CAFFEINE AND NEURODEGENERATIVE DISORDERS

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Abstract

Neurodegenerative disorders are amongst the most dangerous diseases in modern society. At the end of 1990, adenosine receptor antagonists were used to block the adenosine A1 and A2A receptors causing less physical, cellular and molecular damage caused by Alzheimer's and Parkinson's diseases. In recent years, an increase in death rate caused by these diseases has been observed among people under 74. Caffeine, as NMDA receptor antagonist, prevents an uncontrolled influx of calcium ions into the interior of the cells exerting a neuroprotective effect and beneficial procognitive effects. There is much evidence that caffeine intake is associated with a reduced risk of Alzheimer's and Parkinson's diseases.

Keywords: caffeine, adenosine, Alzheimer's disease, Parkinson's disease

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Caffeine

Caffeine is an organic chemical compound present in coffee, tea and various beverages. It is often consumed as a psychoactive substance [1]. Caffeine is one of the many constituents found in food [2]. Natural sources of caffeine are coffee beans, tea leaves, cocoa beans, guarana and mate which are added as ingredients to beverages (e.g. Coca Cola, Red Bull), food and medications (analgesic drugs, slimming drugs) [3, 4].

The main action mechanism of caffeine is to block the adenosine A_1 and A_{2A} receptors [5]. In low doses caffeine increases the activity of the central nervous system [6]. Caffeine causes stimulation of the adenylate cyclase activation and, as a result, it increases cAMP concentration in the cells. Inhibition of adenosine A_1 receptors is associated with an increased release of many neurotransmitters such as acetylcholine and dopamine [7,8]. In the case of Alzheimer's disease, compounds which block the breakdown of the neurotansmitter acetylcholine play a major role. Adenosine A_1 receptors are found in almost all brain areas especially in the hippocampus, the cerebral and the cerebellar cortex [9]. Adenosine A_{2A} receptors are present in the dopamine–rich regions of the brain, the striatum and the nucleus accumbens [9]. Inhibition of the adenosine A_{2A} receptor, unlike that of the A_1 receptor, leads to a decreased cAMP concentration in the cell [10]. In large doses, caffeine inhibits the phosphodiesterase which converts cyclic AMP (cAMP) in the cells into non–cyclic form, which causes an increased cAMP intracellular concentration [10].

Caffeine is completely (99%) absorbed in the gastrointestinal track after ingestion. Maximum caffeine concentration in the plasma is observed between 15 and 120 minutes after oral ingestion. Caffeine is distributed through the body, it penetrates all biological membranes, including the blood – brain barrier and the placental barrier [11]. Caffeine has a half–life elimination of approximately 4–6 hours. Its metabolism occurs almost completely in the liver [1, 12].

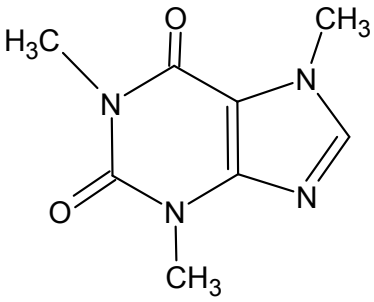

Fig. 1. The chemical structure of caffeine

Alzheimer's disease

Alzheimer's disease affects people mostly over the age of 65 and the risk rises quickly with age. If the

loss of neuronal cells is bigger than 60%, the brain cannot compensate for it and cognitive impairment becomes obvious[13]. It is a neurodegenerative disorder, which is manifested in progressive cognitive impairment [14]. It is diagnosed based on DSM–V diagnostic criteria [15]. Alzheimer's disease is neuropathologically characterized by the presence of extracellular amyloid plaques, which are composed of the β–amyloid (Aβ) protein and intracellular neurofibrillary tangles [16]. The amyloid plaques affect the calcium regulation of the cells, damage mitochondria, increase the amount of free radicals, induce of inflammation (activation of microglia and astrocytes) and degenerate cellular protein and DNA [17].

Tau protein is characteristic for nerve cells, is able to bind to microtubules, is responsible for the formation of the cytoskeleton of cells and ensures their stability. In normal conditions, tau protein is phosphorylated by protein kinase, which is the condition under which it works. If tau phosphorylation is too strong, it leads to patological changes in its structure. Instead of binding to microtubules, the particles of the protein begin to form aggregates called neurofibrillary tangles. Their accumulation leads to disruption of communication within the neurons, disorder in their functions and the death of cells. Tau tangles and β–amyloid are the most characteristic feature of Alzheimer's disease [18]. An experiment was carried out in mice with a genetically modified version of the tau gene, producing an abnormal form of the tau protein which tends to form tangles. The animals were divided into two groups: control, which was given a placebo and the other, provided with 0.3 grams of caffeine per litre of drinking water for several weeks. The studies showed, that the mice receiving caffeine regularly achieved a better result in a memory test. Imaging studies also showed a much smaller accumulation of harmful tau tangles in the brain of these animals compared with the control group [18].

Mice studies showed that adenosine receptor antagonists prevent the accumulation of β–amyloid peptide (Aβ peptide) in around the cerebral blood vessels. Moreover, permanent caffeine consumption can reverse cognitive impairment and decrease Aβ levels in mice's brain [16].

Zeitlin showed that caffeine treatment in transgenic model of Alzheimer diseases stimulate PKA activity, increases phospho–CREB level and decreases phospho–JNK level and phospho–ERK expression in the striatum and frontal cortex. All of this changes are beneficial for the brain function. The results suggest that caffeine increases neuronal survival and reduces neurodegenerative process [19]. Eskelinen and Kivipelto demonstrated that middle aged people, who drink 3–5 cups of coffee per day had decreased the risk of Alzheimer's disease to about 65% [20].

Another study shows the effect of different doses of caffeine on cognitive impairment and the expression of hippocampal BDNF (brain neurotrophic derived factor) and TrkB (main functional receptor) in transgenic mouse models. The results showed that low (0,75 mg/day) and high (1,5 mg/day) doses of caffeine increase memory, learning ability and expression of hippocampal BDNF and TrkB in mice [14].

Animal data show that caffeine intake has a positive effect on cognitive abilities, but in humans the data aree inconsistent. A control study carried out in men in Honolulu and Asia shows that caffeine consumption in midlife cannot be associated with AD after 25 years, but a lower risk of neuropathological lesions has been observed [21].

A case control study from Portugal has shown that caffeine consumption caused a lower risk of Alzheimer's disease [22]. Further studies from Finland have demonstrated that caffeine intake in midlife decreased the risk of AD and dementia [23], but there were no such associations among Finnish twins [24]. Cohort studies from France [25] and Portugal [26] have shown that caffeine intake prevented a decrease in cognitive functions among women and men under 65 years for four consecutive years.

Parkinson's disease

Four milion people around the world, including half a million in Europe suffer from Parkinson's disease (PD). It is one of the most common diseases of the nervous system. The recent results of epidemiological studies show that men tend to suffer from PD more frequently than women [27].

The basis of Parkinson's disease is a selective degeneration of dopaminergic neurons in the brain's nigrostriatal system [28]. It results in the imbalance between dopaminergic neurotransmitters (mainly between dopamine and acetylcholine) in the central nervous system. The characteristic symptoms of this disease are motor deficits like rigidity, bradykinesia and tremor which are the results of striatal dopamine deficiency [29].

The pathogenesis of Parkinson's disease is not fully understood. Among the factors leading to the death of dopaminergic neurons are neurotoxins and oxidative stress. Degeneration of the dopaminergic neurons occurs due to the cooperation of different mechanisms, exerting an influence on one another. Oxidative stress happens to be a result of the release of a large number of free radicals (e.g. iron ions) which degenerate the nerve cells by lipid peroxidation

membranes or apoptosis [30]. It has been shown that the active metabolite of MPTP (MPP+) selectively taken up by dopaminergic cells is an inhibitor of mitochondrial complex 1 in the respiratory chain and then starts the process leading to cell death [28].

Studies have shown that A_{2A} receptors cause antagonist interaction between adenosine and dopamine. Moreover, this receptor can affect the motor efficiency regardless of the dopamine receptors (D2) [31]. It was shown that A_{2A} receptors in animals causes sedation, catalepsy and that they are a motoric depressors as a consequence of dopamine receptor stimulation and reduce the agonistic affinity to D2 receptors [32]. Many reports show an important role of the A_{2A} receptor, over selective antagonists of these receptors (e.g. istradefylline, preladenant, SYN 115) and their potential use in Parkinson's disease [33]. It was shown that istradefylline reduces extrapyramidal movement disorders induced by MPTP [34]. Clinical studies in patients with Parkinson's disease have shown that preladenant was well–tolerated, shortened „off"–, prolonged „on"–periods and did not increase dyskinesias [35].

In recent treatment of Parkinson's disease besides levodopa dopamine agonists are also used. The advantage of the agonist use is a smaller risk of developing dyskinesias and motor fluctuation [36].

Epidemiological studies showed an inverse relationship between caffeine intake and the risk of Parkinson's diseases, which suggests that caffeine can exert neuroprotective action on humans [37]. Caffeine is bound to a neurotoxine (MPTP) which is responsible for the development of the disease in an animal model and this complex is discharged from the body, avoiding it's deposition in the brain. Ulanowska et al. have shown that caffeine forms insoluble complexes with the neurotoxin. Such complexes may be present in the alimentary canal, when the neurotoxin and the caffeine will be there together. Compounds which are dangerous for the body are removed so they do not get into other parts of the body. These complexes can be eliminated from the body, since they are insoluble and there is no absorption [29]. Chen et al. described treatment of mice where caffeine protected nigrostriatal dopamine neurons from neurotoxicity of 1–methyl–4–phenyl–1,2,3,6–tetrahydropyridine (MPTP), which showed caffeine neuroprotective action [38].

Conclusions

We often use caffeine present in coffee or coca cola. We should pay attention to the caffeine content in food because it can influence the body in various ways.

The information gathered in recent years shows the beneficial effect of caffeine on some neurodegenerative disorders. Moreover, these studies reveal that caffeine consumption can reverse cognitive impairment and improve memory in animal models.

Resumo

Neŭrodegeneradaj malsanoj estas inter la plej danĝeraj malsanoj de moderna societo. Fine de la 90–aj jaroj de la lasta jarcento adenozinreceptoraj antagonistoj estis uzataj por bloki adenozinajn A1 kaj A2A receptorojn, kiu kaŭzis malpli korpan, ĉelan kaj molekulan difekton kaŭze de la alchajmera kaj parkinsona malsano. En la lastaj jaroj pli altiĝo de la mortofteco kaŭze de tiuj malsanoj estis observita inter personoj, kiuj aĝis malpli ol 74 jarojn. Kafeino, NMDA receptorantagonisto, preventas nekontrolitan enfluon de kalciojonoj en la enon de ĉeloj, kiu havas neŭroprotektantan kaj la kognicion helpantan efikojn. Ekzistas multe da indikoj, ke la konsumo de kafeino malpliigas la riskon de alchajmera kaj parkinsona malsano.

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