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Molecular and cellular mechanisms of dopamine-mediated behavioral plasticity in the striatum

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ABSTRACT

The striatum is the input structure of the basal ganglia system. By integrating glutamatergic signals from cortical and subcortical regions and dopaminergic signals from mesolimbic nuclei the striatum functions as an important neural substrate for procedural and motor learning as well as for reward-guided behaviors. In addition, striatal activity is significantly altered in pathological conditions in which either a loss of dopamine innervation (Parkinson's disease) or aberrant dopamine-mediated signaling (drug addiction and L-DOPA induced dyskinesia) occurs. Here we discuss cellular mechanisms of striatal synaptic plasticity and aspects of cell signaling underlying striatum-dependent behavior, with a major focus on the neuromodulatory action of the endocannabinoid system and on the role of the Ras–ERK cascade.

1. Introduction

Amongst brain regions involved in cognitive processing, the dorsal striatum and its ventral extension, the nucleus accumbens, have been implicated in a variety of processes in experimental animal models, including motor control, instrumental learning and habit formation, reward and drug addiction. Importantly, current views maintain that within the same striatal sub-regions specific signaling cascades may simultaneously control distinct (but possibly overlapping) gene expression programs resulting from different forms of learning, including stimulus–response (S–R) and drug of abuse related behaviors. At the same time, it has become clear that a derangement of these molecular mechanisms may occur at the striatal level in neurological conditions in which either dopamine (DA) is lost, like in Parkinson's Disease (PD), or made available through pharmacotherapy with the dopamine precursor L-DOPA or related dopaminergic agonists whose chronic use almost invariably result in aberrant adaptations. Considering the central role of the striatum in the control of movement and some aspects of cognition it is not surprising that aberrant modulation of striatal function is a critical aspect in a number of pathologies besides PD, including L-Dopa induced dyskinesia (LID), Huntington's disease (HD), drug abuse, obsessive compulsive disorder, Tourette's syndrome and schizophrenia.

Importantly, synaptic plasticity mechanisms in different regions of the striatum, including long-term potentiation (LTP) and depression (LTD), as well as depotentiation, are interesting cellular models of striatal function and dysfunction and may provide a link between cellular and system events.

In this review, we will first describe how normal and pathological synaptic plasticity occurs in the striatum and then we will focus on specific molecular mechanisms controlling striatum-dependent behavior.

2. Striatal organization and function

The striatum is a heterogeneous structure that can be subdivided at different levels. The major division is in the dorsal and ventral portions. Dorsal striatum (DS) in primates is composed of the caudate–putamen complex, while in rodents this region is functionally divided into medial and lateral dorsal striatum. The ventral part is referred to as nucleus accumbens (NAc) that may be further divided into core and shell. All these sub-regions have similar histological appearance and no sharp anatomical borders are present. Thus, their distinct functions may arise from specific connections to different brain structures. From the neurochemical point of view, the NAc receives its major glutamatergic excitatory

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inputs from the limbic areas such as the amygdala, prefrontal cortex and hippocampus while the DS receives glutamatergic afferents from cortex and thalamus. Dopaminergic neurons from substantia nigra mostly project to the DS while neurons from ventral tegmental area (VTA) reach the NAc (Berendse & Groenewegen, 1990; McGeorge & Faull, 1989; O'Donnell & Grace, 1995).

The role of the striatum in the modulation of movement, observed in clinical context, has been recognized and studied much before the evidence for its cognitive function has been provided. However, it is now widely accepted that the striatum is also involved in motivation, reward and decision making and that specific types of learning are not secondary to its motor control function. The NAc was for a long time believed to be specifically related to the reward experience and to reward-related learning while the DS is involved in motor control and procedural learning. A unifying theory proposes instead that the striatum as a whole may have a role in the selection of actions based on their predicted value in order to optimize behavior (Redgrave, Prescott, & Gurney, 1999; Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004).

The classical idea of a functional dorso–ventral division of the striatum, proposed almost 40 years ago by Heimer and Wilson, has been highly influential since its introduction and it has had great impact on the conceptualization of the functional neuroanatomy of the basal ganglia (Heimer & Wilson, 1975). Nonetheless, recent evidence has led to challenge this classical view in favor of a more up-to-date version (Voorn et al., 2004). First of all, since there is no histological nor immunohistochemical division between ventral and dorsal striatum and it is difficult to locate a sharp boundary between these two areas, it would be better to consider the distinction between them as relative and not absolute. Indeed, some striatal-dependent tasks activate one sub-region relatively more than the other, suggesting a quantitative gradient of specialization, rather than a net categorical qualitative distinction. Secondly, the slightly oblique orientation of the innervation pattern of cortical and subcortical inputs to the striatum, as well as the gradient of observed density of striatal neurons, lead to think to a division based on a slightly rotated axis, namely an axis extending from ventromedial to dorsolateral regions, which is supported also by behavioral lesion studies. This ventromedial–dorsolateral gradient in specialization, proposed by the revised version of the conventional view, fits best currently available data on striatal function and would explain the partial functional overlap between dorsal and ventral striatum that has been observed in relation to reward-dependent and associative memory tasks. For instance, in a cocaine-induced behavioral sensitization test, dopamine is release after training not only in the shell and core of nucleus accumbens but also in the dorsal striatum, following a ventromedial–dorsolateral gradient, with the dopamine efflux being maximal in the shell, lower in the core and lowest in the dorsolateral striatum (Chambers, Sentir, Conroy, Truitt, & Shekhar, 2010).

From the cellular point of view, medium spiny neurons (MSNs) are the main neuronal population in both dorsal and ventral striatum comprising around 95% of striatal neurons, while the cholinergic and GABAergic interneurons account for less than 5% (Kreitzer, 2009; Tepper, Tecuapetla, Koos, & Ibanez-Sandoval, 2010). Complex information coming manly from cortical and midbrain inputs converges on these neurons and it is conveyed through two different pathways to final basal ganglia outputs. The interspersed subpopulation of MSNs projecting directly to substantia nigra forms the striatonigral or direct pathway, while the MSNs projecting to final outputs through other structures such as the globus pallidus pars externa (GPe) and the subtalamic nucleus (STN) belong to the indirect or striatopallidal pathway. According to the classic Albin-DeLong model the direct pathway activity promotes movement while the indirect pathway inhibits movement (Albin, Young, & Penney, 1989; DeLong, 1990) (Fig. 1).

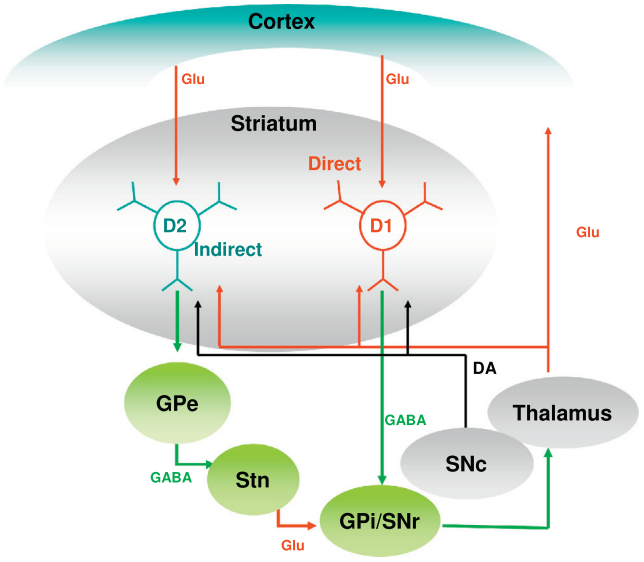

Fig. 1. Simplified model of dorsal striatum (DS) connections. DS receives glutamatergic (GLU) input from the cortex and dopaminergic afferents mainly from substantia nigra pars compacta. The GABA-ergic output from medium spiny neurons (MSNs) expressing D2 dopamine receptors reaches globus pallidus pars externa (GPe), which in turn sends GABAergic projections to subtalamic nucleus (Stn). From Stn, glutamatergic input is conveyed to globus pallidus pars interna (GPi) and substantia nigra pars resticulata (SNr), resulting in a net excitation of these structures. D1 expressing MSNs project directly to the final outputs (GPi and SNr) and have an inhibitory effect. From GPi and SNr the information is sent through thalamus back to cortex.

Several recent studies support the general idea of this model. A picture emerging from studies using innovative approaches such as neuronal type-specific expression of channelrhodopsin-2 (Kravitz et al., 2010) or selective lesions or impairment of striato-pallidal pathway neurons (Durieux et al., 2009; Hikida, Kimura, Wada, Funabiki, & Nakanishi, 2010) seems to be in agreement with the Albin-DeLong theory of modulation of movement. However, this relatively simple classical inhibition/stimulation functional model has been challenged with more recent models proposing that a coordinated activation of both pathways is necessary for action selection. In one of the views, the activation of direct pathway might be necessary to promote desired actions while the activation of the indirect pathway could inhibit unwanted actions (Mink, 2003; Nambu, 2008). To test the possibility of co-activation of direct and indirect pathway, a recent study has used highly innovative in vivo photometry technology based on Cre-dependent viral expression of the genetically encoded calcium indicator in the dorsal striatum in combination with optical stimulation, which enabled scientists to monitor the activity of specific cells deep in the brain during movement (Cui et al., 2013). Activity was recorded in both pathways during movement initiation thus providing the first evidence in support of the new model. Authors suggested that their data are not in disagreement with previous observations from experiments using optogenetics and cell specific lesion techniques. For instance, the massive activation of a large number of indirect pathway neurons would probably inhibit the majority of motor schemes and not only the unwanted ones, resulting in a hypokinetic state while the selective disruption of all indirect pathway neurons would suppress inhibition of unwanted movement leading to hyperkinesia (Cui et al., 2013).

At the molecular level, the direct pathway neurons express predominantly D1 like dopamine receptors, substance P, dynorphin and muscarine M4 acetylcholine receptors, while the indirect pathway neurons express D2 like dopamine receptors, enkephalin and A2A adenosine receptors (Gerfen & Surmeier, 2011). Dopamine is the most important modulator of striatal activity so this segrega-

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