Introduction

Parkinson's Disease is a progressive brain disorder affecting 1% to 3% of the population over 65 years old. As the second most common neurodegenerative disease in the U.S., Parkinson's Disease (PD) is typified by unilateral resting tremor, bradykinesia, rigidity of limbs, and postural dysfunction. While effective therapies using levodopa exist to treat these debilitating symptoms, no treatments are yet available to arrest, slow, or prevent the disease process. As a result, the direct costs of PD in the U.S. alone are estimated to be a devastating $7.1 to $25.1 billion per year, with 80%-90% of PD patients unable to work nine years after diagnosis (1). Moreover, neurodegenerative disease (including PD and dementia) is expected to surpass cancer by 2040 as the second most common cause of death amongst the elderly (2).

Molecularly, PD is characterized by the gradual degeneration of dopaminergic neurons in the pars compacta region of the substantia nigra. Without the release of dopamine, GABA-releasing neurons in the striatum fail to activate, thereby impairing proper function of the basal ganglia circuitry responsible for a number of motor actions. The etiology of how the dopaminergic neurons in the substantia nigra begin to deteriorate is unknown and has spurred intense interest away from simply treating symptoms toward explaining its onset. Presently, the free radical/oxidative stress hypothesis involving an enzyme called monoamine oxidase-B (MAO-B) has become the most accepted theory of PD development (3). Oxidative stress is defined as the production of destructive free radicals (OH.) by MAO-B beyond what the body's antioxidants are able to detoxify.

While much research has focused on the characterization of MAO-B in PD, certain agents have emerged as possible preventive or decelerating agents of PD. Exciting long-term epidemiological studies have begun to establish nicotine and caffeine as promising therapeutic candidates against PD: these two unexceptional substances have been shown preliminarily to improve dopamine transmission to the striatum in PD patients (a symptomatic effect) as well as prevent dopaminergic neuronal loss in the pars compacta (a neuroprotective effect). Although nicotine and caffeine act via different mechanisms, both substances have attracted considerable attention as deterrents against PD onset and progression.

Nicotine

The inverse association between smoking and PD was noted as early as the 1960s (4), and has been since consistently demonstrated in various epidemiological surveys. In a review comparing 46 different studies by Morens et al., the vast majority confirmed this inverse link, with a combined odds measurement of 0.5; that is, PD individuals were only 50% as likely to have smoked than non-PD individuals (5). A more quantitatively detailed case-control study further elucidated the nicotine association by demonstrating a dose-response effect: the heavier the smoker, the less likely the incidence of PD (6). The linkage between cigarette smoking and PD has been hotly contested, with many critics arguing that non-smokers are self-selected into the PD category, and that nonsmoking is characteristic of a Parkinsonian nature. Moreover, since age is the biggest risk factor for

acquiring PD (2), it could be argued that those who do not smoke are more likely to live longer, increasing the chance of PD occurrence. Morens et al. counters these concerns by pointing toward the predominance and consistency of the association in independent studies of unique design, in different ethnicities and nations over an extended period of time (5). More convincingly, credible mechanisms of nicotine action on nicotinic acetylcholine receptors and PD have emerged as the workings of the brain become more fully understood.

Nicotinic Acetylcholine Receptors

Nicotinic acetylcholine receptors (NAchRs) control ligand-gated Ca2+ and Na+ channels, and are comprised of various combinations of twelve different subunits that determine their functional properties (7). NAchRs are found throughout the brain, and in PD patients are degenerative specifically on dopaminergic neurons of the substantia nigra. Stimulation of NAchRs by nicotine or acetylcholine leads to release of monoamines and regulation of functions such as locomotion, cognition, addiction, reinforcement, affect, and anxiety. In addition, it has been well established that administration of nicotine significantly improves memory. These high-level tasks imply that the nicotinic receptors in the central nervous system may play a major role in modifying neuronal excitability, regulating entire neurotransmitter systems beyond direct channel communication (8).

In a number of studies on Parkinson-induced animals, nicotine was found to vastly improve Parkinsonian symptoms, especially locomotion (9). Moreover, in many human PD analyses, nicotine administration moderately reduced most if not all Parkinson symptoms, including rigidity, tremor, locomotor activity, bradykinesia, imbalance, and confusion. These improvements were short-term and in line with the transient nature of nicotine, lasting for 10 to 30 minutes. Interestingly, nicotine chewing gum had a diminished impact on PD patients (9).

In addition to attenuation of PD symptoms, nicotine has also been shown to protect against dopaminergic neuronal loss in the substantia nigra. In animal studies that injected nicotine into dopaminergic neurons or exposed them to tobacco smoke immediately prior to lesioning of PD regions, neuronal loss was significantly (though not completely) counteracted (10). This nicotine pretreatment somehow thwarted glutamate-induced excitotoxicity, a mechanism by which the cells perish as seen in neuronal cultures. The degree of cell death returns to normal PD levels when a nicotine antagonist receptor is applied, further demonstrating the relationship between NAchR action and neuronal rescue.

Mechanisms of Nicotine Action

Several plausible theories have arisen to explain nicotine's beneficial effects. One popular theory suggests that nicotine serves as a potent antioxidant scavenging the free radicals produced by MAO-B. Produced by the body to metabolize monoamines such as dopamine, MAO-B generates hydrogen peroxide by-products, which react with iron to

form free radicals. PD patients typically have an elevated level of iron in the striatum, increasing oxidative stress, neurotoxicity, lipid peroxidation, and DNA injury (3). On the other hand, nicotine may in fact act directly to decrease MAO-B levels, which would lower free radical production.

Another possible mechanism involves growth factors such as fibroblast growth factor-2 (FGF-2) and brain-derived neurotrophic factor, both of which purportedly increase dopaminergic neuron survival in vivo and rescue dopaminergic function (11). The mechanism behind the role of growth factors in PD is still being investigated. Nonetheless, the elevated growth factor levels were muted by nicotinic receptor antagonists, confirming that nicotine is indeed the responsible substance.

Finally, nicotine's neuroprotective properties may arise from its ability to restore cerebral blood flow, which is substantially diminished in the forebrain regions of PD patients. In ultrasonic Doppler studies done on humans, a dose response effect was found, with increased nicotine resulting in increased flow (12). Cholinergic neurons are generally believed to regulate blood flow in the brain, and so destruction of these neurons likely result in the cognitive deficits seen in PD patients. Restoration could have important preventive effects that are still under study.

The possible roles of NAchRs could lead to novel therapeutic treatments for PD, and already have provided dramatic insight on the inception of PD. It is important to note that a small number of studies paradoxically show no change to worsening of PD symptoms upon administration of nicotine, casting doubt on its true effect (7). However, these studies may be faulted for differing dose amounts or means of injection. Activation above or below a certain level might produce the contradictory effects observed in these studies (8).

Caffeine

Perhaps no other psychoactive substance is as universally consumed as caffeine, a non-selective A2A adenosine receptor (A2AR) antagonist. Worldwide, the average person consumes around 75 mg/day, while in the U.S., the figure has climbed to nearly 238 mg/day (13). In contrast to nicotine, neither chronic nor acute coffee consumption has resulted in major health risks, and caffeine addiction is considered relatively mild. Yet similar to nicotine, caffeine has been shown to potently improve PD symptoms and attenuate PD neuronal degeneration. In separate studies, researchers found dose-response effects for coffee, where age-adjusted incidence of PD dropped whenever coffee consumption rose (14). These relationships have been found to be especially strong in men. Significantly, studies have observed that while coffee and tea demonstrate neuroprotective effects, decaffeinated coffee does not. The inverse association between caffeine and PD is hypothesized to result from increased dopamine affinity mediated by the A2A receptor, which is now considered a strong therapeutic candidate for PD.

A2A Adenosine Receptors

Unlike nicotinic receptors that are coupled to ion channels, adenosine receptors are coupled to G-protein pathways that regulate cAMP production. Adenosine receptors exist as four different types and are highly concentrated in CNS areas, including the caudate nucleus, putamen, nucleus accumbens, globus pallidus, and olfactory tubercle (15). In the striatum, A2ARs are specifically co-localized with dopamine (D2) receptors in GABA-releasing neurons, one step downstream from the dopaminergic neurons that nicotine affects.

Consistent with their localization, A2ARs interact with D2 receptors antagonistically to mediate GABA release into the globus pallidus. A2AR stimulation inhibits dopamine transmission, probably by decreasing the affinity of D2 receptors for dopamine (16). While the two receptors do not seem to interact directly, they may interrupt each other's second messenger pathways: A2ARs are known to activate adenylate cyclase, while D2 receptors inhibit it (16).

Mechanisms of Caffeine Action

The relatively recent characterization of A2ARs has begun to clarify the role of caffeine in Parkinson's Disease as a receptor antagonist, defining a scientific basis for caffeine's symptomatic and neuroprotective effects. Both animal and human studies have begun to bear out these molecular theories. In research decreasing the effect of A2ARs using artificial A2AR antagonists (mimicking caffeine) and knockout mice deficient in A2AR expression, locomotor activity in PD animal models dramatically improved, glutamate-induced neurotoxicity significantly dropped, and dopamine neurotransmission was greatly enhanced (17). Human experiments have also begun to show how an A2AR "blockade" set up by caffeine and its analogues have a positive effect on alleviating PD. In trials using theophylline, an A2AR antagonist, all 15 patients in various stages of PD showed marked improvement in motor functions (18). Surprisingly, A2AR antagonists in other studies also protect against cell death during transient focal ischemia (19). This intriguing defense against ischemia suggests a diminished release or blocked effect of an excitatory neurotransmitter like glutamate, a process that may parallel the induction of PD.

The ameliorative effects of caffeine have spurred intense development of more specific A2AR antagonists capable of acting exclusively on diseased regions in PD. Whether by direct or indirect means, A2AR antagonists enhance the effect of dopamine binding on GABA-ergic neurons, with immediate and positive consequences for PD patients (15). Current research seeks to escalate the benefits of caffeine by selectively combining A2AR antagonists with dopamine D2 agonists. The medley of drugs could generate a "double whammy" effect on the GABA-releasing neuron population, favorably manipulating the two co-localized receptors that it expresses in the striatum (17).

Conclusion

Current treatments of Parkinson's Disease depend heavily on levodopa, a form of dopamine replacement therapy that provides substantial improvement of PD's crippling

symptoms. However, levodopa does not slow the progression of PD into its end stages and in fact worsens quality of life through immobilizing side effects. This is likely due to levodopa's enhancement of dopamine metabolization, which increases oxidative stress and free radical production in the basal ganglia (3).

The discovery of caffeine and nicotine as neuroprotective agents shifts the landscape of PD research, not only because they mimic the dopamine-replacement benefits of levodopa but because they also seem to play roles in the prevention of PD onset and progression. The miraculous properties of these everyday, unremarkable substances have been invaluable in characterizing the elusive mechanisms behind how PD begins and develops. And while epidemiological studies have hinted at protective associations with PD (4), it is only now that currently emerging biological theories are able to apply those relationships to sturdy, feasible clinical trials (18).

Of course, nicotine and caffeine by themselves will not cure, prevent, or reverse Parkinson's Disease. Molecularly, the substances are not specific enough to exclusively target the relevant neurons in the basal ganglia. In addition, nicotine and caffeine are well known for their deleterious effects on the body outside of the substantia nigra and striatum: smoking is inextricably linked to atherosclerosis, coronary artery disease, hypertension, stroke, and innumerable forms of cancer. Coffee consumption, while not nearly as severe as smoking, can lead to unpleasant withdrawal effects: weariness, apathy, drowsiness, headaches, and anxiety. Caffeine is also vasoconstrictive and can cause a 20%-30% drop in cerebral blood flow in a subject given a typical day's amount of caffeine (250 mg) (13). The damage done to the body by nicotine especially far outweighs whatever benefits yielded, particularly since the majority of the population will never develop PD. However, the baseline studies conducted using nicotine and caffeine have vividly described tangible pharmacological benefits, enabling researchers to design agents that are more selective, more controlled, and more powerful for those inflicted by and susceptible to PD. As our understanding of Parkinson's Disease increases, these drugs promise to become one of the most effective approaches for prevention and cure.

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