

# A POSSIBLE MECHANISM OF SELECTIVE FUNCTION OF THE BASAL GANGLIA

*Isabella G. Silkis*

Institute of Higher Nervous Activity & Neurophysiology, Russian Academy of Sciences,  
5a Butlerova str, 117485, Moscow, Russia  
isa-silkis@mail.ru

*Alessandro E. P. Villa*

Lab. de Neuroheuristique, Inst. de Physiologie, Université de Lausanne  
Lab. de Neurobiophysique, Université "Joseph Fourier" Grenoble 1, France  
avilla@neuroheuristic.org

## ABSTRACT

The anatomical architecture of the basal ganglia is consistent with their physiological role in the selection of motor programs [7]. Dopaminergic cells with their excitatory responses to presentation of novel or conditioned stimuli have been proposed to play an important role in selecting particular motor responses [8]. Cortical inputs, passing through the basal ganglia via the "direct" pathway provoke a disinhibition of thalamic neurons. Cortical inputs passing via the "indirect" pathway exert mainly an inhibitory effect on thalamic cells. Striatal cells are excited by both neocortical neurons and by Centre Median-parafascicular (CMpf) thalamic neurons, but cholinergic cell excitation is mostly of thalamic origin. Striatal cells are inhibited by Parvalbumin-immunoreactive GABAergic interneurons, which receive only a sparse input from CMpf in comparison to cortical inputs [7]. Cholinergic striatal cells that show a pause in their tonic discharges in response to conditioned sensory simulation [2] are likely to be involved in the selection of motor programs as indicated by impaired behavioral activity following lesions of cholinergic cells [9].

In the present report, we present a model for selection of motor programs by the cortico-basal ganglia-thalamocortical (CX-BG-TH-CX) loop during reinforced learning. The model suggests that conditionally evoked responses occur with opposite effects on the firing pattern of dopaminergic and cholinergic cells. The synergistic combination of these inputs would promote the long-term modulation of cortical inputs to striatal spiny cells, such that the (CX-BG-TH-CX) loop would eventually strengthen the links within a selected cell assembly associated to a significant motor program and weaken the other assemblies of motor cortical cells.

Activation rules for "strong" ("weak") cortical signals that open (close, respectively), postsynaptic N-methyl-d-aspartate (NMDA) receptors of striatal spiny cells are opposite [10,12]. According to the unitary mechanism of synaptic plasticity [10], in the absence of neuromodulators a relative increase/decrease of "strong" ("weak") cortical signals should result in the induction of LTP/LTD (LTD/LTP) in corticostriatal inputs. Modulation of LTP and LTD by dopamine and acetylcholine depends on the type of the activated receptors, as well as on the NMDA channel opening [10,12]. Our model considers that muscarinic  $M_1$  and dopaminergic  $D_2$  receptors are preferentially located on striatopallidal cells. Conversely,  $D_1$  and  $M_4$  receptors are co-expressed on striatonigral neurons and cholinergic interneurons co-express  $D_2$  and  $D_1/D_5$  receptors.

According to the modulation rules that we suggest, when NMDA channels are closed, the activation of  $D_1/D_5$  or  $M_1$  receptors may increase the expression of NMDA-independent LTD. Conversely, the activation of  $D_2$  or  $M_4$  receptors may reduce this LTD or even revert LTP into LTD, when NMDA channels are closed. These effects are in agreement with several experimental results [11,12], in particular with intrastriatal infusion of  $D_1$  receptor agonist that provoked an increase in acetylcholine release, while  $D_2$  receptor agonist provoked the opposite effect [1]. It is important to

emphasize that the inhibitory action of dopamine on acetylcholine release through the D<sub>2</sub> receptors prevail over its facilitatory action through the D<sub>1</sub> receptors [4].

In the model we assume that the activation of NMDA receptors on striatal spiny cells and conditionally evoked increase in dopamine release occur simultaneously with a blockade of acetylcholine release, as supported by experimental results. The latency and the duration of the pause of striatal cholinergic cell discharges evoked by reinforcing stimuli are 100-130 and 200-270, respectively [2,6]. The latencies of dopaminergic cell responses following the presentation of reinforcing stimuli were similar and their duration was 100-150 ms [8]. During the pause of striatal cholinergic cells, nicotinic receptors on inhibitory interneurons cannot be activated. Then, during the pause, disfacilitation of these inhibitory interneurons leads to disinhibition of spiny cells, as observed experimentally [5]. Such disinhibition facilitates the opening of NMDA channels on spiny cells, thus promoting the signal selection of cortical input. Then, dopamine can modulate the propagation of those cortical inputs that converge to the striatum simultaneously with conditionally evoked dopaminergic inputs. If a cortical signal is "strong", the magnitude of LTP of cortical inputs to striatonigral cells is increased by synchronous activation of D<sub>1</sub> receptors on the same striatonigral cells along the "direct" pathway. On the opposite, in the "indirect" pathway, a "strong" input from the cortex to striatopallidal neurons occurring with a dopaminergic activation of D<sub>2</sub> receptors on striatopallidal cells provokes an increase of the magnitude of LTD. The combined effects on direct and indirect pathways provoke a synergistic increase in disinhibition of thalamic and neocortical neurons, thus amplifying certain motor programs [11,12]. Conversely, "weak" cortical inputs to the striatum occurring simultaneously with dopaminergic inputs provoke opposite effects compared to strong cortical inputs. These effects reinforce the inhibition of thalamic and neocortical neurons, thus suppressing other motor programs.

In presence of selected somatotopically organized cortical inputs to basal ganglia, our model shows that the activation of dopaminergic input may play a selective role of motor program by facilitating the activity of neocortical zones associated to particular body parts, while reducing the activity of other cortical zones associated to other body parts. From the suggested modulation rules it may be predicted that similar effects can be achieved by inactivation of acetylcholine muscarinic M<sub>4</sub> receptors on striatonigral cells (as well as by inactivation of acetylcholine muscarinic M<sub>1</sub> receptors on striatopallidal cells). According to this model, if the reward is delivered before the dopaminergic input and a pause in activity of cholinergic interneurons in response to conditioned sensory stimuli, (i.e., the interval between CS and reward is < 100 ms) the basal ganglia cannot select the motor program and the learning cannot take place. In addition, most of the dopaminergic neurons projecting to the associative and motor striatum receive inputs from the limbic striatum [3], thus suggesting that selection of motor programs may depend on the selection of cognitive programs.

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