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You Can't Always Trust Your Gut

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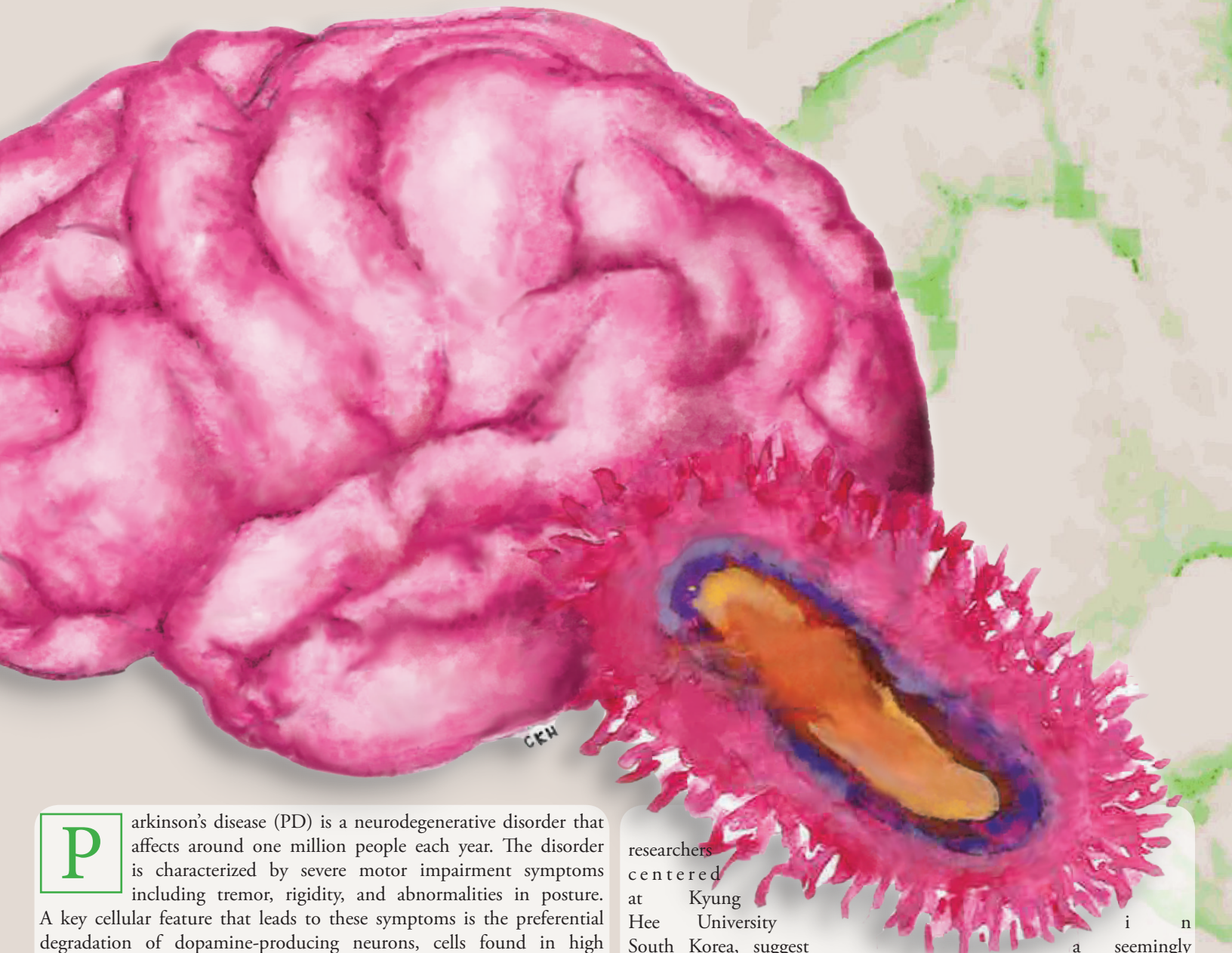

Parkinson's disease (PD) is a neurodegenerative disorder that affects around one million people each year. The disorder is characterized by severe motor impairment symptoms including tremor, rigidity, and abnormalities in posture. A key cellular feature that leads to these symptoms is the preferential degradation of dopamine-producing neurons, cells found in high concentration in areas of the brain such as the substantia nigra and the striatum. The loss of function of these dopaminergic neurons can be moderately rectified by dopamine replacement drugs; unfortunately, these therapies only superficially relieve symptoms and can, paradoxically, further impair motor skills.

The need for more effective therapies for Parkinson's disease is a call for a stronger understanding of what causes it. Choi et al., a group of researchers centered at Kyung Hee University in South Korea, suggest a seemingly unlikely culprit as a contributor to the development of motor impairment symptoms in Parkinson's patients: the gut bacteria Proteus mirabilis. This suggestion stems from the finding that some Parkinson's disease patients suffer from gastrointestinal and urological problems preceding the onset of motor symptoms, which indicates that PD might start in non-neurological tissue. Further, α-synuclein, a protein associated with Parkinson's disease development, has been found in the

intestine of mice before the onset of motor impairment symptoms. There is direct evidence that α-synuclein spreads from the gastrointestinal tract to the brain via the vagal nerve in rats with PD. These discoveries, taken together, suggest that pathological changes in the intestines may induce Parkinson's disease. Analysis of the fecal microbiota of patients with severe PD showed increased amounts of bacteria from the family *Enterobacteriaceae*, suggesting that gut microbial changes may be partially responsible for Parkinson's disease progression. Since there is a dearth of more specific information behind this phenomenon, Choi et al. set out to determine which strain of gut bacteria can influence PD and a possible mechanism for doing so.

To determine which bacteria may be associated with Parkinson's disease, Choi et al., measured the number of bacterial colonies at the family level in animals with PD, then identified the bacteria that were high within specific families. The researchers orally administered these bacteria to the mice, then observed motor behaviors and relevant brain tissues. Finally, the researchers tracked direct damage of dopamine-producing neurons by analyzing change in α-synuclein, a hallmark of Parkinson's disease, levels in the brain. Choi et al. also measured amounts of α-synuclein in the colon to ensure that the protein was indeed coming from the gastrointestinal tract.

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By chemically inducing Parkinson's disease in mice three different ways, Choi et.al. confirmed that the number of *Enterobacteriaceae* was increased in mice with Parkinson's disease; they found that specifically *P. mirabilis* was increased. The researchers then treated mice in the premotor symptom stage (PS) of Parkinson's disease with *P. mirabilis* to see if the bacteria would exacerbate motor symptoms at this early stage of the disease. Treated mice showed severe motor impairment in addition to a significantly lower density of dopaminergic neurons in comparison to both mice in PS not treated with bacteria and control mice. This strongly suggests that *P. mirabilis* may contribute to the onset of motor symptoms in mice with PD. Interestingly, Choi et.al. also found that the increased presence of *P. mirabilis* in healthy mice could also induce motor deficits, further supporting the role of this bacteria in the development of Parkinson's disease.

The researchers connected *P. mirabilis* to Parkinson's disease by showing that the bacteria selectively damages dopamine-producing neurons. Choi et.al. suggest that a possible mechanism for this is that *P. mirabilis* increases α-synuclein production in neurons. Though more experiments are needed to determine the exact mechanism, Choi et.al. observed a significantly higher amount of α-synuclein filaments in the distal colon, substantia nigra, and striatum, which may mean that α-synuclein travels through the vagal nerve to the brain.

The researchers understand how to chemically induce PD in mice, but they are not clear on how the chemical inducers lead to downstream effects such as the increase of *P. mirabilis* in the gut. This raises the question: how do the researchers know that the treated mice actually have PD? Though the mouse models used by Choi et al. were useful for preliminary experiments, the research could benefit from using mice who have naturally developed PD so that the researchers could observe differences in results between mice with naturally occuring PD and chemically induced PD.

The research raises important questions. Is there a protein or other upstream factor that causes the changes seen in Parkinson's disease? Is PD entirely gastrointestinal in nature? The latter seems unlikely as some neurological symptoms of PD, such as memory loss, were not explained by the increase in gut bacteria. Regardless, recent research seems to suggest that the devastating motor effects of Parkinson's disease might simply be surface-level symptoms of pathogenesis that is not even occurring in the brain.

A possible way to determine how much gut bacteria controls PD and its symptoms would be to treat mice with the disease with antibiotics, which would significantly lower the amount of *P. mirabilis* in the gut. This would be accomplished by wiping out the PD gut bacteria and recolonizing the gut with gut bacteria typical of healthy mice. Not only would this experiment allow researchers to gauge the importance of *P. mirabilis*, but it would test the possibility of using antibiotics as a treatment for PD. Antibiotic treatment would likely only treat symptoms of the disease, as much is yet to discovered about the underlying causes of PD. However, antibiotics would not have as severe side effects as dopamine-replacing medications.

We must be cautious extrapolating what was found in chemically controlled mouse models to human patients. Though changes in gut microbiota have been observed in human PD patients, whether or not those changes reflect the extremely simple model shown in Choi et al. is yet to be seen. The chemical that the researchers used to induce Parkinson's disease in mice may have directly increased the amount of *P. mirabilis* in mice. It is possible that this same shift in the gut environment would not be seen in human patients. This question calls for a clinical trial that samples the gut bacteria of human Parkinson's disease patients and analyzes the microbiota to determine which species are being upregulated in the gut.

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Parkinson's disease is most commonly seen as a neurological disease. People associate it with aging and brain deterioration, which is not necessarily incorrect. However, Choi et al. and other researchers have made it clear that this view is an oversimplification. With this knowledge that Parkinson's could be traced back to specific imbalances in the gut microbiota, researchers and physicians have a new basis for future experiments and therapies that could fight PD at the very core, reducing the need for superficial therapies with harmful side effects.