Review

Exercise and Smoking: Yin and Yang Sharing Protective Power for Parkinson's?

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Exercise and Smoking: Yin and Yang Sharing Protective Power for Parkinson's?

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Abstract

Compelling epidemiological evidence suggests that exercise and smoking are modifiable risk factors that are linked to a reduced risk of Parkinson's disease, possibly because they both exert protective effects on neurodegeneration. Like Yin and Yang, these two risk factors represent opposite ends of a spectrum: exercise is universally embraced, while smoking is rightly eschewed. Yet, intriguingly, preclinical evidence suggests that at their biological cores, exercise and smoking may share strikingly similar working mechanisms in favorably modifying the disease course. Here, we deconstruct these overlapping and putative neuroprotective mechanisms. Our aim is to transform this unexpected overlap into an actionable perspective towards identifying novel targets for disease-modifying therapies that can slow the progression of Parkinson's disease. We stress that while both factors may theoretically inform disease-modifying strategies for PD, in practice, only exercise should be promoted for its health benefits, whereas smoking is firmly contraindicated due to its known detrimental health effects.

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Introduction

For decades, studies have fairly consistently reported negative associations between both smoking and exercise (or physical activity) and the risk of developing Parkinson's disease (PD). [1,2] Ever since, smoking has been a hot, intensely debated topic in PD research. [3–7] The inverse association between exercise and PD seems to square with its generally salubrious effects. [8] By contrast, the inverse association between smoking and PD strikes many as paradoxical, as smoking is known to cause or hasten a number of human diseases, including lung cancer and cardiovascular disease. [9] It is therefore critical to underscore that, despite these epidemiological observations, smoking is unequivocally harmful and is not advocated as a preventive or therapeutic strategy for any condition. At its biological core, certain molecular mechanisms engaged by smoking may exert disease-modifying effects that could help explain the reduced risk of PD among smokers. [10–12] This notion has held up in several supportive mendelian randomization studies that allow for causal inferences of a true disease-modifying effect even if tempered by their inherent limitations. [13–15] Interestingly, various molecular mechanisms of action underlying the cellular effects of smoking overlap with those of exercise, including stabilization of hypoxia inducible factor 1α (HIF-1α) and upregulation of anti-oxidative mechanisms and PGC-1α, an important mitochondrial regulator. [16–22] As such, we find exercise and smoking to be biological brethren through their putative neuroprotective mechanisms, yet paradoxically situated at opposite extremes of the overall health

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risk-to-benefit spectrum among potential interventions for PD. Unravelling the shared mechanisms underlying these two putative disease-modifying behaviors for PD might inform further therapeutic pursuits. Notably, several interventions linked to one or more of these mechanisms have been or are now being explored in PD, including several small-molecule compounds, and even controlled exposure to nicotine, low-dose carbon monoxide and moderate hypoxia. [23–26]

Here, we discuss the presumed neuroprotective mechanisms of smoking and exercise and then demonstrate the commonalities between those mechanisms. Finally, we highlight recent research investigating these pathways in the context of PD, and describe several trials of interventions tailored to these insights that may have potential to prevent or slow the disease. We emphasize that the discussion into putative disease-modifying mechanisms behind smoking is intended solely to inform mechanistic understanding and guide the search for safe and targeted disease-modifying therapies, not to promote a smoking habit in any condition.

Epidemiology of Potentially Protective Effects of Smoking and Exercise

Evidence for an Association

The inverse association between smoking and the subsequent diagnosis of PD is among the most consistent lifestyle links across all of neuroepidemiology, and certainly among risk factors for PD. The first reports about smoking in PD were published over 50 years ago, and a twenty-year old landmark twin study showed a negative correlation between smoking dose and PD within twin pairs, even with a 10-year lag time before PD diagnosis. [10] Several studies report a dose-dependent association between smoking and risk of PD, with heavy smokers having the lowest risk to develop PD [20] and former and current smokers having a lower risk of PD compared to participants who never, or occasionally, smoked. [2,13,27–30] Whether second-hand smoking is also inversely associated with risk of PD, [31–33] and whether smoking behavior is associated with PD phenotype and progression, remain topics of debate. For example, some studies suggest that smokers have a later age of PD onset [34–36], lower (better) MDS-UPDRS-III [37] and a different non-motor symptom spectrum [38,39], but other studies report no associations with PD phenotype. [40] Lastly, although smoking is one of the most important risk factors for dementia in the general population, population studies report lower neurology-related mortality in current smokers compared to never-smokers. [41,42]

On the other hand, exercise is a widely advised non-pharmacological intervention in PD management. Exercise offers symptomatic benefits, and may also exert potential disease-modifying effects, although intervention studies addressing the hypothesized preventive effects of exercise in prodromal cohorts are just beginning [NCT06193252]. One synthesis of meta-analyses demonstrated that greater premorbid amounts of physical activity were associated with a dose-dependent reduced risk of developing PD. [1] In one study stratifying for task-related physical activity, only household and commuting-related physical activity were associated with a reduced PD risk, and leisure or occupation-related physical activity were not. [43] Exercise has dose-dependent positive effects on gait and postural stability, independence in activities of daily living and several cognitive symptoms. [44,45] Physical activity levels also correlate inversely with deterioration of dopamine transporter (DAT) imaging. [46] Finally, two randomized controlled trials showed that aerobic exercise resulted in a stabilization of motor progression in PD. [47,48] In one of these studies, this was associated with adaptive plasticity of the brain, which coincided with cognitive improvement. [49]

Limitations

Several limitations exist for observational studies that investigated the association between smoking and PD. First, the association could also be attributed to an intact and higher-than-average dopaminergic state which might make one more prone to addiction-based behaviors like smoking (differences in premorbid personality). *[50]* This enhanced dopaminergic state might directly protect against PD onset. Similarly, caloric restriction induced by smoking may be a confounding factor,

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among others, in this association. Evidence suggests caloric restriction may have preventive effects for neurodegenerative disease through reduced oxidative stress, improved autophagy and mitochondrial function, and neurotrophic effects. [51]

On the other hand, the reduced risk of PD among smokers may result from reverse causation, such that in the early, prodromal phase of PD, addictive behaviors such as smoking are less likely to develop or more likely to halt. Indeed, PD patients quit smoking with less difficulty than controls, possibly due to attenuated addictive effects of nicotine due to dopaminergic loss. [52] As noted above, Mendelian randomization studies report comparable risk reductions to observational studies. [13–15] Both Mendelian randomization studies and case-control studies remain susceptible to survival bias across groups. For example, putative anti-apoptotic smoking-induced effects on Bcl-2 or p53 lead to higher risk for malignancies and might lead to unbalanced drop-out in the smoking group. However, such problems are not as prominent in prospective cohort studies, where smoking's association with PD risk reduction remains strong. [2] Similar arguments regarding prodromal behavioral differences and selective survival exist for exercise. Lastly, the lack of mechanistic clarity hinders the identification of putative therapeutic targets, hampering the development of experimental or translational studies of candidate compounds without the associated harm of tobacco use.

Protective Mechanisms in Smoking and Exercise?

Several hypotheses have been proposed for the mechanisms underlying a putative neuroprotective effect of smoking. [53] First, as non-smokers who used snus (smokeless tobacco) have a substantially lower risk of PD, nicotine or other components of tobacco leaves have been suggested to be the mediating factor. [41,54] Briefly, nicotine may act as a stimulant that inhibits the action of striatal DAT, increasing dopamine levels in the synaptic gap [55] and reducing levodopa-induced dyskinesias [56]. However, a recent trial did not show neuroprotective effects of nicotine patches. [24] Second, preclinical studies report neuroprotective effects of carbon monoxide at the low doses seen in smokers, as it activates protective signaling cascades including HIF-1α and heme oxygenase 1 (HO-1), and reduces α-synuclein pathology. [57] Third, perhaps as a result of carbon monoxide exposure, smoking's benefits on PD risk may be mediated by intermittent hypoxia.[17,58,59] Preclinical evidence demonstrates neuroprotective effects of moderate intermittent hypoxia through activation of the hypoxia response pathway [26]. Fourth, smoking reduces MAO-B activity, which increases dopaminergic activity. Indeed, current smoking is associated with increased DAT binding. [60,61] Lastly, smoking induces cytochrome P450 1A2 (CYP1A2), which plays important roles in detoxification of toxins, whose activity is highest in mitochondria of the striatum. [60,62]

Of note, there is overwhelming evidence that smoking increases the risk of Alzheimer's disease (AD). [63,64] While this finding might cast doubt about the established relation between smoking and PD as both are usually slowly progressive neurodegenerative diseases occurring in later life, it should be noted that AD and PD have widely differing risk factors, most notable in divergent genetic, lifestyle, environmental and vascular risk factors. [63,65]

Several studies have aimed to elucidate the neuroprotective mechanisms of exercise in the light of PD. These include increase in neuronal resilience through improving adaptive response to energetic stress, primarily through anti-inflammatory control mechanisms and improved mitochondrial turnover, and anti-oxidant response. [8] Furthermore, preclinical evidence substantiates the induction of various growth factor-related mechanisms, including IGF-1, clusterin, irisin, Nrf2, BDNF, VEGF and the hypoxia response pathway (through both HIF-1α and HIF-1α independent mechanisms). [26,66] Such mechanisms seem able to strengthen functional connectivity or alternatively induce compensatory mechanisms, improving function. [8,49]

Overlapping Mechanisms

Recent studies suggest a mechanistic overlap between the putative protective effects of smoking and exercise. In Figure 1, we visualized these overlapping mechanisms, which we discuss below.

 doi:10.20944/preprints202507.1110.v1

Hypoxia response pathway (HIF-1)

The most compelling link between smoking and exercise lies in the innate response to hypoxia, which is mainly mediated by hypoxia-inducible factor (HIF) 1α. [26,67] Exercise leads to increased HIF-1 levels due to increased muscle oxygen consumption, and preclinical studies suggest HIF-1 is essential for the exercise-induced anti-apoptotic effects in neurons. [68–70]

Cigarette smoke, carbon monoxide, and nicotine all induce HIF-1 activation, the former in a reactive oxygen species-dependent manner, carbon monoxide via hemoglobin binding and secondary hypoxia, and the latter through the activation of the nicotinic acetylcholine receptor (nAChR)-mediated signaling pathway. [16,17] Preclinical studies suggest that activation of this hypoxia-response pathway through stabilizing HIF-1α has potential beneficial effects on pathophysiological mechanisms in PD, most importantly mitochondrial function, oxidative stress and potentially neuro-inflammation. [26]

Nrf2/HO-1

The second mechanistic connection between exercise and smoking involves the activation of Nrf2 (nuclear factor erythroid 2-related factor 2), which could control the development of PD by mediation of oxidative stress. [71] Exercise induces a systemic Nrf2-mediated redox stress response in an age- and dose-dependent manner. [72–77] However, evidence for the effects of tobacco smoke exposure on Nrf2-ARE activation are conflicting. Some studies demonstrate activation and translocation of Nrf2, potentially as a compensatory protective response to tobacco-induced oxidative stress [18], whereas other studies indicate impaired Nrf2 signaling and the promotion of inflammation in response to tobacco smoke exposure. [78] Both exercise and smoking induce HO-1, an anti-oxidative response element (ARE) downstream from Nrf2. [53,79–82]

PGC-1α

Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) is induced by exercise and promotes mitochondrial biogenesis and neuronal survival. [19–22] Regarding smoking, preclinical evidence suggests that PGC-1α is downregulated in response to tobacco-induced TNF-α activation. [83] However, active smokers have upregulated PGC-1α expression, possibly as a conditioning response of smoking behavior. [84] Nicotine might be a mediating factor in this longer-term response. [85] Contrarily, asthma-related research suggests adverse effects of nicotine on mitochondrial structural integrity in airway smooth muscle. [86]

 doi:10.20944/preprints202507.1110.v1

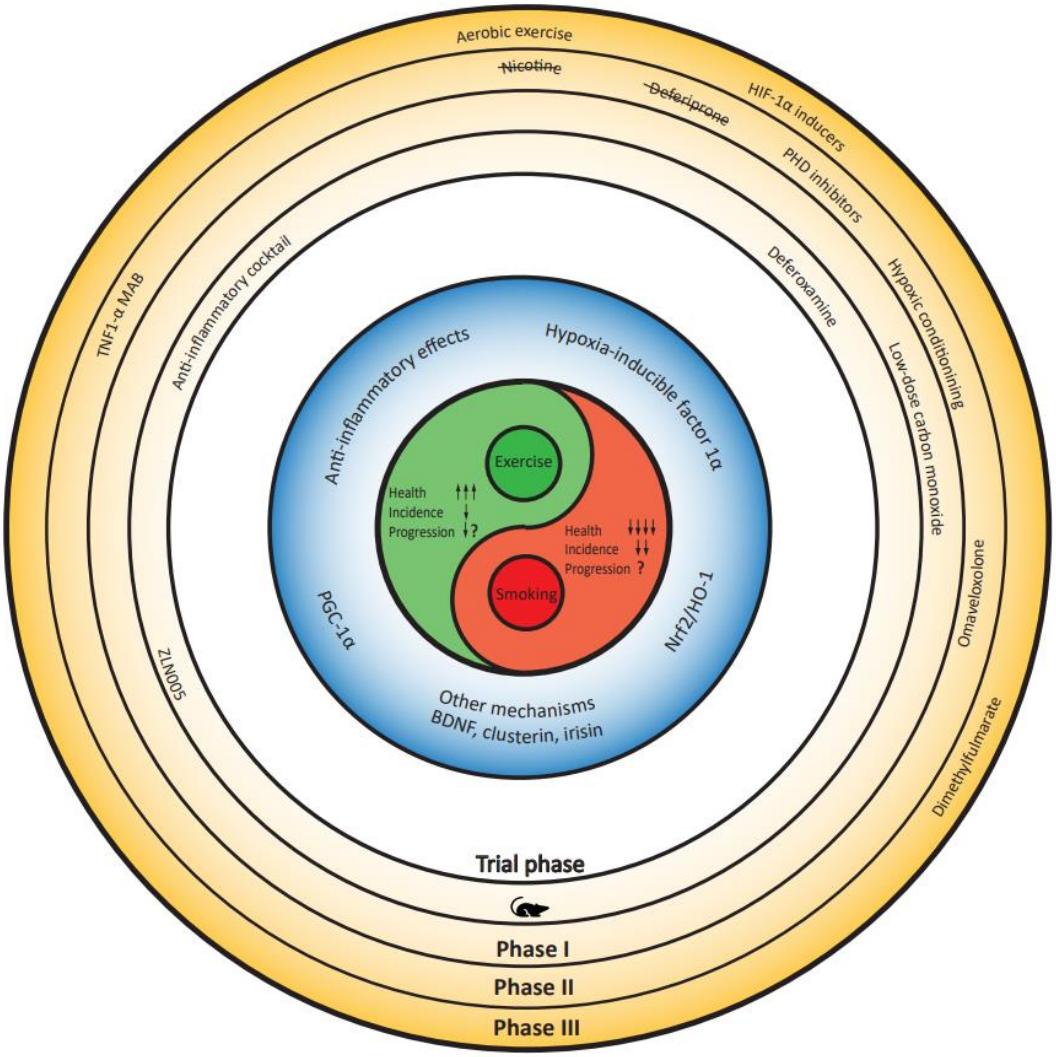

Figure 1. Conceptual framework postulating overlapping mechanisms and therapeutic opportunities shared by - or resulting from - smoking and exercise. Stages of translation are centered around common underlying mechanisms and span from preclinical work (rodent silhouette) to clinical study phases (I, II, and III). BDNF: brain-derived neurotrophic factor, HIF1-α: hypoxia inducible factor 1α, Nrf2: nuclear factor erythroid 2-related factor 2, PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-α, TNFα: Tumor Necrosis Factor-α.

Anti-inflammatory effects

Exercise suppresses pro-inflammatory markers such as TNF-α, IL-6 and IL-1β, while activating anti-inflammatory markers, such as IL-10 and TGF-β. [87–92] Evidence for smoking is more conflicting. Whereas carbon monoxide has a similar profile to exercise [93] and nicotine induces inhibition of microglia and reduces TNF-α activation through the activation of α7 nAChR [22,92,94–97], tobacco exposure exerts acute pro-inflammatory effects by inducing the production of IL-1 and TNF-α. [98,99]

Other mechanisms

Some mechanisms that are considered important for the neuroprotective effects of exercise are minimally explored in smoking. For example, the anti-inflammatory protein clusterin is of recent interest in the neuroinflammatory pathophysiology of PD [66] and increases with exercise. [100] Evidence on its relation with smoking is sparse, although some studies suggest that cigarette smoke induces clusterin expression. [101] One study suggests a relation between smoking intensity and

 doi:10.20944/preprints202507.1110.v1

salivary clusterin levels. [71] Similarly, brain-derived neurotrophic factor (BDNF) is potently activated by aerobic exercise in a dose-dependent fashion. Acute effects are unclear, but smokers have higher BDNF than non-smokers, and some studies suggest a dose-dependent increase in BDNF with duration of smoking behavior. [102,103] Irisin, a myokine, is one of the candidate mediators for increased BDNF expression with exercise. [104] Irisin already showed preventative potential in a mouse model of PD. [105]

Translation of Evidence into Therapeutic Opportunities

First, we stress our unequivocal discouragement of smoking and our wholehearted support for exercise, especially aerobic exercise, for all. However, the evidence above warrants further consideration of potential beneficial effects behind smoking that might inform translational or early-phase trials. Despite their behavioral origins, several experimental phase 1 and 2 trials are currently underway or have recently been published that target one or more of smoking's components and have overlapping pathways with exercise.

Nicotine

Several trials have investigated whether nicotine is the prime mediating mechanism responsible for the neuroprotective effects of smoking. Evidence suggests nicotine is neuroprotective through nicotinic cholinergic activation, which is a proposed mediating pathway for neuroprotective (and neuroplasticity-related) effects of exercise. [106] Inhibition of pro-inflammatory cytokine production, modulation of mitochondrial function through improved mitophagy and increased complex I activity, and stimulation of neurotrophic factors such as BDNF are alternative proposed pathways. However, as recent studies did not show clinical improvement, further initiatives are currently considered futile. [24,107]

Low-Dose Carbon Monoxide

With nicotine trials in PD demonstrating no clear benefit on PD symptoms or progression, carbon monoxide has emerged as a potential novel target. Low-dose carbon monoxide exposure in smokers induces Nrf2/HO-1 and secondary hypoxia causing HIF-1α release, two critical overlapping mechanisms of smoking and exercise, as we mentioned above. Indeed, a recent preclinical study reported neuroprotective effects of low dose carbon monoxide in animal models of PD. They showed protection of dopamine cells and reduced alpha-synuclein pathology in association with engagement of HIF-1α, HO-1 signaling, the lysosomal enzyme cathepsin D, and Polo-like kinase 2, the latter two proteins that contribute to α-synuclein degradation [23]. The application of controlled carbon monoxide exposure as an interesting therapeutic strategy is especially apparent by recent advances in elite sports, that combine carbon monoxide with altitude exposure (see hypoxic conditioning hereafter). [108] An oral liquid formulation of carbon monoxide with completed Phase 1 safety study [NCT03926819] and demonstrated pharmacokinetic and safety markers is slated for evaluation in a pending phase 2a clinical trial in PD.

Hypoxic Conditioning

Recent evidence suggests that evolutionarily preserved adaptive neuronal responses to hypoxia, including the hypoxia-inducible factor (HIF) cascade, impact beneficially on pathophysiological mechanisms in PD. [109] Exercise increases HIF-1 because of increased metabolic demand [110] and HIF-1 is necessary for exercise-induced nigral neuroprotection. [68] This provides a compelling argument for hypoxic conditioning, i.e. repeated exposure to moderate levels of hypoxia, as a non-pharmacological intervention in PD. Exposure to carbon monoxide-induced hypoxia or hypoxia directly reduces oxidative stress and rescues nigrostriatal degeneration and parkinsonism in a preclinical model of complex I deficiency. [111,112] Furthermore, exposure to hypoxia activates HIF-independent pathways that increase mitochondrial volume and decrease oxidative damage. [113]

 doi:10.20944/preprints202507.1110.v1

Notably, chronic intermittent hypoxia, for example in obstructive sleep apnea, is associated with accelerated cognitive decline and PD. [114–116]

Small-Molecule Approaches

Several small-molecule compounds target mechanisms discussed in the previous section. For the hypoxia response pathway, these mechanisms have been summarized elsewhere. [26] Briefly, stabilization of HIF-1α as the prime mediator of the hypoxia response pathway is effectively exerted by prolyl hydroxylase domain (PHD) inhibitors (e.g. daprodustat, dimethyloxalylglycine or *DMOG*, roxadustat), HIF-1α inducers (e.g. albendazole, agmatine) and, less specific in its target, iron chelators (deferoxamine or *DFO*, deferiprone). Out of these, only deferiprone has been investigated in PD. Deferiprone decreased substantia nigra iron levels, [117] but in a phase 2 trial, the participants treated with deferiprone showed worse scores on a gold-standard motor scale for PD. [118] The latter was perhaps caused by a reduction in dopamine synthesis in the drug-naïve participants, so possible beneficial effects in levodopa-treated patients cannot be excluded.

NRF2 stabilizers are small molecules that disrupt Keap1-mediated Nrf2 ubiquitination, decreasing its breakdown and increasing Nrf2 translocation into the nucleus. [119] Several compounds are known and tested in preclinical PD, most prominently sulforaphane [120–122] (an anti-oxidant available as a supplement) and dimethylfumarate (commercially available as Tecfidera® in multiple sclerosis) [123–126]. Omaveloxolone is a KEAP1 inhibitor, currently under investigation in Friedreich's ataxia and mitochondrial myopathy. [127,128] Comparisons between the potency of inducing downstream effects have yet to be conducted, and safety studies in PD are needed.

Some PGC-1α small molecules have been proposed [129,130], primarily for use in diabetes mellitus as a mediator of glucose metabolism. One of these small molecules (ZLN005) has been explored in preclinical parkinson models and demonstrates increased expression of mitochondrial respiratory chain-associated genes, and reduced loss of α-synuclein- or rotenone-induced dopaminergic neuron loss. [131] Notably, diabetes, as opposed to smoking and exercise, is a medical condition associated with *increased* PD incidence of 25-40%. [132]

Lastly, given the anti-inflammatory properties of exercise and some components of tobacco smoke described above, a mixture of anti-inflammatory agents could be explored, targeting multiple pathways all at once. Such a pathophysiology-agnostic regimen avoids the single pathway paradigm that might underlie the failure of many disease-modifying efforts in unselected populations. [133] However, what such a cocktail should include, is currently unknown.

Conclusion

Smoking and exercise are two of the most disparate, yet compelling human behaviors associated with reduced incidence of PD. While on the surface these are Yin and Yang, given their overall opposite health effects, at their biological cores these exposures share some striking similarities in their putative neuroprotective mechanisms. Understanding these overlapping mechanisms provides insight into proposed therapeutic strategies using non-pharmacological interventions or small molecules, many of which have already been tested in human trials in other fragile populations such as anemia or cardiovascular disease. Future proof-of-concept endeavors aimed at translating such insights into the PD population will inform larger clinical trials.

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