Neuroscience Letters 589 (2015) 73–78

Contents lists available at ScienceDirect

Neuroscience Letters

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

Research article

Glutamate and GABA concentration changes in the globus pallidus internus of Parkinson's patients during performance of implicit and declarative memory tasks: A report of two subjects

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HIGHLIGHTS

- Direct neurochemical evidence of the involvement of the GPi in memory function.
- Increased task-contingent levels of Glu and GABA in the GPi during implicit memory.
- Decreased levels of Glu and GABA in the GPi during a declarative memory task.
- Further evidence of potential dissociable learning and memory networks.
- Consistent with our prior report on neurotransmitter changes during tasks in STN.

ARTICLE INFO

Article history:
Received 26 November 2014
Received in revised form 9 January 2015
Accepted 12 January 2015
Available online 14 January 2015

Keywords:
Globus pallidus internus
Basal ganglia
In-vivo microdialysis
Glutamate
GABA
Memory tasks

ABSTRACT

The basal ganglia, typically associated with motor function, are involved in human cognitive processes, as demonstrated in behavioral, lesion, and noninvasive functional neuroimaging studies. Here we report task-contingent changes in concentrations of the neurotransmitters glutamate (Glu) and gamma-aminobutyric acid (GABA) in the globus pallidus internus (GPi) of two patients with Parkinson's disease undergoing deep brain stimulation surgery by utilizing in-vivo microdialysis measurements during performance of implicit and declarative memory tasks. Performance of an implicit memory task (weather prediction task–WPT) was associated with increased levels of glutamate and GABA in the GPi compared to their concentrations at baseline. On the other hand, performance of a declarative memory task (verbal learning task–VLT) was associated with decreased levels of glutamate and GABA in GPi compared to baseline during the encoding and immediate recall phase with less conclusive results during the delayed recall phase. These results are in line with hypothesized changes in these neurotransmitter levels: an increase of excitatory (Glu) input from subthalamic nucleus (STN) to GPi during implicit memory task performance and a decrease of inhibitory inputs (GABA) from globus pallidus externus (GPe) and striatum to GPi during declarative memory performance. Consistent with our previous report on in-vivo neurotransmitter changes during tasks in STN, these data provide corroborative evidence for the direct involvement of basal ganglia in cognitive functions and complements our model of the functional circuitry of basal ganglia in the healthy and Parkinson's disease affected brain.

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http://dx.doi.org/10.1016/j.neulet.2015.01.028
0304-3940/

1. Introduction

The involvement of basal ganglia (BG) in cognitive processes in humans has been shown in several studies in the literature utilizing behavioral, noninvasive functional imaging, electrical stimulation, and lesion approaches [1–4]. Functional magnetic resonance imaging (fMRI) studies in healthy individuals have shown increased activity in basal ganglia during performance of implicit memory tasks [2,5]. Additionally, Parkinson's patients show deficits in implicit memory, with researchers indirectly implicating the basal ganglia, which are known as the most severely affected structure in this disease [1]. Therefore, the basal ganglia are primarily involved in non-declarative memory, such as procedural or habit learning, in contrast to the role of the medial temporal lobes in declarative memory [6]. Moreover, the basal ganglia play an important role in motivation and decision making [6]. Along with the prefrontal cortex, the basal ganglia also support cognitive control of memory retrieval [7]. The prefrontal cortex and basal ganglia activation precede the filtering of irrelevant information and are associated with inter-individual differences in working memory capacity [8]. The output of basal ganglia provides a gating function by enhancing selective consolidation of memories via targeted disinhibition of cortex [9]. Particularly, the activity in the globus pallidus has been found to predict the extent to which only relevant information is stored [8].

Evidence suggests that during learning, basal ganglia and medial temporal lobe memory systems are activated simultaneously. In habit learning situations [10,11], and probabilistic classification such as the weather prediction task [5,12], a competitive interference exists between these two systems [11], pointing also to distinct and dissociable contributions of medial temporal lobe and basal ganglia structures to learning and memory [13].

Networks of basal ganglia–thalamocortical circuits subserve different functions, where the striatal structures of the caudate and putamen serve as the input stage, while the globus pallidus internus (GPi) and the substantia nigra pars reticularis (SNpr) are the output nodes [14]. Motor processes occupy central basal ganglia structures, working-memory processes elicit less lateralized widespread responses, and executive processes engage anterior and ventral regions to those elicited by working-memory processes [15]. Other techniques (such as positron emission tomography [PET], single-photon emission computed tomography [SPECT], and magnetic resonance spectroscopy [MRS]) measure in-vivo metabolic changes in the human brain, but provide more qualitative than quantitative estimates. In-vivo microdialysis on the other hand provides direct quantitative estimates of the neurotransmitter levels in the extracellular space of the human brain. Microdialysis during DBS surgery is a feasible method for assessing extracellular levels of glutamate, GABA and dopamine within the human basal ganglia [16].

The globus pallidus regulates voluntary movements at a subconscious level. It consists of two major parts: the external (GPe) and the internal (GPi). Neither of these structures receives direct input from cortex. The striatum is the main gateway to these structures, including its three major functional territories receiving inputs from motor, associative, and limbic cortical areas. The GPi receives GABAergic inputs from striatum and GPe, as well as glutamatergic inputs from subthalamic nucleus (STN). The direct striatofugal pathway involves inhibitory afferents from striatum and the indirect pathway involves both GPe and STN as intermediary nodes in the circuit. Additionally, STN receives glutamatergic inputs from the associative and limbic cortical areas (hyperdirect pathway), further exerting an excitatory effect on globus pallidus structures (Fig. 1). The output from GPi is conveyed to various ventral thalamic nuclei, some of which project to cortical areas.

The loss of dopaminergic neurons in the substantia nigra (SN) in Parkinson's disease (PD) dramatically alters the delicate dynamic balance among the direct, indirect and hyper-direct control loops of the cortico–striato–thalamic circuitry. The enhanced excitation from the STN combined with the decreased GABAergic input form both the striatum and GPe result in the hyperactivity of the GPi [17].

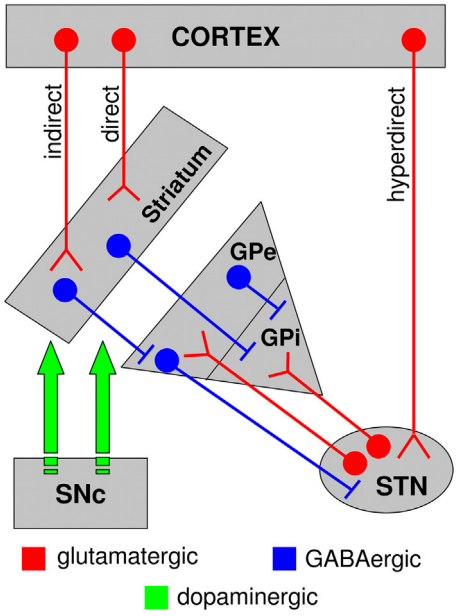

Fig. 1. Diagram of the main glutamatergic (excitatory), GABA-ergic (inhibitory), and dopaminergic pathways (arrows) in human basal ganglia. GPe: globus pallidus externus; GPi: globus pallidus internus; STN: subthalamic nucleus; and SNc: substantia nigra pars compacta.

In this study, we aimed to provide direct neurochemical evidence of the involvement of the GPi in memory processing by using in-vivo microdialysis measurements in two Parkinson's patients undergoing DBS surgery. We hypothesized the following changes in these neurotransmitter levels: an increase of excitatory (Glu) input from STN to GPi during implicit memory task performance (Fig. 2A) and a decrease of inhibitory inputs (GABA) from GPe and striatum to GPi during declarative memory performance (Fig. 2B). This report complements our previous study in five patients with PD [18], which provided the first direct neurochemical evidence of the involvement of the STN in memory function.

2. Methods

Glutamate and GABA concentration levels from GPi were measured in two right-handed female patients with PD undergoing DBS surgery. The study was approved by the local Institutional Review Board at University of Texas Health Science Center San Antonio and was carried out following the guidelines for proper conduct in human research in accordance with the Declaration of Helsinki. The surgical candidates underwent a comprehensive neuropsychological evaluation in order to rule out dementia and psychiatric disorders. Those who meet criteria to undergo deep brain stimulation (DBS) surgery were informed about the risks and benefits of the DBS operation. Patients who decided to proceed with the operation were told about the Institutional Review Board approved intra-operative study. Informed consent was obtained from those participants who decided to participate, explaining the research procedures and their right to withdraw at any time without any penalty of consequence.