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Caffeine and Parkinson's Disease: A Comprehensive Review

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Abstract

Introduction: Parkinson's disease is one of the most common neurodegenerative disorders, affecting 1% of the population older than 60 years. In search for a novel treatment and prevention of PD in the last two decades, research studies on both humans and mice have discovered the neuro protective effects of caffeine. These studies indicate an inverse relationship between the caffeine and PD which point towards the positive effects of moderate caffeine consumption on Parkinson's onset and symptoms. **Objective:** This article explores and analyzes data from the last two decades of published research conducted on both humans and mice to understand the potential molecular mechanisms responsible for the neuro protcetive effects of caffeine , and how it improves motor and non motor deficits related to PD .**Results:** The neuro protective effects of caffeine have been found to depend on various factors, including sex, caffeine metabolism rate, and smoking. For example , caffeine is beneficial in preventing and slowing down the progression of PD in all tested cohorts of men, but only in varying cohorts of women, owing to the competition between estrogen and caffeine for metabolism via CYP1A2. The cohort with the least positive outcome for caffeine was post-menopausal women who were actively taking hormone-replacement therapy (HRT). Similarly, variation in the rate of caffeine metabolism from individual to individual and smoking induce an increase in hepatic enzymes affect the caffeine out come in Parkinson disease (PD). **Conclusion:** Due to the complexity of biological mechanisms and the methodology of scientific research, it is difficult to fully elucidate the benefits of caffeine on PD development and progression despite substantial evidence indicating a lower incidence of PD among caffeine users.

Keywords: Caffeine intake; Parkinson's disease; Parkinson's risk; Parkinson's; Neuro protection; Caffeine effect; Caffeine use.

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1. Introduction

Parkinson's disease (PD) is a progressive , incurable neurodegenerative disorder that causes characteristic motor impairments and varying degrees of non-motor symptoms. The loss of dopaminergic neurons due to oxidative stress, mitochondrial dysfunction, and neuro-inflammation in the substantia nigra pars compacta and the striatum results in deficits of the cortical striatal thalamocortical or nigrostriatal pathways, and the accumulation of alpha-synuclein enriched intracellular proteins called Lewy bodies in the brain [1,2,3]. These impairments result in motor symptoms, such as bradykinesia (slowness of movement), muscle rigidity, postural instability, gait problems, and tremors at rest. Evidence shows that the involvement of other brain areas with non-dopaminergic degeneration can cause non-motor symptoms of the disease, which precede the classical motor symptomatology of PD years before the onset of the disease [4]. Parkinson disease non-motor symptoms include autonomic dysfunction, fatigue, balance impairment, cognitive-dysfunction, sleep disturbance, altered attention, episodic memory loss, working memory deficits, and problems with executive function [5,6]. There has been increased research interest in recent years regarding life-style modifications, particularly dietary factors, as potential disease modifying agents for PD. Therefore caffeine has received attention as a beneficial agent owning to its anti-inflammatory, anti-oxidant, and anti-apoptotic properties [7]. Studies of caffeine done in both humans and animals indicate a strong link between consumption and the prevention of the dopaminergic neuron loss, leading to the slow progression of Parkinson-like symptoms [1,2,8]. Caffeine is the most commonly consumed beverage worldwide, second only to water. The average daily dose of caffeine consumed in the US was 135 mg, corresponding to 1.5 cups. On average 437 ml of brewed coffee contained 188 mg of caffeine . There is about 10.0-12.0 mg of caffeine per gram of coffee bean [9]. Moderate caffeine intake, defined as 2-4 cups or 200-400 mg of caffeine per day, is currently shown to provide the highest benefits and lowest risk (1,10). In a healthy adults, caffeine is readily absorbed in the GI tract, and peak blood levels are reached within 30-60 minutes after consumption. Similar amounts of caffeine are also found within the brain, indicating the hydrophobic nature of caffeine, which allows it to cross the blood-brain barrier quickly [11,12,13]. The half life of caffeine is between 3-7 hours. The Cytochrome-P4501A2 (CYP1A2) is responsible for 95% of caffeine's metabolism in the liver. CYP1A2 metabolizes caffeine into dimethylxanthines like paraxanthine (81.5%), theobromine (10%) and theophylline (5.4%) [11,14]. The remainder of caffeine is metabolized by two other enzymes, Xanthine-Oxidase and N-acetyltransferase2 (NAT2). Caffeine is predominantly excreted from the kidney, with 0.5% - 2% excreted unmetabolized in the urine. Caffeine exerts neuroprotective effects by targeting multiple biochemical mechanisms at the molecular level, such as manipulating neuroinflammation, excitotoxicity, and mitochondrial function. These effects are mediated by endogenous adenosine antagonism at its receptors (A1AR and A2AR) in the brain[15]. Caffeine can also acts as a Ryanodine-receptor agonist, increasing calcium release from the endoplasmic reticulum in neural tissue and causing phosphodiesterase inhibition, this cascade of events results in the blockade of GABA receptors. To exert these effects the concentration of caffeine required is much higher than the known nontoxic dose of caffeine [16]. Caffeine decreases cerebral blood flow, causing hypoperfusion and simultaneously increasing energy metabolism [17]. Growing evidence shows that the mediation of alpha-synuclein causes reactive microglial activation, which plays a critical role in the neurodegeneration of dopaminergic neurons in PD. Caffeine attenuates microglial activity by exerting anti neuro-inflammatory effects [18]. Interestingly, caffeine

may also slow the development of Parkinson disease via the gut microbiome, which is discussed in detail further below [19]. Brain function is based on electromotor forces delivered by chemical transmitters flowing between synapses. These synaptic functions can be modified by agents with identical affinities for receptors or modulators that work on these neuronal circuits. Caffeine influences several biochemical mechanisms by invading the synaptic cleft and modifying synaptic-activity, producing effects opposite to some biochemicals mechanisms responsible for Parkinson disease [20]. Through its pharmacodynamics, caffeine leads to the synaptic mobilization and reorganization of the cortical-network function; which enables neurons to increase synaptic transmission and enhance their morphology [21]. At the network level, cortical neural oscillators are activated by caffeine which sends signals for surrounding areas via repetitive N-methyl-D aspartate to strengthen long range intercortical communications. According to Yoshimura & Hiroshi and his colleagues [22].

1.1. Effect of caffeine on adenosine Receptor

The primary mechanism of the caffeine mediated modulation of neurotransmitters is the blockade of G-protein coupled (GPCR) adenosine receptors, specifically A1AR which is an inhibitory receptor, and A2AR which is a facilitatory receptor in the brain. These receptor complexes display antagonistic properties to each other [23,24,25]. A1AR receptors are expressed densely in the hippocampus and the neocortex along with dopamine D1 receptors and the A2AR receptors which coexists with the D2 receptor [26,27]. A1AR-A2AR functions as an adenosine concentration-dependent switch that is responsible for opposing the actions of adenosine on neurotransmitter release based on the predominant activation of A1R or A2AR [28, 29]. By modulating Adenosine receptors, caffeine exerts an indirect central effect on the noradrenergic, dopaminergic, serotonergic, cholinergic, glutaminergic, and GABAergic systems.

1.2. Effect of Caffeine on Reducing Oxidative Stress

An important pathophysiological mechanism contributing to the development of PD is the elevated oxidative stress levels in the brain, which is dictated by increased lipid peroxidation and decreased endogenous antioxidant system resulting in the damage to organelles, macromolecules and cell-death [30,31]. Cells are physiologically protected from damage by these oxidative stresses through the endogenous antioxidant pathways and cytoprotective enzyme expression . Nuclear factor erythroid 2-related factor 2 (Nrf-2) is a short-lived protein associated with heme Oxygenase-1 (HO- 1); a gene that encodes a transcription factor which is responsible for the cytoprotective pathway by up regulating the antioxidant response. Studies have shown that caffeine positively modulates Nrf-2 expression and therefore down regulates the lipid peroxidation (LPO) and reactive oxygen species (ROS) levels , thereby reducing oxidative DNA damage [32,33].

1.3. Effect of Caffeine on PD related Genes

PD occurs sporadically in the vast majority of cases; however, genetic risk has been increasingly identified due to the genome-wide polymorphisms associated with the development of familial PD. Recent advancements in genetic research have identified many gene loci associated with familial PD. Among these are LRRK2 (leucine-

rich repeat kinase 2) which is the most prevalent [30, 31]. Mutations in the gene encoding the LRRK2 influences the accumulation of alpha-synuclein [32]. This gene mutation is a known cause of autosomal dominant PD with incomplete penetrance [33]. Some studies have shown that caffeine metabolites are linked to resistance toward pathogenic protein mutations and might be responsible for variable penetrance associated with LRRK2 mutation, specifically interacting with the rs2896905 loci located on the SLC2A13 & LRRK2 gene [34]. A patient control study on a sample population of ethnic Swedes reported a link between a single nucleotide polymorphism, GRIN2A rs4998386 (a gene encoding the NMDA-glutamate-receptor subunit), and caffeine intake[35]. They found that 200-400 mg/day of caffeine intake was associated with a 58% risk reduction of Parkinson's disease development over time in those with the genotype rs4998386 and concluded that 400-600 mg/day of caffeine caused the greatest reduction (80%) in diagnosis compared to the similar group who consumed 0-200 mg. A caffeine intake >600 mg/day did not cause any reduction (>79%) [36]. In another study, the R1628P variant of LRRK2 (high genetic susceptibility) in non-caffeine takers was found to be associated with 15 times higher risk of PD development, whereas 3 times lower risk of disease was observed in caffeine takers with R1628P [37].

1.4. Effect of Caffeine on CREB (cAMP-response element binding protein)

A dopaminergic protein that caffeine positively affects in preventing Parkinson's disease is CREB (cAMP-response element binding protein). CREB is a binding protein in dopaminergic neurons such as Brain-derived growth factors (BDNF). It mediates the gene transcription essential for the central nervous system by increasing synaptic activity and plasticity [38]. In vitro, caffeine-mediated CREB stimulation resulted in a bell-shaped dose response curve, with optimal caffeine activity at 10 mM [39].

1.5. Effect of Caffeine on Gut Microbiome

Clinical evidence indicates the role of caffeine in influencing the gut microbiota and its role in the development of PD in humans and mice. Mounting evidence suggests that behavior and brain function are influenced by the gut microbiome. These microbiomes are responsible for neuro-immune mechanisms and brain homeostasis via gut-brain communication [40, 41]. The accumulation of misfolded alpha-synuclein protein in the enteric nervous system leads to the spread of these proteins along the gut-brain axis via the vagus nerve, and resulting in the development of PD [42, 43]. The fact that full truncal vagotomy decreases the risk of subsequent PD further supports this hypothesis [44]. The stomach and small intestine are the main sites for caffeine absorption, however, when it reaches the colon, it is fermented by gut-bacteria. Long-term caffeine consumption favorably alters the intestinal flora to prevent alpha-synuclein accumulation and spread.

1.6. Effect of Caffeine in vitro studies of MPTP treated Mice

A study of the effects of caffeine treatment in mice who had been injected with MPTP was carried out and showed favorable results [45, 46]. MPT (1-methyl-4phenyl-1,2,3,6- tetrahydropyridine) is an artificial substance meant to mimic Parkison's disease by destroying neurons in the basal ganglia by inhibiting the electron transport chain. Caffeine pre-treatment before MPTP administration normalize the inhibitory and excitatory

activity of neurons. It preserves the function of neurotransmitters in the Olfactory bulb and Striatum by preventing disruption of the blood-brain barrier. There is also evidence suggesting the protection of basal ganglia dopaminergic neurons and inhibition of microglial activity against MPTP neurotoxicity [47]. A separate study on chronic MPTP infusion indicated that caffeine protected against dopamine neuro degeneration even when administered after the onset of the neurodegenerative process [48]. Synergistic interactions between caffeine and L-DOPA (the precursor to dopamine) in separate mouse study showed that caffeine also favorably changes the L-DOPA induced response in PD [49]. Caffeine a competitive antagonist of adenosine receptors, removes the adenosine modulation of dopamine receptors and therefore enhances dopaminergic activity [33]. An In vitro mouse study suggested that caffeine might attenuate inflammatory chemokines such as tumor necrosis factor-α, interleukin 6, interferon-γ, and transforming growth factor-β [45].

2. Materials and Methods

To investigate the role of caffeine in protecting against PD, the PubMed and NCBI databases were searched. Pertinent articles describing the role of caffeine in Parkinson's disease(PD) and its effects on related symptoms in different settings, both in in vivo and in vitro models were selected. Only reviews, analyses, meta-analyses, and randomized control-based studies were included in the search criteria. The focus of the search was on adults, regardless of specific age, race, or gender with Parkinson's disease. Only articles written in English with free access were included.

3. Discussion

Parkinson disease was first described by James Parkinson in the tenth century. Aging is the most important risk factor as incidence of PD increases with age. It is likely that incidence of PD will increase in the near future as life expectancy has improved. Since the early 1960's Dopamine replacement therapy has been the mainstay of treatment of PD. Dopamine replacement therapy offers effective motor deficit relief particularly if introduced early in the treatment . Dopamine therapy does not alleviate the underlying dopaminergic neuron degeneration as well as lose their efficacy within a period of time [4]. Another limitation with Dopaminergic agent therapy is the development of undesirable side effects like dyskinesia (abnormal involuntary movements), psychosis, and compulsive behaviors. The neurodegenerative process in PD precedes the onset of motor symptoms by many years and involves the loss of cholinergic, adrenergic, and serotonergic neurons and their neurotransmitters. This variety of neural loss leads to memory impairment, sleep abnormalities, depression, olfaction, and gastrointestinal disturbances. These symptoms are collectively called non motor symptoms of PD and they do not respond effectively to Dopamine replacement therapy. To bridge this gap scientists are in search of a modality to curb the onset and progression of PD and caffeine has received a lot of scientific attention to be investigated as a novel non-dopaminergic agent which can potentially be used as alternative or adjunctive treatment with low profile of side effects. As the author attempts to examine reported studies and their results in clinical and animal studies conducted to comprehend the potential of caffeine as a disease modifying agent for PD it is noted that several of these studies in the human cohorts do not have well defined caffeine measurement, strength, and potency. Borcelos, R.P, and his colleagues conclude that caffeine impart several health related benefits in humans by altering cellular redox and anti-inflammatory mechanisms in a dose dependent manner

[12]. Most studies in the review calculated caffeine consumption ambiguously such as “cups” and did not give an exact criteria for measurement, nor specify the type of caffeine drinks being consumed or the source of caffeine in them. Only a few experimental studies have avoided this ambiguity in language and provided the exact unit of measurement in milligrams. For instance , Postuma and his colleagues conducted a 6 week long randomized control trial of caffeine on symptoms of PD such as daytime somnolence. In their study patients were given 100mg of caffeine twice daily for 3 weeks then 200 mg twice daily for another 3 weeks or a matching placebo. Study concluded borderline improvement in excessive daytime somnolence but much improved motor benefits , suggesting a need for a larger long term trial [6]. In another study Sian J, Youdim MBH, Riederer P, and his colleagues experiment regarding MPTP-induced dopamine loss in male mice showed decreased psychomotor loss via dose-dependent pretreatment with caffeine; 10 mg/kg of caffeine was the most effective dose. Ohmichi, Takuma et al found that in male humans, 120 mg/day consumption of caffeine leads to a significantly lower risk of PD by 38% compared to those who consumed very little caffeine [49]. A major factor disrupting the relationship between caffeine and PD is estrogen levels , which attenuate the efficacy of caffeine due to competition for metabolism via CYP1A2. This results in the inability of caffeine to break down into metabolites because of competition between estrogen and the same enzyme. Estrogen’s competition with caffeine is most markedly seen in both premenopausal women and postmenopausal women on hormone-replacement therapy(HRT) [4]. Estrogen has been shown to exert neuroprotective effects through their very own mechanism; however, in a study of male mice by Kolahdouzan, Mahshad, and Mazen J Hamadeh, mice treated with both estrogen and caffeine simultaneously showed that no dose of caffeine could attenuate dopamine loss in the striatum [30].

A distinction must be made between women who use hormone replacement therapy (HRT) and those with naturally occurring estrogen produced by the body. A large prospective study on a group of men and women not only confirmed the protective effect of caffeine intake on PD incidence but also showed an attenuating influence on women who were taking HRT [50,4]. A prospective study conducted by Palacios, Natalia and his colleagues assessed the caffeine intake and risk of PD found a significant risk reduction in women who never used hormone replacement therapy as compared to ever users. Their results are consistent with attenuating influence of HRT [51]. According to Ritchie, K and his colleagues women who are on HRT and consume the highest amount of caffeine intake among the sample group still had a 50% increased risk of PD compared to women who were non-users [52]. In a large prospective cohort of female nurses in the British National Health Service, no association was found between the risk of PD and caffeine intake overall; however, women who did not use post menopausal estrogen were at a lower risk of PD, while the risk was higher in HRT users. Among the women in the top quintile of this study, the mean caffeine intake was 436 g/day, corresponding to approximately 3 cups of coffee per day. The risk is lowest at moderate intakes (1-3 cups of coffee per day). Women below this amount correspond to the highest level of eventual diagnosis [50, 52].

Smokers have almost double the amount of caffeine metabolism than non-smokers, leading to a reduced half-life of caffeine in smokers. In a study conducted by William D. Parson and his colleagues elimination of caffeine in saliva of healthy smoker and non-smoker was compared. The body clearance of caffeine in the smoker was found to be higher than the nonsmokers reflecting the induction of hepatic aryl hydrocarbon

hydroxylase (AHH) activity in smokers[54]. Polycyclic aromatic hydrocarbons contained in cigarettes promote liver enzyme activity such as hepatic aryl hydrocarbon hydroxyl (AHH) activity, leading to increased caffeine metabolism [53]. Smoking also accelerates the presynaptic (i-e first pass) and systemic (i-e second pass) metabolism of caffeine and the hepatic microsomal oxidative enzymes, which causes faster demethylation and decrease in caffeine neuroprotective effects [55]. The pharmacokinetics of caffeine vary among individuals owing to polymorphisms in important enzymes expression that are responsible for metabolism, such as CYP1A2, which is an isoform of cytochrome P450, and N-acetyltransferase 2 [51]. Variations in CYP1A2 gene encoding alter its ability to be induced, thus affecting the rate of caffeine's metabolism.

Enhanced caffeine metabolism is seen in individuals with the homozygous A/A allele; such individuals are called fast metabolizers, whereas C allele carriers (A/C and C/C) have slow caffeine metabolism and are slow metabolizers [56]. Slow metabolizers have a prolonged half-life of caffeine in their body , thus, they have both longer-lasting and more pronounced effects. Several pharmacodynamic level polymorphisms are found at the main brain targets such as adenosine A2A receptors or ADORA2. The individual physiological differences in gene encoding and gene expression in various population groups can potentially play a prominent role in the degree of the neuroprotective effect of caffeine observed clinically [57].

4. Conclusion

Further investigative research is required on the various biological and environmental factors that affect caffeine pharmacokinetics and pharmacodynamics. The positive neuro-protective effects of caffeine are attributed to its ability to counteract neuroinflammation and oxidative stress. Its antioxidant effects are achieved by reducing the expression of Nrf-2 ; the anti neuro-inflammatory effects are mediated through the suppression of the activated microglial receptor adenosine A2A. These effects of caffeine hold significant promise for restoring both motor and non-motor deficits in PD. However, in the literature reviewed, sex showed pronounced differences in the therapeutic benefits of reducing PD symptoms as endogenous or exogenous estrogen compete with caffeine for receptor sites. Smoking has also been shown to onfeer resistance to caffeine benefit by accelerating its metabolism. Race and ethnicity in terms of gene expression and enzyme induction also had a significant effect on the outcome in terms of gene expression and enzyme induction. Most studies have been conducted on homogenous sample groups, with sex being the only difference. Future research should test various demographic groups and estimate their caffeine metabolic rate before trial to determine both the optimum therapeutic dose of caffeine and the required duration of treatment via quantitative studies and response over longer period of time (i.e. longitudinal studies). The use of caffeine as a preventive-agent may require caffeine initiation years prior to the median age of PD onset in susceptible individuals. However, further research is required to identify gene markers to identify individuals at risk for PD. For now it can said that caffeine is safe to be consumed in moderation with potential neuro-protective effects.

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