BioSystems 142-143 (2016) 25–31

Contents lists available at ScienceDirect

BioSystems

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

A model of dopamine regulation of glutamatergic synapse on medium size spiny neurons

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ARTICLE INFO

Article history:
Received 11 November 2015
Received in revised form 10 February 2016
Accepted 1 March 2016
Available online 5 March 2016

Keywords:
Dopamine regulation
Synaptic model
Glutamatergic synapse
AMPA
NMDA
EPSC
EPSP

ABSTRACT

Spiny neurons of striatum receive glutamatergic synapses on dendritic spines on the neck of which project dopaminergic synapses. Dopamine modulates, by D1 type receptors, the glutamatergic synapses by inducing the phosphorylation of AMPA and NMDA receptors which produces an increased amplitude response. Herein we present a model where, in addition to phosphorylation, the direct modulation by dopamine of the spine resistance can cooperate in producing the observed effect on some of these synapses.

1. Introduction

Pyramidal neurons of the brain cortex show complex patterns of activity which are regulated by complex circuitries. For some areas the information starting from the cortex flow by excitatory projections to the deep nuclei before returning, after the appropriate "manipulations", to the same or to a different area of the cortex. The manipulation of information flow involves both excitatory and inhibitory neurons. Along these pathways, special neurotransmitters, as for example serotonin or dopamine, play a regulatory action on the information flow. A classical example of such kind of circuit is the cortico-striato-thalamo-cortical circuitry where cortical pyramidal neurons project on GABAergic Medium size Spiny Neurons (MSNs) (Surmeier et al., 1996; Kreitzer and Malenka, 2008; Cui et al., 2013; Rothwell et al., 2015). They represent the major target of cortical projections in the striatum that is the main of a group of highly interconnected nuclei of the dorsal basal ganglia. The MSNs terminals form the direct (striatonigral) pathway which is characterized by an abundance of dopamine type 1 receptors (D1R). This pathway directly projects to the internal globus pallidus (GPi) and the substantia nigra reticulata (SNr) before returning to the cortex (Surmeier et al., 1996). A second pathway (indirect or striatopallidal pathway) has abundance of dopamine type 2 receptors (D2R) and projects onto two intermediate relay stations [external globus pallidus (GPe) and sub thalamic nucleus (STN)] before returning to the cortex (Surmeier et al., 1996). The MSNs represent 90% of the neurons of the neostriatum and they have a key role in the regulation of the motor control (Umemiya and Raymond, 1997; Flores-Barrera et al., 2011). Moreover, projections of dopaminergic neurons directly modulate the excitation (glutamatergic synapses) on MSNs depending on the dopaminergic receptor type (Umemiya and Raymond, 1997; Hallett et al., 2006; Kristensen et al., 2011). In the case of the direct pathway and D1R the regulatory effect consists essentially in the phosphorylation of both α-amino-3-hydroxy-5-methyl-D-aspartate receptors (AMPARs) and N-methyl-D-aspartate receptors (NMDARs) (Umemiya and Raymond, 1997; Price et al., 1999; Banke et al., 2000; Hallett et al., 2006; Kristensen et al., 2011). Although some authors found different results (Nicola and Malenka, 1998; Calabresi et al., 1987, 1995), the overt effect of the phosphorylation mediated by cAMP-dependent protein Kinase seems to be the increase of the peak of the glutamatergic Excitatory Post Synaptic Current (EPSC) of about 30% with respect to the non-phosphorylated receptors (Price et al., 1999; Banke et al., 2000; Hallett et al., 2006; Kristensen et al., 2011). Moreover, dopamine activity seems to be effective on a large range around the synaptic space (Sphere of Influence of 2–8 μm of diameter) due to the spillover ((Mitkovski et al., 2012), for a review) such

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http://dx.doi.org/10.1016/j.biosystems.2016.03.001
0303-2647/

that the release of a single vesicle from the dopaminergic terminal influences the excitability of tens to thousands of neighboring glutamatergic synapses (Cragg et al., 2001, 2004; Cragg and Rice, 2004; Arbuthnott and Wickens, 2007).

Modulation of motor control by dopamine through these pathways is fundamental and its lack is involved in severe chronic pathologies as for example the Parkinson's disease (François et al., 2000).

In a recent paper (Di Maio et al., 2015), we used our model of a glutamatergic synapse (Ventriglia and Di Maio, 2000b,a, 2002, 2003a,b, 2013a,b; Ventriglia, 2011) to test three parameters which could be involved in the dopamine-dependent increase of the EPSC peak observed by Price et al. (1999), Banke et al. (2000), and Hallett et al. (2006). We concluded that the increased EPSC amplitude experimentally observed most likely depends on the increase of the single receptor conductance, probably due to a different 3D configuration of the pore of the phosphorylated receptors (Di Maio et al., 2015). The results obtained by simulating the increase of the binding time of Glu to receptors, in fact, did not produced results comparable with those experimentally obtained also when this parameter was increased of 100% with respect to the basic value. We excluded also the single receptor open probability (another of the parameters we have tested) because we got results comparable with those experimentally observed only for an improbable increase of ∼40% of this parameter. This kind of increase, in fact, would correspond to an unrealistic value of the open probability of ∼1 which would mean that receptors are permanently active (Di Maio et al., 2015).

The structural organization of glutamatergic synapses on MSNs dendrites suggests the possible role of other factors that could influence the observed experimental results (Price et al., 1999; Banke et al., 2000; Hallett et al., 2006). While some (but not all) of the glutamatergic synapses receive a direct dopaminergic input on the neck of the spine, others are indirectly modulated because of dopamine spillover (sphere of influence). A schematic description of the dopaminergic input is shown in Fig. 1 showing that some Glu synapses, being directly connected by the dopaminergic one, can have a more relevant role in the total modulation of the MSN neuron. This idea is supported by the fact that the spine can be considered as a separate high resistance dendritic compartment (Segev, 1998; Harnett et al., 2012; Tonnesen et al., 2014; Di Maio et al., 2015, 2016) and that the neck can be the best candidate for a transient regulation of the total spine resistance. A high spine resistance (R_s) can, in fact, produce a localized variation of membrane potential such to promote the activation of the NMDARs influencing the amplitude and the time course of the total EPSC (Di Maio et al., 2016). These receptors, in fact, at resting level are blocked by Mg^{2+} in a voltage dependent way (Jahr and Stevens, 1990; Vargas-Caballero and Robinson, 2004; Di Maio et al., 2015, 2016).

In the present paper we hypothesize that the direct effect of dopamine on the neck of spines can produce a variability of the synaptic resistance such to produce an additional regulatory effect on the glutamatergic response. This regulatory effect can be different among the synapses included in the sphere of influence of a dopaminergic synapse. We surmise that a dopaminergic synapse can regulate the glutamatergic one receiving the direct contact by a combined effect of receptor phosphorylation and spine resistance modulation while the other glutamatergic synapses are modulated, probably with a different degree depending on the distance, only by the receptors phosphorylation.

To test the effect of these two important parameters, we performed a series of computational experiments by using different values of the spine resistances. For each of them we tested the effect of the phosphorylation by modifying the single receptor conductance. In addition, since our previous results where obtained for a single value of R_s, we tested also the receptor open probability as a possible parameter influenced by phosphorylation of AMPARs and NMDARs.

2. Model

For the present paper we used our previous model with a fine description of the synaptic space, a Brownian diffusion of Glu in the synaptic cleft, and the simulation of the post-synaptic response which includes the NMDA voltage dependent contribution (Ventriglia and Di Maio, 2000b,a, 2002, 2003a,b, 2013a,b; Ventriglia, 2011; Di Maio et al., 2016).

2.1. The geometrical model

In short, the synaptic space is modeled as formed by two flat concentric cylinders sharing the same central axis and the same height (the synaptic cleft which is ∼20 nm). The inner cylinder represents on the pre-synaptic side the Active Zone (AZ)

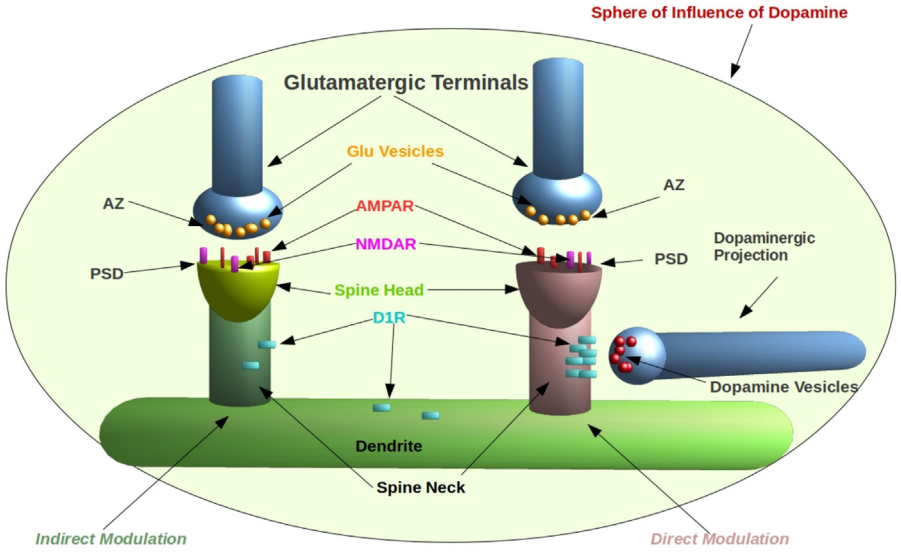

Fig. 1. Schematic representation of dopamine modulation of glutamatergic synapses in medium spiny neurons.