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The basal ganglia as a substrate for the multiple actions of amphetamines

Reka Natarajan, Bryan K. Yamamoto *

Department of Neurosciences, University of Toledo College of Medicine Toledo, OH 43614, United States

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ABSTRACT

Amphetamines are psychostimulant drugs with high abuse potential. Acute and chronic doses of amphetamines affect dopamine (DA) neurotransmission in the basal ganglia. The basal ganglia are a group of subcortical nuclei that are anatomically positioned to integrate cognitive, motor and sensorimotor inputs from the cortex. Amphetamines can differentially alter the functioning of specific BG circuits to produce neurochemical changes that affect cognition, movement, and drug seeking behavior through their effects on DA neurotransmission. This review focuses on how alterations in dopaminergic neurotransmission within distinct basal ganglia pathways can modify their functional output to predict and explain the acute and long term behavioral consequences of amphetamine exposure.

1. Introduction

The amphetamines are a class of psychoactive compounds that have been classified as schedule I–II drugs due to their high abuse potential. Methamphetamine (METH) and 3,4-methylenedioxymethamphetamine (MDMA) are substituted amphetamines that are commonly abused for their euphoric effects which are the result of elevated dopamine (DA) levels at dopaminergic (DAergic) synapses [1–3]. Addiction to amphetamines results in compulsive drug use with frequent relapse in abstinent users, especially in the presence of a drug related context. This drug compulsion is thought to be due to dysfunctions in cortically mediated executive control over impulsive behaviors caused by abnormal signaling of basal ganglia (BG) output to the cortex [4–6]. A current view is that amphetamines dysregulate BG output through their effects on DA neurotransmission in the dorsal striatum, a BG input structure. Changes in striatal signaling affect downstream BG pathways resulting in altered output to the cortex. Because the BG plays an important role in integrating associative, sensorimotor and limbic afferents from the cortex and outputs of the BG affect cortical function through the thalamo-cortical pathway, abnormal BG activity could affect cortically mediated executive control over behavior. This review will discuss how amphetamines influence each neuroanatomical component of the BG and their respective output.

The BG are comprised of topographically organized, functionally segregated, parallel cortico-striato-pallidonigral-thalamo-cortical loops that are essential for cognitive, motor, and sensorimotor function. Dysfunctions of the BG have been implicated in cognitive, motor and impulse control diseases such as Parkinson's (PD), Huntington's (HD), obsessive compulsive disorder (OCD), and Tourette's syndrome (TS) [7]. While it is well recognized that serotonin plays an important modulatory role in the BG, striatal DA neurotransmission is a major factor in the function of the BG and in the initiation, development and maintenance of dependence to addictive drugs [6,8]. Therefore, this review will focus on the integration of amphetamine induced DAergic alterations in the BG with distinct BG pathways and their neurochemical output that could explain the behavioral consequences resulting from amphetamine exposure.

2. Amphetamines and the basal ganglia

This section discusses the anatomical structures that constitute the BG and how amphetamines influence the afferents and efferents of these regions.

2.1. Striatum

The striatum is a major input structure of the BG. It can be divided into dorsal and ventral regions. This review will focus mainly on the dorsal striatal projections rather than the more ventral limbic associated regions of the BG. In primates and some non- primates, the striatum is separated into the caudate and putamen by the internal capsule. The striatum receives DAergic inputs from the SNc and glutamatergic (GLUergic) inputs from the cortex. Within

Abbreviations: BG, basal ganglia; METH, methamphetamine; DA, dopamine; GLU, glutamate; GABA, gamma-aminobutyric acid; GP, globus pallidus; GPi, globus pallidus internal; GPe, globus pallidus external; GPv, globus pallidus ventral; STN, subthalamic nucleus; SN, substantia nigra; SNc, substantia nigra compacta; SNr, substantia nigra reticulata; NA, nucleus accumbens; PD, Parkinson's disease; OCD, obsessive compulsive disorder; vGLUT, vesicular glutamate transporter.

* Corresponding author. Address: Department of Neurosciences, Mail Stop 1007, University of Toledo College of Medicine, 3000 Arlington Avenue, Toledo, OH 43614, United States.

E-mail address: Bryan.Yamamoto@utoledo.edu (B.K. Yamamoto).

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the striatum, GABAergic soma and cholinergic interneurons are the predominant cell types [9]. The GABAergic neurons of the striatum can be classified as either parvalbumin positive interneurons or medium spiny projection neurons (MSN) that send efferents to the GPi, GPe and SNr. These efferent projections can be divided into two GABAergic neuronal subtypes: (1) Substance P and dynorphin positive, D1 receptor containing neurons and (2) Enkephalin positive, D2 receptor containing neurons. Kiyatkin and Rebec [10,11] have shown that DA and GABA have important modulatory effects on corticostriatal glutamatergic input through D1 and GABA receptors by enhancing the relative strength of glutamatergic input onto striatal neurons and thus controlling the information flow from the cortex and subsequent output from the BG to affect relevant neurobehavioral circuits. Dopamine binding to D1 generally activates the direct pathway from the striatum to the internal segment of the globus pallidus (GPi) leading to the disinhibition of the thalamus. By contrast, D2 receptor binding activates the indirect pathway such that striatal output to the GPi detour through the inhibitory projections of the external segment of the globus pallidus (GPe) and the excitatory projections of subthalamic nucleus (STN), ultimately resulting in the inhibition of the thalamus. Thus the striatum regulates and coordinates the activity of the BG through its dopaminergic and glutamatergic input and the regulation of striatal interneurons to affect output to other BG structures (Fig. 1).

2.1.1. Amphetamine induced neurochemical effects in the striatum

A major neurochemical effect of the amphetamines is their influence on dopamine transmission. Dopamine released in the striatum is enhanced by amphetamines through the increased release of DA from intracellular stores and the reversal of the DA transporter (DAT) that otherwise function to take up released DA from the synaptic cleft and into the cell [12]. Administration of single or multiple large doses of amphetamine results in an initial increase in DA release, followed by long lasting depletions in DA, and long-term decreases in the expression of phenotypic markers of DAergic neurons such as DAT, tyrosine hydroxylase (TH), and vesicular monoamine transporter-2 (VMAT2) [13–15].

Amphetamines not only affect neurochemical markers of DAergic neurons but also cause morphological changes in these cells. Continuous infusions of d-amphetamine via subcutaneous minipumps that deliver at least 20 mg/kg/day for 2 days produced axonal swelling and damage to TH positive terminals in the striatum. In addition, dark, shrunken profiles were observed in some glial processes, non-myelinated axons, and postsynaptic dendrites suggesting non-DAergic, terminal degeneration in the striatum [16,17]. Moreover, escalating doses of METH over a 1 month period have been shown to increase the number of mushroom and thin spines on MSN in the dorsolateral striatum, but decreased the number of mushroom spines in the dorsomedial striatum at 3 months after the drug treatment [18]. Thus, neurochemical as well as region-dependent morphological changes are produced by chronic high dose of amphetamines.

The effects of the amphetamine are not limited solely to morphological changes but can also cause cell death in the striatum. Striatal cell cultures exposed to METH treatments exhibit apoptosis [19]. Likewise, in vivo studies employing a single high dose of METH to mice have reported GABAergic and cholinergic cell loss in the striatum [20,21]. Striatal cell loss is thought to be dependent on both DA and GLU neurotransmission. In regard to GLU transmission, Mark et al. [22] have shown that enhanced GLU release in the striatum by METH is mediated by increases in DA in the striatum and the subsequent activation of the direct striatonigral pathway resulting in inhibition of GABAergic nigrothalamic projection. Activation of this BG direct pathway therefore disinhibits the thalamus, resulting in increased activation of the thalamocortical GLUergic projections which in turn, activate the GLUergic corticostriatal innervations causing increased GLU release in the striatum. Furthermore, simultaneous iontophoretic application of DA and GLU into the striatum of freely moving rats synergistically increase the firing rate and phasic activation of striatal neurons, suggesting that DA in the striatum enhances GLU activation of striatal neurons [23,24]. The increase in extracellular glutamate can produce a large Ca^{2+} influx into the cell via ionotropic glutamate receptor activation. The influx of Ca^{2+} activates mitochondrial cell death cascades, leading to increased

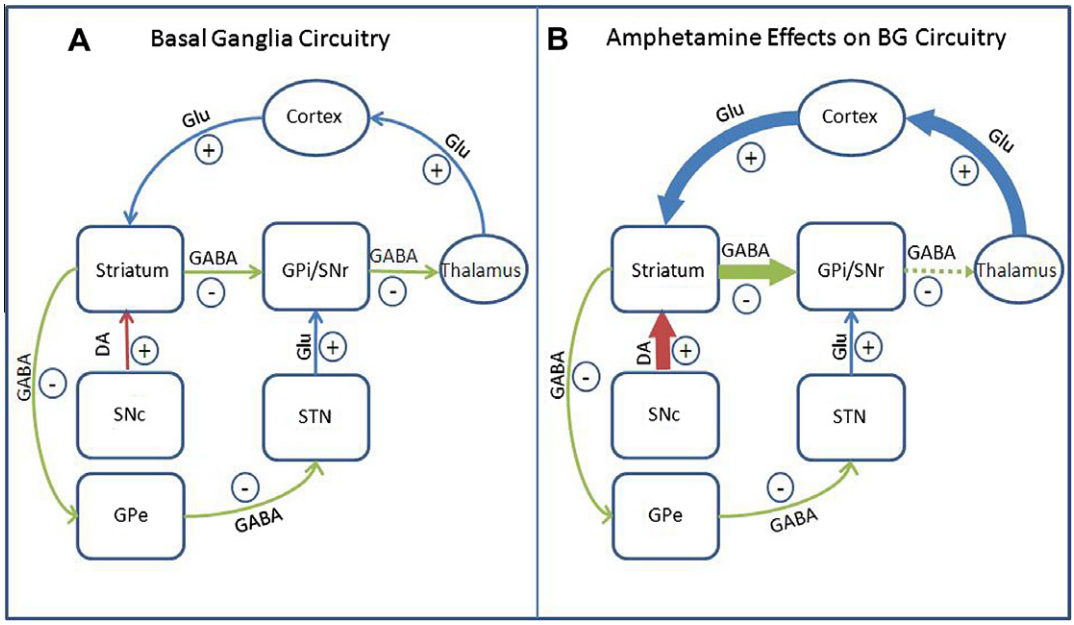

Fig. 1. (A) Schematic representation of the major pathways of the BG. Rectangular boxes denote basal ganglia structures and oval shapes denote brain structures related to the BG. (B) Schematic representation of amphetamine induced changes in neurotransmission in the BG. Wide arrows represent increased activity, and dotted arrow indicate decreased activity in the pathway.