Progressive loss of striatal dopamine terminals in MPTP-induced acute parkinsonism in cynomolgus monkeys using vesicular monoamine transporter type 2 PET imaging ([\(^{18}\)F]AV-133)

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ABSTRACT

The 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP)-induced parkinsonism model, particularly in non-human primates, remains the gold-standard for studying the pathogenesis and assessing novel therapies for Parkinson’s disease. However, whether the loss of dopaminergic neurons in this model is progressive remains controversial, mostly due to the lack of objective in vivo assessment of changes in the integrity of these neurons. In the present study, parkinsonism was induced in cynomolgus monkeys by intravenous administration of MPTP (0.2 mg/kg) for 15 days; stable parkinsonism developed over 90 days, when the symptoms were stable. Noninvasive positron emission tomographic neuroimaging of vesicular monoamine transporter 2 with 9-\(^{18}\)F fluoropropyl-(+)-dihydrotetabenazine ([\(^{18}\)F]AV-133) was used before, and 15 and 90 days after the beginning of acute MPTP treatment. The imaging showed evident progressive loss of striatal uptake of [\(^{18}\)F]AV-133. The dopaminergic denervation severity had a significant linear correlation with the clinical rating scores and the bradykinesia subscores. These findings demonstrated that [\(^{18}\)F]AV-133 PET imaging is a useful tool to noninvasively evaluate the evolution of monoaminergic terminal loss in a monkey model of MPTP-induced parkinsonism.

Keywords: Parkinson’s disease; non-human primate; [\(^{18}\)F]AV-133; VMAT2; positron emission tomography

INTRODUCTION

Parkinson’s disease (PD) is one of the most common neurodegenerative disorders and affects ~2% of the world’s population aged over 65\(^{[1]}\). The cardinal clinical symptoms are bradykinesia, tremor, rigidity, and postural instability with the pathological characteristic of evolutional nigrostriatal dopaminergic neurodegeneration\(^{[2, 3]}\). 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a neurotoxin that induces parkinsonism in both humans\(^{[4]}\) and non-human primates\(^{[5]}\) with the cognitive, biochemical, histological and classical behavioral changes that occur in PD\(^{[6]}\). Therefore, MPTP-lesioned monkeys have been used to evaluate the efficacy of anti-parkinsonian therapy. However, whether the acute MPTP-induced loss of dopaminergic neurons is a progressive process remains controversial, so a biomarker...
that can non-invasively monitor this change longitudinally is critical.

Increasing evidence has suggested that single photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging can be used to sensitively and objectively evaluate the integrity of the nigrostriatal dopaminergic system and may be useful tools for providing diagnostic information on PD\[^{[7-10]}\]. There are numerous SPECT and PET imaging tracers for monitoring the integrity of dopaminergic neurons. 6-\[^{[18]F}\]fluoro-DOPA has been used to evaluate dopamine synthesis\[^{[11, 12]}\] and labeled 2β-carbomethoxy-3β-(4-\[^{[123]I}\]iodophenyl)tropane targets the membrane dopamine transporter\[^{[12, 13]}\], \[^{[13]}C\]raclopride\[^{[14]}\] specifically binds to dopamine receptors, and \[^{[18]F}\]AV-133 targets the vesicular monoamine transporter type 2 (VMAT2). VMAT2, located on vesicle membranes in monoaminergic neurons, carries out the reuptake and packaging of monoamines (including dopamine, norepinephrine, and serotonin) into vesicles.

Increasing numbers of studies have found that the former three biomarkers are susceptible to disease-related compensation and dopaminergic drug-induced regulation, limiting their utility for accurately quantifying the lesion severity in PD. VMAT2-binding sites are not readily affected by dopaminergic regulation. Further, their density correlates well with the number of nigrostriatal dopaminergic neurons\[^{[15-17]}\]. Thus, neuroimaging with markers targeting VMAT2 may be a more reliable and sensitive tool to monitor the progression of dopaminergic neuronal degeneration. Previous immunohistochemical analysis of VMAT2 showed that dopaminergic terminals are responsible for \(>95\)% of VMAT2 expression\[^{[18]}\]. Multi-tracer PET imaging in a monkey model of PD induced by chronic MPTP treatment at a low dose shows progressive nigrostriatal dopaminergic neurodegeneration, and this results in a reduced storage capacity of VMAT2 and decreased uptake of \[^{[13]}C\]DTBZ in the nigrostriatal system. The level of VMAT2 staining with \[^{[1]}H\]DTBZ in MPTP-treated animals is reduced in tyrosine hydroxylase-positive neurons compared with that in controls\[^{[19]}\], suggesting that VMAT2 binding sites are proportionally associated with the presence of functional dopaminergic neurons. Imaging VMAT2 is thus regarded as an effective tool to follow the degeneration of dopaminergic terminals. 9-\[^{[18]F}\]fluoropropyl-(+) -dihydrotetrabenazine (\[^{[18]F}\]AV-133) is a novel \[^{[18]F}\] labeled tetrabenazine derivative that selectively binds to VMAT2 with high affinity\[^{[20, 21]}\].\[^{[18]F}\]AV-133 PET studies in an MPTP-lesioned PD mouse model indicate that the specific uptake ratio (SUR) of \[^{[18]F}\]AV-133 declines significantly in the striatum. The imaging results correlate well with the results of immunohistochemical studies of tyrosine hydroxylase\[^{[22]}\]. Moreover, preliminary clinical studies clearly demonstrate that \[^{[18]F}\]AV-133 sensitively detects VMAT2 reduction in PD patients, supporting \[^{[18]F}\]AV-133 as a potential tool to identify presymptomatic patients with nigrostriatal movement disorders\[^{[23]}\].

So far, no study has used \[^{[18]F}\]AV-133 as a biomarker to evaluate parkinsonism in non-human primates, particularly in the model using the acute intravenous infusion of MPTP which has been extensively used for the preclinical evaluation of anti-parkinsonian drugs. The current study was designed to investigate the utility of \[^{[18]F}\] AV-133 as a biomarker for assessing the longitudinal loss of VMAT2 function and dopaminergic terminal degeneration in monkeys with acute MPTP-induced parkinsonism.

MATERIALS AND METHODS

Animals
Nine 10–15-year-old cynomolgus monkeys (5.2–8.0 kg, 2 females and 7 males) were purchased from Grandforest Co. (Nanning, China), a local primate-breeding company. All the animals were healthy, without any physical injury. For MPTP administration, the animals were anesthetized with a mixture of 3\% isoflurane and 97\% \(O_2\) prior to treatment, and a low level of isoflurane (1\%) was continued for maintenance. MPTP was injected intravenously as MPTP-HCl (Sigma Aldrich, St. Louis, MO) diluted in sterile saline at 0.2 mg/kg. Injection was performed daily for 15 days. No animal was euthanized in this study.

Ethics Statement
All animals were housed with a 12:12 h light/dark cycle at the facility of Wincon TheraCells Biotechnologies Co., Ltd., which is certified by and meets the guidelines of the Council on Accreditation of the Association for Assessment and Accreditation of Laboratory Animals Care (International). The ambient temperature was 24 ± 2 °C, and humidity was 65 ± 4%. RO (Reverses Osmosis) water was available