Basal Ganglia 5 (2015) 1–6

Contents lists available at ScienceDirect

Basal Ganglia

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

Review

Cause of parkinsonian symptoms: Firing rate, firing pattern or dynamic activity changes?

Atsushi Nambu *, Yoshihisa Tachibana, Satomi Chiken

Division of System Neurophysiology, National Institute for Physiological Sciences and Department of Physiological Sciences, Graduate University for Advanced Studies, Myodaiji, Okazaki 444-8585, Japan

ARTICLE INFO

Article history:
Received 27 January 2014
Received in revised form 7 November 2014
Accepted 9 November 2014
Available online 15 November 2014

Keywords:
Direct and indirect pathways
Dystonia
Hyperdirect pathway
Movement disorder
Oscillation
Parkinson's disease

ABSTRACT

Malfunctions of the basal ganglia cause movement disorders, such as Parkinson's disease and dystonia. Several models have been proposed to explain the pathophysiology of these disorders: (1) firing rate model: activity imbalance between the *direct* and *indirect* pathways changes the mean firing rates of the output nuclei of the basal ganglia and induces hypokinetic or hyperkinetic movement disorders; (2) firing pattern model: oscillatory and/or synchronized activity observed in the diseased basal ganglia disturbs information processing in the basal ganglia, resulting in motor symptoms; (3) dynamic activity model: abnormal neuronal modulations through the *hyperdirect*, *direct* and *indirect* pathways interfere with the sequential, dynamic activity changes, and disrupt the balance between the movement-related inhibition and its surrounding excitation in the output nuclei, leading to motor symptoms. In this mini-review, we will critically discuss the three models.

Contents

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of nigrostriatal dopaminergic (DAergic) neurons originating from the substantia nigra pars

* Corresponding author at: Division of System Neurophysiology, National Institute for Physiological Sciences, 38 Nishigonaka, Myodaiji, Okazaki 444-8585, Japan. Tel.: +81 564 55 7771.
E-mail address: nambu@nips.ac.jp (A. Nambu).

http://dx.doi.org/10.1016/j.baga.2014.11.001

compacta (SNc). The loss of DAergic neurons induces severe motor and non-motor dysfunctions, such as akinesia, tremor, rigidity, postural instability, cognitive impairments and depression. There have been two major hypotheses that explain the pathophysiology of PD. First, the "firing rate model" was originally proposed based on firing rate changes of the basal ganglia (BG) neurons in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD monkeys [1]. These changes are considered to finally increase mean firing rates in the output nuclei of the BG, i.e., the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr), along the BG pathways, and induce motor dysfunctions. However, some recent electrophysiological studies using MPTP-induced PD monkeys have failed to detect expected firing rate changes in the BG neurons [2–4]. Second, unit activity and local field potentials (LFPs) recorded from PD animals and patients have shown oscillatory and synchronized activity in the BG [3,5–8]. These firing pattern changes may cause the disturbance of information processing in the BG, resulting in motor dysfunctions [5]. This "firing pattern model" seems to have now largely supplanted the "firing rate model". In this mini-review, we would like to compare and critically discuss these two models. In addition, we would like to introduce a novel "dynamic activity model" [9] that seems to better explain the pathophysiology of PD and may eventually replace the preceding two models.

Firing rate model

One of the earliest studies using MPTP-treated PD monkeys demonstrated a reduction of activity in the external segment of the globus pallidus (GPe) and increased activity in the subthalamic nucleus (STN) and GPi [1]. Together with the *direct* and *indirect* pathways model of the BG [10–13], the pathophysiology of PD is explained as follows (Fig. 1A). Dopamine (DA) depletion reduces tonic excitation to striatal *direct* pathway neurons projecting to the GPi and tonic inhibition to striatal *indirect* pathway neurons projecting to the GPe [10,12–14]. Both of these changes are thought to increase mean firing rates of GPi/SNr neurons through the inhibitory striato-GPi/SNr *direct* pathway and the net excitatory striato-GPe-STN-GPi/SNr *indirect* pathway. Such increased activity in the BG output nuclei seems to induce decreased activity in thalamic and cortical neurons, resulting in akinesia. A number of studies subsequent to the original one confirmed similar activity changes: reduced firing rates in the GPe and increased firing rates in the STN and GPi in the PD state [15–21]. A recent optogenetic study has elegantly shown that facilitating striatal *direct* pathway neurons in PD mice ameliorates akinesia, and that facilitating striatal *indirect* pathway neurons in normal mice induces akinesia [22].

The "firing rate model" seems to be applicable to hyperkinetic disorders that exhibit involuntary movements, as well. Neuronal activity recording in hyperkinetic disorders revealed reduced activity in the GPi. The development of the involuntary movements can be explained as the result of reductions in inhibitory BG outputs to the thalamus. In dystonia, a number of single cell recording studies in patients undergoing functional neurosurgery have reported that firing rates in the GPe and GPi are low [23–26], although some study reported that firing rates were found to be as high as in PD patients [27]. An animal model of dystonia also reported decreased firing rates and the appearance of burst firings in the GPe and GPi [28]. In addition, in experimental models of hemiballism induced by electrolytic lesion, chemical lesion or chemical inactivation of the STN [29–31], ballistic movements were accompanied by substantial reduction of firing rates in the GPe and GPi. It is a consequence of reduced glutamatergic inputs from the STN to the GPe and GPi. The injection of a GABA-receptor blocker into the GPe also induced dyskinetic movements [32–34], probably through STN inhibition by enhanced inhibitory GPe-STN transmission.

Mechanism of firing rate changes

The "firing rate model" assumes that DA has excitatory effects on striato-GPi *direct* pathway neurons through DA D1 receptors (D1Rs) and inhibitory effects on striato-GPe *indirect* pathway neurons through D2 receptors (D2Rs) (Fig. 1A). DA effects were originally proposed on the basis of indirect measurement of neuronal activity, such as alterations in gene expression, glucose utilization and receptor binding [13,35], and have also been confirmed electrophysiologically [35–38]. In addition, DA regulates corticostriatal synaptic plasticity: D1R signaling induces

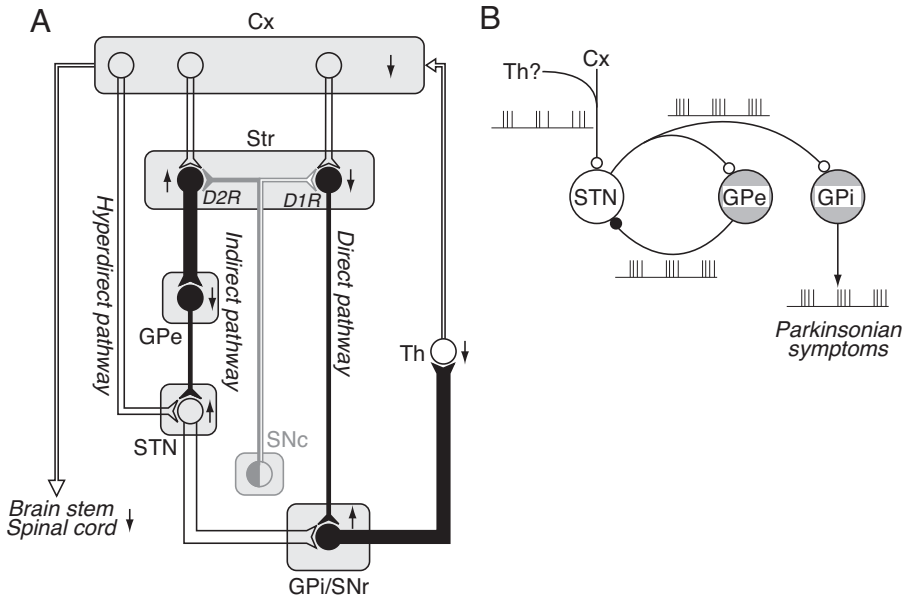

Fig. 1. "Firing rate" (A) and "firing pattern" (B) models explaining the pathophysiology of Parkinson's disease. Open and filled symbols represent excitatory and inhibitory neurons, respectively. Cx, cerebral cortex; D1R, D2R, dopamine D1 and D2 receptors; GPe and GPi, external and internal segments of the globus pallidus; SNc and SNr, substantia nigra pars compacta and reticulata; STN, subthalamic nucleus; Str, striatum; Th, thalamus.
(A) Modified from DeLong [12]; (B) modified from Tachibana et al. [46].