Journal of Nuclear Medicine, published on July 22, 2021 as doi:10.2967/jnumed.121.262300

ARadionuclide imaging of the gut-brain axis in Parkinson's disease

Jacob Horsager[1], Karoline Knudsen[1], Per Borghammer[1]

[1] Department of Nuclear Medicine and PET, Aarhus University Hospital, Denmark

Total word count: 1498

Running Title: Imaging of gut-brain axis in PD

The gut-brain axis is a bidirectional communication system between the enteric- and central nervous system, comprising neuronal, hormonal, and immunological mechanisms. For instance, the autonomic nervous system allows bidirectional communication through parasympathetic and sympathetic efferent and afferent neurons. Compelling evidence support that enteric microbiota has a considerable influence on this intricate system. Thus, potential targets for radionuclide imaging of the gut-brain axis comprise the autonomic nervous system and gut microbiota, including microbiota-specific substances.

Gut microbiota compositional changes in patients with Parkinson's disease (PD) have been reported in several studies, and may influence pathogenesis in several ways. For instance, curli-producing *Escherichia coli* bacteria have been documented to induce α-synuclein aggregation in the gut (*1*). These aggregates may then spread via autonomic neurons to the central nervous system including the substantia nigra (and many other structures), eventually causing PD (*2*). To date, no microbiota-related imaging studies have been published, but validated methods to visualize the autonomic nervous system exist. We have previously hypothesized that PD comprises two subtypes: one that originates in the enteric nervous system and spreads via the autonomic nervous system to the brain (body-first); and one that originates within the central nervous system and spreads via neuronal connections to other parts of the brain and the autonomic nervous system (brain-first). In this framework, the autonomic nervous system is affected at very different time points of the disease depending on the subtype. Thus, radionuclide imaging of the autonomic nervous system may serve as an essential tool to get a detailed understanding of the temporal development of PD.

Parasympathetic innervation can be measured with the PET radiotracer 5-^{11}C-methoxy-donepezil (^{11}C-donepezil), an acetylcholinesterase inhibitor. It is a reproducible method to quantify the cholinergic terminals in the gastrointestinal tract. Kinetic modeling of several internal organs shows strong correlation between tracer volume-of-distribution and standard uptake value (SUV) (*3*). Therefore, a simple static image 45 minutes after ^{11}C-donepezil injection yields high-quality

images of the gastrointestinal acetylcholinesterase density mirroring known cholinergic innervation (Fig. 1). The first comparative study in early-to-moderate stage PD patients showed a significantly decreased signal in the pancreas (22% loss) and the small intestines (35% loss) (*4*). The colon was not investigated in that study. Next, in early-stage PD patients a 22% loss was detected in the colon, and 14% loss in the small intestine and renal cortex (*5*). In a study of patients with isolated REM-sleep behavior disorder (iRBD), the strongest prodromal marker for PD, the colon and small intestine ^{11}C-donepezil SUV was decreased to the same extent as in patients with PD (*6*) (Fig. 1). This firmly suggests that some PD patients (those who develop RBD before parkinsonism) exhibit severe autonomic denervation years before they get a PD diagnosis. This hypothesis was tested in a recent study where *de novo* PD patients were allocated to a brain-first group (without premotor RBD) and a body-first group (with premotor RBD) (*7*). Brain-first patients should, according to the hypothesis, have almost intact parasympathetic innervation of the colon. Conversely, body-first patients should exhibit severe parasympathetic denervation. Indeed, the body-first group had significantly lower colon ^{11}C-donepezil SUV than the brain-first group. Also, the brain-first group showed only minimally reduced SUVs compared to healthy controls (Fig. 1). This finding supports the hypothesis that PD consists of a brain-first- and a body-first subtype. Recently, the ^{11}C-donepezil PET method was further validated by studying patients with bilateral vagotomy following esophageal cancer surgery. Such patients lack vagal cholinergic innervation of the abdominal organs, except pelvic organs and the descending colon. Indeed, the ^{11}C-donepezil SUV was lower in both colon and small intestine in this patient group (*8*) (Fig. 1). Interestingly, the colonic SUV reduction was most prominent in the proximal part of the colon, mirroring the vagal parasympathetic projections. To summarize, ^{11}C-donepezil PET is a reliable method to quantify acetylcholinesterase density, believed to reflect at least in part the parasympathetic innervation of the gastrointestinal tract.

Future studies of the parasympathetic nervous system should include ^{18}F-fluoroethoxybenzovesamicol (^{18}F-FEOBV), a promising PET tracer to evaluate the cholinergic system. ^{18}F-FEOBV is a vesicular acetylcholine transporter ligand, which is a more specific cholinergic target compared to acetylcholinesterase. Thus, ^{18}F-FEOBV may replace ^{11}C-donepezil in future studies of gastrointestinal parasympathetic innervation.

Radionuclide imaging can also be utilized to assess functional abnormalities in the gastrointestinal tract. Up to 50% of PD patients suffer from symptoms, most likely caused by gastric dysfunction. Despite this, studies using gastric emptying scintigraphy, the gold standard method for objective evaluation of gastric emptying time, have shown considerable heterogeneity and only a modest delay in PD patients (*9*). Also, no robust association with subjective symptoms seems to exist (*9*).

Radionuclide imaging is often accompanied by a CT scan where additional important information can be obtained. Since constipation is one of the most frequently reported non-motor symptoms in PD, several efforts have been made to objectively quantify the degree of colonic dysfunction. Colonic transit time (CTT) can be assessed by the radiopaque marker (ROM) method, where the number of retained markers can be counted on CT scans, and a CTT estimate calculated (*10*). Also, total colon volume is easily obtained from even a low-dose CT scan, and is considered another objective biomarker for colonic dysfunction. In support, CTT and colon volume is tightly correlated (*10*). Comparative studies have shown that patients with PD generally have longer CTT and increased colon volume compared to healthy controls (*10*). Even patients with iRBD have considerably prolonged CTT and increased colon volume (*11*) (Fig. 1). Interestingly, body-first PD patients exhibit significantly increased colon volume and CTT in comparison to brain-first PD patients. Collated, these studies illustrate that objective colonic dysfunction is present years *before* the PD diagnosis in some patients, whereas other patients develop colonic dysfunction *after* the PD diagnosis.

In summary, radionuclide imaging of the parasympathetic nervous system is a reproducible method to investigate autonomic degeneration in patients with PD. CT imaging provides additional information of gut dysfunction. Future radionuclide studies of the gut-brain axis in PD should explore new molecular targets, e.g. targets in the sympathetic nervous system, enteric nervous system, and microbiota-specific substances. Such studies will further elucidate the importance of the gut-brain axis in PD and other important disorders including diabetic neuropathy.

Disclosure

No potential conflicts of interest relevant to this article exist.

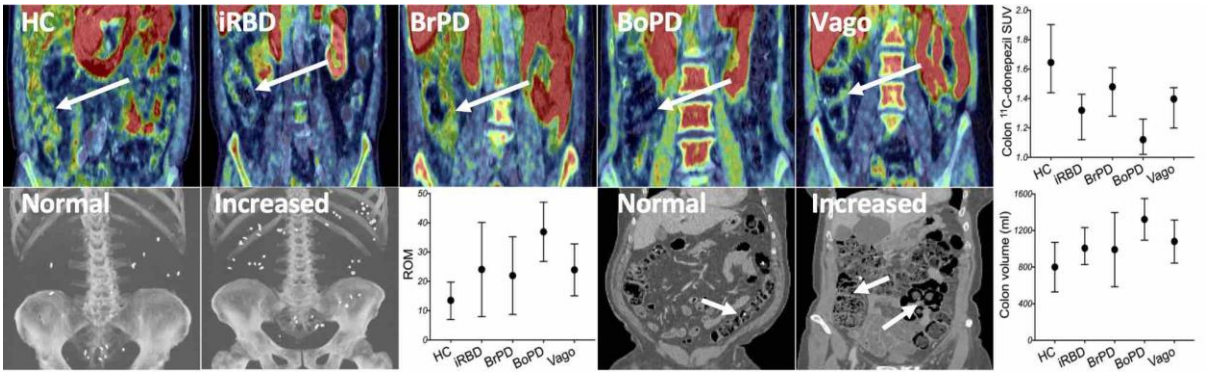

Figure 1. Upper row: Representative ^{11}C-donepezil SUV images of a healthy control (HC), a subject with isolated REM-sleep behavior disorder (iRBD), a brain-first PD patient (BrPD), a body-first PD patient (BoPD), and a vagotomized patient (Vago). See text for details. Note the high signal in the healthy control and brain-first PD patient. Images are scaled from 0-3 SUV. Plot shows ^{11}C-donepezil data for the five different groups (median with interquartile range). Bottom row, left: CT images of a normal and an increased number of retained radiopaque markers (ROM), i.e. normal and increased colon transit time. Plot shows ROM data for the five groups from the upper row (median with interquartile range). Bottom row, right: CT image of a normal and an increased colon volume. Plot shows colon volume data for the five groups from the upper row (median with interquartile range).

References

1. Sampson TR, Challis C, Jain N, et al. A gut bacterial amyloid promotes alpha-synuclein aggregation and motor impairment in mice. *Elife.* 2020;9:e53111.

2. Braak H, Rub U, Gai WP, Del Tredici K. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. *J Neural Transm (Vienna).* 2003;110:517-536.

3. Gjerloff T, Jakobsen S, Nahimi A, et al. In vivo imaging of human acetylcholinesterase density in peripheral organs using 11C-donepezil: dosimetry, biodistribution, and kinetic analyses. *J Nucl Med.* 2014;55:1818-1824.

4. Gjerloff T, Fedorova T, Knudsen K, et al. Imaging acetylcholinesterase density in peripheral organs in Parkinson's disease with 11C-donepezil PET. *Brain.* 2015;138:653-663.

5. Fedorova TD, Seidelin LB, Knudsen K, et al. Decreased intestinal acetylcholinesterase in early Parkinson disease: An (11)C-donepezil PET study. *Neurology.* 2017;88:775-781.

6. Knudsen K, Fedorova TD, Hansen AK, et al. In-vivo staging of pathology in REM sleep behaviour disorder: a multimodality imaging case-control study. *Lancet Neurol.* 2018;17:618-628.

7. Horsager J, Andersen KB, Knudsen K, et al. Brain-first versus body-first Parkinson's disease: a multimodal imaging case-control study. *Brain.* 2020;143:3077-3088.

8. Fedorova TD, Knudsen K, Hartmann B, et al. In vivo positron emission tomography imaging of decreased parasympathetic innervation in the gut of vagotomized patients. *Neurogastroenterol Motil.* 2020;32:e13759.

9. Knudsen K, Szwebs M, Hansen AK, Borghammer P. Gastric emptying in Parkinson's disease - A mini-review. *Parkinsonism Relat Disord.* 2018;55:18-25.

10. Knudsen K, Fedorova TD, Bekker AC, et al. Objective colonic dysfunction is far more prevalent than subjective constipation in Parkinson's disease: A colon transit and volume study. *J Parkinsons Dis.* 2017;7:359-367.

11. Knudsen K, Fedorova TD, Hansen AK, et al. Objective intestinal function in patients with idiopathic REM sleep behavior disorder. *Parkinsonism Relat Disord.* 2019;58:28-34.