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Serotonergic Dysfunction in Parkinson's Disease and Its Relevance to Disability

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Growing evidence suggests that Parkinson's disease is not solely affecting the dopaminergic system. Results from biochemical, animal, *postmortem*, and functional imaging studies have revealed that other neurotransmitter systems are affected as well, including the serotonergic system. With the use of *in vivo* positron emission tomography functional imaging, it has been shown that serotonergic terminals are affected at a varying, nonlinear degree starting early in the clinical course of Parkinson's disease. Tremor and the majority of nonmotor symptoms do not seem to respond adequately to dopaminergic medication. Recent studies suggest that serotonergic dysfunction has a direct relevance to Parkinson's disease symptoms, the so-called nonmotor symptoms, including depression, fatigue, weight changes, and visual hallucinations. These *in vivo* findings indicate that agents acting on the serotonergic system could help towards alleviating these symptoms. This paper aims to review the current literature and to highlight the need for further *in vivo* investigations.

KEYWORDS: PET, serotonin, nonmotor, PD

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1. INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder of the elderly and is clinically characterized by the motor symptoms of tremor, bradykinesia, and rigidity. The pathological hallmark of PD involves the presence of Lewy bodies, resulting in the degeneration of dopamine (DA) neurons in substantia nigra pars compacta (SNc) and subsequently, the striatum. According to Braak's staging of Lewy body deposition [1], the pathological process begins in the dorsal motor nucleus, proceeding in an ascending fashion to the midbrain (including caudal raphe nuclei) and forebrain.

However, growing lines of evidence suggest that PD is not solely a DA-ergic disease but that there is a more diffuse pathology involving other, non-DA neurotransmitter systems, such as the serotonergic. Serotonin (5-HT) neurons in the dorsal raphe nuclei project mainly to the basal ganglia, particularly the striatum, but also to the frontal cortex and the limbic system. The serotonergic system is thought to be involved in the modulation of various cognitive and physiological processes, such as, mood, emotion, sleep, and appetite; thus altered serotonergic neurotransmission is likely to be implicated in both motor and nonmotor disturbances observed in PD [2]. Both motor and nonmotor symptoms are troublesome for patients and affect their quality of life. A recent study outlined the most troublesome symptoms for PD patients following self-report assessments [3], and it was found that both early and advanced PD patients consider tremor, depression, and problems with appetite, weight, and visual hallucinations in their top ten most bothersome symptoms.

Postmortem, animal, and functional imaging studies [4–8] have demonstrated serotonergic dysfunction in PD. The use of functional imaging techniques, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) allows the investigation of 5-HT neuronal integrity across the clinical course of PD and also allows the investigation of correlations between imaging and clinical data.

2. STAGING OF SEROTONERGIC DYSFUNCTION IN PARKINSON'S DISEASE

Functional imaging has been implemented to assess the integrity of the serotonergic terminals in PD and has used the availability of the 5-HT transporter (SERT) as an index. However, functional imaging investigations of SERT have resulted in contradictory data due to the use of radiotracers not specific to SERT (^{123}I-β-CIT) [6, 9, 10] or with high nonspecific binding (^{11}C-McN5652) [6] making it difficult to measure SERT binding in brain regions of low serotonergic innervation. ^{123}I-β-CIT is a SPECT ligand with affinity for the DA transporter (DAT), norepinephrine transporter (NAT), and SERT. Also, ^{11}C-McN5652 PET has relatively high nonspecific binding for SERT in regions of low to moderate SERT density. ^{11}C-DASB currently offers the best selective marker for SERT with high specificity and sensitivity for SERT (nanomolar affinity) and a low affinity for DAT and NAT (micromolar affinity) [11]. Therefore, it is likely that ^{11}C-DASB binding reflects the functional loss of SERT in SERT-expressing terminals due to the denervation of serotonergic pathways. However, despite the ability of current radiotracers to measure 5-HT receptors and SERT, without the knowledge of which cells the 5-HT receptors or SERT are on, interpretation of results can be viewed in a number of ways.

A decrease of striatal 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) has been detected in *postmortem* PD brains [5]. However, striatal hyperinnervation has been observed in a recent PD *postmortem* study [12] and animal models of PD [13]. These findings may be reflective of a compensatory mechanism due to the loss of striatal DA as it has been demonstrated that 5-HT neurons are able to convert L-DOPA to DA, although in an unregulated manner [14], with recent animal studies providing evidence of oversprouting 5-HT neurons [15, 16]. Therefore, this phenomenon should be taken into account when interpreting functional imaging findings considering that the majority of PD patient entering these studies will be undergoing L-DOPA therapy. However, for all studies reviewed here, the patients will have withdrawn from L-DOPA therapy for at least 12–18 hours prior to scanning, resulting in patients undergoing scanning in the practically defined "OFF" condition.

^{11}C-DASB has been used in two preliminary studies [7, 8]. Guttman et al. [7], studied nine clinically advanced nondepressed PD patients (mean disease duration 12 years) and 13 healthy controls. It was reported that PD patients displayed an overall decrease in SERT binding levels (between 7–30%) with significant decreases in orbitofrontal cortex (22%), caudate (30%), putamen (26%), and midbrain (29%). This study presented evidence advancing the knowledge from previous *postmortem* and neuroimaging studies by demonstrating that a decrease in SERT binding cannot solely be an end-stage phenomenon in PD. Albin et al. [8] studied five non-depressed PD patients (H&Y staging between 1–2.5) and eight healthy controls. This study reported symmetrically reduced SERT binding throughout the forebrain and brainstem of PD patients. The greatest reductions of ^{11}C-DASB binding were observed in the cingulate cortex and insula (40–50%) followed by the amygdala, hippocampus, thalamus, basal ganglia, rostral brainstem nuclei (30–35%), and caudal brainstem structures (−20%). This was the first study to consider the caudal brain stem regions in relation to serotonergic denervation in PD and demonstrated symmetrical rather than asymmetrical binding reductions as usually demonstrated nigrostriatal terminal markers. It is important to note that these preliminary studies did not account for any other nonmotor symptoms in their patients such as fatigue, sleep, or appetite problems which may have influenced the findings. Furthermore, neither study addressed the effect of chronic exposure to DA replacement therapy (DRT) (either as mono- or polytherapy with DA agonists and/or L-DOPA) on SERT binding as this may influence the SERT availability [17].

A recent study from our group using *in vivo* ^{11}C-DASB PET as a marker of presynaptic serotonergic terminal integrity aimed to assess the serotonergic dysfunction in early (0–5 years disease duration), established (5–10 years), and advanced (more than 10 years of PD) PD patients [18]. This study reported global reductions of presynaptic serotonergic terminals, which did not correlate with disease duration or motor disability. For the first time, this study addressed the question whether chronic exposure to DRT influences 5-HT terminal functioning; no correlation was found in any of the examined brain regions. It was demonstrated that early PD patients displayed reduced ^{11}C-DASB in the caudate, thalamus, hypothalamus, and anterior cingulate cortex. PD patients with established disease showed additional reductions in the putamen, insula, posterior cingulate cortex, and prefrontal cortex. Advanced PD patients had further reductions in the ventral striatum, raphe nuclei and amygdala. Furthermore, it was demonstrated that there is a preferential loss of SERT in the caudate (early = 28.2%, established = 29.8%, advanced = 34.4%) versus the putamen (early = 13.3%, established = 23.0%, advanced = 30.0%) in all stages of PD studied. This is consistent with an earlier *postmortem* study showing a preferential loss of 5-HT markers in the caudate versus the putamen (−56% versus −30%) [5]. DA dysfunction in the caudate seems to be comparable to the serotonergic dysfunction (−40%) found by Politis et al. [18] but attenuated, compared to DA dysfunction found in the putamen (70–80%) with ^{18}F-DOPA PET [19]. The authors conclude that there is a nonlinear loss of SERT in the PD brain across the course of the disease, which is not related to disease duration, disability, or DRT [18].

The results from this study suggest that the pattern of serotonergic denervation is different to that observed in the DA system. ^{18}F-DOPA and ^{18}F-CFT have detected greater reductions in the posterior putamen, which inversely correlates with disease progression [20–22] and differs from ^{11}C-DASB where the putamen appears to be affected later. Braak et al. [1] suggest that the pathological process of PD begins in the dorsal motor nucleus and progresses in an ascending fashion with midbrain and forebrain structures affected later. At stage 2 of this process, Lewy body and neurite deposition occur within the raphe nuclei with the substantia nigra, amygdala, and hypothalamus affected at stage 3. According to this hypothesis, caudal serotonergic brainstem neurons are affected prior to DA-ergic midbrain neurons. However, the *in vivo* PET data [18] suggest that there is a relative preservation of caudal and rostral raphe nuclei until a later stage of the disease process. Thus far, there is little knowledge regarding the density and functional effect of Lewy body and neurite deposition in the serotonergic neurons. It is possible that alpha-synuclein accumulates in 5-HT neurons at an early stage but the effect is less toxic than in DA neurons.

3. SEROTONERGIC DYSFUNCTION AND PARKINSON'S DISEASE SYMPTOMATOLOGY

3.1. Tremor

Tremor is one of the most challenging symptoms to manage in the parkinsonian patient with a poorer response to DA-ergic therapy compared to bradykinesia and rigidity [23]. It is likely that a system other than the DA-ergic may play a role in its pathophysiology. In this context, both animal and functional imaging studies have failed to reveal any correlation between denervation of the DA-ergic system and tremor. Brooks et al. [24] and Asenbaum et al. [25] utilising ^{18}F-DOPA PET and ^{123}I-β-CIT SPECT, respectively, have demonstrated that reductions in striatal DA terminal function correlate with the severity of bradykinesia and rigidity but not with tremor.

Resting tremor can be evoked in primates by lesioning the midbrain tegmentum [26]. Such lesions interrupt the serotonergic and noradrenergic projections, thus possibly accounting for the development of tremor in the primates. In this animal study, it was observed that 5-HT levels were reduced ipsilateral to the lesion in the brainstem and that tremor and bradykinesia manifested contralateral to the lesion.

To date, only one PET imaging study has been conducted to investigate the association between tremor and dysfunction in the 5-HT system in 26 PD patients and eight healthy controls using ^{11}C-WAY-100635 PET, a selective marker of 5-HT$_{1A}$ receptors [27]. It was demonstrated that midbrain raphe 5-HT$_{1A}$ binding was reduced by 27% in PD patients compared to healthy controls. The authors also report a correlation between reduction of midbrain raphe 5-HT$_{1A}$ binding and severity of tremor as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) but not rigidity or bradykinesia. The authors suggest that the reductions in 5-HT$_{1A}$ binding could reflect loss of 5-HT neuronal cell bodies, likely due to Lewy body pathology. However, further *in vivo* studies are required to explore the influence of serotonergic dysfunction in tremorgenesis.

3.2. Depression

Depression in PD is one of the most common nonmotor symptoms and it is estimated to affect approximately 40–50% of patients [28, 29]. Clinically identifying depressive symptomatology in PD is a challenging process because several features of depression overlap with PD symptomatology.

^{11}C-RTI 32 PET is a marker of both DAT and NAT bindings. A study using this PET technique showed reduced putaminal ^{11}C-RTI 32 uptake in PD patients without a history of depression. PD patients with a history of depression (but antidepressant-free for at least three months) demonstrated additional reductions in the locus coeruleus, thalamus, and the limbic system (amygdala, ventral striatum, and anterior cingulate) [30]. Measures of anxiety severity also inversely correlated with ^{11}C-RTI 32 binding in these regions. The DA-ergic system is shown to be less affected in the ventral striatum compared to more dorsal regions in PD, although it receives most of the noradrenergic afferents from the striatum [31]. Therefore, these findings indicate that the noradrenergic system may be implicated in depression in PD.

However, ^{11}C-RTI 32 has a very low affinity for SERT and therefore, cannot assess the serotonergic system. ^{123}I-β-CIT SPECT in non-PD depressed patients has shown increased uptake in the striatum compared to healthy controls [32]. There have been a few attempts to investigate, *in vivo*, serotonergic involvement in the pathophysiology of depression in PD. Doder et al. [33] used ^{11}C-WAY-100635 PET in a pilot study of PD patients with and without depression and healthy controls. Although the authors reported a decrease in midbrain raphe 5-HT$_{1A}$ receptor binding in the PD patients compared to healthy controls, there were no differences between depressed and nondepressed PD patients.

Another study utilizing the nonspecific marker for SERT, ^{123}I-β-CIT SPECT, studied seven PD patients with depressive symptoms as measured by the Hamilton Depression Rating Scale (HDRS), who were not receiving any antidepressant medications. The authors reported no differences in midbrain ^{123}I-β-CIT binding compared to healthy controls and no correlation between ^{123}I-β-CIT binding and HDRS scores in the PD with depression group [9].

^{11}C-DASB PET has been utilised in a pilot study of seven early-stage PD patients (mean disease duration 4 years) with current depressive disorder as classified by the structured clinical interview DSM-IV Axis I Disorders (SCID-I) who did not receive antidepressant medication [34]. This study reported an overall increase in extrastriatal SERT binding ranging between 8–68% with specific increases in dorsolateral (37%) and prefrontal (68%) cortices compared to a group of seven healthy controls. Correlating ^{11}C-DASB binding with depression symptom severity as measured by the Hamilton Depression Scale (HDS-21) was significant only for the orbitofrontal cortex.

Recently, our group used ^{11}C-DASB PET and a larger cohort of 34 antidepressant-naïve PD patients and 10 age- and sex-matched healthy controls in order to investigate associations between *in vivo* serotonergic dysfunction and depressive symptomatology [35]. All participants were assessed using the Beck Depression Inventory-II (BDI-II), HRSD, and the SCID-I. It was demonstrated that PD patients with depressive symptoms had significantly increased ^{11}C-DASB binding in the amygdala, hypothalamus, caudal raphe nuclei, and posterior cingulate cortex compared to matched-PD patients without depressive symptomatology but not compared to healthy controls. The ^{11}C-DASB binding increases in these regions in the PD group with depression correlated with depressive symptomatology. The findings from this study suggest that relatively increased SERT binding in raphe and limbic regions is implicated in PD depression possibly due to a combined loss of 5-HT terminals and upregulation of SERT function in these regions. This provides evidence for the use of agents acting on SERT for the treatment of PD depression.

3.3. Weight Alterations

PD patients characteristically lose body mass index (BMI) [36], a phenomenon observed among 52–65% of patients. It has been suggested that weight loss in PD patients occurs as a continuous process starting several years prior to diagnosis [37]. Conversely, weight gain has been observed in PD patients on L-DOPA and following deep brain stimulation (DBS) [38]. Appetite regulation has been associated with the serotonergic system [39], and functional imaging studies in non-PD individuals with high BMI have demonstrated decreased cerebral SERT binding as measured with ^{11}C-DASB PET [40].

There is only one study to date which has investigated *in vivo* the relationship between BMI changes and serotonergic dysfunction in PD [41]. This study calculated BMI changes over a 12-month period and compared ^{11}C-DASB binding in PD patients with normal and abnormal BMI alterations, and a group of healthy controls with stable BMI. The results showed that PD patients with abnormal BMI alterations had an increase of SERT binding in raphe nuclei, caudate, hypothalamus, and ventral striatum compared to PD patients without abnormal BMI alterations. The ^{11}C-DASB binding increases in these regions correlated with BMI alterations in the PD group with abnormal BMI changes over the 12-month period. Moreover, PD patients who gained BMI demonstrated raised SERT availability in the anterior cingulate cortex (ACC). The authors suggest that lower levels of 5-HT resulting from an increased clearance in the synapse, in an otherwise affected 5-HT system, could play a primary role in the pathophysiology of fluctuating BMI in PD.

3.4. Fatigue

It is estimated that approximately one third of PD patients experience disabling fatigue [42]. Studies of non-PD patients with chronic fatigue syndrome have demonstrated that the serotonergic system may contribute to its pathophysiology [43].

Serotonergic transmission in PD patients with fatigue has been investigated in a combined ^{18}F-DOPA and ^{11}C-DASB PET study [44]. This study investigated 20 PD patients; 10 with fatigue and 10 without fatigue. Results showed that PD patients with fatigue had a significant reduction of ^{11}C-DASB binding in the putamen (−83%), caudate nucleus (76%), ventral striatum (−74%), and thalamus (−66%), and also the cingulate and amygdala compared to the PD patients without fatigue. Due to basal ganglia receiving sensory and motor input from cortical regions, the authors suggest that their result of reduced SERT expression supports the pathophysiological model that a disruption of the neurotransmitter balance within the basal

ganglia and associated regions influences the integration of emotional and motor information in limbic regions, thus resulting in fatigue symptoms.

3.5. Visual Hallucinations

Visual hallucinations are reported to occur up to approximately 60% of PD patients [45]. Reduction of DA medication dose does not always attenuate visual hallucinations, and no correlation has been shown so far between visual hallucinations and DA medication type or dose. Therefore, it is likely that visual hallucinations in PD are not purely drug-induced and may be due to a neuropathological dysfunction affecting terminals other than DA monoaminergic terminals such as the 5-HT.

A recent PET study utilising ^{18}F-setoperone, a marker for 5-HT$_{2A}$ receptors availability, compared seven PD patients with visual hallucinations and seven PD patients without visual hallucinations [46]. It was reported that PD patients with visual hallucinations had increased 5-HT$_{2A}$ binding in ventral visual pathway, dorsolateral prefrontal cortex, medial orbitofrontal cortex, and insula. These regions have been associated with typical aspects of visual hallucinations in PD, such as objective and subjective perception and recognition [47, 48] and the phenomenology of complex nonstationary scenarios [49, 50]. Thus, the authors suggest that their findings provide justification for the use of selective 5-HT$_{2A}$ receptor antagonists in the treatment of visual hallucinations in PD.

4. CONCLUSIONS

In vivo evidence from functional imaging studies suggests that the recently demonstrated serotonergic dysfunction in PD is related to tremor, depressive symptomatology, weight and appetite problems, fatigue, and visual hallucinations. The degeneration of serotonergic terminals is a process that starts early in the course of PD, however, it does not follow the extent nor the linearity of the degeneration observed in the DA-ergic system. Alterations in the serotonergic system may be a contributing factor to PD symptomatology and in particular, the nonmotor symptoms observed in PD. Further research should carefully delineate correlations between clinical data and serotonergic dysfunction in order to elucidate the underling mechanisms of these symptoms, thus providing vital information regarding novel interventions for their management.

ABBREVIATIONS

PET:	Positron emission tomography
SPECT:	Single-photon emission computed tomography
5-HT:	Serotonin; 5-hydroxytryptamine
SERT:	Serotonin transporter
PD:	Parkinson's disease
DA:	Dopamine
DA-ergic:	Dopaminergic
SNc:	Substantia nigra pars compacta
^{18}F-DOPA:	Fluorine-18-L-dihydroxyphenylalanine
^{123}I-β-CIT:	[^{123}I]-2b-carbomethoxy-3b-(4-iodophenyl)tropane
L-DOPA:	levodopa
DBS:	Deep brain stimulation.

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