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From epidemiology to pathophysiology: what about caffeine in Alzheimer's disease?

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Abstract

Alzheimer's disease (AD) is the most prevalent form of dementia in the aged population. Definitive diagnosis of AD is based on the presence of senile plaques and neurofibrillary tangles that are identified in post-mortem brain specimens. A third pathological component is inflammation. AD results from multiple genetic and environmental risk factors. Among other factors, epidemiological studies report beneficial effects of caffeine, a non-selective antagonist of adenosine receptors. In the present review, we discuss the impact of caffeine and the adenosinergic system in AD pathology as well as consequences in terms of pathology and therapeutics.

Keywords

Alzheimer's disease; caffeine; adenosine receptors; adenosine; epidemiology; A2A

1. Alzheimer's disease pathology

AD is the most frequently encountered form of dementia. In most cases, AD appears as a sporadic multifactorial disease resulting from the interaction of different environmental, epigenetic and genetic factors [1]. Various epidemiologic studies have allowed the identification of "risk factors" and "protective factors". High blood pressure, diabetes and obesity are detrimental factors [2–4]; while physical and intellectual activities, as well as fish consumption have protective effects [5 and references herein, 6].

The definitive diagnosis of AD is based on the observation of characteristic brain lesions: senile plaques and neurofibrillary tangles. Senile plaques are characterized by the extracellular accumulation of the amyloid-beta peptide (A β) while neurofibrillary degeneration is due to the pathological accumulation in the neurons of the naturally present Tau protein. A β peptides derive from a precursor called β APP (β -Amyloid Precursor Protein) through the combined action of two distinct proteolytic enzymatic activities, β - and γ -secretase releasing N- and C-terminal fragments of A β peptides, respectively [7, 8]. Notably, soluble A β oligomers are thought to be the most neurotoxic species driving the detrimental impact of amyloid pathology [9 and references herein]. Neurofibrillary degeneration arises from the intraneuronal accumulation of proteinaceous fibrils in paired helical filaments (PHF) made of hyperphosphorylated Tau proteins, forming flame-shaped neurons [for reviews see 10, 11]. Tau is a neuronal protein located within the axonal compartment, essential for the organization, stabilization and dynamics of microtubules [10, 11], but recent data also emphasize that Tau has additional important neuronal functions at the dendritic and nuclear levels [12–14]. The physiologic and pathologic functions of Tau are also regulated by post-translational modifications, such as phosphorylation. Changes in Tau phosphorylation may affect multiple Tau functions and facilitate Tau aggregation [10, 11]. Importantly, spreading of the neurofibrillary lesions in the cortex (first entorhinal cortex, then hippocampus, and lastly neocortex), corresponds to the progression of the symptoms [15]. This supports that Tau pathology is instrumental in cognitive alterations as stressed by observations that it impairs various forms of synaptic plasticity and cognitive tasks in mouse models [16–21]. Finally, neuroinflammatory processes are considered as a third pathological component in AD as recently pointed out by several genetics studies [13, 22]. While their respective contribution to the amyloid and Tau sides of AD remain unclear so far, astrogliosis and neuroinflammatory events, especially those mediated by microglial cells, have an instrumental role in AD. Extensive description of their role in AD is beyond the scope of the present paper and has been reviewed elsewhere [23, 24].

2. Caffeine and Alzheimer's disease: from epidemiology to pathophysiology

The methylxanthine caffeine (1,3,7-trimethylxanthine) is the world's most popular psychoactive drug. The reason for this popularity lies in its psychostimulant properties combined with the absence of substantial negative side effects. Caffeine is contained in coffee, tea, soft drinks and chocolate. Overall, the psychostimulant properties of caffeine are due to its ability to interact with neurotransmission in different regions of the brain, thereby promoting behavioural functions, such as vigilance, attention, mood and arousal as well as improvement of cognition [25].

In Humans, cognitive benefits of caffeine have been reported [26]. Brief exposure improves memory and cognitive function in paradigms of scopolamine-induced impairments [27]. Caffeine also improves attention and information processing [28]. In rodents, evidence from the past few years support the cognition-enhancing properties of caffeine in a variety of behavioural tasks that evaluated learning and memory [29]. Different longitudinal studies have investigated the relationship between coffee consumption, cognitive decline or

dementia/AD. In the Finland, Italy and the Netherlands Elderly (FINE) Study, among elderly men, drinking three cups of coffee per day was associated with the least 10-year cognitive decline [30]. Further, results from the Three City Study among 65 years old persons indicated that a consumption over three cups per day was associated with less decline in verbal memory and to a lesser extent in visuospatial memory among women [31].

Interestingly, other studies support that caffeine consumption might prevent AD. A retrospective study has shown an inverse correlation between coffee intake and the occurrence of AD later on in life since patients with AD had an average daily caffeine intake of 73.9 ± 97.9 mg during the 20 years that preceded diagnosis of AD, whereas the controls had an average daily caffeine intake of 198.7 ± 135.7 mg during the corresponding 20 years of their lifetimes [32]. In the prospective Canadian Study of Health and Aging (CSHA), daily coffee drinking decreased the risk of AD by 31% during a 5-year follow-up [33]. In line with those findings, another study from the CAIDE (Cardiovascular Risk Factors, Aging and Dementia) population reports that coffee drinkers at midlife had lower risk of dementia and AD later in life compared with those drinking no or only little coffee. The lowest risk (65% decreased) was found in people who drank 3–5 cups per day [34]. Finally, recent prospective data proposed that high plasma caffeine levels were associated with a reduced risk of dementia or a delayed onset in patients with mild cognitive impairment (MCI) [35]. It is noteworthy that in a recent study from the Honolulu-Asian Aging Study, authors did not find a significant association between caffeine intake and dementia risk [36]. However, they interestingly reported that, at autopsy, patients in the highest quartile of caffeine intake (>277.5 mg/d) were less likely to have any of the neuropathological lesions, such as AD-related lesions, microvascular ischemic lesions, cortical Lewy bodies, hippocampal sclerosis, or generalized atrophy. Therefore, available epidemiological data support that caffeine consumption is able to slow down cognitive decline in the elderly and reduces the risk to develop AD. Of note, while this looks also to be the case in Parkinson's Disease [37], caffeine has been recently suggested to exhibit detrimental effects in Huntington's Disease [38], suggesting that caffeine is not protective in all neurodegenerative conditions and its effects depends on underlying instrumental mechanisms.

Several scientific studies support that caffeine is beneficial also in animal models, which mimic the amyloid or Tau sides of AD. Caffeine mitigates cognitive decline induced by A β and reduced the amyloid burden in transgenic mice overexpressing mutant APP (APP^{sw}) in preventative but also in therapeutic paradigms. Indeed, APP^{sw} mice chronically treated from 4 to 9.5 months of age with caffeine (300mg/L by drinking water) were cognitively improved in several behavioural tasks that evaluated working and spatial memory and exhibited reduction of hippocampal A β_{1-40} and A β_{1-42} [39]. Importantly, a similar treatment of APP^{sw} mice at late pathological stages (18–19 months) for 4–5 weeks reversed memory deficits and reduced amyloid deposition as well as soluble A β levels in both entorhinal cortex and hippocampus [40]. Such beneficial effects of caffeine against A β production were recently confirmed by a different group using an experimental model of sporadic AD based on feeding rabbits with cholesterol enriched-diet that elevates both A β levels and Tau phosphorylation in the brain [41]. In this study, rabbits fed with cholesterol-enriched diet were treated with low doses of caffeine (0.5 to 30 mg/d) through drinking water, corresponding to a maximal 60mg/d consumption in humans. In this paradigm, caffeine

significantly decreased A β production in accordance with Arendash's results. Interestingly, reduced production of A β ₁₋₄₀ and A β ₁₋₄₂ was also observed in a neuroblastoma model overexpressing mutant APP following treatment with concentrations of caffeine below 10 μ M [39], further supporting the notion that caffeine impacts on mechanisms underlying amyloid peptide production. In accordance, chronic caffeine treatment of APPsw mice has been associated with decreased PS1 (Presenilin 1) and beta-site APP cleaving enzyme 1 (BACE1) protein expression as well as increased Insulin-Degrading enzyme (IDE) levels, the latter presumably contributing to enhanced A β degradation [39, 41]. The effect of caffeine on BACE1 expression could relate to its ability to reduce c-Raf1 activity, possibly through protein kinase A (PKA) activation [40]. In addition, caffeine would reduce Glycogen synthase kinase 3 (GSK3) expression and/or activity and thereby influence A β production [40]. However, a direct effect of caffeine on γ -secretase activity remains elusive and mechanisms linking caffeine and A β production/clearance deserve further evaluation. It is finally noteworthy that although the beneficial effects of coffee on cognitive decline and decreased AD risk in human has been mostly ascribed to caffeine, other coffee constituents may also play an important role. Indeed, two recent studies support that non-caffeine components of coffee display neuroprotective effects in *D. melanogaster* and *C. elegans* amyloid models through activation of the Nrf2 detoxification pathway [42, 43]. Further, recent data indicate that caffeine may also impact on Tau phosphorylation. Indeed, cultured neuronal cells exhibited reduced Tau phosphorylation under caffeine treatment [44]. While caffeine doses used are far above the levels normally obtained following habitual consumption, this indicates a possible relationship to Tau. In accordance, we recently observed that chronic caffeine consumption by Tau transgenic animals (THY-Tau22 strain) developing neurofibrillary lesions, prevented memory alterations as well as decreased Tau phosphorylation in the hippocampus [45].

3. Caffeine targets and Alzheimer's Disease: the role of adenosine receptors

Only at high millimolar concentrations, which are irrelevant for normal consumption, caffeine can act at the level of ryanodine receptors and cyclic nucleotide phosphodiesterases, but it is now well established that under normal habitual caffeine consumption, the effects exerted in the brain by caffeine depend on its ability to block adenosine A₁ and A_{2A} receptors [25]. Adenosine receptors have a crucial neuromodulatory role and regulate both synaptic transmission and plasticity either by directly modulating synaptic responses or by interfering with other receptors [46].

During ageing, we and others have found compelling evidence of cortical and hippocampal upsurge of A_{2A}R expression/function. Specifically, in the hippocampus of aged rats, A_{2A}R expression is nearly two fold higher compared to young rats [47, 48]. More importantly, the A_{2A}R-dependent activation of glutamate release becomes more pronounced as ageing progresses and shifts from protein kinase C-mediated signaling to cAMP-dependent effects [48, 49]. This is accompanied by clear behavioural deficits in hippocampus-dependent tasks, such as spatial memory in rats [50]. Accordingly, rats overexpressing hippocampal A_{2A} receptors also exhibit behavioural deficits including spatial memory defects as well as LTP

impairments [Lopes et al., unpublished; 51]. Interestingly, other detrimental conditions associated to cognitive impairment, such as hypoxia, diabetes or epilepsy share similar A_{2A}R overactivation [48, 52, for review see 53]. Recently, we demonstrated decreased adult hippocampal long-term potentiation (LTP) and cognitive/memory impairment in a chronic stress induced ageing-like model, generated by maternal separation during the early post-natal period, in association with increased hippocampal A_{2A}R expression [52]. Strikingly, we observed, in adults, a normalization of synaptic and cognitive dysfunctions following A_{2A}R blockade with the selective antagonist KW6002 [52], supporting an instrumental role of A_{2A} receptor dysregulation in the genesis of synaptic dysfunctions underlying cognitive impairment within an ageing context.

Importantly, additional convergent data indicate that caffeine protects against the synapto-neurotoxicity induced by A β through blockade of A_{2A} receptors. In primary cultures of cerebellar granule cells, low doses of caffeine (1–25 μ M) -comparable with those achieved following caffeine treatment in animals or coffee consumption in Humans [25]- are able to counteract A β ₂₅₋₃₅ toxicity, an effect mimicked by ZM241385, an A_{2A} receptor antagonist but not CPT, a selective A₁ receptor antagonist [54]. These protective effects were confirmed *in vivo*. Subchronic treatment with caffeine 30mg/kg was shown protective against aversive and working memory deficits induced by intra-cerebroventricular (icv) injection of A β ₂₅₋₃₅ in mice [55] and mimicked by administration of SCH58261, a selective A_{2A} receptor antagonist. A_{2A} receptor blockade, through intraperitoneal injection of SCH58261 and KW6002 or genetic knock-out, was also shown to prevent working memory impairment as well as synaptic loss induced by icv injection of A β ₁₋₄₂ [56, 57]. Working memory improvement observed following A_{2A} receptor blockade was thought to be related to the prevention of synaptotoxicity promoted by A β through modulation of p38 MAPK and mitochondrial function [57]. Interestingly, it has been demonstrated that memory improvement promoted by A_{2A} receptor blockade following icv injection of A β was not observed in amnesic conditions induced by MK801 or scopolamine [56]. A_{2A} receptor blockade would then mitigate detrimental synaptic effects of A β . So far, no studies have been published on the impact of A_{2A} receptor modulation upon Tau pathology in AD. However, we recently demonstrated the beneficial impact of A_{2A} receptor deletion in a transgenic mouse model of AD-like Tau pathology [45].

Besides its direct action on synapses, the effects of A_{2A} receptor modulation upon AD pathophysiology could be non-neuronal. The role of A_{2A} receptors expressed by astro- and microglial cells is far from understood [for review see 58]. However, few studies indicate that A_{2A} receptors are upregulated in both microglial and astroglial cells treated by A β [59, 60]. A_{2A} receptors may promote activation and proliferation of astroglial cells [61, 62], and thereby regulate their ability to release glutamate [63] by controlling glutamate uptake [60], or affect the homeostasis of the endogenous neuroprotectant adenosine via adenosine kinase [64]. Increased astroglial A_{2A} receptor may thus contribute to the pathophysiology of AD. This idea is in line with the observation of the reinstatement of glutamate uptake in A β -treated glial cells following A_{2A} receptor blockade [60]. In addition, it has been shown that A_{2A} receptor stimulation causes microglial activation [59] and potentiates the release of nitric oxide as well as prostaglandine E2 release from these cells [65, 66]. Different

experimental evidence supports the anti-inflammatory effect of A_{2A} receptor blockade in different neuropathological situations [67–69]. Further, A_{2A} receptor blockade mitigates LTP defects as well as microglial activation and IL1 β release following LPS administration [69]. Then, blocking microglial A_{2A} receptor could be beneficial in AD. However, as microglia may play a janus role in AD [24], this conclusion needs further evaluation. In particular, the role of A_{2A} receptor activation towards the pathophysiology of AD will require further *in vivo* studies with appropriate and reliable cell-type specific models.

5. Conclusion

While recent data indicate that perinatal caffeine may impair interneuron migration and hippocampal network function [70], epidemiological and pre-clinical data, including ours, support the notion that caffeine might be not only be a cognitive enhancer but also a disease modifier in AD. The qualities of caffeine as a safe [71], inexpensive, and brain-penetrating agent deserves the translation of these findings into a pilot clinical trial in AD patients. Despite epidemiological data on the effects of caffeine in aged and AD subjects, and data from animal studies, no clinical trials have been performed to date to evaluate the extent by which caffeine can slow down disease progression in patients that have already developed AD. In addition, encouraging preliminary experimental data have been obtained related to the role of A_{2A} receptors in AD. While more work is still needed to uncover specific A_{2A} receptor functions in AD, all findings so far indicate that antagonists tested in human trials, even when not optimal in terms of efficacy, have reliably been shown to be safe and tolerable [72, for reviews see 73, 74]. Therefore, A_{2A}-based trials will be feasible in the future, if we are able to better delineate the function of A_{2A}Rs in the pathophysiology of AD.

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