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Candidate mechanisms of caffeine improving memory dysfunction

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Received August 1, 2019; accepted August 30, 2019

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Pharmazie 74: 705-710 (2019) *doi: 10.1691/ph.2019.9711*

Caffeine is the most common psycho-stimulant that is broadly known to cause peripheral effects. Caffeine is well known as an adenosine receptor antagonist. Adenosine receptors are present in all areas of the brain, which makes caffeine's effects very prevalent. The main goal of this review is to summarize recent studies that are investigating the mechanism of action of acute and chronic caffeine treatment of to alleviate the cognitive deficits and synaptic plasticity. This review discusses the effect of caffeine on the brain functions including learning and memory, and synaptic plasticity in case of various diseases.

1. Introduction

Caffeine has been used for centuries and it is suggested that it enhances various central nervous system (CNS) functions, but the exact mechanism is still elusive. Caffeine is contained in many beverages such as coffee, tea, and soft drinks. Many people intend to drink coffee or tea to consume caffeine, believing that it increases cognitive function, attention, and alertness. Studies have shown that two hours after consuming coffee the caffeine concentration reaches the peak levels (Carrillo and Benitez 2000), causing several effects such as increasing blood pressure (Mesas et al. 2011), and dopamine, glutamate (Solinas et al. 2002), epinephrine, norepinephrine, and cortisone levels (Lovallo et al. 2005; Minana and Grisolia 1986).

Caffeine is used as a CNS stimulant and plays a vital role in learning and memory modulation. Studies revealed that caffeine enhanced the cognitive function in both clinical and experimental studies (Cunha and Agostinho 2010; Han et al. 2013). Furthermore, the administration of caffeine improved memory impairment caused by multiple brain disorders and diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and sleep deprivation (Alkadhi et al. 2013; Han et al. 2013; Roshan et al. 2016).

Caffeine belongs to methylxanthine class which mainly acts as central nervous system (CNS) stimulant (Nehlig et al. 1992). It is a white crystalline purine, a methylxanthine alkaloid which is the world's most abundantly consumed psychoactive drug. It is chemically 1,3,7-trimethylpurine-2,6-dione with molecular formula $C_8H_{10}N_4O_2$ and correlated to the adenine and guanine nitrogen bases of deoxyribonucleic acid and ribonucleic acid. Due to the absence of stereogenic centers, caffeine is identified as an achiral molecule (Fig. 1). It is weakly basic (pKa of 10.4 at 40 at 25°C (Rodopoulos et al. 1995).

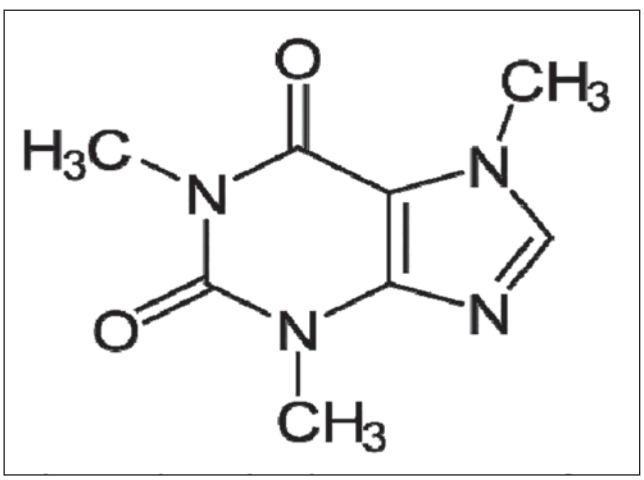

Fig.: Chemical structure of caffeine

Caffeine is regarded to have many different effects like memory enhancing (Borota et al. 2014; Cunha and Agostinho 2010), anticancer (Tomita and Tsuchiya 1989), and antioxidant effects (Azam et al. 2003). It is lipophilic in nature and this property allows for rapid absorption into the bloodstream where it freely crosses the blood-brain barrier (BBB) (Alzoubi et al. 2013). In this review, most recent studies on caffeine, linked to the effect of memory function such as behavioral tests, electrophysiological assessment, and molecular signaling are discussed as a potential therapy for some disease conditions.

2. Caffeine and synaptic transmission

At the synaptic level, caffeine is found to be a competitive blocker for adenosine receptors, mainly A_1 and A_{2A} subtypes (Biaggioni et al. 1991; Costenla et al. 2010). Once caffeine blocks the adenosine receptors, this action leads to increase in the release of other neurotransmitters such as dopamine, noradrenalin, and glutamate (Solinas et al. 2002). Thus, these neurotransmitters are highly expressed in the brain and this in turn will play an important role in regulating memory processes (Myhrer 2003). Several lines of evidence showed that a reduction in dopamine, noradrenaline, and glutamate levels results in cognitive deficits (Coradazzi et al. 2016; Diggs-Andrews et al. 2013; Merritt et al. 2013). Caffeine blocks adenosine receptors, and increases the levels of other neurotransmitters in the synapse.

Electrophysiology is a technique, which is used to mimic the physiological function of tissues or cells. The major electrophysiological test that is used to evaluate memory function in the synaptic level is long-term potentiation (LTP), which measures memory at cellular level (Bliss and Collingridge 1993). This test mainly evaluates the strength of neuronal communication, particularly synaptic strength and weakening (Chang et al. 1999). Electrophysiological studies using LTP have shown that cognitive dysfunction is associated with some neurological disorders and diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and sleep deprivation (Alkadhi et al. 2013; Chiaravalloti et al. 2014; Jahn 2013). Interestingly, chronic caffeine treatment revealed to rescue the LTP in many neurological disorders. For instance, sleep deprivation, AD, and PD caused a decrease in LTP and the research findings revealed that caffeine can improve the reduction in the LTP and memory function.

3. Caffeine and stress

Chronic exposure to stress increases stress hormones, which may cause several problems to the body including the brain (Magarinos et al. 1997). Likewise, studies have shown that acute caffeine consumption leads to elevate cortisol levels (Lovallo et al. 2005). Severe and long-term increase of stress hormones can change normal brain structure and function and these changes might result in cognitive impairment (Magarinos et al. 1997; McEwen et al. 1997). In experimental animals, stress alters protein expression and functions of proteins such as BDNF and CaMKII (Gerges et al. 2004; Mondelli et al. 2011; Murakami et al. 2005) that affects memory function. Nevertheless, chronic treatment with caffeine rescues the cognitive impairment and elevates the expression of BDNF and CaMKII proteins, which are reduced by stress and sleep deprivation in the hippocampus (Alzoubi et al. 2013). Therefore, caffeine is acting against the effect of stress in the brain by reducing the side effects caused by the of stress.

4. Caffeine and CNS disorders

CNS disorders, including neurodegenerative disease such as AD and PD are characterized by primary alteration in brain function causing cognitive impairment (Jahn 2013; Leverenz et al. 2009). Generally, AD and PD are found to develop neurodegeneration by increasing pro-apoptotic markers (Yalcinkaya et al. 2016; Ye and Fortini 1999). Contrarily, caffeine acts to decrease the pro-apoptotic and increased the anti-apoptotic markers, which ultimately increases the survival rate of cells (Blandini et al. 2003; Zeitlin et al. 2011).

4.1. Alzheimer's disease (AD)

AD is a common neurodegenerative disease in elderly people causing dementia, and is characterized by deposition of β-amyloid (Aβ) and tau protein in the brain. Aβ oligomers and plaques are considered potent neurotoxins. Accumulation of β-amyloid inhibits mitochondrial activities, blocks proteasome function, increases intracellular Ca^{++} levels, and stimulates inflammatory processes. Studies have revealed that alteration in physiological function of Aβ contributes to neuronal dysfunction. Aβ accumulation is interacted with signaling pathways that are important to regulate phosphorylation of the microtubule-associated tau protein, and also generate reactive oxygen species (ROS) resulting in oxidative stress. In addition, hyperphosphorylation of tau protein disrupts its normal function to regulate axonal transport and results in the accumulation of neurofibrillary tangles into the neurons. Moreover, Aβ accumulation inhibits the ability of the proteasome to degrade hyperphosphorylated tau protein. AD is also known to be associated with insulin resistance (Talbot 2014).

Strategies to slow the progression of AD includes: using drugs such as acetylcholinesterase inhibitors, blockage of N-methyl-D-aspartate receptor (NMDAR), and antioxidants (Mendiola-Precoma et al. 2016). Caffeine has radical scavenging properties which is responsible for its antioxidant potential. Also, studies have revealed that caffeine is increasing insulin sensitivity in Alzheimer patients, slows down the progression of the disease, and alleviates cognitive impairment (Eskelinen and Kivipelto 2010). Also, caffeine is found to reduce hippocampal tau phosphorylation and neuroinflammation in Alzheimer's transgenic models resulting in improved memory function (Laurent et al. 2014). In addition, caffeine has proven to reduce the neuronal damage in the brain following high oxygen exposure in case of hyperoxia (Endesfelder et al. 2014). All these studies have supported the assumption that there could be a chance that caffeine could slow down the progression of AD.

4.2. Parkinson's disease (PD)

Parkinson's disease is the second most common progressive neurodegenerative disorder affecting older adults leading to dementia (Sherer et al. 2012). This disease is affecting approximately 1% of population with age more than 60 years (Bezard et al. 2001). Pathologically, this disease is characterized by selective dopaminergic neuronal degeneration in the substantia nigra of the midbrain and the development of neuronal Lewy Bodies. PD is associated with risk factors including aging, family history, pesticide exposure and environmental chemicals. However, the exact cause of PD is still unclear and is characterized by both motor and non-motor system manifestations. PD could associate with neurobehavioral disorders such as depression, anxiety, cognitive impairment, and autonomic dysfunction. Studies have reported that correcting the dopamine deficiency in PD with levodopa (L-dopa) significantly attenuates the motor symptoms (Guttman 1992). However, definitive disease-modifying therapy is still lacking. The diagnosis of PD is based on the symptom signs such as rigidity, bradykinesia, and tremors as well as cognitive impairment (Ng 1996), and it initiates in the loss or degeneration of the dopaminergic neurons (dopamine-producing) in the substantia nigra (Barber et al. 2001). This loss of dopamine producing neurons leads to impairment of motor control and memory function (Kinoshita et al. 2015). Besides causing motor symptoms, PD (Braak et al. 2003) is involved in non-motor symptoms such as cognitive impairment (Aarsland et al. 2012). Preclinical studies have revealed that caffeine has improved both motor and non-motor symptoms of PD patients through synergetic effect between the adenosine and dopamine receptors (Manalo and Medina 2018). Thus, caffeine may represent as a promising preventive strategy for cognitive impairment associated with PD.

4.3. Caffeine and attention deficit hyperactivity disorder (ADHD)

ADHD is a neurodevelopmental disorder affecting subjects of all age groups. ADHD patients could have difficulty preserving attention or they may exhibit some hyperactivity that affect their daily life of children such as school performance (Loe and Feldman 2007). These symptoms commences around the age of seven years in between 4 to 12% of students in the world and it lasts for few months (Wilens and Spencer 2010). To date, ADHD is usually diagnosed based on behavioral symptoms (Reason and Working Party of the British Psychological Society 1999) that because of lack of accurate biological test for this disorder (Edwards et al. 1995). The exact etiology of the ADHD pathway is still elusive. Studies have reported that in patients with ADHD, the concentration of the neurotransmitter dopamine is reduced and the expression of dopamine transporter is increased. This increased dopamine transporter caused the reduction of dopamine levels. So, the dopamine transporter takes back dopamine to the same neurons immediately after release and blocks further transportation to the next neurons. Thus, the major strategy to treat ADHD disorder is increasing dopamine levels by blocking the dopamine transporters preventing dopamine reuptake (Schmeichel et al. 2013; Wang et al. 2013). This alteration in the dopamine levels is affecting the dopamine receptors expression in ADHD patients ultimately resulting in changes in brain function (LaHoste et al. 1996). Caffeine administration is typically considered to be safe for healthy adults; however, treating children with ADHD is controversial. Caffeine is reported to increase the dopamine levels by increasing the release when adenosine receptors are blocked (Daly et al. 1994; Ferre 2016), and also by blocking the dopamine transporter (Pandolfo et al. 2013). Therefore, more investigation of the effects of caffeine effect on ADHD disorder may help to develop new therapeutic strategies.

5. Caffeine effects on protein expression and phosphorylation

Protein expression and phosphorylation levels are essential for regulating cell function. Alteration of some protein expression and phosphorylation is associated with brain disorders such as AD. Phosphorylation changes the structural conformation of a protein, causing it to become switch on/off or by modifying its function and this depend on the site of phosphorylation. Here, we illustrate how the proteins are altered in brain disorders and how these alterations were recovered by caffeine treatment.

5.1. Brain derived neurotrophic factors (BDNF)

BDNF gene is encoding for BDNF protein, which is important for the central nervous system function, enhancing growth, survival, and differentiation of newly born and grown neurons as well as synaptic plasticity (Bramham and Messaoudi 2005; Vaynman et al. 2004). BDNF is expressed not only in brain tissue but also in the peripheral nervous system and skeletal muscle (Porcelli et al. 2010). BDNF is a ligand for tyrosine receptor kinase B (TrkB) and both of the BDNF and TrkB receptors play an essential role in regulating brain development, and learning and memory processes (Yoshii and Constantine-Paton 2010). Evidence has implicated that BDNF also plays an important role in LTP induction and maintenance in the hippocampus (Ying et al. 2002). Studies revealed that memory consolidation are accompanied with an increase in *BDNF* mRNA expression and activation of TrkB receptors in the hippocampus (Novkovic et al. 2015).

Accordingly, BDNF and TrkB receptor expressions are increased during hippocampal learning and memory dependent tasks and synaptic plasticity (Yoshii and Constantine-Paton 2010). Hence, alteration of BDNF or TrkB expression in the central nervous system will lead to cognitive dysfunction (Erickson et al. 2010). Experimental studies have identified that BDNF levels are reduced in sleep deprivation using rodent models. Thus, this reduction in the BDNF levels is rescued by caffeine treatment (Alhaider et al. 2010). So, this result justifies the memory dysfunction in sleep deprivation and the improvement of memory after caffeine consumption. Based on this result, caffeine may have an effect to improve memory function in case of memory dysfunction caused by BDNF reduction. Therefore, more research in this area could exert a new therapeutic potential to treat memory impairment caused by BDNF reduction. Researches have revealed that caffeine alleviates BDNF expression and memory function following reduction in BDNF caused by sleep deprivation (Alzoubi et al. 2013).

5.2. Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII)

CaMKII is expressed as a multimeric protein, and comprises 12 subunits in the most physiological states. CaMKII expression plays a crucial role for memory function specifically upstream cellular events into downstream physiological effects. Similarly, it functions as a regulator in neuronal excitability and synaptic transmission in the hippocampus. Moreover, autophosphorylation of CaMKII has been recognized as an important factor in learning and memory processes besides the importance of total expression. Remarkably, in several diseases resulting in downregulation of CaMKII, it was found that caffeine upregulates CaMKII expression and phosphorylation (Alzoubi et al. 2013).

5.3. Cyclic-AMP response element binding protein (CREB)

CREB is a transcription factor that regulates the expression of CRE-containing genes and it facilitates gene transcription crucial for the development and function of the central nervous system. CREB is an essential regulator underlying synaptic plasticity (Benito and Barco 2010). CREB is also known to intermediate the transcription of the BDNF gene that stimulates neuron development, survival, and synaptic plasticity.

The activity of CREB as a transcriptional factor occurs by phosphorylation of the Ser^{133} residue by other protein kinases (Shaywitz and Greenberg 1999). Depolarization of neurons opens voltage-gated calcium channels allowing Ca^{++} to influx into the cells. Ca^{++} in a high concentration activates calcium calmodulin kinase II/IV (CaMKII/IV). Autophosphorylation of CaMKII activates CREB in ser^{133} residue that is vital for learning and memory processes (Sun et al. 1994). Activation of CREB is required to generate LTP and synaptic plasticity (Ahmed and Frey 2005). In contrast, inhibition of CREB impairs the long-term memory process (Vitolo et al. 2002). In case of AD, expression of CREB is downregulated (Pugazhenthi et al. 2011). On the other hand, caffeine increases the expression of endogenous CREB and thus it could be a potential neuroprotective agent in AD (Connolly and Kingsbury 2010).

6. Caffeine and catecholamines

Epinephrine, norepinephrine, and dopamine are crucial for learning and memory function. Studies have reported that endogenous epinephrine enhances long-term memory in human even though it is not crossing the blood brain barrier (Cahill and Alkire 2003; McIntyre and Roozendaal 2007). Epinephrine has indicated in many experiments that it improves memory consolidation through peripheral β-adrenoceptor activation (Cahill and Alkire 2003; McGaugh et al. 1996). Interestingly, caffeine is found to enhance the release of epinephrine and norepinephrine (Yamada et al. 1989).

The dopaminergic system is one of the major players in learning and memory processes (Berry et al. 2012; Kempadoo et al. 2016; Puig et al. 2014). When dopamine is released, it binds to two types of dopaminergic receptors widely expressed in the brain (Beaulieu et al. 2015). These two receptors can either have stimulatory or inhibitory effects (Baik 2013). Therefore, many studies showed that alteration in dopamine release affects memory function (Willard et al. 2015). For example, PD is associated with reduced dopamine release as a result of the dopaminergic death in area of the substantia nigra (Hoang 2014; Michel et al. 2016). Increased levels of dopamine formed from levodopa, which is a precursor of dopamine, partly rescued the deficit in memory in parkinsonism patients (Beigi et al. 2016; Floel et al. 2008; Peterson and Horak 2016). Agonism of adenosine A_1 receptors located in the presynaptic neurons is known to inhibit dopamine and glutamate release, and it results in decreased dopaminergic neurotransmission in the postsynaptic neurons. Thus, caffeine is antagonizing the effects of endogenous adenosine and enhances the release of dopamine neurotransmission to activate dopamine receptors (Solinas et al. 2002).

7. Caffeine and acetylcholine

The cholinergic system is an important regulator for most of the body mechanisms including brain function. Acetylcholine functions as both excitatory and inhibitory neurotransmitter in the brain. Previous studies have shown that both muscarinic and nicotinic acetylcholine receptors play a role in memory encoding and synaptic plasticity (Hasselmo 2006). Blockage of muscarinic and nicotinic cholinergic receptors impairs learning and memory processes (Atri et al. 2004). However, activation of nicotinic receptors is found to enhance memory function (Buccafusco et al. 2005). In addition, in the medial septal nucleus area of the brain, acetylcholine is reported to be the first neurotransmitter that was affected in AD (Kihara and Shimohama 2004).

The medial septum innervates the hippocampus, which is the part of the brain that initiates memory formation. Moreover, acetylcholinesterase is the enzyme that breaks down the acetylcholine to choline and acetyl. Several studies indicate that acetylcholinesterase (AChE) activity is increased in Alzheimer's patients. This increase in AChE activity results in cognitive dysfunction and the inhibition of AChE is considered one of the major therapeutic strategies for Alzheimer's and cognitive dysfunction (Tabet 2006). Moreover, caffeine administration interestingly is able to decrease AChE activity and thus it slows down the progression of AD (Pohanka and Dobes 2013).

8. Caffeine and estrogen

Estrogen is a hormone that plays significant roles in the development and function of sexual and reproductive system. Estrogen is a hormone that converted from testosterone by the aromatase enzyme (Cui et al. 2013). Estrogen is involved in fetal development processes as well as regulatory role in the cardiovascular, musculoskeletal, immune, and central nervous systems function (Gustafsson 2003). Estrogen is lipophilic and it acts through estrogen receptors, and these receptors are nuclear receptors. There are several lines of evidence implicating that estrogen receptors regulate learning and memory processes (Luine et al. 1998), The blocking of estrogen receptors leads cognitive impairment (Inagaki et al. 2012). Menopausal women exhibit cognitive impairment and memory dysfunction, whereas several studies correspond this memory dysfunction as a result of reduced estrogen production (Sliwinski et al. 2014). On the contrary, postmenopausal women treated with estrogen exhibited significant improvement of memory function (Newhouse et al. 2010). Moreover, the direct relationship between caffeine and estrogen levels is still controversial, whereas some studies revealed that caffeine administration decreases estrogen levels and caffeinated drinks increases the circulating levels of estrogen (Schliep et al. 2012). Therefore, regular consumption of caffeine may have a positive effect on cognitive function and might be used to treat diseases or physiological changes resulting from reduced estrogen levels.

9. Caffeine and chromatin modification

In eukaryotic cells, DNA is packed highly around a protein inside the nucleus called chromatin (Shilatifard 2006). Chromatin is composed of subunits known as histones (Kouzarides 2007). Each of these histones plays a complicated role for gene regulation and transcription. Chromatin modification occurs by different processes such as acetylation, methylation, and phosphorylation (Kouzarides 2007). Phosphorylation of certain histone subunits at a particular site can increase or inhibit gene transcription (Brehove et al. 2015; Zhang et al. 2004). Inhibition of histone deacetylase (HDAC), which is the enzyme that enhances histone acetylation, enhances memory function and synaptic plasticity (Vecsey et al. 2007). The direct relation between caffeine, HDAC inhibition, and memory is not well understood. However, studies have revealed that HDAC-1 is inhibited in cancer cells leading to death of the cells following caffeine treatment (Chen and Hwang 2016). Addition to that, myoblasts, for example, showed an increase in GLUT4 expression by acetylating the myocyte enhancer factor-2 (MEF2) site to increase MEF2A binding, which is required for GLUT4 gene expression (Thai et al. 1998) via CaMKII signaling following caffeine treatment (Mukwevho et al. 2008). Therefore, further studies are needed to investigate more mechanisms of caffeine effect on memory function related to chromatin modulation.

10. Caffeine and inflammation

Inflammation is a natural response to protect the body from foreign antigens. Chronic inflammation can be dangerous and contribute to health problems such as cardiovascular disease, certain types of cancer and rheumatoid arthritis (Araki and Mimura 2016; Golia et al. 2014; Multhoff et al. 2011). When a foreign antigen attacks the cells or tissue damage, which activates leukocytes leading to release of pro-inflammatory cytokines (Amaya et al. 2013). Cytokines play an important role regulating physiological function, but they can also result in undesirable effects such as memory impairment (Johnson et al. 2017; Menza et al. 2010; Pomykala et al. 2013; Sartori et al. 2012). It was reported that peripheral cytokines are able to penetrate the BBB via an active transport mechanism or vagal nerve stimulation (Yarlagadda et al. 2009). Activation of the hypothalamic-pituitary-adrenal (HPA) axis can facilitate learning and memory processes by enhancing glucocorticoids, norepinephrine, epinephrine, and dopamine release (Yirmiya and Goshen 2011). However, over-activation of the HPA axis caused by cytokines is associated with cognitive impairment (Wilson et al. 2002; Yirmiya and Goshen 2011).

It is well understood that there is a significant relationship between inflammation and elevated levels of cytokines and cognitive impairment (Ahles and Saykin 2007; Murray et al. 2012). Therefore, regulation of cytokines levels is important for general brain function. In normal persons, caffeine administration increased the interleukin-6 (IL-6) (Tauler et al. 2013) in the circulating blood when compared with the persons who consume alcohol.

11. Caffeine and phosphodiesterases (PDEs)

Phosphodiesterases are enzymes that break down the phosphodiesteric bond of cyclic adenosine monophosphate (cyclic AMP) and cyclic guanosine monophosphate (cyclic GMP) in the cells. Hormones and neurotransmitters activate their receptors that activate second messengers such as cyclic AMP and cyclic GMP. These secondary messengers regulate the signal transduction of many biological activities (Yan et al. 2016). Phosphodiesterase-5 (PDE-5) inhibition is used clinically to treat chronic heart failure (Vecchis et al. 2017) and erectile dysfunction (Rosen and Kostis 2003). In terms of learning and memory, PDE-5, PDE-4 inhibition is playing a vital role in synaptic plasticity and memory function (Blokland et al. 2006; Werenicz et al. 2012). One of the investigated mechanisms of caffeine is that it acts as a phosphodiesterase inhibitor (Francis et al. 2011; Nehlig et al. 1992). Therefore as well, caffeine may potentially be useful for the improvement of cognitive impairment.

12. Conclusion

This paper reviews publications regarding of the impact of several diseases on brain function that interfere with memory encoding. The reader will relatively observe more emphasis on how different mechanisms of caffeine affect learning and memory processes and synaptic plasticity as well as molecular signaling. The discussion also includes the impacts of caffeine on health conditions and some disease states that obviously result in alleviation of memory function.

Dedication: I dedicated this review paper to address how caffeine could improve the memory function in different cases of disorders and state some potential mechanisms behind its effect.

Conflict of interest: There is no conflict of interest in this review paper.

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