Microbiome and neurodegeneration

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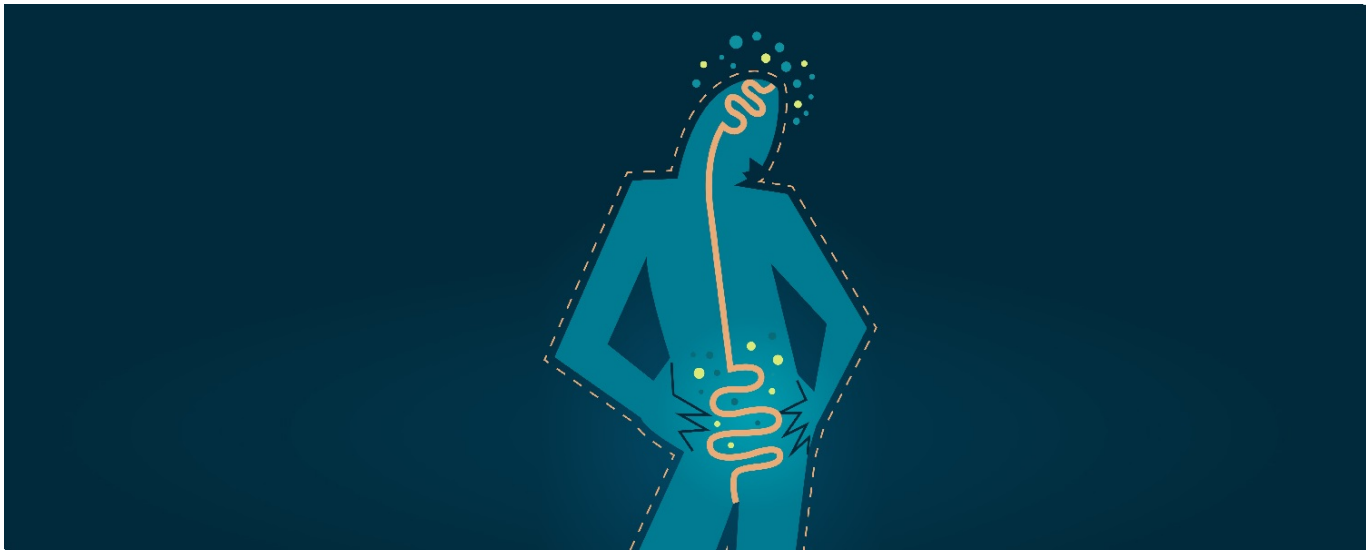

A recent study has established a link between specific gut bacteria species and the physical manifestations of neurodegenerative diseases ([1]).

Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) are characterised by problems with the way proteins are handled in the body. The misfolding and accumulation of proteins in the brain often results in the loss of tissue function that promotes disease progression ([2]). Millions of adults around the world suffer from these "protein conformational diseases" (PCDs), resulting in enormous financial and social burdens on the individuals themselves as well as their carers ([3]). There is still no effective treatment or cure for PCDs, and the cause is still largely unknown ([4]).

Factors such as age, diet, stress, trauma, toxins, infections, or antibiotics, have been shown to increase the risk of PCDs. These triggers are also associated with changes in the microbiome which suggests that bacteria may contribute to the pathogenesis of PCDs. However, the relationship between the microbiome and disease progression remains poorly defined.

Evidence has established a link between human gut dysbiosis or direct intestinal infection and exacerbation of PCDs ([5],[6],[7]). Commensal residents of the human microbiota, specifically those involved in the synthesis of short-chain fatty acids (SCFAs) such as butyrate, are beneficial in brain disorders ([8]).

Environmental factors and the complexity of the human microbiome make the complex study of the effect of the microbiome on PCDs difficult ([9]). This latest study was carried out on *C. elegans* and showed that specific species of bacteria play a role in the development of PCDs. Commensal butyrate-producing bacteria can counteract these pathogenic strains ([1]).

Pathogenic strains

Among all of the strains that were tested, *Klebsiella* spp. and *P. aeruginosa* were the most potent inducers of misfolded protein aggregation. Both of these species are ubiquitous in the environment, and multidrug-resistant strains of these bacteria are often associated with nosocomial and opportunistic infections ([10]). While these strains are often associated with infections, they are also present in the intestines of healthy individuals, which may possibly support their contribution to neurodegenerative diseases ([11],[12]). In fact, both of these microbes have recently been associated with neurodegenerative diseases in humans ([13],[14]). The increasing prevalence of antibiotic resistance among *Klebsiella* spp. and *P. aeruginosa* strains may specifically encourage their growth within the human microbiome during antibiotic treatment while decreasing the abundance of beneficial bacteria. Population-based studies of patients with PD and ALS support this hypothesis, revealing that a history of antibiotic treatment is associated with an elevated risk for these diseases ([15],[16]). However, more research is required before we can understand what, if any, connection there is between antibiotic resistance and neurodegenerative diseases.

Another notable strain that induced aggregation by more than three-fold is *P. mirabilis*. This gram-negative bacterium is part of human commensal microbiota but can also become an opportunistic pathogen, most often leading to urinary tract infections, and eventually, bacteraemia ([17]).

A surprising and interesting finding from this study is the fact that the offspring of affected *C. elegans* also showed increased protein aggregation, even though these offspring never encountered the bacteria originally associated with the condition. This suggests that these bacteria generate some sort of a signal that can be passed along to the next generation.

Butyrate

The depletion of butyrate-producing bacteria in the gut establishes an environment in which pathogenic bacteria can flourish ([18]). In addition, butyrate itself has been found to suppress the growth of pathogenic bacteria and was shown to protect against neurodegeneration ([19],[20]). SCFA-producing bacteria are common residents of the human gut microbiota. Many of these bacteria, such as those belonging to the Firmicutes phylum, are known to produce butyrate ([21]). Butyrate has been demonstrated to provide numerous health benefits against a variety of ailments, and neurodegenerative diseases are no exception ([20]). Results from this recent study demonstrate that butyrate can suppress protein aggregation and the associated toxicity when supplied exogenously or produced by intestinal bacteria ([1]).

Results also indicate that butyrate may inhibit bacteria-induced aggregation by activating protective stress responses, in particular, oxidative stress responses. Bacteria are known to trigger oxidative stress, which can contribute to protein aggregation ([22]). It is possible that various bacteria introduce different levels of oxidative stress and the strongest contributors affect host protein homeostasis, consequently leading to misfolding and aggregation of proteins. In fact, oxidative stress is one of the major contributors to PCDs ([23]).

Limitations

The results in this study demonstrate that bacteria alone do not cause major toxicity in control animals that do not express metastable aggregation-prone proteins, which indicates that other factors are at play in the aetiology of neurodegenerative diseases. However, in those that do express aggregate-prone proteins, gut bacteria play a role in disease progression.

Conclusion

These latest results indicate that endogenous butyrate synthesised by butyrate-producing bacteria can enhance host protein homeostasis and suppress protein misfolding in the brain. Butyrate and butyrate-producing bacteria also show potential benefits in the suppression of bacteria-induced protein-associated toxicity. This highlights the importance of having a balance between commensal butyrate-producing and intestinal pathogenic microbes.

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