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Review

Neurobiology of chronic caffeine use and withdrawal: Mechanisms, effects and implications

Yu Zhao Lee [a], Ker Ni Chua [b], Fui-Ling Voon [c], Chau Ling Tham [d,e], Yu-Cheng Ho [f,*], Ming Tatt Lee [g,h,**]

[a] Faculty of Medicine and Health Sciences, UCSI University, Kuala Lumpur, 56000, Malaysia
[b] Faculty of Pharmaceutical Sciences, UCSI University, Kuala Lumpur, 56000, Malaysia
[c] Faculty of Resource Science and Technology, Universiti Malaysia Sarawak, Kota Samarahan, 94300, Malaysia
[d] Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, 43400, Selangor, Malaysia
[e] Future Foods, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, 43400, Selangor, Malaysia
[f] School of Medicine, College of Medicine, I-Shou University, Kaohsiung City, 82445, Taiwan
[g] Office of Postgraduate Studies, UCSI University, Kuala Lumpur, 56000, Malaysia
[h] College of Health Sciences, Chang-Jung Christian University, Tainan, 711301, Taiwan

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ABSTRACT

Caffeine is the most widely consumed psychoactive substance worldwide and is increasingly being explored for its potential pharmacological applications, including in neurodegenerative diseases, cognitive enhancement, and pain modulation. However, chronic caffeine use leads to neuroadaptive changes that underlie dependence and a well-characterized withdrawal syndrome, which includes symptoms such as headache, fatigue, cognitive impairment, and mood disturbances. This review critically examines the neurobiology of chronic caffeine exposure and withdrawal, focusing on its interaction with adenosine receptor systems, neural plasticity, and the role of genetic and time-course variability in modulating individual responses. Evidence from human and animal studies is discussed to highlight mechanisms driving tolerance, sensitisation, and withdrawal symptoms. We further discuss the broader implications for public health and society, particularly in relation to substance use patterns, cessation strategies, and the safe integration of caffeine into therapeutic applications. As caffeine continues to be investigated as a therapeutic agent, understanding its dependence potential and withdrawal effects is essential to ensure safe and effective clinical applications. This paper underscores the importance of integrating neurobiological, behavioural, and genetic insights to fully evaluate the implications of long-term caffeine consumption.

1. Introduction

Caffeine is a plant alkaloid classified as a methylxanthines. It is also known as 1,3,7-trimethylxanthine and, when pure, appears as a bitter white powder (Institute of Medicine (US) Committee on Military Nutrition Research, 2001). It is a well-known and most consumed psychoactive stimulant across the globe (Reddy et al., 2024). It performs biological activities by stimulating the central nervous system (CNS). Its consumption may increase arousal and alertness, altering mood and catecholamine release (Unsal and Sanlier, 2025a). Caffeine can be naturally extracted from some 63 plant species, including coffee beans, cocoa beans, and tea leaves (Siow et al., 2022). Coffee, tea, caffeinated soft drinks, and energy beverages are the predominant sources of caffeine for the general populace (Song et al., 2023). Study indicated that some 69 % of US population ingest caffeine daily (Mitchell et al., 2025). The study also revealed that the mean daily caffeine intake is 210 mg.

The recreational use of caffeine typically involves deliberate intake to improve alertness, cognitive function, or mood, frequently within social or professional settings (Moreira-Silva et al., 2025). However, the distinction between use and misuse or dependency can become ambiguous, particularly if individuals acquire tolerance, encounter withdrawal, or increase consumption to mitigate fatigue and cognitive deterioration. The risk for caffeine misuse is frequently undervalued

* Corresponding author. School of Medicine, College of Medicine, I-Shou University, No.8, Yida Rd., Yanchao District, Kaohsiung City, 82445, Taiwan.
** Corresponding author. Office of Postgraduate Studies, UCSI University, No 1, Jalan Menara Gading, Cheras, Kuala Lumpur, 56000, Malaysia.
E-mail addresses: r96443003@ntu.edu.tw (Y.-C. Ho), mingtatt7286@outlook.com, leemt@ucsiuniversity.edu.my (M.T. Lee).

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owing to its legal status, extensive accessibility, and assumed safety profile (Cappelletti et al., 2018). Excessive use, especially in amounts beyond 400 mg/day for adults or 2.5 mg/kg/day for adolescents, has been linked to negative effects such as anxiety, sleeplessness, tachycardia, gastrointestinal issues, and, in rare instances, toxicity necessitating medical treatment (Wikoff et al., 2017). The unregulated consumption of high-caffeine supplements and pre-workout products, which may include caffeine alongside other stimulants, presents an increasing concern, especially among young adults and sports (Harty et al., 2018). Instances of caffeine intoxication and unintentional overdose, albeit being rare, highlight the dangers associated with high-dose use, particularly when ingested rapidly or in powdered form (Cappelletti et al., 2018).

The bulk of large cohort studies have not found significant health risks associated with coffee or tea intake because of the general public's modest exposure levels (Fredholm et al., 2017). Nonetheless, approximately 17 % of caffeine users are dependent on the drug, indicating that it should be taken responsibly even though it is less addictive than alcohol, nicotine, and other drugs of abuse (Griffiths and Mumford, 1996; Reich et al., 2024). Additionally, at least 85 commercially available medications have been shown to interact with caffeine (Reich et al., 2024). These interactions may alter the metabolism of caffeine and result in potentially fatal side effects like seizures and cardiac arrhythmias (Carrillo and Benitez, 2000; Temple et al., 2017). Prolonged caffeine consumption is linked to the onset of dependence and a clearly defined withdrawal syndrome (Booth et al., 2020). Despite its prevalent use, the enduring neurobiological effects of caffeine use and withdrawal are not well elucidated, particularly concerning mood regulation, cognitive resilience, and individual heterogeneity influenced by genetic and metabolic factors (Rikitake et al., 2022). The processes driving these alterations have increasingly been the focus of neurological and genetic research. Symptoms include headache, weariness, diminished alertness, drowsiness, and impaired cognitive ability frequently emerge after quitting caffeine, indicating the neuroadaptive alterations in the CNS due to regular caffeine consumption (Davoudi et al., 2025).

The normalisation of everyday caffeine dependence in many societies masks the potential burden of withdrawal symptoms and the cyclical pattern of consumption, resulting in under-recognition in therapeutic contexts. Despite caffeine's inclusion in The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as a substance that can cause withdrawal, healthcare providers seldom test for or address caffeine-related issues unless significant symptoms manifest (Harstad et al., 2016). Epidemiological studies indicated that up to 30 % of habitual caffeine users fulfil the criteria for caffeine use disorder according to proposed DSM definitions, which encompass persistent cravings or unsuccessful attempts to reduce intake, continued consumption despite adverse effects, and clinically significant withdrawal symptoms upon cessation (Booth et al., 2020). This gap highlights the need for greater clinical awareness, standardized intake assessments, and public education regarding safe consumption thresholds.

This review aims to summarise current evidence on the neurobiology of chronic caffeine use and withdrawal, focusing on the molecular and neural mechanisms, behavioural and cognitive consequences, individual genetic variability, and clinical and public health implications. In doing so, it seeks to provide a comprehensive framework for understanding the complex interplay between chronic caffeine exposure, neuroadaptation, and withdrawal in humans. The review emphasises the necessity of comprehending the long-term brain adaptations and withdrawal effects of caffeine, as it is increasingly examined for pharmacological uses, which is crucial for its safe and successful therapeutic use (Janakiraman et al., 2024; Reddy et al., 2024).

2. Caffeine's mechanism of action

2.1. Antagonism of adenosine receptors

The late 1970s saw the development of the theory that methylxanthines, like theophylline and caffeine, work by blocking adenosine's activities (Smellie et al., 1979). Adenosine and caffeine share structural similarities (Song et al., 2023). This resemblance allows caffeine and its metabolite act as competitive antagonists of adenosine receptors, demonstrating CNS effects and facilitating the neuromodulation of adenosine (Lopes et al., 2019). Adenosine is an inhibitory neuromodulator that accumulates during awake and facilitates sleep by interacting with adenosine receptors in several brain areas (Huang et al., 2024). Caffeine indiscriminately bind to and inhibit G-protein coupled adenosine receptors, promoting arousal, alertness, and cognitive ability by inhibiting the action of adenosine (Solinas et al., 2005; Xu et al., 2022). It has been estimated that up to 50 % of the brain's adenosine receptors can be occupied by regular doses of caffeine consumption (Elmenhorst et al., 2012).

G-protein coupled adenosine receptors are classified into four subtypes: A_1, A_{2A}, A_{2B}, and A_3 receptors. Among the subtypes, the brain predominantly express A_1 and A_{2A} receptors. A_1 subtypes are ubiquitous throughout the CNS with the hippocampus, cerebellum, and cortex showing the highest expression (Sheth et al., 2014). They regulate excitatory transmission at both pre- and postsynaptic sites (Fritz et al., 2021). A_{2A} subtypes are predominantly expressed in the striatum and function on striato-pallidal medium spiny neurones. They are crucial in presynaptically releasing glutamate by modulating synaptic plasticity (Ferreira et al., 2025). Caffeine can antagonise all types of adenosine receptors (ARs), including A_1 and A_{2A} receptors with highest affinity for adenosine, the high-affinity A_3 receptor, and the lower-affinity A_{2B} receptor (Daly et al., 1983). It eliminates adenosinergic tone and demonstrates antagonistic effects against adenosine binding to these receptors (Do et al., 2021). Adenosine modulates various physiological activities via G protein-coupled receptors by modifying cellular levels of cyclic adenosine monophosphate (cAMP). Adenosine binding to the A_1 receptor inhibits adenylyl cyclase through a guanyl nucleoside binding protein (Gi), resulting in a reduced quantity of intracellular cAMP (Dunwiddie and Fredholm, 1989; Ramkumar et al., 1988). Upon adenosine's binding to the A_{2A} receptor, adenylyl cyclase is activated by a distinct guanyl nucleoside binding protein (Gs), resulting in an elevated intracellular concentration of cAMP (Pleli et al., 2018). The modulation of cAMP levels can initiate various metabolic, cardiovascular, and neurological responses (Shi et al., 2025; Theparambil et al., 2024). Caffeine's antagonistic action obstructs the binding of adenosine to its receptors, hence inhibiting receptor activation (Lopes et al., 2019).

Caffeine's adenosine receptor antagonistic effect indirectly leads to the release of neurotransmitters such as acetylcholine, noradrenaline, dopamine, serotonin, glutamate, and gamma-aminobutyric acid (GABA), which are essential for cognition, alertness, memory, and mood regulation (Alasmari, 2020). The blockade of A_1 receptors by caffeine enhances excitatory neurotransmission, particularly affecting glutamate release (John et al., 2014). The caffeine-induced inhibition of adenosine A_1 receptors eliminates the receptors' persistent inhibitory effects on presynaptic glutamate release, resulting in heightened excitatory neurotransmission (Quarta et al., 2004a). Glutamate serves as the principal excitatory neurotransmitter in the brain and is crucial for synaptic plasticity, learning, and memory formation (Tan et al., 2020). Caffeine affects Ca^{2+} homeostasis at the post-synaptic level by increasing Ca^{2+} entry through N-methyl-D-aspartate receptor (NMDAR) via A_1 receptors inhibition. The release of glutamate was promoted by the Ca^{2+} signalling. On the other hand, caffeine inhibits glutamate release at the pre-synaptic level by blocking A_{2A} receptor, which may offset the excitatory activity and help preserve synaptic transmission balance (Martins et al., 2020). Different overall impacts of caffeine on NMDAR-mediated responses may result from variations in the relative