American Journal of Alzheimer's Disease & Other Dementias®
Volume 23 Number 5
October/November 2008 417-422

10.1177/1533317508320083
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Caffeine: Neuroprotective Functions in Cognition and Alzheimer's Disease

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Alzheimer's disease is a common problem in our elderly population. Although research is leading to improvements in our understanding of the underlying biology, we still have little understanding of the environmental risk factors associated with this disorder. Caffeine, an easily modifiable environmental factor, may have a protective effect on the likelihood of developing Alzheimer's disease. This article reviews the association between caffeine from both a biologic and epidemiologic perspective. Further studies are needed to determine whether caffeine consumption could have a major affect on the development of Alzheimer's disease or age-related cognitive decline.

Keywords: caffeine; Alzheimer's disease; aging; cognition; adenosine receptors; epidemiology; risk factors

Alzheimer's disease (AD) is a medical, economic, and emotional burden on affected individuals and their families. The cumulative burden of AD is expected to increase substantially in the coming decades, with a projected prevalence by 2050 of between 6 and 10 million persons in the United States.[1] There are currently no cures and only limited treatment options for this disease; consequently, much recent research has focused on the prevention of AD.

Caffeine, a widely consumed methylxanthine, is well characterized as a neuromodulator, with known effects on motor behavior, information processing, and cognitive performance. In addition, some evidence suggests that caffeine can enhance learning and memory and may have neuroprotective properties. A protective role for caffeine has been hypothesized or studied for a number of neurodegenerative diseases, including Parkinson disease,[2,3] ischemic damage, [4] Huntington disease,[5] and fetal methylmercury poisoning.[6] Research has indicated that caffeine or coffee consumption may improve cognition in the elderly and may protect against AD.[7-12] Other studies, however, have shown no such role for caffeine.[13,14]

Much work has been done on the basic physiology of caffeine in the brain, and these results have supported the theory that caffeine plays a neuroprotective role in the aging brain. This article presents the existing evidence for caffeine's neuroprotective functions in cognition and AD. First, the physiologic properties of caffeine relevant to these are presented. Laboratory findings related to AD pathology and cognition are reviewed. Finally, human experimental and epidemiologic studies are summarized and reviewed. Given the widespread use, social acceptability, and the relative lack of side effects from its consumption, caffeine use may prove to be an important, modifiable, protective factor for AD and cognitive decline with aging.

Physiologic Properties

Caffeine has been shown to have a variety of effects in the brain. At the ranges of normal daily consumption, which is approximately 2.4 to 4.0 mg/kg (2 to 4 cups of coffee) per person,[15] the primary physiologic action of caffeine is nonselective antagonism of adenosine receptors. Of particular importance are the high-affinity A_1

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and A_{2A} receptors and, to a lesser extent, the widespread, low-affinity A_{2B} and the high-affinity low-density A_3 receptors.[16] The physiologic role of these receptors and their agonists and antagonists has been widely studied in recent years.[15-17]

Adenosine is a ubiquitous nucleoside that is considered a homeostatic regulator.[16] It has important biochemical actions, including signal transduction and energy transfer, and is directly involved in communication between nerve cells. Adenosine and its receptors have been implicated in a range of neurologic properties, including regulation of sleep, anxiety, memory, and cognitive performance.[16]

The most widely distributed adenosine receptors in the brain are the A_1 receptors. They are found in nearly all regions of the brain and in relatively high concentrations in the hippocampus, cortex, and cerebellum.[16] The A_1 receptors are inhibitory, and the excitatory effects of caffeine can largely be explained by antagonism of these receptors. The A_1 receptors have been found to inhibit excitatory neurotransmitter release and reduce the firing rate of neurons in the central nervous system.[15] Therefore, blockade of these receptors by caffeine may explain the increased cognitive abilities seen with caffeine consumption.

The A_{2A} receptors are found less frequently in the nervous system and are most dense in the basal ganglia.[16] In contrast with A_1 receptors, the A_{2A} receptors are largely excitatory. Blockade of these receptors has consistently been shown to be neuroprotective.[6,17-19] This role likely occurs through a combination of actions, including anti-inflammatory effects, glial activation, and enhanced glutamate outflow.[20] Blockade of both A_1 and A_{2A} receptors has been posited to protect against AD and enhance cognitive performance in the elderly. A combination of effects from both receptors is likely responsible for the observed results.

The A_{2B} and A_3 receptors have been less well characterized, but there is some evidence that their blockade could play a role in caffeine's effects on cognition. The A_{2B} receptors are excitatory and are involved in long-term potentiation.[21] Activation of the A_3 receptor enhances inflammatory processes in the brain,[16] indicating that A_3 antagonists are likely neuroprotective. In addition, a high level of A_3 receptor activation has been demonstrated to trigger cell death.[16]

Other properties of caffeine-containing beverages have been hypothesized to play a part in neuroprotection. Coffee is the primary source of antioxidants in Western diets, and tea is also a significant contributor.[22] The polyphenols found in these beverages counteract free-radicals that can cause oxidative damage to neurons and other cells.[22] In addition, caffeine has been demonstrated to increase the transcription factors activating protein (AP)-1 and *c-fos*, which enhance cell proliferation and defend against cell damage.[23] Caffeine also increases the rate of cerebral glucose utilization,[15] which could contribute to enhanced cognitive functioning.

The potential neuroprotective effects of caffeine consumption are likely explained through long-term intake rather than the short-term exposures that have typically been assessed in experimental models. Long-term intake of caffeine, typically 2 to 6 weeks of free access for in vivo models, leads to favorable adaptive changes in the brain.[15] In contrast, short-term administration of caffeine and other adenosine receptor antagonists at the time of neurologic insult can have negative affects. Administration of caffeine at the time of an ischemic event has consistently been shown to enhance neuronal damage.[17] In contrast, when caffeine was given long-term to experimental animals in the few weeks before ischemic insult, neuronal damage was lessened and survival was enhanced.[17] Changes in receptor densities have been demonstrated after long-term, but not short-term, administration of caffeine in animal models. In particular, adenosine A_1 and acetylcholine receptors are up-regulated in animals that have been given caffeine, whereas A_{2A} receptors remain unchanged.[23] However, human positron emission tomography studies have not confirmed these findings for A_1 receptors.[24]

Of particular interest in AD, adenosine antagonists appear to have an enhanced neuroprotective role in the presence of β-amyloid deposition or cholinergic deficits. Experiments in both animal models and in vitro cultures have demonstrated that caffeine can reduce the negative effects of β-amyloid. Cultured cells exposed to β-amyloid had reduced rates of death in the presence of caffeine.[19] Long-term caffeine treatment of mice prevents cognitive decline after injection of β-amyloid compared with animals with no pretreatment.[18] In addition, suppression of β-amyloid production has been demonstrated in Alzheimer's (APPsw) transgenic mice, with a concurrent increase in cognitive performance after long-term exposure to caffeine.[25] No similar improvement in wild-type mice with long-term caffeine administration was observed. These effects appeared to be mediated through reduced expression of presenilin-1 and β-secretase.[25] In

comparison, agonists of the A_1 receptor increased production of soluble forms of the amyloid precursor protein in cell culture.[26]

Caffeine also has an affect on acetylcholine and its receptors in the brain. Both long- and short-term administration of caffeine to rats increased the acetylcholine concentration in the prefrontal cortex.[27] Unlike the response seen for dopamine, the acetylcholine response showed no tendency to tolerance. The increase in prefrontal cortex acetylcholine concentration did not taper with prolonged caffeine exposure.[27] This may occur through either inhibitory effects on acetylcholinesterase or increased release of acetylcholine, both of which have been demonstrated in experimental models at concentrations of caffeine comparable with human consumption.[28,29] Further, long-term ingestion of caffeine by mice increased the number of muscarinic and nicotinic receptors in the brain and may also have increased their cholinergic function.[30] However, the concentration of caffeine given to these animals was higher than would normally be ingested by humans.

Our understanding of the effects of caffeine in the brain is fairly comprehensive. However, much of the research that relates to protection from AD has been completed in in vivo models and some at concentrations much higher than are typical for people. Replication in human tissue of results relevant to AD pathology from animal and cell culture studies should be the primary focus of ongoing research. Specifically, changes in adenosine and cholinergic receptors need to be further assessed in humans. In addition, the provocative evidence for the protective effects of caffeine in the presence of β-amyloid should be extended to human studies.

Human Studies

A number of observational and experimental human studies have been conducted to determine the role of caffeine in neuroprotection and maintenance of cognitive abilities. Although there is no consensus from the results, several studies have demonstrated improved cognition after long-term caffeine consumption. The effects on cognition have consistently been greatest among the oldest age groups and in women.

Several studies of the effect of caffeine on human cognition have focused on the effects from short-term exposures.[15] These studies have largely found that caffeine response is limited to increased attention and response times rather than improvements in higher-level functions such as memory or information processing.[15,31] Brief exposures to caffeine have been shown to improve memory and cognitive function in the presence of scopolamine-induced impairments.[32] Scopolamine creates cholinergic blockades that mimic the deficits in memory and cognition seen in AD. This suggests that caffeine may be most important in overcoming cholinergic deficits rather than improving function in cognitively normal individuals.

In contrast to the results seen with short-term exposures, multiple studies have shown that long-term consumption of caffeine, or coffee, for decades may result in improved cognitive abilities or may reduce the decline of cognition and memory that are part of the pathologic aging process. Studies that have assessed cognitive abilities longitudinally have consistently shown the greatest effect of long-term caffeine consumption among the oldest individuals.

The Three Cities Study, a longitudinal study of 7017 French men and women, found a lower loss of cognitive abilities, as assessed at the 4-year data collection, among women who consumed high levels of caffeine compared with low consumption and nonconsumers.[7] No comparable effect was seen among men in their study.

A cross-sectional analysis of the Rancho Bernardo cohort, consisting of 1528 participants, found a similar association between both current and lifetime consumption of coffee and cognitive function among women, but not among men.[9] The strongest associations were found for women aged older than 80 years, with high consumers in this group performing significantly better on 11 of the 12 administered cognitive tests than nonconsumers and low consumers.[9]

A study conducted with 676 men in Finland, Italy, and the Netherlands found a significant association between coffee consumption and cognitive function after 10 years, with those consuming 3 cups of coffee a day having the smallest decline.[11]

An analysis of the Maastricht Aging Study found a cross-sectional association between habitual caffeine consumption and long-term memory for its 1875 participants, who were aged 24 to 81 years.[33] However, these results were not replicated in a longitudinal follow-up of 75.6% of the original cohort 6 years later.[14] In addition, neither Maastricht analysis found improvements in short-term memory or an effect by age. No analyses by sex were reported.[14]

The combined human and animal data demonstrating a role for caffeine in overcoming cholinergic deficits and β-amyloid insults has led to the hypothesis that habitual caffeine consumption is protective against AD. Limited data have been published regarding this association, and results have been inconclusive. Further, it is unclear from these data whether caffeine may be affecting AD incidence or delaying progression. The most cited article on caffeine and AD prevalence is based on a case–control study performed in Portugal in which 54 cases were compared with 54 controls.[10] The authors found a significantly lower average daily intake of caffeine during the previous 20 years among cases compared with controls (odds ratio, 0.40; 95% confidence interval, 0.25-0.67). A number of other factors, such as diabetes mellitus, vitamin E intake, and family history of dementia, were assessed, and contrary to other studies, no associations with AD were found.[10]

The results of longitudinal data have been less consistent. Results from the Canadian Study of Health and Aging (CSHA) found a lower incidence of AD during 5 years among coffee consumers compared with nonconsumers, but not among tea drinkers.[12] In this study, AD risk was lowered by 30% among coffee drinkers after adjustment for age, sex, and education.[12] The Manitoba Study of Health and Aging (MSHA), a parallel study to the CSHA with some subjects enrolled in both, found no difference in AD incidence during 5 years by coffee consumption after adjustment for age, sex, and education.[13] A nonsignificant protective effect was seen for tea drinkers (odds ratio, 0.46; 95% confidence interval, 0.20-1.06). However, these results from the MSHA were based on a small number of AD cases (36 of the 694 subjects),[13] and neither the MSHA nor the CSHA was specifically designed to assess caffeine intake or AD risk.

The Three Cities study that found a longitudinal protective role for caffeine in maintaining cognitive ability in women found no association with dementia or AD incidence over 4 years.[7] Unlike the other studies described here, the Three Cities study used *Diagnostic and Statistical Manual of Mental Disorders-IV* criteria for the dementia diagnosis rather than the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association riteria.[7,10,12,13]

A comparison of studies that have investigated the associations between caffeine consumption and both cognitive decline and AD is complicated by methodologic differences. Some studies measured only coffee consumption,[9,11] whereas others assessed multiple sources of caffeine, including medications and energy drinks. Among the studies that assessed several sources of caffeine, some reported separate associations for coffee and tea,[12,13] and others reported associations for combined sources.[7,10,14,33] Consumption has been measured as milligrams per day,[10] cups per day,[7,9,11,14,33] and as "regular" consumption.[12,13] In addition, only 2 studies have attempted to measure lifetime consumption[9,10] rather than consumption at the study's baseline. Mental status has been measured using a broad range of cognitive tests, with only limited overlap between studies, and AD assessment has been completed using different diagnostic criteria.

Despite the difficulties in comparing studies, some conclusions appear warranted. The Rancho Bernardo study,[9] which found an inverse association between coffee consumption and decline in cognitive performance among women, and the Portuguese case–control study,[10] which found a protective effect for caffeine in AD prevalence, were best designed for assessing the effect of long-term caffeine consumption. Both asked about consumption over the lifetime rather than current use at the study baseline. Caffeine consumption has been shown to decrease as people age[10]; therefore, baseline measures may not accurately reflect the lifetime consumption patterns that are more likely to result in significant adaptive changes in the brain. However, both of these studies are vulnerable to the inherent biases related to retrospective data collection, namely recall bias and misclassification due to inaccurate recall.

Conclusions

The combined evidence for a protective effect from caffeine on cognitive functioning and AD incidence is promising. In vitro and animal studies have provided compelling physiologic support for caffeine's neuroprotective effects against and in the presence of AD pathology. Human studies have begun to demonstrate the presence of similar associations in the aging population. However, because of the conflicting results from some longitudinal studies, there is no consensus about the role of caffeine in AD onset. In addition, comparison of results between

studies is complicated by the lack of standard methodology for the measurement of caffeine consumption and cognitive capacity, and the diagnostic criteria for AD.

The published research raises additional questions; does caffeine prevent AD onset or simply slow progression? Why have the greatest effects been found among the oldest individuals (typically older than 80) and among women? Are the effects seen caused by caffeine's antagonism of adenosine receptors or to other properties of coffee and tea, the primary sources of caffeine in the studied populations? Also, does caffeine alter the effect of cholinesterase inhibitors in the AD population?

Elucidating the mechanisms by which caffeine or caffeine-containing beverages affect cognitive decline and pathologic changes specific to AD could lead to new avenues of research in pharmacologic treatments or preventive strategies for AD. Further research specifically designed to answer these questions is needed. The reported effects of caffeine on AD incidence have been on the order of a 30% to 60% decrease.[10,12,13] Such a significant decrease could represent a substantial reduction or delay in AD incidence from a socially acceptable and generally safe compound.

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