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Editorial

Concluding Remarks

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CONCLUDING REMARKS

Substantial evidence from epidemiological studies suggests that caffeine may be protective against the cognitive decline seen in dementia and Alzheimer's disease (AD). This evidence was reappraised by the authors of the original studies in this special issue of the *Journal of Alzheimer's Disease* [1,2], and, despite methodological differences between the studies, the data was confirmed by the valuable meta-analysis of Santos and colleagues [3]. Notably, epidemiological studies corroborated by meta-analysis [4] also suggest that caffeine may be protective against Parkinson's disease [5].

An inverse relationship between caffeine consumption and neurodegenerative disorders thus appears compelling based on these epidemiological studies. However, epidemiological studies have significant limitations. Even though the studies mentioned above were controlled for many confounding factors, unknown factors may have influenced the experimental results. In this regard, the study by Lawrence Whalley's group [6] is particularly interesting. They used a Scottish dataset to examine the mental ability of the participants when they were children and compared it to their present caffeine intake. Since mental abilities in the young may be strong predictors of the development of AD at an old age [7], it could be that brighter children, presumably carrying a lower risk, would consume more caffeine during their lifetime to meet high intellectual and occupational demands, thus driving the association between caffeine and cognitive decline. The present study clearly rules out this hypothesis, and, in fact, those subjects with *higher* childhood mental ability, who would later spend more time in full time education, had *lower* present daily caffeine intake. Even with this supporting data, epidemiological studies finding associations between risk factors and health conditions cannot establish a causality relationship.

The causal relationship, however, is fostered by animal studies. It was found that caffeine prevented deterioration of memory performance in a transgenic mouse model for AD [8]. Animal studies also indicate that caffeine may interfere with key processes associated with memory dysfunction, since the consumption of caffeine prevented memory impairment in different animal models of neurodegenerative disorders [9]. This is further emphasized by the seminal studies of Takahashi's group showing an ability of caffeine to reverse age-related memory impairment, without evident effects in younger animals [10]. Overall, these animal studies provide a strong causal relation supporting the ability of chronic consumption of caffeine to counteract memory impairment.

The obvious next step should therefore be to move from observational studies to randomized, placebo-controlled clinical trials. In selecting participants, the expected biological *window of opportunity* [11] must be considered, that is to say, it should be determined when the administration of caffeine would be most effective in counteracting the neurodegenerative process. In this respect, caffeine could potentially interfere with the initial stages of the neurodegenerative processes involving the neurovascular unit [1,12], blood-brain barrier dysfunction [13], insulin regulation [14], and synaptotoxicity [9]. Despite the current hypotheses, however, much of the mechanistic interactions underlying the

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effect of caffeine remains unknown. As in other neurodegenerative disorders, it was proposed that adenosine A_{2A} receptors might be the target of caffeine (discussed in [9]), but other studies, such as that of Jiang-Fan Chen and colleagues [15], identified other possible targets [16]. Elucidating the mechanisms of action of caffeine in neurodegeneration is crucial for the proper design of a clinical trial to instruct us of when and how (the dose and timing of) caffeine should be introduced to gain maximal benefit.

Another key question to consider is the design of a trial to test the beneficial effects of caffeine in a select patient population. That is, a primary prevention trial could be designed involving participants who are not cognitively impaired. People above a certain age, at which cognitive decline is more probable, should be selected [17]. There is evidence that the effects of caffeine can be different in men and women [1,18], as well as in individuals carrying particular polymorphisms of the adenosine A_{2A} receptor [19–21]. Animal studies have indeed identified estrogens as important modulators of caffeine neuroprotection [22]. There are also polymorphisms of other elements controlling the adenosine neuromodulation system (e.g., adenosine kinase), which have not yet been tested. Certainly, an adequate profiling of the susceptibility to caffeine could help us interpret the results of a future trial.

Two primary outcomes could be considered for an initial trial designed to probe the effectiveness of caffeine consumption for AD management: either conversion to dementia/AD or cognitive decline, for instance in a specific memory test [23]. These primary outcomes were also used in the epidemiological studies described in this special issue. Although conversion to dementia/AD is a very significant outcome from a clinical point of view, the use of cognitive decline as the primary outcome is a sensitive and objective method, sparing the number of participants (from a few thousand to a few hundred) and the time of follow-up (from a few years to maybe one or two years) [23].

For the planning of such a clinical trial, caffeine as an experimental drug represents a special challenge. The fact that the intake of caffeine is common among most populations is both advantageous and disruptive. Since it has been widely consumed for many years, concerns about toxicity are minimal. On the other hand, because people *enjoy* caffeine-containing beverages, and have ready access to them, they may not easily abstain from caffeine intake. This means that the placebo group would not be free from the experimental drug, and that the treated group could have variable amounts of caffeine added to the experimental dose. This situation is different from primary prevention trials with nutritional supplements, i.e., vitamins, in which a high dose of the specific nutrient is usually administered as compared to the regular dietary intake. An alternative strategy would be to recruit participants who do not usually take caffeine. However, this sample would presumably be enriched in people who have unpleasant symptoms with caffeine, like palpitations and anxiety, or may be for some reason resistant to the effects of caffeine. In other words, the trial would tend to have a higher probability of side effects, and a lesser probability of finding a beneficial effect.

Other concerns about the planning of such a trial, such as the proposed dosage, are worth mentioning. Evidence from some but not all epidemiological studies (reviewed in [3,4]) may suggest a beneficial effect for moderate doses of caffeine but a possible deleterious effect for larger doses. It should also be kept in mind that the finding of consistent objective effects for the acute administration of low doses of caffeine in humans (100–200 mg, equivalent to about 1–2 cups of coffee), namely on central electrophysiological measures [24], as well as functional neuroimaging studies [25], does not necessarily mean that these are the relevant doses for the neuroprotective effects of chronically-administered caffeine. Clearly, basic research is required to provide a rationale for the choice of the adequate dose of caffeine to be tested. Choosing a proper dose requires merging two key pieces of information: data from pharmacodynamics and that from pharmacokinetics. Thus, the main target of caffeine action must be determined to define the optimal dosage for therapeutic use. Notably, this information will be revealed in animal studies. While A_{2A} receptors emerge as the most likely candidate to mediate the effects of caffeine on neurodegeneration and memory impairment (see discussion in [9]), there seems to be a different involvement of distinct adenosine A_{2A} receptors in behavior and neuroprotective effects [26]. Similarly, more detailed information on the pharmacokinetics of caffeine is necessary, with particular emphasis on the brain distribution of caffeine [27]. Again, preliminary animal studies will be an invaluable starting point to tackle these questions in humans.

An alternative clinical research approach could involve a restricted proof-of-concept trial to confirm in humans the beneficial effects of caffeine on the pathological processes of neurodegeneration so far observed in experimental animal models. In this issue, after reviewing the evidence that mice models of AD given caffeine during their lifetime were protected against

memory impairment and had lower brain levels of amyloid-β, Arendash and colleagues presented preliminary data showing that acute oral caffeine administration (400 mg, equivalent to about 4 cups of coffee) decreases blood amyloid-β levels in both young adult and aged humans [8]. Furthermore, it is now possible to detect and measure amyloid-β plaques *in vivo* using Positron Emission Tomography (PET) imaging and different radiotracers, particularly the [^{11}C]-labeled Pittsburgh compound B (PIB). The PIB retention values are quite stable in AD, with a small annual rate of change [28]. It would be interesting to design a proof-of-concept randomized clinical trial, of 6–12 months duration, in a small number (tens) of PIB-positive AD patients, to detect the expected effect of caffeine on the reduction of the brain amyloid burden, as compared to the subjects administered placebo. Sub-studies using PET with PIB are now being incorporated in larger disease-modifying clinical trials. In a small number of participants, the control of caffeine-containing beverage intake and the regular monitoring of caffeine plasma levels should be easier.

The daily follow-up of patients with AD has taught us that improvement of daily living may be a more significant indicator of amelioration than slight improvements in objective measures of memory performance. One of the most prevalent complications of AD is depression of mood, and the recent observations that caffeine might be a mood normalizer are of particular interest [29]. Given that the consumption of caffeine is associated with a reduced risk of depression [30], this may be a further potential confounding factor to be taken into account when designing a study to probe the ability of caffeine to preserve memory function in AD patients. Likewise, several other beneficial effects of caffeine on arousal and motivation [31,32] as well as other psychiatric conditions [29] should also be considered.

Ultimately, the time has come to decisively test the putative neuroprotective effects of caffeine in clinical trials. Certainly, important consequences for health recommendations and prevention of neurodegenerative disorders would result. However, starting clinical trials without adequately addressing the issues raised in this commentary may only 'kill the goose', as sadly witnessed by the attempts to establish clinical proof of A_{2A} receptor antagonists as anti-Parkinsonian drugs, without adequate support for a clear mechanism of action.

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