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The relationship between the stomach and the brain: investigating *Helicobacter Pylori* infection pathways and its association with Parkinson's disease

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Abstract

Parkinson's disease (PD) is a chronic neurodegenerative disorder primarily diagnosed based on its clinical manifestations. Reactive oxygen species (ROS) and inflammatory factors play crucial roles in triggering and developing PD. Helicobacter pylori (H. pylori) is a common gastrointestinal infection typically associated with peptic ulcers. However, recent studies have revealed associations between H. pylori and various other disorders. While the exact mechanism remains unclear, H. pylori can disrupt drug absorption and modulate pathways such as inflammatory responses. Patients with PD have shown a high prevalence of H. pylori. Furthermore, H. pylori can induce motor symptoms by interfering with the absorption of levodopa, the primary drug used in PD treatment. Eradicating H. pylori in PD patients through antibiotic therapy can enhance levodopa absorption and alleviate motor symptoms.

Keywords: Parkinson's disease, Helicobacter pylori, Oxidative stress, Drug absorption, Inflammatory factors.

Introduction

Parkinson's disease (PD), the second most commonly diagnosed neurological disorder among individuals over 60 years old, is closely linked to age, following Alzheimer's disease.[1,2] In PD, there is a significant reduction in dopamine production in the Substantia Nigra region due to neuronal death. Diagnosis of PD typically involves assessing motor symptoms like bradykinesia, muscle stiffness, tremors, and gait issues, as well as non-motor symptoms such as stress, anxiety, insomnia, constipation, and digestive and swallowing difficulties.[1,3] Notably, digestive issues were first described by James Parkinson in 1817 and have gained prominence in recent years as key non-motor symptoms of PD.[4,5]

Heredity is believed to play a major role in PD, with environmental factors like pathogenic infections also influencing disease progression.[6] Recent research has highlighted the potential impact of the brain-stomach axis, particularly through gut bacteria, on PD.[7,8] Study by Sampson et al. have suggested that intestinal microbiota may contribute to neuro-inflammation in PD, leading to the proposal of the "brain-gut axis" theory.[9] Additionally, α-synuclein, a prion-like protein, has been implicated in PD pathophysiology and has been found in the enteric nervous system of PD patients.[10] Sampson et al.'s study further supports the idea that gut bacteria can exacerbate α-synuclein-mediated motor disorders and that eliminating gut bacteria could reduce neuro-inflammation in animal models of PD.[11]

Helicobacter pylori (*H. pylori*), a gram-negative bacterium present in approximately half of the global population, is known to cause gastric ulcer disease and chronic stomach inflammation, with implications for other gastrointestinal conditions.[12,13] H. pylori infection triggers immune responses involving neutrophils, macrophages, dendritic cells, T cells, and B cells in the stomach's mucous membrane, leading to the release of various chemokines and interleukins.[14] The production of

reactive oxygen species (ROS) and reactive nitrogen species (RNS) by neutrophils and macrophages can induce gene expression changes in stomach mucosal cells, potentially contributing to PD development [Figure 1].[15] Physiological functions like gastric acid secretion can modulate inflammatory responses in chronic H. pylori-induced gastric defects and impact drug absorption and gastric motility.[16,17] Research by Lahner et al., has suggested an association between drug metabolism disorders and H. pylori infection, proposing that H. pylori can affect the bioavailability of levodopa through the duodenal mucosa.[18,19]

Objectives

This study focuses on exploring the pathways of H. pylori infection and its role in PD pathogenesis. Given the high prevalence of H. pylori infection (32-70%), we suggest that targeted treatment for PD addressing H. pylori infection could enhance disease management with greater precision and efficiency by eradicating the bacterium.

Methods

We conducted a search on the PubMed database to compile the current article using terms and Boolean operators such as "(Helicobacter Pylori OR H. pylori OR HP) AND (Parkinson's disease OR Parkinson disease OR Parkinsonian OR Parkinsonism OR PD)." The search was conducted in English without limiting it to specific publications or years.

Link between H. pylori Virulence Factors and PD

The etiology of PD remains elusive, leading to the availability of only symptomatic treatments. Recent developments have suggested interactions between genetic predispositions and exposure to environmental agents, with toxins and infectious factors potentially contributing to the selective but widespread multisystem loss of neurons in PD. Some researchers argue that the gastrointestinal system may play a pivotal role in the etiology and progression of PD.[20] Several factors may support the pathogenesis of H. pylori, including its association with virulence components such as Flagella, LPS, vacuolating cytotoxin A (VacA), and CagPAI cavity poison.[21] In the genome of H. pylori, there are coding regions spanning 40 kbp known as CogPAI,[22] which can encode the cytotoxin-associated gene A (CagA) virulence factor. CagA is a protein transferred from H. pylori to host epithelial cells and activated by tyrosine phosphorylation by the host src kinase, leading to cellular responses by targeting host proteins.[22,23] H. pylori possesses various virulence factors that compromise the host immune system, with one extensively studied factor being CagA. Upon entry into host cells, CagA can induce changes in cellular proliferation.[24-26] Additionally, H. pylori secretes another factor called VacA, a toxin that triggers inflammatory cytokines upon entering host cells [Figure 2].[27] Studies have indicated an elevated concentration of hydrogen peroxide (H_2O_2) in positive CagA species during DNA damage in the nervous system.[28,29] Research on Egyptian PD patients demonstrated a significantly higher frequency of H. pylori infection among PD patients compared to healthy controls, consistent with previous studies reporting a high prevalence of H. pylori in PD patients.[20,30] H. pylori may induce an inflammatory state, trigger autoantibody/molecular mimicry mechanisms, and/or cause apoptosis of nerve cells via circulating monocytes, potentially leading to dopaminergic neuron destruction.[31,32] Previous findings have shown greater severity of parkinsonism in H. pylori-infected patients compared to those without H. pylori infection based on clinical scales. There is a possibility that H. pylori's interference with L-dopa absorption is linked to the presence of the CagA gene as a virulence factor in this bacterium.[33] VacA can stimulate calcium influx and ROS generation, leading to NF-kβ activation, thereby triggering a pro-inflammatory immune response that may play a crucial role in the initiation and progression of PD.[34]

Impact of H. pylori on Levodopa Absorption

The initial absorption of levodopa occurs in the duodenum, making it susceptible to influence by H. pylori infection, which can affect both the drug absorption through mucosal damage in this area and the production of ROS.[35] Levodopa solubility is pH-dependent, and alterations in intestinal pH can hinder its absorption [Figure 3]. By eradicating the bacteria in the duodenum, acid secretion returns to normal, enhancing levodopa uptake and improving clinical symptoms of PD.[36,37] Studies have demonstrated that H. pylori eradication leads to increased levodopa concentration in the serum of PD patients. Given that the duodenum is a preferred site for levodopa absorption,[38] inflammation in this region may disrupt levodopa absorption through secretions produced by inflammatory cells, potentially reversible upon eradication of H. pylori.[39] Notably, levodopa absorption can increase by 21-54% post H. pylori eradication, with PD patients experiencing motor dysfunction if eradication treatment fails.[11]

With the significant rise in H. pylori incidence among PD patients over the years, an epidemiological link appears to exist between impaired levodopa absorption and H.

pylori-induced inflammation.[41] Consequently, elderly PD patients often exhibit reduced response to levodopa treatment.[40] A randomized placebo-controlled double-blind trial on PD patients revealed that H. pylori eradication led to improved clinical symptoms and serum levodopa concentration compared to the placebo group receiving only antioxidants, indicating enhanced levodopa absorption post-eradication as the primary reason for improvement.[39] Previous studies have proposed various mechanisms through which H. pylori infection affects levodopa absorption. It has been suggested that H. pylori-induced gut changes may disrupt gastric acid secretion by releasing pro-inflammatory cytokines.[42] Since levodopa solubility is pH-dependent, alterations in gastric acidity can impact its absorption, with eradication treatment potentially normalizing gastric acid release and improving levodopa absorption and clinical outcomes.[37] Furthermore, H. pylori infection can disrupt gastric myoelectric function, leading to gastric motility issues and changes in gastric emptying, further negatively affecting levodopa absorption.[44]

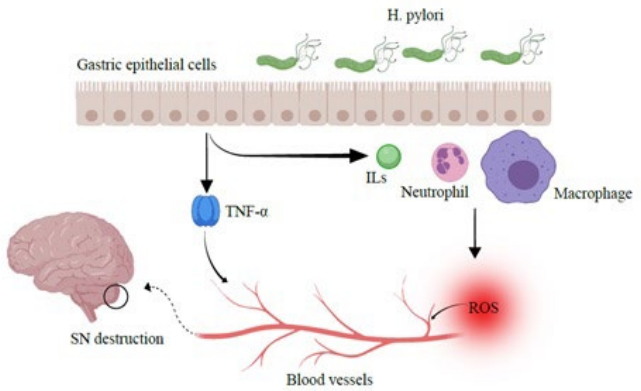

Figure 1. Gastric cells immune response in *H. pylori* infection. Damage to gastric epithelial cells by *H. pylori* bacteria leads to the secretion of TNF-α and interleukins followed by these secretions the ROS will be elevated and then transferred to the brain via blood vessels.

The most common problems of gastrointestinal in PD are as follow:

1; Mouth problems, Inability to collecting saliva, dysphagia, and jaw tremors.

2; Salivary glands problems, decreased saliva creation, but swallowing disorder causes drop saliva uncontrollably from the salivary glands.

3; Pharynx problems, oropharyngeal dysphagia augments risk of aspiration.

4; Oesophagus problems, slow oesophageal passing, oesophageal spasm, spontaneous contractions of proximal oesophagus, air trapping, aperistalsis, and gastro-oesophageal reflux.

5; Stomach problems, gastroparesis, nausea, bloating, early satiety, and weight loss.

6; Small intestine problem, dilatation in the intestine.

7; Colon problems, motility disorder, constipation, volvulus, and bowel perforation.

8; Rectum problems, anorectal dysfunction leads to disorder in excretion.

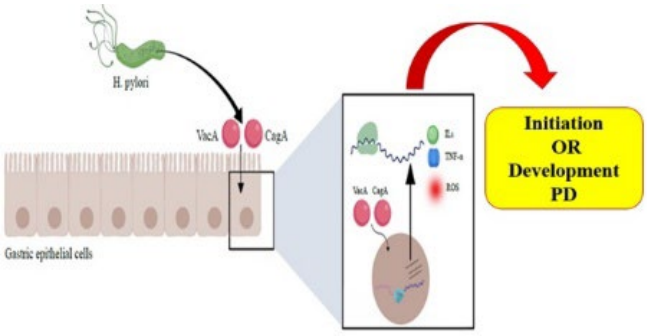

Figure 2. The effect of *H. pylori* secretory proteins on the host cells. Attack of the H. pillory bacteria to the gastric epithelial cells by two specific proteins (Vac A and Cag A) leads to elevated ROS. Vac A and Cag A are two proteins that are produced by H. pillory. These proteins could transfer to the nucleus of gastric epithelial cells and then attach to the host cell's DNA making these host cells produce ROS and initiation or development of PD.

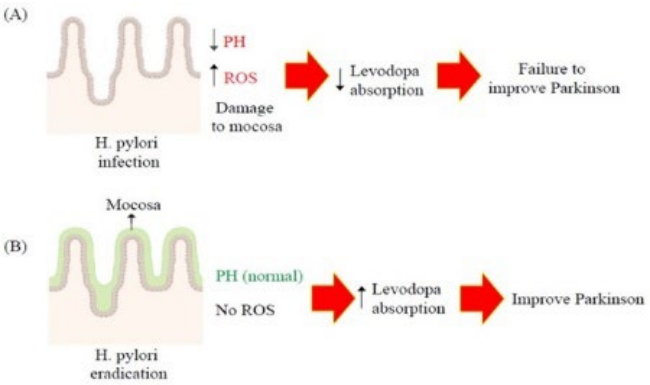

Figure 3. The effect of PH changes induced by *H. pylori* infection on levodopa absorption. H. pillory infection leads to a change in pH to an acidic pH and ROS elevation. These situations are not prepared place to the absorption of levodopa as an anti-PD drug, thus; it leads to unsuccessful PD treatment (A). After eradication of H. pillory by anti-bacterial drugs the gastric mucosa get back to the normal pH and non-ROS status and then, levodopa absorption will be increased (B).

The link between Parkinson's disease and cytokine secretion following H. pylori infection

Chronic inflammatory responses to gastric mucosa caused by H. pylori infection are a major factor in the onset and progression of stomach issues. H. pylori triggers inflammatory processes in gastric epithelial cells and immune cells in the infected area, leading to an increase in interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α) levels.[45] These cytokines play a significant role in gastric pathophysiology, with NF-κβ playing a prominent role in gastric inflammation.[46] Research by Zahaglia et al., has highlighted the transformation of natural gastric mucus into inflammation through the TNF-α gene and other inflammatory factors.[47] TNF-α, specifically associated with H. pylori infection, disrupts gastric acid secretion, which can contribute to digestive issues associated with H. pylori through pH alterations in the stomach.[48,49] These inflammatory processes can lead to the excessive production and accumulation of inflammatory cells and factors in the brain. Studies on inflammation in PD have indicated that microglia and astrocyte cells play a significant role in this process. Microglia, located in the midbrain substantia nigra region, are activated by interferon-gamma (IF-8), inducible nitric oxide synthase (iNOS), IL-1β, and TNF-α. Activated microglia are crucial in the progression of PD.[50] NF-κβ activity in astrocytes in the midbrain region can result in the loss of dopamine-producing neurons in PD-induced mice.[51] Activated microglia can negatively impact dopamine-producing neurons by increasing the production of pro-inflammatory factors like nitric oxide (NO) and cytokines such as IL-6, TNF-α, and IL-1.[52]

The effects of TNF-α are mediated through two receptors, TNFR-55kDa and TNFR-75kDa, expressed throughout the central nervous system (CNS) by neurons, astrocytes, and microglia cells.[53] In Parkinson's disease models, the release of both TNF-α receptors reduced dopamine production in the striatum region while increasing dopamine transport.[54] Studies have shown a significant increase in TNF-α concentration and receptor reactivity in cerebrospinal fluid (CSF) and substantia nigra of PD patients.[50] Binding of TNF-α to these receptors can activate crucial signaling pathways.[55]

Lipopolysaccharide (LPS), a bacterial endotoxin, can increase the secretion of inflammatory factors in cultured microglia and astrocytes.[56] These factors, derived from microglia and other non-neuronal cells, can lead to the degeneration of dopaminergic neurons.[57] Furthermore, inflammation triggered by bacteria has been suggested to initiate misfolding in the α-synuclein structure and its accumulation.[58] Previous studies have shown that inoculation of LPS into the substantia nigra of a mouse model led to the accumulation of α-synuclein.[59] Additionally, an overgrowth of gut bacteria may play a major role in activating degenerative processes in the nervous system related to H. pylori infection.[56] In patients with PD, an overgrowth of gut bacteria is highly prevalent and independently predicts worse motor function.[57]

An IL-1 receptor antagonist can significantly reduce the damage to dopamine-producing neurons induced by LPS or 6-OHDA (an inducer of PD models). Studies have also indicated that IL-6 is associated with motor function in PD patients.[50] Building on this theory, one study demonstrated that men with higher levels of IL-6 had a higher risk of developing PD.[60] The mechanism of the effect of LPS includes 1) the activation of astrocytes and microglia, 2) damage to dopamine-producing neurons, and 3) the release of pro-inflammatory responses.[61,62] Xiao-Yan et al., in a meta-analysis, reported that serum levels of IL-1β, IL-6, and TNF-α are higher in patients with PD. These findings strongly suggest that the clinical symptoms of PD are associated with inflammatory responses.[63]

The IL-1 family consists of three members, including IL-1α, IL-1β, and an IL-1 receptor antagonist. Among these, IL-1α and IL-1β are pro-inflammatory cytokines. IL-1β plays a crucial role in cellular responses to damage in the central nervous system.[64] Some studies have indicated that stimulating IL-1β with LPS induces Parkinson's symptoms, which do not occur in animal models lacking IL-1β.[65,66] Furthermore, administration of high doses of IL-1β has been shown to induce PD symptoms and the destruction of dopamine-producing cells in the midbrain.[67, 68]

IL-6 is a neuropathic cytokine with the ability to stimulate glial cells and affect the differentiation, survival, development, and proliferation of neurons in the central nervous system.[69,70] On the other hand, IL-6 is involved in the production of acute phase proteins and the protection of neurons.[70] Studies have revealed increased levels of IL-6 in post-mortem brains and cerebrospinal fluid of PD patients.[71] Conversely, IL-8 is a chemokine synthesized in response to pro-inflammatory factors in macrophages. IL-8 mediates interactions between glial cells and neurons and can lead to neuronal damage.[72] IL-8 is recognized as an important pro-inflammatory factor influenced by various factors such as hypoxia, ROS, bacterial components, and other cytokines.[73]

Oxidative stress resulting from H. pylori infection is linked to Parkinson's disease (PD)

H. pylori can stimulate the production of ROS and RNS through inflammatory cells and host epithelial cells.[74] Moreover, the oxidation of polyamine spermine by spermine oxidase in gastric epithelial cells can lead to DNA damage and cell death via CogA stimulation.[75]

NADPH oxidase, an intracellular enzyme, is involved in ROS production and bacterial cell death.[76,77] By utilizing electrons from NADPH, NOX can generate O_2 radicals and the hydroxyl radical OH to eliminate bacteria within neutrophils. Prolonged NOX activity aimed at killing bacteria can result in chronic inflammation during persistent infections.[78] Additionally, oxidative stress is believed to be a significant factor in the loss of dopamine-producing cells and the progression of PD.[79-81] Studies on PD patients have identified oxidative stress-related factors as potential prognostic indicators for the disease.[1]

Oxidative stress occurs when there is an excess of free radicals in the body and the antioxidant defense system is insufficient to counteract them. The NOX enzyme is recognized as a key source of ROS production in neurons.[82,83] While the exact etiology of PD remains unknown, factors such as advanced age, genetic predisposition, mitochondrial dysfunction, and exposure to environmental toxins are considered contributors to the imbalance between oxidant and antioxidant systems.[84] The oxidation of dopamine leads to ROS production, and an imbalance in ROS production and removal ultimately results in oxidative stress and neuronal loss.[85]

Conclusions

PD predominantly affects the elderly population and significantly impacts their quality of life. Identifying underlying factors contributing to the disease's development and addressing them can enhance PD treatment outcomes. H. pylori infection is a crucial factor implicated in the onset, progression, and potentially ineffective treatment of PD through various pathways. Therefore, evaluating PD patients for H. pylori infection and implementing eradication therapy when positive can be beneficial. Understanding how H. pylori influences various bodily systems may offer new insights into optimizing PD treatment strategies. Further comprehensive research is needed to elucidate the association between H. pylori and PD for improved patient care in the future.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

Parkinson's disease: PD; Reactive oxygen species: ROS; Reactive nitrogen species: RNS; Nitric oxide: NO; Interleukin-1: IL-1; Interleukin-6: IL-6; Interleukin-8: IL-8; Interferon-gamma: IF-8; Inducible nitric oxide synthase: iNOS; Cerebrospinal fluid: CSF; Lipopolysaccharide: LPS.

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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Availability of data and materials

The data used in this study are available from the corresponding author on request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. Institutional Review Board approval was obtained.

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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