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The Basal Ganglia as a Substrate for the Multiple Actions of Amphetamines

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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.

1.1 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], [2], [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], [5], [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,

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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.

1.2 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.

1.2.1 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 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 (1999a and 1999b) [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 (Figure 1).

Amphetamine induced neurochemical effects in the striatum—A major neurochemical effect of the amphetamines is their effect 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], [14], [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 one 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 three 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 (2004) [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 caspase activity resulting in apoptosis and dopamine terminal degeneration [21], [25]. Therefore, elevations in GLU and DA concentrations in the striatum and the subsequent activation of polysynaptic pathways in the BG could mediate the long term DA toxicity observed after METH [26], [27], [28], [29].

Long term changes in the brain involve transcriptional regulation and amphetamines are known to affect gene transcription. Kodama et al (1998), have shown that arc mRNA levels increase in the striatum after acute METH administration. Pretreatment with a D1 antagonist or NMDA antagonist abolished increases in arc mRNA suggesting a DA or GLU mediated transcriptional regulation in MSN neurons in the striatum. In addition, amphetamine induced phosphorylation of the ERK pathway results in ERK1/2 protein nuclear translocation and activation of transcription factors such as CREB and Elk-1 in a DA and GLU dependent manner in MSN [30],[31]. Moreover, striatal neurons show increased G-protein coupled receptor activity, PI3K, PKA, and ERK/MAPK pathway activity in d-amphetamine sensitized rats [32]. This suggests that the ERK – CREB pathway may be involved in behavioral sensitization due to d-amphetamine exposure [33], [34] and other evidence indicates that the behavioral sensitization to d-amphetamine is context dependent and involves distinct striatal pathways. For example, d-amphetamine administered in the home cage increased c-fos expression in dynorphin positive MSNs, whereas d-amphetamine administered in a novel environment increased c-fos in enkephalin and dynorphin positive cells [35]. Therefore, d-amphetamine induces differential gene expression based on the environmental context in which the drug is taken and is mediated by dopamine and glutamate.

Amphetamine effects on behavior—Amphetamine induced behavioral affects such as enhanced locomotion and stereotypy is influenced by neuronal activity at the striatum. Single unit recording of striatal neurons show a positive correlation between the rate of cell firing and locomotor activity after systemic d-amphetamine administration and this response

was decreased by DA antagonist eticlopride [36], [37], [38], suggesting a direct relationship between dopamine and striatal activity. The striatal effects of amphetamine on behavior are not limited simply to changes in locomotion. Because the striatum is essential for the development of instrumental responding such as lever pressing for a reward, and continued instrumental conditioning can shift behavior from goal directed to habitual responses [39] amphetamines can influence drug taking behavior by affecting both goal directed and habitual responding [40], [41]. A behavior is considered goal directed if devaluation of reward decreases the action to obtain the reward. However, if the animal continues responding despite devalued reward, the behavior is considered habitual responding. The dorsolateral or sensorimotor striatum appears to mediate habitual responding and motor aspects of amphetamine derived behavior. In contrast, the dorsomedial or associative striatum is involved in mediating cognition and goal directed behavior [42, 43] and is required for learning new motor tasks but not previously learned and established tasks [44, 45]. This is evidenced by studies showing that the temporary inactivation or lesions of this region affect only new learning [46, 47] and produce a shift from goal directed to stimulus-response habitual behavior such as that which occurs with extended training [42], [48].

The associative learning function of the BG appears to be dependent on DA in the striatum such that DA acts as a reward error signal by increasing or decreasing release after an unexpected reward or in the absence of an expected reward, respectively [49]. It is possible that the increased or decreased DA release is related to the enhanced or decreased activity of corticostriatal projections [48] to influence goal directed behavior. In this regard, activation of cortical synapses can be caused by amphetamine induced elevations of DA in the striatum that can in turn, enhances reward value and accelerates the transition from goal-directed to habitual responses in amphetamine-sensitized rats [40], [41]. These changes can also be accompanied by structural modifications in the MSN that ultimately result in increased control of behavior by the dorsolateral striatum represented by a shift from goal directed to habitual behavior after prolonged METH exposure [18]. Thus, sustained molecular and morphological changes in the striatum could produce persistent alterations in goal directed and habitual behavioral response to rewarding stimuli.

Goal directed and habitual learning occurs through modulation of the synaptic pathways resulting in the induction of long term potentiation (LTP) or long term depression (LTD) at the GLUergic synapses in the striatum [50]. The activation of NMDA receptors by GLU is one of the requirements for the induction of LTP. NMDA and AMPA receptors on MSNs induce LTP and LTD. The induction of LTP increases gene transcription and protein synthesis resulting in persistent neurochemical and morphological changes at the synapse. LTP induction at the GLUergic synapses in the striatum is D1/D5 receptor dependent [51], [52] and LTD is dependent on retrograde endocannabinoid signaling via D2 and metabotropic glutamate receptors [53], [54]. LTP in the striatum is induced by repeated low doses of METH [55] and by intrastriatal infusions of d-amphetamine resulting in improved striatal dependent learning [56], [57]. Conversely, rats that receive multiple large doses of METH exhibit significant DA depletions in the medial and lateral striatum at 9 weeks after drug treatment and show impaired performance on a sequential motor learning task that correlated with the degree of striatal DA depletion [58]. Overall, the above studies of the striatum suggest that amphetamines can appropriate neural plasticity mechanisms underlying learning through their influence on DA or glutamate release in the striatum to produce strong associations between drug, context and reward in a manner that can result in a habitual responding to drugs.

1.2.2 Globus Pallidus

The globus pallidus is comprised of external (GPe) and internal (GPi) segments in primates, and in non-primates these segments are known as the globus pallidus (GP) and

entopeduncular nucleus [59] [60]. The GPi is a component of the direct pathway of the BG, whereas the GPe is part of the indirect pathway. Together these nuclei can mediate the output of the BG.

Globus Pallidus Internal (GPi)—The GPi receives GABAergic afferent from the striatum, GLUergic afferents from the STN, DAergic afferents from SNc, and sends GABAergic efferents to the thalamus. Activation of the direct pathway from the striatum decreases inhibitory output of the GPi on the thalamus, whereas the activation of the GPi by the indirect pathway through GLUergic projections from the STN increases output of the GPi. Therefore, there exists a balance of disinhibitory and inhibitory inputs to the GPi that modulates inhibitory output to the thalamus.

Globus Pallidus External (GPe)—The GPe receives GABAergic innervations from the striatum, GLUergic innervations from the STN and DAergic innervations from the SNc, and sends GABAergic projections to STN, GPi and SNr [61], [62], [63], [64]. The GPe sends massive inhibitory projections to the output nuclei that terminate as groups of large varicosities that are closely positioned around the soma and proximal dendrites of GPi and SNr [60] [65]. These synapses are thought to be ideally situated to oppose signals from the striatum and the STN, thereby positioning the GPe as a critical integrator of input signals and regulator of BG output rather than a simple relay station for striatal output [66].

Amphetamine effects on the GP—Amphetamines can modulate the GP through their effects on DA release. Bergstrom and Walters (1981) [67] have shown that d-amphetamine administration dose dependently increased GP cell firing. DA depletion with reserpine pretreatment or inhibition of TH by pretreatment with alpha-methyl-p-tyrosine attenuated d-amphetamine induced increases in GP neuronal activity. d-Amphetamine and the D1/D2 agonist apomorphine have been shown to dose dependently increase spontaneous cell firing in the GP, the effects of which were partially blocked by D1 antagonist SCH23390 and completely blocked and reversed by D2 receptor antagonist haloperidol [68], [69]. These observations suggest that amphetamine induced DA release in the GP activates the D1 and D2 receptors and affects the firing of the GP neurons.

Direct microinjection of amphetamine into the GP [70], or systemic administration of DA agonist or DA releasers such as d-amphetamine is known to produce acute stereotypic behavior and hyperactivity in rodents [71]. Electrolytic, 6-hydroxydopamine, quinolinic acid lesions of GP or administration of D1/D2 antagonists have been shown to decrease d-amphetamine induced stereotypy [70], [72], [73], [74]. In addition, GP lesions with quinolinic acid reversed catalepsy induced by systemic administration of D1 and D2 antagonist SCH23390 and raclopride, respectively. These findings are especially interesting since inactivation of the GP decreased locomotor activity after DA receptor stimulation and increased locomotor activity after DA receptor inhibition, suggesting opposing roles played by the GP on locomotion. The opposing outcome of GP inactivation could be due to differential activation of neuronal subpopulations within the GP [74]. The GP is known to contain two distinct GABAergic subpopulations, one mediating increased activation after systemic administration of D1/D2 agonist apomorphine, and the other mediating increased inhibition [75], [76]. It is possible that activity of one type disinhibits the other and affects the degree of inhibition of the pallido-thalamic outputs [74], [77], thereby explaining the opposite effects of the GP on motor function.

There is also some evidence suggesting that the GP is involved in functions that are non-motor related. Ennaceur et al. 1998 [78], have shown that bilateral electrolytic GP lesions in rats resulted in poor performance in a novel object recognition task. In this experiment, rats were exposed to an object for a few minutes, followed by re-exposure to the now familiar

object along with a novel object after a 15 min interval. The GP lesioned rats spent equal amount of time exploring the familiar and novel object, whereas the sham operated controls spent more time exploring the novel object [78]. This suggests disruption of short term memory formation in GP lesioned rats. Furthermore, electrolytic lesions to the GP increased the time taken to perform in a radial maze task as a result of the animals making more errors by revisiting previously visited arms. d-Amphetamine treatment decreased the time taken to complete the radial maze task in GP lesioned animals, but increased the number of errors in both the GP lesioned and sham lesioned animals [78]. This could be due to increased motor activity causing the rats to move from one arm to another without regard for reward or previously learned criteria for the completion of the task. These results suggest that amphetamines affect GP function and thereby influence its effects on attention, motivation and motor control. Similarly, pallidotomy or deep brain stimulation of GP in PD patients affects memory, verbal fluency, attention, information processing and executive functioning [79], [80], [81]. Nevertheless, little is known about the specific involvement of GP in non-motor behaviors. Further research using animal models is required to better understand the GP involvement in non-motor related functions.

1.2.3 Subthalamic Nucleus

The STN is the only excitatory nucleus of the BG, and it sends GLUergic efferents to the GPi, SNc, and SNr. It receives GABAergic innervations from GPe, cholinergic inputs from the pedunculopontine nucleus, DAergic inputs from SNc, and GLUergic inputs from the cortex [82], [83]. The cortical afferents of the STN are topographically organized projections from the motor and premotor regions [84, 85]. These excitatory cortical projections have a shorter conduction time than the direct and indirect pathways originating at the striatum, hence have been collectively termed the hyperdirect pathway [86].

Amphetamine effects on the STN—The hyperdirect pathway is thought to provide rapid inhibitory output that acts as a “stop signal” to an already initiated response [86], [87–89], [90], [91]. Human METH abusers show significant deficits in the stop response latency compared to tobacco users and normal control subjects [92], suggesting a role for STN in timing the execution of a response [90]. Additionally, d-amphetamine has been shown to dose dependently increase impulsive behavior in STN lesioned animals compared to controls, suggesting that the STN provides inhibitory control over impulsive behavior [93]. Therefore, another function of the STN could be to alter the inhibitory control of behavior and the reward value attributed to the amphetamines could be related to their ability to disrupt the function of the STN.

Amphetamines can disrupt STN function by affecting DA and GLU in the BG. Cortical ablations or chronic DA depletions, such as those observed after large doses of amphetamines alter the rate and pattern of activity of the STN [94]. Deep brain stimulation of the STN has been shown to increase DA release in the striatum [95], [96, 97], the latter being related to development of incentive salience and increased motivational and emotional value for drugs of abuse and the environmental context in which they are generally taken [98], [99]. Stimulation of the STN induces the development of LTP in the SNc cell bodies [100], which could increase DA released from terminals in the striatum, and provide a molecular substrate for behavioral sensitization caused by psychostimulant drugs [101], [100]. In unilateral 6-hydroxydopamine lesioned rats, repeated low dose amphetamine administration in either the home cage or a novel environment generated enhanced behavioral sensitization in animals tested in the novel context compared to the home cage [102, 103]. Furthermore, low dose amphetamine increased c-fos mRNA in the STN when administered in a novel environment and upon re-exposure to a previously drug-paired environment suggesting a role for the STN in encoding drug-context relationship[104], [35,

105]. Overall, these findings support the ability of amphetamines to alter motor and cognitive output by affecting the STN and its efferents.

1.2.4 Substantia Nigra

The SN is comprised of two distinct subregions – the pars compacta (SNc) and pars reticulata (SNr). The SN primarily receives GABAergic inputs from the striatum and GLUergic inputs from the STN. The SNc provides DAergic innervations to the striatum and STN of the BG, and the SNr provides GABAergic innervations to SNc and the thalamus.

Amphetamine effects on the SN—The SNc contains DAergic cell bodies and is the primary source of DAergic innervation in the BG. Amphetamines are known to increase the release of DA from the soma and the dendrites of the neurons in this region [106], [107]. Somatodendritically released DA at the SNc stimulates D1 receptors on striatal and pallidal GABAergic terminals within the SN and decreases SNr output to affect motor behavior [108] [109] [110] [111]. In addition, Hatzipetros and Yamamoto (2006) [112], have shown that somatodendritically released DA at the SNc can activate D1 and D2 heteroreceptors in the STN terminals in the SNc. Activation of D1 regulates basal GLU levels in the STN, whereas D2 receptor activity decreases GLU released by the STN terminals into the SNc. Furthermore, DA depletion produced by 6-hydroxydopamine induced lesions of the SNc resulted in a large increase in STN activity [94], [113] suggesting that STN activity is modulated through somatodendritic and presynaptic terminal DA released from the SNc. A similar enhancement in STN activity could occur after chronic amphetamine use, as neurotoxic amphetamine doses produce sustained DA depletions in the midbrain [114] [115]. The resultant increase in STN GLU neurotransmission could be hypothesized to affect the cell bodies of the SN as evidenced by DAergic cell loss in mouse SNc, 5 days after a neurotoxic METH administration paradigm [115]. Therefore, it can be predicted that there would be an increased risk for development of PD-like symptoms due to amphetamine abuse however, this has been debated [116], [117], [118].

The SNr is the other GABAergic output nucleus of the BG. Amphetamines induce c-fos expression in SNr [119], [120, 121], and a repeated high dose regimen of METH increases GAD67 mRNA and extracellular GABA levels in the SNr in a D1 dependent manner [22]. More specifically, intranigral perfusions of $GABA_A$ antagonist bicuculline, blocked METH induced decreases in GABA release from the SNr terminals in the thalamus, and also blocked METH induced increases in VGLUT1 mRNA in the cortex and striatum. Perfusion of a D1 or $GABA_A$ receptor antagonist during METH treatment decreased DA depletions seen in the striatum 7 days later [22, 122]. These results show that METH affects the direct pathway by increasing D1 signaling dependent striatonigral GABA transmission. The striatal GABA released into the SNr activates the $GABA_A$ receptors leading to disinhibition of the thalamus, which increases output of the thalamic GLUergic neurons projecting to the cortex, resulting in enhanced cortical activity and GLU release in the striatum. In this manner, amphetamines can increase GLU and DA levels and contribute to the toxicity to DA terminals in the striatum [28], [22, 122].

Whereas DA toxicity and DAergic cell loss have been observed in the SNc, there is no evidence of GABAergic cell loss in the SNr after amphetamine exposure alone. However, Hatzipetros et al (2006), have shown evidence of GABA cell loss in the SNr but not SNc, after haloperidol treatment subsequent to exposure to METH. Haloperidol is a D2 antagonist that is commonly used in the treatment of METH induced psychosis. The loss of GABA cells in the SNr could result in an increase thalamocortical activity and increase the risk for the development of movement disorders [112]. Therefore, D2 modulation of amphetamine action can also affect BG circuitry and output.

1.3 Amphetamine Influence on the Overall Functions of the Basal Ganglia

The BG is thought to play a major role in cognitive, sensorimotor and emotional aspects of behavior through the activation BG-thalamo-cortical loop. Associative and sensorimotor outputs of the cortex primarily project to the dorsal striatum, whereas the limbic and prelimbic cortical afferents mainly project to the limbic striatum comprised of the ventral striatal regions and nucleus accumbens (NA) [66]. The cortical inputs to the striatal regions are topographically organized, and the efferents of these areas continue to project in a segregated manner to output nuclei such that the GPi receives primarily sensorimotor innervations, the SNr receives mainly associative innervations, and the ventral globus pallidus (GPv) receives innervations from the limbic striatal region [66], [123, 124], [125], [126]. The SNr, GPi and GPv project extensively to ventroanterior, ventromedial, ventrolateral and mediodorsal regions of the thalamus, which in turn project extensively to the cortex, thereby completing the cortico-basal ganglia-thalamo-cortical loop [66], [127]. The BG therefore acts as a center for integrating and processing several functionally distinct inputs from the cortex (Figure 2). Consequently, amphetamines can affect cognitive, limbic, and sensorimotor function through their effects on the BG.

Amphetamines and other addictive compounds alter brain neurotransmission to facilitate drug use. The initial stages of the development of drug dependence are thought to involve the limbic cortical and limbic striatal regions, where DA modulation of the NA-amygdala pathway alters stimulus response and reward associations by affecting the motivational and emotional salience of a drug [128], [129], [130, 131]. Rats have been shown to lever press for intra-accumbens infusions of d-amphetamine, whereas DA depletions caused by 6-hydroxydopamine lesions of the limbic striatum but not the dorsal striatum attenuated lever pressing, suggesting that the limbic striatum is involved in mediating reward value for the drug in a DA dependent manner [132]. Continued drug exposure recruits the dorsomedial striatum to execute goal-directed motor and cognitive behaviors with regards to drug seeking and drug taking. With further drug use, there is additional activation of the dorsolateral striatum such that drug use shifts from goal-directed to progressively more automatic and habitual behavior [44], [45], [57]. Along these lines, the development of habitual behavior has been shown to be facilitated by amphetamines [41], [40]. Likewise, other addictive drugs like cocaine and alcohol have been shown to engage habitual responding more rapidly than natural rewards [133], [134].

A shift to habitual behavioral responses alone is insufficient to explain the compulsive drug seeking behavior exhibited by addicts. Abusers are reported to be preoccupied with their next drug use to the extent that these thoughts and their resultant actions could be considered obsessive and compulsive. Compulsive behavior could be due to an abnormally large incentive salience assigned to drug reward by the limbic striatum, or due to the over activation of the habitual response circuitry of the BG. Along these lines BG dysfunction has been implicated in impulse control diseases such as OCD and TS [135]. Amphetamines could change neurotransmission in the BG to generate neuroadaptations that would support compulsive drug seeking, such as those observed in impulse control diseases. The compulsive thoughts and behavior are believed to be mediated by the limbic cortical projections from orbitofrontal cortex and the anterior cingulate regions to the limbic striatum, BG, and its projections to the thalamus [135]. Along these lines, striatal or pallidal lesions are known to produce OCD-like behavior and there is evidence of decreased neuronal density in the striatum of OCD patients [136], [137]. In fact, GABAergic cell loss in the mouse striatum caused by large doses of METH [20], [21] could result in disinhibition of the BG output to the thalamus. Such a disinhibition is observed in compulsive disorders such as TS and OCD [138] such that the disinhibition of thalamus is thought to produce compulsive behavior that could be due to disruption of neurotransmission in the striatum or

through the disruption in the functioning of the direct and indirect pathway resulting in uncontrollable, repetitive habitual actions [138]. Thus, amphetamines and other drugs of abuse that affect striatal DA could alter BG neurotransmission to favor compulsive drug seeking behavior.

In a compulsive drug use state, large doses of drugs are chronically taken due to decreased inhibitory control of drug intake behavior. Chronic amphetamine use is known to cause psychotic episodes that include verbal and visual hallucinations and paranoia [139], [140]. The psychotic episodes are thought to be due to elevated DA in the striatum that ultimately disinhibits thalamic function and decreases the filtering of information delivered by the thalamus to the cortex [141], [142]. Moreover, chronic high dose exposure to amphetamines could lead to neurotoxicity as evidenced by long-term decreases in monoamines and their phenotypic markers in the striatum and other brain regions to affect normal function, cognition and behavior [143], [144]. Thus, higher doses and continued use of amphetamines may differentially activate BG structures that contribute to the progression of drug use beginning with the initiation of drug seeking followed by drug dependence, compulsive drug use, and in some cases, psychosis and neurotoxicity (Figure 2).

1.4 Conclusion

Knowledge of the BG circuitry has contributed substantially to our understanding of movement disorders and their treatment. In this review, we conclude that amphetamines alter the neurochemistry of distinct pathways within BG circuit to produce biochemical and behavioral perturbations that could manifest as harmful neuro-psychopathological conditions. Therefore, it is important to further our understanding of the neurochemical substrates of BG function as they relate to the action of the amphetamines and other psychostimulant drugs of abuse.

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Abbreviations

BG	basal ganglia
METH	methamphetamine
DA	dopamine
GLU	glutamate
GABA	gamma-aminobutyric acid
vGLUT	
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

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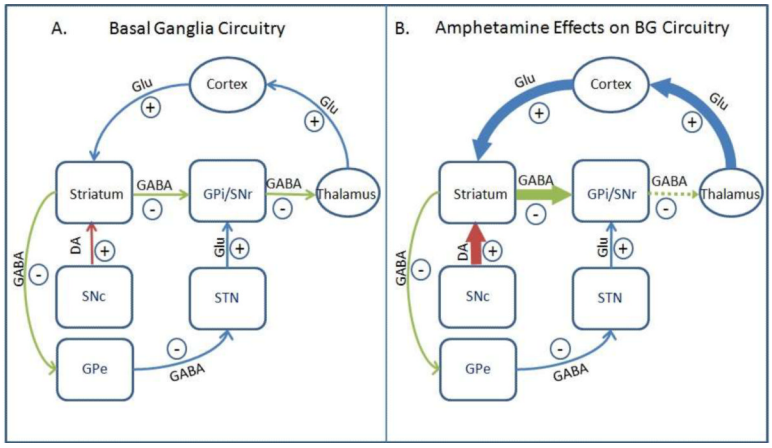

Figure 1.

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.

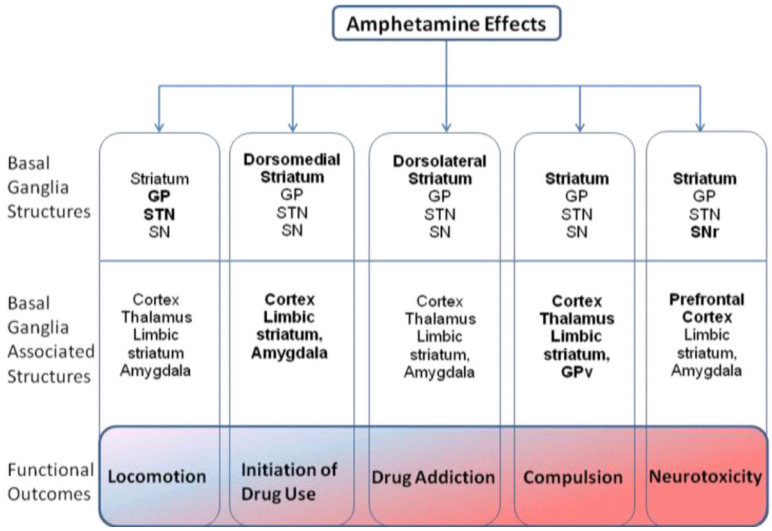

Figure 2.

Model of amphetamine influence on BG and its related structures resulting in differential functional output. Amphetamines can affect specific components of the BG and other structures closely associated with the BG to mediate behavioral outcomes associated with drug use. The bold print denotes increased involvement of these structures in the behavioral outcome.