^{18}F-AV-133: A Selective VMAT2-binding Radiopharmaceutical for PET Imaging of Dopaminergic Neurons

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KEYWORDS

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The early detection and monitoring of neurodegenerative diseases, including Parkinson disease (PD), Alzheimer disease (AD), dementia with Lewy bodies (DLB) and other dementias, and movement disorders, represent a significant unmet medical need. Disease mechanisms are gradually becoming understood, and disease-modifying drugs that target the specific molecular pathology underlying each of these diseases are emerging. Tools for accurate and early differential diagnosis are thus necessary to determine the appropriate treatment for patients and to minimize inappropriate use of potentially harmful treatments. In addition, such diagnostic imaging tools are expected to permit monitoring of disease progression and will thus accelerate testing and development of disease-modifying drugs. Furthermore, the new imaging tests may be useful as prognostic tools by identifying humans with neurodegenerative diseases before the clinical manifestations become evident.

Most of the motor deficits that represent the cardinal symptoms of PD are caused by the progressive degeneration of dopaminergic neurons of the midbrain, which project to the basal ganglia of the forebrain and synaptically release the transmitter dopamine (DA) on target neurons there. The midbrain dopaminergic neuronal population also undergoes degeneration in patients with DLB, thereby generating parkinsonian symptoms. Given the essential role of DA neurons in these diseases, the development of suitable imaging tools has been an active research endeavor in recent years.

APPROACHES TO DA NEURON IMAGING

The 3 types of imaging agents that have been developed so far are (1) agents imaging the enzymatic activity of aromatic amino acid decarboxylase (AADC), which converts L-dihydroxyphenylalanine (L-DOPA) to DA; (2) agents imaging the dopamine transporters (DAT) that are located at the extracellular membrane and responsible for the reuptake of DA from the synaptic cleft, and (3) agents imaging vesicular monoamine transporter type 2 (VMAT2) located on the membranes

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of the intracellular vesicles storing DA for synaptic release.

[^{18}F]6-Fluoro-DOPA

[^{18}F]6-Fluoro-DOPA (FDOPA) is the PET imaging agent for dopaminergic neuron function and it is a commonly used PET agent. FDOPA is a false substrate for the enzyme AADC. PET imaging with [^{18}F]6-FDOPA reflects the in situ synthesis of DA.[1,2] Because AADC is not only localized in dopaminergic neurons and AADC enzyme appears to be up-regulated in the parkinsonian brain, and because the O-methylated derivatives are contributing to background noise, [^{18}F]6-FDOPA imaging may underestimate the degree of neuronal loss caused by compensatory changes.[3–5]

DAT Ligands

Several ligands for DAT, which is responsible for the reuptake of DA from the synaptic cleft, have been pursued as radiopharmaceuticals. These ligands include iodine-123-fluoropropyl-β-carbomethoxy-3β-(4-iodophenyltropane) (^{123}I-FP-CIT, DaTSCAN), which has been approved as a single photon emission computed tomography (SPECT) radiopharmaceutical. Most of the DAT imaging agents are tropane (or cocaine) derivatives, which have varying degrees of affinity to serotonin and norepinephrine transporters.[6–13] These agents are likely to be superior to FDOPA as imaging agents. A review by Ravina and colleagues[14] pointed out the deficiencies in imaging dopaminergic neuron function based on DAT tracers. There is evidence from animals suggesting that DA agonist therapy, given to most patients with PD, may affect the expression of DAT, and thus limit their utility to accurately reflect the structural integrity of dopaminergic systems. The currently broadly available DAT SPECT radiopharmaceuticals provide images of lower spatial resolution than is possible with ^{18}F-PET. Quantization of dopaminergic neuronal changes over time is also anticipated to be better with ^{18}F agents because of the inherent higher image resolution achievable with PET compared with SPECT.

VMAT2 Ligands

The third type of imaging agent for dopaminergic neurons is VMAT2-specific tracers. ^{11}C-labeled tetrabenazine (TBZ) derivatives, including [^{11}C]dihydrotetrabenazine ([^{11}C]DTBZ), have been successfully tested in humans. An ^{18}F-labeled agent, [^{18}F]9-fluoropropyl-DTBZ (^{18}F-AV-133) is in early stages of clinical development as a commercial radiopharmaceutical. These VMAT2-specific tracer molecules are discussed in detail in the following sections.

VMAT2 AS PET IMAGING TARGET

VMAT2 is an integral part of the mechanism for vesicular packaging and storage of monoamine neurotransmitters in the synapses of the brain (**Fig. 1**, see Refs.[15–19] for reviews). After synthesis of monoamines in the presynaptic terminals, the

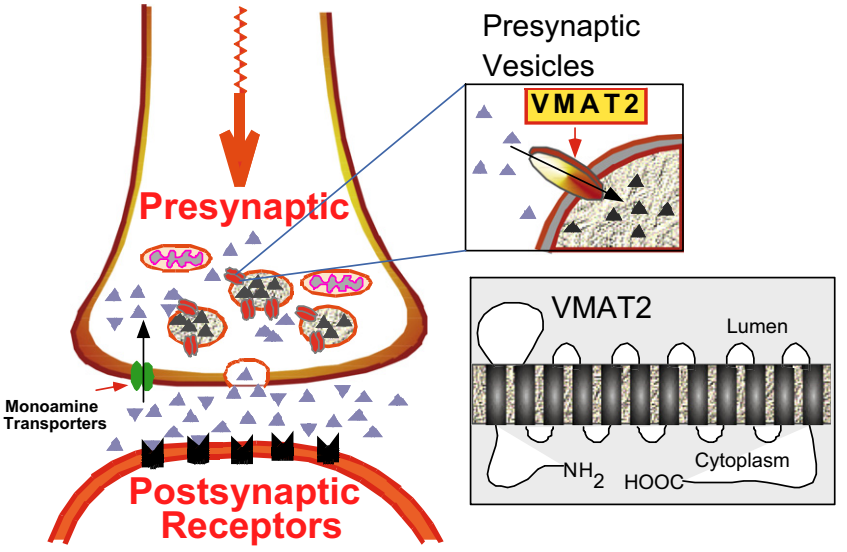

Fig. 1. VMAT2, the molecular target of ^{11}C-DTBZ and ^{18}F-AV-133. Schematic drawing of a typical monoamine neuron (*left*). VMAT2s are located in the presynaptic neurons that are responsible for storing and packing the neurotransmitters (*small triangles*) inside the vesicles. VMAT2 is a 12-domain transmembrane protein that selectively transports monoamines (DA, serotonin, norepinephrine) into transmitter storage vesicles.