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Initiation of calorie restriction in middle-aged male rats attenuates aging-related motoric decline and bradykinesia without increased striatal dopamine

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ABSTRACT

Aging-related bradykinesia affects ~15% of those reaching age 65 and 50% of those reaching their 80s. Given this high risk and lack of pharmacologic therapeutics, noninvasive lifestyle strategies should be identified to diminish its risk and identify the neurobiological targets to reduce aging-related bradykinesia. Early-life, long-term calorie restriction (CR) attenuates aging-related bradykinesia in rodents. Here, we addressed whether CR initiation at middle age could attenuate aging-related bradykinesia and motoric decline measured as rotarod performance. A 30% CR regimen was implemented for 6 months duration in 12-month-old male Brown-Norway Fischer 344 F_1 hybrid rats after establishing individual baseline locomotor activities. Locomotor capacity was assessed every 6 weeks thereafter. The ad libitum group exhibited predictably decreased locomotor activity, except movement speed, out to 18 months of age. In contrast, in the CR group, movement number and horizontal activity did not decrease during the 6-month trial, and aging-related decline in rotarod performance was attenuated. The response to CR was influenced by baseline locomotor activity. The lower the locomotor activity level at baseline, the greater the response to CR. Rats in the lower 50th percentile surpassed their baseline level of activity, whereas rats in the top 50th percentile decreased at 6 weeks and then returned to baseline by 12 weeks of CR. We hypothesized that nigrostriatal dopamine tissue content would be greater in the CR group and observed a modest increase only in substantia nigra with no group differences in striatum, nucleus accumbens, or ventral tegmental area. These results indicate that initiation of CR at middle age may reduce aging-related bradykinesia, and, furthermore, subjects with below average locomotor activity may increase baseline activity. Sustaining nigral dopamine neurotransmission may be one component of preserving locomotor capabilities during aging.

1. Introduction

The risk of significant and clinically diagnosable locomotor impairment in those 65 years and older is increasing. In the United States alone, the number of retirees will double in the next 20 years. The growing elderly population is presenting an increasing challenge to the biomedical enterprise of industrialized nations. Viewed as a cardinal symptom of Parkinson's disease (PD), bradykinesia (slowness or poverty of movement and difficulty in movement initiation) is also a significant health risk to the elderly, affecting 15% by age 65 and 50% by age 80 (Bennet et al., 1996; Murray et al., 2004; Prettyman, 1998; Rosano et al., 2012). Recent evidence points to an association between social activity and motor decline (Buchman et al., 2009) and genetic loci contributing to vulnerability to age-related Parkinsonism (Shulman et al., 2014). This impairment greatly compromises an individual's ability to navigate the daily environment, and concomitantly, the risk of severe injury greatly increases (Fleischman et al., 2007). To fully elucidate the neurobiological basis for aging-related bradykinesia, it must also be recognized that ~50% of the elderly do not exhibit signs of bradykinesia (Bennet et al., 1996; Buchman et al., 2014; Rosano et al., 2012). Therefore, it is important to frame questions that recognize that aging-related bradykinesia, while different in origin compared with PD, shares a common locomotor deficit, bradykinesia, with PD. Thus, identification of a common neurobiological basis for bradykinesia in either condition would be highly important. Second, it is

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imperative to understand if potential lifestyle practices may underlie the neurobiological basis as to why bradykinesia affects roughly half of the elderly, but not the other half, by age 80.

Thus, 3 priorities can be recognized: (1) determine if there are inherent behavioral (in this case, locomotor activity tendencies) traits that may predispose or increase risk of aging-related locomotor impairment; (2) determine if there is a neurobiological basis for predisposing individuals to locomotor impairment with aging; and (3) evaluate noninvasive lifestyle strategies that can be practically implemented to reduce the significant risk of locomotor impairment associated with aging. To address whether inherent locomotor capacity at middle age could be a predictive factor for the likelihood of bradykinesia onset, we hypothesized that a lower than average activity level at middle age would predispose that subset to aging-related bradykinesia. In established rat models of aging, studies indicate that a significant decline in locomotor activity occurs somewhere between 6 and 18 months of age, when evaluating the entire cohort for each age group (Hebert and Gerhardt, 1998; Salvatore et al., 2009; Yurek et al., 1998). However, considerable variance in individual differences in locomotor activity at a young age could predict eventual bradykinesia onset (Salvatore et al., 2009), particularly if a test subject's relative ranking in locomotor activity level at an earlier age is maintained with advancing age. Therefore, we predicted that bradykinesia would be more evident in the bottom 50th percentile with advancing age. This tendency may portend to increased morbidity as well because rodent studies have demonstrated that lower locomotor activity at advanced ages is predictive of earlier death (Ingram and Reynolds, 1986).

Attempts to understand the neurobiological basis of impaired locomotor function with aging have been approached from the hypothesis that deficits in dopamine (DA) neurotransmission could underlie aging-related bradykinesia. Indeed, bradykinesia is a cardinal symptom of PD itself and occurs when striatal DA or tyrosine hydroxylase (TH) loss reaches or exceeds 80% (Bernheimer et al., 1973; Bezard et al., 2001; Hornykiewicz and Kish, 1986). However, in the typical course of aging, striatal DA loss has been reported to reach a maximum of 60% in human (Haycock et al., 2003; Kish et al., 1992) or the nonhuman primate (Collier et al., 2007). Notably in established models of aging, there are more numerous reports indicating less than 30%–40% striatal DA loss in nonhuman primate (Gerhardt et al., 2002; Irwin et al., 1994) and rat models of aging (Cruz-Muros et al., 2007; Emerich et al., 1993; Marshall and Rosenstein, 1990; Ponzio et al., 1982; Salvatore and Pruett, 2012; Salvatore et al., 2009; Yurek et al., 1998). The loss of striatal DA required for the onset of bradykinesia, at least in PD models, is tightly defined, as 60% loss of DA in striatum in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine PD model is not associated with bradykinesia, but rather a loss exceeding 80% is seen in bradykinetic test subjects (Bezard et al., 2001). Thus, numerous studies support that age-related decreases in striatal DA do not meet, let alone exceed, the threshold of striatal DA loss associated with bradykinesia onset in PD. Furthermore, more recent reports indicate that although striatal markers of DA show virtually complete loss in some PD patients, the severity of locomotor impairment still increases over time (Kordower et al., 2013; Tabbal et al., 2012). Therefore, at the very least, the confluence of these results suggests that striatal DA content may not serve as a reliable index of locomotor impairment or capability.

Nigral DA function has been an oft-ignored barometer of locomotor function in such studies. In the comparatively smaller number of studies, aging-related DA loss in the substantia nigra is approximately 40%–60%, similar to that reported in PD (Bezard et al., 2001; Marsden, 1990) and may be in association with the onset of bradykinesia (Cruz-Muros et al., 2007; Salvatore et al., 2009; Yurek et al., 1998). Interference with DA signaling, specifically in the substantia nigra, has been shown to inhibit open-field locomotor activity (Andersson et al., 2006; Bergquist et al., 2003; Trevitt et al., 2001) Therefore, involvement of the entire nigrostriatal pathway must be considered as the primary neural system underlying aging-related bradykinesia.

Noninvasive strategies that may reduce the risk of aging-related bradykinesia include exercise and calorie restriction (CR). Long-term CR when initiated at a relatively young age in the lifespan preserves locomotor activity in aged rodents or nonhuman primates to levels associated with younger cohorts (Fitting et al., 2008; Ingram et al., 1987; Weed et al., 1997). Some evidence suggests that initiation of CR at middle age may also preserve locomotor function (Kastman et al., 2010). Furthermore, CR may protect nigrostriatal function, as such intervention has shown to mitigate locomotor impairment from a neurotoxic insult with some protection against severe striatal DA loss (Maswood et al., 2004). Here, we determined if a 30% reduction in calorie intake, when initiated in middle-aged Brown-Norway/Fischer 344 F_1 (BNF) hybrid male rats previously fed ad libitum (AL), could maintain baseline activity for 6 months out to 18 months of age, an age where locomotor and nigral DA deficits have been reported in rodents on AL diets. We also determined if any response to CR to prevent aging-related bradykinesia might be affected by the individual test subject's baseline locomotor activity at the time of intervention. Additionally, we evaluated the effects of CR on motor function via longitudinal assessment of performance in a rotarod task and a 1-time assessment of cognitive performance as assessed in a novel location memory task at the end of the study. The other major objective was to test the hypothesis that DA levels in the nigrostriatal pathway would increase in CR rats relative to AL rats, given evidence of CR-associated protection against aging-related bradykinesia, at the conclusion of the study.

2. Methods

2.1. Test subjects and weight determinations

All procedures involving rats were conducted under the auspices of approved protocols at the LSU Health Sciences Center (Shreveport) and Pennington Biomedical Research Center (PBRC) Institutional Animal Care and Use Committees. We used 12-month-old male BNF hybrid rats obtained from the National Institute on Aging contract facility at Harlan Laboratories (Indianapolis, IN, USA). The BNF hybrid strain exhibits aging-related changes in striatal and midbrain DA tissue content comparable with that reported in nonhuman primates and the outbred Sprague-Dawley rat (Cruz-Muros et al., 2007; Pruett and Salvatore, 2013; Salvatore et al., 2009; Yurek et al., 1998). Concomitantly, aging-related decreases in locomotor activity and function are well documented in this strain (Pruett and Salvatore, 2013; Salvatore et al., 2009; Spangler et al., 1994; Yurek et al., 1998) and its positive behavioral responses to lifelong CR (Fitting et al., 2008).

Body weights were determined on a weekly basis for all subjects for the duration of involvement in the study (control group, 5 measures; AL and CR groups, 24 or 25 measures after baseline). Body composition was measured by nuclear magnetic resonance (NMR) (Bruker Minispec) about 2–3 days before euthanasia. This procedure involves placement of unanesthesized rat into a small cylinder that is placed into the calibrated NMR for about 90 seconds to provide estimates of fat mass, lean estimates, and water content.

2.2. Calorie restriction regimen

The rats arrived at PBRC at 11 months of age. Since weaning, they had been maintained on an AL diet (NIH-31). After arrival, the rats