Neurobiology of Aging 34 (2013) 1497–1503

Contents lists available at SciVerse ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Higher iron in the red nucleus marks Parkinson's dyskinesia

Mechelle M. Lewis [a,b,1], Guangwei Du [a,1], Michal Kidacki [a], Nisargkumar Patel [a], Michele L. Shaffer [c], Richard B. Mailman [a,b], Xuemei Huang [a,b,d,e,f,*]

[a] Department of Neurology, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey, PA, USA
[b] Department of Pharmacology, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey, PA, USA
[c] Department of Public Health Sciences, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey, PA, USA
[d] Department of Radiology, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey, PA, USA
[e] Department of Neurosurgery, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey, PA, USA
[f] Department of Kinesiology, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey, PA, USA

ARTICLE INFO

Article history:
Received 10 May 2012
Received in revised form 22 October 2012
Accepted 25 October 2012
Available online 21 November 2012

Keywords:
Parkinson's disease (PD)
Red nucleus
Transverse relaxation rate (R2*)
Magnetic resonance imaging (MRI)

ABSTRACT

Dopamine cell loss and increased iron in the substantia nigra (SN) characterize Parkinson's disease (PD), with cerebellar involvement increasingly recognized, particularly in motor compensation and levodopa-induced dyskinesia (LID) development. Because the red nucleus (RN) mediates cerebellar circuitry, we hypothesized that RN iron changes might reflect cerebellum-related compensation, and/or the intrinsic capacity for LID development. We acquired high resolution magnetic resonance images from 23 control and 38 PD subjects (12 with PD and history of LID [PD+DYS]) and 26 with PD and no history of LID (PD−DYS). Iron content was estimated from bilateral RN and SN transverse relaxation rates (R2*). PD subjects overall displayed higher R2* values in both the SN and RN. RN R2* values correlated with off-drug Unified Parkinson's Disease Rating Scale-motor scores, but not disease duration or drug dosage. RN R2* values were significantly higher in PD+DYS compared with control and PD−DYS subjects; control and PD−DYS subjects did not differ. The association of higher RN iron content with PD-related dyskinesia suggests increased iron content is involved in, or reflects, greater cerebellar compensatory capacity and thus increased likelihood of LID development.

1. Introduction

Parkinson's disease (PD) is characterized by loss of dopaminergic neurons in the substantia nigra (SN) of the basal ganglia (BG). Levodopa corrects the primary motor dysfunction, but with continuing use and disease progression is associated with levodopa-induced dyskinesia (LID). The classic striato-thalamo-cortical model posits that dopamine deficiency leads to primary motor dysfunction via excessive inhibition of the thalamus resulting in reduced excitatory thalamo-cortical output. Functional somatotopy after pallidotomy, however, suggests PD primary motor symptoms have a different anatomic substrate from LID (Kishore et al., 2000) that cannot be explained purely by traditional striato-thalamo-cortical models.

In recent years, we (Lewis et al., 2007, 2011; Sen et al., 2009) and others (Cerasa et al., 2006; Yu et al., 2007) have suggested cerebellar pathways might be important in the pathophysiology of PD, particularly in compensating for BG dysfunction with increased functional activity. Increased cerebellar function might contribute to the development of LID in PD (Brusa et al., 2011; Koch et al., 2009), as shown by increased cerebellar activity during PD progression (Sen et al., 2009) and by more LID in PD subjects with younger onset age (Jankovic, 2005), possibly because of more robust compensatory mechanisms (Fuente-Fernandez et al., 2011). In addition, di- and trisynaptic connections between the striatum and cerebellum have been demonstrated (Bostan et al., 2010; Hoshi et al., 2005), and in the context of our previously proposed model of motor control (Lewis et al., 2007), these data lead to a testable hypothetical model for motor control (Fig. 1A, gray arrows) in which motor tasks are processed through combined activity of cortico-striato-cortical and cortico-cerebello-cortical circuits. The model also suggests that the subcortical striato-cerebellar and cerebello-striatal pathways might modulate function in a parallel fashion (the implications for PD [Fig. 1B and C] are addressed in the Discussion).

The red nucleus (RN) receives significant somatotopically-organized input from ipsilateral motor cortex and contralateral cerebellum (Habas and Cabanis, 2007), thus providing a pivotal intersection between primary and cerebellar motor pathways

* Corresponding author at: Department of Neurology, Pennsylvania State University-Milton S. Hershey Medical Center, 500 University Drive, H-037, Hershey, PA 17033-0850, USA. Tel.: +1 717 531 1803; fax: +1 717 531 0266.
E-mail address: xuemei@psu.edu (X. Huang).
[1] These authors contributed equally to this work.

0197-4580/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2012.10.025

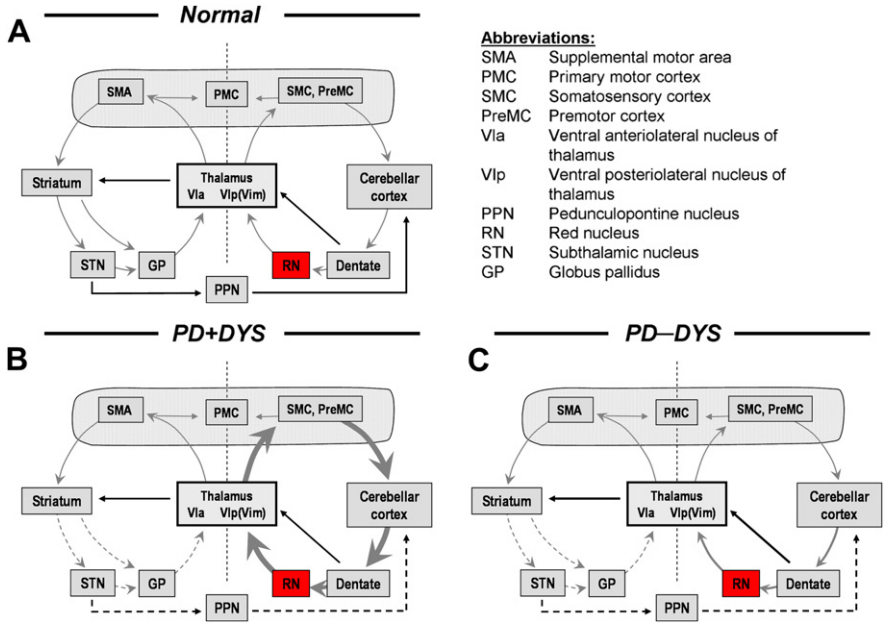

Fig. 1. Model of motor function. (A) Normal subjects: motor tasks are accomplished through combined activity in striato- and cerebello-thalamo-cortical circuits (gray arrows) with modulation from striato-cerebellar and cerebello-striatal subcortical pathways (solid lines). (B and C, See Discussion): Model of motor dysfunction in Parkinson's disease (PD) with and without dyskinesia. In subjects with PD and history of levodopa-induced dyskinesia (LID, PD+DYS), decreased input from dysfunctional striatal circuits (dotted lines) leads to markedly increased activity in cerebellar circuits that set the stage for LID development (B). In subjects with PD but no history of LID (PD−DYS), the slightly increased recruitment of cerebellar circuits is not dysfunctional enough to result in predisposition for development of LID (C).

(Bird and Shaw, 1978; Lapresle and Hamida, 1970). Animal studies suggest that RN output provides important compensation after corticospinal lesions (Belhaj-Saif and Cheney, 2000; Kanagal and Muir, 2009). In PD, the RN might increase its function to fulfill cerebellar compensation in the presence of BG dysfunction (see Fig. 1B), although the exact mechanism is not known.

Iron is a cofactor for the synthesis and degradation of several neurotransmitters (Beard et al., 1993), and occurs in high concentration in many subcortical nuclei with high metabolic demands (e.g., SN, globus pallidus). In the face of oxidative stress challenges, there is an induction of ferritin intracelluarly (possibly as a "sink" for toxic iron) and an upregulation of heme oxygenase (increasing iron sequestration into glia). These changes, however, might promote iron "trapping" or "overload" (Zukor et al., 2009). We thus hypothesized that RN iron content might be increased in PD, particularly in patients with higher cerebellar compensation (i.e., higher metabolic demand) in the presence of oxidative stress; these subjects would be hypothesized to have increased likelihood of developing LID.

Iron is paramagnetic and causes a strong reduction in T2* relaxation time. Several magnetic resonance imaging (MRI) studies have demonstrated that the SN transverse relaxation rate ($R2^* = 1/T2^*$) is correlated with iron concentration in vivo (Gelman et al., 1999), is increased in PD (Sofic et al., 1988), and discriminates PD from control subjects (Du et al., 2011). The RN lies near the SN, is similarly iron-rich (Drayer et al., 1986), and is recognized easily in midbrain MRI images (see Fig. 2). This is the first MRI study focused on the RN to test the hypothesis that RN iron might mark the intrinsic capacity of PD subjects to develop LID.

2. Methods

2.1. Subjects

Thirty-eight PD (12 with PD and history of LID [PD+DYS]) and 26 with PD and no history of LID [PD−DYS]) and 23 control subjects (Controls) were recruited from patients and their companions presenting to a tertiary movement disorders clinic (Table 1). PD diagnosis was confirmed by a movement disorder specialist (XH) according to published criteria (Calne et al., 1992), and PD medications optimized before enrollment in the study. Disease duration from time of diagnosis and history of dyskinesia were obtained from subject history. All 12 PD+DYS subjects were medically optimized such that dyskinesia was either minimal or totally absent at the time of study enrollment. Thus, the brain MRI results are unlikely to be influenced by abnormal movements per se.

Unified Parkinson's Disease Rating Scale part III-motor scores (UPDRS-III; Goetz et al., 2008) were obtained for each PD subject after withholding all PD medication overnight (approximately 12 hours). Levodopa-equivalent daily dose (LEDD) was estimated (Tomlinson et al., 2010), and total levodopa dose (tLD) calculated by summing the amount of levodopa taken per day. All subjects were free of major acute medical issues such as liver, kidney, or thyroid abnormalities, or deficiencies of B12 or folate. A medical history on all subjects, noting any previous or current conditions, was obtained. Each brain MRI (vide infra) was inspected and reviewed by a board-certified neurologist, and deemed to be free of any cerebral white matter or ischemic changes. All subjects gave written informed consent, and the study was reviewed and approved by the Penn State Hershey Institutional Review Board.

2.2. MRI data acquisition

All subjects were scanned using a 3.0 Tesla MR Scanner (Trio, Siemens Magnetom, Erlangen, Germany) and high-resolution T2-weighted and multigradient-echo T2*-weighted images were collected. T2-weighted images were acquired using a fast spin-echo sequence with TR/TE = 2500/316, field of view = 256 mm × 256 mm, matrix = 256 × 256, slice thickness = 1 mm (with no gap), and slice number = 176. A multigradient-echo sequence was used to estimate the proton transverse relaxation rate, $R2^*$ ($R2^* = 1/T2^*$). Six echoes with a TE ranging from 7 to 47 ms and an interval of 8 ms were