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Assessing the role of dopamine in limb and cranial-oromotor control in a rat model of Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder primarily characterized by sensorimotor dysfunction. The neuropathology of PD includes a loss of dopamine (DA) neurons of the nigrostriatal pathway. Classic signs of the disease include rigidity, bradykinesia, and postural instability. However, as many as 90% of patients also experience significant deficits in speech, swallowing (including mastication), and respiratory control. Oromotor deficits such as these are underappreciated, frequently emerging during the early, often hemi-Parkinson, stage of the disease. In this paper, we review tests commonly used in our labs to model early and hemi-Parkinson deficits in rodents. We have recently expanded our tests to include sensitive models of oromotor deficits. This paper discusses the most commonly used tests in our lab to model both limb and oromotor deficits, including tests of forelimb-use asymmetry, postural instability, vibrissae-evoked forelimb placing, single limb akinesia, dry pasta handling, sunflower seed shelling, and acoustic analyses of ultrasonic vocalizations and pasta biting strength. In particular, we lay new groundwork for developing methods for measuring abnormalities in the acoustic patterns during eating that indicate decreased biting strength and irregular intervals between bites in the hemi-Parkinson rat. Similar to limb motor deficits, oromotor deficits, at least to some degree, appear to be modulated by nigrostriatal DA. Finally, we briefly review the literature on targeted motor rehabilitation effects in PD models.

Learning outcomes: Readers will: (a) understand how a unilateral lesion to the nigrostriatal pathway affects limb use, (b) understand how a unilateral lesion to the nigrostriatal pathway affects oromotor function, and (c) gain an understanding of how limb motor deficits and oromotor deficits appear to involve dopamine and are modulated by training.

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1. Introduction

Regular physical exercise is widely advocated as an important component of health and may reduce the risk of certain diseases (Nelson et al., 2007). A beneficial effect of exercise has been reported in patients with PD (Chen, Zhang, Schwarzschild, Hernan, & Ascherio, 2005). Specifically, exercise has been shown to improve motor performance (Miyai et al., 2000; Sunvisson, Lökk, Ericson, Winblad, & Ekman, 1997), increase daily activity (Miyai et al., 2000), and decrease mortality (Kuroda, Tatara, Takatorige, & Shinsho, 1992). Regular exercise may even delay the appearance of motor impairment in people diagnosed with PD (Tsai et al., 2002). Exercise is associated with a lower risk of PD, although it may be that people who exercise less already have subclinical neurodegeneration (Chen et al., 2005). Animal models may help to clarify whether some types of motor rehabilitation can protect against degeneration of DA neurons. Given the potential beneficial effects of exercise in PD, it may seem surprising that physical exercise is not always a component of therapy for PD. In fact, studies have shown that although persons with PD reduce their level of physical activity, only 12–15 percent of diagnosed individuals are referred to physical therapy for an exercise intervention (Goodwin, Richards, Taylor, Taylor, & Campbell, 2008; Thacker et al., 2008). However, optimal levels, quality, and timing of PD-specific therapies remain unclear.

Animal models have provided a means for investigating the potentially positive effects of exercise on the brain, including neurogenesis, synaptogenesis, angiogenesis, increased neurotrophic factors, and increased levels of DA (Faherty, Shepherd, Herasimtschuk, & Smeyne, 2005; Jones & Schallert, 1994; Poulton & Muir, 2005; Schallert & Jones, 1993; Swain et al., 2003; van Praag, Shubert, Zhao, & Gage, 2005). Animal models of stroke have been instrumental in helping to guide the experimental use of exercise therapy by suggesting that forced use of the upper limb improves motor recovery and neural plasticity (Jones, Kleim, & Greenough, 1996; Jones & Schallert, 1994; Kleim, Jones, & Schallert, 2003; Nudo, Miliken, Jenkins, & Merzenich, 1996). However, very intense or prolonged levels of motor training very early after injury may be toxic (Kozlowski, James, & Schallert, 1996; Schallert, Fleming, & Woodlee, 2003). Animal models of PD afford us the opportunity to examine experience-dependent plasticity in the nervous system as a result of sensorimotor training. Our labs focus on a rat model of PD that is created by unilateral infusion of the catecholamine neurotoxin 6-hydroxydopamine (6-OHDA) into the medial forebrain bundle. During a short window, this procedure leads to death of DA neurons that have their cell bodies in the substantia nigra and terminate in the striatum, which models primary disease pathology of PD (Fulceri et al., 2006; Marshall, 1979; Tillerson et al., 2001; Ungerstedt & Arbuthnott, 1970). Several studies suggest that intensive training that includes behaviors that are highly vulnerable to DA neurotoxins may reverse or slow disease progression (Anstrom, Schallert, Woodlee, Shattuk, & Roberts, 2007; Cohen, Tillerson, Smith, Schallert, & Zigmond, 2003; Smith & Zigmond, 2003; Tillerson et al., 2001, 2002). For example, in unilateral 6-OHDA models, rats show deficits in forelimb use (Allred et al., 2008; Calne & Zigmond, 1991; Schallert, Fleming, Leasure, Tillerson, & Bland, 2000), but forced use of an impaired forelimb yields behavioral sparing in that limb and may prevent the degeneration of dopaminergic neurons when training is initiated before or early enough after introduction of the neurotoxin (Anstrom et al., 2007; Cohen et al., 2003; Tillerson et al., 2001, 2002). However, if initiation of intervention is delayed by 7 days, then the effect of behavioral sparing is not apparent or as robust (Tillerson et al., 2001, 2002).

Until recently, the body of animal model rehabilitation literature has focused on the forelimb. However, even in the early stages of PD, significant voice and swallowing deficits emerge that negatively impact quality of life, often leading to loss of employment and social isolation (Athlin et al., 1989; Bird et al., 1994; Fuh, Lee, & Wang, 1997; Miller et al., 2006). Up to 90% of people with PD experience a voice or swallowing problem and as the disease progresses, these deficits can cause debilitating health complications, including aspiration pneumonia, which is the leading cause of death in PD (Beyer, Herlofson, Arsland, & Larsen, 2001; D'Amelio et al., 2006; Fox, Morrison, Ramig, & Sapir, 2002; Ho, Iansek, Marigliani, Bradshaw, & Gates, 1998; Plowmann-Prine et al., 2009). Despite these significant clinical issues, there is not a clear understanding of the underlying neurobiological mechanisms of voice and swallowing disorders in regard to PD. Thus, a goal of this paper is to review tests commonly used in our labs to model PD deficits, focusing on those that involve DA, and tests of oromotor functions including voice, mastication and swallowing. New preliminary data on the control of biting will be presented in some detail.

2. Methods, preliminary results and discussion

2.1. Parkinson's disease model

Moderate to severe degeneration of presynaptic dopaminergic striatal neurons is induced by unilateral infusion of 6-OHDA (a catecholamine neurotoxin; Sigma) into the medial forebrain bundle (Fulceri et al., 2006; Marshall, 1979; Tillerson et al., 2001; Ungerstedt & Arbuthnott, 1970). Rats are anesthetized with a combination of ketamine (90 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.) and placed in a stereotaxic frame. Pre-operative analgesia [5 mg/kg 0.25% (w/v) Marcaine] is injected underneath the scalp prior to making the initial incision. Animals receive unilateral infusions of 7 μg (free base weight) 6-OHDA hydrobromide dissolved in 3 μl artificial cerebrospinal fluid (composition: NaCl, KCl, $CaCl_2$, $MgCl_2 \cdot 6H_2O$) containing 0.05% (w/v) ascorbic acid. Injection coordinates are measured from bregma (−4.3 AP; ±1.5 ML; −8.0 DV from dural surface), and the solution is infused at a rate of 0.5 μl/min for a total of 6 min. At the end of the 6-min infusion, the needle is left in place for an additional 2 min before being slowly retracted. Infusions are directed into the nigrostriatal projections in the hemisphere opposite to the preferred forelimb as determined from baseline scores on the limb-use asymmetry test (see below).