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Gut feelings about smoking and coffee in Parkinson's Disease

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Abstract

Strong epidemiological evidence suggests that smokers and coffee drinkers have a lower risk of Parkinson's disease (PD). The explanation for this finding is still unknown and the discussion has focused on two main hypotheses. The first suggests that PD patients have premorbid personality traits associated with dislike for coffee-drinking and smoking. The second posits that caffeine and nicotine are neuroprotective. We propose an alternative third hypothesis in which both cigarette and coffee consumption change the composition of the microbiota in the gut in a way that mitigates intestinal inflammation. This, in turn, would lead to less misfolding of the protein alpha-synuclein in enteric nerves, reducing the risk of PD by minimizing propagation of the protein aggregates to the central nervous system where they otherwise can induce neurodegeneration.

Background

A striking epidemiological feature of Parkinson's disease (PD) is that it is less common among cigarette smokers and coffee drinkers. The first case-control study suggesting such an inverse association was published more than 40 years ago. The finding has, since then, been confirmed by several other surveys.[1] In their systematic review and meta-analysis of 61 case-control and cohort studies published on the topic in 2001, Hernan and colleagues showed that the risk of PD is 60% lower among current cigarette smokers than among never smokers, and 30% lower among coffee drinkers than among non–drinkers.[2] These data, mainly obtained from retrospective studies were confirmed in four large prospective studies for either coffee and cigarette consumption (reviewed in [3]). A recent study has shown that the consumption of caffeine-containing beverages other than coffee, such as black tea and Japanese and Chinese teas, is also inversely related to PD risk.[4]

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Authors Roles

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Although the high number of studies conducted and the magnitude of the observed associations provide unequivocal epidemiological evidence that the risk of PD is lower in smokers and coffee drinkers, the explanations for these findings still remain controversial.[3] Several small case-control studies have suggested that PD patients display specific personality traits such as cautiousness, high harm avoidance and lack of novelty seeking even before the onset of motor symptoms. This has lead to the suggestion that people who later develop PD are constitutionally less likely to feel the need for the type of stimulation provided by tobacco and coffee.[5] Another possible explanation comes from the observations that substances present in coffee and tobacco, among which caffeine and nicotine are the most obvious candidates, are neuroprotective in experimental settings. Indeed, both nicotine and caffeine have, for example, been found to reduce MPTP-induced neurotoxicity in animal models of PD.[6,7] Albeit plausible, these two hypotheses are still contested. The idea that PD patients exhibit a premorbid personality has never been explored in a large prospective study[8] and there are obvious and well-known limitations inherent in animal models of PD.[9]

The hypothesis

Is there an alternative explanation to the inverse association between the risk of PD and coffee and cigarette consumption? We think so and we suggest that it lies hidden in digestive tract and more precisely in the gut microbiota. The intestinal microbiota consists of around a hundred trillion microorganisms that reside primarily in the lower gastro-intestinal tract, largely outnumbering our eukaryotic cells and surpassing the metabolic potential of our body.[10] Interestingly, the influence of microbiota is not limited to local effects but also extends to remote organs, particularly the brain.[11,12] Several recent studies have tried to shed light on the influence of gut flora on the brain by using germ-free animals or disrupting existing microbiota, and exposing the animals to specific microorganisms.[11] Although the precise mechanisms through which signals from gut bacteria are communicated to the brain are still largely unknown, evidence obtained from vagotomy experiments point toward a key role for the vagus nerve in the interplay between the microbiota and the brain.[11]

In healthy subjects, the intestinal microbiota is generally stable over time, but compositional changes might occur following antibiotic usage or dietary modifications.[10] Diseases associated with impaired gastrointestinal motility, such as diabetes mellitus and PD, predispose for small intestinal bacterial overgrowth (SIBO), a malabsorption syndrome associated with increased bacterial density in the gut.[13,14] Interestingly, three reports recently addressed the role of smoking and coffee on the composition of gut microbiota. A marked shift in the composition of the intestinal microbiota was observed in humans after smoking cessation[15] while consumption of coffee in both mice and humans induced a significant increase in the *Bifidobacterium* population without major impact on the dominant microbes.[16,17] We postulate that the changes in gut bacteria observed after coffee consumption and cigarette smoking affect the risk of PD being triggered in the gastrointestinal tract.

In their comprehensive anatomopathological survey published in 2003, Braak and coworkers postulated that α-synuclein-positive Lewy pathology initially appears, during the pre-motor

stage of PD, in the dorsal motor nucleus of the vagus.[18] Subsequent work from the same group along with two studies using gastrointestinal biopsies[19,20] suggested that the enteric neurons, which synapse with both afferent and efferent vagal neurons, are also affected by Lewy pathology early in the disease.[21] These and other observations led Braak to put forth the so-called "dual hit hypothesis" stipulating that PD may be triggered by an hitherto unknown neurotropic agent, presumed to be a virus, which initially affects the gut and the olfactory system causing α-synuclein aggregation.[22] Thereafter, according to the hypothesis, the neurotropic agent propagates through the nervous system, giving rise to Lewy pathology on the way and eventually after several years, reaching the substantia nigra. More recent observations showing in experimental models that misfolded α-synuclein can propagate from one neuron to another in a prion-like fashion has led to the hypothesis that it is misfolded α-synuclein itself that is the propagating agent.[23] Thus, the initial event would be α-synuclein misfolding and aggregation in neurons of the submucosal plexus whose terminal axons are only micrometers away from the gut lumen and flora.[24,25] Several detailed pathological studies have indeed consistently shown that these nerve terminals were affected by Lewy path The pathological process would further spread to the CNS via the vagal preganglionic innervation of the gut[24,26], as this has been already demonstrated for prion[27] and neural tracers[28].

If the beneficial effects of smoking and coffee consumption on PD are mediated through the modulation of the microbiota-gut-brain axis, what role might the microbes play in Braak's scenario? A possible explanation comes from the anti-inflammatory properties of some bacterial stains such as *Bifidobacterium* whose activity and proportion are upregulated by coffee-drinking.[17] One might therefore suggest that in the absence of coffee drinking and cigarette smoking, the microbiota would shift toward a pro-inflammatory state (Figure 1). This would promote chronic gastrointestinal inflammation and an enteric glial reaction, which actually have been shown to occur in the early stage of PD.[29] The local inflammation would in turn initiate the neuropathological process by making α-synuclein more prone to aggregate within the adjacent submucosal neurons.[30,31] As an alternative explanation, coffee and tobacco might promote microbes that counteract certain forms of chronic gastrointestinal infection such as that caused by *Helicobacter Pylori*, which is overrepresented in PD patients as compared to controls subjects.[32]

Besides the vagal neuronal pathway, a putative mechanism by which gut flora bacteria may influence the brain include bacterial products that gain access to the brain via the bloodstream and the *area postrema*[12]. Systemic inflammation has been demonstrated in PD patients[33,34] and evidence from animal models supports a role for peripheral inflammation in the exacerbation of neurodegeneration.[35] It could thus be proposed that smoking and coffee consumption, by decreasing the release of pro-inflammatory cytokines from the gut to the bloodstream, may reduce central nervous system neurodegeneration.

Testing the hypothesis

Complex studies would be required to determine whether a link exists between tobacco and coffee-drinking, changes in the gut microbe composition and a lower risk of PD. Our hypothesis suggests that in people who develop PD the crucial changes in the gut

microbiome might occur several years before they present with motor symptoms. These changes might therefore no longer be apparent at the time of PD diagnosis, making it challenging to test the hypothesis. Consequently, the first critical and more feasible studies could explore if changes in the gut microbiome are capable of modifying the evolution profile in experimental parkinsonism. Disrupting the microbiome or adding probiotics in toxin-induced or genetic models of PD would provide interesting answers. It could be also relevant to compare the neurodegenerative changes induced by a neurotoxin, such as MPTP and rotenone, between germ-free and specific pathogen-free animals, an approach that successfully has revealed that gut microbiota is critically involved in the development of experimental autoimmune encephalomyelitis in mice.[36] If a first set of experiments in animal models of PD is encouraging, further work will be needed to determine whether the specific changes in microbiota composition induced by coffee and tobacco are sufficient to prevent neurodegeneration in experimental parkinsonism and whether these effects are vagal-dependent. Combined with clinical studies on the gut microbiota in PD, the results of such studies in animal models of PD should help us find out if the truth lies in the gut.

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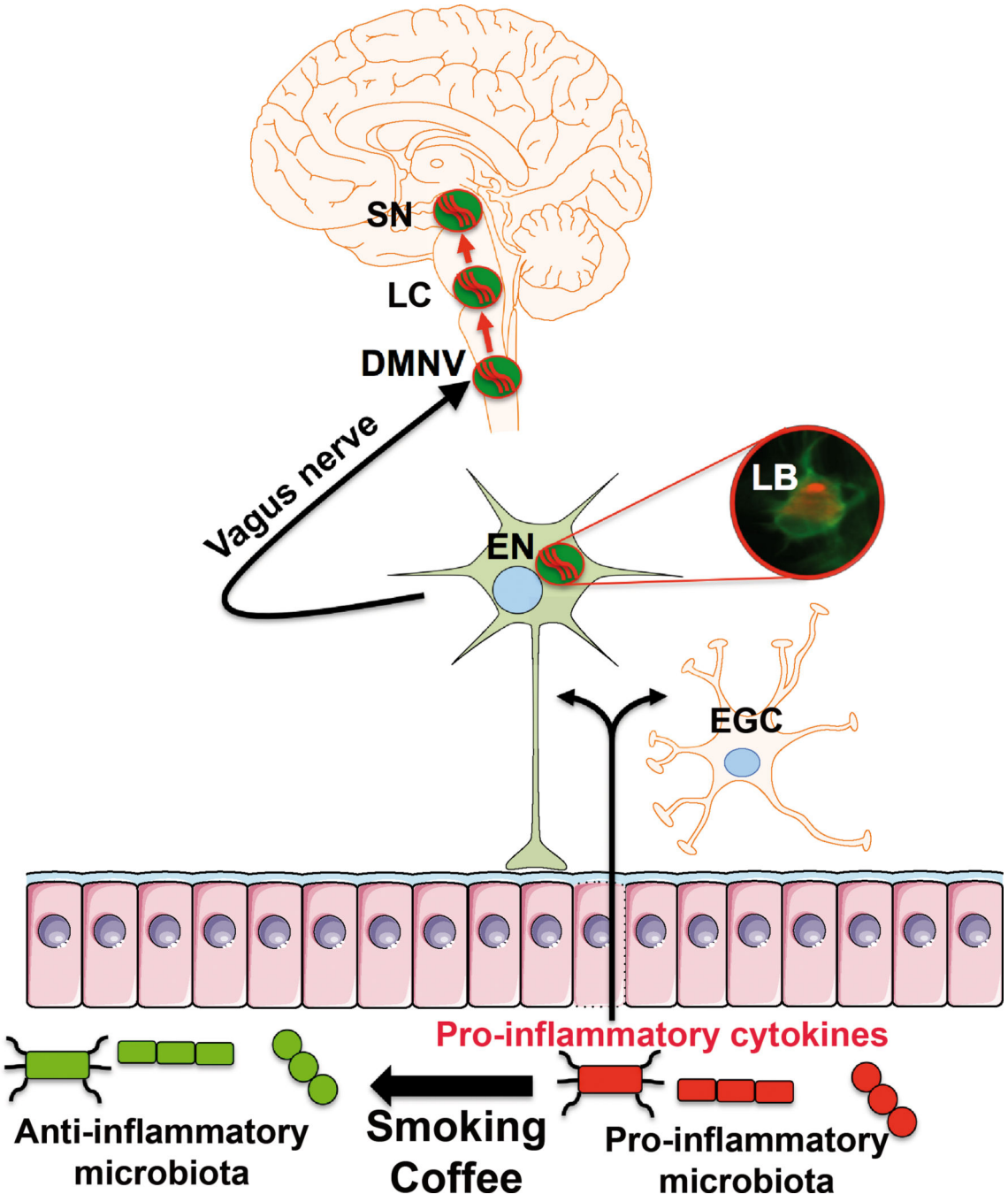

Figure 1. Possible role of smoking and coffee consumption on microbiota-gut-brain-axis and the development of Parkinson's disease

We propose that both cigarette smoking and coffee consumption may induce changes in the composition of microbiota with a shift toward a more anti-inflammatory state. In the absence of coffee and cigarette smoking, more pro-inflammatory cytokines are produced by immunologically competent cells and by enteric glial cells (EGC) in the gut. This would promote α-synuclein aggregation (Lewy bodies, LB) within enteric neurons (EN) that may spread further to the central nervous system via the vagal preganglionic innervation of the

gut and the dorsal motor nucleus of the vagus (DMNV). After several years, the pathological process would reach the *locus coeruleus* (LC) and the *substantia nigra* (SN).