-1 levels and reduces. Caffeine reduces phosphorylated IκBα and NF-κB levels, as well as the translocation of NF-κB into the nucleus, back to control levels (McCusker et al., 2003). In human neuroblastoma cells, caffeine reduced harmful reactive oxygen species (ROS) by 51% and boosted levels of the antioxidant superoxide dismutase (SOD) by 50%. It also normalized protein levels involved in cell survival. Additionally, caffeine protected against cell death better than an A2AR-specific antagonist. In mice with Alzheimer's, caffeine increased energy production in brain cells and improved blood flow, contributing to its protective effects (Giunta et al., 2014; Sato et al., 2005).

These interventions also prevent ataxin-3-induced synaptotoxicity. Upcoming investigation is needed to enhance caffeine's impact in MJD at different doses and across genders (Kolahdouzan and Hamadeh, 2017). Caffeine's impact on dopaminergic systems in both humans and animals has been noted across various investigations, including those spearheaded (Garrett and Griffiths, 1997; López-Cruz et al., 2018; Manalo and Medina, 2018; Pandolfo et al., 2013; Solinas et al., 2002; Volkow et al., 2015). Manalo and Medina (2018) highlight its ability to modulate adenosine A receptors. Caffeine influences the glutamatergic system in diverse brain regions (John et al., 2014; Owolabi et al., 2017; Smith, 2002; Solinas et al., 2002; Vyleta and Smith, 2008).

Pandolfo et al. (2013) suggests caffeine's potential to alleviate specific neurological disorders by modifying dopaminergic pathways. Investigations by Vyleta and Smith (2008) indicate that caffeine exposure alters glutamate levels and affects receptors and transporters associated with glutamatergic signaling. Further, research by Manalo and Medina (2018) proposes that caffeine may protect against dopaminergic neuron loss, potentially offering therapeutic benefits for conditions like Parkinson's disease. Moreover, caffeine's impact on GABAergic systems, including GABA receptor regulation, is highlighted in studies led by Ferreira et al. (2014); Hahn et al. (2017); Isokawa (2016); Lopez et al. (1989) and Roca et al. (1988). These collective findings suggest that caffeine's effects on the glutamatergic system may contribute to the development of neurological disorders (Volkow et al., 2015).

6.1 Adenosine and sleep pattern

Adenosine, a neurotransmitter involved in sleep-wake regulation, exerts its effects by suppressing the activity promoting neurons in various brain region, including hypothalamus. This inhibition contributes to cortical

disfacilitation, characterized by decreased activation resulting from reduced input from metabolic pathways. Adenosine activates hypothalamic neurons and also present in the preoptic area by GABAergic inputs. Such neurons exhibit heightened firing rates following sleep deprivation, indicating their activity is regulated by mechanisms reflecting the body's need for sleep (Sherin et al., 1996; Urry and Landolt, 2014). While it has been suggested that high adenosine levels in the forebrain play a significant role in increasing sleepiness and the urge for sleep following sleep deprivation, recent research challenges this view. Studies indicate that adenosine's effects are not confined to the BF, and its buildup in this region is not necessary for initiating sleep. Furthermore, BF cholinergic nerve cells are not pivotal for promoting drive in sleep. Instead, evidence suggests that adenosine acts as a signal across the neuronal network spanning both subcortical and cortical structures, regulating essential aspects of sleep pattern (Porkka-Heiskanen and Kalinchuk, 2011).

Nonetheless, this is generally recognized the predominant impact of adenosine on wakefulness, particularly in humans, is mediated by the effective-affinity A1 and A2A receptors (Dias et al., 2013). Adenosine A2A receptors are implicated in regulating cellular activity by elevating adenyl cyclase an effector molecule through Gs (G-stimulatory) proteins, resulting in the activation of protein kinase A and the formation of inositol phosphates. Unlike the A1 receptor, the A2A subtype not much distributed within the brain, with its over-expression noted in the nerve ganglion nuclei. Recent performed exeriments suggested A2A receptors are involved in sleep regulations (Elmenhorst et al., 2007). Interestingly, preliminary evidence suggests that mice lacking functional A2A receptors exhibit reduced sleep indicating their role in regulating sleep homeostasis in mammals.

Human studies further corroborate these findings, indicating that genetic variations in the A2A receptor gene induced the increase in electroencephalogram (EEG) slow-wave activity (SWA) during NREM sleep following sleep deprivation. Overall, both adenosine A1 and A2A receptor subtype are likely involved in mediation of adenosine, although the specific effects may vary depending on the site and type of receptor involved (Basheer et al., 2004). In the CNS, adenosine regulates sleep and wakefulness (Ferré, 2010). It promotes sleep by increasing in the forebrain during wakefulness and declining during sleep. It reduces cortical activity via A1 receptor modulation and affects the hypothalamus through A2A receptors (Scammell et al., 2001). Caffeine-induced wakefulness depends on blocking A2A receptors, leading to increased arousal (Huang et al., 2005). Both A1 and A2A receptors play

roles in adenosine's sleep-promoting effects (Lazarus et al., 2011). Caffeine, known as the most widely consumed stimulant globally, act as competitive antagonist at A1 and A2A receptors when reaching plasma microliter concentrations post-moderate consumption. Elmenhorst et al. (2012) found through recent PET imaging studies that the consumption of 5 cup of coffee, equivalent to approximately 450 mg of caffeine displace endogenous adenosine. Conversely, other impacts of caffeine observed including inhibition of phosphodiesterase and calcium ion concentrations, blockage of GABA receptor.

6.2 Pain modulation

The analgesic effects of caffeine may pose a challenge in comparison to those of adenosine (Johansson et al., 2001). Elevated adenosine levels during stress and noxious stimuli have been linked to pain reduction, while adenosine receptor agonists demonstrate pain-relieving effects in various models (Li et al., 2003). In a study, mice lacking A1 receptors display heightened anxiety and increased sensitivity to pain, with the pain-relieving effects of adenosine absent in these mice. A1 receptors are found in peripheral nerve cells, suggesting that peripheral pain relief via A1 receptor activation may involve the inhibition of calcitonin (Sawynok, 1998). Experimental data under inflammatory conditions suggest that adenosine's analgesic effect involves reducing hypersensitivity through a central mechanism (Eisenach et al., 2002).

It has been suggested that caffeine, when consumed in typical human doses, may potentially have analgesic effects, potentially through the inhibition of A2A receptors (Sawynok, 2011). Central dopaminergic mechanisms may also play a role, according to some propositions. Similar to other pain-relieving substances, caffeine is believed to increase dopamine release, potentially by inhibiting A2A receptors. Interestingly, it has been observed that A2A receptor antagonists did not have an effect on dural meningeal vasodilation induced by calcitonin related gene (CGRP) (Ferré et al., 1992). Although A2A receptors are not typically found in the spinal cord, Brooks et al. demonstrated a specific inhibition of intermediolateral cell column activity (sympathetic system), suggesting a possible presence of A2A receptors on presynaptic (Brooke et al., 2004).

7. The influence of caffeine on sleep patterns and migraine occurrence

It has been stated that there is a definite connection between sleep and migraine (Holland, 2014). It has also been suggested that caffeine can indeed disrupt sleep (Wesensten, 2014). Disrupted sleep patterns have been

proposed to predispose individuals to migraines, while sleep itself is considered to offer protection against migraines (Alstadhaug, 2009). It has been noted that the likelihood of experiencing a migraine attack is minimized during sleep, but there is a notable increase in the morning, particularly when accompanied by insomnia. Afternoon peaks in migraine occurrences are thought to be linked to stress. Menstrual migraine and headaches are best examples of this periodicity (Couturier et al., 1992). 35 children experiencing chronic headaches, history of migraine, were found to consume excessive amounts of caffeine primarily through cola drinks, averaging around 190 mg of caffeine per day. Following a gradual withdrawal from caffeine consumption, 33 of these children fully recovered (Hering-Hanit and Gadoth, 2003). It is generally observed that chronic headache are associated with migraines (Hershey, 2003). Caffeine has been considered as a potential risk factor for episodic migraine progressing into chronic migraine. Studies indicate a significant positive relationship in both chronic and episodic migraine. Various study have explored the correlation among the caffeine consumption and headache. Some studies found no significant relationship between current caffeine intake and headaches, while others identified a higher likelihood of heavy caffeine consumption among headache sufferers compared to non-sufferers (Boardman et al., 2005). It has been observed generally that chronic consumption of caffeine appears to be linked with an elevated migraine burden. It remains uncertain whether chronic caffeine consumption raises the risk of migraines or, conversely, offers beneficial effects for individuals severely impacted by migraines.

8. Impact of maternal caffeine consumption on fetal brain development

In 1989, a single-blind crossover study was conducted by Salvador and Koos, involving eight patients, to investigate how caffeinated and decaffeinated coffee affect breathing rate in fetus. The study enrolled pregnant ladies, all non-smokers, in their 32–36 weeks of gestation. Among them, four were assigned to the control group, consuming decaffeinated coffee, while the remaining four constituted the experimental group, consuming caffeinated coffee. Following caffeine intake, epinephrine levels escalated from 200 picograms per milliliter (pg/mL) to 455 pg/mL within 30 min. Moreover, maternal caffeine consumption corresponded to a importance upsurge in fetal breathing rate ($P < 0.01$). This heightened fetal breathing rate may potentially be attributed to the physiological effects of caffeine on the maternal body. It is essential to emphasize that caffeine's vasoconstrictive

characteristics may diminish blood flow to the fetus, prompting the fetus to compensate by elevating its breathing rate (Lakin et al., 2023).

Additionally, it was observed that the rise in maternal epinephrine levels following the consumption of caffeinated coffee contributed to the increase the rate of fetus. Nonetheless, there is a need for studies with larger sample sizes to delve deeper into this evidence (Salvador and Koos, 1989).

A non-randomized controlled trial aimed at delving deeper into the effects of maternal caffeine. Approximately 13 healthy pregnant women, with an average age of 29 years, were enlisted for the study. These women, who were not classified as obese, presented unremarkable obstetric histories and no history of smoking, alcohol consumption, or any use of medication or drugs. Caffeine sources were included in the diary. Additionally, there was a notable increase in the number of fetal heart rate accelerations and general fetal movements. However, conclusive evidence regarding the impact of maternal caffeine intake on fetal breathing rate remained elusive. It is important to acknowledge that the researchers did not offer a precise definition of "normal conditions" for the control group, and the study sample was relatively small. Nevertheless, these findings shed light on the fact that maternal caffeine consumption can indeed alter fetal functionality, thereby highlighting its influence on the fetal environment (Mulder et al., 2010).

Pregnancy is a pivotal time for both the mother-to-be and her unborn child. In order to ensure a smooth pregnancy journey, health care providers commonly advise against the use of certain medications and consumption of particular foods, alcohol, and beverages, including those containing caffeine. Although generally deemed safe during pregnancy, there is still much to be learned about the effects of caffeine on fetal development, current clinical evidence suggests that maternal caffeine intake may impact the fetus by increasing its breathing rate and time spent awake. Furthermore, it appears to elevate the fetal heart rate and potentially lead to lower birth weight, affecting overall infant growth. While there isn't conclusive evidence linking caffeine to gestational length or hypertension, it is believed to heighten uterine contractions, which could lead to complications like spontaneous abortion or pre-eclampsia. However, the exact relationship between caffeine consumption and congenital malformations remains unclear. Therefore, it's crucial to conduct further clinical trials with larger participant pools to thoroughly investigate the effects of caffeine on infant congenital disabilities. Additionally, delving into the underlying mechanisms by which caffeine impacts fetal development and pregnancy is essential.

9. Caffeine and neurodegenerative diseases

The central nervous system (CNS) comprises neuronal network responsible for nerve impulse transmission all the parts of body which is responsible for coordination. Nerve cells or neurons are the basic structural and functional unit of nervous system. Progressive loss of these cells leads to cause abnormalities with the brain and CNS including Parkinson's disease, Huntington's disease, Sclerosis, epilepsy and Alzheimer's disease. Neuronal dysfunction or neuronal death is the main outcome of these diseases. Such selective neuronal loss affects the both central and peripheral nervous system.

9.1 Parkinson's disease (PD)

The disease is related to postural instability which may result in the loss of dopamine secreting nerve cells. The main reason behind this dysfunction is due to damaged DNA molecules and reactive oxygen species (ROS). Caffeine, known for its role as an antagonist to adenosine receptors, has been found to improve motor activity among individuals diagnosed with Parkinson's Disease (Cunha and Agostinho, 2010). 1-Mehtyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) a neurotoxic compound which inhibits the complex I system of electron chain and leads to cause energy depletion resulting in progressive loss of neurons. Caffeine reduces the toxic effect of MPTP based neuronal damage hence are potent inhibitor in neuronal death pathway. It has been observed that it reduces neuroinflammatory responses and lower nitric oxide (NO) production, suggesting potential neuroprotective effects (Camilo and Goldstein, 2004). Studies indicate that caffeine are helpful in preventing the loss of nigral dopaminergic neurons, a salient feature of Parkinson's Disease progression. Furthermore, research suggests that caffeine exhibits efficacy integration prevention of the blood–brain barrier, which could potentially slow down the advancement of the disease (Yadav et al., 2012).

9.2 Huntington's disease (HD)

The term Huntington's chorea also be used for this dysfunction and is one of the main genetic cause of chorea. In the 1872, this an inherited disease was first coined by George Huntington. The main reason behind this disorder is due to dominant Mutation in huntingtin gene (HTT) Leads to cause this disorders. Initial symptoms involves jerky movement Known as chorea. It is characterized by bradykinesia and triplet repeats. Excessive influx of

calcium ions (Ca^{2+}) cause to release of pro-apoptotic factors from mitochondria which result in apoptosis of neurons. Caffeine have antioxidant property therefore, it reduces the oxidative stress. Caffeine consumption as an antagonist has been proven beneficial in the HD. Previous study suggested that it boosts neuroprotective effect in the brain.

9.3 Alzheimer's disease (AD)

It is associated with memory impairments and behavioral disabilities and involves histopathological characters such as deposition of plaques and neurofibrillary dysfunctions. These features leads to cause selective loss of nerve cells in the hippocampal and cortical region. Caffeine has shown promise in inhibiting the deposition of amyloid-β-peptide (Aβ), a key pathological feature. It has been found to reverse cognitive decline and decrease brain Aβ levels in animal models. Caffeine appears to offer protective effects against metabolic stress and pathological abnormalities in the hippocampal region. Additionally, observational studies have linked moderate coffee consumption during midlife to a decreased risk of dementia later in life. Caffeine's ability to enhance mitochondrial activity and suppress signaling of melatonin, further contributes to its potential neuroprotective properties (Chen et al., 2010). Caffeine become central area of scientific researches as it consist of antioxidant property against the AD. It improves the functional task, reduces the accumulation of amyloid granules and oxidative stress.

9.4 Machado-Joseph disease (MJD)

In this disease the number of CAG codon increases, leading to disrupt of the CAG in the MJD1 gene, which express the polyQ in the ataxin-3 protein. The disease is recognized by mature individual and features progressive ataxia, motor dysfunction, walking instability, and few characters of PD also ultimately resulting in premature death. Glutamate stimulation contributes to the protein degradation and accumulation of ataxin-3. Research indicates that high dosage of caffeine consumption and deletion in gene of A2AR reduce degeneration, neuronal death, dysfunction, and gliosis in MJD (Table 1).

9.5 Amyotrophic lateral sclerosis (ALS)

A dysfunction involves progressive degeneration of both (upper and lower) motor neurons. This histopathological effect result in muscles atrophy and also respiratory failures. It is rapidly progressing disease can be caused by

Table 1 Neuroprotection of caffeine in neurodegenerative disorders.

S. No.	Neurdegenerative disease	Mechanism of actions
1.	Alzheimer's Disease	Decreases (Aβ) aggregation, blocks melatonin signaling
2.	Machado-Joseph disease	Inactivation of adenosine receptors
3.	Parkinson's Disease	Decreases loss of dopaminergic neurons and downregulation of neuroinflammatory response
4.	Migraine	Increases CSF production
5.	Huntington's Disease	Decreases oxidative stress
6.	Multiple Sclerosis	Inducing integrity of blood brain barrier
7.	Amyotrophic lateral Sclerosis	Decreases microglial activation

single gene mutation such as Cu^{2+}/Zn^{2+} superoxide dismutase (SOD)-1 mutation. Instead of glutamate stimulation, calcium ions concentration increases resulting in reactive oxygen species and inflammation. Caffeine seems to plays significant role in ALS through mechanism of actions. It attenuate the microglial cells and down regulate the risk factor of disease.

9.6 Cons of caffeine consumption

In accordance with the DSM-5 and the International Classification of Diseases (ICD-10) (Verheul et al., 1999) by the World Health Organization, caffeine intoxicity is acknowledged as a syndrome. It is characterized by specific symptoms that manifest directly due to caffeine consumption. Symptoms of caffeine intoxication, which may mirror those associated with anxiety and other affective disorders, encompass stress, tension, insomnia, intestinal abnormalities, tachycardia and in some instances, death. Commonly observed features of caffeine intoxication, also termed "caffeinism" to indicate chronic toxicity from excessive caffeine intake, include these symptoms. Consumption of energy drinks may heighten the risk of caffeine overdose among individuals abstaining from caffeine, as well as habitual caffeine use. It was stated that the ingestion of abundant amount of caffeine, more than 600 mg equal to approximately 4–7 cups/day, can result in symptoms such as anxiety, tremors, and increased heart rate

(tachycardia). However, it was noted that reaching such high concentrations of caffeine typically requires intake beyond what is commonly found in dietary sources. In most cases of life-threatening caffeine overdoses, it was observed that the culprit is the uptake of caffeine having medicinal value rather than caffeinated foods or drinks (Nawrot et al., 2003). It was highlighted that this instance of multichemical death underscores the potential interaction between these substances within body tissues, leading to rapid toxicity and premature demise (Bryant, 1981). Average amount of caffeine consumption is alright for health but when the amount of dosage increases it induce negative effects such as anxiety and insomnia. Hence one should consume caffeine according to necessity (Table 2).

10. Conclusion

Adenosine, often referred to as the "sleep regulator" is produced in response to neuronal function and interacts with A1 and A2A receptors in the brain, including the basal ganglia and cortex. Its actions involve inducing global cortical disfacilitation and stimulating sleep-active neurons in the hypothalamus, thereby modulating brain functions associated with the regulation of sleep pattern, such as mental and physical attention. Accumulated evidence from pharmacological and genetic studies conducted in individuals suggests that variations in adenosinergic activity primarily impact vigilant attention, irrespective of sleep status. Caffeine, acting as a non-selective antagonist of A1 and A2A receptors, mitigates the physiological and behavioral aspects related to neuronal activity, effects of sleep deprivation. However, it does not serve as a complete substitute for sleep, and standard doses fail to enhance cognitive learning and memory are compromised by severe sleep loss. It was noted that the hazards associated with caffeine are

Table 2 Average daily intake of caffeine as per age group.

Age group	Dosage of caffeine
Very elderly (75 years and above)	22–417 mg
Elderly (65–75 years)	23–362 mg
Adults (18–65 years)	37–319 mg
Adolescents (10–18 years)	0.4–1.4 mg bw
Children (3–10 years)	0.2–2.0 mg/kg bw
Toddlers (12–36 years)	0–2.1 mg/kg bw

linked to its widespread availability, which often leads to unintentional excessive consumption. This is due to the difficulty in accurately gauging daily intake and predicting specific effects. It was also observed that, similar to other psychoactive substances, caffeine has the capability to induce dependence. Unlike alcohol and tobacco, though, there are fewer controls or restrictions on the sale of high-concentration caffeine products such as drinks or tablets. Recently, researches provide a way to determine the effect of caffeine on mood swing and majority of studies to help enable the memory and cognitive learning tasks. It has been reported that caffeine plays crucial role in short-term as well as long-term memory.

Acknowledgment

The authors wish to thank Principal, S. S. Khanna Girls' Degree College (A Constituent College of University of Allahabad, Prayagraj) and DST-CURIE Grant of Department of Science and Technology, New Delhi GOI (DST/CURIE-PG/2022/10G) for providing all the necessary facilities in college.

References

Alasmari, F., 2020. Caffeine induces neurobehavioral effects through modulating neurotransmitters. Saudi Pharm. J. 28 (4), 445–451. https://doi.org/10.1016/j.jsps.2020.02.005.

Alstadhaug, K.B., 2009. Migraine and the hypothalamus. Cephalalgia 29 (8), 809–817. https://doi.org/10.1111/j.1468-2982.2008.01814.x.

Ansari, A., Singh, D., Singh, S., 2024. Effect of plant-based diets on the brain., https://doi.org/10.1016/B978-0-443-18951-7.00014-1.

Arendash, G.W., Schleif, W., Rezai-Zadeh, K., Jackson, E.K., Zacharia, L.C., Cracchiolo, J.R., Tan, J., 2006. Caffeine protects Alzheimer's mice against cognitive impairment and reduces brain β-amyloid production. Neuroscience 142 (4), 941–952. https://doi.org/10.1016/j.neuroscience.2006.07.021.

Basheer, R., Strecker, R.E., Thakkar, M.M., McCarley, R.W., 2004. Adenosine and sleep–wake regulation. Prog. Neurobiol. 73 (6), 379–396. https://doi.org/10.1016/j.pneurobio.2004.06.004.

Boardman, H.F., Thomas, E., Millson, D.S., Croft, P.R., 2005. Psychological, sleep, lifestyle, and comorbid associations with headache. Headache 45 (6), 657–669. https://doi.org/10.1111/j.1526-4610.2005.05133.x.

Brooke, R.E., Deuchars, J., Deuchars, S.A., 2004. Input-specific modulation of neurotransmitter release in the lateral horn of the spinal cord via adenosine receptors. J. Neurosci. 24 (1), 127–137. https://doi.org/10.1523/jneurosci.4591-03.2004.

Bryant, J., 1981. Suicide by ingestion of caffeine. Arch. Pathol. Lab. Med. 105 (12), 685–686. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/6895464.

Butt, M.S., Sultan, M.T., 2011. Coffee and its consumption: benefits and risks. Crit. Rev. Food Sci. Nutr. 51 (4), 363–373. https://doi.org/10.1080/10408390903586412.

Camilo, O., Goldstein, L.B., 2004. Seizures and epilepsy after ischemic stroke. Stroke 35 (7), 1769–1775. https://doi.org/10.1161/01.str.0000130989.17100.96.

Cappelletti, S., Daria, P., Sani, G., Aromatario, M., 2015. Caffeine: cognitive and physical performance enhancer or psychoactive drug? Curr. Neuropharmacol. 13 (1), 71–88. https://doi.org/10.2174/1570159x13666141210215655.

Chee, H.K., Oh, S.J., 2013. Molecular vibration-activity relationship in the agonism of adenosine receptors. Genomics Inform. 11 (4), 282. https://doi.org/10.5808/gi.2013.11.4.282.

Chen, X., Ghribi, O., Geiger, J.D., 2010. Caffeine protects against disruptions of the blood-brain barrier in animal models of Alzheimer's and Parkinson's diseases. J. Alzheimer's Dis. 20 (s1), S127–S141. https://doi.org/10.3233/jad-2010-1376.

Clifford, M.N., Gibson, C.L., Rakotomalala, J.-J.R., Cros, E., Charrier, A., 1991. Caffeine from green beans of Mascarocoffea. Phytochemistry 30 (12), 4039–4040. https://doi.org/10.1016/0031-9422(91)83461-s.

Couturier, E.G.M., Hering, R., Steiner, T.J., 1992. Weekend attacks in migraine patients: caused by caffeine withdrawal? Cephalalgia 12 (2), 99–100. https://doi.org/10.1046/j.1468-2982.1992.1202099.x.

Cunha, R.A., Agostinho, P.M., 2010. Chronic caffeine consumption prevents memory disturbance in different animal models of memory decline. J. Alzheimer's Dis. 20 (s1), S95–S116. https://doi.org/10.3233/jad-2010-1408.

dePaula, J., Farah, A., 2019. Caffeine consumption through coffee: content in the beverage, metabolism, health benefits and risks. Beverages 5 (2), 37. https://doi.org/10.3390/beverages5020037.

Dias, R.B., Rombo, D.M., Ribeiro, J.A., Henley, J.M., Sebastião, A.M., 2013. Adenosine: setting the stage for plasticity. Trends Neurosci. 36 (4), 248–257. https://doi.org/10.1016/j.tins.2012.12.003.

Dórea, J.G., da Costa, T.H.M., 2005. Is coffee a functional food? Br. J. Nutr. 93 (6), 773–782. https://doi.org/10.1079/bjn20051370.

Eisenach, J.C., Hood, D.D., Curry, R., 2002. Preliminary efficacy assessment of intrathecal injection of an American formulation of adenosine in humans. Anesthesiology 96 (1), 29–34. https://doi.org/10.1097/00000542-200201000-00011.

Elmenhorst, D., Meyer, P.T., Winz, O.H., Matusch, A., Ermert, J., Coenen, H.H., Bauer, A., 2007. Sleep deprivation increases A(1) adenosine receptor binding in the human brain: a positron emission tomography study. J. Neurosci. 27 (9), 2410–2415.

Elmenhorst, D., Meyer, P.T., Matusch, A., Winz, O.H., Bauer, A., 2012. Caffeine occupancy of human cerebral A1 adenosine receptors: in vivo quantification with 18F-CPFPX and PET. J. Nucl. Med. 53 (11), 1723–1729. https://doi.org/10.2967/jnumed.112.105114.

Evans, J., Richards, J.R., Battisti, A.S., 2023. StatPearls. StatPearls Publishing.

Ferré, S., 2010. Role of the central ascending neurotransmitter systems in the psychostimulant effects of caffeine. J. Alzheimer's Dis. 20 (s1), S35–S49. https://doi.org/10.3233/jad-2010-1400.

Ferré, S., Fuxe, K., von Euler, G., Johansson, B., Fredholm, B.B., 1992. Adenosine-dopamine interactions in the brain. Neuroscience 51 (3), 501–512. https://doi.org/10.1016/0306-4522(92)90291-9.

Ferreira, D.D.P., Stutz, B., de Mello, F.G., Reis, R.A.M., Kubrusly, R.C.C., 2014. Caffeine potentiates the release of GABA mediated by NMDA receptor activation: involvement of A1 adenosine receptors. Neuroscience 281, 208–215. https://doi.org/10.1016/j.neuroscience.2014.09.060.

Frary, C.D., Johnson, R.K., Wang, M.Q., 2005. Food sources and intakes of caffeine in the diets of persons in the United States. J. Am. Diet. Assoc. 105 (1), 110–113. https://doi.org/10.1016/j.jada.2004.10.027.

Fried, N., Elliott, M., Oshinsky, M., 2017. The role of adenosine signaling in headache: a review. Brain Sci. 7 (12), 30. https://doi.org/10.3390/brainsci7030030.

Garrett, B.E., Griffiths, R.R., 1997. The role of dopamine in the behavioral effects of caffeine in animals and humans. Pharmacol. Biochem. Behav. 57 (3), 533–541. https://doi.org/10.1016/s0091-3057(96)00435-2.

Giunta, S., Andriolo, V., Castorina, A., 2014. Dual blockade of the A1 and A2A adenosine receptor prevents amyloid beta toxicity in neuroblastoma cells exposed to aluminum chloride. Int. J. Biochem. Cell Biol. 54, 122–136. https://doi.org/10.1016/j.biocel.2014.07.009.

Gökcen, B.B., Şanlier, N., 2019. Coffee consumption and disease correlations. Crit. Rev. Food Sci. Nutr. 59 (2), 336–348. https://doi.org/10.1080/10408398.2017.1369391.

Hahn, S., Kim, Y.H., Seo, H.S., 2017. Immediate decrease in γ-AminoButyric acid after caffeine intake in adolescents: a preliminary MRS study. Investig. Magn. Reson. Imaging 21 (2), 102. https://doi.org/10.13104/imri.2017.21.2.102.

Herbst, R.S., Eckhardt, S.G., Kurzrock, R., Ebbinghaus, S., O'Dwyer, P.J., Gordon, M.S., Mendelson, D.S., 2010. Phase I dose-escalation study of recombinant human Apo2L/TRAIL, a dual proapoptotic receptor agonist, in patients with advanced cancer. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 28 (17), 2839–2846. https://doi.org/10.1200/jco.2009.25.1991.

Hering-Hanit, R., Gadoth, N., 2003. Caffeine-induced headache in children and adolescents. Cephalalgia 23 (5), 332–335. https://doi.org/10.1046/j.1468-2982.2003.00576.x.

Hershey, A.D., 2003. Chronic daily headaches in children. Expert Opin. Pharmacother. 4 (4), 485–491. https://doi.org/10.1517/14656566.4.4.485.

Higdon, J.V., Frei, B., 2006. Coffee and health: a review of recent human research. Crit. Rev. Food Sci. Nutr. 46 (2), 101–123. https://doi.org/10.1080/10408390500400009.

Holland, P.R., 2014. Headache and sleep: shared patho physiological mechanisms. Cephalalgia 34 (10), 725–744. https://doi.org/10.1177/0333102414541687.

Horrigan, L., Kelly, J., Connor, T., 2006. Immunomodulatory effects of caffeine: friend or foe? Pharmacol. Ther. 111 (3), 877–892. https://doi.org/10.1016/j.pharmthera.2006.02.002.

Huang, Z.-L., Qu, W.-M., Eguchi, N., Chen, J.-F., Schwarzschild, M.A., Fredholm, B.B., Hayaishi, O., 2005. Adenosine A2A, but not A1, receptors mediate the arousal effect of caffeine. Nat. Neurosci. 8 (7), 858–859. https://doi.org/10.1038/nn1491.

Isokawa, M., 2016. Caffeine-induced suppression of GABAergic inhibition and calcium-independent metaplasticity. Neural Plast. 2016, 1–7. https://doi.org/10.1155/2016/1239629.

Johansson, B., Halldner, L., Dunwiddie, T.V., Masino, S.A., Poelchen, W., Giménez-Llort, L., Fredholm, B.B., 2001. Hyperalgesia, anxiety, and decreased hypoxic neuroprotection in mice lacking the adenosine A_1 receptor. Proc. Natl. Acad. Sci. U. S. A. 98 (16), 9407–9412. https://doi.org/10.1073/pnas.161292398.

John, J., Kodama, T., Siegel, J.M., 2014. Caffeine promotes glutamate and histamine release in the posterior hypothalamus. Am. J. Physiol. Regul. Integr. Comp. Physiol. 307 (6), R704–R710. https://doi.org/10.1152/ajpregu.00114.2014.

Kolahdouzan, M., Hamadeh, M.J., 2017. The neuroprotective effects of caffeine in neurodegenerative diseases. CNS Neurosci. Ther. 23 (4), 272–290. https://doi.org/10.1111/cns.12684.

Lakin, H., Sheehan, P., Soti, V., 2023. Maternal caffeine consumption and its impact on the fetus: a review. Cureus. https://doi.org/10.7759/cureus.48266.

Lazarus, M., Shen, H.-Y., Cherasse, Y., Qu, W.-M., Huang, Z.-L., Bass, C.E., Chen, J.-F., 2011. Arousal effect of caffeine depends on adenosine A2A receptors in the shell of the nucleus accumbens. J. Neurosci. 31 (27), 10067–10075. https://doi.org/10.1523/jneurosci.6730-10.2011.

Lazarus, M., Oishi, Y., Bjorness, T.E., Greene, R.W., 2019. Gating and the need for sleep: dissociable effects of adenosine A1 and A2A receptors. Front. Neurosci. 13. https://doi.org/10.3389/fnins.2019.00740.

Li, X., Conklin, D., Pan, H.-L., Eisenach, J.C., 2003. Allosteric adenosine receptor modulation reduces hypersensitivity following peripheral inflammation by a central

mechanism. J. Pharmacol. Exp. Ther. 305 (3), 950–955. https://doi.org/10.1124/jpet.102.047951.

Lopez, F., Miller, L.G., Greenblatt, D.J., Kaplan, G.B., Shader, R.I., 1989. Interaction of caffeine with the GABAA receptor complex: alterations in receptor function but not ligand binding. Eur. J. Pharmacol. 172 (6), 453–459. https://doi.org/10.1016/0922-4106(89)90028-x.

López-Cruz, L., Salamone, J.D., Correa, M., 2018. Caffeine and selective adenosine receptor antagonists as new therapeutic tools for the motivational symptoms of depression. Front. Pharmacol. 9. https://doi.org/10.3389/fphar.2018.00526.

Manalo, R.V.M., Medina, P.M.B., 2018. Caffeine protects dopaminergic neurons from dopamine-induced neurodegeneration via synergistic adenosine-dopamine D2-like receptor interactions in transgenic *Caenorhabditis elegans*. Front. Neurosci. 12. https://doi.org/10.3389/fnins.2018.00137.

Marchi, M., Raiteri, L., Risso, F., Vallarino, A., Bonfanti, A., Monopoli, A., Raiteri, M., 2002. Effects of adenosine A_1 and A_{2A} receptor activation on the evoked release of glutamate from rat cerebrocortical synaptosomes. Br. J. Pharmacol. 136 (3), 434–440. https://doi.org/10.1038/sj.bjp.0704712.

McCusker, R.R., Goldberger, B.A., Cone, E.J., 2003. Caffeine content of specialty coffees. J. Anal. Toxicol. 27 (7), 520–522. https://doi.org/10.1093/jat/27.7.520.

Mulder, E.J.H., Tegaldo, L., Bruschettini, P., Visser, G.H.A., 2010. Foetal response to maternal coffee intake: role of habitual versus non-habitual caffeine consumption. J. Psychopharmacol. 24 (11), 1641–1648. https://doi.org/10.1177/0269881109106310.

Nawrot, P., Jordan, S., Eastwood, J., Rotstein, J., Hugenholtz, A., Feeley, M., 2003. Effects of caffeine on human health. Food Addit. Contam. 20 (1), 1–30. https://doi.org/10.1080/0265203021000007840.

Owolabi, J.O., Olatunji, S.Y., Olanrewaju, A.J., 2017. Caffeine and cannabis effects on vital neurotransmitters and enzymes in the brain tissue of juvenile experimental rats. Ann. Neurosci. 24 (2), 65–73. https://doi.org/10.1159/000475895.

Pandolfo, P., Machado, N.J., Köfalvi, A., Takahashi, R.N., Cunha, R.A., 2013. Caffeine regulates frontocorticostriatal dopamine transporter density and improves attention and cognitive deficits in an animal model of attention deficit hyperactivity disorder. Eur. Neuropsychopharmacol. 23 (4), 317–328. https://doi.org/10.1016/j.euroneuro.2012.04.011.

Porkka-Heiskanen, T., Kalinchuk, A.V., 2011. Adenosine, energy metabolism and sleep homeostasis. Sleep Med. Rev. 15 (2), 123–135. https://doi.org/10.1016/j.smrv.2010.06.005.

Roca, D.J., Schiller, G.D., Farb, D.H., 1988. Chronic caffeine or theophylline exposure reduces gamma-aminobutyric acid/benzodiazepine receptor site interactions. Mol. Pharmacol. 33 (5), 481–485. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/2835648.

Salvador, H.S., Koos, B.J., 1989. Effects of regular and decaffeinated coffee on fetal breathing and heart rate. Am. J. Obstet. Gynecol. 160 (5), 1043–1047. https://doi.org/10.1016/0002-9378(89)90157-9.

Sato, A., Terata, K., Miura, H., Toyama, K., Loberiza Jr., F.R., Hatoum, O.A., Gutterman, D.D., 2005. Mechanism of vasodilation to adenosine in coronary arterioles from patients with heart disease. Am. J. Physiol. Heart Circ. Physiol. 288 (4), H1633–H1640. https://doi.org/10.1152/ajpheart.00575.2004.

Saud, S., Salamatullah, A.M., 2021. Relationship between the chemical composition and the biological functions of coffee. Molecules 26 (24), 7634. https://doi.org/10.3390/molecules26247634.

Sawynok, J., 1998. Adenosine receptor activation and nociception. Eur. J. Pharmacol. 347 (1), 1–11. https://doi.org/10.1016/s0014-2999(97)01605-1.

Sawynok, J., 2011. Caffeine and pain. Pain 152 (4), 726–729. https://doi.org/10.1016/j.pain.2010.10.011.

Scammell, T.E., Gerashchenko, D.Y., Mochizuki, T., McCarthy, M.T., Estabrooke, I.V., Sears, C.A., Hayaishi, O., 2001. An adenosine A2a agonist increases sleep and induces Fos in ventrolateral preoptic neurons. Neuroscience 107 (4), 653–663. https://doi.org/10.1016/s0306-4522(01)00383-9.

Sherin, J.E., Shiromani, P.J., McCarley, R.W., Saper, C.B., 1996. Activation of ventrolateral preoptic neurons during sleep. *Science* (New York, N.Y.) 271 (5246), 216–219. https://doi.org/10.1126/science.271.5246.216.

Smith, A., 2002. Effects of caffeine on human behavior. Food Chem. Toxicol. 40 (9), 1243–1255. https://doi.org/10.1016/s0278-6915(02)00096-0.

Socała, K., Szopa, A., Serefko, A., Poleszak, E., Wlaź, P., 2020. Neuroprotective effects of coffee bioactive compounds: a review. Int. J. Mol. Sci. 22 (1), 107. https://doi.org/10.3390/ijms22010107.

Solinas, M., Ferré, S., You, Z.-B., Karcz-Kubicha, M., Popoli, P., Goldberg, S.R., 2002. Caffeine induces dopamine and glutamate release in the shell of the nucleus accumbens. J. Neurosci. 22 (15), 6321–6324. https://doi.org/10.1523/jneurosci.22-15-06321.2002.

Urry, E., Landolt, H.-P., 2014. Adenosine, caffeine, and performance: from cognitive neuroscience of sleep to sleep pharmacogenetics. In: *Current Topics in Behavioral Neurosciences. Sleep, Neuronal Plasticity and Brain Function*, pp. 331–366, https://doi.org/10.1007/7854_2014_274.

Verheul, R., van den Brink, W., Geerlings, P., 1999. A three-pathway psychobiological model of craving for alcohol. Alcohol Alcohol. 34 (2), 197–222. https://doi.org/10.1093/alcalc/34.2.197.

Vidyasagar, R., Greyling, A., Draijer, R., Corfield, D.R., Parkes, L.M., 2013. The effect of black tea and caffeine on regional cerebral blood flow measured with arterial spin labeling. J. Cereb. Blood Flow Metab. 33 (6), 963–968. https://doi.org/10.1038/jcbfm.2013.40.

Volkow, N.D., Wang, G.-J., Logan, J., Alexoff, D., Fowler, J.S., Thanos, P.K., Tomasi, D., 2015. Caffeine increases striatal dopamine D2/D3 receptor availability in the human brain. Transl. Psychiatry 5 (4), e549. https://doi.org/10.1038/tp.2015.46.

Vyleta, N.P., Smith, S.M., 2008. Fast inhibition of glutamate-activated currents by caffeine. PLoS One 3 (9), e3155. https://doi.org/10.1371/journal.pone.0003155.

Wesensten, N.J., 2014. Legitimacy of concerns about caffeine and energy drink consumption. Nutr. Rev. 72, 78–86. https://doi.org/10.1111/nure.12146.

Xue, Y., Huang, F., Tang, R., Fan, Q., Zhang, B., Xu, Z., Ruan, Z., 2019. Chlorogenic acid attenuates cadmium-induced intestinal injury in Sprague–Dawley rats. Food Chem. Toxicol. 133 (110751), 110751. https://doi.org/10.1016/j.fct.2019.110751.

Yadav, S., Gupta, S.P., Srivastava, G., Srivastava, P.K., Singh, M.P., 2012. Role of secondary mediators in caffeine-mediated neuroprotection in maneb- and paraquat-induced Parkinson's disease phenotype in the mouse. Neurochem. Res. 37 (4), 875–884. https://doi.org/10.1007/s11064-011-0682-0.

Further reading

Bjorness, T.E., Kelly, C.L., Gao, T.S., Poffenberger, V., Greene, R.W., 2009. Control and function of the homeostatic sleep response by adenosine A(1) receptors. J. Neurosci. 29 (5), 1267–1276.

Fredholm, B.B., Chen, J.-F., Cunha, R.A., Svenningsson, P., Vaugeois, J.-M., 2005. Adenosine and brain function. Int. Rev. Neurobiol. 63, 191–270. https://doi.org/10.1016/S0074-7742(05)63007-3.

Scher, A.I., Stewart, W.F., Lipton, R.B., 2004. Caffeine as a risk factor for chronic daily headache. Neurology 63 (11), 2022–2027. https://doi.org/10.1212/01.wnl.0000145760.37852.ed.

van Gelder, B.M., Buijsse, B., Tijhuis, M., Kalmijn, S., Giampaoli, S., Nissinen, A., Kromhout, D., 2007. Coffee consumption is inversely associated with cognitive decline in elderly European men: the FINE study. Eur. J. Clin. Nutr. 61 (2), 226–232. https://doi.org/10.1038/sj.ejcn.1602495.