ELSEVIER

Neurobiology of Aging 29 (2008) 267–279

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Levodopa increases memory encoding and dopamine release in the striatum in the elderly

A. Floel [a,b,c,*], G. Garraux [d], B. Xu [a], C. Breitenstein [b,c], S. Knecht [b,c], P. Herscovitch [e], L.G. Cohen [a]

[a] *Human Cortical Physiology Section, National Institute of Neurological Disorders and Stroke, NIH, Bethesda, USA*
[b] *Department of Neurology, University of Münster, Albert-Schweitzer-Str. 33, 48129 Münster, Germany*
[c] *IMF Münster, University of Münster, Münster, Germany*
[d] *Human Motor Control Section, National Institute of Neurological Disorders and Stroke, NIH, Bethesda, USA*
[e] *Positron Emission Tomography Department, Clinical Center, NIH, Bethesda, USA*

Received 23 June 2006; received in revised form 13 September 2006; accepted 7 October 2006
Available online 13 November 2006

Abstract

Normal aging is associated with a decrease in dopaminergic function and a reduced ability to form new motor memories with training. This study examined the link between both phenomena. We hypothesized that levodopa would (a) ameliorate aging-dependent deficits in motor memory formation, and (b) increase dopamine availability at the dopamine type 2-like (D2) receptor during training in task-relevant brain structures. The effects of training plus levodopa (100 mg, plus 25 mg carbidopa) on motor memory formation and striatal dopamine availability were measured with [^{11}C]raclopride (RAC) positron emission tomography (PET). We found that levodopa did not alter RAC-binding potential at rest but it enhanced training effects on motor memory formation as well as dopamine release in the dorsal caudate nucleus. Motor memory formation during training correlated with the increase of dopamine release in the caudate nucleus. These results demonstrate that levodopa may ameliorate dopamine deficiencies in the elderly by replenishing dopaminergic presynaptic stores, actively engaged in phasic dopamine release during motor training.

Keywords: Aging; Motor; Memory formation; Positron emission tomography; Neuropharmacology; Neurotransmitter; Neurorehabilitation

1. Introduction

Normal aging is associated with decreased ability to form new memories (Hedden and Gabrieli, 2004; Jay, 2003; Kandel and Pittenger, 1999; Li and Sikstrom, 2002), most notably episodic encoding (Bailey et al., 2000; Hedden and Gabrieli, 2004; Kandel and Pittenger, 1999). A similar deficit is expressed in the motor domain, impairing the ability to encode the kinematic features of a previously practiced motor task in the primary motor cortex as a function of training (Floel et al., 2005a; Sawaki et al., 2003).

Dopamine is a major neurotransmitter that strengthens the specificity and duration of formed memories (Goldman et al., 1998; Jay, 2003; Kandel, 2001; Williams and Goldman-Rakic, 1995). Dopaminergic function, including dopaminergic receptors, transporters and overall dopaminergic metabolic activity, are reduced with normal aging (Deisseroth et al., 1995; Emborg et al., 1998; Fearnley and Lees, 1991; Jay, 2003; Li and Sikstrom, 2002; Luo and Roth, 2000; Roth et al., 1995; Volkow et al., 1998). Previous work showed that administration of the dopamine precursor levodopa could enhance training effects on motor memory formation in healthy elderly subjects (Floel et al., 2005a) and stroke patients (Floel et al., 2005b), and appears to enhance motor rehabilitation (Scheidtmann et al., 2001), as do noradrenergic agents (Martinsson et al., 2003). One

* Corresponding author. Tel.: +49 251 83 45699; fax: +49 251 83 48181.
E-mail address: floeel@uni-muenster.de (A. Floel).

0197-4580/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.neurobiolaging.2006.10.009

relative advantage in using dopaminergic agents versus, for example, amphetamines is that they exhibit fewer side-effects and may be safer (Feeney et al., 2004; Walker-Batson et al., 2004).

The findings of enhanced memory encoding in the elderly after administration of levodopa (Floel et al., 2005a) raise the hypothesis of a mechanistic link between dopaminergic function and training-induced motor memory formation. We reasoned that if such a link exists, administration of levodopa – which increases the presynaptic availability of endogenous dopamine – prior to training would lead to parallel increments in dopaminergic neurotransmission in task-relevant brain structures (Mawlawi et al., 2001; Schlosser et al., 1998) and in motor memory formation (Butefisch et al., 2000; Classen et al., 1998). Molecular imaging using the competitive D2 receptor ligand raclopride (RAC-positron emission tomography, PET) allows direct assessment of the brain dopamine system (Cropley et al., 2006). Endogenous release of dopamine increases synaptic dopamine concentration, resulting in increased occupancy of D2 receptors, and consequently decreased availability of dopamine D2 receptors for binding the radiotracer raclopride (Laruelle, 2000).

In the present study, we evaluated the effects of training plus levodopa on motor memory formation and on dopamine availability in the striatum. We also assessed levodopa effects on resting RAC-PET in the absence of training.

2. Methods

2.1. Subjects

Eleven healthy elderly subjects gave written informed consent and participated in this double-blind, placebo-controlled and randomized cross-over study. Four of them (age range 53–75 years, mean ± S.D.: 61 ± 10, one woman) participated to determine effects of levodopa on resting RAC-PET ($\text{CONDITION}_{\text{resting dopamine release}}$). Seven volunteers (age range 55–86 years, mean ± S.D.: 65 ± 10, three women) participated in the main study to identify training effects with and without levodopa on RAC-PET ($\text{CONDITION}_{\text{training dopamine release}}$) and motor memory formation ($\text{CONDITION}_{\text{motor training}}$). The study was approved by the Institutional Review Board of the National Institute of Neurological Disorders and Stroke and by the National Institutes of Health Radiation Safety Commission Committee.

2.1.1. Inclusion criteria

All subjects fulfilled the following inclusion criteria for testing of motor memory formation (Classen et al., 1998): (1) transcranial magnetic stimulation (TMS) applied to the primary motor cortex elicited isolated thumb movements in the absence of movements of any other digits, wrist, or arm; (2) there was a consistent (reproducible) direction of TMS evoked thumb movements in the baseline condition; (3) no medication was administered prior to the study that would affect the central nervous system (e.g., anti-psychotics and anti-depressants, or drugs interfering with the absorption of levodopa from the gastrointestinal tract; Nutt and Fellman, 1984); (4) routine medical and neurological examinations were normal and (5) handedness test showed strong right-handedness (handedness score ≥70; Oldfield, 1971).

In each session, subjects fasted for at least 2 h preceding levodopa or placebo intake to prevent interference with drug absorption (Nutt and Fellman, 1984). RAC-PET scans started 60 min after the oral intake of levodopa or a placebo to achieve appropriate peak plasma concentrations (Robertson et al., 1989). Measurements of systolic and diastolic blood pressures and heart rates, and subjects' ratings of attention to the task and general level of fatigue using visual scales with good internal consistency, reliability and objectivity (Chibnall and Tait, 2001; Floel et al., 2004; Folstein, 1973) were taken three times during each session. Motor training kinematics were monitored during the experiment in all sessions involving training.

Subjects also received a high-resolution structural 3D magnetic resonance image (MRI) (Deichmann et al., 2000) of the brain using a 3 T Signa System (General Electric, Milwaukee, WI) for co-registration with PET images (Woods et al., 1993), and to rule out lesions or brain abnormalities (Good et al., 2001).

2.2. Study design

2.2.1. Effects of levodopa on training-dependent formation of a motor memory

Each subject was studied in two separate sessions to determine the effects of levodopa (100 mg levodopa plus 25 mg carbidopa, p.o.) and placebo (identical capsule, p.o.; see Fig. 1A) on formation of a motor memory ($\text{CONDITION}_{\text{motor training}}$). Order of sessions (levodopa, placebo) was counterbalanced between subjects. Motor memory formation was tested using the methods described in several published studies that included the following procedures (Butefisch et al., 2000, 2002; Classen et al., 1998).

2.2.1.1. Baseline determination. Prior to training, 60 TMS stimuli were delivered to the scalp position that elicited optimal thumb movements at 0.1 Hertz (Hz), a rate that does not affect cortical excitability (Chen et al., 1997). Subjects occasionally realized that the thumb had moved but could not determine its direction. In these trials, the baseline direction was defined as the direction of the mean angle of TMS-evoked movements (Fig. 1A, hand on the left, thin lines). Subjects' muscle relaxation was closely monitored by electromyography (EMG). Trials with background EMG activity were discarded from analysis (less than 5% of the data).

2.2.1.2. Motor training. After identifying the baseline TMS-evoked movement direction (Fig. 1A, hand on the left, training target zone, "TTZ"), subjects began the training period performing voluntary brisk thumb movements at a