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Mechanisms underlying cognitive impairment induced by prenatal caffeine exposure

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Abstract. – OBJECTIVE: Caffeine is one of the most commonly used stimulants among pregnant women. Human and animal studies have shown that prenatal caffeine exposure affects fetal brain development and results in persistent cognitive deficits in offspring. Studies have found that caffeine consumption during pregnancy may alter many activities that are ultimately associated with cognitive dysfunction in offspring. Despite these important findings, there is a fundamental gap in understanding the mechanism underlying cognitive impairment due to prenatal caffeine exposure. Filling this knowledge gap would provide further insights into caffeine-mediated cognitive dysfunction. The objective of this review was to evaluate the findings of studies showing that prenatal caffeine exposure induces cognitive dysfunction and the potential underlying mechanisms.

Key Words:
Caffeine, Cognitive dysfunction, Protein kinase, Memory impairment.

Introduction

Caffeine has been used as a stimulant, as well as for medical purposes for thousands of years. To date, there are several sources of caffeine, including tea, coffee, and caffeinated drinks. Children of mothers who consume caffeine during pregnancy are at higher risk of severe adverse health effects[1,2]. Specifically, chronic neurobehavioral changes, such as learning and memory deficits and impaired social development, have been linked to caffeine exposure during pregnancy. Studies have demonstrated a strong correlation between maternal use of caffeine and cognitive deficits in young children[3,4]. These findings have been confirmed by animal studies[3].

Several lines of evidence have demonstrated neurobehavioral alterations in children of women who consumed caffeine during pregnancy[3,5]. Caffeine intake exogenously activates adenosine receptors in the brain[6], which alter the action of several other neurotransmitters such as glutamatergic, dopaminergic, and serotonergic neurotransmitters[7-10]. Chronic exposure of the adenosine receptors to caffeine could potentially lead to chronic suppression of neuronal plasticity in the hippocampus, as well as the neighboring brain regions and reduced cognitive function. These findings indicate that the alteration of adenosine receptors by caffeine has a functional role in synaptic plasticity processes and plays an important role in the cognitive impairment of offspring.

Caffeine is a neuromodulator and is similar in structure to adenosine (Figure 1), which is produced primarily from ATP metabolism and its formation is dependent on the relative rates of ATP breakdown and synthesis[11]. There are four types of adenosine receptors, A_1, A_{2A}, A_{2B} and A_3, and all of these receptors belong to the superfamily of G-protein-coupled receptors[12]. This class of receptors comprises seven transmembrane α-helical structures, of which the extracellular and intracellular structures are the amino-terminus and carboxy-terminus, respectively[13]. Adenosine receptors are classified based on their differences in coupling to adenylyl cyclase to regulate cyclic AMP levels. The A_1 and A_3 adenosine receptors are coupled to inhibitory $G_{i/o}$ proteins, whereas A_{2A} and A_{2B} adenosine receptors are coupled to stimulatory G_s proteins. At low doses, caffeine blocks the A_1 and A_{2A} adenosine receptors[14].

Both the A1 and A_{2A} adenosine receptors are highly expressed in the central nervous system and are believed to play a major role in neurodevelopment and cognitive function[15,16]. Adenosine A_1 receptors are predominantly expressed in the hippocampus, cortex, cerebellum, and hypothalamus [17-19], whereas the A_{2A} subtype is present in the striatum and nucleus accumbens[20]. Adenosine receptor activation appears to inhibit the release of many neurotransmitters in the central nervous system[19]. Adenosine A_1 receptor agonists have been shown to inhibit the release of glutamate[21-23], serotonin[24],

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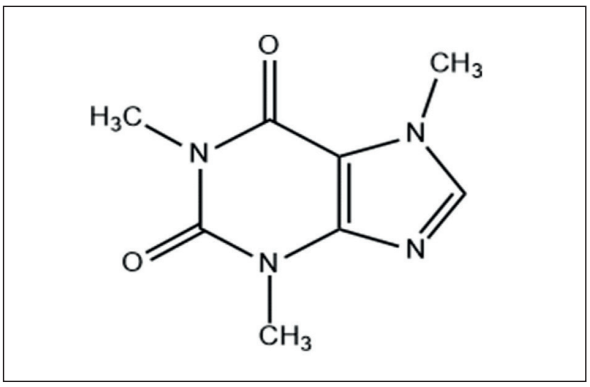

Figure 1. Chemical structure of caffeine.

acetylcholine[25,26], noradrenaline[27], and dopamine[28] in animal models. Caffeine acts as an adenosine receptor antagonist; therefore, it enhances the release of various neurotransmitters. For example, caffeine has been linked to behavior modulation through its inhibitory effects on other neurotransmitters[6].

Adenosine receptors are abundantly expressed in the hippocampus[29]. Some of the G-proteins expressed earliest during the embryonic stage are A1 receptors[30,31]. Caffeine is believed to regulate synaptic plasticity and memory formation in the hippocampus[32]. The regulatory role of caffeine in neuronal circuit development and synapse formation can be impaired by chronic caffeine exposure during fetal development[33,34]. During early development, caffeine exposure appears to result in alterations of the neuronal morphology of certain brain regions, including decreased neuronal area of the hippocampal and cortical neurons[35]. Chronic exposure to caffeine significantly decreases the levels of synaptic plasticity by modulating adenosine receptors[36].

Both clinical and experimental studies have demonstrated that prenatal caffeine exposure induces memory impairment[3]. However, the exact etiology of this impairment is still not fully understood. In this review, we discuss the potential mechanisms behind memory impairment in the children of mothers consuming caffeine.

Prenatal caffeine exposure and adenosine receptors

Adenosine receptors play an important role in the regulation of memory function. Some studies[15,37,38] have reported that the alteration of adenosine receptor expression in transgenic animals impairs memory function. Overexpression of the adenosine A_{2A} receptor resulted in impairment of performance in novel object recognition tasks[39]. In addition, knockout of adenosine A1 receptors did not affect performance in spatial memory tasks; however, habituation was slow, and long-term potentiation and paired-pulse facilitation in the hippocampus was impaired[40]. Therefore, prenatal caffeine exposure chronically altered adenosine receptor expression in offspring, which may be one of the potential mechanisms underlying the cognitive dysfunction caused by caffeine.

Prenatal caffeine exposure and behavioral tasks

Behavioral tests such as novel object recognition, the Morris water maze task, and the radial arm maze task are commonly used approaches to evaluate cognitive function[41]. Several lines of evidence demonstrate that alterations in behavioral tests can be classified as cognitive deficits[42,43]. Prenatal caffeine exposure has been shown to be associated with memory impairment in animals in the novel object recognition task. However, in the water maze task, the caffeine-treated animals found the platform faster. This result is probably due to the development of stress or anxiety, as reported by previous studies[3,44,45]. In the radial arm maze task, the caffeine-treated animals exhibited memory impairment, and the caffeine-treated animals' performance demonstrates that the caffeine-treated animals had significantly more references and working memory errors than the control animals. These results indicate that prenatal caffeine exposure alters brain development and thus affects memory function in adults.

Prenatal caffeine exposure and protein kinases

Protein kinases play an important role in regulating cellular function. They have essential functions in proliferation, signal transduction, metabolism, and apoptosis[46-48]. In the brain, these enzymes regulate general brain function as well as memory formation and synaptic plasticity[49-51]. For instance, the PI3K/Akt pathway regulates cell survival and is involved in receptor and transporter trafficking to the cell surface. It also regulates other proteins that function as transcriptional factors, which enhance gene transcription. In addition, the brain-derived neurotrophic factor (BDNF) plays a role in regulating memory function by activating tropomyosin receptor kinase B (TrkB) receptors[52].

The BDNF is reported to be involved in glutamate receptor trafficking[53]. Therefore, alterations in BDNF expression lead to memory impairment and reduce synaptic plasticity[54].

In addition, the cAMP response element-binding protein (CREB) mediates protein synthesis, which is important for neurogenesis, synaptic plasticity, and memory formation[55]. Notably, CREB is elevated in tumor cells and thus increases cell division[56]. In addition, CREB phosphorylation is increased during memory formation[57]. CREB has been shown to be downregulated under oxidative stress in both the hippocampus and cortical areas of the brain, which impairs memory function[58]. Therefore, alterations in CREB expression or phosphorylation change cognitive function[59].

Interestingly, a recent report showed that CREB and BDNF expression is reduced in the offspring of rats exposed to prenatal caffeine[4], which is shown to be one of the mechanisms by which prenatal caffeine exposure causes memory dysfunction.

Effect of prenatal caffeine exposure on heart development and function

Heart failure is a major health problem, and it is caused by blood flow deficiency to the rest of the body, including the brain, which results in hypoxia[60]. Shortage of brain oxygenation alters brain functions as well as learning and memory processes[61]. Prenatal caffeine exposure has been shown to change cognitive function, and studies have shown that the children of mothers taking caffeine during pregnancy have a lower Intelligence Quotient (IQ)[62]. Cognitive impairment is one of the most common chronic conditions in heart failure patients[63]. The reported occurrence of cognitive impairment with heart failure shows a wide range from 25% to about 70%[64,65]. In adults, caffeine consumption has been reported for multiple types of neurological disorders such as Alzheimer's disease, Parkinson's disease, and sleep deprivation, since it improves the cognitive dysfunction caused by these disorders[6]. However, prenatal caffeine exposure alters cardiac morphology. These changes are induced by altered expression of the *MYH7* gene, whose expression is increased during heart failure or stress[66]. Increased *MYH7* expression causes cardiomyopathy by modulation of the adenosine receptor A_1 by caffeine, and thus results in heart failure[67]. Therefore, one of the potential mechanisms by which caffeine impairs cognitive function is through its effect on heart development and function.

Conclusions

Both clinical and experimental studies have shown that prenatal caffeine exposure alters some aspects of learning and memory performance[3,62]. Caffeine can cross the placental and blood-brain barriers, which allows it to reach the fetal brain and act through adenosine receptors. Therefore, caffeine causes changes in brain development by altering the expression of proteins such as BDNF and CREB in the hippocampus and cortex; this leads to alteration of learning and memory functions.

Informed consent

There is no informed consent required for this study.

Ethical approval

The ethics and protocol are not required for this study.

Conflict of Interests

The authors declare no conflict of interest.

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