Chronic caffeine treatment reverses memory impairment and the expression of brain BNDF and TrkB in the PS1/APP double transgenic mouse model of Alzheimer's disease

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Abstract. The objective of this study was to investigate the effects of varying doses of caffeine on memory impairment and the expression of brain neurotrophic derived factor (BNDF) and TrkB in PS1/APP double transgenic mouse models. PS1/APP double transgenic mice were administrered 0.3 ml/day of saline, 1.5 mg/day of caffeine or 0.75 mg/day of caffeine for eight weeks. A water maze test and western blotting were used to determine the memory capability and expression of hippocampal BNDF and TrkB of the mice. The results demonstrated that 0.75 mg/day and 1.5 mg/day doses of caffeine significantly increased memory capability and the expression of hippocampal BDNF and TrkB in PS1/APP mice with a dose-response effect. The results suggested that chronic caffeine treatment may reverse memory impairment in PS1/APP transgenic mice, and BDNF and its receptor TrkB, may be involved in this process.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder resulting in progressive cognitive impairment. It has been reported that AD is the most common form of dementia among older people and the worldwide prevalence of the disease is estimated at >24 million cases (1). Medical treatment for AD patients is placing an increasing burden on physicians and families every year. Clinically, there are a variety of drugs available for AD, such as cholinesterase inhibitors, glutamate receptor antagonist and free radical scavengers. However, these drugs cannot target the pathogenesis of the disease closely and have significant side-effects (2). Therefore, it is important to find a new type of drug and to clarify the mechanism of AD pathophysiology. Caffeine is one of the most widely consumed psychoactive substances in the world (3). Recently, studies have demonstrated that caffeine intake may reduce the cognitive impairment in elderly patients and the risk of AD in later life (4,5). It also has been revealed that AD patients consume markedly less caffeine than people without AD (6). Elevated levels of β-amyloid (Aβ) in the brain and progressive cognitive impairment are the main characteristics of AD. Several studies have indicated that caffeine intake (1.5 mg/day) may reverse cognitive impairment and decrease brain Aβ levels in aged AD mice (7,8).

Brain neurotrophic derived factor (BDNF), a member of the neurotrophin family, is essential for growth, survival and the differentiation of neurons. Furthermore, BDNF is involved in learning and memory by binding to its main functional receptor (TrkB), in the hippocampus, cortex and basal forebrain (9). The levels of BDNF and TrkB have been reported to be lower in AD patients (10,11). It has been demonstrated that BDNF signaling, through TrkB, is involved in the pathophysiology and cognitive deficits of AD (12). PS1/APP double transgenic mice expressing the human APPsw and PS1-A246E mutations are a widely used AD model which may imitate the main pathophysiology process of AD. The present study was conducted in order to investigate the effect of varying caffeine doses on memory impairment and the expression of brain BNDF and TrkB in PS1/APP double transgenic mice.

Materials and methods

Drugs. Caffeine (lot number, 1001176428) was purchased from Sigma Corporation (St. Louis, MO, USA).

Animals. PS1/APP double transgenic mice (genetic background C57BL/6J), containing the human APPsw and PS1-A246E mutations, were obtained from the Institute of Laboratory Animals at the Chinese Academy of Medical Sciences (Beijing, China). Wild-type C57/BL6J mice were used as controls. All mice were housed in the Laboratory Animal Center of Liaoning Medical University (Jinzhou, Liaoning, China). All mice were maintained in an air-conditioned room with a 12-h
Cognitive ability of AD mice decreased and 1.5 mg/day of caffeine was capable of reversing cognitive impairment (7,8). The present study not only confirmed previous studies but also investigated the effect of caffeine intake (1.5 mg/day) on the cognitive impairment of hippocampal BDNF and TrkB in PS1/APP mice with a dose-response effect.

**Discussion**

Several studies have demonstrated that caffeine intake (1.5 mg/day) is capable of reversing cognitive impairment in AD mice (7,8). As the effect of different doses of caffeine on cognitive impairment and the expression of hippocampal BDNF and TrkB in PS1/APP mice have been poorly investigated, the present study was conducted. The results demonstrated that low (0.75 mg/day) and high (1.5 mg/day) doses of caffeine increased spatial learning ability and the memory expression of hippocampal BDNF and TrkB in PS1/APP mice with a dose-response effect.

It had been shown that the cognitive ability of AD mice decreased and 1.5 mg/day of caffeine was capable of reversing the cognitive impairment (7,8). The present study not only confirmed previous studies but also investigated the effect of low doses of caffeine (0.75 mg/day) on the cognitive impairment...
of AD mice. The results revealed that 0.75 mg/day of caffeine for eight weeks was capable of increasing spatial learning ability and memory in 12 month old PS1/APP transgenic mice. It has been reported that the oral administration of 3 mg/day of caffeine for two weeks was capable of improving cognitive impairment of 9.5 month old PS1/APP double transgenic mice (14). A previous study has demonstrated that 0.5 mg/day of caffeine in drinking water reduced the cholesterol-induced increase in Aβ and phosphorylated τ, which suggests that even particularly low doses of caffeine may protect against sporadic AD-like pathology (15). The varying doses of caffeine treatments in different studies may be caused by differences in the ages of mice or treatment time.

Studies have revealed that caffeine intake may reverse memory impairment and decrease the levels of Aβ in the brains of AD mice (7,8,14,16); however, the exact mechanism for the role of caffeine in memory impairment is unclear. Previous studies have indicated that the mechanism may be complex and involve a variety of aspects of memory ability. Long-term caffeine administration may improve memory by reducing the levels of Aβ through the suppression of the Aβ-producing enzymes, β- and γ-secretase (7,17). In another study, it has been demonstrated that caffeine is capable of decreasing the expression of pro-apoptotic phospho-JNK...
and phospo-ERK in the striatum and cortex, and stimulated PKA signaling in the striatum of APPswe mice. BDNF is crucial in neuronal plasticity, learning and memory. The levels of BDNF, and its main receptor TrkB, have been reported to decrease in AD. We hypothesized that BDNF and its receptor may be involved in the protective role of caffeine against memory impairment. Results of the present study have demonstrated that caffeine intake significantly increased the expression of BDNF, and its main receptor TrkB, in the brain, which is in agreement with our hypothesis. There is evidence to support our results. It has been demonstrated that BDNF, and TrkB, are capable of protecting against memory impairment and regulate neurogenesis in the hippocampus of AD (18). A recent study also supports the role of BDNF signaling through TrkB in the pathophysiology and cognitive deficits of AD (12). However, the exact mechanism of BDNF and its receptor involving caffeine in AD remains unclear and requires further investigation.

In conclusion, the present study reveals that 0.75 mg/day and 1.5 mg/day of caffeine for eight weeks is capable of reversing memory impairment in 12 month old PS1/APP transgenic mice, and BDNF and its receptor TrkB may be involved in the protective role of caffeine against memory impairment in AD.

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