Neuroscience Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience Research

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

Review article

Neural mechanism of the nucleus accumbens circuit in reward and aversive learning

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ARTICLE INFO

Article history:
Received 14 October 2015
Received in revised form 19 January 2016
Accepted 20 January 2016
Available online xxx

Keywords:
Dopamine
Drug addiction
Plasticity
Basal ganglia
Reversible neurotransmission blocking
Dopamine receptor

ABSTRACT

The basal ganglia are key neural substrates not only for motor function, but also cognitive functions including reward and aversive learning. Critical for these processes are the functional role played by two projection neurons within nucleus accumbens (NAc); the D1- and D2-expressing neurons. Recently, we have developed a novel reversible neurotransmission blocking technique that specifically blocks neurotransmission from NAc D1- and D2-expressing neurons, allowing for *in vivo* analysis. In this review, we outline the functional dissociation of NAc D1- and D2-expressing neurons of the basal ganglia in reward and aversive learning, as well as drug addiction. These studies have revealed the importance of activation of NAc D1 receptors for reward learning and drug addiction, and inactivation of NAc D2 receptors for aversive learning and flexibility. Based on these findings, we propose a neural mechanism, in which dopamine neurons in the ventral tegmental area that send inputs to the NAc work as a switch between D1- and D2-expressing neurons. These basal ganglia neural mechanisms will give us new insights into the pathophysiology of neuropsychiatric diseases.

Contents

Abbreviations: NAc, nucleus accumbens; GPi, globus pallidus interna; GPe, globus pallidus externa; VP, ventral pallidum; STN, subthalamic nucleus; SNr, substantia nigra pars reticulate; SNc, substantia nigra pars compacta; VTA, ventral tegmental area; MSN, medium spiny neuron; SP, substance P; Enk, enkephalin; MDT, mediodorsal thalamus; RNB, reversible neurotransmission blocking; D1-RNB, D1-expressing neuron-specific RNB; D2-RNB, D2-expressing neuron-specific RNB; CPP, conditioned place preference; LTP, long-term potentiation; LTD, long-term depression.

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http://dx.doi.org/10.1016/j.neures.2016.01.004
0168-0102/

1. Introduction

The basal ganglia constitute an important brain region not only for motor function, but also for higher functions such as emotion, motivation, cognitive behavior, learning, and decision-making. Neuropathologies that damage the basal ganglia include neurodegenerative diseases that cause motor impairment such as Parkinson's disease and Huntington's disease (Albin et al., 1989; DeLong, 1990; Wichmann and DeLong, 1996), and psychiatric disorders such as drug addiction, schizophrenia, and depression (Hyman et al., 2006; Simpson et al., 2010; Ikemoto et al., 2015). These conditions highlight the importance of research into basal ganglia neural mechanisms.

The basal ganglia consist of a series interconnected subcortical nuclei: the dorsal striatum, the ventral striatum (primarily consisting of the nucleus accumbens (NAc)), the globus pallidus interna (GPi) and externa (GPe), the ventral pallidum (VP), the subthalamic nucleus (STN), the substantia nigra pars reticulata (SNr) and pars compacta (SNc), and ventral tegmental area (VTA) (Albin et al., 1989; Haber, 2003). These structures also connect with the cerebral cortex and thalamus to form a series of parallel circuit loops (Alexander et al., 1986; Alexander and Crutcher, 1990). Output from the dorsal striatum to the SNr, an output nucleus to the thalamus, has broadly been divided into two pathways: (1) the direct pathway, a monosynaptic projection to the SNr, and (2) the indirect pathway, a polysynaptic projection to the SNr via the GPe and STN (Graybiel, 2000). Additionally, dorsal striatal direct and indirect pathway medium spiny neurons (MSNs) differ in their expression of dopamine receptors and releasable peptides. Direct pathway striatonigral neurons have been demonstrated to express dopamine D1 receptors and substance P (SP), while indirect pathway striatopallidal neurons express dopamine D2 receptors and enkephalin (Enk) (Gerfen et al., 1990; Surmeier et al., 1996).

MSNs within the NAc can also largely be divided into dopamine D1 receptor and SP expressing, or dopamine D2 receptor and Enk expressing neurons (Lu et al., 1998; Bertran-Gonzalez et al., 2008). However, anatomically, NAc output circuits differ from those of the dorsal striatum. The NAc projects to the VP, which unlike the GP, projects directly to the mediodorsal thalamus (MDT) as well as to the SNr, and is thus an output nucleus (Zahm et al., 1987; Tripathi et al., 2013). Innervation of MDT-projecting VP neurons could lead to disinhibition of the thalamus, similar to that produced by accumbonigral MSN activation. Recent evidence indicates that the vast majority of SNr- and MDT-projecting VP neurons receive innervation from D2-expressing NAc MSNs, while approximately 42% of SNr-projecting and 58% of MDT-projecting VP neurons receive inputs from D1-expressing NAc MSNs (Kupchik et al., 2015). These findings suggest that the selectivity of dopamine D1 and D2 receptors to 'direct' and 'indirect' pathways, respectively, as seen in the dorsal striatum, does not apply to the NAc.

In addition to their differing efferent projections, NAc and dorsal striatal neurons also receive modulatory inputs from discrete dopaminergic pathways. D1-expressing and D2-expressing MSNs in the NAc receive a mesolimbic dopamine pathway input from the VTA (Fallon and Moore, 1978; Nauta et al., 1978; Swanson, 1982), whereas dorsal striatum MSNs are innervated by a nigrostriatal dopamine projection from the SNc (Fallon and Moore, 1978; Beckstead et al., 1979; Veening et al., 1980).

Recently, bacterial artificial chromosome (BAC) and viral transgenic technologies have allowed the creation of activity blocking and activation techniques for specific striatal neurons, including optogenetics (Deisseroth, 2011), pharmacogenetics (Dong et al., 2010) and reversible neurotransmission blocking (Hikida et al., 2010). Kravitz et al. (2010) created mice expressing channelrhodopsin specifically in dorsal striatal direct or indirect pathway neurons, and showed that mice in which the direct pathway was activated with light stimuli exhibited increased locomotion, while mice in which the indirect pathway was activated exhibited increased freezing, bradykinesia, and decreased locomotor initiations. In addition, light stimulation of the dorsal striatal direct pathway was able to ameliorate freezing and bradykinesia symptoms in a mouse model of Parkinson's disease (Kravitz et al., 2010). Behavioral and electrophysiological experiments on mice with specific immunotoxic damage to the dorsal striatal indirect pathway have showed that this pathway plays an important role in stopping motion through activation of the SNr (Sano et al., 2013). These observations are consistent with classic models of striatal motor control, which stipulate that movement is promoted when the dorsal striatal direct pathway is activated, while movement is inhibited when the dorsal striatal indirect pathway is activated (Alexander and Crutcher, 1990; DeLong, 1990; Kravitz and Kreitzer, 2012). While these findings indicate that these two pathways of the basal ganglia are functionally independent, recent rodent data has revealed that the direct and indirect pathways of the dorsal striatum are actually activated concurrently during the initiation of movement, suggesting that the control of movement may be more complex than originally hypothesized (Cui et al., 2013; Isomura et al., 2013)

While the study of dorsal striatal output pathways has received considerable attention in recent years, the roles of ventral striatal direct and indirect pathways are still relatively unknown. For the remainder of this review we will focus on the role of NAc projection neurons in controlling reward and aversive learning, and drug addiction.

2. Functional dissociation of the NAc D1- and D2-expressing neurons in reward and aversive learning

The basal ganglia, specifically the NAc, is associated with higher functions such as reward and aversive learning, social behavior, and addictive behavior. In order to examine the role of NAc projection neurons in learning, we developed a reversible neurotransmission blocking (RNB) technique that allows specific inhibition of neurotransmission from the D1- and D2-expressing MSNs (Hikida et al., 2010). This method uses promoters of SP and Enk that are specifically expressed in D1- and D2-expressing MSNs to control expression of tetanus toxin specifically in these neural circuits. This method is able to block neurotransmission over a long period of time without inducing cell death; thus, it is an ideal method to identify the neural circuitry involved in learning behavior. Additionally, as this technique utilizes tetTag technology, it is reversible by administration of the antibiotic doxycycline. Using this RNB technique, we analyzed reward and aversive learning in mice in which neurotransmission from NAc D1-expressing MSNs (D1-RNB) or NAc D2-expressing MSNs (D2-RNB) was specifically blocked (Hikida et al., 2010).

A conditioned place preference (CPP) paradigm was employed to explore the roles of the NAc projection neurons in reward learning. Following conditioning, wild-type and D2-RNB mice expressed a strong place preference for a chamber associated with a reward (chocolate). In contrast, preference for the reward-associated chamber was significantly attenuated in D1-RNB mice. The role of NAc pathways in aversive learning was explored in an inhibitory avoidance paradigm. During conditioning, entry into a dark room was paired with delivery of an aversive electric foot shock. Then 24 h later, in the absence of foot shocks, the time it took for these mice to enter into a dark room was measured. Both wild-type and D1-RNB, but not D2-RNB mice took longer to enter the dark room compared to pre-conditioning entry times.

Please cite this article in press as: Hikida, T., et al., Neural mechanism of the nucleus accumbens circuit in reward and aversive learning. Neurosci. Res. (2016), http://dx.doi.org/10.1016/j.neures.2016.01.004