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The Rationale of Using Coffee and Melatonin as an Alternative Treatment for Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a devastating neurodegenerative disease with no current cure. FDA approved drugs have been widely used to address symptoms of AD, but none have been successful in preventing or reversing its effects. As the prevalence of AD increases due to the increased lifespan of the population, it is becoming essential to discover new drugs or find alternative treatment approaches to overcome the potential toxicity induced by current medications. We have noted that coffee and melatonin can play a role in delaying disease onset and improving memory for AD patients. Once these independent discoveries were made, we tested the possibility of using them in combination as therapy for AD. In this review, we are going to summarize the results from various investigations testing caffeine, coffee, and melatonin and present a method for their combined use for maximum treatment efficacy against AD pathogenesis.

Keywords: Alzheimer's disease; Coffee; Melatonin

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that afflicts the majority of the estimated 24-million dementia cases worldwide [1]. The disease is characterized by hyperphosphorylation of tau protein, accumulation of β-amyloid (Aβ) into senile plaques caused by the processing of amyloid precursor protein (APP), and an increase in oxidative stress [2]. However, AD etiology is still unknown, and drugs approved by FDA only alleviate symptoms instead of preventing disease pathogenesis. Additionally, current treatments are costly and are accompanied by unpredictable toxicity associated with long-term use. The use of an affordable and efficacious compound against AD with low chances of toxicity will allow the consumers to shift towards methods of prevention instead of beginning treatments after disease onset. This review will summarize the effects of coffee and melatonin and conclude with a proposed mechanism of their combined use for maximum treatment efficacy against AD pathogenesis.

Role of Coffee and Caffeine in Alzheimer's Disease

Coffee is the most consumed beverage in the world, and many of its health benefits have been widely reported in various research studies [3-6]. Coffee consumption is generally considered safe, but a few studies have reported it as a suspected cause of hypertension and increased vulnerability to abortion in pregnant women consuming more than 6 cups/day [7]. In relation to AD, it has been found that people who consumed 3-5 cups of coffee per day at midlife were associated with a decreased risk of dementia/AD later in life [8]. Until recently, most studies about the effects of coffee have been retrospective studies [9,10]. Various studies have indicated that caffeine has some function in treating various diseases, thus these benefits have at times been incorrectly generalized to include coffee. This vague terminology produces confusion between the effects of coffee and caffeine because caffeine is only one of the many active compounds in coffee. However, we accept that caffeine does have many functions in the modification and treatment of various diseases, but many of the other compounds in coffee may be essential components in treatments [11-13].

It has been observed that doses of caffeine, a main component in coffee, can lower plasma Aβ levels within several hours post-treatment [14]. The ability of caffeine to reduce Aβ levels is attributed to its ability to reduce both beta- and gamma-secretase levels in the hippocampus of caffeine-treated Tg mice [13]. This reduction of beta- and gamma-secretase levels is of importance because they are responsible for Aβ deposition via the processing of APP. A recent study suggests that caffeine may also exert a protective role through a peripheral mechanism involving red blood cells. In this study, caffeine fully eliminated PKCα activation induced by Aβ through a mechanism involving acetylcholinesterase on the external face of the red blood cell plasma membrane [15]. An additional study investigating the effects caffeine reported a reduction in several proinflammatory and oxidative stress biomarkers typically upregulated in the hippocampus of THY-Tau22 transgenic mouse model [16]. These significant findings indicate caffeine's ability to act via the various hypothesized mechanisms of AD pathology.

Previous research, has indicated that granulocyte colony-stimulating factor (GCSF) has therapeutic effects against cancer [17,18] and neurodegenerative diseases such as AD [19,20] and ALS [21]. Long-term GCSF treatment has been reported to enhance cognitive performance in AD mice through three possible mechanisms: the recruitment of microglia from bone marrow, synaptogenesis, and neurogenesis [22]. Interleukin 10 (IL-10) is an anti-inflammatory cytokine suspected to play a protective function against AD pathogenesis due to the characteristic accompaniment of inflammation with disease progression. Another cytokine, interleukin 6 (IL-6), is presumed

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to play a protective role against AD by differentiating microglia into phagocytic macrophages capable of degrading Aβ peptide [23]. Our research has demonstrated that coffee can increase plasma GCSF, IL-10, and IL-6 levels in mice three hours post treatment, while neither decaffeinated coffee nor caffeine alone were able to induce this effect [22]. Additionally, it was noted that these favorable effects lasted much longer than the half-life of caffeine indicating that the function is not attributed to caffeine alone and components in coffee have a synergistic effect with caffeine. As of yet, the exact component of coffee providing synergistic effects with caffeine has not been identified [22]. Although there are numerous components in coffee to be investigated, studies isolating individual components such as eicosanoyl-5-hydroxytryptamide (EHT) have demonstrated neuroprotective benefits in an AD rat model [24]. This inspired us to further test coffee along with other molecules such as melatonin that might synergistically play a role against Aβ toxicity.

Melatonin and Alzheimer's Disease

Melatonin is a hormone produced in the pineal gland of the brain [25]. The pineal gland has been shown to exhibit calcification correlating with increasing age [26]. In accordance, melatonin levels have been found to decrease with age after a peak in production during human adolescence [27]. Plasma melatonin levels are further lacking in AD patients due to a dysfunction in noradrenergic regulation and the depletion of serotonin by increased monoamine oxidase [28,29]. The cerebrospinal fluid testing of 121 subjects, confirmed that CSF melatonin levels were significantly decreased in the aged subjects with early neuropathological changes in the temporal cortex where AD pathology begins [30]. This decrease and irregular secretion of melatonin may also be attributed to the impairment of CLOCK genes in AD patients amongst other factors [31]. Trials attempting to minimize the effects of reduced melatonin levels have proven melatonin replacement to be effective in treating sleep wake disorders and "sundowning" in Alzheimer's patients [32-34]. Fortunately, melatonin replacement is a low-risk treatment as it considered relatively devoid of toxicity, with 6-9 mg of fast-release melatonin preparations being considered safe for humans [2,32].

Melatonin has several critical functions such as the ability to induce sleep based on light abundance and the regulation of the circadian rhythm. The hormone is generated in the hypothalamic suprachiasmatic nuclei (SCN), at the site of the circadian clock, and is synchronized by interactions between transcription factors known as CLOCK genes to ensure its production during the dark phase of the circadian cycle [31,35]. Although it has only recently been noted as a means to alleviate the effects of neurological disorders and diseases, it has been demonstrated that it can assist in the regulation of tau phosphorylation, reduce Aβ aggregation, and act as a powerful antioxidant to protect the brain from free radical damage [36-38].

Regulation of tau phosphorylation

Tau hyperphosphorylation is considered one of the underlying causes of AD pathology. In its normal state, tau promotes the assembly and stabilization of microtubules, but causes cytoskeletal disruption in its hyperphosphorylated state. A study by Yang in 2010 tested the *in vivo* effects of melatonin on changes associated with AD by administering the indoleamine for nine consecutive days before the addition of calyculin A, an inhibitor of protein phosphatase (PP)-2A and PP-1. The inhibition of PP-2A and PP-1 alleviated hyperphosphorylation of tau, and the addition of melatonin proved to further regulate the process while reducing oxidative stress [39]. Accordingly, a reduction in melatonin levels has been correlated with increased tau phosphorylation and spatial memory impairment in rats while supplementation with melatonin has exhibited efficacious effects [40].

Reduction of amyloid beta aggregation

Melatonin exhibits the ability to prevent Aβ aggregation, which causes senile plaques in AD patients [41]. The Aβ monomer is derived from APP, but only its aggregated form is toxic to the brain. The administration of melatonin was shown to increase survival rates in transgenic mice due to the partial inhibition of the expected time-dependent elevation of β-amyloid [42]. Another recent study was conducted to investigate the location and environment of Aβ peptides in a lipid bilayer in order to examine the peptides interaction with cholesterol and melatonin. The study found two locations in the hydrophilic head group region of anionic lipid bilayers and one located in between the membranes. Melatonin molecules were also found in the same vicinity as Aβ with melatonin supplementation drastically reducing the embedded Aβ populations [43].

Our research supports the neuronal benefits of administering melatonin for reducing Aβ toxicity. In our study, 100 mg/L of melatonin was given to 2.5 month old APP+PS1 double transgenic mice for 6 weeks. After the supplementation period, treated mice demonstrated improvements in cognitive tasks, up to a 43% reduction of Aβ aggregation in the hippocampus of the brain, and suppressed levels of inflammatory cytokines. Thus, melatonin treatment displayed positive results that may treat specific symptoms in AD patients [44].

Melatonin as an antioxidant

Research has also shown melatonin to be neuroprotective due to its capacity to act as a free radical scavenger with antifibrillogenic properties. Free radicals are highly reactive due to the unpaired electron in their outermost orbital allowing them to react with stable molecules to produce another free radical, leading to a self-propagating destructive cycle. Given that melatonin can cross the blood-brain barrier, it can promote antioxidant proteins and enzymes to fight against free radical damage in the brain and eventually avoid neuronal loss [45]. The activation of enzymes by melatonin makes use of their ability to metabolize toxic reactants into less harmful products [46].

An important feature contributing to the antioxidant properties of melatonin is its ability to cross the mitochondrial membrane. The hormone can act at the mitochondrial level to improve cellular respiration and increase ATP synthesis. It's antioxidant properties can also protect the mitochondria from oxidative damage by scavenging nitrogen and oxygen-based reactants generated within the organelle [32,47]. An experiment testing the effect of melatonin treatment on Aβ levels in brain mitochondria of APP/PS1 transgenic mice reported decreased Aβ toxicity levels in several brain regions after one month of treatment. Mitochondrial dysfunctions were alleviated if not fully treated in young mice, but a lack of response in the mitochondrial functions of aged mice signifies the importance of utilizing melatonin supplements in the early stages of AD [48].

Due to the correlation between mitochondrial dysfunction and apoptosis (programmed cell death), melatonin is able to reduce the number of apoptotic neurons by alleviating mitochondrial dysfunction [49,50]. Although apoptosis is a natural process, excessive cell death is an indication of neurodegenerative diseases. Melatonin affects the intrinsic signaling pathway of apoptosis through the mitochondria by improving the cholinergic system function [2,51]. The unique features of melatonin allow it to play a protective role in the accumulation of Aβ

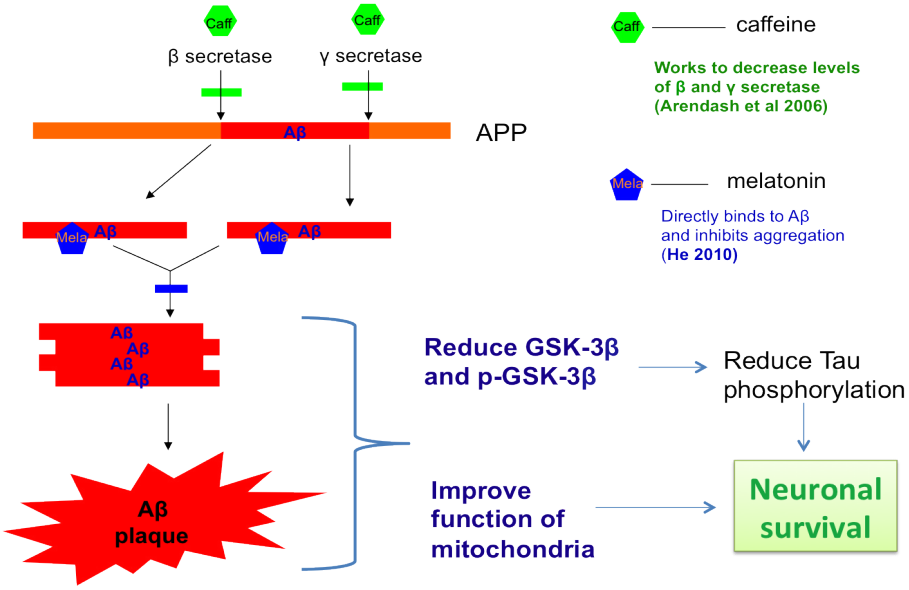

Figure 1: Mechanism of caffeine and melatonin in the prevention of Alzheimer's disease.

in the mitochondria which typically leads to severe axonal harm and eventually apoptosis [52].

Caffeine Counteracts Melatonin when Delivered Simultaneously

Attempts to use a combination therapy of caffeine and melatonin demonstrated little to no therapeutic benefit. Further analysis of the caffeine and melatonin combination in the Neuro-2a/amyloid precursor protein (N2a/APP) cell line indicated that caffeine may inhibit melatonin's function in mitochondrial enhancement. This result demonstrated that caffeine should not be combined and administered simultaneously with melatonin as a therapy for AD [53].

Alternative Treatment with Caffeine and Melatonin has Beneficial Effects on N2a/APP Cells

Since caffeine was found to inhibit the function of melatonin, we decided to test an alternative treatment regimen in the N2a/APP cell lines. An effective treatment schematic was found when treating the cells with caffeine in the morning and then switching to melatonin treatment in the evening [53]. Implementation of this regimen produced an additive and synergistic effect on extracellular Aβ40/42 levels compared to the other regimens tested. This schematic provides the framework for future investigations on the effective use of caffeine and melatonin by elucidating the importance of chronotherapy in AD treatments.

Mechanism of Caffeine and Melatonin against AD

Due the positive results in the study and the added benefits of using coffee instead of caffeine alone, it is supposed that using the chronotherapy of coffee in the morning and melatonin in the evening will aid in combatting AD progression. As previously presented, caffeine acts to decrease both beta- and gamma-secretase levels, leading to reduced levels of Aβ by decreased cleavage of APP [13]. The resulting Aβ peptide that is produced via the processing of APP binds to melatonin, which is able to improve mitochondrial function by entering the mitochondria and preventing the aggregation of the Aβ peptide into toxic plaques [36]. The consequent reduction of Aβ aggregation leads to a reduction of GSK-3 activation and ultimately reduced tau phosphorylation [54,55].

Although the ability of coffee to induce beneficial effects not caused by caffeine alone have been reported, the possible interaction between the many compounds in coffee has not allowed for a clear mechanism in its prevention of AD. However, given the benefits of coffee and those of caffeine, it is proposed that caffeinated coffee should be used in treatments to take advantage of all the benefits. Figure 1 illustrates our proposed mechanism of caffeine and melatonin in using coffee and melatonin as an alternative treatment approach for AD:

Conclusion

Coffee has been used for hundreds of years worldwide as the traditional beverage to promote wakefulness. In addition to its cognitive benefits, coffee can act to prevent AD pathology by inhibiting Aβ production and increasing GCSF, IL-6 and IL-10 levels more effectively than caffeine alone. Melatonin also has many qualities that make it an excellent candidate for future AD treatments, such as its ability to improve mitochondrial function by acting as an antioxidant, its inhibition of Aβ aggregation, and its regulation of tau phosphorylation. The combination of using both drugs as a treatment for AD with respect to the timing of drug administration presents an interesting and potentially effective way to approach further treatment methods for AD and other neurological disorders.

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