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Recent Progress of Imaging Agents for Parkinson's Disease

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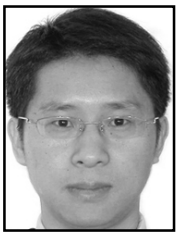

Abstract: Parkinson's disease (PD) is a common progressive, neurodegenerative brain disease that is promoted by mitochondrial dysfunction, oxidative stress, protein aggregation and proteasome dysfunction in the brain. Compared with computer tomography (CT) or magnetic resonance imaging (MRI), non-invasive nuclear radiopharmaceuticals have great significance for the early diagnosis of PD due to their high sensitivity and specificity in atypical and preclinical cases. Based on the development of coordination chemistry and chelator design, radionuclides may be delivered to lesions by attaching to PD-related transporters and receptors, such as dopamine, serotonin, and others. In this review, we comprehensively detailed the current achievements in radionuclide imaging in Parkinson's disease.

Keywords: Neurodegenerative, Parkinson's disease, radiopharmaceuticals.

INTRODUCTION

As the second most widespread neurodegenerative disease in elderly people, Parkinson's disease (PD) is characterized by cardinal motor symptoms, including tremor, rigidity, bradykinesia and postural instability [1]. The histopathological hallmarks of PD are dopamine depletion in the striatum, which results from the progressive degeneration of the substantial nigral dopamine neurons in patient brains [2, 3]. Certain etiopathogenic processes, such as mitochondrial dysfunction, oxidative stress, protein aggregation and proteasome dysfunction, are thought to promoted PD, which can lead to nigrostriatal cell dysfunction and death [4].

The prevalence rate of PD increases with age, and the overall prevalence of PD has recently been increasing because of an aging population [5]. Currently, the diagnosis of PD is primarily based on clinical symptoms, in addition to a favorable response to levodopa therapy [6, 7]. Therefore, rigorous diagnostic criteria are necessary to ensure that the diagnosis is applied consistently and reliably.

Almost 25% of PD patients with an antemortem clinical diagnosis were found to have no PD during postmortem examinations in clinical-pathological studies [8]. PD patients manifest symptoms only when 50 to 80% of the nigrostriatal neurons are lost. Clinical methods are not able to provide an early diagnosis before a significant loss of dopamine neurons has occurred. Computer tomography or magnetic resonance imaging can be used to diagnose Parkinson's disease, but they have obvious disadvantages, such as low sensitivity and specificity, particularly in certain atypical or preclinical cases. However, PD patients would benefit from early diagnosis, particularly before severe dopamine neuron loss. Therefore, improvements to the accuracy of PD clinical diagnoses are necessary, and non-invasive nuclear imaging agents and nuclear imaging technology may provide these improvements.

Nuclides-based positron imaging tomography (PET) or single photon emission computed tomography (SPECT) imaging methods are emerging techniques for the diagnosis, staging and evaluation of PD as many new types of nuclear imaging agents are being developed and clinically applied [8]. After decades of research in the field, some progress has been made and imaging agents that are targeted to PD have become a popular research topic in the field of nuclides-based imaging.

The study of PD imaging agents has developed for decades and has greatly progressed [9-12]. PD imaging agents, including positron imaging agents and single photon imaging agents using different nuclide types ([^{123}I], [^{131}I], [^{99m}Tc], [^{11}C], [^{18}F], *etc.*) may be categorized as dopamine transporter imaging agents, dopamine receptor imaging agents, serotonin transporter imaging agents and other receptor imaging agents.

[^{18}F]FDG

[^{18}F]Deoxyglucose ([^{18}F]FDG) is the most popular PET imaging agent for detecting glucose metabolism. Because the analogue of glucose, [^{18}F]Deoxyglucose (Fig. **1**), has the same cellular transport and phosphorylation processes as glucose [13-16] and glucose metabolism is very active in the brain, the partial or whole glucose metabolism in the brain can be measured *via* the dynamic distribution of [^{18}F]FDG PET scanning [13, 14].

[^{18}F]FDG PET is useful for early PD diagnosis [17-19], progression assessment [20] and rehabilitation evaluation [21]. Generally, [^{18}F]FDG PET imaging indicates normal or increased glucose metabolism in the striatum and,

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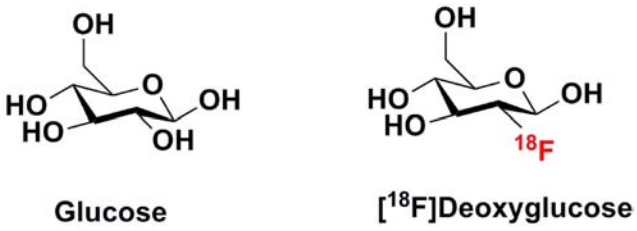


Fig. (1). Structures of Glucose and [^{18}F]FDG.

occasionally, hypometabolism signs in the temporal parietal region. Therefore, an [^{18}F]FDG PET imaging evaluation may be a useful adjunct for clinical examinations when performing a differential diagnosis for Parkinsonism [22]. Research performed by Juh *et al* [22] demonstrated that significant hypometabolism had occurred in the cerebral neocortex of PD patients. Twenty-four patients with idiopathic Parkinson's disease (IPD), progressive supra nuclear palsy (PSP), and multiple system atrophy (MSA) and 22 age-matched normal controls were assessed in this research. A total of 21 Parkinsonism patients with final clinical diagnoses were visually and quantitatively evaluated using NeuroQ software in a study performed by Akdemir ÜÖ *et al*; their results indicated that brain [^{18}F]FDG PET imaging could be a useful reference during the differential diagnosis of PD patients [23]. To track metabolic glucose uptake during brain activity, Olmo [24] and Haegelen *et al* [25] performed [^{18}F]FDG PET on PD patients after the completion of a rehabilitation program. These authors observed glucose changes in several cerebral regions.

DOPAMINERGIC SYSTEM IMAGING AGENTS

[^{18}F]DOPA

As described above, Parkinson's disease results from brain cell dysfunction in the region that controls movement. This dysfunction induces a shortage of dopamine, a neuro-transmitter that regulates important physiological functions, such as cognitive, learning, memory, body movement, *etc*. Dopamine (DA) is synthesized by tuberoinfundibular dopaminergic neurons in the hypothalamic dorsal medial arcuate nucleus (dmARN), is released from the median eminence, and is then delivered to the anterior pituitary by hypothalamohypophysial portal vessels. Dopamine loss results in the characteristic symptoms of Parkinson's disease.

In past decades, [^{18}F] fluoro-3, 4-dihydroxyphenyl-Lalanine ([^{18}F]DOPA) has been used as an imaging probe to examine DA synthesis, storage, and turnover in the human brain using PET visualization [26-31]. [^{18}F]DOPA (Fig. **2**) traces the levodopa (LDOPA) metabolic pathway and provides metabolic information about LDOPA, which is quite distinct from the information provided by ligands of dopamine receptors, transporters or other targets within the dopaminergic system [28]. Kyono and Walker have successfully used [^{18}F]DOPA PET to study DA dysfunctional rat models of PD [32, 33]. [^{18}F]DOPA was also proved and used as an effective tool to study the pathogenesis of PD and the projection systems of dopaminergic neurons by Sharma and co-workers [34-37]. Additionally, Sharma reported the connection between coenzyme Q(10) and PD in mice by examining complex-1 and [^{18}F]DOPA [38]. Asymmetric low radioactive uptake in the bilateral putamen and caudate nucleus can be observed in PD patients using [^{18}F]DOPA PET scanning. [^{18}F]DOPA PET also has been used in several studies to examine neuropathology, psychological cognition, PD evaluation and long-term follow-up in Parkinson's disease. A study performed by Pavese and co-workers revealed significant DA metabolism changes in the brain between early PD patients and healthy controls using [^{18}F]DOPA [39]. Saito [40] performed multiple regression using an [^{18}F]DOPA and [^{18}F]FDG PET analysis to determine the specific cognitive and motor symptoms of brain regions in non-demented patients with PD. Their study demonstrated that changes in striatal [^{18}F]DOPA uptake and corresponding FDG metabolic changes in the primary motor cortex

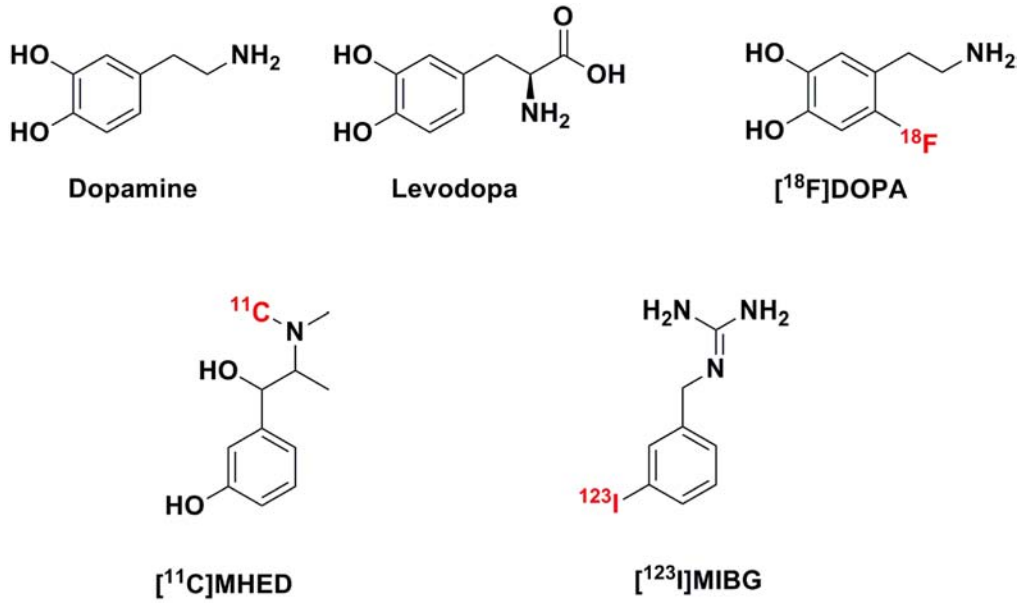


Fig. (2). Structures of dopamine, levodopa, [^{18}F]DOPA [^{11}C]MHED and [^{123}I]MIBG.

represented dysfunction in the corticobasal ganglia-thalamocortical loop in the motor system; however, the change of [^{18}F]DOPA uptake in the anterior cingulate gyrus may be affected by increased dopamine synthesis in the surviving dopamine neurons.

However, [^{18}F]DOPA is rapidly cleared from peripheral tissues after intravenous injection, limiting its imaging timing and utility [40]. Consequently, alternative radiotracers have been investigated. In addition to [^{18}F]DOPA [31-44], the sympathoneuronal imaging agents [^{11}C]-meta-hydroxyl-ephedrine (MHED) [45, 46] and [^{123}I]-meta-iodobenzyl-guanidine (MIBG) (Fig. **2**) [47-51] have also been used to evaluate cardiac sympathetic loss in PD [52].

Dopamine Transporter

The dopamine transporter (DAT) is a transmembrane protein that transports dopamine out of the neuron synapse and into the presynaptic cytoplasm. DAT is specifically expressed in DA neurons and its density highly corresponds to the number of DA neurons; therefore, DAT may be used to reflect the functional changes in DA neurons [53]. Physiological studies have indicated that DAT facilitates consistence of cellular DA, regulates DA signal intensity, and controls DA cleaning in synaptic gaps [54]. It has been demonstrated that in idiopathic Parkinson's disease patients, DAT dramatically declined in the brain along with dopaminergic system degeneration; therefore, DAT nuclear imaging is thought to be a potential biomarker for the diagnosis of DA degeneration [55-59].

The presynaptic terminals in the central nervous system (CNS) can be imaged using DAT probes, such as cocaine analogs, [^{123}I]-N-2-carbomethyl-3-(4-iodophenyl)-tropane ([^{123}I]FP-CIT, [^{123}I]-Ioflupane, [^{123}I]β-CIT-FP), [^{123}I]-β-carbomethoxy-3β-(4-iodophenyl)tropane ([^{123}I]β-CIT), [^{11}C]-N-2-carbomethoxy-3-(4-fluorophenyl)-tropane ([^{11}C]CFT) [60-63], [^{123}I]-Altropane [64, 65],2-β-carbomethoxy-3β-(4-chlorophenyl)-8-(2-[^{18}F]-fluoroethyl)-nortropane ([^{18}F]FECNT) [66-68], [^{99m}Tc]TRODAT-1 [69, 70], [^{123}I]PE2I, and other types of radiotracers, such as [^{11}C]-methylphenidate ([^{11}C]DMP) [71, 72] and others (Fig. **3**). Consequently, dopamine release can be evaluated indirectly to diagnose Parkinson's disease because DAT levels at the presynaptic site are able to be quantified.

[^{99m}Tc]TRODAT-1 and [^{123}I]FP-CIT SPECT are commonly used to evaluate the impairment of the nigrostriatal pathway in Parkinson's disease. These radioligands are also used for the early diagnosis and evaluation of clinical symptom severity in Parkinson's disease because of their steady uptake, long retention time in the brain and their ability to clearly display DAT density in the striatum. Felicio *et al* [73] reported that SPECT using [^{99m}Tc]TRODAT-1 had 100% sensitivity and 70% specificity in clinically unclear Parkinsonian syndromes (CUPS). [^{123}I]FP-CIT has been used for the differential diagnosis of essential tremor or Parkinson's disease and predicts the clinical symptom severity of Parkinson's disease. [^{123}I]FP-CIT has also been used for the early diagnosis, PD follow-up and monitoring DAT changes in Parkinson's disease patients [74-77]. A [^{11}C]FE-CIT PET assessment demonstrated that the severity of nigrostriatal damage was not dependent on the age at onset during the early disease phase of sporadic PD patients [78]. Furthermore, [^{18}F]FECNT evaluation indicated that PD heritability may be associated with more severe and widespread genetic dopaminergic injury [79]. The β-CIT striatal-to-nonspecific binding ratios in patient brains were evaluated using [^{123}I]β-CIT and a significantly increased S/N ratio was observed after selective serotonin reuptake inhibitor (SSRI) treatment [80-83]. A more recent study determined that SSRI paroxetine treatment was able to significantly increase the quantification of striatal [^{123}I]FP-CIT binding to DAT in humans. These results indicate that *in vivo* [^{123}I]FP-CIT and [^{123}I]β-CIT are able to bind DATs as well as central serotonin transporters (SERTs) [84].

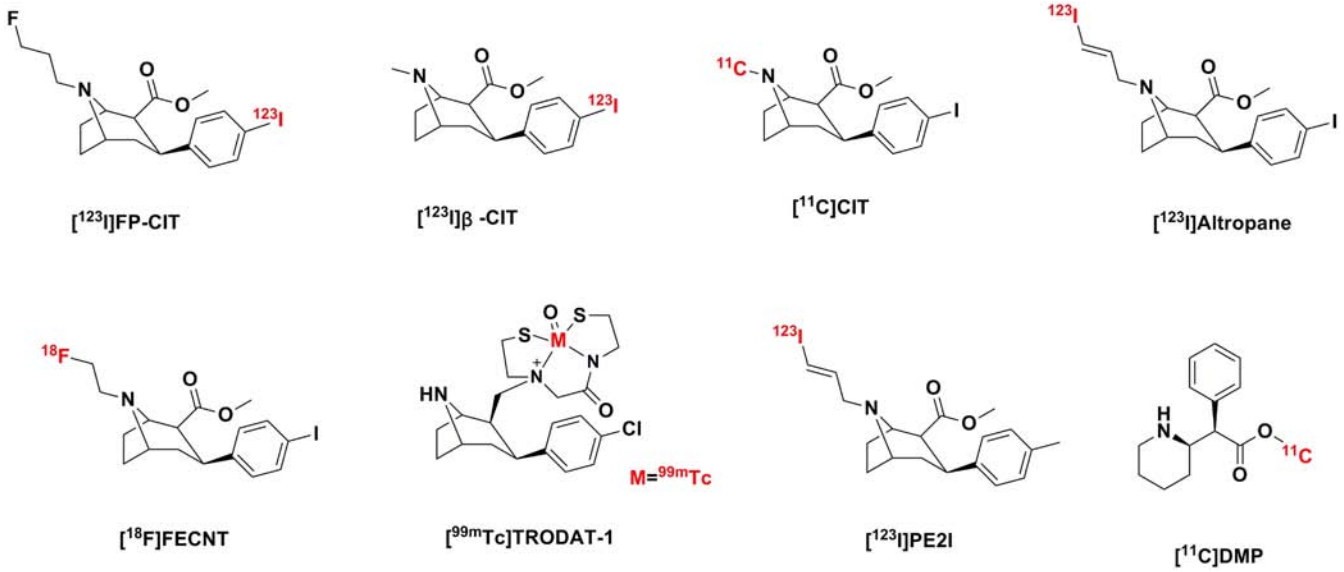


Fig. (3). Structures of DAT radioligands.

Masilamoni *et al* [78] validated the use of [^{18}F]FECNT as a PET radiotracer to assess the degree of striatal dopamine terminal denervation and midbrain dopaminergic cell loss in MPTP-treated Parkinsonian monkeys. Because humans and other primates are highly similar, [^{18}F]FECNT, a highly sensitive and specific dopamine transporter ligand, may be effective for DAT imaging in PD patients.

Dopamine Receptor Imaging Agents

Dopamine is synthesized in the CNS; however, the complicated neuronal dopamine physical functions are mediated in combination with different dopamine receptors (DA Receptor) in the brain.Although dopamine receptors are widely distributed in the brain, different subtypes of DA receptors presumably reflect different functional roles. Five subtypes of DA receptors have been investigated to date. Based on their pharmacological properties, the D_2, D_3, and D_4 receptors are classified as D_2-like receptors, which are able to directly induce physical functions after DA and DA receptor binding; and the D_1 and D_5 receptors, classified as D_1-like receptors, have permissive and synergistic actions with D_2-like receptors but do not have clear physical functions. Histochemical observations have indicated that dopamine receptors are classified with respect to connectivity; dopamine D_1-like receptors are mainly expressed on striatal neurons that project into the substantia nigra, whereas D_2-like receptors are mainly localized on striatal–pallidal neurons [85].

Particularly, the occurrence of PD with dopamine dysfunction is closely related to D_2-like receptors, which are distributed in the cerebral hypothalamus, striatum, substantia nigra, and anterior pituitary. D_2-like receptors have attracted much attention in the field of nuclear imaging. D_2-like receptor imaging agents are primarily comprised of [^{11}C]Raclopride [86-88], [^{123}I]IBZM [89-92], [^{18}F] Desmethoxyfallypride ([^{18}F]DMFP) [93, 94], [^{11}C]MNPA [94, 95], [^{131}I]Epidepride and [^{124}I]Epidepride [96-99], [^{11}C] (+)-PHNO [100, 101], [^{11}C]NMSP [102, 103], [^{18}F]MCL-524 [104], *etc* (Fig. **4**).

D_2-like receptor imaging agents may contribute to the early diagnosis, differential diagnosis, disease course, therapeutic efficacy monitoring and follow-up of PD. Verstappen *et al* [105] confirmed that there was asymmetric D_2 receptor upregulation in PD in a study using [^{123}I]IBZM and [^{123}I]FP-CIT SPECT, but the sensitivity of the contralateral higher striatal [^{123}I]IBZM binding was only 56%. Therefore, the presence of contralateral higher striatal [^{123}I]IBZM uptake did not have sufficient diagnostic accuracy for PD and an independent assessment using [^{123}I]IBZM SPECT cannot determine the PD risk in patients with Parkinsonism that also have no contralateral up-

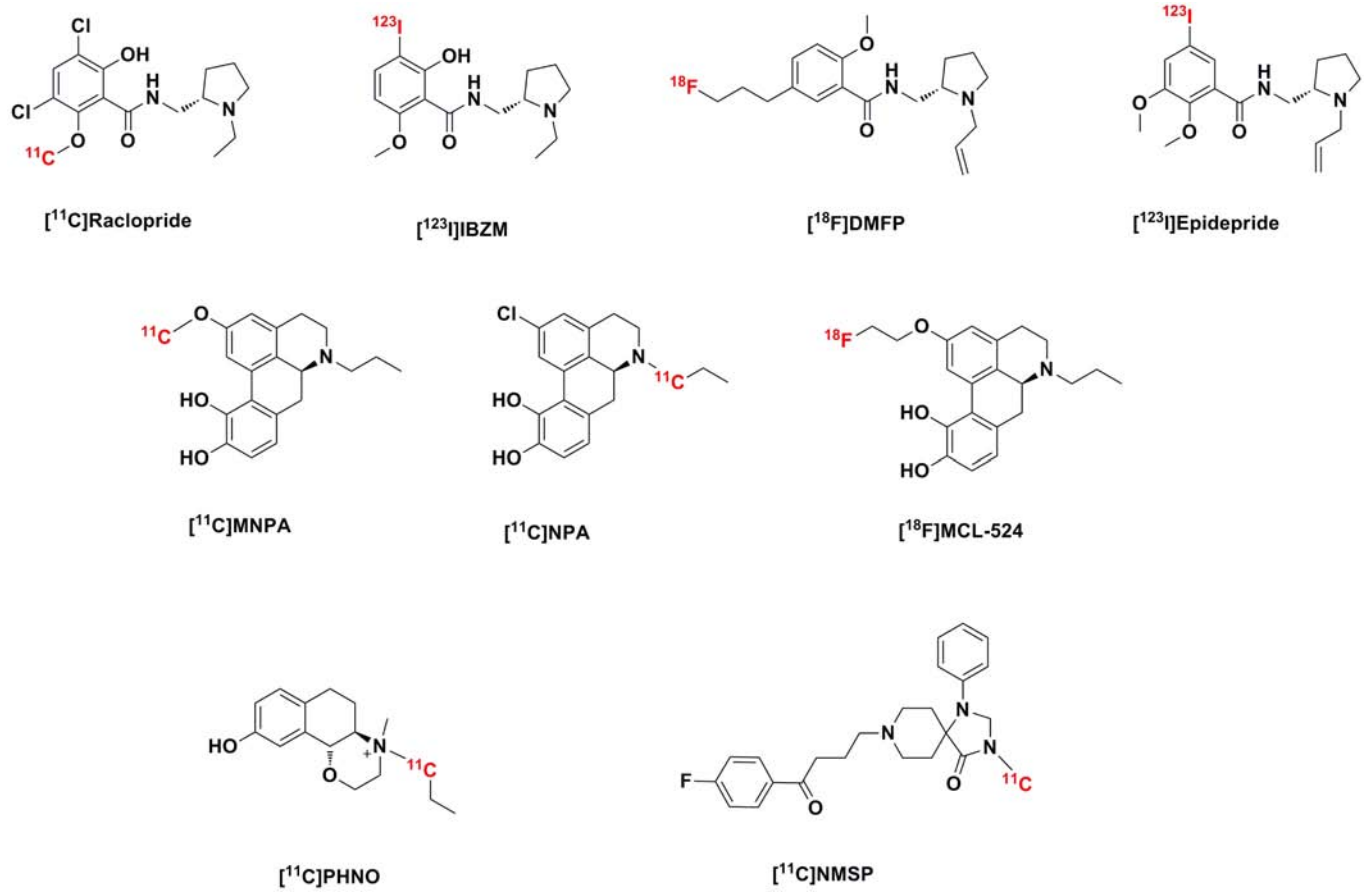


Fig. (4). Structures of DA receptor radioligands.

regulation of D_2 receptors. Politis reported a significant reduction in the mean hypothalamic [^{11}C]Raclopride binding potentials of PD patients compared with normal controls (0.2714+/-0.06 vs. 0.3861+/-0.04; mean+/-SD; $p<0.05$) [106]. However, D_2 receptor imaging may be influenced by certain drugs, such as levodopa; therefore, some researchers believe that D_2-like receptor imaging should be combined with DAT or other imaging methods for PD diagnosis. In recent research, the combined striatal D_2R BP and cerebral influx ratio information from a single dynamic [^{11}C]Raclopride PET imaging analysis successfully distinguished patients with PD or multiple-system atrophy with predominant Parkinsonism (MSA-P) with high accuracy [107].

PET studies of dopamine D_2 and D_3 receptors (D_2/D_3) have predominantly been conducted using antagonists analogues, such as [^{11}C]Raclopride. [108-110]. However, more recently developed agonist radioligands have demonstrated enhanced sensitivity to endogenous dopamine, such as [^{18}F]DMFP [93], [^{11}C]N-propyl-norapomorphine ([^{11}C]NPA) [111], [^{11}C]MNPA [112], [^{11}C]4-propyl-9-hydroxynaphthoxazine [113]. A recent study indicated that [^{11}C]Raclopride binding in the striatum of PD patients was prominently associated with the reduced endogenous dopamine and that [^{11}C]NMSP demonstrated a smaller association with endogenous dopamine compared with [^{11}C] Raclopride [113]. [^{18}F]MCL-524, a [^{11}C]MNPA analog, appears suitable for D_2/D_3 receptor binding quantification *in vivo*, encouraging future translation to human studies when compared with [^{11}C]Raclopride [104].

Vesicular Monoamine Transporter Imaging Agent

The vesicular monoamine transporter (VMAT) is a transport protein complex that is responsible for transporting monoamine neurotransmitters into the synaptic vesicles, which are releasing neurotransmitters into monoaminergic neurons. VMAT is known to transport several neuro-transmitters, such as dopamine, serotonin, norepinephrine, epinephrine, histamine and others. One subtype of VMAT, $VMAT_2$, is primarily expressed in a variety of monoaminergic cells in the CNS, such as mast cells, the sympathetic nervous system brain, and cells that contain histamine in the gut [114]. Because of these properties $VMAT_2$ was considered to be a novel PD imaging probe. $VMAT_2$ targeting produced excellent image quality and had the ability to differentiate reduced $VMAT_2$ uptake sites in patients with PD; these properties have made non-invasive nuclear $VMAT_2$ imaging a leader in the frontier of current PD imaging research.

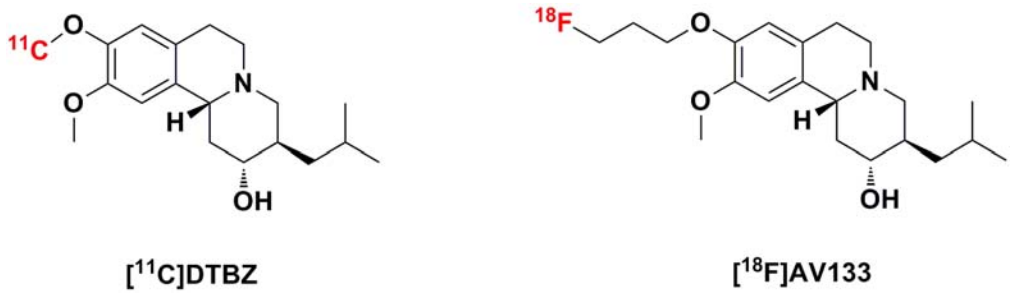
There are two PD imaging agents that target $VMAT_2$: [^{11}C]DTBZ and [^{18}F]AV-133. Both of these agents are based on a dihydrotetrabenazine scaffold (Fig. **5**). Koeppe *et al* [115] performed PET imaging using [^{11}C] Dihydrotetrabenazine ([^{11}C]DTBZ) to examine blood-to-brain ligand transport and striatal monoaminergic presynaptic binding in patients with DLB (dementia with Lewy bodies), PD, and AD and in 57 healthy elderly controls. The imaging results indicated that a single PET neuroimaging analysis using [^{11}C]DTBZ was able to differentiate DLB from both PD and AD. Furthermore, [^{11}C]DTBZ combined with [^{18}F]DOPA imaging has made significant progress in evaluating dopamine system damage and prognosis in animal models [115].

[^{18}F]AV-133 is another ^{18}F labeled dihydrotetrabenazine radiotracer that has a propanediol linker that is used for $VMAT_2$ imaging. Okamura *et al* [116] analyzed the binding potential (BP) of [^{18}F]AV-133 to VMAT2 in 17 PD patients and 6 healthy controls and determined that the BP of $VMAT_2$ in PD patients was dramatically decreased in the posterior putamen, anterior putamen, and caudate nucleus; furthermore, the $VMAT_2$ BP in caudate nuclei was closely correlated with clinical severity in PD patients. These results indicated that the novel ^{18}F-labeled ligand [^{18}F]AV-133 can sensitively detect monoaminergic reductions in neuronal termini in PD patients [117].

5-HYDROXYTRYPTAMINE RECEPTOR AND TRANSPORTER IMAGING AGENTS

5-hydroxytryptamine (5-HT or serotonin) is an important monoamine neurotransmitter that is widely distributed in the brain. 5-HT is synthesized in the serotonergic neurons of the CNS and contributes to feelings of happiness. As neuropathology, neurochemistry and other related subjects have developed, there is the belief that 5-HT metabolic changes are important in the mechanism of PD. Recent research has determined that there is a significant decrease of the 5-HT transporter (SERT) in the striatum and other brain areas in PD patients [118-122]. Currently, there are several types of 5-HT relevant radiotracers available for imaging studies, including 5-HT_{1A} receptor imaging agents and 5-HT transporter (SERT) imaging agents [123], *etc*.

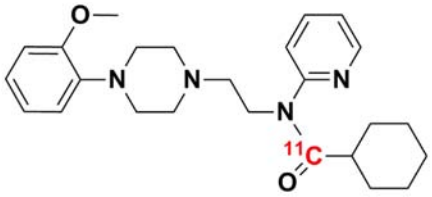
The 5-HT_{1A} receptor is the most widespread subtype of 5-HT receptor, which is a G protein-coupled receptor and mediates inhibitory neurotransmission. 5-HT_{1A} receptor activation has been proven to increase dopamine release and may be useful for improving PD symptoms. [^{11}C]WAY-100635 (Fig. **6**) was a commonly used 5-HT_{1A} receptor imaging agent. A PET study using [^{11}C]WAY-100635 in 23



[^{11}C]DTBZ [^{18}F]AV133

Fig. (5). Structures of [^{11}C]DTBZ and [^{18}F]AV-133.

patients with PD and 8 age-matched healthy volunteers was performed by Doder *et al* [124]; they observed a 30% reduction of 5-HT_{1A} binding potential in the midbrain raphe in PD patients, which strongly supported previous indirect *in vivo* evidence that implicated decreased serotonergic neurotransmission in PD.



[^{11}C]WAY100635

Fig. (6). Structure of [^{11}C]WAY 100635.

Currently, there are several SERT imaging agents available, including [^{11}C]DASB [125-127], [^{123}I]ADAM [128, 129], [^{11}C]McN5652 [130, 131], [^{11}C] MADAM[132, 133], [^{11}C]HOMADAM [134, 135] (Fig. **7**). However, ^{18}F has some advantages over ^{11}C, notably, ^{18}F-labeled radiopharmaceuticals can be delivered if a cyclotron is not available. Therefore, numerous ^{18}F-labeled SERT imaging agents have been developed and evaluated in animal models, such as [^{18}F]McN5652 [136-141], [^{18}F]ACF [142], 4-[^{18}F]ADAM [143-145], 5-[^{18}F]ADAM [146], [^{18}F]AFM [147], [^{18}F] FBASB [148] and [18F]FPBM [149] (Fig. **8**). Among these agents, [^{18}F]McN5652 has been demonstrated to be suitable for SERT quantification using PET analysis in humans in *in vivo* studies [150]. The ^{18}F-labeled SERT radioligand, 4-[^{18}F]ADAM, has also been reported as a viable agent for both preclinical [143] and human studies [151-154].

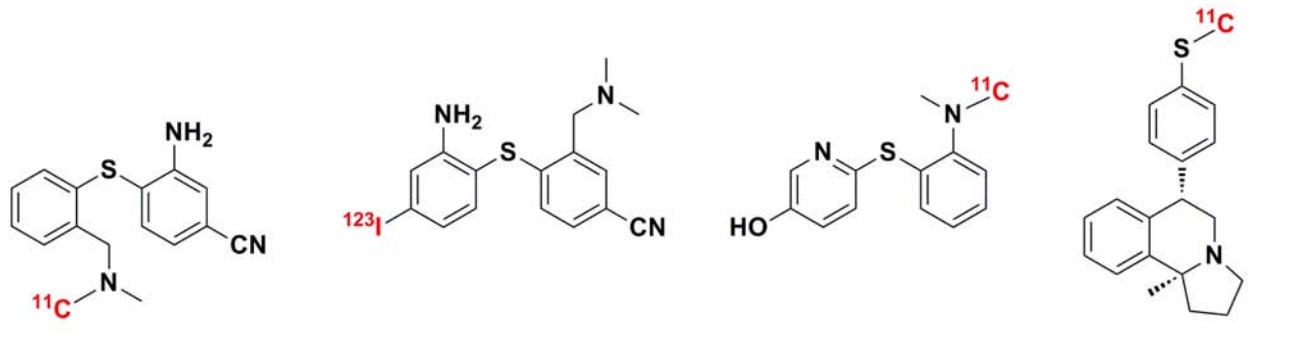
Politis *et al* [126] observed significant [^{11}C]DASB binding reductions in the striatal, brainstem, and cortical regions in PD patients using [^{11}C]DASB PET in 30 PD patients. Progressive non-linear serotonergic dysfunction was investigated in PD patients, which appeared not to influence SERT binding and did not determine disability levels or chronic exposure to dopaminergic therapy. Li and co-workers [155] performed [^{99m}Tc]TRODAT-1 and [^{123}I] ADAM SPECT in four healthy and one 6-OHDA-induced PD monkey. Their study demonstrated that [^{99m}Tc]TRODAT-1 uptake in the striatum of the PD monkey was remarkably lower than in the normal monkeys and that the thalamic and striatal uptake of [^{123}I]ADAM was decreased in the PD monkey. The successful use of a dual-isotope SPECT using [^{99m}Tc]TRODAT-1 and [^{123}I]ADAM suggests that it is possible to simultaneously evaluate dopaminergic and serotonergic system changes in PD models.

OTHER IMAGING AGENTS

There are a variety of agents that may be used in non-invasive nuclear PD imaging that are currently being tested in animal experiments or preclinical trials, such as [^{11}C] MP4A [156] targeted acetylcholinesterase, [^{123}I]5IA [157] and [^{18}F]2FA [158] targeted nicotinic acetylcholine receptors *in vivo* (nAChRs), [^{123}I]QNB [159] targeted muscarinic acetylcholine receptors (mAChRs), [^{11}C](R)-PK11195 [160] targeted peripheral benzodiazepine sites (PBBS) and others (Fig. **9**).

Recent results have demonstrated that in PD patients without dementia [161], as well as de novo or early PD patients, AchE is particularly reduced in the posterior cingulate and posterior temporo-parieto-occipital associative cortex [162]. It has been proven that PD patients without dementia have more severe cholinergic deficits in these areas compared with patients with AD [156, 160]. Brain cholinergic dysfunction was observed at a very early stage of PD using [^{11}C]MP4A PET studies; furthermore, this dysfunction may precede the manifestation of motor symptoms. Interestingly, lower AChE activity in the cerebral cortex was also observed in the early PD group compared with the advanced PD group without dementia [156, 159]. A [^{18}F]2FA PET study in PD patients observed decreasednicotinic receptors (nAChRs) in the nigrostriatal system, indicating that [^{18}F]2FA could be a useful tool to study post-synaptic cholinergic transmission [158].

In vivo SPECT imaging of muscarinic acetylcholine receptors using [^{123}I]QNB in patients with dementia with Lewy bodies and Parkinson's disease dementia determined that significantly elevated mAChRs in the occipital lobe were associated with DLB and PD [157]. A [^{11}C](R)-PK11195 PET study in patients with idiopathic Parkinson's



[^{11}C]DASB [^{123}I]ADAM [^{11}C]HOMADAM [^{11}C]McN5652

Fig. (7). Structures of [^{11}C] or [^{123}I] -labeled SERT radioligands.

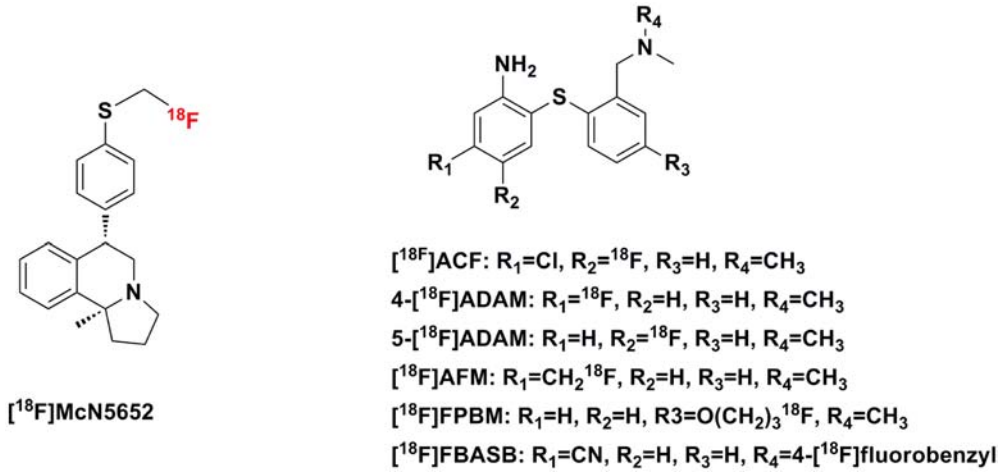


Fig. (8). Structures of [^{18}F] labeled SERT radioligands.

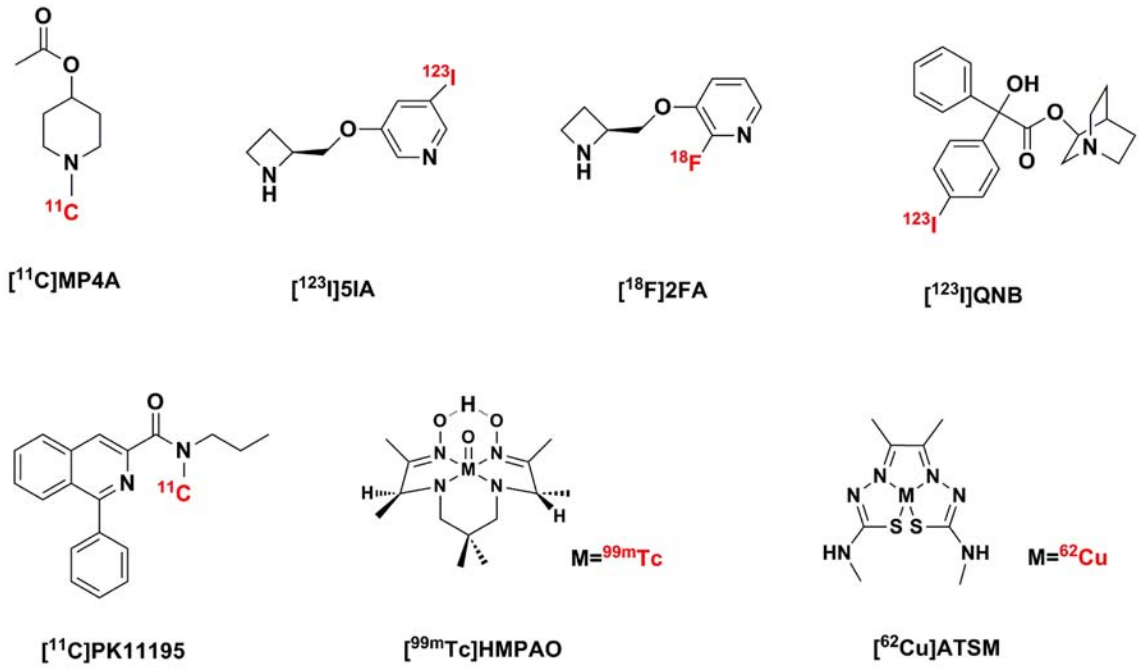


Fig. (9). Structures of other imaging agents.

disease confirmed that widespread microglial activation is associated with the PD pathological process [160].

Parkinson's disease itself is not associated with a consistent pattern of cerebral blood flow alterations in the basal ganglia, but reduced parietal blood flow is often reported [163]. A recent study determined that hypo-perfusion in the inferior frontal region can be observed in patients with Parkinson's disease with dementia using [^{99m}Tc]HMPAO SPECT [164] (Fig. **9**). Brain perfusion imaging agents, such as [^{99m}Tc]HMPAO, can also be used to measure cerebral tissue perfusion in PD patients [163-165].

Several novel imaging approaches have been proposed that examine mitochondrial oxidative stress. Ikawa *et al* [166] evaluated a PET method using [^{62}Cu]-diacetyl-bis (N(4)-methyl-thiosemicarbazone) ([^{62}Cu]ATSM) (Fig. **9**) to evaluate oxidative stress and the accompanying mitochondrial dysfunction during PD pathogenesis. Their study observed enhanced striatal oxidative stress, particularly in the contralateral striatum of PD patients compared with control subjects. Additionally, this increased oxidative stress was associated with the progression of disease severity. These findings indicate a potential correlation between oxidative stress and striatal neurodegeneration in PD.

CONCLUSIONS

During the past three decades, nuclear brain imaging has proven to be a promising, powerful and unique method for the evaluation of brain function during normal and disease states. Research investigating Parkinson's disease diagnosis has occurred in tandem with the rapid evolution of molecular imaging technologies and their applications in preclinical

studies and clinical practice. Compared with traditional anatomical imaging technologies, PET nuclear imaging assessments provide spatial localization of metabolic changes as well as accurate and consistent quantification of their distribution. These properties have allowed PET nuclear imaging to be employed as a valuable tool during clinical neuro-disease examinations. These personalized highly sensitive and specific evaluations will be useful for the early diagnosis, prognosis and long-term follow up of Parkinson's disease.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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LIST OF ABBREVIATIONS

5-HT	=	5-hydroxytryptamine
BP	=	binding potential
CNS	=	central nervous system
CT	=	computer tomography
CUPS	=	clinically unclear Parkinsonian syndromes
DA	=	dopamine
DAT	=	dopamine transporter
IPD	=	idiopathic Parkinson's disease
LDOPA	=	levodopa
mAChR	=	muscarinic acetylcholine receptor
MRI	=	magnetic resonance imaging
MSA	=	multiple system atrophy
MSA-P	=	multiple-system atrophy with predominant Parkinsonism
nAChR	=	nicotinic acetylcholine receptor
PD	=	Parkinson's disease
PET	=	positron imaging tomography
PBBS	=	peripheral benzodiazepine site
PSP	=	progressive supra nuclear palsy
SERT	=	serotonin transporter
SPECT	=	single photon emission computed tomography
SSRI	=	selective serotonin reuptake inhibitor
VMAT	=	vesicular monoamine transporter

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