Saudi Pharmaceutical Journal 28 (2020) 445–451

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Review

Caffeine induces neurobehavioral effects through modulating neurotransmitters

Fawaz Alasmari

Department of Pharmacology and Toxicology, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia

ARTICLE INFO

Article history:
Received 19 November 2019
Accepted 12 February 2020
Available online 17 February 2020

Keywords:
Caffeine
Neurobehavioral effects
Neurotransmitters
Dopamine
Glutamate
GABA

ABSTRACT

Evidence demonstrates that chronic caffeine exposure, primarily through consumption of coffee or tea, leads to increased alertness and anxiety. Preclinical and clinical studies showed that caffeine induced beneficial effects on mood and cognition. Other studies using molecular techniques have reported that caffeine exhibited neuroprotective effects in animal models by protecting dopaminergic neurons. Moreover, caffeine interacts with dopaminergic system, which leads to improvements in neurobehavioral measures in animal models of depression or attention deficit hyperactivity disorder (ADHD). Glutamatergic receptors have been found to be involved on the neurobiological effects of caffeine. Additionally, caffeine has been found to suppress the inhibitory (GABAergic) activity and modulate GABA receptors. Studies have also found that modulating these neurotransmitters leads to neurobehavioral effects. The linkage between the modulatory role of caffeine on neurotransmitters and neurobehavioral effects has not been fully discussed. The purpose of this review is to discuss in detail the role of neurotransmitters in the effects of caffeine on neurobehavioral disorders.

Contents

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

E-mail address: ffalasmari@ksu.edu.sa

https://doi.org/10.1016/j.jsps.2020.02.005
1319-0164/

1. Introduction

Studies have found that consumption of products-containing caffeine such as coffee is widespread in United States and varies according to multiple factors (Loftfield et al., 2016). There has been a huge increase in the manufacturing of these products. Caffeine is the major active ingredient in coffee, tea, hot chocolate, and other beverages. Recent evidence demonstrates that caffeine addiction is becoming popular worldwide [For review see (Meredith et al., 2013). It is known that both chronic and acute exposure to caffeine impairs the central nervous system (CNS), at least in part, by modulating neuronal pathways (Nancy et al., 2017; Blaise et al., 2018). Caffeine, at non-toxic doses, exerts neuropharmmacological actions through blocking adenosine A receptors in the brain. This effect led to blockade of adenosine kinase decreasing the release of adenosine (Fredholm et al., 1999). More importantly, adenosine A2 receptor is linked to dopaminergic transmission and receptors, which indicate that caffeine can affect the symptoms of neurological disorders caused by dysregulated dopaminergic system. Recent studies have focused on the effects of chronic caffeine exposure and have indicated that chronic caffeine exposure affects the CNS and its molecular pathways, including neurotransmitters systems (López-Cruz et al., 2018; Manalo and Medina, 2018; John et al., 2014; Owolabi et al., 2017; Hahn et al., 2017; Isokawa, 2016). In this article, we review the effects of caffeine on the dopaminergic, glutamatergic, and GABAergic systems. We discuss whether there is a link between modulating these neurotransmitters and the development/attenuation of neuropsychiatric and neurological disorders in animal models exposed to caffeine. A review discussed the beneficial effects of caffeine on symptoms of Alzheimer's disease and attention deficit hyperactivity disorder (ADHD) and these effects might be mediated by blocking adenosine A2 receptor, localized in synaptic neurons (Cunha and Agostinho, 2010). The review also discussed that the caffeine-blocked adenosine A2 receptor could affect glutamatergic transmission and receptors plasticity.

1.1. Caffeine and neurotransmitters

Caffeine exposure has been reported to induce changes in dopaminergic systems in humans and animals (Volkow et al., 2015; Solinas et al., 2002; Manalo and Medina, 2018; López-Cruz et al., 2018; Pandolfo et al., 2013; El Yacoubi et al., 2001; Garrett and Griffiths, 1997). These effects may be mediated by modulation of adenosine A receptors (Manalo and Medina, 2018). It has been reported that caffeine attenuated certain neurological diseases through modulating dopaminergic pathways (El Yacoubi et al., 2001; Pandolfo et al., 2013). In addition, caffeine induces protection effects against dopaminergic neuronal loss (Manalo and Medina, 2018), suggesting that caffeine may have therapeutic activity against neurodegenerative diseases, including Parkinson's disease. Moreover, caffeine has also shown the ability to modulate the glutamatergic system in different brain regions (Solinas et al., 2002; John et al., 2014; Owolabi et al., 2017; Vyleta and Smith, 2008). Prior reports have found that caffeine exposure increases glutamate concentrations (John et al., 2014; Solinas et al., 2002) and modulates glutamatergic receptors and transporters (De Freitas et al., 2016; Vyleta and Smith, 2008). These effects of caffeine exposure on glutamatergic systems may explain the development of neurological diseases that involve dysregulated glutamatergic signaling. Caffeine has also been found to induce various effects on GABAergic systems, including GABAergic receptors (Ferreira et al., 2014; Hahn et al., 2017; Isokawa, 2016; Lopez et al., 1989; Roca et al., 1988).

1.2. Caffeine and neurobehavioral effects

Caffeine induces neuroprotective effects through attenuating dopaminergic neuronal loss (Manalo and Medina, 2018). This effect may result in positive responses against neurodegenerative diseases such as Parkinson's disease. It is important to note that the disruption of blood brain barrier integrity was inhibited by caffeine treatments in animal models of Parkinson's and Alzheimer's diseases (Chen et al., 2010). Importantly, a study reported dysfunction in memory and mood as well as alterations in synaptic plasticity in mice exposed to chronic (3 weeks) unpredictable stress (CUS) and that caffeine drinking (1 g/L), starting 3 weeks before and during CUS could inhibit these alterations (Kaster et al., 2015). In addition, ADHD or depressive-like behaviors were improved following treatments with caffeine (Pandolfo et al., 2013; López-Cruz et al., 2018; El Yacoubi et al., 2001). Improvements in these neurobehavioral disorders could be attributed to the modulatory effects of caffeine on dopaminergic system. Caffeine can also modulate the GABAergic activity (Isokawa, 2016; Yang et al., 2015). Since GABAergic system is dysregulated in animals with epilepsy, caffeine can be involved in other neurological diseases such as epileptic disorders.

Less is known about the relationship between neurotransmitters and neurobehavioral effects after exposure to caffeine. The neurological mechanisms, focusing on neurotransmitters, underlying the beneficial effects of caffeine on memory, mood and cognition could provide pharmacological therapies against certain neurological diseases. In this review article, we discuss associations between the modulatory effects of caffeine on neurotransmitters and the attenuation/development of neurological diseases in clinical and preclinical studies.

2. Effects of caffeine on dopaminergic systems

2.1. Effects of caffeine on dopaminergic neurons and dopamine concentrations as well as dopamine receptors and transporters

Several studies have found that exposure to caffeine modulates dopaminergic systems (Volkow et al., 2015; Solinas et al., 2002; Manalo and Medina, 2018; López-Cruz et al., 2018; Pandolfo et al., 2013; El Yacoubi et al., 2001). A previous study reported that caffeine can induce marked changes in certain behaviors, including high level of alertness and poor sleep, in humans (Volkow et al., 2015). This effect was associated with an increase in the availability of dopamine receptors 2/3 in the left and right striatum (Volkow et al., 2015). This finding indicates that dopaminergic receptor activity is highly sensitive to caffeine. However, another study found that there were no significant changes in the levels of dopamine receptor 1 or 2 in the striatum of male Swiss strain mice after chronic exposure to caffeine (Shi et al., 1994). Caffeine has also been shown to affect dopamine metabolism in some brain regions but did not induce stimulatory effects on dopaminergic receptors in rats (Watanabe and Uramoto, 1986).

With regard to dopaminergic neurons and dopamine concentrations, it has been shown, using a microdialysis technique, that caffeine exposure elevates extracellular concentrations of dopamine and glutamate in the nucleus accumbens shell in male Sprague Dawley rats (Solinas et al., 2002). This study showed that these alterations in glutamate and dopamine concentrations were inhibited following administration of an adenosine A1 receptor antagonist. These findings indicate that caffeine may modulate dopamine and glutamate release through blocking adenosine A1 receptors. Caffeine has also been found to exhibit protective effects in dopaminergic neurons in *Caenorhabditis elegans* (Manalo and Medina, 2018). This study discussed that this protection may be

occurring due to the modulatory effects of caffeine on the interaction between adenosine and dopamine-2 receptors. These findings suggest that caffeine may attenuate the loss of dopaminergic neurons in neurodegenerative diseases such as Parkinson disease.

2.2. Caffeine modulates neurobehavioral effects through acting on dopaminergic system

Chronic caffeine treatments has been reported to modulate dopaminergic transporters in animal models (Pandolfo et al., 2013). For instance, caffeine administration (2 mg/kg twice a day for 21 days) normalizes the function of dopaminergic transporters in frontocortical areas in animal models of ADHD (Pandolfo et al., 2013). This study reported that there are improvements in neurobehaviors such as cognitive dysfunction and attention in Wistar Kyoto rats. This indicates that caffeine may attenuate the symptoms of neurodevelopmental disorders such as ADHD through modulating dopaminergic transporters. In parallel to this, a recent review discussed the potential therapeutic effects of caffeine in attenuating major depressive disorder through reversing anergia induced by dopaminergic depletion or antagonism [For review see (López-Cruz et al., 2018)]. It is important to note that an adenosine A2 antagonist showed ability to attenuate depression-like behaviors in an outbred CD1 mouse model (El Yacoubi et al., 2001). This study reported that these effects were abolished following treatments with haloperidol, a dopamine-2 receptor antagonist. These findings highlight the importance of modulating dopaminergic signaling in attenuating neurological diseases in animals exposed to caffeine. In humans and animals, dopamine plays a critical role in behavioral effects of caffeine [for review see (Garrett and Griffiths, 1997)].

Taken together, it appears that caffeine induces neuroprotection and attenuates neurological diseases in animal models. These positive effects might be due to the ability of caffeine to combat the loss of dopaminergic neurons. However, less is known about the effects of caffeine on extracellular dopamine concentrations as well as the expression of dopaminergic receptors and transporters in animal models of neurodevelopmental disorders. Accordingly, targeting dopaminergic pathways using caffeine may elicit positive effects, and will further improve neuropharmacological research.

3. Effects of caffeine on glutamatergic systems

3.1. Effects of caffeine on glutamatergic neurons and glutamate concentrations as well as glutamate receptors and transporters

Caffeine increases extracellular glutamate concentrations in the nucleus accumbens shell of male Sprague Dawley rats in part by blocking adenosine A1 receptor (Solinas et al., 2002). Moreover, caffeine has been shown to increase the concentration of glutamate in the posterior hypothalamus of adult male Sprague-Dawley rats (John et al., 2014). These effects were confirmed by a separate study that found that caffeine at both low and high doses increased the concentration of glutamate in the brain of Wistar rats (Owolabi et al., 2017). These observations indicate that caffeine induces glutamate excitotoxicity in the brain. Future studies should explore mechanisms by which caffeine exposure causes an elevation in extracellular glutamate concentrations.

These findings have raised questions about the effects of caffeine on glutamate release and/or uptake. It is noteworthy to mention that chronic exposure to alcohol, nicotine, and cocaine decreases the expression of proteins, such as glutamate transporter 1, that uptake the majority of glutamate from synapses into astrocytes (Goodwani et al., 2015; Hammad et al., 2017; Alasmari et al., 2017; Das et al., 2015; Alasmari et al., 2018; Hammad et al., 2017; Hakami et al., 2016, 2017; Alhaddad et al., 2014). For example, chronic exposure to alcohol reduced the expression of glutamate transporter 1 in the nucleus accumbens, an effect associated with a marked increase in the extracellular glutamate concentration (Das et al., 2015). This increase in the extracellular glutamate concentrations might be involved in the development of alcohol addiction. It is important to note that a single dose of caffeine (200 or 500 μM) can modulate the uptake of glutamate/aspartate transporters in rat retina, which is mediated by blocking adenosine A2 receptor (De Freitas et al., 2016). Little is known about the effects of chronic exposure to caffeine on protein and gene expression of glutamate transporter 1 in the central reward brain regions involved in the development of drug addiction. Investigating the effects of chronic caffeine exposure will provide important information on whether astroglial glutamate transporters might be involved in the development of caffeine addiction. Studies have shown that upregulation of astroglial glutamate transporters in the mesocorticolimbic system can decrease alcohol and nicotine seeking behaviors (Sari et al., 2016; Rao and Sari, 2014; Sari et al., 2013a; Rao et al., 2015; Sari et al., 2013b; Abulseoud et al., 2014).

Additionally, caffeine has been found to reverse the reduction of postsynaptic current amplitude in neocortical neurons using whole-cell patch-clamp techniques (Vyleta and Smith, 2008). This study also found that caffeine reversed the increase of excitatory postsynaptic current frequency. It has been highlighted that these effects were occurred due to the ability of caffeine to block non-N-Methyl-D-aspartic acid receptor (NMDAR) (Vyleta and Smith, 2008). However, low dose caffeine treatment inhibited amnesia and memory dysfunction induced by treatment with MK-801, a NMDAR antagonist, in male Wistar rats (Diler et al., 2013). By contrast, a clinical study did not suggest an interaction between caffeine intake and a polymorphism of a NMDAR subunit, GRIN2A, in the risk of Parkinson's disease (Kim et al., 2018). Interestingly, chronic caffeine consumption during the gestational period reduced the expression of metabotropic glutamate receptors (mGluRs) in the hearts of both fetal and maternal rats (Iglesias et al., 2006). More research is necessary to study whether the downregulatory effects of chronic exposure to caffeine on mGluRs in hearts can be generalized into the brain.

A previous study found that chronic caffeine consumption could attenuate blast-induced memory deficit in part by reducing neuroinflammation and glutamate excitotoxicity (Ning et al., 2015). Moreover, caffeine consumption was found to restore diabetes-induced memory dysfunction (Duarte et al., 2012). This study found that caffeine could also restore the loss of glutamatergic nerve terminals (vesicular glutamate transporters) in the hippocampus. The increase of hippocampal adenosine A2 receptor expression caused memory deficit in depression-prone mice, an effect associated with marked decrease in synaptic glutamatergic and GABAergic markers (Machado et al., 2017). Accordingly, chronic caffeine intake reversed these effects possibly by blocking adenosine A2 receptor. These observations indicate that there is a possible interaction between caffeine and glutamatergic signaling. This interaction might be involved in the attenuation or development of neurobehavioral symptoms. Future work is required to provide more data regarding the effects of caffeine on modulating glutamatergic transporters and receptors in animal models of neurological diseases.

4. Effects of caffeine on GABAergic systems

4.1. Effects of caffeine on GABAergic neurons and dopamine concentrations receptors and transporters

Several studies have found that caffeine interacts with GABAergic systems (Isokawa, 2016; Lopez et al., 1989; Mukhopadhyay and

Poddar, 1998; Yang et al., 2015; Hahn et al., 2017; Roca et al., 1988; Ferreira et al., 2014). For example, it has been found that caffeine induces a transient suppression of inhibitory postsynaptic currents in GABAergic pathways in hippocampal CA1 pyramidal cells (Isokawa, 2016). This effect was associated with metaplasticity, which was mediated through opening multiple channels in the plasma membrane (Isokawa, 2016). These observations were further supported by a previous report that investigated the effects of caffeine on postsynaptic currents of GABAergic pathways in rat primary sensory neurons (Yang et al., 2015). This study demonstrated that pretreatment with caffeine (10 μM) caused suppression of GABA receptor-mediated currents. This effect, caffeine-induced suppression of GABA receptor currents, was mainly mediated through phosphodiesterase pathways (Yang et al., 2015). Suppression of inhibitory GABAergic signaling may lead to an enhancement of dopaminergic system activity. Alternatively, the release of GABA has been found to be potentiated by caffeine treatments (500 μM) in chick retina (Ferreira et al., 2014). This effect was abolished by NNC-711, a GABA transporter 1 blocker and MK-801, an NMDA receptor antagonist (Ferreira et al., 2014). The study suggested that the potentiating effect of caffeine on GABA release is mediated by blocking adenosine A1 receptor.

Regarding the pharmacokinetic properties of caffeine, a prior study found that nontolerant caffeine conditions decreased the activity of GABAergic systems in multiple brain regions, including the hypothalamus, cerebellum, corpus striatum, cerebral cortex, pons, and medulla (Mukhopadhyay and Poddar, 1998). Interestingly, the reduction in GABAergic activity was normalized under conditions of caffeine tolerance, supporting the hypothesis that caffeine doses and duration of treatment play a role in modulating of GABAergic signaling (Mukhopadhyay and Poddar, 1998). Therefore, optimizing the dose and duration of exposure of caffeine has the potential to modulate the activity of the GABAergic system. Additionally, the effect of caffeine consumption on the levels of GABA in three high school adolescents has been investigated in a previous clinical study (Hahn et al., 2017). This clinical study used magnetic resonance spectroscopy techniques and found that the ratio of GABA/creatine was reduced in the anterior cingulate cortex after caffeine consumption (Hahn et al., 2017).

Caffeine can also modulate GABAergic receptors (Lopez et al., 1989; Roca et al., 1988). It has been suggested that chloride transport through $GABA_A$ receptors is altered with exposure to caffeine (Lopez et al., 1989). This effect was associated with increased t-b utylbicyclophosphorothionate sites in unwashed membrane in *ex-vivo* experiments (Lopez et al., 1989). It is important to consider that GABA/benzodiazepine receptor sites have been found to be reduced significantly following chronic exposure to caffeine (Roca et al., 1988). This study concluded that the downregulatory effects of caffeine on GABA receptors is mediated by adenosine receptors. It is important to note that the pathophysiology of certain neurological disorders, such as sleep disorders and epilepsy, involve dysregulated GABAergic signaling indicating that studies are warranted to explore the effects of caffeine on sleep disorders in respect to GABAergic activity.

5. Potential therapeutic effects of caffeine against neurological diseases through modulating neurotransmitter systems

In this section, we review whether the modulatory effects of caffeine on neurotransmitters can attenuate symptoms of some diseases such as depression and ADHD (Pandolfo et al., 2013; Kalda et al., 2006; Chen et al., 2008). For example, it has been found that there are marked improvements in behavioral responses in a rat model of ADHD following exposure to caffeine (Pandolfo et al., 2013). This study found that caffeine modulated dopaminergic transporters in frontocorticostriatal brain regions and improved cognition and attention in spontaneously hypertensive rats (ADHD animal model). A prior study also reported that a chronic treatment with caffeine induced anxiolytic and antidepressant activities assessed by elevated plus maze and forced swim assays in rats (Pechlivanova et al., 2012). These improved behavioral responses were associated with increased dopamine levels in the hippocampus (Pechlivanova et al., 2012). Wakefulness has been found to be enhanced after exposure to caffeine in *Drosophila*, an effect mediated through dopaminergic pathways (Nall et al., 2016). Together, caffeine may have therapeutic efficacy for attenuating the progression of ADHD or depression through acting on dopaminergic pathways.

Moreover, it has been suggested that caffeine treatments protect against MPTP-induced disruption of the blood brain barrier in a Parkinson's disease mouse model (Chen et al., 2008). This study found that caffeine could rescue MPTP-decreased tyrosine hydroxylase numbers in dopaminergic neurons of mice. The protective effect of caffeine against dysfunction of blood brain barrier integrity is in agreement with a another report showing that caffeine exhibited neuroprotective effects against disruption of the blood brain barrier in animal models of Parkinson's and Alzheimer's diseases (Chen et al., 2010). We conclude here that the protective effects of caffeine on dopaminergic neurons is associated with an improvement in blood brain barrier integrity in neurodegenerative models.

Importantly, caffeine and nicotine co-administration could improve impairments in learning and memory in rats models of Alzheimer's disease (Azza et al., 2016). Neurodegeneration was also prevented in the striatum and hippocampus (Azza et al., 2016), suggesting an involvement of dopaminergic neurons on the ability of caffeine to induce neuroprotective effects against neuronal degeneration. Additionally, dopamine neurotoxicity was attenuated by treatments with caffeine in animal models of Parkinson's disease (Kalda et al., 2006). This effect was mediated mainly by the inhibitory effects of caffeine on adenosine A receptors (Kalda et al., 2006). Moreover, a review article has also discussed the promising therapeutic effects of caffeine against Parkinson's disease (Prediger, 2010).

In regard to glutamatergic and GABAergic neurons, pretreatment with caffeine exhibited an ability to improve the motor function in a rats treated with MPTP (Bagga et al., 2016). These improvements in neurobehavioral responses were mediated by caffeine-induced protection effects on GABAergic and glutamatergic neurons (Bagga et al., 2016). Moreover, caffeine treatments have also been reported to induce sleep disturbances, in part by downregulating $GABA_A$ receptors in the mouse hypothalamus (Ko et al., 2018). NMDAR antagonists and glutamate antagonists did not affect the hyperlocomotion activity induced by caffeine, suggesting that caffeine increased locomotion activity through acting on other neurotransmitters systems such as dopaminergic pathways (Pulvirenti et al., 1989, 1991).

6. Potential clinical uses of caffeine

In addition to preclinical studies, clinical findings showed promising effects of caffeine against neurological diseases (Lucas et al., 2011; Kahathuduwa et al., 2019; Haskell et al., 2005; Borota et al., 2014). The risk of depression, for example, was reduced with increasing caffeine consumption in women (Lucas et al., 2011). This study reported lower relative risk of depression in women consume more than 4 cups/day compared to those who consume 2–3 cups/day. Moreover, another study investigated the effects of caffeine on ADHD symptoms, including impulsivity and attention in children (Kahathuduwa et al., 2019). After

consumption of caffeine, continuous performance task and cognition were improved in children with ADHD (Kahathuduwa et al., 2019). Importantly, studies showed that moderate consumption of caffeine (less than 6cups/day) exhibited ability to attenuate cognitive failure, suicide and symptoms of major depressive disorder while high doses of caffeine may lead to psychosis and anxiety (Lara, 2010). Studies also reported that caffeine was able improve the alertness and performance in attention and memory-based tasks (Haskell et al., 2005). Using post-study caffeine administration, memory consolidation has been found to be improved in humans (Borota et al., 2014). These positive effects were observed in habitual caffeine consumers and non-consumers. These findings indicate that there is a possible role of dopaminergic system, since it is involved in these disorders, in attenuating these conditions in caffeine-exposed humans. More pharmacological research should further explore the role of dopaminergic system in caffeine-attenuated ADHD or depression symptoms in humans.

At high doses, caffeine-sensitive individuals develop caffeinism, which is characterized by insomnia agitation, excitement, nervousness and other symptoms (Gilliland and Andress, 1981). Consuming high amount of caffeine resulted in psychosis and psychotic-like symptoms (Hedges et al., 2009; Goiney et al., 2012). Moreover, a case report showed that exposure to a low dose of caffeine was able to exacerbate symptoms of psychosis in a schizophrenic patient (Peng et al., 2014). In addition, it has been concluded that patients with generalized anxiety disorder were sensitive to caffeine (Bruce et al., 1992). Accordingly, it has been suggested that caffeine intake should be monitored carefully in patients with neuropsychiatric disorders (Wang et al., 2015). Taken together, caffeine at low to moderate doses might have pharmacotherapeutic properties against certain neurological diseases such as ADHD and major depressive disorder in human. However, consumption large amount of caffeine may induce psychosis anxiety and other central nervous system side effects. These dose responses of the behavioral effects of caffeine has been discussed in a previous clinical study (Cunha and Agostinho, 2010).

7. Caffeine induces neurotoxicity effects

In addition to the beneficial effects, exposure to high dose of caffeine can lead to neurotoxicity (Gepdiremen et al., 1998; Kang et al., 2002). Neurotoxicity has been observed in cerebellar granular cell isolated from rat pups (Gepdiremen et al., 1998). This study found that this effect was abolished following pre-treatment (45 min prior to caffeine treatment) with nimodipine, a calcium channel blocker. The study concluded that newborn apneas due to neurotoxicity, which is induced by high dose of caffeine, could be prevented by nimodipine (Gepdiremen et al., 1998). Another study found that intraperitoneal administration of caffeine, at dose of 50 mg/kg 3 times daily, induced marked neuronal death in different brain regions in neonatal rats (Kang et al., 2002). This study also investigated the effect of caffeine exposure through *in vitro* assay using in murine cortical cell. *Kang et al.,* study reported significant neurotoxicological effects in murine cortical cell exposed to more than 300 μM of caffeine. The authors reported that these neurotoxicity effects of caffeine using *in vivo* and *in vitro* experiments could be occurred through activation of pro-apoptotic protease caspase-3 pathway (Kang et al., 2002). Together, caffeine at high doses may induce neuronal death through modulating various pathways.

Additionally, acute caffeine exposure has been found to increase the risk of development of seizures or epilepsy due to development of neurotoxicity (Yasuhara and Levy, 1988; Vesoulis et al., 2016). For instance, theophylline at lower doses showed ability to produce seizures following acute caffeine exposure as compared to rats received theophylline alone (Yasuhara and Levy, 1988). It is important to note that a recent systematic review found that caffeine can increase or decrease the susceptibility of seizures depending on several factors, including the dose, duration of treatment (acute or chronic) and the time at which caffeine treatments start (van Koert et al., 2018). For example, long term exposure to a low dose of caffeine was associated with low seizures susceptibility in young and adult pre-clinical models. However, clinical studies showed that preterm infants exhibited high incidence of seizures with high doses of caffeine (Vesoulis et al., 2016). The potency of antiepileptic drugs was reduced in animals exposed to caffeine indicating the potential interaction between caffeine and antiepileptic drugs (van Koert et al., 2018). These findings provide evidence about the ability of caffeine to produce positive and negative effects on the brain based on different factors.

8. Conclusion

Caffeine, which is present in many products, modulates neurotransmitter systems in mesocorticolimbic brain regions. Studies have found that caffeine induces positive effects in animal models of certain neurological diseases, in part by modulating dopaminergic signaling. These results are further supported by previous findings demonstrating that neurobehavioral reactions are improved in animals exposed to caffeine, an improvement mediated by modulation of dopaminergic pathways. Caffeine can also affect the activity of glutamatergic and GABAergic neurons, which may lead to improved neurobehavioral disorders. However, the role of glutamatergic signaling in the development of caffeine dependence needs further investigation. Based on this knowledge, caffeine treatments can be developed and tested for effectiveness against certain neurological and neuropsychiatric diseases. However, these pharmacological studies should consider that exposure to overdose of caffeine may induce neurotoxicity and negative neurobehavioral effects. Moreover, caffeine, at high doses, induces undesirable health responses on other systems, including cardiovascular, skeletal and muscular systems.

Declaration of Completing of Interest

The author declares no conflicts of interest.

Acknowledgments

The author extend his appreciation to the deanship of scientific research and the research center, College of Pharmacy, King Saud University for financial support.

References

Abulseoud, Osama A., Camsari, Ulas M., Ruby, Christina L., Kasasbeh, Aimen, Choi, Sun, Choi, Doo-Sup, 2014. Attenuation of ethanol withdrawal by ceftriaxone-induced upregulation of glutamate transporter EAAT2. Neuropsychopharmacology 39, 1674.

Alasmari, Fawaz, Alexander, Laura E. Crotty, Nelson, Jessica A., Schiefer, Isaac T., Breen, Ellen, Drummond, Christopher A., Sari, Youssef, 2017. Effects of chronic inhalation of electronic cigarettes containing nicotine on glial glutamate transporters and α-7 nicotinic acetylcholine receptor in female CD-1 mice. Prog. Neuro-Psychopharmacol. Biol. Psychiatr. 77, 1–8.

Alasmari, Fawaz, Bell, Richard L., Rao, P.S.S., Hammad, Alaa M., Sari, Youssef, 2018. Peri-adolescent drinking of ethanol and/or nicotine modulates astroglial glutamate transporters and metabotropic glutamate receptor-1 in female alcohol-preferring rats. Pharmacol. Biochem. Behav. 170, 44–55.

Alhaddad, Hasan, Kim, Nathaniel T., Aal-Aaboda, Munaf, Althobaiti, Yusuf S., Leighton, James, Boddu, Sai H.S., Wei, Yangjie, Sari, Youssef, 2014. Effects of MS-153 on chronic ethanol consumption and GLT1 modulation of glutamate levels in male alcohol-preferring rats. Front. Behav. Neurosci. 8, 366.

Azza, A.A., Ahmed, H.I., El-Samea, H.A.A., El-Demerdash, E., 2016. The potential effect of caffeine and nicotine co-administration against aluminum-induced

Alzheimer's disease in Rats. J. Alzheimers Dis Parkinsonism 6 (2161–0460), 100023.
Bagga, Puneet, Chugani, Anup N., Patel, Anant B., 2016. Neuroprotective effects of caffeine in MPTP model of Parkinson's disease: a 13C NMR study. Neurochem. Int. 92, 25–34.
Blaise, J. Harry, Park, Jee E., Bellas, Nicholas J., Gitchell, Thomas M., Phan, Vy, 2018. Caffeine consumption disrupts hippocampal long-term potentiation in freely behaving rats. Physiol. Rep. 6, e13632.
Borota, Daniel, Murray, Elizabeth, Keceli, Gizem, Chang, Allen, Watabe, Joseph M., Ly, Maria, Toscano, John P., Yassa, Michael A., 2014. Post-study caffeine administration enhances memory consolidation in humans. Nat. Neurosci. 17, 201.
Bruce, Malcolm, Scott, Nigel, Shine, Philip, Lader, Malcolm, 1992. Anxiogenic effects of caffeine in patients with anxiety disorders. Arch. Gen. Psychiatry 49, 867–869.
Chen, Xuesong, Ghribi, Othman, Geiger, Jonathan D., 2010. Caffeine protects against disruptions of the blood-brain barrier in animal models of Alzheimer's and Parkinson's diseases. J. Alzheimers Dis. 20, S127–S141.
Chen, Xuesong, Lan, Xun, Roche, Ian, Liu, Rugao, Geiger, Jonathan D., 2008. Caffeine protects against MPTP-induced blood-brain barrier dysfunction in mouse striatum. J. Neurochem. 107, 1147–1157.
Cunha, Rodrigo A., Agostinho, Paula M., 2010. Chronic caffeine consumption prevents memory disturbance in different animal models of memory decline. J. Alzheimers Dis. 20, S95–S116.
Das, Sujan C., Yamamoto, Bryan K., Hristov, Alexandar M., Sari, Youssef, 2015. Ceftriaxone attenuates ethanol drinking and restores extracellular glutamate concentration through normalization of GLT-1 in nucleus accumbens of male alcohol-preferring rats. Neuropharmacology 97, 67–74.
De Freitas, Adriana Pinto, Ferreira, Danielle Dias Pinto, Fernandes, Arlete, Martins, Robertta Silva, Borges-Martins, Vladimir Pedro Peralva, Sathler, Matheus Figueiredo, dos-Santos-Pereira, Maurício, Paes-de-Carvalho, Roberto, Giestal-de-Araujo, Elizabeth, de Melo Reis, Ricardo Augusto, 2016. 'Caffeine alters glutamate–aspartate transporter function and expression in rat retina. Neuroscience 337, 285–294.
Diler, A. Sarper, Ziylan, Y. Ziya, Üzüm, Gülay, 2013. N-methyl-D-aspartate receptors are involved in caffeine-induced facilitation on memory retention of passive avoidance learning in rats. J. Caff. Res. 3, 169–174.
Duarte, João M.N., Agostinho, Paula M., Carvalho, Rui A., Cunha, Rodrigo A., 2012. Caffeine consumption prevents diabetes-induced memory impairment and synaptotoxicity in the hippocampus of NONcZNO10/LTJ mice. PLoS ONE, 7.
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.
Fredholm, Bertil B., Bättig, Karl, Holmén, Janet, Nehlig, Astrid, Zvartau, Edwin E., 1999. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacol. Rev. 51, 83–133.
Garrett, Bridgette E., Griffiths, Roland R., 1997. The role of dopamine in the behavioral effects of caffeine in animals and humans. Pharmacol. Biochem. Behav. 57, 533–541.
Gepdiremen, A., Sönmez, S., Ikbal, M., Düzenli, S., Tuna, S., 1998. Response to nimodipine in caffeine-induced neurotoxicity in cerebellar granular cell culture of rat pups. Pharmacol. Res. 38, 239–242.
Gilliland, Kirby, Andress, Dara, 1981. Ad lib caffeine consumption, symptoms of caffeinism, and academic performance. Am. J. Psychiatry.
Goiney, Christopher C., Gillaspie, Devin B., Villalba, Clara L. Alvarez, 2012. Addressing caffeine-induced psychosis: a clinical perspective. Addict. Disord. Treat. 11, 146–149.
Goodwani, Sunil, Rao, P.S.S., Bell, Richard L., Sari, Youssef, 2015. Amoxicillin and amoxicillin/clavulanate reduce ethanol intake and increase GLT-1 expression as well as AKT phosphorylation in mesocorticolimbic regions. Brain Res. 1622, 397–408.
Hahn, Sanghyun, Kim, Yun Ho, Seo, Hyung Suk, 2017. Immediate decrease in γ-aminobutyric acid after caffeine intake in adolescents: a preliminary MRS study. Investig. Magn. Reson. Imag. 21, 102–105.
Hakami, Alqassem Y., Alshehri, Fahad S., Althobaiti, Yusuf S., Sari, Youssef, 2017. Effects of orally administered Augmentin on glutamate transporter 1, cystine-glutamate exchanger expression and ethanol intake in alcohol-preferring rats. Behav. Brain Res. 320, 316–322.
Hakami, Alqassem Y., Hammad, Alaa M., Sari, Youssef, 2016. Effects of amoxicillin and augmentin on cystine-glutamate exchanger and glutamate transporter 1 isoforms as well as ethanol intake in alcohol-preferring rats. Front. Neurosci. 10, 171.
Hammad, Alaa M., Alasmari, Fawaz, Althobaiti, Yusuf S., Sari, Youssef, 2017a. Modulatory effects of Ampicillin/Sulbactam on glial glutamate transporters and metabotropic glutamate receptor 1 as well as reinstatement to cocaine-seeking behavior. Behav. Brain Res. 332, 288–298.
Hammad, Alaa M., Althobaiti, Yusuf S., Das, Sujan C., Sari, Youssef, 2017b. Effects of repeated cocaine exposure and withdrawal on voluntary ethanol drinking, and the expression of glial glutamate transporters in mesocorticolimbic system of P rats. Mol. Cell. Neurosci. 82, 58–65.
Haskell, Crystal F., Kennedy, David O., Wesnes, Keith A., Scholey, Andrew B., 2005. Cognitive and mood improvements of caffeine in habitual consumers and habitual non-consumers of caffeine. Psychopharmacology 179, 813–825.
Hedges, Dawson W., Woon, Fu Lye, Hoopes, Scott P., 2009. Caffeine-induced psychosis. CNS Spectr. 14, 127–131.
Iglesias, I., León, D., Ruiz, M.A., Albasanz, J.L., Martín, M., 2006. Chronic intake of caffeine during gestation down regulates metabotropic glutamate receptors in maternal and fetal rat heart. Amino Acids 30, 257–266.
Isokawa, Masako, 2016. Caffeine-induced suppression of GABAergic inhibition and calcium-independent metaplasticity. Neural Plasticity.
John, Joshi, Kodama, Tohru, Siegel, Jerome M., 2014. Caffeine promotes glutamate and histamine release in the posterior hypothalamus. Am. J. Physiol.-Regul., Integr. Comp. Physiol. 307, R704–R710.
Kahathuduwa, Chanaka, Wakefield, Sarah, West, Blake, Blume, Jessica, Mastergeorge, Ann, 2019. L-theanine and caffeine improve sustained attention, impulsivity and cognition in children with attention deficit hyperactivity disorders by decreasing mind wandering (OR29-04-19). Curr. Develop. Nutr. 3. nzz031 OR29-04-19.
Kalda, Anti, Liqun, Yu, Oztas, Emin, Chen, Jiang-Fan, 2006. Novel neuroprotection by caffeine and adenosine A2A receptor antagonists in animal models of Parkinson's disease. J. Neurol. Sci. 248, 9–15.
Kang, Sang Hwan, Lee, Young Ae, Won, Seok Joon, Rhee, Ki-Hyeong, Gwag, Byoung Joo, 2002. Caffeine-induced neuronal death in neonatal rat brain and cortical cell cultures. NeuroReport 13, 1945–1950.
Kaster, Manuella P., Machado, Nuno J., Silva, Henrique B., Nunes, Ana, Ardais, Ana Paula, Santana, Magda, Baqi, Younis, Müller, Christa E., Rodrigues Lisiane, Ana Lúcia S., Porciúncula., O., 2015. Caffeine acts through neuronal adenosine A2A receptors to prevent mood and memory dysfunction triggered by chronic stress. Proc. Natl. Acad. Sci. 112, 7833–7838.
Kim, Iris Y., O'Reilly, Éilis J., Hughes, Katherine C., Gao, Xiang, Schwarzschild, Michael A., McCullough, Marjorie L., Hannan, Marian T., Betensky, Rebecca A., Ascherio, Alberto, 2018. Interaction between caffeine and polymorphisms of glutamate ionotropic receptor NMDA type subunit 2A (GRIN2A) and cytochrome P450 1A2 (CYP1A2) on Parkinson's disease risk. Mov. Disord. 33, 414–420.
Ko, Yong-Hyun, Shim, Kyu-Yeon, Lee, Seok-Yong, Jang, Choon-Gon, 2018. Evodiamine reduces caffeine-induced sleep disturbances and excitation in mice. Biomol. Therap. 26, 432.
Lara, Diogo R., 2010. Caffeine, mental health, and psychiatric disorders. J. Alzheimers Dis. 20, S239–S248.
Loftfield, Erikka, Freedman, Neal D., Dodd, Kevin W., Vogtmann, Emily, Xiao, Qian, Sinha, Rashmi, Graubard, Barry I., 2016. Coffee drinking is widespread in the United States, but usual intake varies by key demographic and lifestyle factors. J. Nutr. 146, 1762–1768.
López-Cruz, Laura, Salamone, John D., Correa, Mercè, 2018. Caffeine and selective adenosine receptor antagonists as new therapeutic tools for the motivational symptoms of depression. Front. Pharmacol., 9
Lopez, Fred, Miller, Lawrence G., Greenblatt, David J., Kaplan, Gary B., Shader, Richard I., 1989. Interaction of caffeine with the GABAA receptor complex: alterations in receptor function but not ligand binding. Eur. J. Pharmacol. Mol. Pharmacol. 172, 453–459.
Lucas, Michel, Mirzaei, Fariba, Pan, An, Okereke, Olivia I., Willett, Walter C., O'Reilly, Éilis J., Koenen, Karestan, Ascherio, Alberto, 2011. Coffee, caffeine, and risk of depression among women. Arch. Intern. Med. 171, 1571–1578.
Machado, Nuno J., Simões, Ana Patrícia, Silva, Henrique B., Ardais, Ana Paula, Kaster, Manuella P., Garção, Pedro, Rodrigues, Diana I., Pochmann, Daniela, Santos, Ana Isabel, Araújo, Inês M., 2017. Caffeine reverts memory but not mood impairment in a depression-prone mouse strain with up-regulated adenosine A 2A receptor in hippocampal glutamate synapses. Mol. Neurobiol. 54, 1552–1563.
Manalo, Rafael V.M., Medina, Paul, 2018. Caffeine protects dopaminergic neurons from dopamine-induced neurodegeneration via synergistic adenosine-dopamine D2-like receptor interactions in transgenic Caenorhabditis elegans. Front. Neurosci. 12, 137.
Meredith, Steven E., Juliano, Laura M., Hughes, John R., Griffiths, Roland R., 2013. Caffeine use disorder: a comprehensive review and research agenda. J. Caff. Res. 3, 114–130.
Mukhopadhyay, S., Poddar, M.K., 1998. Is GABA involved in the development of caffeine tolerance?. Neurochem. Res. 23, 63–68.
Nall, Aleksandra H., Shakhmantsir, Iryna, Cichewicz, Karol, Birman, Serge, Hirsh, Jay, Sehgal, Amita, 2016. Caffeine promotes wakefulness via dopamine signaling in Drosophila. Sci. Rep. 6, 20938.
Nancy, Y. Yu, Bieder, Andrea, Raman, Amitha, Mileti, Enrichetta, Katayama, Shintaro, Einarsdottir, Elisabet, Fredholm, Bertil B., Falk, Anna, Tapia-Paez, Isabel, Daub, Carsten O., 2017. Acute doses of caffeine shift nervous system cell expression profiles toward promotion of neuronal projection growth. Sci. Rep. 7, 11458.
Ning, Ya-Lei, Yang, Nan, Chen, Xing, Zhao, Zi-Ai, Zhang, Xiu-Zhu, Chen, Xing-Yun, Li, Ping, Zhao, Yan, Zhou, Yuan-Guo, 2015. Chronic caffeine exposure attenuates blast-induced memory deficit in mice. Chin. J. Traumatol. 18, 204–211.
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, 65–73.
Pandolfo, Pablo, Machado, Nuno J., Köfalvi, Attila, Takahashi, Reinaldo N., Cunha, Rodrigo 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, 317–328.

Pechlivanova, Daniela M., Tchekalarova, Jana D., Alova, Liana H., Petkov, Vesselin V., Nikolov, Rumen P., Yakimova, Krassimira S., 2012. Effect of long-term caffeine administration on depressive-like behavior in rats exposed to chronic unpredictable stress. Behav. Pharmacol. 23, 339–347.

Peng, Po-Jui, Chiang, Kuo-Tung, Liang, Chih-Sung, 2014. Low-dose caffeine may exacerbate psychotic symptoms in people with schizophrenia. J. Neuropsychiat. Clin. Neurosci. 26. E41-E41.

Prediger, Rui DS., 2010. Effects of caffeine in Parkinson's disease: from neuroprotection to the management of motor and non-motor symptoms. J. Alzheimer's Dis. 20, S205–S220.

Pulvirenti, Luigi, Swerdlow, Neal R., Koob, George F., 1989. Microinjection of a glutamate antagonist into the nucleus accumbens reduces psychostimulant locomotion in rats. Neurosci. Lett. 103, 213–218.

Pulvirenti, Luigi, Swerdlow, Neal R., Koob, George F., 1991. Nucleus accumbens NMDA antagonist decreases locomotor activity produced by cocaine, heroin or accumbens dopamine, but not caffeine. Pharmacol. Biochem. Behav. 40, 841–845.

Rao, P.S.S., Sari, Youssef, 2014. Effects of ceftriaxone on chronic ethanol consumption: a potential role for xCT and GLT1 modulation of glutamate levels in male P rats. J. Mol. Neurosci. 54, 71–77.

Rao, P.S.S., Saternos, Hannah, Goodwani, Sunil, Sari, Youssef, 2015. Effects of ceftriaxone on GLT1 isoforms, xCT and associated signaling pathways in P rats exposed to ethanol. Psychopharmacology 232, 2333–2342.

Roca, Dominic J., Schiller, Grant D., Farb, David H., 1988. Chronic caffeine or theophylline exposure reduces gamma-aminobutyric acid/benzodiazepine receptor site interactions. Mol. Pharmacol. 33, 481–485.

Sari, Youssef, Franklin, Kelle M., Alazizi, Adnan, Rao, P.S.S., Bell, Richard L., 2013a. Effects of ceftriaxone on the acquisition and maintenance of ethanol drinking in peri-adolescent and adult female alcohol-preferring (P) rats. Neuroscience 241, 229–238.

Sari, Youssef, Sreemantula, Sai N., Lee, Moonnoh R., Choi, Doo-Sup, 2013b. Ceftriaxone treatment affects the levels of GLT1 and ENT1 as well as ethanol intake in alcohol-preferring rats. J. Mol. Neurosci. 51, 779–787.

Sari, Youssef, Toalston, Jamie E., Rao, P.S.S., Bell, Richard L., 2016. Effects of ceftriaxone on ethanol, nicotine or sucrose intake by alcohol-preferring (P) rats and its association with GLT-1 expression. Neuroscience 326, 117–125.

Shi, D., Nikodijević, O., Jacobson, K.A., Daly, J.W., 1994. Effects of chronic caffeine on adenosine, dopamine and acetylcholine systems in mice. Arch. Int. Pharmacodyn. Ther. 328, 261.

Solinas, Marcello, Ferre, Sergi, You, Zhi-Bing, Karcz-Kubicha, Marzena, Popoli, Patrizia, Goldberg, Steven R., 2002. Caffeine induces dopamine and glutamate release in the shell of the nucleus accumbens. J. Neurosci. 22, 6321–6324.

van Koert, Rick R., Bauer, Prisca R., Schuitema, Ilse, Sander, Josemir W., Visser, Gerhard H., 2018. Caffeine and seizures: a systematic review and quantitative analysis. Epilepsy Behav. 80, 37–47.

Vesoulis, Zachary A., McPherson, Christopher, Neil, Jeffrey J., Mathur, Amit M., Inder, Terrie E., 2016. Early high-dose caffeine increases seizure burden in extremely preterm neonates: a preliminary study. J. Caff. Res. 6, 101–107.

Volkow, N.D., Wang, G.J., Logan, J., Alexoff, D., Fowler, J.S., Thanos, P.K., Wong, C., Casado, V., Ferre, S., Tomasi, D., 2015. Caffeine increases striatal dopamine D 2/D 3 receptor availability in the human brain. Transl. Psychiatr. 5, e549.

Vyleta, Nicholas P., Smith, Stephen M., 2008. Fast inhibition of glutamate-activated currents by caffeine. PLoS ONE 3, e3155.

Wang, Hee Ryung, Woo, Young Sup, Bahk, Won-Myong, 2015. Caffeine-induced psychiatric manifestations: a review. Int. Clin. Psychopharmacol. 30, 179–182.

Watanabe, H., Uramoto, H., 1986. Caffeine mimics dopamine receptor agonists without stimulation of dopamine receptors. Neuropharmacology 25, 577–581.

El Yacoubi, Malika, Ledent, Catherine, Parmentier, Marc, Bertorelli, Rosalia, Ongini, Ennio, Costentin, Jean, Vaugeois, Jean-Marie, 2001. Adenosine A2A receptor antagonists are potential antidepressants: evidence based on pharmacology and A2A receptor knockout mice. Br. J. Pharmacol. 134, 68–77.

Yang, J.Y., Yang, G., Ren, J., Zhao, J., Li, Sh., 2015. Caffeine suppresses GABA receptor-mediated current in rat primary sensory neurons via inhibition of intracellular phosphodiesterase. Neurophysiology 47, 108–114.

Yasuhara, Masato, Levy, Gerhard, 1988. Caffeine as a potential risk factor for theophylline neurotoxicity. J. Pharm. Sci. 77, 745–747.