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REVIEW

# DISTINCT DOPAMINERGIC CONTROL OF THE DIRECT AND INDIRECT PATHWAYS IN REWARD-BASED AND AVOIDANCE LEARNING BEHAVIORS

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**Abstract—The nucleus accumbens (NAc) plays a pivotal role in reward and aversive learning and learning flexibility. Outputs of the NAc are transmitted through two parallel routes termed the direct and indirect pathways and controlled by the dopamine (DA) neurotransmitter. To explore how reward-based and avoidance learning is controlled in the NAc of the mouse, we developed the reversible neurotransmission-blocking (RNB) technique, in which transmission of each pathway could be selectively and reversibly blocked by the pathway-specific expression of transmission-blocking tetanus toxin and the asymmetric RNB technique, in which one side of the NAc was blocked by the RNB technique and the other intact side was pharmacologically manipulated by a transmitter agonist or antagonist. Our studies demonstrated that the activation of D1 receptors in the direct pathway and the inactivation of D2 receptors in the indirect pathway are key determinants that distinctly control reward-based and avoidance learning, respectively. The D2 receptor inactivation is also critical for flexibility of reward learning. Furthermore, reward and aversive learning is regulated by a set of common downstream receptors and signaling cascades, all of which are involved in the induction of long-term potentiation at cortico-accumbens synapses of the two pathways. In this article, we review our studies that specify the regulatory mechanisms of each pathway in learning behavior and propose a mechanistic model to explain how dynamic DA modulation promotes selection of actions that achieve reward-seeking outcomes and avoid aversive ones. The biological significance of the network organization consisting of two parallel transmission pathways is also discussed from the point of effective and prompt selection of neural outcomes in the neural network.**

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**Key words: nucleus accumbens, neural circuit, dopamine D1 and D2 receptors, neural plasticity, reward and aversive learning, learning flexibility.**

Contents



## INTRODUCTION

Reward-based and aversive forms of learning are essential for animals to survive in different environments. Animals possess the innate ability to effectively gain rewards such as food but also to rapidly avoid uncomfortable or dangerous situations. However, when rewards are present in dangerous environments, the animal needs to select actions as to whether it will still seek rewards or avoid dangerous places. The basal ganglia are the key neural substrate that controls not only motor balance but also decision making based on reward-based and aversive forms of learning (Graybiel, 2008; Bromberg-Martin et al., 2010; Gerfen and Surmeier, 2011; Aggarwal

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*Abbreviations:* AAV, adeno-associated virus; aRNB, asymmetric reversible neurotransmission blocking; CB1, cannabinoid receptors type 1; CPP, conditioned place preference; DA, dopamine; DOX, doxycycline; DREADD, designer receptors exclusively activated by designer drugs; LTD, long-term depression; LTP, long-term potentiation; NAc, nucleus accumbens; NMDA, *N*-methyl-D-aspartate; PKA, protein kinase A; RNB, reversible neurotransmission blocking; SNr, substantia nigra pars reticulata; TRE, tetracycline-responsive element; TRP, transient receptor potential; tTA, tetracycline-repressive transcription factor; VCT, visual cue task; VP, ventral pallidum; VTA, ventral tegmental area; wt, wild-type.

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et al., 2012; Salamone and Correa, 2012). This circuitry receives and integrates neural information from the cerebral cortex and thalamus and facilitates selection of actions that achieve reward-seeking outcomes and avoid aversive ones (Graybiel, 2000, 2008; Bromberg-Martin et al., 2010). Dysfunction of the basal ganglia leads to severe cognitive and learning impairments as exemplified in Parkinson's disease, schizophrenia, and drug addiction (Hyman et al., 2006; Israel and Bergman, 2008; Simpson et al., 2010; Wichmann et al., 2011; Grueter et al., 2012).

In the basal ganglia circuitry, the projection neurons in the striatum are divided into two subpopulations, i.e., striatonigral neurons of the direct pathway and striatopallidal neurons of the indirect pathway (Albin et al., 1989; Alexander and Crutcher, 1990) (Fig. 1A). The outputs of these two parallel pathways converge at substantia nigra pars reticulata (SNr) and ventral tegmental area (VTA) and control the dynamic balance of the basal ganglia-thalamocortical circuitry (Graybiel, 2008; Wickens, 2009; Bromberg-Martin et al., 2010; Gerfen and Surmeier, 2011). In this circuit, dopamine (DA) from the VTA and substantia nigra pars compacta is essential for controlling both pathways by dichotomously modulating glutamatergic synaptic plasticity of striatal neurons (Grace et al., 2007; Surmeier et al., 2007, 2009; Kreitzer and Malenka, 2008; Shen et al., 2008; Flores-Barrera et al., 2011). In the dorsal striatum, the striatonigral neurons selectively express D1 receptors and the substance P neuropeptide; and this expression is in marked contrast to the predominant expression of D2 receptors and the enkephalin neuropeptide in the striatopallidal neurons (Gerfen et al., 1990; Flajolet et al., 2008; Heiman et al., 2008). The difference in expression profile as well as the distinct ligand affinities of D1 receptors (μM order) and D2 receptors (nM order) is thought to be critical for differential modulation of transmission of these two pathways (Surmeier et al., 2007; Graybiel, 2008; Kreitzer and Malenka, 2008). However, the transmission circuit is more complicated in the nucleus accumbens (NAc), the ventral part of the striatum. The D2 receptor/enkephalin-expressing NAc neurons project to the ventral pallidum (VP), but the D1 receptor/substance P-expressing NAc neurons innervate not only the SNr (from the NAc core) and the VTA (from the NAc shell) but also the VP (Lu et al., 1998; Zhou et al., 2003; Nicola, 2007; Smith et al., 2013). Thus, the SNr and the VTA exclusively receive inputs from the D1 receptor-expressing NAc neurons via the direct pathway, but the VP receives inputs from both D1 receptor- and D2 receptor-expressing NAc neurons. Interestingly, it has been discussed that the VP neurons that receive inputs from the D1 receptor-expressing NAc neurons could directly transmit their outputs to the thalamus, thereby retaining segregated transmission characteristic of the direct and indirect pathways (Smith et al., 2013), although this possibility needs to be further investigated.

The two types of striatal projection neurons are morphologically indistinguishable and it remains a key question as to how these different types of DA receptors in the two pathways control reward-based and aversive learning behaviors. To address this fundamental question regarding control of the basal ganglia circuitry, we

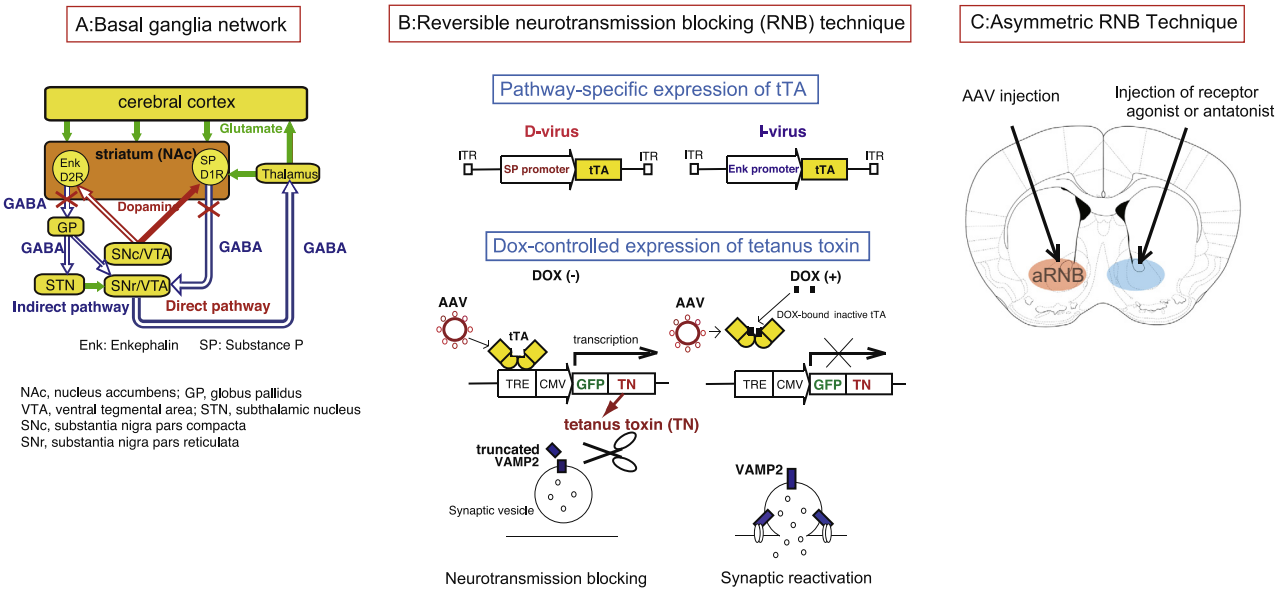


**Fig. 1.** The basal ganglia circuitry and the RNB and asymmetric RNB techniques. (A) In the basal ganglia circuitry, transmission of either the direct pathway or the indirect pathway is blocked by specific expression of tetanus toxin (TN) in the respective pathway. Filled arrows, excitatory transmission; unfilled arrows, inhibitory transmission. (B) In the RNB technique, the D-virus and the I-virus incorporate the flag-tagged tTA gene following the SP and Enk promoters, respectively. The RNB transgenic mice contain the GFP–TN fusion gene. When the striatum is transfected with the recombinant virus, the expression of the GFP-TN is driven by the interaction of the tTA with the TRE under the DOX-free condition, but this expression is abolished by DOX treatment. The expression of TN is confined to the striatonigral neurons of the direct pathway and the striatopallidal neurons of the indirect pathway by transfection with D-virus and I-virus, respectively. (C) In the asymmetric RNB technique, one side of transmission of the direct or indirect pathway in the NAc was blocked by the RNB technique and the other intact side of the NAc was injected with saline or an agonist or an antagonist specific for the targeted receptor. D1R, D1 receptor; D2R, D2 receptor; ITR, inverted terminal repeat, CMV, cytomegalovirus promoter.