ELSEVIER

Neurobiology of Aging 28 (2007) 156–165

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Bilateral effects of unilateral intrastriatal GDNF on locomotor-excited and nonlocomotor-related striatal neurons in aged F344 rats

John A. Stanford [a,b,c,d,*], Michael F. Salvatore [e,h,i], Barry M. Joyce [e,h,i], Hongyu Zhang [a], Don M. Gash [e,i], Greg A. Gerhardt [e,f,g,h,i]

[a] *Department of Molecular & Integrative Physiology, University of Kansas Medical Center, Kansas City, KS 66160, USA*
[b] *Department of Physical Therapy & Rehabilitation Sciences, University of Kansas Medical Center, Kansas City, KS 66160, USA*
[c] *Landon Center on Aging, University of Kansas Medical Center, Kansas City, KS 66160, USA*
[d] *Smith Mental Retardation Research Center, University of Kansas Medical Center, Kansas City, KS 66160, USA*
[e] *Department of Anatomy & Neurobiology, The University of Kentucky Chandler Medical Center, Lexington, KY 40536-0098, USA*
[f] *Department of Neurology, The University of Kentucky Chandler Medical Center, Lexington, KY 40536-0098, USA*
[g] *Department of Psychiatry, The University of Kentucky Chandler Medical Center, Lexington, KY 40536-0098, USA*
[h] *Center for Sensor Technology, The University of Kentucky Chandler Medical Center, Lexington, KY 40536-0098, USA*
[i] *Morris K. Udall Parkinson's Disease Research Center of Excellence, The University of Kentucky Chandler Medical Center, Lexington, KY 40536-0098, USA*

Received 15 September 2005; received in revised form 20 October 2005; accepted 21 October 2005
Available online 28 November 2005

Abstract

In order to determine its effects on locomotor-related striatal electrophysiology in aged rats, glial cell line-derived neurotrophic factor (GDNF) was infused (vehicle or 30 μg) into the right striatum of 24–25-month-old Fischer 344 (F344) rats. Multi-wire electrode arrays were then chronically implanted in striatum bilaterally. Thirty days later, striatal electrophysiological activity was recorded during freely moving conditions. Individual neurons were classified as locomotor-excited if they exhibited significant increases in firing rates during locomotor bouts versus periods of nonmovement. GDNF produced a significant increase in overall firing rates in locomotor-excited striatal neurons. This effect was observed in both the infused and the contralateral striatum. GDNF also attenuated the bursting activity of nonlocomotor-related striatal neurons, an effect that was also present bilaterally. These results suggest that GDNF's antiparkinsonism effects are associated with increased excitability of motor-related striatal neurons and diminished activity of neurons that do not exhibit explicit motor-related changes in activity. Such studies may aid in understanding the mechanism of potential therapies for movement disorders seen in aging and Parkinson's disease.

Keywords: Dopamine; Neurotrophic; Striatum; Aging; Freely moving; Multiunit; Basal ganglia; Electrophysiology; Behaving; Awake

1. Introduction

In humans and in animals, normal aging is accompanied by progressive decreases in motor function [3,24]. The most common finding in animal studies of age-related changes in motor function is a decrease in spontaneous locomotor activity [14,21,24,41,45]. Because the basal ganglia are involved in motor function [19], it is possible that changes in basal ganglia nuclei contribute to the decreases in locomotor activity observed in aging. This hypothesis is supported by a number of studies reporting age-related changes in nigrostriatal dopamine (DA) function in humans and animals (for a review, see [40]). Although these studies provide little evidence for decreases in the number of DA neurons or whole tissue DA content in normal aging, they do provide substantial evidence for alterations in the functional status of the nigrostriatal DA circuit. The most commonly reported

* Corresponding author. Present address: Department of Physiology, Mailstop 3051, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160, USA. Tel.: +1 913 588 7416.
E-mail address: jstanford@kumc.edu (J.A. Stanford).

0197-4580/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.neurobiolaging.2005.10.015

alterations include decreases in the number of post-synaptic DA receptors in the striatum and alterations in evoked DA release [23,40]. Because DA released from nigrostriatal terminals regulates motor-related corticostriatal glutamatergic input to the medium spiny neuron [4,33], alterations in pre- or post-synaptic striatal DA function may disrupt the normal processing of these signals.

Previous studies examining extracellular striatal electrophysiological activity in aged rats support this hypothesis [5,38,39]. These studies report increased striatal activity in aged rats compared to young controls. These increases are similar to what has been reported in 6-hydroxydopamine-depleted rats [11,27], and are thought to result from disrupted dopaminergic modulation of corticostriatal glutamate projections [6]. Results from a number of labs have demonstrated that individual striatal neurons can be characterized according to their relationship to motor activity [15,35,38,43,44]. In an attempt to study functionally characterized striatal neurons in aged rats, we recently examined electrophysiological activity in locomotor-related striatal neurons in young versus aged Fischer 344 (F344) rats. We found that the effects of normal aging were limited to striatal neurons that did not exhibit locomotor-related changes in activity [38]. Striatal neurons that exhibited locomotor-related changes in activity did not differ between the two age groups. This finding supports the hypothesis that age-related motor deficits result not from changes in striatal circuits that are explicitly linked to motor activity, but rather from changes in what may be striatal background activity.

Recent preclinical studies from our laboratory and others have demonstrated that age-related motor deficits can be reversed by intracranial administration of glial cell line-derived neurotrophic factor (GDNF) [5,18,20,29]. These studies also report an upregulation of nigrostriatal DA function in the GDNF-treated animals. It is unclear, however, whether the upregulation of nigrostriatal DA function is accompanied by normalization of striatal electrophysiological activity in GDNF-treated aged rats. In a previous attempt to address this issue, one group found that while intrastriatal GDNF administration improved motor function in aged rats, it did not normalize striatal neural activity [5]. In this study, however, electrophysiological activity was measured in anesthetized rats. Furthermore, although striatal neurons were classified according to their waveform shapes, no functional classification of recorded neurons was made.

The goal of the current study was to determine the effects of intrastriatal GDNF on functionally characterized striatal neurons under freely moving conditions. Specifically, we wanted to determine whether unilateral intrastriatal GDNF normalizes the increased electrophysiological activity of nonlocomotor-related striatal neurons in aged rats. Also, because our previous studies have reported bilateral motor improvement following unilateral GDNF administration [18,29,37], an additional aim was to determine whether any effect observed for GDNF occurs bilaterally.

2. Materials and methods

2.1. Animals

Nineteen aged (24–25-month-old) virgin male F344 rats were obtained from NIA colonies. Animals were housed in laminar flow units with ad libitum access to food (Harlan Teklad Rodent Diet) and water. The vivarium was on a 12-h light:12-h dark cycle and animals were tested during the light portion of the cycle. The body weights of the animals averaged 378 ± 6 g on the day of recording. Protocols were approved by the local Institutional Animal Care and Use Committee and procedures adhered to the *Guide for the Care and Use of Laboratory Animals*.

2.2. GDNF infusion

On the day of surgery, animals were anesthetized with sodium pentobarbital (37.5 mg/kg i.p.; our experience suggests that aged F344 rats require ~75% of the dose administered to a young adult rat) and placed in a stereotaxic frame. Body temperature was maintained at 37 °C using an isothermal heating pad. Burr holes were drilled through the skull and an incision was made in the dura. A 26-gauge dome-tipped infusion needled was then lowered into the right-side striatum according to the following coordinates versus bregma: +1.0 mm AP, +4.0 mm ML, and 5.0 mm ventral to the brain surface [34]. Animals then received either GDNF or citrate vehicle (both from AMGEN, Thousand Oaks, CA, USA). The vehicle group ($n = 12$) received a 5 μL infusion of citrate vehicle. The GDNF group ($n = 7$) received 30 μg GDNF (a 5 μL infusion of 6 μg GDNF/μL vehicle). All solutions were infused at a flow rate of 0.25 μL/min, and needles were left in place for 5 min following the infusion before they were removed.

2.3. Chronic electrode implantation

Headstages and multi-wire stainless steel Teflon-coated microelectrode arrays (50-μm diameter per wire) were obtained from NB Labs (Dennison, TX). Following the removal of the infusion needle, electrodes were slowly lowered into the brain according to the following coordinates versus bregma: +1.2 to −0.8 mm AP, ±2.5 to ±3.5 mm ML, and 4.0 mm ventral to the brain surface [34]. Two arrays, each comprised of 16 electrodes (2 rows × 8 wires), one in each striatum of each animal, were implanted. Arrays were implanted such that their long axis was oriented in the anterior–posterior direction of the striata. The electrodes were permanently attached to the skull using skull screws and dental acrylic.

2.4. Electrophysiological recordings

After a recovery period of 30 days, rats were placed in a shielded recording chamber (15 in. × 15 in. × 33 in.) and