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Research Report

Linking Smoking, Coffee, Urate, and Parkinson's Disease – A Role for Gut Microbiota?

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Abstract. While the etiology and pathogenesis of Parkinson's disease (PD) is still obscure, there is evidence for lifestyle factors influencing disease risk. Best established are the inverse associations with smoking and coffee consumption. In other contexts there is evidence that health effects of lifestyle factors may depend on gut microbiome composition. Considering the gastrointestinal involvement in PD, it was recently speculated, that the associations between smoking, coffee, and PD risk could be mediated by gut microbiota. Here we review such a possible mediatory role of gut microbiota taking into account recent findings on microbiome composition in PD and extending the scope also to urate.

Keywords: Gut-brain axis, risk factors, non-motor symptoms, gut motility, constipation, nicotine, caffeine, inflammation, gut permeability, dietary fiber

RELATIONS OF SMOKING, COFFEE CONSUMPTION, AND SERUM URATE LEVELS TO PD RISK AND THEIR PROPOSED MECHANISMS

A history of smoking reduces the risk of PD by about 36%–50% and there is an inverse dose-response relationship while for coffee consumption the risk reduction is about 33% [1, 2]. The exact mechanisms behind these associations are not known, but cigarette smoke and coffee contain possibly neuroprotective compounds such as nicotine and caffeine, respectively [1, 3–5]. Coffee is also rich in potentially neuroprotective polyphenols [6].

On the molecular level, nicotine is a potent agonist to nicotinic acetylcholine receptors (nAChR) whereas caffeine is a nonselective adenosine receptor antagonist. It has been suggested that mainly nAChRs and Adenosine A(2A) receptors mediate the neuroprotective effects of nicotine and caffeine, respectively [3, 4, 7, 8]. Another mechanism could be prevention of misfolding and fibril formation of α-synuclein [9, 10]. It is still unclear whether these molecules are solely responsible for the observed risk reduction. Challenging common interpretations related to neuroprotection, a recent study suggested that the reduced risk of PD in smokers could instead be explained by reverse causation in terms of a greater ease of smoking cessation in the prodromal phase of PD related to the loss of nicotinic rewards [11]. More generally it has been speculated that personality traits associated with PD, in particular low sensation seeking, could be the cause for reduced cigarette smoking and caffeine consumption in subjects later diagnosed with PD [12].

Although the number of publications addressing urate levels and PD risk is rather small, the results have been relatively consistent [2, 13]. These studies indicate a protective effect of high versus low serum uric acid levels with a risk reduction of 33% [13].

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Furthermore, urate levels were inversely associated with disease progression. Since urate is a powerful antioxidant and oxygen radical scavenger it has been speculated that its protective effect against PD is based on a reduction of oxidative stress [13].

THE GUT AND ITS MICROBIOTA IN PD

In recent years, one important focus of PD research has been on gut related pathology, pathophysiology, and symptoms. Gastrointestinal dysfunction, in particular constipation, affects up to 80% of PD-patients and idiopathic constipation is one of the strongest risk-factors for PD [1, 14]. In PD, prolonged intestinal transit time and constipation are associated with α-synuclein accumulation and neurodegenerative changes in the enteric nervous system [15]. Furthermore, there are signs of local inflammation, oxidative stress, and increased mucosal permeability [16, 17]. These changes can be found in earliest stages of PD, sometimes years before the appearance of motor symptoms, lending support to the hypothesis that environmental factors relevant for PD pathogenesis might act primarily via the gut [14, 18–21]. One proposed pathophysiological pathway in this context is the induction of intestinal mucosal inflammation leading to accumulation of misfolded α-synuclein in enteric nerves which thereafter could act in a prion-like fashion leading to propagation of the neuropathological changes via autonomic connections to the central nervous system [16, 17, 22].

The human gut is home to 1-2 kg of bacteria, contains 10-times more microbial cells than human cells and these microbes carry approximately 100–200-times more protein coding genes than the human genome [23]. Gut microbiota influence the immune system and the absorption of nutrients, vitamins, medications, and toxic compounds [24–28]. Changes in gut microbiota have been found in a multitude of human diseases fuelling hope for better understanding and new treatments for these disorders [29]. There is an intense bidirectional interaction between gut microbiota and the nervous system influencing brain activity, behavior, as well as levels of neurotransmitter receptors and neurotrophic factors [30–34]. Recently, in a case-control study we identified alterations of gut microbiota in PD, in particular a reduced abundance of bacteria from the Prevotellaceae family [35]. *Prevotella* are mucous degrading diet sensitive bacteria. Some studies have reported an association between higher *Prevotella* abundance and a less developed mucous layer and a higher sensitivity to experimentally induced colitis as well as associations with rheumatic diseases [36–39]. This, however, is in contrast to the strong evidence that a diet rich in fiber, fruit, and vegetables is associated with higher intestinal Prevotellaceae abundance, lower risk for the development of inflammatory bowel disease, and higher production of health promoting short-chain fatty acids (SCFAs) [40–42]. Furthermore, several studies have demonstrated lower *Prevotella* abundance in type 1 diabetes and it has been suggested that this could be related to impairment of mucin synthesis and barrier function [43, 44]. We found no evidence for decreased *Bifidobacteria* levels in PD [45]. However, our analyses were restricted to the taxonomic family level and therefore do not exclude alterations at genus or species levels [35]. In our study, the abundance of Enterobacteriaceae bacteria was related to the severity of postural instability and gait difficulty. The relevance of these bacterial families for PD is supported by previous reports of colonic mucosal invasion by coliform bacteria, increased mucosal permeability, and increased systemic endotoxin exposure in PD subjects [16].

RELATIONS BETWEEN SMOKING AND GUT MICROBIOTA AND THEIR RELEVANCE FOR GUT INFLAMMATION AND PERMEABILITY

The best documented gastrointestinal effect of smoking, after carcinogenesis, is immunomodulation by nicotine and carbon monoxide [46, 47]. Smoking increases the risk for and severity of Crohn's disease, but the opposite is seen with respect to ulcerative colitis [48]. There is also some evidence for an increased risk for gastric ulcers and dose dependent effects on gut motility [49, 50]. Effects of cigarette smoke on intestinal barrier function seem to differ between gut segments. After cigarette smoke exposure mice showed impairment of the intestinal barrier and bacterial translocation in the small bowel, but unchanged or even improved barrier function in the large bowel [51, 52]. Improved gut barrier function has been reported also in human subjects [53]. Overall, the effect of smoke and its constituents on the small bowel seems deleterious, increasing susceptibility for inflammatory stimuli. Instead, in the colon, both pro- and anti-inflammatory effects are seen, possibly depending on genetic and environmental factors and cytokine environment [47]. Importantly, smoking also seems to have an effect on gut microbiome

composition. Not only do smokers have higher abundance of *Bacteroides/Prevotella* in their feces, but this abundance decreases together with that of *Proteobacteria* after smoking cessation while levels of Firmicutes and Actinobacteria increase [54, 55]. Furthermore, improvements in colonic barrier function and inflammation caused by cigarette smoke were associated with a decrease of *Ruminococcus albus* and Enterobacteriaceae [52]. Less smoking in PD subjects alone does, however, not explain decreased Prevotellaceae and increased Ruminococcaceae levels since these findings were independent of smoking status [35]. Reduced inflammation and gut permeability combined with a decrease in Enterobacteriaceae abundance after smoke exposure fits to the co-occurrence of *Escherichia coli* invasion, mucosal inflammation, and permeability increase reported in PD [16, 52]. Even the abovementioned hypothesis of the inverse association of smoking and PD being explained by certain personality traits or loss of nicotine reward is not in contradiction with an involvement of gut microbiota [11, 12]. The gut microbiome influences reward seeking behavior and could therefore influence the propensity to smoke [56].

In summary, smoking affects gut microbiome composition and this seems to go along with improved barrier function and anti-inflammatory effects in the colonic mucosa. It remains to be established whether these simultaneous changes are causally related to each other and eventually to PD. Also a possible reverse effect of gut microbiota on smoking propensity and its relevance for PD is an interesting field for future studies.

THE TRIANGLE OF COFFEE, GUT MOTILITY, AND MICROBIOTA – IS IT RELEVANT FOR GUT DYSFUNCTION IN PD?

Regarding coffee the best documented effects on the gastrointestinal tract are promotion of gastro-oesophageal reflux, stimulation of gallbladder contraction and an increase of colonic motor activity [57]. Distal colonic motility increases as early as 4 minutes after coffee ingestion [58]. These effects are unlikely mediated by caffeine, instead an indirect action on the colon mediated by neural mechanisms or gastrointestinal hormones has been suspected. Coffee consumption is also inversely associated with the prevalence of self-reported constipation [59]. Some effects of coffee might be related to constituents such as alkaloids, phenolic compounds, fibers, and minerals. Dietary fiber contained in coffee has marked effects on gut microbiota. It is rapidly metabolized into SCFAs and causes a marked expansion of *Bacteroides/Prevotella* bacteria [60]. *In vivo*, one study found a decrease of *Bacteroides* after coffee consumption while another did not find changes of *Bacteroides/Prevotella* [61, 62]. This could, however, indicate an expansion of *Prevotella* bacteria since their abundance is inversely associated with that of *Bacteroides* [63]. *In vivo*, coffee caused an increase of anti-inflammatory *Bifidobacteria* and a decrease of *Clostridium spp.* and *Escherichia coli* that invade the gut mucosa in PD [16, 61, 62, 64].

It is important to consider that alterations in gut motility, as found in PD, and gut microbiome composition could be independently related to each other. Decreased *Prevotella* abundance and, more consistently, a decreased abundance of *Bifidobacteria* were found in constipated subjects [65–67]. In our recent study, however, we did not find such associations. Instead, constipation was associated positively with abundance of Verrucomicrobiaceae and negatively with levels of Bradyrhizobiaceae [35]. Apparently, constipation itself may predispose to microbiome alterations, increased mucosal permeability, and inflammation [66].

In summary, there seem to be complex interrelations between coffee and more generally the amount and type of consumed polysaccharides, gastrointestinal transit, and microbiome composition that are not well understood, but may have connections to mucosal permeability and inflammation [68]. All these domains are known to be altered also in PD and in the few studies available, microbiome changes induced by coffee somewhat resemble what has been seen in the microbiome of control subjects versus PD patients [16, 35]. Although direct evidence for the relevance of these interactions for phenomena seen in PD is still missing, there is an intriguing framework for hypothesis generation.

GUT MICROBIOTA ARE RELATED TO SERUM URATE LEVELS, BUT LITTLE IS KNOWN ABOUT LOCAL EFFECTS IN THE GUT

Although relatively scarce, data regarding the relationship between gut microbiota and urate metabolism mostly corroborate recent microbiome findings and lower urate levels in PD. In particular, it has been

Table 1
Summary table of bacterial taxa that have been reported to show altered abundances in the colon or feces in relation to PD and/or PD risk modifiers (includes *in vitro* as well as *in vivo* studies on humans and animal models)

Taxon	Abundance in PD vs. Controls	Effect of smoking	Effect of coffee	Association with higher urate levels	Remarks	References
Bacteroidetes					Together with Firmicutes constitute over 90% of distal gut microbiota.	[72]
Prevotellaceae	↓				Positively associated with levels of the neuroprotective gut hormone Ghrelin. Increased abundance reported in ankylosing spondylitis.	[35, 39, 73]
Prevotella		?	↑?	↑	Breakdown of carbohydrates and mucous. Abundance correlates with fiber, fruit, and vegetable consumption and is inversely related to *Bacteroides* abundance. *Prevotella copri* has been associated with rheumatoid arthritis. Low abundance has been associated with autism and type I diabetes.	[36–38, 40, 42–44, 54, 55, 60–63, 69, 74]
Bacteroidaceae						
Bacteroides		?	↓	↓	Abundance positively associated with protein- and animal-fat-rich "western" diet and inversely related to *Prevotella* abundance.	[40, 54, 55, 60–63]
Firmicutes		↓			Together with Bacteroidetes constitute over 90% of distal gut microbiota.	[72]
Ruminococcaceae	↑				Higher abundance was not PD specific in confounder adjusted analysis.	[35]
Ruminococcus albus		↓			Obtain nutrients by breaking down cellulose. Ferments glucose and xylose.	[52]
Lactobacillaceae	↑				May perform several beneficial roles including immunomodulation, interference with enteric pathogens, and maintenance of healthy intestinal microflora. Inversely associated with levels of the neuroprotective gut hormone Ghrelin. Modulate activity of enteric neurons.	[35, 73, 75, 76]
Clostridiaceae (IV)	↑				↓ in confounder adjusted analysis	[35]
Clostridium			↓		Around 100 species that include common free-living bacteria, as well as important pathogens.	[62]
Proteobacteria		↑				[54, 55]
Enterobacteriaceae		↓			A large family of bacteria that includes, along with many harmless symbionts, also familiar pathogens. Abundance associated with PIGD symptoms in PD patients. Increased abundance reported in autistic children.	[35, 52, 77]
Escherichia coli			↓		Includes hundreds of different strains that are involved in food digestion, but some can cause intestinal and extra-intestinal infections. Invade gut mucosa in PD.	[16, 62]
Bradyrhizobiaceae	↑				Was negatively related to constipation in PD microbiota study.	[35]
Actinobacteria		↓				[54, 55]
Bifidobacteriaceae						
Bifidobacterium			↑		Ubiquitous, endosymbiotic inhabitants of the gastrointestinal tract, vagina, and mouth. Some strains are considered important probiotics. May exert beneficial health effects such as immune modulation, inhibition of pathogens, and bioconversion of dietary compounds into bioactive molecules. Improve gut mucosal barrier and lower levels of lipopolysaccharide in the intestine.	[61, 62, 64, 78]
Verrucomicrobia						
Verrucomicrobiaceae	↑				Was positively related to constipation in PD microbiota study.	[35]

Taxonomic levels: **Phylum**, Family, *Genus/Species*. ↑/↓ = Direction of bacterial abundance difference related to the respective factor. ? = Alterations of abundance have been reported, but reports are inconclusive since *Bacteroides/Prevotella* were analyzed as one group although abundances of these genera are usually inversely related to each other.

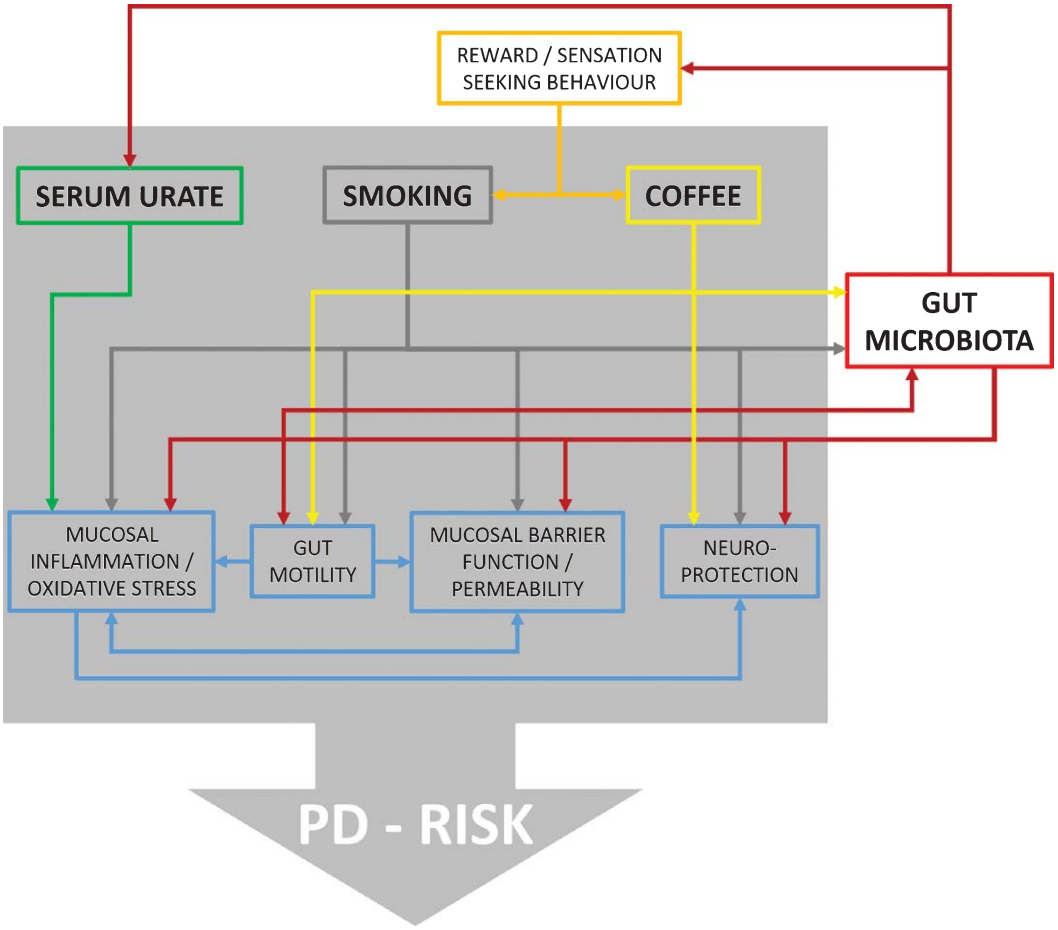

Fig. 1. Flow chart illustrating reported effects between urate, smoking, coffee, and different physiological domains with possible relevance for PD risk. Furthermore, it is shown which of these factors are also related to changes in gut microbiota providing ground for interactions. However, at present direct evidence for such interactions is missing and information is derived from *in vitro* as well as *in vivo* studies on humans and animal models.

shown that the *Prevotella* dominated enterotype, which seems to be underrepresented in PD subjects, is associated with higher serum uric acid levels [35, 69]. This could be due to a lower activity of hydroxyisourate hydrolase, which is involved in the conversion of uric acid to allantoin (intestinal uricolysis) [69]. With respect to effects of uric acid on gut physiology, mainly oxidative stress and inflammation have been studied, but results are heterogeneous and cannot necessarily be extrapolated to systemic or central nervous compartments. In plasma, uric acid accounts for about half of the antioxidant capacity, while in colonic biopsies, it has only a small contribution [70]. In the gut mucosa, xanthine oxidase is upregulated in response to oxidative stress [52]. However, in addition to producing uric acid, this enzyme also produces reactive oxygen species. Therefore, an increase in uric acid production may actually go along with increases in oxidative stress and inflammation, at least in the gut mucosa [70, 71]. The *Prevotella* enteroype produces high amounts of the anti-inflammatory SCFA butyrate which likely influences colonic uric acid levels [40, 43, 70]. Thus, in particular Prevotellaceae, that mainly determine microbiome differences between PD patients and controls, seem to be related also to urate metabolism, providing ground for further studies.

CONCLUSIONS

Considering the well established gastrointestinal abnormalities in PD and the vast interactions of gut microbiota with the human host, it seems mandatory to explore whether gut microbiota are involved in this devastating disorder. The recent discovery of gut microbiome alterations in PD is a promising first step, but obviously only a scrape on the surface. Intriguing

associations have been reported based on which microbiota could indeed play a role at the interface between environmental and lifestyle factors and PD. Figure 1 gives an overview of these possible connections and Table 1 provides a list of the taxa mentioned in this context. However, data about the mechanisms behind these associations and their relevance for PD is scarce. The most promising domains seem to be related to gut barrier function, inflammation, oxidative stress, gut motility, and metabolism. By studying these we may gain more insight into the hugely complex network of microbiome-host-interactions underlying the observed associations. Longitudinal studies integrating metagenomic, transcriptomic, metabolomic, and systems biology approaches with clinical parameters and eventually interventional studies will hopefully elucidate the temporal and mechanistic relationships between established risk modifiers, gut microbiota, and PD.

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