J Physiol 00.0 (2020) pp 1–2

The Journal of Physiology

PERSPECTIVES

Can we trust the gut? The role of the intestine in neurodegeneration

Karl-Herbert Schäfer, Anne Christmann and Manuela Gries
Working Group Enteric Nervous System, University of Applied Science Kaiserslautern, Zweibrücken, Germany

E-mail: karlherbert-schaefer@hs-kl.de

Edited by: Kim Barrett & David Grundy

Linked articles: This Perspectives article highlights an article by Sun *et al.* To read this paper, visit https://doi.org/10.1113/JP279919.

A 2500-year-old statement by the ancient Greek physician Hippocrates claims that 'All disease begins in the gut'. While conservative medicine kind of ignored the primacy of the gut, traditional medical systems always acknowledged that it plays a central role in a broad range of diseases and provided – sometimes strange – treatments such as purgatives to get rid of toxins or anal tobacco fume infusions to heal acute abdominal pain.

Since the gut harbours an intrinsic nervous system containing more neurons than the spinal cord, it is obvious that it might also be involved in neurological disorders. Patients with Parkinson's disease (PD) suffer from constipation or delayed gastric emptying long before 'typical motoric' Parkinson's symptoms occur. These findings together with experimental data provided evidence that PD might even start in the gut. It appears plausible that PD affects not only neuromuscular functions in the skeletal muscle system, but also impacts the intrinsic nervous system of the gut, the enteric nervous system (ENS), and thus gastrointestinal motility. In contrast, this seems to be completely different when we talk about neurodegeneration of the cognitive system, as we see it in Alzheimer's disease (AD). The idea of the gut taking part in AD is not new, but it still needs more evidence to confirm this long-widespread suspicion. The deposition of amyloid β (Aβ), one of the hallmarks of AD in the brain, could already be shown in the gastrointestinal tract of AD patients about 30 years ago, but without prompting further investigations for a long time. Maybe the cognitive aspect of motor dysfunction in the gut was too visionary to be taken seriously.

Either we suppose that we do think with the gut, or we believe that AD might also compromise gastrointestinal motoric functions; both seem to be true. The gastrointestinal motoric activity goes along with a dedicated cross-talk between macrophages and the ENS in the gut wall, while we know at the same time that the gastrointestinal immune system is also impaired in AD. But what exactly is altered in the immune system in AD conditions within the gut? Puig *et al.* (2012) used an APP-/- model to impressively demonstrate the alterations in immune cell secretions and their phenotype. APP, the amyloid-precursor-protein, is a ubiquitous molecule in all cells, and is located in the cell membrane. It can be sliced by specific enzymes either within the membrane or out of the cell, thus generating pathological Aβ peptides. Morphological alterations of the macrophages in the gut wall were also present in an APP/PS1 overexpressing AD mouse model (Semar *et al.* 2013). In this model, both the Alzheimer's-relevant peptide APP and presenilin-1 (PS1) are overexpressed and induce an Alzheimer's morphology in the central nervous system. In this longitudinal study, alterations of inflammatory (Toll-like-receptor 4, TLR4) and reactive gliosis (glial acidic fibrillary protein, GFAP) markers were found in the ENS, long before these changes appeared in the brain. Moreover, the amount of neuronal tissue in the ENS tissue was reduced in both myenteric and submucosal plexus in the adult animals and their gastrointestinal motility was significantly reduced.

Since we know from prion diseases that there is a direct highway from the gut to the brain, we have to consider that neurodegeneration might also start in the gut and progress to the brain. While these routes have been described for PD, it is a completely different story to argue that a cognitive disease might also start from the gut and travel along the vagal nerve to induce AD in the brain. A novel exciting study (Sun *et al.* 2020) delivers amazing insights and perspectives towards a shift in paradigms concerning AD. The authors injected A$\beta_{1–42}$ into both the stomach and colon, and investigated its distribution at different time points. Within 3 h, the peptide could be localized in cholinergic neurons of the myenteric plexus. This corresponds to findings in the human brain and also to the fact that A$\beta_{1–42}$ binds selectively to α_7 nicotinic acetylcholine receptors. So tobacco fume infusions might find their targets! While these findings are interesting, the data from the cognitive test one year after the gastrointestinal injections of A$\beta_{1–42}$ are spectacular: the injected mice showed both significant cognitive deficits and impaired long-term spontaneous memory. Aβ plaques were widely distributed all over the brain and were found especially in the hippocampus cortex and amygdala. Furthermore, Aβ was found in both the vagal nerve and blood vessel walls of the brain. While these findings nicely demonstrate the progression of Aβ from the gut to the brain we still need to know how the Aβ enters or appears in the gut in the first place, without being injected there.

There are many potential players that might induce an Aβ pathology into the gut; for example, by preventing the clearance of the peripheral Aβ load. Starting from nutrition, intoxication, dysbiosis or others, there seems to be a complex cross-talk between the individual players and factors. Any imbalance or synergistic and accumulative aggravation of isolated harmless factors can trigger the fatal event. There might be a vicious circle starting with a defective mucosal barrier or fatal signals from the microbiome or its metabolites using the neuroendocrine sensor system (enteroendocrine cells, Bohorquez *et al.* 2015) that alters the local neuroimmunological environment inducing a fatal cascade that ends up with pathological aggregated peptides such as Aβ or alpha-synuclein.

Similar to PD, the microbiome in AD seems to be one of the key players in this fatal game and is found to be altered in AD mouse models and patients. Unfortunately, it is still unknown what is triggering what; AD the microbiome changes or the microbiome changes AD. Interestingly, a recent study proves that Aβ exposition to the gut microbiome does rapidly lead to significant alterations (Dos Santos *et al.* 2020).

So we have to look at the big picture and study the ENS, the immune system and the microbiome as an interacting unity to understand the role of the gut in the aetiology of neurodegenerative diseases. This might enable us not only to understand

DOI: 10.1113/JP280336

what is going on in the gut while neurodegenerative processes occur, but additionally provide us with the tools to diagnose the disease early enough in the gut to open up new options for early treatment.

References

Bohorquez DV, Shahid RA, Erdmann A, Kreger AM, Wang Y, Calakos N, Wang F & Liddle RA (2015). Neuroepithelial circuit formed by innervation of sensory enteroendocrine cells. *J Clin Invest* **125**, 782–786.

Dos Santos Guilherme M, Todorov H, Osterhof C, Möllerke AAS, Cub K, Hankeln T, Gerber S & Endres K (2020). Impact of Acute and Chronic Amyloid-β Peptide Exposure on Gut Microbial Commensals in the Mouse. *Front Microbiol*, https://doi.org/10.3389/fmicb.2020.01008. eCollection.

Puig KL, Swigost AJ, Zhou X, Sens MA & Combs CK (2012). Amyloid precursor protein expression modulates intestine immune phenotype. *J Neuroimmune Pharmacol* **7**, 215–230.

Semar S, Klotz M, Letiembre M, Van Ginneken C, Braun A, Jost V, Bischof M, Lammers WJ, Liu Y, Fassbender K, Wyss-Coray T, Kirchhoff F & Schäfer KH (2013). Changes of the enteric nervous system in Amyloid Precursor Protein transgenic mice correlate with disease progression. *J Alzheimers Dis* **36**, 7–20.

Sun Y, Sommerville N, Liu JYH, Ngan M, Poon D, Ponomarev ED, Lu Z, Kung JSC & Rudd JA (2020). Intra-gastrointestinal amyloid-β1-42 oligomers perturb enteric function and induce Alzheimer's disease pathology. *J Physiol*, https://doi.org/10.1113/JP279919.

Additional information

Competing interests

There are no competing interests.

Author contributions

KHS designed and wrote the text. MG and AC worked on the manuscript and discussed the content.

Funding

AC was supported by a DFG grant: SCHA/11-1.

Acknowledgements

Open access funding enabled and organized by Projekt DEAL.

Keywords

Alzheimers disease, brain-gut axis, enteric nervous system