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Dual-isotope single-photon emission computed tomography for dopamine and serotonin transporters in normal and parkinsonian monkey brains☆

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Abstract

Introduction: Parkinson's disease (PD) affects both dopaminergic and serotonergic systems. In this study, we simultaneously evaluated dopamine and serotonin transporters in primates using dual-isotope single-photon emission computed tomography (SPECT) imaging and compared the results with traditional single-isotope imaging.
Methods: Four healthy and one 6-OHDA-induced PD monkeys were used for this study. SPECT was performed over 4 h after individual or simultaneous injection of [^{99m}Tc]TRODAT-1 (a dopamine transporter imaging agent) and [^{123}I]ADAM (a serotonin transporter imaging agent).
Results: The results showed that the image quality and uptake ratios in different brain regions were comparable between single- and dual-isotope studies. The striatal [^{99m}Tc]TRODAT-1 uptake in the PD monkey was markedly lower than that in normal monkeys. The uptake of [^{123}I]ADAM in the midbrain of the PD monkey was comparable to that in the normal monkeys, but there were decreased uptakes in the thalamus and striatum of the PD monkey.
Conclusions: Our results suggest that dual-isotope SPECT using [^{99m}Tc]TRODAT-1 and [^{123}I]ADAM can simultaneously evaluate changes in dopaminergic and serotonergic systems in a PD model.

Keywords: Parkinson's disease; Dopamine transporter; Serotonin transporter; Dual-isotope SPECT; [^{99m}Tc]TRODAT-1; [^{123}I]ADAM

1. Introduction

Neuropathological alterations in Parkinson's disease (PD) are thought to be due to degeneration of the nigrostriatal dopaminergic pathway, leading to a progressive decrease of dopaminergic neurons [1]. The dopamine transporter (DAT), located in the presynaptic dopaminergic neurons, is the principal site for regulating synaptic dopamine levels in the synaptic cleft and may serve as a marker for dopaminergic neurons [2]. In normal human brains, high density of DAT was found in the striatum [3,4].

On the other hand, the serotonergic system is thought to play a crucial role in neuropsychiatric disorders [5]. The serotonin transporter (SERT), located in the presynaptic serotonergic neurons, modulates synaptic serotonin levels [6]. Recent human postmortem neuropathological and neurochemical studies further revealed that the brain serotonergic neurons were also affected in PD [7]. A previous study indicated that neuronal degeneration in the dorsal raphe nucleus is more severe in PD patients with depression than in those without depression [8]. Abnormalities in SERT have been demonstrated in depressive PD patients by imaging modalities such as PET and single-photon emission

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computed tomography (SPECT) [5,9-11]. The role of SERT in depression is of particular interest because it is a major target for antidepressant medications [12-14].

The depression has become the most common psychiatric symptom in PD patients with a prevalence of 20–45% [15], causing a negative influence on patients' quality of life and becoming one of the most important risk factors for rapid disease progression [5,16,17].

The radioligands [^{99m}Tc]TRODAT-1 ([2-[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo[3,2,1]oct-2-yl] methyl](2-mercaptoethyl)amino]ethyl]amino]ethanethiolato (3-)-*N2,N2′,S2,S2′*]oxo-[1*R*-(*exo-exo*)]) and [^{123}I]ADAM (2-([2-([dimethylamino]methyl)phenyl]thio)-5-[^{123}I] iodophenylamine) are potent DAT and SERT imaging agents, respectively. These radioligands have been extensively studied individually in the past [3,4,18-23], but combined use of [^{99m}Tc]TRODAT-1 and [^{123}I]ADAM, to our knowledge, has not yet been published.

The goal of this study was to evaluate the feasibility of using dual-isotope SPECT imaging to study DATs and SERTs simultaneously by simultaneous injection of [^{99m}Tc]TRODAT-1/[^{123}I]ADAM in normal monkeys and in a monkey with 6-OHDA-induced PD [4]. This PD model has been assessed by SPECT imaging using [^{99m}Tc]TRODAT-1 and [^{123}I]ADAM SPECT individually [24].

2. Materials and methods

2.1. Animal model

The creation of parkinsonian model in the Formosan rock macaque (*Macaca cyclopis*) has been described previously [4]. Briefly, four previously healthy monkeys, weighing 5–7 kg, received bilateral injections of 30 μl 6-OHDA at the following concentrations — 1, 2, 3 and 5 μg/μl, respectively — into the medial forebrain bundle (MFB) using MR image guidance. MR image was performed before and after the injection to confirm the location of the lesion. The monkey that received 5 μg/μl 6-OHDA injection developed persistent parkinsonian symptoms after 4 days.

After 6 years, this PD monkey along with four other normal monkeys was chosen for dual-isotope SPECT study; all monkeys were matched for age and sex. All the research protocols were approved by the local animal care committee.

2.2. Radiopharmaceuticals

The radioligands [^{99m}Tc]TRODAT-1 and [^{123} I]ADAM were provided by the Institute of Nuclear Energy Research (Lung-Tan, Taiwan) as described previously [4,25].

2.3. Image data acquisition and analyses

The four normal and one PD monkeys were fasted overnight and anesthetized with ketamine injection (10 mg/kg im), followed by passive inhalation of O_2 (2 L/min) containing 1.8% isoflurane. The monkeys were placed supine, with their heads fixed in a holder and aligned with an installed laser beam. An intravenous line was established in the cephalic vein for hydration (0.9% NaCl, 5 ml/kg per hour), and radioligand was administered through the same line. Potassium perchlorate (200 mg) was given orally 30 min before radioligand injection to minimize ^{123}I uptake in the thyroid gland.

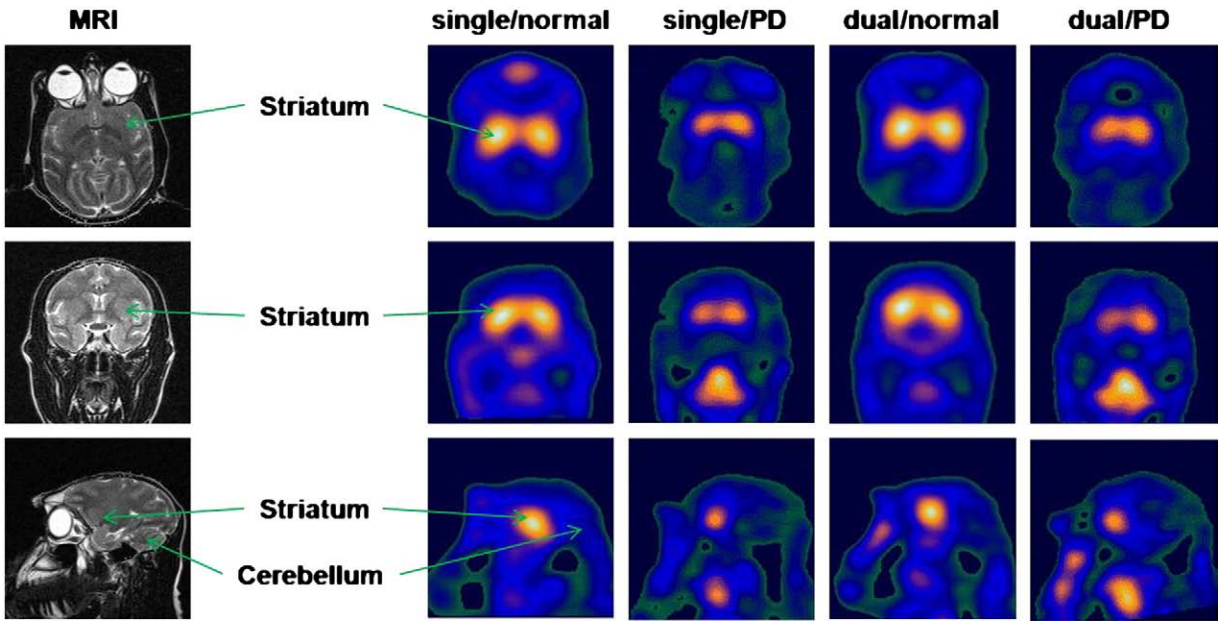

Fig. 1. [^{99m}Tc]TRODAT-1 SPECT seen on single- and dual-isotope images of one normal and one PD monkeys at 180–210 min after injection of 20 mCi [^{99m}Tc]TRODAT-1, showing the comparable image quality between single- and dual-isotope images. There is a marked lower striatal [^{99m}Tc]TRODAT-1 uptake in the PD monkey than that of the normal monkey. The transaxial, coronal and sagittal SPECT images are coregistered to the MR images.