The Effects of Coffee Consumption on Cognition and Dementia Diseases

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Abstract

Normal aging is accompanied by diminishing motor and cognitive performances that are exacerbated or accelerated in neurodegenerative diseases such as Alzheimer’s disease (AD) or Parkinson’s disease (PD). Coffee/caffeine is regularly consumed by many people around the world providing a psychoactive stimulant resulting in enhanced alertness, arousal and improvement of cognitive performance. This review presents the science surrounding coffee, caffeine and its impact on cognition for the elderly. There is now considerable knowledge obtained from epidemiological evidence and animal studies, that 3 to 5 cups of caffeine-coffee improves-corrects, positively changes the trajectory of age-related neurodegenerative decline, supporting the healthy aging effects of coffee consumption for dementia prevention and AD. With time, life doesn’t get better by chance - it gets better by change.

Keywords: Caffeine; Healthy aging; Neurodegeneration; Neuroprotection

Introduction

Alzheimer’s disease (AD) is the most common disease of aging, currently incurable with a long and progressive course. The first defined pathological features of AD are extracellular amyloid plaques and intracellular neurofibrillary tangles in the hippocampus. Studies related to autosomal dominant AD [1] found that the disease process starts 20 years prior to the onset of dementia. The incremental neuronal damage caused by non-sequestered amyloid oligomers is the early pathological event and accumulates over time eventually leading to neurodegeneration and then widespread cognitive impairment [2,3]. Therefore for aging societies, AD is no longer a growing threat but a global health problem and it is a problem for and of our age. The World Health Organization [4] reported that in 2010 an estimated 35.6 million people were suffering from dementia and the 2050 projection of people living with dementia is 115 million. Now every 4 seconds there is a reported case of dementia. The biggest challenge facing scientists is the human brain and sustaining healthy brain aging.

Nature is not only inspirational, but may have created therapeutic agents for combating AD. Plant derived dietary-medicinal compounds termed nutraceuticals represent classes of molecules/phytochemicals that are generally less potent and have fewer side effects than pharmaceuticals. A snapshot of some nutraceuticals [5-18] in common usage to combat AD is shown in Figure 1. The multiple binding modes of EGCG, curcumin and resveratrol to Aβ, specifically to the 17-42 peptide [19,20] portion, derived from sequential cleavage of APP by α-, γ-secretases present in AD amyloid plaques has been described using computational studies. This indicated that the dominant interaction occurs with the central hydrophobic core region involving Aβ residues [17-21] with the implication that these nutraceuticals may interfere with Aβ oligomerization. The nutraceutical aromatic ring hydrophobic π-π interactions with like residues of the Aβ peptide can inhibit the early stages of the molecular recognition-structural transition of the monomers that results in the formation of amyloid protein toxicity.

Figure 1: Some nutraceuticals that reduce Aβ toxicity in AD.

Caffeine Characteristics

Caffeine in coffee is the most popular natural drug in the world [21,22] with more than 2.25 billion cups consumed daily. Some of its characteristic effects are listed in Table 1. It has multiple molecular targets [23] and therefore exhibits many affects, and is regarded as a safe substance for most people. It can easily pass the BBB and it appears to directly affect cognitive processes. This review examines the evidence and the surrounding science of coffee, its consumption and its therapeutic value to combat neurocognitive impairments and AD with aging.

There are many compounds present in coffee [24] with caffeine, caffeic acid and chlorogenic acid (CGA) the three most abundant components. For a regular coffee consumer [three cups per day] this amounts to an approximate daily intake of 500 mg, 500 mg, 1000 mg of these natural products [25-27]. Coffee roasting via the Maillard reaction converts some free CGAs into melanoidin-CGAs combinations, with this bound form contributing 25-47% of the brews antioxidant activity [28]. The potential formation of polyphenol-protein complexes with simultaneous coffee-milk consumption [29] may limit the bioavailability of CGAs and trans-cinnamic acid derivatives. Computational studies of the various mechanisms by which caffeine and caffeic acid are involved in scavenging hydroxyl...
free radicals concluded that radical adduct formation as the most likely mechanism involved. However it was found that caffeine is inefficient in directly scavenging oxygen superoxide anion, \( O_2^- \) and methylperoxyl \( \cdot \text{OOCH} \) radicals and most likely other alkylperoxyl radicals. The C8 atom for caffeine [30] and the phenolic-C4-atom of caffeic acid [31] are the most reactive sites for adduct formation with hydroxyl radicals that are further stabilized by resonance delocalization.

### Table 1: Caffeine characteristics.

| Description                                                                 | Caffeine conclusions                                                                 |
|----------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Caffeine absorption from the GI tract [32,33]                             | Peak concentration is reached after 30 minutes of ingestion with a half-life period of approximately 4 h. |
| One effect of caffeine is in the lengthening the post firing duration in the hippocampus [34,35] | This effect lasts longer than the changes induced by caffeine on the EEG.             |
| Caffeine and persuasion [36]                                               | Evidence exists for caffeine increasing the systematic processing of persuasive messages. |
| Does the ingestion of a controlled amount of caffeine improve Working Memory? [37] | Caffeine was associated with a significant increase in alertness. Significantly shorter response times were recorded with caffeine compared to placebo. |
| Does caffeine consumption improve cognition?                               | Functional magnetic resonance imaging data suggests an effect on brain areas engaged in specific cognitive processes rather than a general effect due to the influence of caffeine on the vasculature [38] |
| Does caffeine improve accuracy?                                            | Caffeine has fewer side effects than other treatments for cognitive decline, and it requires a relatively small amount for a beneficial effect. The benefits increased with age – coffee drinkers being 30 percent less likely to have memory decline at age 65 and rising to 70 percent less likely over age 80. |
| Elderly women [85 years and older] who drank three cups of coffee or more a day had better [less cognitive decline] working and storage memory compared to controls [39] | Caffeine consumers did not seem to have lower rates of dementia. |
| A longer study is required to examine if caffeine prevents dementia; perhaps caffeine slows the dementia process rather than preventing it. | The age-related memory deficit was reversed by treatment with caffeine or SCH58261. Treatment also significantly normalized oxygen and nitrogen reactive species levels that are increased in brains of aged rats. |
| The effects of caffeine and SCH58261, a selective A2A receptor antagonist, on memory impairment and oxidative stress generated by aging in rats were investigated [40] | Caffeine in a performance bar can significantly improve endurance performance and complex cognitive ability during and after exercise. |
| Examination of the effects of ingesting a performance bar, containing caffeine, before and during cycling exercise on physical and cognitive performance [41] | Habitual consumers of only high doses (400 mg) of caffeine can produce beneficial changes in visual attention. These results carry implications for the theorized interactions between caffeine, acetylcholine release via blockade of A1 adenosine receptor [53,54]. |
| Can low caffeine consumption enhance both vigilance and the executive control of visual attention? Examination of the effects of four caffeine doses (0 mg, 100 mg, 200 mg, 400 mg) | Does caffeine consumption improve accuracy? Caffeine had no significant effect on cognitive performance. |
| Consumption of coffee was significantly related to slower cognitive decline [48]. | Not only caffeine but also the bioactive compounds in coffee consumed in reasonable amounts, may reduce both motor and cognitive deficits in aging [50]. |
| Chronic caffeine administration to APP transgenic mice significantly improved cognitive performance and reduced levels of A\(\beta\)40 and A\(\beta\)42 production [49]. The intake also caused an attenuation in PS1 and BACE1 protein expression. | Is a non-selective A1 and A2 adenosine receptor antagonist leads to increased cognitive performance with habitual consumption [51]. |
| Neuroprotective actions of caffeine                                         | Is neuroprotective toward A\(\beta\) induced neurotoxicity in cultured neurons of rats [51]. |
| Coffee consumption in stressful situations inversely correlates with the incidence of depression [44]. | Is protective against A\(\beta\) induced neuronal damage in mice [52]. |

### Coffee may reduce the risk of T2DM

Evidence from epidemiological research suggests that coffee consumption is inversely related with the risk of type 2 diabetes mellitus (T2DM). Recent in vitro studies of the suppression of oligomerization and fibrillation of human islet amyloid polypeptide (hIAPP), a key indicator of T2DM by 3-caffeoylquinic acid supports this assertion [43]. This is not without precedence since the green tea polyphenol (\(\cdot\)epigallocatechin-3-gallate (EGCG) and black tea theaflavins (Figure 1) can inhibit the toxic amyloid aggregation [10] of A\(\beta\) in AD and a-synuclein in PD. Further studies are required to determine the molecular mechanisms of the coffee constituents on inhibition of the toxic aggregation of hIAPP.
Prevented neuronal damage, synaptotoxicity and cognitive deficit in rats induced by Aβ, comparable to the actions of the A2 adenosine receptor antagonist SCH 58261 [55].

Has been shown to attenuate Aβ production in APPswe mice [49,56] and also a high cholesterol-fed rabbit model of sporadic AD [57].

Modulates tau phosphorylation in human neuroblastoma SHSY5Y cells via Akt pathway, regulating the activity of the tau kinase glycogen synthase kinase 3β [58].

Stimulates an increase in Aβ production from ryanodine receptor-regulated intracellular calcium release channels [59].

In cellular models [60,61] to probe neurodegeneration and cell death evoked by Aβ and aggregated tau, caffeine was the most promising therapeutic drug candidate showing high efficacy in both the APP (77%) and tau-induced models (72%) recovery.

Studies have indicated [62] that the immunomodulatory actions of caffeine are mediated via nonselective inhibition of cyclic adenosine monophosphate (cAMP)–phosphodiesterase (PDE). It raises intracellular cAMP, activates PKA [63,64] inhibits TNF-α [60,65] leukotriene synthesis [66] and reduces inflammation. The claim that many of these effects occur at concentrations that are relevant to normal human coffee consumption is controversial [62].

A2A antagonists and the receptor pathways of PD

The neurological effects of caffeine are due in large part to its activity at human hA2A receptors, which are abundant in the nucleus accumbens, olfactory tubercle, and striatum, where they are co-localized with dopamine D2 receptors [67]. Epidemiological studies [68] have illustrated that caffeine consumption is associated with a decreased risk of developing PD making A2A adenosine receptors an important pharmacological target for PD therapy. Furthermore antagonists of A2A receptors in the striatum can potentiate the response of dopamine agonists acting at D2 receptors in the same location. Indeed preclinical and clinical studies have provided evidence of the ability of A2A antagonists such as istradefylline, an analogue of caffeine (Scheme 3) improvement in the mobility of PD patients [69-72] by enhancing the therapeutic effects of L-DOPA and reduce motor complications such as wearing off, dyskinesias and on/off phenomena deriving from its pulsatile long-term treatment [73,74]. It has been established that A2A receptors are co-expressed with dopaminergic D2 receptors in striatopallidal GABA neurons, where they form hetero-dimeric complexes able to decrease the D2 affinity for dopamine when the A2A receptors are stimulated [70, 75,76]. The A2A antagonists therefore enhance the therapeutic index of L-DOPA and D2 agonists by blocking the A2A receptors in these A2A–D2 heteromers [76,77] Moreover, A2A antagonists are able to reduce the L-DOPA induced dyskinesias by restoring the appropriate balance between A2A receptors and D2 receptors [78-80]. The neuroprotective effects of A2A antagonists are considered as potentially useful in preventing the onset and development of PD [81-83] The A2A antagonists emerge, therefore, as a class of efficacious antiparkinsonian drugs for the future, whose co-administration with L-DOPA appears significant for both the early stage and long-term treatment of PD.

There is a productive focus to discover selective and potent A2A antagonists for drug development that either alone or as multi-target antiparkinsonian strategies for the treatment of neurodegenerative movement disorder.

Human Studies of the effects of coffee consumption on dementia and AD (Table 2)

| Human Studies                                                                 | Outcomes                                                                                     |
|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Findings of two large cross-sectional population studies investigated regular  | Improvement of cognitive performance in older subjects (55+).                               |
| coffee intake                                                                  |                                              |
| The Maastricht Aging Study in southern Netherlands [86]                        | Confirmed the link between coffee consumption and enhancement of cognitive function in healthy individuals. |
| Survey of coffee drinking habits 20 years prior AD diagnosis [87]              |                                              |
| Canadian Study of Health & Aging                                              | AD patients consumed less caffeine than age-matched individuals without AD.                  |
| survey of 4,615 subjects, 5-year follow up with 194 AD plus 3,894 healthy     |                                              |
| controls [88]                                                                  |                                              |
| The FINE study of 667 healthy men born [1900-1920] in Finland, Italy,         | Confirmed that the men with intake of 3 cups of coffee had the least cognitive decline.     |
| Netherlands [89]                                                              |                                              |
| The French Three Cities studied of the coffee drinking habits of 4,197 women,  | Found that women without dementia drinking over 3 cups of coffee per day, the psycho-stimulant properties of caffeine appear to reduce cognitive decline, especially at higher ages. No impact was observed on dementia incidence. |
| 2,820 men [39]                                                                |                                              |
| The Cardiovascular Risk Factors, Aging, and Dementia study examined the       | The coffee drinkers at midlife were 65% less likely to develop dementia and AD in later life relative to persons drinking little or no coffee. Scope of study: 1,409 aged 65-79; 21-year follow up with 61 cases demented, 48 AD patients. |
| causal connection between coffee/tea intake at midlife and consequent         |                                              |
| development of dementia [90]                                                  |                                              |
| Studies on a cohort of 648 Portugal subjects aged >65 years was conducted to   | Cognitive evaluations indicated that caffeine intake >62 mg/day supported the negative association between caffeine and cognitive decline in women. |
| quantify the association between caffeine intake and cognitive decline [91]     |                                              |
| Despite methodological heterogeneities, the systematic review and meta-analysis of four studies [89] published [2004] suggests an inverse relation of coffee consumption and AD. |                                              |

Caffeine – analogues.

Scheme 1: Snapshot of the neuroprotective actions of coffee – caffeine – analogues.
The latest case-control studies of 124 elderly (65-88 years) subjects equated blood plasma caffeine values \([92,93]\) with dementia progression rates. The incidence of dementia was higher in subjects with plasma caffeine levels below 1200 ng/mL (\(\approx 6 \mu M\)) and the analysis of 3 cytokine biomarkers \([GCSF, \text{ IL-10 and IL-6}]\) were also found to be lower.

Table 2: The evaluation of human coffee consumption studies on dementia and AD.

| Summary |
|---|
| Low doses of caffeine non selectively block inhibitory adenosine A1 and A2A receptors resulting in increases in CNS activity and stimulation. Adenosine A2A is co-localized with DA receptors and occurs mainly in the striatum. The antagonistic A2A-D2 receptor interactions underlie the anti-PD effects of caffeine and those of more potent A2A antagonists. Structure based drug design, fragment based drug design and other technologies have injected a new productive focus into A2A antagonist discovery. Epidemiological data reveal that caffeine appears to reduce cognitive decline in the elderly, has fewer side effects, with relatively small amounts providing a beneficial effect. Importantly, the cognitive benefits increase with age - coffee drinkers being 30 percent less likely to have memory decline at age 65 and rising to 70 percent less likely over age 80. The mechanisms and influences of dietary molecules such as caffeine/coffee on brain health, mental function and cognitive ability are not completely understood. Further research on how natural products influence cognition will help to optimize the nature of diets to increase and extend the longevity of mental fitness with aging and resist dementia and AD. There are limited and inconsistent findings from longitudinal studies. Many of the studies that proposed a causal relationship between coffee consumption or plasma caffeine levels with incident mild cognitive impairment and its progression to dementia were too limited to draw any conclusion \([94]\). Coffee is readily available, low in cost with multiple benefits. Caffeine’s prophylactic effects in slowing cognitive decline are promising in humans, and compelling in animal studies. The impact of potential caffeine-coffee molecular synergies on biomarker patterns and their changes with aging needs further investigation and should be included in further studies \([95]\). In vitro and pre-clinical animal models have identified and suggested potential neuroprotective mechanisms of action of some or many of the bioactive components of coffee, however to the best of our knowledge, no evidence has been gathered from randomized controlled trials. It is difficult to obtain definitive evidence for the cognitive corrections and brain-benefits derived from caffeine consumption, as there are currently no adenosine receptor antagonists or therapeutic options approved for the treatment of patients with dementia or AD to compare and evaluate the effects of caffeine on these receptors. As the global growth of dementia continues, coffee can turn down dementia. However this needs to be confirmed with RCT evidence. More translational research is needed to make available FDA approved A1A, A2A receptor antagonists. In the meantime we should encourage safe and regular coffee consumption [3 cups daily] be included with other dietary health approaches across the lifespan, for neuroprotection and for promotion of healthier old age. Acknowledgments The work presented in this perspective is part of our ongoing interdisciplinary research collaboration with colleagues at RMIT University and around the globe. We are grateful for their contributions of high quality research to study dementia and AD. There is sufficient scientific evidence to suggest that making small changes such as increasing coffee consumption by the elderly will make a big positive cognitive impact and providing the healthy way to ‘living longer, living better’ aged care welfare strategy for our society. This is an innovative self-help way of preventing cognitive decline, fighting dementia and AD that empowers the aged, enabling them to cope with a better cognitive future. The low cost-high benefit, and the direct human impact of this natural product, has quite enormous future implications for everyone. References 1. Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, et al. (2012) Clinical and biomarker changes in dominantly inherited Alzheimer’s disease. N Engl J Med 367: 795-804.
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