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Pharmacologic MRI (phMRI) as a tool to differentiate Parkinson's disease–related from age-related changes in basal ganglia function

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ABSTRACT

The prevalence of both parkinsonian signs and Parkinson's disease (PD) per se increases with age. Although the pathophysiology of PD has been studied extensively, less is known about the functional changes taking place in the basal ganglia circuitry with age. To specifically address this issue, 3 groups of rhesus macaques were studied: normal middle-aged animals (used as controls), middle-aged animals with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–induced parkinsonism, and aged animals (>20 years old) with declines in motor function. All animals underwent the same behavioral and pharmacologic magnetic resonance imaging (phMRI) procedures to measure changes in basal ganglia function in response to dopaminergic drug challenges consisting of apomorphine administration followed by either a D1 (SCH23390) or a D2 (raclopride) receptor antagonist. Significant functional changes were predominantly seen in the external segment of the globus pallidus (GPe) in aged animals and in the striatum (caudate nucleus and putamen) in MPTP-lesioned animals. Despite significant differences seen in the putamen and GPe between MPTP-lesioned versus aged animals, a similar response profile to dopaminergic stimulations was found between these 2 groups in the internal segment of the GP. In contrast, the pharmacologic responses seen in the control animals were much milder compared with the other 2 groups in all the examined areas. Our phMRI findings in MPTP-lesioned parkinsonian and aged animals suggest that changes in basal ganglia function in the elderly may differ from those seen in parkinsonian patients and that phMRI could be used to distinguish PD from other age-associated functional alterations in the brain.

1. Introduction

Human aging is a universal phenomenon. Parkinson's disease (PD), an important example of an age-related movement disorder, is clinically characterized by slowness of movement, rigidity, tremor, and postural and balance instabilities. The prevalence of PD rises with increasing age from 0.6% in 65- to 69-year-old individuals to 3.6% in 80-year-old individuals (de Rijk et al., 1997). In normal aging, nearly 15% of individuals between the ages of 65–75 years old were found to display ≥2 parkinsonian signs, and the incidence rose to >50% in those >85 years old (Bennett et al., 1996; Buchman et al., 2012). Bennett et al. (1996) reported that motor symptoms with the highest prevalence included bradykinesia (37%), gait disturbance (51%), and rigidity (43%) whereas resting tremor, a cardinal symptom of idiopathic PD, had the lowest prevalence (5%) in the elderly. Although the expression of movement dysfunctions, often called "mild parkinsonian signs," is more prevalent in older people who otherwise have no definite neurologic disease (Louis and Bennett, 2007), those so-called "mild PD signs" are in fact not benign. Rather, they are associated with a wide range of adverse health outcomes including an increased risk of death and the development of disability, mild cognitive impairment, Alzheimer's disease, and cognitive decline (Buchman et al., 2012). Furthermore, dopaminergic replacement therapies, in contrast with their use in PD, are ineffective at relieving the burden associated with age-related parkinsonism (for a review, see Darbin, 2012).

For over half a century, it has been hypothesized that age-associated decline in movement functions is caused by changes in "central processes initiating, shaping, and monitoring movements" (Welford, 1958). Because the primary cause of PD is the degeneration of the nigrostriatal dopaminergic system (Hornykiewicz and Kish, 1987), there has long been a suspicion that the mechanisms underlying motor decline in normal aging also involve the central

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dopaminergic system (for a review, see Darbin, 2012). Although the movement disorders seen with advancing age resemble those seen in PD, it is still not clear whether similar changes in the central nervous system circuitry underlie these similar behavioral impairments. Emerging evidence demonstrates that the basal ganglia dopaminergic system, which degenerates in PD, is also altered in normal aging processes in humans but with some distinct differences. For instance, dopamine (DA) cell loss in PD is more severe and mainly occurs in the ventral tier of the substantia nigra pars compacta (SNc), whereas it is milder and located in the dorsal tier of the SNc in normal aging. Also, DA levels are higher in the SNc and putamen in normal age-matched controls than in PD patients (Bokobza et al., 1984; Kish et al., 1988). Thus, dopaminergic pathways are changing in the basal ganglia in PD and in normal aging, but the underlying mechanisms may be different. Although the effects of PD on basal ganglia functions have been extensively studied, much less is known about the functional consequences because of normal aging. As a result, the treatments for age-associated motor dysfunctions are even more limited than for PD (Buchman et al., 2012). Differentiating idiopathic PD from atypical PD syndromes, especially in the early disease stages, has proven to be difficult because of an overlap of clinical signs and symptoms. This may explain, at least in part, the high rate of misdiagnosis for PD (for a review, see Mahlknecht et al., 2010).

Positron emission tomography (PET) and single-photon emission computed tomography imaging with radioactive tracers such as [^{11}C] SCH23390 (SCH) and [^{11}C] raclopride (RAC) have been increasingly used clinically to study PD (Sioka et al., 2010). Striatal DA receptor binding has been investigated in vivo with PET in patients with early PD using the D1 receptor antagonist [^{11}C] SCH23390 and the DA D2 receptor antagonist [^{11}C] RAC (Rinne et al., 1990). In that study, abnormal bindings of D2 but not D1 receptors were found in early PD. In general, idiopathic PD patients usually show a normal or unregulated postsynaptic DA D2 receptor profile, whereas atypical parkinsonian syndromes like multiple system atrophy or progressive supranuclear palsy present with decreased postsynaptic binding (Schreckenberger et al., 2004). However, alternative noninvasive imaging methods that avoid ionizing radiation would be preferable for screening a large number of individuals at risk for developing PD and/or to differentiate PD from other neurologic disorders (Zhang et al., 2006). After carefully examining the previously published studies using PET and single-photon emission computed tomography in PD research, we hypothesize that pharmacologic magnetic resonance imaging (phMRI) could be used to investigate the underlying mechanism of age-associated parkinsonism and propose to explore the feasibility of using this imaging modality for the differential diagnosis of PD in future clinical trials.

The present study was designed to use phMRI to investigate the differences in basal ganglia function in aged and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–lesioned rhesus monkeys in response to DA receptor agonists and antagonists. For example, compared with young rhesus monkeys, DA agonists including apomorphine (APO) and D-amphetamine significantly increased neuronal activity in the external segment of the globus pallidus (GPe) of aged animals indicating that the altered responses in the aged GPe may contribute significantly to the motor dysfunctions characterizing advanced age (Zhang et al., 2001). Based on our previously published studies (Cass et al., 2007; Hardy et al., 2005; Zhang et al., 2001, 2006), we hypothesized that age-related pathophysiological changes would be concentrated in the pallidal regions, particularly in the GPe, whereas changes related to DA denervation induced by MPTP would be dominant in the nigrostriatal regions.

2. Materials and methods

2.1. Animals

A total of 10 female rhesus monkeys (*Macaca mulatta*) ranging in age from 15 to 22 years old and weighing between 5.5 and 7.5 kg were obtained from a commercial supplier (Covance, Alice, TX, USA) and used for this study. All animals were housed in individual cages in a temperature-controlled room and maintained on a 12-hour light and dark cycle. Throughout the entire study, water was available ad libitum. They were divided into 3 test groups: normal middle-aged (12 - to 14-year-old, $n = 3$) animals, middle-aged (15- to 16-year-old, $n = 4$) animals with unilateral MPTP lesions, and normal aged (>20-year-old, $n = 3$) animals. The 4 parkinsonian animals received unilateral administration of 0.12-mg/kg MPTP via the right carotid artery 12 months before entering the present study using previously described surgical procedures (Ding et al., 2008). All procedures were conducted in the Laboratory Animal Facilities of the University of Kentucky, which are fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. All experimental protocols were approved by the University of Kentucky Animal Care and Use Committee and followed National Institutes of Health and US Department of Agriculture guidelines.

2.2. Standardized rating of movement dysfunctions

As per the previously described procedures (Zhang et al., 2000), all animals were videotaped to assess motor functions, and the MPTP-treated animals were video-recorded pre- and post-MPTP administration before entering the present study. Briefly, the monkeys were transferred into a customized videotaping cage at 9 AM on the day of testing and allowed to adapt to the environment for a few hours. The videotaping segment started at 1:00 and 2:00 PM, and each video segment lasted for 45 minutes. Motor dysfunctions were rated independently in quarter-point increments by 2 experienced observers (RCG and ZZ) using our previously published rating scale (Zhang et al., 2000). Motor dysfunctions including bradykinesia, rigidity, and postural and balance instabilities were rated from 0 (normal) to 3 (severe disability). The rating from the middle-aged controls was considered to be the normal baseline (rating as "0").

2.3. PhMRI procedure

The complete methodology for conducting MRI scanning and minimizing head motion in alert rhesus monkeys has been detailed elsewhere (Andersen et al., 2002). The methodology includes (1) acclimating awake animals to the MRI environment before scanning; (2) using custom head frame and head pins to secure the head; (3) using ear bars to reduce ambient scanning noise levels; and (4) using multivariate methods of image data analysis suitable for detecting and deleting outlying observations because of motion artifacts. The phMRI scans were conducted in fully conscious and alert animals on a Siemens Vision 1.5-T clinic scanner using the body coil to transmit radio frequency and an 8-cm diameter surface coil for signal reception. The anatomic structures of interest were visualized using a 3D fast low angle shot (FLASH) sequence with 1-mm isotropic resolution (time repetition and/or echo time [TE] = 21/6 ms, flip angle = 30°, image matrix size = 128 × 128 × 90, field of view = 128 mm). The functional MR images from pharmacologic challenges were acquired continuously at a temporal sampling rate of 30 seconds using a FLASH 2-dimensional (2D) multiple gradient–recalled echo navigator sequence (Chen et al., 1996). Slices were acquired interleaved for 3 noncontiguous coronal slices: the