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The Relation Between the Brain-Gut Axis and Parkinson's Disease

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Abstract: This article is intended to cover the connection between the brain-gut axis and Parkinson's Disease (PD). Neurodegenerative diseases are currently a major area of research in neuroscience, and many have sought to uncover the underlying causes behind these disorders. Many scientific studies suspect that gut bacteria are involved in neurological disorders, but no clear role has been defined. A better understanding of how the intestinal microbiota interact with the brain would be a major advance in neuroscience and could lead to the development of important new treatments for diseases that currently lack effective remedies. This work will cover PD and its specific relationship to the brain-gut axis.

Discussion

Examining the relationship between the brain-gut axis and PD requires analyzing multiple factors. Specifically, three facts must be proven to establish a link between the brain-gut axis and PD. First is the theory that the α-synuclein (αSyn) protein is produced in the gut, misfolds, then travels to the brain through the vagus nerve, as if it were a prion (Del Tredici & Braak, 2008). The second is that α-synuclein aggregations (Lewy bodies) in the brain damage the substantia nigra pars compacta (SNc), which plays a role in movement, leading to PD. The last is that these aggregations also induce an overreaction from the brain's microglia, leading to a pro-inflammatory environment and further damage to the brain as the microglia destroy healthy neurons. An examination of these assertions leads one to find that there are many complications in how the brain-gut axis and PD are linked and that there is still much information that remains unknown.

Several observations support the idea that the vagus nerve transports αSyn. Cell degradation in the vagus nerve often precedes PD by several years, as do intestinal inflammation and constipation. Comparisons of the gut microbiota of healthy individuals and those of individuals with PD have yielded significant differences in which bacteria are present (Sampson et al., 2016). Surgical removal of the vagus nerve has been shown to be effective at preventing PD (Cryan et al., 2019). Researchers have even demonstrated that injecting αSyn fibrils into the gut tissue of healthy rodents will cause dopamine loss

and PD pathology in the vagus nerve and brainstem (Holmqvist et al, 2014; Kim et al, 2019). However, the link between the vagus nerve and brain remains a subject of debate.

Recent research has also shed more light on the exact mechanisms behind αSyn aggregation. Microbiota-containing fecal matter of mice with PD was transplanted to the digestive tract of wildtype mice and compared to mice who received fecal matter from healthy control mice. The experimental group saw an increase in short-chain fatty acid–producing bacteria and short-chain fatty acids (SCFA) in the gut, as well as αSyn aggregations in the brain. It was hypothesized that SCFA accelerate αSyn aggregations, and indeed, once another group of mice was fed with a SCFA-rich diet, they demonstrated an increase in tumor necrosis factor alpha (an indication of inflammation) and αSyn aggregation, as well as a reduction in motor function (Sampson et al., 2016).

Mice who received anti-inflammatory antibiotics did not demonstrate motor dysfunction along or αSyn aggregation (Sampson et al., 2016). The group also noted that SCFA do not accelerate αSyn aggregation in-vitro, indicating that SCFA-mediated αSyn aggregation is likely more complicated than a direct cause-and-effect structure, but rather a series of mechanisms (Sampson et al., 2016). Researchers should further examine currently understood αSyn-related processes to uncover possible mechanisms that can explain the relationship between SCFA and αSyn aggregation. For example, it is well-documented that lipopolysaccharide (LPS), a byproduct produced by gut bacteria, modulates αSyn aggregation in-vitro by forming intermediate nucleating species that assist in αSyn clumping (Bhattacharyya et al., 2019). How LPS could influence PD development in-vivo should be explored by scientists.

Contrasting Findings

However, some reports have contradicted these findings on SCFA. This paragraph will briefly explore the evidence that has challenged the link between SCFA and αSyn aggregation.

One study extracted microbiota from human PD patients and compared them to those of healthy control subjects. The researchers focused on specific bacteria in order to compare them with past studies. They found a reduction in SCFA-producing bacteria in PD patients (Ungel et al., 2016). They also observed a statistically significant decrease in butyrate and propionate (two SCFA) rather than the increase reported by the Sampson study. Bacteroidetes and Lactobacillaceae (both SCFA-producing) bacteria levels were decreased in PD patients, while Bifidobacterium and Enterobacteriaceae levels were higher, potentially indicating that the last two bacteria may be linked to PD development (Ungel et al., 2016). Lactobacillaceae is known to be anti-inflammatory, supporting the idea that inflammation is also linked to PD.

The findings on Bacteroidetes contradicted other studies, but the Lactobacillaceae results are consistent with other studies that indicate that inflammation is positively correlated with PD, and the authors indicate that the Bacteroides results

can be attributed to differences in mean age, disease duration and medication status between the participants in the different studies. Still, more research is needed on how SCFA-bacteria affect αSyn aggregation and PD development.

Discussion Cont.

Returning to the final link between PD and the brain-gut axis, it has also been shown that αSyn produced by SCFA trigger the immune response of the central nervous system (CNS), thereby inducing neuroinflammation (Erny et al., 2015). The Sampson study found that mice treated with SCFAs had smaller microglia but more branches and a longer average branch length than those of mice with depleted gut bacteria (Sampson et al., 2016), indicating that they were more mature.

The authors hypothesize that SCFA increase microglial activation, possibly by passing the blood brain barrier (BBB) and activating SCFA-responsive genes in CNS cells, such as histone deacetylase, thereby altering their physiology. Alternatively, it is possible that the activated genes create peripheral effects that activate microglia by some currently unknown mechanism. This immune response further damages the SNc as microglia overreact and attack healthy neurons, accelerating the onset of PD.

Conclusion

The link between the brain-gut axis and PD is an important but complex topic. Discoveries made in this area could lead to greatly improved medical techniques for treating PD by allowing researchers to understand how PD development occurs. Currently, it is known that gut microbiota, especially SCFA-producing bacteria, affect αSyn aggregation, where αSyn either aggregates in the gut before migrating to the brain via the vagus nerve or triggers αSyn aggregation in the brain through a yet-unknown mechanism (Ungel et al., 2016).

This triggers a pro-inflammatory state in the brain where microglia release chemicals that destroy healthy nerves, leading to PD (Ungel et al., 2016). Much is still unknown about the exact mechanisms involved in each of these steps, as well as if SCFA-levels increase or decrease during PD development. Additionally, many of these experiments have only been carried out in mice or in-vitro, while research involving human subjects has not always yielded consistent data (likely due to differences in the sample populations).

More studies that control for different demographic factors in humans need to be carried out to resolve differences in findings (for example, multiple studies of people with PD in the same age group, living in similar areas and under similar medication). In sum, more in-vitro research is needed to analyze the chemical mechanisms that link the brain-gut axis on a basic level, while more animal and human research is needed to analyze how these mechanisms play out in living creatures.

One focus should be on how SCFA-producing bacteria leads to αSyn aggregation, which plays an important role in PD development. This can be studied by adding chemicals of interest found in the gut and

vagus nerve to an in-vitro culture of SCFA and αSyn to see which allow for αSyn aggregation, as it has already been shown that SCFA cannot induce this by itself. Other research should analyze how this process leads to microglial activation and PD pathology. This can be achieved by analyzing the genes in the CNS that potentially allow αSyn to activate microglia, as well as studying interactions between αSyn and dopaminergic neurons to discover how αSyn damages the SNc.

Much of this research connects to fundamental PD concepts. For example, the reason why damage to the SNc leads to PD is that this region of the basal ganglia (BG) facilitates the BG's direct pathway with its dopaminergic neurons, which allows for voluntary movement. When this region is damaged, it cannot properly carry out its functions, so activity in the direct pathway decreases, which makes voluntary movement more difficult (Holmqvist et al, 2014). In addition, activity in the indirect pathway increases, making it more difficult for patients to inhibit their involuntary movements.

The main result of these changes is bradykinesia, one of the main symptoms of PD. Bradykinesia is characterized by slow movement, where patients have difficulty initiating voluntary movements and carrying them out. However, movements triggered by external stimuli (see as seeing that oneself is about to be hit by a flying object) are generally easier for PD patients. Overall, PD patients experience a reduction in automaticity, as they must concentrate heavily on performing movements that an unaffected person would do with little effort. These ailments mainly stem from damage to the SNc, showing that motor functions are closely tied to this region of the brain.

This research also connects to how neurodegenerative diseases generally occur. Many of these diseases result from the misfolding of a protein, αSyn in the case of PD. The misfolded proteins then aggregate, leading to one of several results. One is loss-of-function, where the protein cannot perform its normal function, or experiences a reduction in function.

Another is gain-of-function, where the protein gains an ability that it did not have previously (for better or worse). Finally, both effects can take place in the protein concurrently. In PD, αSyn seems to gain the ability to damage dopaminergic neurons in the BG. By connecting PD to broader topics within neuroscience, this paper can serve as a starting point for exploring the similarities between the pathological mechanisms of different neurodegenerative diseases.

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