

Received: 23 March, 2020

Accepted: 20 April, 2020

Published: 21 April, 2020

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Keywords: Microbiota; Neurodegenerative disease; Parkinson; Alzheimer

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Mini Review

Intestine microbiota and neurodegenerative diseases: Can microbiota affect the brain?

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Abbreviations

PD: Parkinson's Disease; AD: Alzheimer's Disease; α -Syn; α -synuclein; BBB: Blood Brain Barrier.

Short reviews

The communication between the digestive tract and the brain is an important aspect to the regulation and maintenance of its functionality. This communication is made by a network of signals that the brain sends to the gastrointestinal tract and vice-versa through the gut-brain axis. These signals can be direct or indirect, direct is a signal sent by the pathogen to the brain, while indirect is a signal originated from the alterations that the pathogen triggers. Even though it is not yet completely clear of what it consists, the gut-brain axis is a connection between the intestinal epithelium and the brain, connected by the Vagus nerve, as well as metabolic and nervous pathways [1]. In humans, the intestine is sterile after birth, being colonized by several microbes, by the contact of the mouth with surfaces and food. The gut's microbiota also plays a major role in digestion, being responsible for fermenting proteins and carbohydrates, which are not metabolized by the body. The enzymes produced by these microbes are also known as factors of biotransformation of exogenous molecules such as low solubility drugs, that may not be fully absorbed by the upper parts of the intestine [2]. The imbalance of the microbiota can cause several problems, such as irritable bowel

syndrome, gastrointestinal disorders, imbalance in immune responses. In addition, the imbalance is linked with the cause or the aggravation of neurodegenerative disease such as Parkinson's (PD) and Alzheimer's (AD).

In this short review we utilized the platforms Scencedirect, NCBI and the US National Library of Medicine, where it was selected 11 articles with the keywords microbiota, alzheimer, parkinson, biotransformation and gut-brain axis. Only free full text articles were selected.

Parkinson's disease is a neurodegenerative disorder characterized by the aggregation of α -synuclein (α -Syn), a protein also present in presynaptic terminals, and the degeneration of dopaminergic neurons in the striatum, resulting in motor responses to severely decrease due to lack of dopamine in the brain. Patients with PD present a very distinct intestinal flora in comparison with healthy patients when evaluating the microbial content of fecal matter and gut mucosa. In germ-free models, it has been reported a reduced aggregation of α -Syn, which may suggest that the content of the intestinal flora serves a virulence factor for PD [3]. The intestine microbial imbalance associated with PD can cause several non-motor conditions, such as dysphagia and constipation [4]. Early symptoms of PD can be detected many years before motor ones, the most common symptoms is intestinal inflammation, which causes the differentiation of



immune cells of the intestine, regulated by the intestinal flora, another evidence that the microbiota is a virulence factor for PD [2].

Alzheimer's Disease (AD) is another common neurodegenerative disorder in people older than 60 years, the main symptoms are motor damage and memory loss, consequence of the tauopathy. The main histopathological alteration is the neurofibrillary tangles and beta-amyloid deposits. These deposits are composed of hyperphosphorylated tau protein, which causes neuroinflammation and neuronal death. AD causes progressively memory loss, difficulty in communication and culminating in severe dementia leading to loss of basic psychomotor skills [5]. Moreover, a group from China showed that non lysed bacterial filtrate of *Helicobacter pylori* has shown induction signs of hyperphosphorylation of tau protein *in vivo* and *in vitro*. This suggests that possibly exotoxins produced by this bacteria are capable of passing through the Blood Brain Barrier (BBB), leading to the phosphorylation of tau directly [6, 7].

Although studies regarding the exact content of the intestine microbiota are very recurrent, it is not yet known the amount of bacterial specimens of the guts, and since their location is also difficult to reach, whereas the colon prevents a further examination of the activity in the lower parts of the guts, it is also testing to develop ways of experiment with biotransformation of xenobiotics and endogenous molecules [2]. In AD patients some post-mortem studies found a reduced abundance of *Akkermansia muciniphila*, one of the bacteria responsible for thickening the gut mucosa, its absence has also been previously associated with other dementia hallmarks, such as type II diabetes. It's been found that other bacteria present in AD patients disrupt tight junctions in the intestine, such as *H. pylori*, and some *Escherichia coli* strains. These disruptions might lead to transport of disruptive molecules and bacteria to the bloodstream, thus breaching the BBB, and ultimately to the brain [8]. Additionally, in PD patients the predominance of *H. pylori* leads to motor dysfunctions by blocking the absorption of levodopa, and important medication for PD treatment. Also, it's been found that in PD patients there's a reduced abundance in fecal bacteria of the genus *Blautia*, *Coprococcus* and *Roseburia* [9]. Furthermore, the ingestion of *Proteus mirabilis* in mice has shown an aggravation in motor symptoms caused by PD in mammal models, since bacteria of the family *Enterobacteriaceae* is known to be increasingly present in the colon of PD patients and can cause intestinal inflammation [10].

Finally, epidemiologic studies point to the fact that there's no global pattern to microbial contents, instead, for each region of the globe this pattern shifts. Also, there's no consensus about what specific bacteria is directly capable of causing a pathology due to lack of multicentric studies. It's necessary to realize studies that compare an ample variety of places, including cities, states and countries. This way, it will be possible to reach a consensus about the interaction of the microbe with the pathology.

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Citation: Meirelles EF, Coste Grahl MV (2020) Intestine microbiota and neurodegenerative diseases: Can microbiota affect the brain? *Open J Biol Sci* 5(1): 022-023. DOI: <https://dx.doi.org/10.17352/ojbs.000019>