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Addiction-Related Gene Regulation: Risks of Exposure to Cognitive Enhancers vs. Other Psychostimulants

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Abstract

The psychostimulants methylphenidate (Ritalin, Concerta), amphetamine (Adderall), and modafinil (Provigil) are widely used in the treatment of medical conditions such as attention-deficit hyperactivity disorder and narcolepsy and, increasingly, as “cognitive enhancers” by healthy people. The long-term neuronal effects of these drugs, however, are poorly understood. A substantial amount of research over the past 2 decades has investigated the effects of psychostimulants such as cocaine and amphetamines on gene regulation in the brain because these molecular changes are considered critical for psychostimulant addiction. This work has determined in some detail the neurochemical and cellular mechanisms that mediate psychostimulant-induced gene regulation and has also identified the neuronal systems altered by these drugs. Among the most affected brain systems are corticostriatal circuits, which are part of cortico-basal ganglia-cortical loops that mediate motivated behavior. The neurotransmitters critical for such gene regulation are dopamine in interaction with glutamate, while other neurotransmitters (e.g., serotonin) play modulatory roles. This review presents (1) an overview of the main findings on cocaine- and amphetamine-induced gene regulation in corticostriatal circuits in an effort to provide a cellular framework for (2) an assessment of the molecular changes produced by methylphenidate, medical amphetamine (Adderall), and modafinil. The findings lead to the conclusion that protracted exposure to these cognitive enhancers can induce gene regulation effects in corticostriatal circuits that are qualitatively similar to those of cocaine and other amphetamines. These neuronal changes may contribute to the addiction liability of the psychostimulant cognitive enhancers.

Keywords

amphetamine; cocaine; cognitive enhancer; cortex; dopamine; gene regulation; methylphenidate; psychostimulant; striatum

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Conflict of interest statement

There is no conflict of interest.

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1. Introduction

Cognitive enhancers, sometimes called “smart drugs” or “memory enhancers,” are substances taken with the expectation that they increase mental functions such as attention, concentration, alertness, memory, motivation, planning, and decision making (Svetlov et al., 2007; Lanni et al., 2008; Husain and Mehta, 2011). The most widely used cognitive enhancers include the psychostimulant medications methylphenidate (Ritalin, Concerta), amphetamine (Adderall), and modafinil (Provigil). The oldest of these drugs is amphetamine, which was first synthesized in 1887 and has been used in the clinic since the 1930s (Berman et al., 2009). Methylphenidate, first produced in 1944, has also been used as a medication for many decades (Leonard et al., 2004), whereas modafinil was introduced only in the early 1990s (Minzenberg and Carter, 2008).

1.1. Medical and nonprescription uses of psychostimulants

These psychostimulant medications are valued and widely prescribed for their efficacy in controlling symptoms of attention-deficit hyperactivity disorder (ADHD) (methylphenidate, amphetamine) or excessive daytime sleepiness associated with narcolepsy and other sleep disorders (modafinil, amphetamine, methylphenidate) (Leonard et al., 2004; Minzenberg and Carter, 2008; Berman et al., 2009). Furthermore, there is a rationale for the use of methylphenidate and modafinil in the treatment of behavioral deficits associated with psychostimulant addiction (e.g., Goldstein et al., 2010; Volkow et al., 2010; Loland et al., 2012; Reichel and See, 2012; for reviews, see Brady et al., 2011; Sofuoglu et al., 2012). But these medications are also recognized by the US Drug Enforcement Administration (DEA) for their abuse potential and are therefore classified as Schedule II (amphetamine, methylphenidate) or Schedule IV (modafinil) controlled substances.

ADHD is among the most common neurobehavioral disorders and, in the United States, affects approximately 7.8% of children aged 4 to 17 and 4.4% of adults (Kollins, 2008). It is arguably the dramatic increase in diagnosis and pharmacological treatment of ADHD over the past 2 decades that has led to a parallel increase in production of these psychostimulants (Biederman et al., 2007; Kollins, 2008; Swanson and Volkow, 2008; Berman et al., 2009). For example, the number of prescriptions for amphetamine increased 16-fold during the 1990s, and in 2000 the US annual production of amphetamine reached 30,000 kg (Berman et al., 2009). Likewise, the DEA aggregate production quotas for methylphenidate increased from 5,000 kg in 1993 to 15,000 kg in 2000 to 50,000 kg in 2009.¹

Not surprisingly, with increasing availability came increasing diversion and use of psychostimulant medications as cognitive enhancers or party drugs (Kollins et al., 2001; Svetlov et al., 2007; Kollins, 2008; Swanson and Volkow, 2008; Wilens et al., 2008; Mache et al., 2012). It is difficult to accurately estimate the amounts and extent of their use as cognitive enhancers, but surveys indicate that students are frequent consumers of these drugs (Svetlov et al., 2007). Thus, studies of the misuse and diversion of prescription ADHD medications found that rates of self-reported past-year use range from 4% to 30% among college students (Kollins et al., 2001; Kollins, 2008; Wilens et al., 2008; Berman et al., 2009) and 5% to 9% in grade school- and high school-aged children (Wilens et al., 2008). The most often reported motives for illicit use among college students are to increase attention, concentration, or alertness (to help study), and to a lesser extent to get “high” (Babcock and Byrne, 2000; Teter et al., 2006; White et al., 2006). Furthermore, the trend for using cognitive enhancers is growing not only among students (Greely et al., 2008): in a recent poll of 1,400 academics (*Nature* readers), 20% indicated that they had used

¹Data available at the DEA website, www.deadiversion.usdoj.gov/fed_regs/quotas/2009/fr10212.htm, accessed August 2, 2012.

methylphenidate (62%) or modafinil (44%) to combat jet lag, to improve general concentration, or to assist them in a particular task (Maher, 2008).

1.2. Neurobehavioral and molecular impacts of psychostimulant use

It remains controversial whether the medical use of psychostimulants is completely safe (Kollins, 2008; Wilens et al., 2008; see Section 8), especially in children and adolescents (Carlezon and Konradi, 2004; Andersen, 2005; Berman et al., 2009). Even less clear are the potential long-term effects of cognitive enhancer use in the healthy, in part because widespread use is a relatively new phenomenon and adverse effects of early drug exposure may appear only late in life (e.g., Bolanos et al., 2003; Tropea et al., 2008; Warren et al., 2011). There is concern especially that long-term exposure to psychostimulants during the sensitive period of brain development may increase the risk for maladaptive neurobehavioral changes that may facilitate drug addiction and other neuropsychiatric disorders (Bolanos et al., 2003; Warren et al., 2011; for reviews, see Carlezon and Konradi, 2004; Andersen, 2005; Carrey and Wilkinson, 2011; Marco et al., 2011).

There is little doubt that changes in gene regulation produced by illicit psychostimulants such as cocaine play a critical role in addiction (Hyman and Nestler, 1996; Nestler, 2001) because only these molecular changes endure long enough to mediate behavioral pathologies that can last a lifetime such as addiction (Renthal and Nestler, 2008). Therefore, the addiction liability of medical psychostimulants most likely also rests on their propensity to induce altered gene regulation.

In this article, we review changes in gene regulation produced by medical amphetamine (Adderall), methylphenidate, and modafinil as determined in animal models. We discuss these findings in the context of the known molecular changes that are produced by illicit psychostimulants (e.g., cocaine) and are considered part of the molecular basis for drug addiction.

2. Neurochemical effects of psychostimulant cognitive enhancers

2.1. Changes in monoamine transmission

Psychostimulants cause, among other effects, amplification of monoamine neurotransmission by promoting release and/or blocking reuptake of monoamines and thus prolonging their actions (Natarajan and Yamamoto, 2011; Sulzer, 2011). Psychostimulant-induced potentiation of the dopamine transmission (Di Chiara and Imperato, 1988) is considered critical to the addiction process, whereas serotonin and norepinephrine play modulatory roles (Berke and Hyman, 2000; Nestler, 2001).

Adderall is a mixture of D- and L-amphetamine salts (Berman et al., 2009) and, like cocaine, amphetamines produce elevated extracellular levels of the monoamines dopamine, norepinephrine, and serotonin (Di Chiara and Imperato, 1988; Hurd and Ungerstedt, 1989; Ritz et al., 1990; Kuczenski and Segal, 1997, 2001). Modafinil seems to primarily inhibit dopamine and norepinephrine reuptake (Madras et al., 2006; Volkow et al., 2009; Schmitt and Reith, 2011; Loland et al., 2012) but, probably indirectly, affects other neurotransmitters as well (e.g., histamine, orexin and serotonin; see Minzenberg and Carter, 2008). Better established are the effects of methylphenidate. Methylphenidate binds to and blocks the dopamine and norepinephrine transporters (Schweri et al., 1985; Gatley et al., 1996) and thus produces overflow of these two monoamines (Hurd and Ungerstedt, 1989; Kuczenski and Segal, 1997; Volkow et al., 1998; Gerasimov et al., 2000; Bymaster et al., 2002; Berridge et al., 2006). In contrast, methylphenidate has low affinity for the serotonin transporter (Pan et al., 1994; Wall et al., 1995; Gatley et al., 1996; Bymaster et al., 2002)

and produces minimal or no effects on serotonin levels, even with high doses (30 mg/kg, i.p.) (Kuczenski and Segal, 1997; Segal and Kuczenski, 1999; Kankaanpää et al., 2002).

In vivo microdialysis studies demonstrate that these psychostimulant-induced neurochemical effects are very robust in the prefrontal cortex and in parts of the basal ganglia (Figure 1), especially the striatum (dorsal striatum/caudate-putamen, ventral striatum/nucleus accumbens) (Di Chiara and Imperato, 1988; Hurd and Ungerstedt, 1989; Kuczenski and Segal, 1997, 2001; Gerasimov et al., 2000; Berridge et al., 2006). Low, clinically relevant doses of cognitive enhancers seem to preferentially boost extracellular levels of dopamine and norepinephrine in the prefrontal cortex (Berridge and Devilbiss, 2011, but see Volkow et al., 2001). Higher doses (presumably associated with abuse) predominantly affect dopamine in the striatum due to orders of magnitude higher levels of dopamine tissue content in the striatum.

2.2. Other effects

In addition to the direct neurochemical effects described above, all of these drugs have a number of other acute effects that can, directly or indirectly, further modify monoamine (and other) transmission (see Yano and Steiner, 2007). The following examples pertain to methylphenidate: (1) Recent studies showed that acute methylphenidate administration alters the distribution and function of the vesicular monoamine transporter-2 (VMAT-2) in the striatum (Sandoval et al., 2002, 2003), similar to cocaine (Fleckenstein et al., 2009). (2) Methylphenidate produces enhanced phosphorylation of glutamate receptors (GluR1) in the prefrontal cortex, similar to amphetamine (Pascoli et al., 2005). (3) Methylphenidate affects second messenger cascades that mediate dopamine signaling. Thus, acute methylphenidate was found to increase and decrease phosphorylation of DARPP-32 at Thr34 and Thr75, respectively, in striatal slices from adult mice, an effect that was dependent on D₁ dopamine receptor stimulation (Fukui et al., 2003). These findings demonstrate that there are several independent mechanisms by which cognitive enhancers can affect addiction-related neurotransmission.

Chronic perturbation of neurotransmission by psychostimulants often elicits compensatory (homeostatic) neuroadaptations, which are considered critical for addiction and dependence (Hyman and Nestler, 1996). Thus, repeated treatment with such drugs produces neuronal changes ranging from altered cell signaling (Yano and Steiner, 2007; McGinty et al., 2008) to structural modifications (e.g., in dendritic spine density; Robinson and Kolb, 1997; Jedynak et al., 2007; Kim et al., 2009), and the longevity of these alterations likely requires adaptations in gene expression (Renthal and Nestler, 2008).

Many excellent reviews have surveyed the effects of psychostimulants (primarily amphetamines and cocaine) on gene regulation and their role in addiction in general (e.g., Hyman and Nestler, 1996; Harlan and Garcia, 1998; Torres and Horowitz, 1999; Berke and Hyman, 2000; Nestler, 2001; Kelley, 2004; Hyman, 2005; McGinty et al., 2008; Renthal and Nestler, 2008). In this review we first summarize the molecular changes produced by amphetamine² and cocaine to provide context for a discussion of findings on the effects of medical amphetamine (Adderall), methylphenidate, and the little that is known about modafinil. Most of these findings were obtained in rat and mouse models.

²We do not specifically address the molecular effects of methamphetamine and related compounds, which are also approved by the US Food and Drug Administration for the treatment of ADHD and other conditions (Berman et al., 2009). Many methamphetamine effects on gene regulation are similar to those of amphetamine; we refer the interested reader to a recent review by Keefe and Horner (2010[0]) on this topic.

3. Gene regulation by amphetamine and cocaine in corticostriatal circuits

Most studies on the molecular effects of psychostimulants have focused on gene regulation in dopamine target areas, especially the striatum, which displays particularly robust changes in gene regulation after treatments with amphetamine, cocaine, and other abused drugs (Harlan and Garcia, 1998; Berke and Hyman, 2000).

The striatum, the main input nucleus of the basal ganglia, is an important component of cortico-basal ganglia-cortical circuits (Gerfen and Bolam, 2010; Figure 1), which play a critical role in motivational, executive, and motor aspects of all goal-directed behavior and thus in addiction (Steiner, 2010). Psychostimulant-induced molecular changes in these circuits through the striatum are important for various aspects of addiction, including abnormal reward processing, habit formation, and compulsive behavior (Robbins and Everitt, 1999; Berke and Hyman, 2000; Hyman and Malenka, 2001; Gerdeman et al., 2003; Everitt and Robbins, 2005; Belin and Everitt, 2010). However, some of the most affected (dorsal) striatal circuits (Willuhn et al., 2003; Yano and Steiner, 2005a; 2005b; Unal et al., 2009) also participate in frontostriatal attentional networks and may thus be a therapeutic target in ADHD (Robbins et al., 1998; Solanto, 2002). We therefore focus on psychostimulant-induced gene regulation in corticostriatal circuits.

Microarray investigations indicate that hundreds of genes are affected by dopamine and psychostimulants in these circuits (Berke et al., 1998; McClung and Nestler, 2003; Konradi et al., 2004; Yuferov et al., 2005; Adriani et al., 2006a; Adriani et al., 2006b; Black et al., 2006; Yano and Steiner, 2007; Heiman et al., 2008). However, the vast majority of studies have assessed effects on the expression of neuropeptide transmitters and immediate-early genes (IEGs). Neuropeptides are often selectively contained in specific neuronal subtypes and thus serve as cell type markers (see Section 3.1.3), but they also modulate basal ganglia functions on several levels (e.g., Steiner, 2010). IEGs are useful as markers for cell activation due to their rapid and transient induction by neuronal activity and drug treatments (Sharp et al., 1993; Chaudhuri, 1997; Harlan and Garcia, 1998). They are thus frequently used to map drug effects in the brain.

Immediate-early genes are also of interest because of their direct involvement in neuroplasticity. Many IEGs encode transcription factors that regulate the expression of other genes (e.g., *c-Fos*, *Zif268*; Knapska and Kaczmarek, 2004). Others (e.g., *Homer 1a*) code for members of a family of scaffolding proteins that anchor receptors to the postsynaptic density and play a role in receptor trafficking, dendritic spine formation, and other processes of synaptic plasticity (Xiao et al., 2000; Thomas, 2002). These latter processes may be involved in the abnormal spine formation in striatal neurons produced by psychostimulant treatment (Robinson and Kolb, 1997; Ferrario et al., 2005; Jedynak et al., 2007; Kim et al., 2009).

In the following sections, we first describe the functional domains of the striatum and then present studies that illustrate psychostimulant-induced effects on gene regulation in these domains. The findings reveal which cortico-basal ganglia-cortical circuits (functional domains, cell types) are affected by these drugs and establish a cellular framework for evaluating and understanding the effects of cognitive enhancers such as methylphenidate and modafinil. We then provide examples of molecular changes induced by repeated psychostimulant treatment and discuss their potential functional significance.

3.1. Corticostriatal circuits affected

3.1.1. Functional domains of the striatum—The functional domains of the striatum are defined by their cortical inputs (Figure 1). According to current models of basal ganglia

function, the basal ganglia and cortex are interconnected by several parallel anatomical circuits/loops that arise in the cortex and project in a topographical manner to the striatum and from there via the basal ganglia output nuclei and thalamus back to the cortex (Alexander et al., 1986; Albin et al., 1989; Alexander et al., 1990; Groenewegen et al., 1990; Haber, 2003; Joel and Weiner, 1994; Redgrave et al., 2010). Functionally, these circuits can be roughly categorized as limbic, associative, and sensorimotor, arising, respectively, in the limbic, associative, and sensory and motor regions of the cortex and projecting to their associated domains in all basal ganglia nuclei. The behavioral consequences of psychostimulant-induced molecular changes (or indeed of any pathological changes) in the basal ganglia are therefore dependent on the particular circuits affected. Thus there is interest in determining which circuits/functional domains in the striatum are altered by these drugs.

3.1.2. Topography of psychostimulant-induced gene regulation—Early descriptions of the regional distribution of psychostimulant-induced gene regulation in the striatum were in relatively vague terms anatomically (e.g., dorsolateral quadrant, dorsal vs. ventral). Nevertheless, the findings were clear and consistent between laboratories that these effects differ considerably between the different striatal regions. This variability is characteristic of the effects of amphetamine, cocaine (Figure 2A), and methylphenidate (Figure 2B).

Graybiel and colleagues (1990) first showed that *c-Fos* induction by acute cocaine treatment, although widespread in the striatum, had a distinctive topography. It was most pronounced in the dorsal central portion of the sensorimotor striatum and was fairly limited (or absent) in parts of the ventral (limbic) striatum, including the nucleus accumbens (Figure 2A). Other early studies confirmed this general pattern for *c-Fos* and other genes (e.g., Young et al., 1991; Hope et al., 1992; Moratalla et al., 1992; Bhat and Baraban, 1993; Steiner and Gerfen, 1993; Johansson et al., 1994; see Harlan and Garcia, 1998 for a review of the early work).

Many investigators found an overall similar (dorsal-ventral) distribution for amphetamine effects (Graybiel et al., 1990; Moratalla et al., 1992; Wang et al., 1994a; Badiani et al., 1998; Adams et al., 2001), but there are also differences between amphetamine and cocaine effects, for example, in their distribution across the striatal patch/matrix compartments (Harlan and Garcia, 1998). In contrast to the rather uniform gene induction by cocaine in terms of patch/matrix distribution, the IEG response to amphetamine appears reduced in the matrix relative to that in the patches (striosomes) (Graybiel et al., 1990; Graybiel et al., 2000). This finding was confirmed by many (e.g., Moratalla et al., 1992; Nguyen et al., 1992; Wang et al., 1995) but not all (Johansson et al., 1994; Wang et al., 1994b; Jaber et al., 1995) subsequent studies.

To better relate psychostimulant-induced molecular changes to specific corticostriatal circuits/functional domains in the rat, we mapped striatal gene regulation using 23 sampling areas (sectors)—based largely on their predominant cortical inputs—on three rostrocaudal levels (Figure 1A) (Willuhn et al., 2003; Yano and Steiner, 2005a, b; Cotterly et al., 2007; Unal et al., 2009). These studies revealed the following patterns (see Steiner, 2010 for review):

1. The most robust cocaine-induced changes in gene regulation occur in sensorimotor sectors of the middle and caudal striatum (Figure 2A) (e.g., Steiner and Gerfen, 1993; Willuhn et al., 2003; Unal et al., 2009). A similar regional distribution has been shown for amphetamine (e.g., Badiani et al., 1998).
2. Within the sensorimotor striatum, maximal changes occur in the dorsal sectors (approximately the dorsal third) (Figure 2A). These sectors are unique in that they

receive the densest input from the medial agranular cortex (M2; Figure 1A) (Reep et al., 2003) in addition to convergent inputs from the somatosensory (or visual) and primary motor cortex (cf. Willuhn et al., 2003). Surrounding tissue that is, to a lesser extent, also targeted by medial agranular projections also shows robust changes in gene expression. The rat medial agranular cortex has mixed prefrontal/premotor features (Reep et al., 1987; Passingham et al., 1988; Preuss, 1995; Reep et al., 2003; Uylings et al., 2003) and can therefore be considered a prefrontal/motor interface. Our findings thus indicate that sensorimotor striatal circuits under the influence of medial agranular (prefrontal/premotor) input are particularly prone to psychostimulant-induced neuroplasticity.

3. Medial and rostral striatal sectors (associative sectors) were affected to a lesser degree (Figure 2A). These sectors receive inputs from prefrontal regions including the cingulate, prelimbic, and orbital cortex (Figure 1A) (e.g., Berendse et al., 1992).
4. On all three rostrocaudal levels, minimal or no changes in gene regulation were seen in ventral striatal sectors (Figure 2A) that receive inputs mostly from the dorsal agranular insular cortex (Figure 1A) (e.g., Berendse et al., 1992).
5. Psychostimulant-induced molecular changes in the nucleus accumbens are well appreciated in the addiction literature (e.g., Graybiel et al., 1990; Hope et al., 1992; Hope et al., 1994; for reviews, see Berke and Hyman, 2000; Nestler, 2001) because they are implicated in motivational (reward) processes (Pierce and Kalivas, 1997). However, consistent with the earlier literature (see above), our studies show that gene regulation effects of cocaine in the nucleus accumbens (Figure 2A) are modest compared with those in the sensorimotor striatum (Steiner and Gerfen, 1993; Willuhn et al., 2003; Unal et al., 2009). This effect reflects the finding that cocaine strongly activates only a small proportion of sparsely distributed neurons in the nucleus accumbens (as well as in the most rostral striatum) (Mattson et al., 2008). The nucleus accumbens shell appears more affected than the core, and the most robust effects were seen in the lateral part of the shell (Unal et al., 2009), which also receives medial agranular input (Reep et al., 1987) in addition to inputs from the ventral agranular insular cortex (Berendse et al., 1992) and other limbic areas (e.g., McGeorge and Faull, 1989; Brog et al., 1993; Wright and Groenewegen, 1996). The functional significance of these lateral shell effects is not known, but it is of interest to note that the insular cortex, one of the input regions of that part of the nucleus accumbens, is associated with craving in drug addiction (Naqvi et al., 2007), which often drives relapse.

In summary, amphetamine and cocaine produce changes in gene regulation in limbic striatal regions, but these are relatively modest. These changes are likely involved in altered reward processing in addiction (e.g., Belin and Everitt, 2010). Studies that compared effects in different striatal regions demonstrate that more robust drug-induced changes in gene regulation occur in the sensorimotor striatum. These molecular changes probably mediate the functional changes seen in these regions as the addiction disorder progresses (Porrino et al., 2007). Behaviorally, sensorimotor striatal changes may be responsible for habitual and compulsive aspects of drug taking (Berke and Hyman, 2000; Gerdeman et al., 2003; Everitt and Robbins, 2005; Belin and Everitt, 2010), and are likely also important for relapse to drug seeking after abstinence (Vanderschuren et al., 2005; Fuchs et al., 2006; See et al., 2007).

3.1.3. Striatal cell types—The main cell type of the striatum is the medium-sized spiny projection neuron (“medium spiny neuron”); in the rat, interneurons account for less than 3% of striatal neurons (Oorschot, 2010, 2013). Colocalization studies indicate that

psychostimulants affect gene regulation in projection neurons but have minimal or no effect in interneurons (Berretta et al., 1992). For example, cholinergic interneurons showed cocaine-induced IEG expression only in the ventromedial striatum and the medial shell of the nucleus accumbens but not in the core or in the dorsolateral striatum (Berlanger et al., 2003).

Striatal projection neurons are divided into two subtypes that are intermingled and approximately equal in number and that give rise to two different striatal output pathways (Figure 1B). The “direct pathway” (striatonigral neurons) connects the striatum directly to the basal ganglia output nuclei (substantia nigra pars reticulata, entopeduncular nucleus/internal pallidum); the “indirect pathway” begins with the striatopallidal neurons and projects to the output nuclei indirectly via the globus pallidus (external pallidum) and subthalamic nucleus (Gerfen and Bolam, 2010).

Both subtypes of striatal projection neurons use γ -aminobutyric acid as their main neurotransmitter, but they differ in a number of receptors and neuropeptides they express (Steiner and Gerfen, 1998; Heiman et al., 2008). Striatonigral neurons contain predominantly the D₁ receptor subtype and the neuropeptides substance P and dynorphin (Figure 1B), whereas striatopallidal neurons mostly express the D₂ receptor and the neuropeptide enkephalin. (Because of this differential receptor/neuropeptide distribution, these neurons are sometimes referred to as D₁ or D₂ neurons, respectively, and these neuropeptides often serve as markers to differentiate effects of drug treatments between these striatal output pathways).

These two striatal output pathways have opposite effects on basal ganglia output and motor control. According to current models of basal ganglia function (Figure 1B), activity in the direct pathway inhibits basal ganglia output, thus disinhibiting thalamocortical (and brainstem) activity (Chevalier and Deniau, 1990) and facilitating behavior, whereas activity in the indirect pathway (i.e., in striatopallidal neurons) results in disinhibition of basal ganglia output, thus arresting behavior (Albin et al., 1989; DeLong, 1990; Redgrave et al., 2010). It is thought that activity in the direct pathway (the “Go pathway”) functions to initiate (or facilitate selection of) motor programs, whereas activity in the indirect pathway (the “Stop pathway”) interrupts motor programs and/or suppresses unwanted (or incompatible) movement. (For an elegant recent demonstration of this oppositional movement control, see Kravitz et al., 2010.) Although these concepts were initially derived from anatomical findings in the dorsal/sensorimotor striatum (Alexander et al., 1986; Albin et al., 1989), recent results confirmed such antagonistic functions of these two pathways for cocaine-induced behavior mediated by the dorsal striatum (Ferguson et al., 2011) and reward processes mediated by the limbic/ventral striatum (Lobo et al., 2010).

Given the differential functional roles of the two subtypes of striatal projection neurons, it was of considerable interest to determine whether psychostimulants alter gene regulation in both subtypes or whether one is preferentially affected. Early clues were obtained from drug effects on the expression of the neuropeptides that are differentially localized in these neurons and thus serve as cell type markers (Steiner and Gerfen, 1998). Many studies showed that amphetamine and cocaine robustly induce expression of substance P and dynorphin (e.g., Hanson et al., 1987; Sivam, 1989; Hurd and Herkenham, 1992; Hurd and Herkenham, 1993; Steiner and Gerfen, 1993; Daunais and McGinty, 1994; Wang and McGinty, 1995a; Drago et al., 1996; Adams et al., 2001; Frankel et al., 2008), which are contained in striatonigral neurons. In contrast, enkephalin expression (in striatopallidal neurons) is only modestly affected by psychostimulants (Steiner and Gerfen, 1993; Jaber et al., 1995; Wang and McGinty, 1996a; Spangler et al., 1997; Mathieu-Kia and Besson,

1998). (It should be noted, however, that enkephalin expression is readily induced by glutamate receptor stimulation or D₂ receptor blockade [e.g., Steiner and Gerfen, 1999].)

Colocalization studies using neuropeptide messenger RNAs (mRNAs) or tract tracers as markers confirmed this differential gene regulation for IEGs as well. Amphetamine and cocaine induce IEGs predominantly in striatonigral neurons (Berretta et al., 1992; Cenci et al., 1992; Johansson et al., 1994; Jaber et al., 1995; Kosofsky et al., 1995; Badiani et al., 1999). However, depending on the treatment conditions (i.e., with enough cortical activation/glutamate input; see Steiner, 2010), some IEG induction also occurs in striatopallidal neurons (e.g., Jaber et al., 1995; Badiani et al., 1999; Uslaner et al., 2001; Ferguson and Robinson, 2004).

3.1.4. Dopamine receptor subtypes—The differential effects on striatonigral versus striatopallidal neurons are likely based on the differential distribution of dopamine receptor subtypes between the two projection neuron subtypes (Figure 1B): As mentioned above, D₁ receptors are predominantly expressed in striatonigral neurons, and D₂ receptors mostly in striatopallidal neurons (Gerfen et al., 1990; Le Moine et al., 1990; Le Moine et al., 1991; Curran and Watson, 1995; Le Moine and Bloch, 1995). Numerous studies show that D₁ receptor stimulation and resulting activation of second messenger signaling cascades (Bronson and Konradi, 2010; Caboche et al., 2010) are critical for psychostimulant-induced gene regulation in striatal neurons. Thus, IEG expression induced by amphetamine and cocaine is eliminated either by systemic or intrastratial administration of D₁ receptor antagonists (Graybiel et al., 1990; Young et al., 1991; Moratalla et al., 1992; Cole et al., 1992; Steiner and Gerfen, 1995) or by targeted deletion of the D₁ receptor (D₁ receptor knockouts) (Drago et al., 1996; Moratalla et al., 1996b; Zhang et al., 2004).

D₂ receptors also affect gene regulation in striatal neurons. In contrast to D₁ receptors, however, stimulation of D₂ receptors *inhibits* gene expression in striatopallidal neurons (e.g., Gerfen et al., 1990; Le Moine et al., 1997; Pinna et al., 1997), whereas *blockade* of D₂ receptors (e.g., by antipsychotic drugs) increases gene expression in these neurons (e.g., Steiner and Gerfen, 1998). This difference in effect presumably reflects the fact that D₂ receptors inhibit second messenger signaling, as opposed to the stimulatory action of D₁ receptors (Bronson and Konradi, 2010). However, stimulation of D₂ plus D₁ receptors potentiates D₁ receptor-mediated gene regulation in striatonigral neurons (D₁–D₂ receptor synergy; e.g., Paul et al., 1992; LaHoste et al., 1993; Gerfen et al., 1995). Consistent with this observation, a full gene response to psychostimulants requires combined stimulation of D₁ and D₂ receptors (Ruskin and Marshall, 1994). This interaction between D₁ and D₂ receptors is thought to be mediated by cholinergic interneurons (Wang and McGinty, 1996b; Pisani et al., 2007)—for example, via a D₂ receptor-mediated inhibition of inhibitory cholinergic input to striatonigral neurons (Wang and McGinty, 1996b).

In addition, D₃ receptors modify such molecular effects. These receptors are predominantly present in ventral striatal regions where they are partly coexpressed with D₁ receptors in striatonigral neurons (Le Moine and Bloch, 1996; Schwartz et al., 1998). Because they also exert opposite (inhibitory) effects on second messenger signaling (Zhang et al., 2004), D₃ receptors dampen gene induction by D₁ receptor stimulation (Carta et al., 2000; Zhang et al., 2004).

In summary, these findings demonstrate that (1) amphetamine- and cocaine-induced changes in gene regulation in the striatum occur preferentially (but not exclusively) in direct pathway (striatonigral) neurons (see also Lobo and Nestler, 2011), and (2) D₁ receptors (and their downstream signaling cascades; Caboche et al., 2010) are critical for these molecular changes.

3.2. Relationship between gene regulation in striatum and cortex

Imaging studies in humans and other primates show that exposure to psychostimulants such as cocaine and amphetamine produces functional changes also in various regions of the cortex (e.g., London et al., 1990; Breiter et al., 1997; Beveridge et al., 2006; Porrino et al., 2007). Similarly, systemic administration of cocaine, amphetamine, and other dopamine agonists causes increases in gene expression in the cortex (Figure 2) (e.g., Graybiel et al., 1990; Paul et al., 1992; Dilts et al., 1993; Johansson et al., 1994; Steiner and Gerfen, 1994; Wang and McGinty, 1995a; LaHoste et al., 1996; Badiani et al., 1998). These cortical effects are widespread (Harlan and Garcia, 1998), but a recent detailed mapping study showed that acute and repeated cocaine treatments produce the most robust changes in IEG regulation in sensory and motor regions of the cortex (Unal et al., 2009), thus mirroring the distribution of such molecular changes across striatal functional domains. Other studies have also revealed preferential gene regulation in the sensorimotor cortex for cocaine (e.g., Daunais and McGinty, 1994; Johansson et al., 1994) and amphetamine (e.g., Wang et al., 1994a, 1995; Curran et al., 1996; Badiani et al., 1998; Uslaner et al., 2001).

Some of these cortical effects may be a consequence of drug action directly in the cortex. However, consistent with the models of cortico-basal ganglia-cortical circuits (Figure 1B), many of the cortical changes are caused by drug-induced alterations in basal ganglia output as a consequence of changed activity in the D₁ receptor-regulated direct striatal output pathway (for review, see Steiner, 2007). Thus, stimulation of striatal D₁ receptors produces widespread increases in gene expression throughout the cortex (Steiner and Kitai, 2000; Gross and Marshall, 2009; see Steiner, 2007).

True to the loop architecture of these circuits, reentrant activity from the cortex (or thalamus; Cotterly et al., 2007) to the striatum is also important for psychostimulant-induced gene regulation in the striatum. Studies demonstrated that blockade of glutamate (*N*-methyl-D-aspartate) receptors (e.g., Johnson et al., 1991; Torres and Rivier, 1993; Wang et al., 1994a; Hanson et al., 1995) or elimination of corticostriatal afferents (Cenci and Björklund, 1993; Vargo and Marshall, 1995; Ferguson and Robinson, 2004) attenuates psychostimulant-induced gene expression in striatal neurons. Therefore, striatal effects of psychostimulants are a consequence of drug-induced overstimulation of striatal D₁ receptors in interaction with cortical (glutamate) input (Hyman et al., 1996; Wang and McGinty, 1996b).

Other findings demonstrate that psychostimulants engage cortical and striatal nodes of corticostriatal circuits in a coordinated manner; gene induction in cortical areas and in their associated functional domains in the striatum is correlated (Figure 1A; Cotterly et al., 2007; Yano and Steiner, 2005a). Given their role in neuroplasticity, these gene regulation effects indicate coordinated neuroplastic changes in cortical and functionally related striatal areas.

3.3. Molecular effects of repeated amphetamine and cocaine exposure

Repeated psychostimulant exposure produces a variety of neuroadaptations and other neuronal changes in the basal ganglia (e.g., Hyman and Nestler, 1996; Kuhar and Pilotte, 1996; Berke and Hyman, 2000; Nestler, 2001; Kelley, 2004). In this section, we provide a few examples of such molecular changes for comparison with similar changes induced by cognitive enhancers, presented later. These examples involve the same IEG and neuropeptide markers as discussed in the previous sections.

As would be expected for molecular adaptations, changes after repeated treatments occur in the same striatal regions and neurons that display the acute drug effects and are directly correlated in magnitude with that of the acute effects (Steiner and Gerfen, 1993; Willuhn et al., 2003; Unal et al., 2009).

3.3.1. Blunted gene inducibility—One of the best-established molecular consequences of repeated psychostimulant treatment is blunting (repression) of gene inducibility in the striatum. Thus, after repeated treatments, genes are still inducible by a drug challenge, but this induction is typically attenuated compared with acute induction. Such blunting was first demonstrated after repeated amphetamine and cocaine treatment for several transcription factor IEGs (e.g., *c-Fos* and *Zif268*; Hope et al., 1992, 1994; Persico et al., 1993; Steiner and Gerfen, 1993; Daunais and McGinty, 1994; Moratalla et al., 1996a). Other genes are similarly affected—for example, the effector IEG *Homer 1a* (Unal et al., 2009) and the neuropeptide substance P (Steiner and Gerfen, 1993; Jaber et al., 1995).

Blunting of gene induction is long-lasting. A recent study showed marked attenuation in *Zif268* and *Homer 1a* inducibility even 3 weeks after a 5-day repeated cocaine treatment (Unal et al., 2009).

Consistent with a compensatory neuroadaptation, the degree of blunting is directly related to the magnitude of the initial (acute) gene induction in a given striatal region—the greater the induction after the first drug administration, the more blunted the induction after chronic treatment (Willuhn et al., 2003; Unal et al., 2009). Mapping studies showed that repeated cocaine treatment produces the most robust blunting in the dorsal/lateral (sensorimotor) striatum at middle to caudal striatal levels (Willuhn et al., 2003; Unal et al., 2009). [It should be noted, however, that gene induction is not universally blunted in all striatal areas after repeated psychostimulant treatments; in parts of the nucleus accumbens, increased rather than reduced gene induction has been demonstrated in several studies (Crombag et al., 2002; Todtenkopf et al., 2002; Brandon and Steiner, 2003; Cotterly et al., 2007; Damez-Werno et al., 2012).]

Various mechanisms may contribute to blunting of gene induction after repeated drug treatment, some shorter-lasting, some long-lasting. Investigators have proposed systems-level neuroadaptations as well as intracellular (epigenetic) adaptations. Examples are:

1. Given the importance of excitatory inputs for striatal gene regulation, blunted gene induction may partly reflect dampened inputs from the cortex (and/or thalamus), perhaps involving long-term depression-like synapse modifications (see Graybiel et al., 2000; Unal et al., 2009, for discussion).
2. Neuropeptides such as dynorphin modulate dopamine and glutamate input to striatal neurons and thus indirectly also affect gene regulation (Steiner, 2010). For example, acute IEG induction by cocaine and D₁ receptor agonist treatment is inhibited by stimulation of dynorphin (kappa opioid) receptors in the striatum (Steiner and Gerfen, 1995, 1996). Blunting of gene induction may thus at least in part reflect increased dynorphin function and resulting inhibition of dopamine or glutamate action after repeated psychostimulant treatment (as we discuss below).
3. Epigenetic regulation of gene expression involving chromatin modifications (e.g., histone acetylation and methylation) may best explain the endurance of gene blunting (for reviews see Renthal and Nestler, 2008; Caboche et al., 2010). For example, chromatin modification has been shown to contribute to blunting of *c-Fos* expression after repeated amphetamine treatment (e.g., Renthal et al., 2008) and to blunting/priming of *FosB* expression after repeated cocaine treatment (Damez-Werno et al., 2012).

The exact consequences of blunted gene induction for basal ganglia function are unknown. However, the functional integrity of neurons depends on balanced regulation of gene expression because cellular components have limited half-lives and must be replenished. It is assumed that disruption of such homeostatic regulation by psychostimulants results in

deficient neuronal function that contributes to behavioral manifestations of psychostimulant addiction (e.g., Hyman and Nestler, 1996; Nestler, 2001).

3.3.2. Alternative splicing: accumulation of deltaFosB—Another often described molecular change caused by psychostimulants is accumulation of the transcription factor deltaFosB in striatonigral neurons (McClung et al., 2004). DeltaFosB is induced by many manipulations that involve excessive neuronal activation (McClung et al., 2004). DeltaFosB is a truncated isoform of FosB (member of the AP-1 family of transcription factors) that is produced by alternative splicing (Nakabeppu and Nathans, 1991). The truncation renders the molecule highly stable. With repeated drug treatments, deltaFosB accumulates in cells and displaces other members of the AP-1 family from the AP-1 transcriptional complex, thus altering the function of this complex (Nakabeppu and Nathans, 1991; McClung et al., 2004).

DeltaFosB accumulation is well established for repeated amphetamine and cocaine treatments (Hope et al., 1994; Nye et al., 1995; Renthall et al., 2008). A recent mapping study showed increased deltaFosB levels in many striatal regions, with maximal increases in the dorsal/lateral striatum, after repeated cocaine treatment (Sato et al., 2011).

Findings indicate that many genes (e.g., those with AP-1 and CRE binding sites in their promoter) are affected by this abnormal transcription factor; some are activated and some are repressed, depending in part also on the length of the drug treatment (McClung and Nestler, 2003; McClung et al., 2004). For example, deltaFosB action appears to upregulate dynorphin expression (Andersson et al., 1999; but see McClung et al., 2004), while playing a role in blunting of *c-Fos* induction after repeated amphetamine treatment (Renthall et al., 2008).

3.3.3. Increased dynorphin expression—A third widely demonstrated consequence of repeated psychostimulant treatment is increased dynorphin expression in the striatonigral (direct) pathway (Steiner, 2010; Butelman et al., 2012; Yoo et al., 2012). Many laboratories have reported elevated dynorphin mRNA (e.g., Hurd and Herkenham, 1992; Spangler et al., 1993; Steiner and Gerfen, 1993; Daunais and McGinty, 1994; Wang et al., 1994a; Adams et al., 2003; Willuhn et al., 2003) or peptide levels (e.g., Hanson et al., 1987; Li et al., 1988; Sivam, 1989; Smiley et al., 1990) after repeated amphetamine and cocaine treatment. Notably, increased dynorphin expression has also been found in human cocaine addicts (Hurd and Herkenham, 1993; Frankel et al., 2008).

After a single psychostimulant administration, elevated dynorphin mRNA levels persist in the rat for at least 18 to 30 hours (Smith and McGinty, 1994; Wang and McGinty, 1995). Thus, this mRNA accumulates with daily drug treatments. Indeed, after repeated treatment with a dopamine agonist, elevated dynorphin mRNA levels in the striatum lasted several weeks past cessation of the treatment (Andersson et al., 2003). Again, repeated cocaine treatment produces maximally increased dynorphin expression in the dorsal/lateral (sensorimotor) sectors of the middle to caudal striatum (Steiner and Gerfen, 1993; Willuhn et al., 2003).

What is the functional significance of increased dynorphin expression in the striatum? Findings indicate that opioid peptides such as dynorphin (striatonigral neurons) and enkephalin (striatopallidal neurons) act, at least in part, as negative feedback mechanisms (Steiner and Gerfen, 1998) to limit dopamine and glutamate input to these neurons (Steiner, 2010). Repeated excessive activation of these neurons by pharmacological treatments (or other experimental manipulations) is thought to trigger compensatory upregulation of opioid peptide function to counteract the activation (i.e., to act as a “brake”) and maintain systems homeostasis (Hyman and Nestler, 1996).

In the case of upregulated dynorphin function after repeated psychostimulant exposure, it is thus to be expected that during early withdrawal from drug use the “brake” is still on for some time given the relatively long half-life of changes in dynorphin expression. The increased dynorphin signaling would then excessively inhibit inputs to striatal neurons (Hyman and Nestler, 1996; Steiner and Gerfen, 1998; Shippenberg et al., 2007). There is good evidence that increased dynorphin function in this manner contributes to somatic signs of withdrawal such as dysphoria, anxiety, anhedonia, and depression after discontinuation of drug use (Nestler and Carlezon, 2006; Shippenberg et al., 2007; Butelman et al., 2012; Yoo et al., 2012). These effects are thought to contribute to maintenance of drug use or relapse during abstinence.

4. Gene regulation by oral Adderall

The above reviewed effects of amphetamine in animal studies were mostly obtained with intraperitoneal (i.p.) or subcutaneous (s.c.) administration of relatively high doses (~3–10 mg/kg). How relevant are these findings for therapeutic use of Adderall, which involves lower doses and predominantly oral administration?

Psychostimulant effects on gene regulation are dose-dependent. Higher doses produce greater increases in gene expression across a wide range of doses (e.g., Steiner and Gerfen, 1993; Wang and McGinty, 1995b, 1997; Brandon and Steiner, 2003; Chase et al., 2003; Chase et al., 2005a; Yano and Steiner, 2005b). [Occasionally, very high doses have been found to result in attenuated expression (Wang and McGinty, 1995b, 1997), similar to other neuronal effects (e.g., Hanson et al., 2002), possibly due to receptor inactivation (internalization) by the high dose or other mechanisms.]

Gene regulation is also under the control of the drug delivery rate. For example, fast intravenous (i.v.) delivery of a certain cocaine dose (2 mg/kg) produced greater *c-Fos* induction in the striatum than slower delivery of the same dose (Samaha et al., 2004; Samaha and Robinson, 2005). Similarly, with repeated treatment (self-administration model), faster drug delivery produced more robust blunting of *c-Fos* inducibility (Wakabayashi et al., 2010). These enhanced neuronal changes were associated with indices of a greater addiction liability (greater escalation of drug intake and propensity to relapse; Wakabayashi et al., 2010).

Conversely, oral (or intragastric) administration of drugs produces slower (and lower) uptake (Swanson and Volkow, 2003; Kuczenski and Segal, 2005; Yano and Steiner, 2007), which would thus be expected to produce less molecular changes. Few studies have investigated the molecular effects of oral amphetamine administration in a therapeutic dose range. Researchers recently used a model with prepubertal rats to assess whether a low dose (1.6 mg/kg) of orally (p.o.) administered Adderall (mix of D- and L-amphetamine), which resulted in amphetamine levels in the blood close to those of children treated with amphetamine, caused changes in *c-Fos* expression in corticostriatal circuits (Allen et al., 2010). The results showed that despite the low dose and oral route, acute Adderall administration produced significant *c-Fos* induction in the striatum and cortex (Allen et al., 2010). Moreover, repeated treatment (1.6 mg/kg, p.o., once daily for 14 days) resulted in blunting of *c-Fos* inducibility in these brain regions (Allen et al., 2010). An earlier study in adult cats reported that 1 mg/kg (p.o.) of amphetamine induced *c-Fos* in the cortex and striatum (Lin et al., 1996). Consistent with these findings, another study in young rats showed that repeated treatment with a low dose of amphetamine (0.5 mg/kg, s.c., twice daily for 13 days), which resulted in amphetamine plasma concentrations corresponding to the clinical range used in the treatment of ADHD, produced altered dendritic architecture in the prefrontal cortex (Diaz Heijtz et al., 2003).

In summary, the findings obtained with faster administration and higher doses of amphetamine (and cocaine) may be more relevant for abuse of psychostimulants. But the results described above indicate that therapeutically relevant amphetamine doses and routes of administration can produce qualitatively similar molecular changes in neurons of corticostriatal circuits (Carrey and Wilkinson, 2011).

5. Gene regulation by methylphenidate

Methylphenidate, widely used in the treatment of ADHD and other mental disorders, is also popular as a cognitive enhancer (see Introduction). Although methylphenidate has been effective in the clinic for several decades, assessment of its molecular impacts began only about 10 years ago (Yano and Steiner, 2007). Because both clinical and recreational exposure to methylphenidate occurs predominantly in children and adolescents, preclinical studies often focus on the effects in prepubertal/adolescent animals (Yano and Steiner, 2007; Carrey and Wilkinson, 2011; Marco et al., 2011).

Early microarray studies in adolescent rats showed that acute and repeated treatment with 2 mg/kg (i.p.) of methylphenidate altered the expression of more than 2,000 genes in the striatum (Adriani et al., 2006a,b). Similar to other psychostimulants (Section 3), methylphenidate affected genes that encode transcription factors, neurotransmitter receptors, ion channels, postsynaptic density proteins, and other signaling-related molecules as well as many other classes (e.g., molecules involved in cell migration, survival, maturation, and other forms of neuroplasticity) (Adriani et al., 2006a,b; see also Yano and Steiner, 2007; Carrey and Wilkinson, 2011; Marco et al., 2011). Some of the molecular changes persisted well past the termination of the drug treatment, into the adulthood of the animals (Adriani et al., 2006a,b; for similarly long-lasting changes, see Chase et al., 2007; Warren et al., 2011).

Most of these wide-ranging effects will have to be confirmed in follow-up studies; but the effects on the expression of transcription factors/IEGs and neuropeptides in corticostriatal circuits are well established. We summarize these findings here for comparison with the effects of amphetamine and cocaine described above.

5.1. Regulation of immediate-early genes and neuropeptides

The first demonstration of gene regulation by methylphenidate was through oral administration in adult cats (Lin et al., 1996). This study showed that 2.5 mg/kg (p.o.) induced *c-Fos* expression in many brain areas, including the cortex and striatum. The regional patterns were described as “highly similar” to those produced by 1 mg/kg (p.o.) of amphetamine (these doses were compared because of their similar effects on wakefulness). Importantly, the *c-Fos* expression patterns of both drugs were different from those induced by modafinil (5 mg/kg, p.o.), also chosen for a similar waking effect (Lin et al., 1996). This comparison indicates that these regional patterns reflect the pharmacological targets of these drugs rather than their waking effect. Acute *c-Fos* induction by methylphenidate in the striatum (Figure 2B) was confirmed by many subsequent studies in both mice (Penner et al., 2002; Trinh et al., 2003; Hawken et al., 2004) and rats (Brandon and Steiner, 2003; Chase et al., 2003; Chase et al., 2005b; Yano and Steiner, 2005b).

Examples of other IEGs induced in the striatum include the transcription factors *Zif268* (Figure 2B) (Brandon and Steiner, 2003; Yano and Steiner, 2005a) and *FosB* (Chase et al., 2005a) as well as the effector IEGs *Arc* (Chase et al., 2007; Banerjee et al., 2009) and *Homer 1a* (Figure 2B) (Yano and Steiner, 2005a; Adriani et al., 2006a; Cotterly et al., 2007).

A few studies show that methylphenidate also affects neuropeptide markers in striatal output neurons. These studies indicate that methylphenidate increases substance P expression

(striatonigral neurons) (Figure 3) in a manner similar to other psychostimulants, whereas the opioid peptides dynorphin (striatonigral neurons) and enkephalin (striatopallidal neurons) appear to be less affected (Yano and Steiner, 2007).

We directly compared methylphenidate effects on the expression of these genes by monitoring their mRNA levels between 20 minutes and 24 hours after acute injection of methylphenidate (2–10 mg/kg, i.p., adult rats; Yano and Steiner, 2005b) (Figure 3). Similar to the effects of cocaine/amphetamine (see Section 3.1.3), we found that substance P expression increased in many striatal sectors in a dose-dependent and very robust manner, with elevated mRNA levels present within 20 minutes and lasting for more than 3 hours. Conversely, for dynorphin mRNA, we detected a statistically significant, if modest, increase only in two sectors at 1 hour (Figure 3) (Yano and Steiner, 2005b). This latter finding contrasts with studies on amphetamine and cocaine effects, which showed that significantly increased dynorphin mRNA levels are present within 30 minutes (Willuhn et al., 2003), are prominent at 2 to 3 hours (Hurd and Herkenham, 1992; Smith and McGinty, 1994), and last 18 to 30 hours (Smith and McGinty, 1994; Wang et al., 1995) after acute drug administration.

Enkephalin, which is strongly induced, for example, by D2 receptor antagonists (Steiner and Gerfen, 1998), is only moderately affected by acute cocaine and amphetamine treatments (Hurd and Herkenham, 1992; Steiner and Gerfen, 1993; Wang and McGinty, 1995, 1996a). Acute methylphenidate did not produce consistent effects on enkephalin expression (Yano and Steiner, 2005b).

Neurotensin is another neuropeptide expressed in striatal output pathways; it is contained in both types of projection neurons, and its expression is also regulated by D1, D2 and glutamate receptors (see Hanson et al., 1992; Alburges et al., 2011). Its apparent interactions with the mesolimbic and mesostriatal dopamine systems suggest that neurotensin may influence the addictive properties of psychostimulants (cf. Alburges et al., 2011). Both cocaine and amphetamine treatments produce increased neurotensin expression (e.g., Letter et al., 1987; Hanson et al., 1989; Gygi et al., 1994), and a recent study shows that methylphenidate increases neurotensin expression as well (Alburges et al., 2011).

Overall, the molecular effects of methylphenidate described above typically emerged with doses of 2 mg/kg (i.p. or s.c.), and juvenile/adolescent rodents tended to be more sensitive than adults, as is true with other psychostimulants (Yano and Steiner, 2007; Carrey and Wilkinson, 2011).

5.2. Corticostriatal circuits affected

5.2.1. Functional domains of the striatum—To determine which corticostriatal circuits/functional domains are affected by methylphenidate treatment, we first mapped gene regulation throughout the striatum (Yano and Steiner, 2005a,b; Cotterly et al., 2007). We assessed the same 23 striatal sectors (Figure 1A), reflecting specific corticostriatal circuits from the rostral to the caudal striatum, as in our cocaine studies (Willuhn et al., 2003; Unal et al., 2009) to allow direct comparisons. Our findings show that, overall, methylphenidate- and cocaine-induced gene regulation in the striatum display a similar but not identical topography (Figure 2), as follows:

1. Similar to cocaine, methylphenidate produces the most robust changes in gene expression in sensorimotor sectors of the middle and caudal striatum. Maximal effects are present in the dorsal sectors (Figure 2B) that receive the densest input from the medial agranular cortex. However, unlike cocaine-induced gene regulation, which peaks in the postcommissural caudal striatum (corresponding to

the middle-to-caudal putamen) (Willuhn et al., 2003; Unal et al., 2009), methylphenidate-induced gene regulation peaks in somewhat more rostral parts of the sensorimotor striatum (Figure 2B) (Yano and Steiner, 2005a,b; Cotterly et al., 2007).

2. For both drugs, medial and rostral (associative) sectors are also affected to some extent, although they appear to be more changed by methylphenidate than by cocaine (Figure 2).
3. Similar to cocaine (Willuhn et al., 2003; Unal et al., 2009), small or no effects are seen in ventral striatal sectors on all rostrocaudal levels (Figure 2B). In the nucleus accumbens, methylphenidate-induced gene regulation appears even less robust than that induced by cocaine; however, the most prominent effects were again found in the lateral part of the shell (Figure 2B) (Brandon and Steiner, 2003; Yano and Steiner, 2005a,b; Cotterly et al., 2007). Such differential gene regulation between sensorimotor striatum and nucleus accumbens, with pronounced effects in the former and minor or no effects in the latter, was also found by others (neurotensin, Alburges et al., 2011; IEGs, e.g., Lin et al., 1996; Trinh et al., 2003; Chase et al., 2005b).

5.2.2. Striatal cell types and dopamine receptors—The striatal output pathways affected by methylphenidate require confirmation by double-labeling studies, but the robust effects on substance P expression (Figure 3) (Brandon and Steiner, 2003; Yano and Steiner, 2005b) strongly indicate that, in line with other psychostimulants, methylphenidate alters gene expression in neurons of the D₁ receptor-regulated direct pathway (Figure 1B). This conclusion is supported by dopamine receptor antagonist studies showing that blockade of D₁ receptors in the striatum eliminates methylphenidate-induced IEG (Yano et al., 2006) and neuropeptide expression (Alburges et al., 2011). Again similar to other psychostimulants (Ruskin and Marshall, 1994; see Section 3.1.4), D₂ receptor stimulation also appears to facilitate such gene regulation (Alburges et al., 2011).

Consistent with the above findings, a recent study in bacterial artificial chromosome-transgenic D₁- or D₂-EGFP-expressing³ mice found that repeated methylphenidate treatment increased *FosB* expression in neurons of the direct pathway (D₁) but not the indirect pathway (D₂) (Kim et al., 2009). However, dendritic spine densities in the nucleus accumbens were increased in both subtypes of projection neurons (Kim et al., 2009).

Together with the dearth of effects on enkephalin expression (indirect pathway) (Brandon and Steiner, 2003; Yano and Steiner, 2005b; Van Waes et al., 2012a), these findings indicate that methylphenidate may more selectively affect direct pathway neurons than do amphetamine and cocaine (for possible mechanisms, see Van Waes et al., 2012a).

5.3. Relationship between gene regulation in striatum and cortex

As mentioned above, and as with other psychostimulants, methylphenidate produces IEG induction also in other brain areas, particularly the cortex (Figure 2B) (Lin et al., 1996; Chase et al., 2005b; Yano and Steiner, 2005a; Banerjee et al., 2009).

We mapped methylphenidate-induced IEG expression throughout the major functional subdivisions of the rat cortex (22 areas on four rostrocaudal levels; Figure 1A) (Yano and Steiner, 2005a; Cotterly et al., 2007). Our results show that acute methylphenidate induces IEG expression most robustly in the medial agranular (M2; premotor) and cingulate cortex

³EGFP, enhanced green fluorescent protein

(Figure 2B), followed closely by motor and somatosensory areas, with minor effects in the insular cortex (Yano and Steiner, 2005a). Although the overall topography of these methylphenidate-induced cortical changes was thus similar to that of cocaine, the methylphenidate effects tended to spread more into rostral and medial cortical areas (Yano and Steiner, 2005a; Cotterly et al., 2007) than the effects of cocaine (Unal et al., 2009).

Our results indicate that cortical gene regulation by methylphenidate occurs in similar functional domains as IEG regulation in the striatum (Figure 2B). Indeed, our regional analysis determined that these IEG responses were positively correlated between cortical areas and their striatal target sectors, confirming that specific corticostriatal projections are affected (Figure 1A) (Yano and Steiner, 2005a; Cotterly et al., 2007). Cortical IEG regulation was also correlated with striatal substance P and dynorphin induction (striatonigral neurons) but not with enkephalin expression (striatopallidal neurons) (Yano and Steiner, 2005a). These findings thus indicate coordinated methylphenidate-induced neuroplasticity between the cortex and neurons of the direct (but not indirect) striatal output pathway.

5.4. Effects of repeated methylphenidate treatment

5.4.1. Blunted gene inducibility—As discussed in the section on amphetamine and cocaine effects, a well-established neuroadaptation that occurs during repeated psychostimulant treatment is blunting (repression) of gene inducibility. Repeated methylphenidate treatment produces a similar effect. Methylphenidate-induced blunting of gene induction in the striatum has been demonstrated, for example, for *c-Fos*, *Zif268*, *Arc*, and substance P (Brandon and Steiner, 2003; Chase et al., 2003, 2007; Hawken et al., 2004; Cotterly et al., 2007) and can last more than 4 weeks (Chase et al., 2005a). As with repeated cocaine treatment (Unal et al., 2009), the degree of blunting after repeated methylphenidate treatment is directly related to the strength of the acute gene response in a particular striatal region (Cotterly et al., 2007).

Most often gene blunting after repeated methylphenidate treatment has been demonstrated by the (reduced) response to a subsequent methylphenidate challenge. However, given that these drugs share some of their neurochemical effects (see Section 2.1), it is not surprising that repeated methylphenidate pretreatment also results in blunted gene induction by a cocaine challenge (Brandon and Steiner, 2003).

The mechanisms underlying gene blunting by these two drugs, however, may not be identical. For example, repeated cocaine treatment blunted striatal *Zif268* and *Homer 1a* induction to a similar extent (Unal et al., 2009), while repeated methylphenidate treatment (10 mg/kg, i.p., 7 days) produced significant blunting of striatal *Zif268* induction but minimal changes in *Homer 1a* induction (Cotterly et al., 2007).

5.4.2. Alternative splicing: accumulation of deltaFosB—DeltaFosB accumulation in striatal neurons after repeated amphetamine and cocaine treatment is well established (e.g., Hope et al., 1994; Nye et al., 1995; McClung et al., 2004). Repeated methylphenidate treatment also increases levels of FosB immunoreactivity in the striatum and cortex (Chase et al., 2005a,b; Kim et al., 2009). In the striatum, the increased FosB signal was selectively present in striatonigral (D₁) neurons (Kim et al., 2009). This immunoreactivity is thought to reflect deltaFosB (Kim et al., 2009), but this remains to be confirmed.

5.4.3. Increased dynorphin expression—As mentioned above, in contrast to cocaine and amphetamine, a single methylphenidate injection caused only a modest increase in dynorphin expression in the striatum (Yano and Steiner, 2005b). Consistent with this finding, recent studies indicate that repeated methylphenidate treatment also produces more

modest upregulation of dynorphin expression compared with cocaine and amphetamine. For example, a study using reverse-transcription polymerase chain reaction to measure gene expression failed to find altered striatal dynorphin expression after daily methylphenidate treatment with a low dose (2 mg/kg, i.p.; adolescent rats) for 16 days (Adriani et al., 2006a). Another investigation demonstrated that methylphenidate treatment with a high dose (10 mg/kg, i.p.; adolescent rats) once daily for 7 days, which produced robust blunting of IEG and substance P induction, resulted in a significant but more limited (compared with cocaine and amphetamine effects) increase in dynorphin expression (Brandon and Steiner, 2003). A more aggressive methylphenidate treatment (four injections of 10 mg/kg, s.c., over 6 hours) produced increased dynorphin peptide levels (immunoreactivity) in the striatum and substantia nigra 18 hours later (Alburges et al., 2011). This treatment also enhanced neurotensin expression in striatal output pathways (Alburges et al., 2011).

The findings above, together with the unchanged *Homer 1a* regulation (Cotterly et al., 2007), indicate that some genes are less affected by methylphenidate than by cocaine or amphetamine. Below (Section 7) we discuss potential mechanisms underlying these differential effects and possible clinical relevance.

5.5. Gene regulation by oral methylphenidate treatment

Since the first demonstration of gene regulation by methylphenidate through oral administration (Lin et al., 1996), few studies have assessed oral effects (Carrey and Wilkinson, 2011). Given that therapeutic use of methylphenidate typically involves oral administration, a recent study investigated whether oral treatment (in freely moving prepubertal rats) with doses that produced clinically relevant methylphenidate blood levels would alter gene regulation in the striatum (Chase et al., 2007). The results showed that acute administration of 7.5 to 10 mg/kg (p.o.), but not 2.5 to 5 mg/kg, induced robust IEG expression (*Arc*) in the striatum. However, although repeated s.c. injections of 7.5 mg/kg of methylphenidate did cause blunting of *Arc* induction, 14 days of daily oral treatment with this threshold dose did not attenuate *Arc* inducibility (Chase et al., 2007). The investigators did not examine higher doses (or other genes).

Future studies will have to determine whether this effect reflected a qualitatively different potential for neuroadaptations by oral treatment compared with injected methylphenidate, or was, more likely, simply a consequence of slower uptake and too low methylphenidate plasma levels after oral administration of this threshold dose.

5.6. Methylphenidate effects: conclusions

The reviewed findings indicate that methylphenidate, even in therapeutically relevant doses, can produce changes in gene regulation in cortical and striatal neurons that are qualitatively similar to those of cocaine and amphetamine, although some of the investigated genes seem to be less affected. Methylphenidate also appears to alter the same corticostriatal circuits/functional domains; these are mostly sensorimotor and to some degree associative domains. Overall, these findings are consistent with an addiction liability for methylphenidate, if reduced compared with cocaine and amphetamine (Svetlov et al., 2007).

6. Gene regulation by modafinil

Modafinil is a relatively novel agent that promotes wakefulness and is thus widely used to treat excessive daytime sleepiness associated with narcolepsy and other sleep disorders, but it is also gaining popularity as a cognitive enhancer (see Introduction). Its effects on gene regulation have been described in only a handful of studies.

To our knowledge, the first study to indicate such molecular effects showed increased expression of glutamine synthetase, an enzyme involved in brain metabolism, after a single injection of modafinil in rats (Touret et al., 1994). More recently, a gene microarray study identified several molecule classes affected by modafinil, including transcription factors such as *c-Fos* (Hasan et al., 2009), and thus suggested that modafinil exposure may alter various neuronal processes. However, most studies to date have assessed only *c-Fos* expression (*Fos* immunoreactivity) as a marker to identify neuronal systems involved in the regulation of sleep and wakefulness.

The 1996 study by Lin and colleagues showed that in adult cats modafinil (5 mg/kg, p.o.) produced minor *c-Fos* induction in striatum and cortex (i.e., considerably less than induced by methylphenidate [2.5 mg/kg, p.o.] and amphetamine [1 mg/kg, p.o.], despite causing similar wakefulness), but induced pronounced *c-Fos* expression in the hypothalamus and other brain regions (Lin et al., 1996). A study in rats (300 mg/kg, i.p.; Engber et al., 1998) confirmed these effects.

More recent work found *c-Fos* induction by modafinil (75–300 mg/kg, i.p.) in various nuclei from the hypothalamus to the brainstem, but also described considerable induction in the cortex and striatum in mice (Willie et al., 2005; Hasan et al., 2009) and rats (Scammell et al., 2000; Fiocchi et al., 2009). Based on findings with other psychostimulants, which typically show correlated regulation of several genes (Steiner and Gerfen, 1993; Willuhn et al., 2003; Yano and Steiner, 2005a,b; Unal et al., 2009), it is likely that modafinil alters the expression of various genes in concert in these brain regions.

Little is known about regional variations in the cortex and striatum or about the cell types and receptors involved. Given that less than 3% of striatal neurons are interneurons (Oorschot, 2010), it is clear that striatal *c-Fos* induction in these studies also predominantly occurred in projection neurons. In most studies, *c-Fos* induction in the dorsal striatum was abundant, while the nucleus accumbens showed only modest (Willie et al., 2005) or no induction (Scammell et al., 2000; Fiocchi et al., 2009). A recent mapping study in rats used a modafinil dose (10 mg/kg, i.v.) that produced clinically relevant plasma levels and found the most robust increase in *c-Fos* expression in the dorsomedial striatum, with a significant *c-Fos* response also in the nucleus accumbens shell (but not core) and the cingulate cortex (Gozzi et al., 2012).

Based on the mechanisms underlying gene regulation by other dopamine-enhancing drugs, it can be assumed that dopamine receptors are also important for modafinil-induced gene regulation, although this remains to be determined. However, in support of this notion, recent studies showed that D₁ (and D₂) receptors are important for modafinil-induced increases in motivation and arousal (Qu et al., 2008; Young and Geyer, 2010). Future studies will have to elucidate which corticostriatal circuits are affected and identify the mechanisms underlying these molecular changes.

In summary, knowledge on the molecular effects of modafinil in corticostriatal circuits is currently limited, but early findings suggest that this psychostimulant may have the potential to produce effects that are qualitatively similar to those of cocaine, amphetamine, and methylphenidate.

7. Drug interactions: SSRI antidepressants potentiate methylphenidate-induced gene regulation

As discussed, drug-induced gene regulation in neurons critically depends on the neurochemical effects of the drug. In this section we address an aspect of drug treatments

that is often overlooked in the assessment of addiction liability: drug interactions based on the neurochemical effects.

If a combination drug treatment results in altered net neurochemical effects, modified gene regulation and thus presumably addiction liability should be expected. Such drug interactions in gene regulation have recently been shown for methylphenidate and certain prescription medications that modify serotonin transmission. Methylphenidate alone increases dopamine overflow but does not affect serotonin (e.g., Kuczenski and Segal, 1997; Borycz et al., 2008; see Section 2.1) and appears to have a reduced propensity to produce neuroadaptations compared with cocaine and amphetamine. In contrast to methylphenidate, cocaine and amphetamine elevate extracellular serotonin levels as well (Yano and Steiner, 2007). Would a combination treatment of methylphenidate with a drug that enhances serotonin action therefore produce more cocaine-/amphetamine-like gene regulation?

A host of findings support this possibility. For example, studies have shown that serotonin contributes significantly to various behavioral effects of cocaine (for reviews, see Filip et al., 2005; Muller and Huston, 2006; Carey et al., 2008). Similarly, whereas dopamine is critical for cocaine-induced gene regulation in the striatum (see Section 3.1.4), serotonin facilitates such effects (Bhat and Baraban, 1993). Thus, attenuation of the serotonin transmission by transmitter depletion (Bhat and Baraban, 1993), receptor antagonism (Lucas et al., 1997; Castanon et al., 2000), or receptor deletion (Lucas et al., 1997) reduces IEG induction by cocaine in the striatum. Conversely, direct and indirect serotonin receptor agonists increase the expression of IEGs (Li and Rowland, 1993; Torres and Rivier, 1994; Wirtshafter and Cook, 1998; Gardier et al., 2000) and other genes (e.g., Mijster et al., 1998; Morris et al., 1988; Walker et al., 1996) in the striatum.

We therefore investigated whether enhancing serotonin transmission by an SSRI (selective serotonin reuptake inhibitor) antidepressant in conjunction with methylphenidate treatment would modify methylphenidate-induced gene regulation. Our results show that this is indeed the case: adding an SSRI (fluoxetine or citalopram) to methylphenidate treatment potentiates acute induction of IEGs (Steiner et al., 2010; Van Waes et al., 2010), and substance P and dynorphin (but not enkephalin) (Van Waes et al., 2012a) in the striatum (Figure 4). Moreover, repeated treatment with the methylphenidate+SSRI combination produced potentiated blunting of IEG inducibility and increased dynorphin expression (Van Waes et al., 2012b). This SSRI potentiation of methylphenidate-induced gene regulation was present in most striatal sectors (Figure 4B) but was maximal in the lateral sensorimotor striatum (Van Waes et al., 2010; Van Waes et al., 2012a), mimicking cocaine effects. Behaviorally, these SSRIs potentiated methylphenidate-induced locomotion (Borycz et al., 2008) and stereotypies (Van Waes et al., 2010), and produced other behavioral changes (e.g., enhanced sensitivity to cocaine reward and stress-eliciting situations; Warren et al., 2011; see Section 8.1).

The potential significance of these findings relates to the medical use of methylphenidate and SSRIs. SSRIs such as fluoxetine are among the first-line treatments for several depressive and anxiety disorders (Petersen et al., 2002) and are given to millions of patients in the United States alone every year. As discussed, methylphenidate is used both in the treatment of conditions such as ADHD (Biederman et al., 2007; Swanson and Volkow, 2008) and as a recreational drug and cognitive enhancer (Greely et al., 2008; Kollins, 2008; Wilens et al., 2008). The rate of accidental coexposure due to such overlapping drug use/treatments is unclear, but combination therapies of methylphenidate and an SSRI are indicated for several conditions, including ADHD and anxiety/depression comorbidity (Safer et al., 2003; Bhatara et al., 2004; Kollins, 2008). Methylphenidate is also combined with SSRIs as augmentation therapy in major depressive disorder (e.g., Nelson, 2007; Ishii

et al., 2008; Ravindran et al., 2008), as acceleration treatment for SSRIs (e.g., Lavretsky et al., 2003), and as treatment for sexual dysfunction related to SSRIs (e.g., Csoka et al., 2008).

Further studies are necessary to determine how much methylphenidate-SSRI coexposure occurs due to clinical administration or as a result of uncontrolled cognitive enhancer use by patients on SSRIs and whether such coexposure enhances the addiction liability of methylphenidate, as the potentiated gene regulation effects might suggest.

8. Behavioral consequences and clinical considerations

While the potential benefits and ethics of cognitive enhancer use are being debated (e.g., Farah et al., 2004; Greely et al., 2008; Chatterjee, 2009; Harris, 2009; Outram, 2010; Hyman, 2011), developmental neurobiologists and addiction researchers warn that the long-term consequences of protracted use of these psychostimulants, especially during brain development, are hardly understood (e.g., Carlezon and Konradi, 2004; Andersen, 2005; Swanson and Volkow, 2008; Berman et al., 2009) (for reviews of neurobehavioral effects of SSRI exposure during development, see, e.g., Oberlander et al., 2009; Olivier et al., 2011). What are the known behavioral consequences of exposure to psychostimulant cognitive enhancers?

8.1. Findings in animal models

Results from animal studies suggest that repeated psychostimulant exposure during preadolescence and adolescence may predispose the individual to substance use or other mental disorders later in life (Brandon et al., 2001; Bolanos et al., 2003; Carlezon et al., 2003; Wiley et al., 2009). It is clear that methylphenidate, for example, produces behavioral changes in animals that mimic those induced by cocaine and amphetamine (for reviews, see Kollins et al., 2001; Carlezon and Konradi, 2004; Kuczenski and Segal, 2005; Yano and Steiner, 2007). Best established is that, similar to cocaine and amphetamine, repeated methylphenidate pretreatment increases locomotor activity/stereotypy levels induced by a subsequent methylphenidate or cocaine/amphetamine challenge ("sensitization") (e.g., Kollins et al., 2001; Yano and Steiner, 2007).

Conditioned place preference (CPP) and drug self-administration in animals are two behavioral models that rank among the most relevant for addiction research. The CPP model determines the conditioned rewarding effects of a drug by assessing whether an animal seeks out/prefers (or avoids) a specific environment in which it previously experienced this drug (Tzschentke, 2007). Psychostimulants typically produce conditioned preference, although high doses can be aversive. Pretreatment with cocaine, for example, either facilitates (e.g., Shippenberg and Heidbreder, 1995) or attenuates (or even produces aversion in) subsequent preference conditioning by cocaine (Carlezon et al., 2003), depending on factors such as the conditioning dose and the age of the animal during the pretreatment. Methylphenidate alone also produces conditioned place preference (e.g., Meririnne et al., 2001; Zhu et al., 2011), and methylphenidate pretreatment in adult rats enhances subsequent preference conditioning by methylphenidate (Meririnne et al., 2001). In contrast, studies have shown that methylphenidate pretreatment in preadolescent rats (postnatal day [PND] 20–35) produces place aversion or attenuates preference conditioning by cocaine (Andersen et al., 2002; Carlezon et al., 2003; Wiley et al., 2009), similar to pretreatment with cocaine (Carlezon et al., 2003).

The latter findings are sometimes interpreted as indicating a protective effect of methylphenidate pretreatment during development against psychostimulant abuse later in life. However, according to recent research (Wiley et al., 2009; Warren et al., 2011), such early-life exposure may result in behavioral abnormalities suggestive of impaired mood

functions. These include generally decreased responsiveness to rewarding stimuli (similar to anhedonia; Nestler and Carlezon, 2006) and depression-like states (enhanced sensitivity to anxiety- and stress-inducing situations) (Wiley et al., 2009; Warren et al., 2011). Interestingly, combined treatment with SSRIs appears to enhance some and reverse others of these methylphenidate-induced behavioral deficits (Warren et al., 2011).

Most drugs of abuse are also self-administered by animals, and methylphenidate is no exception (Kollins et al., 2001). Pretreatment with cocaine or amphetamine facilitates the animal's subsequent psychostimulant seeking and self-administration (reviewed in Vezina, 2004). This is also the case for methylphenidate. Thus, repeated methylphenidate pretreatment in preweanling (2 mg/kg, PND 11–20; Crawford et al., 2011), adolescent (2 mg/kg, PND 36–42; Brandon et al., 2001), and adult rats (20 mg/kg; Schenk and Izenwasser, 2002) facilitates subsequent cocaine seeking and self-administration. These findings suggest an enhanced risk for psychostimulant abuse in humans after methylphenidate pretreatment (O'Connor et al., 2011).

Future studies will have to clarify whether the apparently contradictory behavioral findings (aversion in the CPP paradigm vs. enhanced drug self-administration) are related to age differences (developmental stage) during drug exposure, specifics of drug treatments (e.g., dose), or other experimental variables. Alternatively, given access to cocaine, such rats may be more likely to seek and consume the drug despite a diminished rewarding effect—a characteristic of compulsive drug seeking, which is thought to be mediated by the sensorimotor striatum (Vanderschuren and Everitt, 2005).

8.2. Findings in human studies

Do human studies support an increased risk for drug abuse/addiction (substance use disorder, SUD) after exposure to medical psychostimulants? This question has been investigated in young ADHD patients. Despite the remarkably consistent results in animal models, early clinical findings remain equivocal. With the possible exception of an increased risk for smoking, such studies indicated that the risk for SUD was unchanged or even decreased after treatment with psychostimulant medications (e.g., Barkley et al., 2003; Wilens et al., 2003; Kollins, 2008).

However, several issues complicate interpretation of these findings. For one, successful control of symptoms in an ADHD patient likely improves the patient's educational and societal functioning, and resulting socioeconomic advantages may outweigh (and mask) a treatment-inherent biological risk. There are also technical issues. For example, (unmedicated) ADHD patients already show an enhanced risk for SUD (comorbidity; Kollins, 2008), which statistically would be expected to increase the variance, thus favoring the null hypothesis. Another caveat is the often early assessment of outcomes in the clinical studies (a few years after treatment onset in young patients), whereas there is increasing evidence that neurobiological manifestations of early psychostimulant exposure may appear only later in life (e.g., Bolanos et al., 2003; Tropea et al., 2008; Warren et al., 2011). Thus, conclusions will have to await follow-up studies at an older age (see also Kollins, 2008; Wilens et al., 2008; Berman et al., 2009, for further discussions). Importantly, similar studies in healthy humans who were exposed to psychostimulants, either due to ADHD misdiagnosis or because of cognitive enhancer use, have yet to be conducted.

The reviewed molecular findings indicate that risks may be more serious for abuse of medical psychostimulants. As discussed, the molecular changes induced by psychostimulants are dependent on dose and route of administration (Yano and Steiner, 2007). Proper medical psychostimulant treatment almost always involves oral drug administration, which results in lower drug levels in the brain (Swanson and Volkow, 2003;

Kuczenski and Segal, 2005; Carrey and Wilkinson, 2011) and thus a lower risk for neuroadaptations. This contrasts with cognitive enhancer use/abuse. For example, studies show that in recreational settings, intranasal use (snorting of ground-up pills) is not uncommon (e.g., 38.1% prevalence in users among college students; Teter et al., 2006), and intravenous administration also occurs (Parran and Jasinski, 1991; Babcock and Byrne, 2000; Barrett et al., 2005; Teter et al., 2006; White et al., 2006; for a review, see Kollins et al., 2001). These latter routes of administration result in exposure to much faster and higher drug peak levels and are thus expected to have a greater potential for inducing maladaptive neuronal plasticity (Samaha and Robinson, 2005) and enhanced addiction liability. Studies in healthy subjects are needed to evaluate the safety concerns related to cognitive enhancer use and abuse.

9. Conclusions

The findings we have summarized show that psychostimulants such as cocaine and amphetamine produce changes in gene regulation in specific corticostriatal circuits. These effects are most robust in sensorimotor circuits (which are implicated in habit formation and compulsive aspects of drug taking), less pronounced in associative circuits, and more modest in limbic circuits (where they are thought to contribute to altered reward processing in addiction). At the cellular level, psychostimulants alter predominantly neurons of the direct striatal output pathway (“Go pathway”), while the indirect pathway is less affected, and those changes appear to depend on the treatment context (i.e., arousal and associated changes in excitatory striatal input). Overall, these findings support the notion that action selection and initiation are compromised in addiction.

Comparative studies on cognitive enhancers (Adderall, methylphenidate, modafinil) show that they can induce largely similar molecular changes in corticostriatal circuits. Moreover, the same functional domains, cell types, neurotransmitters, and receptors appear to be affected. These effects were mostly explored with high drug doses, but qualitatively similar molecular changes were evident with drug treatments that mimicked medical treatments (oral administration and low drug plasma levels), although it is not clear whether these molecular changes are robust enough to alter behavior. Drug levels associated with cognitive enhancer abuse, however, are likely higher and, with protracted use, likely contribute to molecular changes that increase the addiction liability of these drugs. Further research is necessary to resolve these questions.

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Abbreviations

ADHD	attention-deficit hyperactivity disorder
IEG	immediate-early gene
M2	medial agranular cortex
mRNA	messenger RNA
SUD	substance use disorder

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Highlights

Medical psychostimulants (methylphenidate, amphetamine, modafinil) are used as cognitive enhancers

These drugs can alter gene regulation in corticostriatal circuits similar to cocaine

These molecular changes may contribute to the addiction liability of cognitive enhancers

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Figure 1.

Schematic illustrations of cortico-basal ganglia-thalamocortical circuits. **(A)** Striatal sectors used for mapping gene expression and their main cortical inputs (arrows) are shown for frontal, rostral, middle, and caudal levels of the rat forebrain (for details, see Willuhn et al., 2003; Yano and Steiner, 2005a,b). Psychostimulant-induced gene regulation is maximal in the dorsal sensorimotor sectors of the middle and caudal striatum (darkest shading), which receive inputs from the medial agranular (M2), primary motor (M1), and somatosensory (SS) cortex (see Section 3.1.2). Limbic (white), associative (light grey), and sensorimotor sectors (darker grey) are indicated. The scatterplot (inset upper right) displays the association between methylphenidate-induced *Zif268* expression in individual striatal sectors and *Zif268* expression in their indicated cortical input regions (values averaged if more than one input). Values are differences in gene expression between animals sacrificed 40 minutes after methylphenidate administration (5 mg/kg, i.p.) and controls sacrificed immediately after drug injection, and are expressed as the percentage of maximal increase in the striatum (see Yano and Steiner, 2005a). CG, cingulate; I, insular; IL, infralimbic; I/O, insular/lateral orbital; P, piriform; PL, prelimbic. *** $p < 0.001$. **(B)** Direct and indirect striatal output pathways in the cortico-basal ganglia-thalamocortical circuits. Direct pathway (striatonigral) neurons contain mainly D₁ dopamine receptors and the neuropeptides

substance P (SP) and dynorphin (DYN), whereas neurons that give rise to the indirect pathway (striatopallidal neurons) express mostly D₂ receptors and the peptide enkephalin (ENK), in addition to their main neurotransmitter γ -aminobutyric acid (GABA). + and – denote facilitatory and inhibitory, respectively. GLU, glutamate; GPe, globus pallidus external segment; GPi, globus pallidus internal segment; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus

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Figure 2.

Psychostimulant-induced immediate-early gene expression in corticostriatal circuits as determined by *in situ* hybridization histochemistry. **(A)** Cocaine-induced *c-Fos* expression. Top: Film autoradiographs depict *c-Fos* expression in coronal sections from rostral (top), middle (center), and caudal striatal levels (bottom) in rats that received a vehicle injection (control, left halfbrain) or a cocaine injection (25 mg/kg; right halfbrain) and were sacrificed 30 minutes later (Brandon and Steiner, 2003). Striatum (S) and nucleus accumbens (NAc) are outlined in the cocaine-treated animals. Note the considerable regional differences in the *c-Fos* response. Bottom: Time course of cocaine (30 mg/kg)-induced *c-Fos* and *Zif268* expression in the dorsal striatum on the middle level (mean density, expressed as percentage of maximal induction) (Steiner and Gerfen, 1998). Basal expression is indicated by broken lines. **(B)** Methylphenidate-induced gene expression. Top: Film autoradiographs show *c-Fos* (left), *Zif268* (middle), and *Homer 1a* expression (right) at 0 minutes (control, left halfbrain) and 40 minutes (*c-Fos*) or 1 hour (*Zif268*, *Homer 1a*) after methylphenidate injection (MP, 5 mg/kg, i.p.; right halfbrain) (Yano and Steiner, 2005a,b). Bottom: Time course of methylphenidate (5 mg/kg)-induced expression of *c-Fos*, *Zif268*, and *Homer 1a* for the dorsal striatal sector on the middle level (Yano and Steiner, 2005a,b). LS, lateral shell of nucleus accumbens

Figure 3.

Methylphenidate-induced neuropeptide expression. Top: Film autoradiograms depict substance P expression in the middle striatum at 0 minutes (control, left halfbrain) and 1 hour after injection of methylphenidate (MP, 5 mg/kg, i.p.; right halfbrain). Bottom: Time course of methylphenidate (5 mg/kg)-induced expression of substance P (SP), dynorphin (DYN), and enkephalin (ENK) (in percentage of basal expression) for the dorsal striatal sector on the middle level (Yano and Steiner, 2005b). Note that substance P expression increased in 13 of the 23 striatal sectors, whereas dynorphin and enkephalin expression significantly increased in only two and one sector, respectively (values in area of maximal increase are shown here; see Yano and Steiner, 2005b, for details). ** $p < 0.01$, * $p < 0.05$ versus 0 minutes.

Figure 4.

Fluoxetine potentiates methylphenidate-induced gene regulation. **(A)** Film autoradiograms depict expression of *Zif268* in the middle striatum for rats that received a single injection of vehicle (V), methylphenidate (MP, 5 mg/kg), fluoxetine (FLX, 5 mg/kg), or a combination of methylphenidate plus fluoxetine (Van Waes et al., 2010). **(B)** Association between the potentiation of *Zif268* expression (at 40 minutes; Van Waes et al., 2010) and that of substance P expression (at 90 minutes after drug injection; Van Waes et al., 2012a) in the 23 striatal sectors (open diamonds, sensorimotor; full circles, non-sensorimotor; data expressed as percentage of maximal increase). Potentiation is the difference between MP+FLX and MP groups. The potentiation was most robust in sectors of the sensorimotor striatum (open diamonds). *** $p < 0.001$