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Can Caffeine Reduce the Chances of Parkinson's Disease? A Review

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ABSTRACT

Finding therapies for preventing Parkinson's Disease (PD), a major neurodegenerative disease, remains an important way to improve the quality of life and reduce the total number of those afflicted with PD worldwide. Caffeine, one of the world's most consumed psychoactive drugs, affects neurological pathways that are involved in PD. In this review, we explore the relationship between caffeine and PD, its mechanisms, and how the onset of PD is affected by the consumption of caffeine. We propose that daily caffeine consumption may reduce the risk of developing PD later in life, but that the neuroprotective effect varies by several factors. Understanding the effects of caffeine and how it impacts PD may provide insight into potential treatments or delay the onset of disease.

Introduction

Caffeinated beverages are immensely popular around the globe. Two billion cups of coffee alone are consumed worldwide each day and are among some of the world's most-consumed beverages (Brown 2021) (Chen et al. 2022). Caffeine is present in various other sources, including soda, energy drinks, tea, and chocolate where it continues to be consumed (Evans, Richards, and Battisti 2023); (Katz, Doughty, and Ali 2011). Almost 80 percent of Western Society consumes caffeine to the extent that major physiological effects occur (Daly, Holmén, and Fredholm 1998). As such, research on caffeine and its mechanisms is imperative for understanding the effects it has on human physiology and disease pathogenesis. Caffeine is a stimulant drug that is well known for its physiological effects, such as cognitive enhancement, improved reaction time, alertness, motor coordination, and wakefulness (Department of Health and Human Services, n.d.; Nehlig 2010). After ingestion, most caffeine is absorbed by the gastrointestinal tract and then enters the bloodstream (Institute of Medicine (US) Committee on Military Nutrition Research 2001); ("13C-Caffeine Breath Test Identifies Single Nucleotide Polymorphisms Associated with Caffeine Metabolism" 2020), after which it crosses the blood-brain barrier and begins to affect the body (McCall, Millington, and Wurtman 1982); (McCall, Millington, and Wurtman 1982; "Caffeine" 2020). Biological half-life elimination depends on the individual, but usually takes 1.5 to 9.5 hours (Institute of Medicine (US) Committee on Military Nutrition Research 2001); (Institute of Medicine (US) Committee on Military Nutrition Research 2001; "Caffeine" 2020).

A major mechanism of caffeine is through the suppression of the neurotransmitter adenosine in the striatum (Webster Ross et al. 2000; Ribeiro and Sebastião 2010) (Ferré 2010). When adenosine is suppressed, dopamine and acetylcholine levels are increased (Ribeiro and Sebastião 2010) (Solinas et al. 2002); (Ross and Jill Venton 2015) (Duarte-Araújo et al. 2004), where dopamine is released into both the nucleus accumbens and prefrontal cortex (Olguín et al. 2016) and acetylcholine at the neuromuscular junctions (Sam and Bordoni 2023). The neurotransmitter dopamine is involved in motor control, motivation, and reward (Triarhou 2013; Olguín et al. 2016), while acetylcholine has roles in memory, motivation, sensory information, attention, and arousal (Sam and Bordoni 2023) ("Cognitive Functions of Cortical Acetylcholine: Toward a Unifying Hypothesis" 1997). The short-term effects of caffeine consumption include increased physical capabilities, reduced reaction

time, concentration, motor coordination, wakefulness, stimulation of urine, insomnia, jitters, increased heart rate, and blood pressure increase (Calabresi et al. 1989); (Winston, Hardwick, and Jaberi 2005); (Tarnopolsky 2011) (Green, Kirby, and Suls 1996); (Nehlig 2010); (Conger, Warren, and Hardy 2011). Researchers hypothesize that the increase in dopamine after caffeine consumption is responsible for an increase in locomotor activity (Solinas et al. 2002), while the suppression of adenosine secretion is believed to contribute to feelings of reduced sleepiness (Ribeiro and Sebastião 2010); (Bjorness and Greene 2009; Reichert, Deboer, and Landolt 2022). Caffeine additionally affects human physiology neurologically, with the potential to affect neurodegenerative disorders including Alzheimer's Disease (Eskelinen and Kivipelto 2010). Studies suggest that caffeine acts by reducing oxidative stress and neuroinflammation, therefore potentially attenuating the risk of Alzheimer's disease (AD) (Schreiner and Popescu 2022). Though another significant theory suggests that PD attenuation is due to caffeine decreasing amyloid-beta (Aβ) levels (J. W. Kim et al. 2019), a protein implicated in the progression of AD (Sun, Chen, and Wang 2015). Collectively, these studies suggest caffeine influences human neurophysiology significantly by altering levels of neurotransmitters and reducing factors that contribute to neurodegeneration.

Parkinson's disease (PD) is a neurodegenerative disease that initially affects motor control marked by tremors and difficulty in controlling movement ("Parkinson's Disease," n.d.). PD worsens over time and may eventually result in depression, poor communication abilities, sleep disorders, dementia, psychosis, and a variety of other symptoms ("Parkinson's Disease," n.d., "Parkinson's Disease: Causes, Symptoms, and Treatments," n.d.); (Sveinbjornsdottir 2016). Researchers suggest that PD affects locomotion through the death of neurons in the basal ganglia, which is a region in the brain responsible for producing dopamine ("Parkinson's Disease: Causes, Symptoms, and Treatments," n.d.). It is currently unknown what exactly causes the neurons to die ("Parkinson's Disease: Causes, Symptoms, and Treatments," n.d.), though it is hypothesized to be a complex combination of both genetic and environmental factors ("Parkinson's Disease" 2015). An estimated 8.5 million individuals suffer from PD worldwide (Sveinbjornsdottir 2016; "Launch of WHO's Parkinson Disease Technical Brief," n.d.); (W. Yang et al. 2020).

Similar to AD it has been hypothesized that caffeine may also offer protection against PD. Multiple studies provide evidence that relatively moderate to high caffeine consumption is correlated with a reduction in the risk of PD (Webster Ross et al. 2000); (Hong, Chan, and Bai 2020); (Qi and Li 2014);(R. Liu et al. 2012). Though evidence supporting the reduction in risk of PD following regular moderate to high caffeine consumption is abundant, the mechanism by which this occurs is unclear. In this review, we will highlight the possible mechanisms by which caffeine may prevent or delay the onset of PD.

Mechanisms Involving Caffeine

Following oral caffeine consumption, caffeine is absorbed by the gastrointestinal tract where it is disseminated throughout the body via the bloodstream (Institute of Medicine (US) Committee on Military Nutrition Research 2001); (Walter 2022); ("Emptying and Absorption of Caffeine from the Human Stomach" 1971). Caffeine can then cross the blood-brain barrier due to its lipophilic properties (Institute of Medicine (US) Committee on Military Nutrition Research 2001); (Nehlig 2010). Once it crosses the blood-brain barrier, caffeine antagonizes adenosine receptors and exerts its effects on the brain (Institute of Medicine (US) Committee on Military Nutrition Research 2001).

Neurotransmitters are signaling molecules used by neurons to excite or inhibit other neurons (Sheffler, Reddy, and Pillarisetty 2023). They are released via action potentials, electrical events that alter membrane voltage (Grider, Jessu, and Kabir 2023; Sheffler, Reddy, and Pillarisetty 2023) throughout the whole body, used both in the central and peripheral nervous systems (Teleanu et al. 2022). This is the mechanism by which neuronal communication occurs and thus, is essential for basic biological functioning (Sheffler, Reddy, and Pillarisetty 2023). Stimulant drugs such as caffeine affect the body by modifying or disrupting the functioning of

neurotransmitters (National Institute on Drug Abuse, n.d.). Caffeine exerts physical effects on the consumer by antagonizing adenosine A2A receptors in the nucleus accumbens (Lazarus et al. 2011). Adenosine A2A receptors antagonize dopamine, promote the release of glutamate (Hong, Chan, and Bai 2020), and play a role in the regulation of sleep, locomotion, and general cognition (Shen and Chen 2009). Since adenosine is a dopamine antagonist, caffeine stimulates the transmission of dopamine, most likely through adenosine antagonism (Solinas et al. 2002).

Caffeine causes short-term and long-term physiological effects. Various negative health effects of caffeine are present during the consumption of caffeine. Diuresis, insomnia, and jitters are some of the common short-term negative health effects, (Maughan and Griffin 2003); (Green, Kirby, and Suls 1996) while bone loss in postmenopausal women, exacerbation of anxiety and sleep disorders, and a risk of dependence and withdrawal are associated with long-term caffeine consumption ("Caffeine Intake Increases the Rate of Bone Loss in Elderly Women and Interacts with Vitamin D Receptor Genotypes" 2001); (Winston, Hardwick, and Jaberi 2005); (Temple 2009). Additionally, caffeine increases physical capabilities, including aerobics, stamina, reduced reaction time, concentration, motor coordination, and wakefulness (Tarnopolsky 2011) (B. Lara et al. 2019); (McLellan, Bell, and Kamimori 2004); (Green, Kirby, and Suls 1996); (Nehlig 2010). Many individuals view these physical capabilities as beneficial. Additional benefits from prolonged consumption have also been observed, including a reduced risk of depression, dementia, and liver disease (D. R. Lara 2010; Winston, Hardwick, and Jaberi 2005) (Winston, Hardwick, and Jaberi 2005), suggesting a potential therapeutic quality to caffeine consumption. Lastly, the biological half-life of caffeine (how long it takes for the body to remove one-half of a substance's initial quantity) varies by individual but generally takes 2.5-4.5 hours (Institute of Medicine (US) Committee on Military Nutrition Research 2001); (Institute of Medicine (US) Committee on Military Nutrition Research 2001; "Caffeine" 2020); ("Caffeine," n.d.). Therefore, caffeine is short-acting and may have beneficial properties as a therapeutic in those with neurodegeneration.

Potential Mechanisms in Parkinson's Disease

PD is a neurodegenerative disease characterized by slow progression and a gradual deterioration of motor, and later, cognitive functions (Sveinbjornsdottir 2016); (Zhai et al. 2018); ("Parkinson's Disease," n.d.); ("Parkinson's Disease: Causes, Symptoms, and Treatments," n.d.; Lanciego, Luquin, and Obeso 2012); (Han et al. 2018). In PD, the lack of dopamine has been associated with the main symptoms of the disease ("Dopamine in Parkinson's Disease" 2021). Dopamine is correlated with motivation, reward, and motor control (Triarhou 2013; Olguín et al. 2016). The death of dopaminergic nerve cells in the substantia nigra pars compacta and the resulting deficiency of dopamine in the striatum, a region of the basal ganglia that is responsible for motor planning, decision making, motivation, and reward (Yager et al. 2015);(Taylor, Lewis, and Foster Olive 2013), contributes to the sequelae observed in PD ("Parkinson's Disease: Causes, Symptoms, and Treatments," n.d.) (Zhai et al. 2018); (Lanciego, Luquin, and Obeso 2012) (Lanciego, Luquin, and Obeso 2012; "Functional Changes of the Basal Ganglia Circuitry in Parkinson's Disease" 2000); ("Parkinson's Disease," n.d.). What exactly causes the cells to die is currently unknown, though it is believed to be a combination of genetic and environmental factors ("Parkinson's Disease: Causes, Symptoms, and Treatments," n.d.) ("Parkinson's Disease: Causes, Symptoms, and Treatments," n.d., "Parkinson's Disease" 2023) ("Parkinson's Disease - Causes," n.d.). An estimated 8.5 million people are estimated to have PD worldwide as of 2019 ("Parkinson Disease," n.d.), with PD being the second most common neurodegenerative disease after AD ("Genetics, Coffee Consumption, and Parkinson's Disease" 2022).

Dopamine, acetylcholine, and adenosine all function in the brain as neurotransmitters that have specific functions and play vital roles within the nervous system (Poewe 2006; Marsden 2006; "Dopamine, a Neurotransmitter, Influences the Immune System" 2000; Nirogi et al. 2010) (Y. Liu et al. 2019). Dopamine is

released via the mesolimbic pathway into the nucleus accumbens (Harris and Peng 2020) (Berridge and Kringelbach 2015). This then plays important roles in selecting motor responses used for acquiring reward (Hjelmstad 2004), general motor control (Gepshtein et al. 2014), learning, and memory (Hjelmstad 2004; "Dopamine: A Potential Substrate for Synaptic Plasticity and Memory Mechanisms" 2003),

Acetylcholine has been linked to cognitive functions such as memory, motivation, sensory information, attention, and arousal (Sam and Bordoni 2023) ("Cognitive Functions of Cortical Acetylcholine: Toward a Unifying Hypothesis" 1997). Studies suggest that those with PD have excess acetylcholine (Rizzi and Tan 2017) (Zhang and Cragg 2021) (Calabresi et al. 1989), most likely due to inhibition of acetylcholine release by dopamine (Calabresi et al. 1989) (Vizi et al. 1977).

Adenosine is linked to sleep modulation, arousal, cognition, memory, and learning, (Sebastião and Ribeiro 2009) (Reichert, Deboer, and Landolt 2022). It has already been established that the death of dopamine-producing cells in the basal ganglia is correlated to PD and its resulting motor symptoms (Reichert, Deboer, and Landolt 2022; "Dopamine in Parkinson's Disease" 2021); (S. J. Kim et al. 2003), resulting in insufficient levels of dopamine in the brain (S. J. Kim et al. 2003; Triarhou 2013). The loss of dopamine impairs motor function, therefore exacerbating motor dysfunction apparent in PD. The antagonism of adenosine has been theorized to improve symptoms in those with Parkinson's (Cieślak, Komoszyński, and Wojtczak 2008) (Cieślak, Komoszyński, and Wojtczak 2008), and even to offer neuroprotection against the disease (Cieślak, Komoszyński, and Wojtczak 2008; "Therapeutic Potential of Adenosine A2A Receptor Antagonists in Parkinson's Disease" 2005) ("Targets for Neuroprotection in Parkinson's Disease" 2009).

The substantia nigra, a brain region within the basal ganglia, is responsible for significant dopamine production and therefore large degrees of motor control (Sonne, Reddy, and Beato 2022) (S. J. Kim et al. 2003). The cell death in this region and subsequent lack of dopamine is believed to be the cause of most of the motor issues present in PD, with 60-80% of dopamine-producing cells having died by the time symptoms occur (Jankovic 2008) ("Parkinson's Disease," n.d.). Because both caffeine and PD hold many neurological pathways with dopamine, it is possible that caffeine may influence PD (R. Liu et al. 2012).

Caffeine and Parkinson's Disease

Numerous studies have highlighted the observed neuroprotective effects of caffeine on neurodegenerative diseases and cognitive function (Arendash et al. 2006; "Crude Caffeine Reduces Memory Impairment and Amyloid β1–42 Levels in an Alzheimer's Mouse Model" 2012) (Maia and De Mendonça 2002), including PD (Webster Ross et al. 2000) (Tsuboi 2012). Moderate to high caffeine consumption is associated with a reduced risk of PD (Tsuboi 2012) (Santos et al. 2010), where one study reported that the maximum neuroprotective effect of caffeine consumption against PD occurred when 2-3 cups of coffee (around 60-140 mg of caffeine per cup) ("Caffeine Consumption" 1996) (Lean and Crozier 2012)) were consumed each day (Ren and Chen 2020) (Qi and Li 2014). A study demonstrated that when administered 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) at 5 to 30 mg/kg (a drug used to artificially induce the effects of PD), caffeine attenuated the loss of both striatal and nigral dopamine neurons in rodents, further finding that even just one cup of coffee per day reduces the chances of PD by 50% in men compared to those that do not (Prediger 2010). Therefore, caffeine consumption may reduce the risk of PD, though it is dependent on the amount of caffeine that is consumed and is influenced by individual metabolic factors.

Many human studies further demonstrate the neuroprotective effect of caffeine, with one study reporting a 25% lower chance of PD when one cup of caffeine (defined as 137 mg of caffeine) was consumed per day (Costa et al. 2010), and another stating a similar 25% lower chance of PD when race, age and physical activity were adjusted (R. Liu et al. 2012). A third study compared the likelihood of PD in men who did not drink coffee and those who did, resulting in 10.4 cases of PD per 10,000 and 1.9 cases of PD per 10,000, respectively (Webster Ross et al. 2000). When taken together, these studies suggest that caffeine consumption decreases the risk

of PD, and caffeine consumption is inversely correlated with disease risk. Overall, more studies are needed to determine the therapeutic level of caffeine to achieve maximal reduction in disease risk.

Most studies suggest that the observed neuroprotective effects of caffeine against PD are a result of the antagonism of adenosine A2A receptors (Ren and Chen 2020) (Hong, Chan, and Bai 2020; Costa et al. 2010) (Yamada-Fowler and Söderkvist 2015). In the central nervous system, adenosine A2A receptors antagonize dopamine, promote the release of glutamate (Hong, Chan, and Bai 2020), and are primarily responsible for the regulation of sleep, locomotion, and general cognition (Shen and Chen 2009). In PD, the antagonism of A2A receptors has been shown to improve the management of symptoms (Popoli et al. 2003; Jenner 2014). Because adenosine is a known dopaminergic antagonist (Webster Ross et al. 2000), adenosine antagonism stimulates dopamine release and stimulation in the substantia nigra, nucleus accumbens (inside the basal ganglia), hippocampus and cortex in both mice and humans. (Solinas et al. 2002) (Ferré et al. 1997). (Ferré 2010) (Qi and Li 2014) (R. Liu et al. 2012). Caffeine, an adenosine antagonist, promotes wakefulness by antagonizing adenosine A2A receptors (Lazarus et al. 2011) as well as protecting against glutamate excitotoxicity (Ning et al. 2015) (Kolahdouzan and Hamadeh 2017), the death of neurons due to excessive glutamate or other excitatory amino acid levels. Perhaps, the antagonism of adenosine A2A receptors by caffeine exerts protective effects on dopaminergic neurons, the main cell type affected by PD.

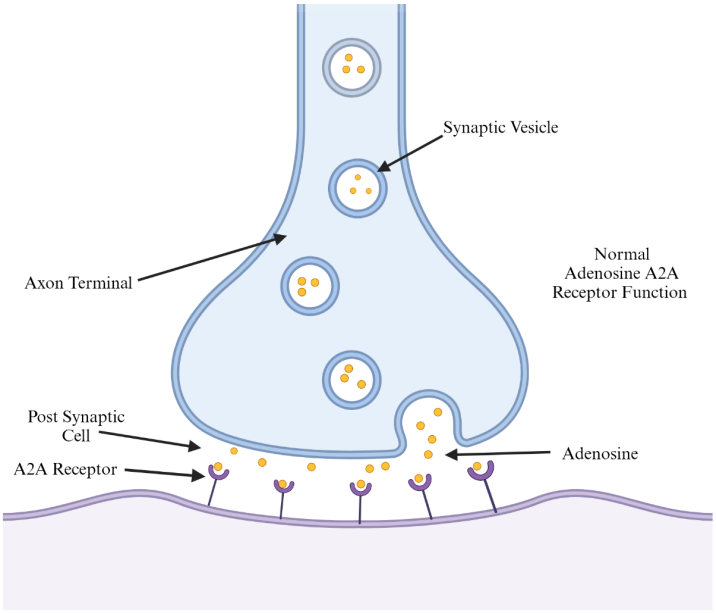

Figure 1. Simplified diagram of normal adenosine A2A receptor function. Adenosine secreted from synaptic vessels binds to A2A receptors, relaying effects to the postsynaptic cell. This allows the intended effects to be communicated across different neurons to the next, and for the physiological changes to occur. Created with Biorender.com

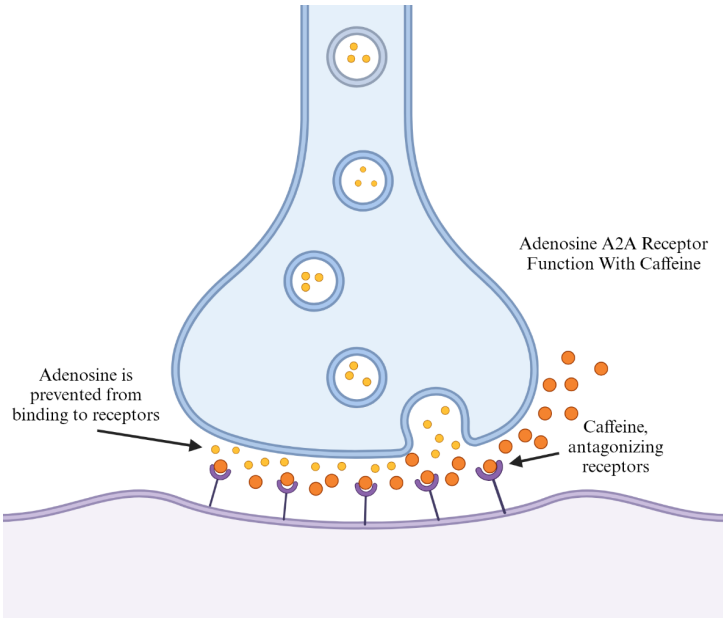

Figure 2. Simplified diagram of adenosine A2A receptor function with caffeine antagonism. Adenosine is prevented from binding to the receptors due to the presence of caffeine, thus it cannot communicate its effects. Created with Biorender.com

Discussion

In this review, we discussed multiple mechanisms by which caffeine may protect against neurodegeneration. These studies suggest that caffeine may be used as an adjunctive treatment for PD. It has been consistently shown to improve motor issues in patients with PD (Altman and Lang 2011; Ren and Chen 2020), and can attenuate the development of Levodopa-induced dyskinesia (Manalo and Medina 2018). However, the administration of caffeine to PD patients can increase gastrointestinal discomfort, tremors, and anxiety (Altman and Lang 2011). Therefore, additional safety profile studies must be completed to understand the full effects of caffeine as an adjunct therapy.

One of the most commonly used medications for the treatment of PD is Levodopa. This dopamine replacement agent can substitute for the loss of dopamine in patients and mitigate the bradykinetic symptoms most commonly associated with PD (Gandhi and Saadabadi 2023). It is currently the most commonly used treatment for PD, with a large number of patients experiencing motor improvement after initial treatment ("Parkinson's Disease" 2022). However, because Levodopa is unable to prevent or slow PD and is associated with numerous adverse effects after prolonged intake (Paoletti, Tambasco, and Parnetti 2019) (Gandhi and Saadabadi 2023), such as Levodopa-induced dyskinesia that typically occurs following prolonged treatment, additional therapies are needed to treat PD. Caffeine has been shown to attenuate Levodopa-induced dyskinesia (Manalo and Medina 2018), therefore, caffeine could be administered in conjunction with Levodopa to aid in mitigating some of Levodopa's significant side effects.

The possibility of caffeine reducing the risk of PD leads to new possibilities as a preventive treatment. Minimizing the risk for PD would not only reduce the amount of people with PD but remove the otherwise required treatment in those individuals. Caffeine could be administered (either as coffee, tea or as a supplement) to certain high-risk individuals, such as those with genetic predispositions to developing PD or predisposing age groups. Still, much care is required to prevent tolerance and dependency of caffeine during routine consumption. Individual genetics, lifestyle factors, and characteristics influence caffeine metabolism and its effects

(A. Yang, Palmer, and de Wit 2010). For example, the enzyme CYP1A2 is responsible for 95% of the primary caffeine metabolism in humans (Thorn et al. 2012). The expression of the CYP1A2 gene can greatly alter caffeine metabolism: those homozygous (to have two identical alleles of a gene) for CYP1A2*1A metabolize caffeine faster, while those carrying the variant CYP1A2*1F have reduced caffeine metabolism (Thorn et al. 2012; Cornelis et al. 2006). The slow caffeine metabolizers have an increased chance of nonfatal myocardial infarction, (Cornelis et al. 2006). Thus, individuals would have to be tested for genetic factors to conclude if caffeine administration is the safest intervention for PD patients.

Further compounding caffeine treatment is the possibility of caffeine intoxication, resulting in various negative health effects that adversely affect the user (Winston, Hardwick, and Jaberi 2005). Symptoms including aggression, anxiety, excessive urination, increased thirst, nausea, tremors, tachycardia, and insomnia are correlated with a caffeine overdose of 1g-1.5g ("Caffeine Overdose," n.d.) (Winston, Hardwick, and Jaberi 2005) (PubChem, n.d.). A lethal dose typically requires roughly 10-14 grams of caffeine to be consumed, (Murray and Traylor 2023; PubChem, n.d.) (Murray and Traylor 2023) or about 150-200 mg/kg of body weight (PubChem, n.d.). For reference, the average cup of coffee contains roughly 100 mg of caffeine and tea contains 50 mg (Winston, Hardwick, and Jaberi 2005). While caffeine overdose from consuming coffee is extremely rare, powdered caffeine supplements or caffeinated medications are significantly more likely to induce intoxication (Murray and Traylor 2023). Due to this, caution must be exercised in the hypothetical administration of caffeine to reduce the chances of PD so as not to negatively degrade the health of a patient. Still, the amount of caffeine required for neuroprotection against PD is currently understood to be well within safe limits (Costa et al. 2010). Additional studies are needed to better determine the amount of caffeine required for and maintaining neuroprotection.

Conclusion

To conclude, caffeine most likely offers neuroprotective qualities against PD. The maximum neuroprotection is posited to occur when about 2-3 cups of coffee are consumed daily, though this varies due to various metabolic factors and can vary. The mechanisms by which this occurs are unknown, yet caffeine's antagonism of adenosine, the prevention of glutamate excitotoxicity, and the prevention of apoptosis may be possible mechanisms by which caffeine is beneficial for those with PD or for reducing the risk of PD. Caffeine could be used to minimize the risk of the disease itself in high-risk groups. This is not without major limitations though, as caffeinism, caffeine tolerance and dependence, and various other genetic or metabolic factors may complicate the effectiveness of using caffeine as treatment. Research at this stage remains highly speculatory and uncertain. Further research is necessary to determine if caffeine should be used to minimize the chances of PD.

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