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Neuroadaptations Involved in Long-Term Exposure to ADHD Pharmacotherapies: Alterations That Support Dependence Liability of These Medications

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Abstract

Repeated administration of addictive drugs causes cellular and molecular changes believed to be the mechanism of pro-addictive behaviors. Neuroadaptations also take place with repeated administration of amphetamine, methylphenidate and atomoxetine, drugs for Attention Deficit Hyperactivity Disorders (ADHD), and it is speculated that these changes may serve as markers to demonstrate the dependence liability of these therapies. In this review, we enumerate the neuroadaptive changes in molecules associated with neuronal signaling and plasticity, as well as neuronal morphology wrought by repeated administration of ADHD medications. We provide the current perspective on the dependence liability of these therapies, and also suggest of some factors that need to be considered in future investigations, so that what is drawn from animal studies would be better consolidated with those known clinically.

Key Words: Neuroadaptations, Amphetamine, Methylphenidate, Atomoxetine, Dependence liability

INTRODUCTION

Substance dependence is one of the most established physiological states following chronic exposure to an addictive drug. It is characterized by a cluster of physio-behavioral and cognitive phenomena which include the persistent desire or unsuccessful efforts to cut down substance abuse, unrestrained drug taking despite harmful consequences, higher priority given to drug use than to other social, recreational activities and obligations, tolerance to the drug's euphorigenic effects and a physical withdrawal state (International Classification of Diseases (ICD)-10).

Measuring the dependence liability of a certain substance is a challenging task as some components of dependence cannot be gauged objectively in the laboratory. Pro-addictive behaviors such as tolerance and withdrawal can be well studied in animal subjects and they have provided us with important information on the effects of drugs on health and long-term consequences of substance use. However, it is difficult to measure the cognitive aspect of dependence (such as drug craving, loss of control and persistent drug use), although this is slowly being addressed by recent neuroimaging techniques (Maganti, 2004). On the other hand, a number of studies have emerged and those investigations center on the molecular and cellular changes in the brain associated with chronic exposure to drugs of abuse. The neuroadaptations identified with repeated drug administration are thought to explain the clinically significant aspects of drug abuse syndromes (Kopnisky and Hyman, 2002).

Of interest in drug addiction studies are investigations which inquire if the standard therapies for the most common neurobehavioral developmental disorder of childhood, Attention Deficit Hyperactivity Disorder (ADHD) (Swanson *et al.*, 1998), also have addiction liability. ADHD, which is also present in adolescent and adult populations, is usually treated with psychostimulants (amphetamines and methylphenidate), and both animal and clinical studies have documented the abuse potential of these substances (for reviews see Kollins *et al.*, 2001; Kollins, 2003; but see also Barkley *et al.*, 2003; Wilens *et al.*, 2003; Evans *et al.*, 2004). This is expected as psychostimulants have profound effects on the brain system responsible for the rewarding efficacy of many drugs (*see below*). Thus, methylphenidate and amphetamines, as they share pharmacological and neurochemical effects like cocaine, have

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been reported to be abused by both healthy and ADHD sufferers (Wilens *et al.*, 2008). On the other hand, ADHD is also treated with a class of drugs, which does not have stimulant properties and devoid of any influence on the brain's reward system (Bymaster *et al.*, 2002; Swanson *et al.*, 2006). By virtue of this property alone, atomoxetine is suggested to be a better ADHD pharmacotherapy (Bymaster *et al.*, 2002; Prasad and Steer, 2008), despite clinical trials documenting its inferiority to amphetamine or methylphenidate in terms of efficacy endpoints (Kemner *et al.*, 2005; Starr and Kemner, 2005; Wigal *et al.*, 2005; Biederman *et al.*, 2006; Faraone *et al.*, 2007; Newcorn *et al.*, 2008). The abuse potential of this compound is not well researched.

Drug addiction or substance dependence is a complex and chronic disease process occurring in the brain modulated by a number of factors which are genetic, developmental and environmental in nature. Despite this complexity and the uniqueness in the neural circuits and molecular targets of the different classes of addictive drugs, it is generally believed that most, if not all of them, activate the mesolimbic dopamine (DA) system which reinforces both pharmacological and natural rewards. The mesolimbic system consists of the dopaminergic neurons in the ventral tegmental area (VTA), and their axonal projections to terminal fields in the nucleus accumbens (NAc) and prefrontal cortex (PFC). The VTA-NAc circuit is of particular importance as it is considered as the key detector of a rewarding stimulus. Accordingly, addictive drugs cause elevation of DA levels in this region, most especially in the shell subregion of the NAc (Chao and Nestler, 2004). It is considered that the neuroadaptive changes in this projection as well as in adjacent neural circuitry mediate the clinically significant aspect of drug abuse syndromes such as tolerance, dependence, sensitization and addiction (Koob *et al.*, 1998; Kopnisky and Hyman, 2002)(Fig. 1). As for psychostimulants, the VTA serves as the primary nucleus at which cocaine and amphetamine activate neurotransmitter pathways that initiate molecular mechanisms (Bonci *et al.*, 2003; Vezina, 2004) while the NAc and the dorsal striatum represent the sites at which molecular adaptations are consolidated following abstinence from drug exposure (Pierce and Kalivas, 1997; Berke and Hyman, 2000; Hyman and Malenka, 2001).

This review focuses on the cellular and molecular changes in certain brain regions produced by chronic administration of ADHD therapies. The neuroadaptive changes in the mesolimbic system are described and they are the information gleaned from years of animal research. This overview places more emphasis on the neuroadaptations caused by the most prescribed stimulant ADHD therapy, methylphenidate (Biederman and Faraone, 2005). Relative to amphetamines, not much is known about the molecular effects of this stimulant therapy. Towards the end of this review, we summarize available literature investigating the neuroadaptive changes associated with repeated administration of the non-stimulant ADHD medication, atomoxetine. Lastly, we mention our viewpoint on the dependence potential of these compounds and recommend some aspects that need to be considered in future research which may facilitate more reliable extrapolations of results in animal studies to those obtained in clinical settings.

MOLECULAR TARGETS OF ADHD DRUGS WHICH MEDIATE THEIR ABUSE LIABILITY

The therapeutic effects of stimulant and non-stimulant ADHD medications are thought to be exerted by their interactions with monoamine transporters, most especially transporters of DA and norepinephrine (NE) (for reviews see Arnsten, 2006; Heal *et al.*, 2009). ADHD is characterized by a dysfunctional cathecholaminergic transmission (Himelstein *et al.*, 2000; Teicher *et al.*, 2000), or perhaps with DA transmission (Goldman-

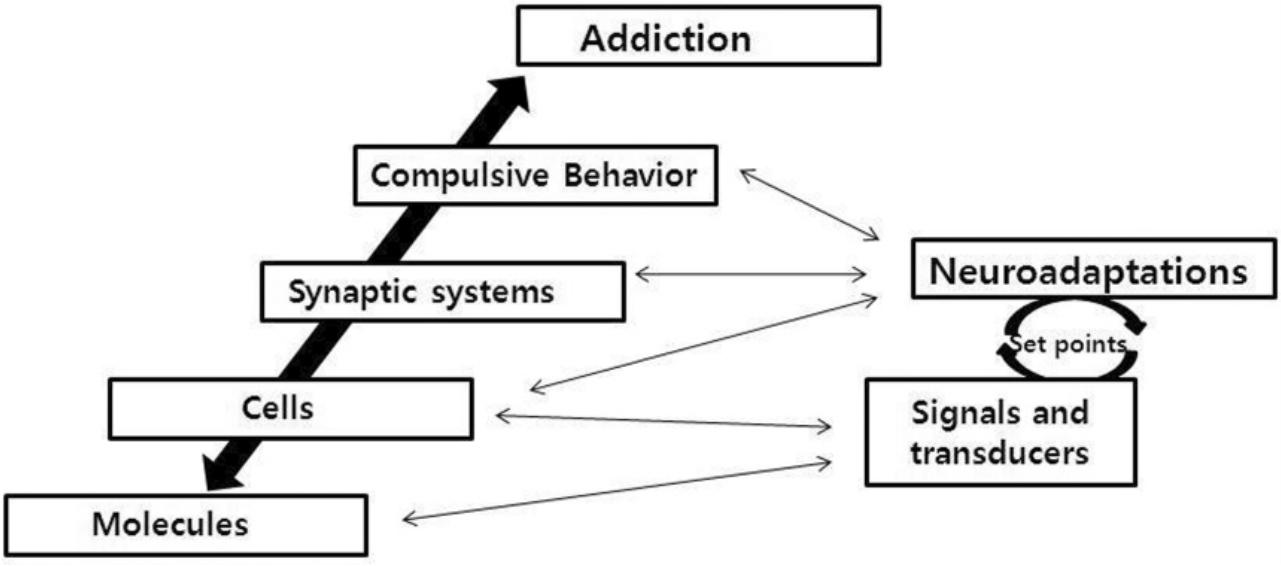

Fig. 1. The role of the neuroadaptive changes in the manifestation of pro-addictive behaviors. Neuroadaptations have long been thought to contribute to compulsive behavior and addiction by acting on the different levels of the spiraling cycle of the development of dependence. Other pro-addiction behaviors (sensitization, tolerance, withdrawal) contribute to changes in hedonic responsiveness and set-points. Reproduced from Koob *et al.*, 1998.

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Rakic, 1996; Volkow and Swanson 2003; Sagvolden *et al.*, 2005b), and ADHD therapeutics may correct this defect by regulating extracellular DA and/or NE concentrations in brain regions associated with motivation, movement and attention (Volkow and Swanson, 2003). Amphetamines, methylphenidate and atomoxetine bind to or block monoamine transporters (DAT and/or NET), inhibit reuptake or stimulate the release of monoamines (DA and/or NE) and thereby increasing their temporal or spatial presence in postsynaptic receptors (Heal *et al.*, 2009). Amphetamines and methylphenidate have strong affinity for both the DA and NE transporters (Arnsten, 2006). Methylphenidate, however, differs from amphetamines as it has low affinity for the serotonin transporter (SERT) (Kuczenski and Segal, 1997; Kankaanpaa *et al.*, 2002). Atomoxetine causes both DA and NE increases in brain cortical regions. However, it is more selective for the NET (Bymaster *et al.*, 2002) than the other transporters. Despite the differences in their properties, the common ground for their therapeutic effects is to facilitate cathecholamine (DA and NE) release in the prefrontal cortex, the brain region mostly associated with the dysfunctions observed in ADHD (Arnsten, 2006).

On the downside, stimulant ADHD therapies can also cause increases of DA levels in the reward-related brain region, the striatum, particularly the NAc (Volkow *et al.*, 1999; Heal *et al.*, 2009). Thus, the abuse liability of these therapies was suspected despite the fact that increase in DA concentrations in striatum can also be attributed for their therapeutic effects (Kiyatkin and Rebec, 1996; Volkow *et al.*, 2003). Indeed, it was demonstrated that high doses of methylphenidate and amphetamines can block the DAT and enhance DA release in the NAc and the dorsal striatum (Kuczenski and Segal, 1997; Segal and Kuczenski, 1999). In human imaging studies, intravenous stimulant administration displaced D2 receptor PET ligands, indicating increased endogenous DA release (Volkow *et al.*, 2002a). The measure of D2 receptor stimulation was reportedly consistent with measures of reinforcement, and it coincided with those found in rodent studies (Volkow *et al.*, 2002b). These information prompted animal studies that determine if low and oral doses of stimulants, corresponding to those given therapeutically in ADHD children would also alter DA release in the NAc. It was found, however, that stimulant medications, given within the clinical range, had little or no effect on DA release in the NAc and that no evidence of sensitization was observed following low-dose chronic usage (Kuczenski and Segal, 2002; Kuczenski and Segal, 2005). This may represent previous clinical investigations detailing that ADHD medications do not cause euphoria and the incidence of drug abuse is reduced in properly medicated ADHD patients (Hechtman and Greenfield, 2003; Katusic *et al.*, 2005). However, a recent clinical survey has reported that stimulant ADHD medications are being abused, not only by "healthy" individuals, but also by ADHD patients themselves (Wilens *et al.*, 2008). It is therefore reasonable to doubt that animal studies conducted in the past have limitations such that results obtained in those work do not harmonize with what is known clinically. Thus, some of the present challenges involve identifying the flaws of previous investigations, and finding out more effective strategies that would better bridge animal and clinical research.

NEUROADAPTATIONS WITH REPEATED ADMINISTRATION OF ADHD THERAPIES

One way to explore if ADHD therapies may cause behavioral responses reminiscent of substance dependence is to compare the neuroadaptations that take place with repeated administration of these drugs to those of other drugs of abuse (cocaine, methamphetamine, etc.). However, we are cautioned not to fully rely on this kind of characterization as identification/comparison of the neuroadaptations alone does not provide us with steadfast evidence to support "dependency" claims (See and Kalivas, 2008). It is said that the functional changes with chronic administration of addictive drugs are "transient" and may not explain the persistent behavioral changes during the addiction process. On the contrary, some argue that the neuroadaptations may serve as a "molecular switch" that may trigger other alterations which are responsible for the maintenance and expression of addiction-related behaviors (White and Wolf, 1991; Hyman and Malenka, 2001; Nestler, 2001). Thus, there is necessity in identifying those changes in drug addiction studies.

Table 1. Neuroadaptive changes following repeated administration of methylphenidate and atomoxetine

ADHD drug	Neuroadaptations
Methylphenidate	In the mesolimbic DA system: transcription factors
	Induction of c-fos expression (Chase *et al.*, 2003; 2005a; 2005b)*+
	Increased delta FosB expression (Chase *et al.*, 2005a; 2005b)*+
	Induction of zif268 expression (Brandon and Steiner, 2003; Cotterly *et al.*, 2007)*+
	Increased basal levels of CREB mRNA and CREB protein levels (Adriani *et al.*, 2006; Andersen *et al.*, 2002)*+
	In opioiod peptide system
	Induction of substance P expression (Brandon and Steiner, 2003)*+
	Induction of dynorphin expression (Brandon and Steiner, 2003)
	In glutamate neurotransmitter system and postsynaptic density-associated proteins
	Increased GluR2/3 expression (Andersen *et al.*, 2002)+
	Elevated Homer1a, Homer1b and Shank2 (Adriani, *et al.*, 2006; Cotterly *et al.*, 2007)*
	In synaptic structures
	Increased dendritic spine density (Kim *et al.*, 2008)*
Atomoxetine	Induction of c-fos expression (Koda *et al.*, 2010)
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*Alterations similar with repeated amphetamine and/or cocaine treatment, +Drug at clinically relevant dose range.

In the succeeding sections, we state the neuroadaptations that have been identified with repeated administration of ADHD therapeutics (Table 1). More emphasis would be given to the functional changes associated with methylphenidate, the most commonly used ADHD medication.

AMPHETAMINE AND METHYLPHENIDATE

Functional changes in the mesolimbic DA system: effects on transcription factors

The mesolimbic DA system is the site of potentiation for the reinforcing effects of many addictive drugs. It is also the brain circuitry that mediates the behavioral responses to repeated exposure to drugs of abuse and therefore, is highly subjected to a variety of functional adaptations (Nestler, 1996). Potentiation of DAergic neurotransmission in this system, especially projections from the VTA to the NAc explains the mechanism underlying acute, reinforcing activities of psychostimulants (for review see White and Kalivas, 1998). The functional alterations with acute exposure to psychostimulants have been reviewed by White and Kalivas (1998). Accordingly, stimulants, acting via the D1 family of receptors, modulated by D2 type receptors (Steiner and Gerfen, 1993; Volkow *et al*., 1999) and in association with glutamate inputs (Vanderschuren and Kalivas, 2000; Everitt and Robbins, 2005; Steketee, 2005; Kalivas and O'brien, 2008), trigger the phosphorylation of cyclic AMP response element-binding protein (CREB) and the expression of a number of immediate early genes (IEGs) such as *c-fos*, *c-jun* and *jun-B* within medium striatal neurons (*for reviews see* Self and Nestler, 1995; Hyman,1996). CREB phosphorylation results to the enhancement of its ability to regulate gene transcription at specific DNA sequences (cAMP response elements or CRE). Induction of IEGs can lead to the formation of homodimeric or heterodimeric complexes which bind to activating protein-1 (AP-1) sites, the known DNA regulatory sequences (Self and Nestler, 1995). It has been asserted that the induction of these functions may have relevant roles in the initiation and maintenance of addictive states as they are crucial for many forms of neuroplasticity (*see below*).

Repeated administration of psychostimulants like cocaine and amphetamines alter significantly DA neurons in the VTA (White and Kalivas, 1998). Among the neuroadaptions are DA autoreceptor subsensitivity (White and Wang, 1984; Ackerman and White, 1990; Gao *et al*., 1998), reduction of inhibitory G protein levels (Nestler *et al*., 1990; Striplin and Kalivas, 1997), enhanced basal levels of extracellular DA (Kalivas and Duffy, 1998), enhanced sensitivity of AMPA receptors on VTA DA neurons (White *et al*., 1995; Zhang *et al*., 1997) and increased tyrosine hyroxylase (TH) expression (Sorg *et al*., 1997). TH is the rate-limiting enzyme in DA synthesis. Overall, these functional changes cause enhancement of the basal activity of DA neurons, altering the mechanisms involved in DA release and post-synaptic DA receptor sensitivity. In the NAc, DA receptor affinity and density are seldom altered with chronic stimulant administration. Nevertheless, there is an upregulation of both adenyl cyclase (AC) and protein kinase A (PKA) systems which may result to a wide array of intracellular cascades relevant to the addiction process (White and Kalivas, 1998).

On the other hand, chronic stimulant exposure, contrasting the effects of acute stimulant exposure, is associated with decreased induction of transcription factor genes (Hope *et al*., 1992; Steiner and Gerfen, 1993). For example, the induction of *c-fos* expression in the striatum is blunted after repeated cocaine challenge although this is not observed in some parts of the NAc and the cortex (Brandon and Steiner, 2003; Cotterly *et al*., 2007). Chronic stimulant treatment however, triggers the production of a truncated form of *FosB*, the delta *FosB*, which is implicated in the manifestation of behavioral sensitization and in long-term adaptations underlying addiction that persists through withdrawal (Hiroi *et al*., 1997). This neuroadaptation is also observed with repeated administration of other addictive drugs (opioids, etc). Delta *FosB* regulates the expression of GluR2, which is specific to the NAc and sensitive to DA (Todtenkopf *et al*., 2006), and cyclin-dependent kinase 5 (Cdk5), which is responsible for desensitization of the neuron to DA (Norrholm *et al*., 2003). Cdk5 has also been implicated in the induction of dendritic spines in the NAc neurons (Robinson and Kolb, 1997). Cocaine-induced dendritic spine formation in the NAc (*see below*) is associated with strengthening of synapses and perhaps sensitized behavioral responses to cocaine (Chao and Nestler, 2004).

Acute exposure to methylphenidate also causes induction of transcription factor genes comparable to the effects of amphetamines and cocaine. The effects of methylphenidate, consistent with the effects of other stimulates, were more profound in the young vs adult animals (Andersen *et al*., 2001). It was first demonstrated that acute oral administration of methylphenidate (2.5 mg/kg) increases *c-fos* protein levels in the striatum of cats (Lin *et al*., 1996). Later, it was shown that acute methylphenidate also induced *c-fos* mRNA or *Fos* expression in rats (Brandon and Steiner, 2003; Chase *et al*., 2003; Yano *et al*., 2005a). Expression of other transcription genes such as *FosB* (Chase *et al*., 2005a) and *zif268* (Brandon and Steiner, 2003; Yano *et al*., 2005a; Yano *et al*., 2006) in the striatum were also observed with acute methylphenidate administration. These effects were mediated by the D1 receptor similar to the effects of cocaine and amphetamine (Yano *et al*., 2006). In addition, expression of these transcription factors was also observed in the cortex (Lin *et al*., 1996; Chase *et al*., 2005a; Yano *et al*., 2005a; Yano *et al*., 2006) and in the NAc (Brandon and Steiner, 2003; Chase *et al*., 2005a; Yano *et al*., 2005b). These neuroadaptations were brought by intraperitoneal (i.p.) or subcutaneous (s.c.) administration of methylphenidate at therapeutically relevant doses (2 mg/kg) and higher.

Repeated methylphenidate exposure also caused a variety of neuroadaptive changes similar with other psychostimulants (for review see Yano and Steiner, 2007). Induction of *c-fos* and *zif268* expression in the striatum (Chase *et al*., 2003; Chase *et al*., 2005b; Cotterly *et al*., 2007) is decreased a day after repeated methylphenidate administration. Conversely, increased gene induction was observed in some parts of the NAc (Brandon *et al*., 2003; Cotterly *et al*., 2007) and the cortex (Cotterly *et al*., 2007). Also, basal CREB mRNA levels in the striatum (Adriani *et al*., 2006) or CREB protein in the NAc (Andersen *et al*., 2002) were increased in adult rats treated with methylphenidate during their adolescence. Delta *FosB* was also expressed in the striatum and cortex with chronic methylphenidate treatment (Chase *et al*., 2005a; Chase *et al*., 2005b) indicating possible delta *FosB* accumulation. Altogether, these results demonstrate that methylphenidate-induced neuroadaptations are similar to that of cocaine and amphetamine (Yano and Steiner, 2007).

Activation of other neurotransmitter systems and cellular signaling molecules

Aside from the mesolimbic DA system, drug-induced changes can also happen in other neurotransmitter systems, which appear to be activated only during chronic psychostimulant exposure (Koob *et al.*, 1998). As stated previously, chronic treatment of psychostimulants upregulates the cAMP-PKA transduction system and this upregulation alters many target genes that contain CREs, including those that encode the neuropetides prodynorphin and protachykinin (Hyman, 1996). In the dorsal and ventral striatum, the levels of dynorphin and *substance P* peptides are significantly elevated following administration of psychostimulants cocaine and methamphetamine while enkephalin levels are subtly affected (Steiner and Gerfen, 1998). Increases of dynorphin levels in the NAc, decreases DA release via presynaptic action on *k* opioid receptors, and therefore opposes the effect of cocaine on reward (Hyman, 1996; Koob *et al.*, 1998). In humans, this phenomenon brings behavioral alterations such as dysphoria, anhedonia and strong drug craving. These behavioral responses are similar to those seen with administration of drugs that act on the *k* opioid receptors (Kopnisky and Hyman, 2002). Increase in *substance P* expression is also implicated in the sensitization process and may contribute to vulnerability to addiction or relapse, although these effects are only compelling in opioids but not with psychostimulant exposure (*for review see* Commons, 2010).

Exposure to methylphenidate causes changes in *substance P* expression in the striatum but it does not significantly alter dynorphin and enkephalin levels (Yano *et al.*, 2005b). *Substance P* expression was, however, blunted with repeated methylphenidate, an effect that can also be observed with repeated cocaine and amphetamine treatment (Steiner and Gerfen, 1998). Methylphenidate (10 mg/kg, adolescent rats administered for 7 days) modestly changed dynorphin levels (Brandon *et al.*, 2003) and did not cause any change in enkephalin expression (Brandon and Steiner, 2003). By contrast, dynorphin and enkephalin levels were elevated with repeated cocaine or amphetamine treatment (Steiner and Gerfen, 1993; Daunais and McGinty, 1994; Spangler *et al.*, 1997; Willuhn *et al.*, 2003) although enkephalin levels were not drastically changed (Spangler *et al.*, 1997).

Repeated psychostimulant administration also enhances expression of glutamate receptor (AMPA and NMDA) subunits (Vanderschuren and Kalivas, 2000; Everitt and Robbins, 2005; Steketee, 2005; Kalivas and O'brien, 2008). In addition, chronically-administered stimulants enhance sensitivity of AMPA receptors on VTA DA neurons (White *et al.*, 1995; Zhang *et al.*, 1997). Transient increases in the glutamate receptor GluR1 subunits in the VTA are important for the expression of behavioral sensitization (Carlezon and Nestler, 2002). Glur2, which is specific to the NAc, is also implicated in sensitization by virtue of its sensitivity for DA (Todtenkopf *et al.*, 2006). Also, NMDA receptors within the NAc modulate the rewarding effects of cocaine as demonstrated in previous studies (Pulvirenti *et al.*, 1992, 1994). Indeed, repeated administration of cocaine increases the capacity of cocaine to elevate extracellular glutamate NMDA receptors within the NAc and VTA that seems to coincide with the time course for behavioral sensitization (Pierce *et al.*, 1996; Reid and Berger, 1996; Kalivas and Duffy, 1998). In case of amphetamine administration, elevated levels of glutamate in VTA and NAc are also observed. However, these do not correlate with the time course of sensitization, or appear to be delayed (Xue *et al.*, 1996). Chronic methylphenidate enhances phosphorylation of glutamate receptor as well as other receptor systems. The acute effects of methylphenidate on glutamate receptor have been reviewed by Yano and Steiner (2007). In contrast with the other stimulants, methylphenidate increases Glur2/3 but not GluR1 protein levels in the NAc of adult rats, 3 weeks after 16 days of treatment (2 mg/kg dose) and this effect was observed in adults but not in adolescent rats (Andersen *et al.*, 2002).

The activity-dependent expression of IEGs more closely related to synaptic activity is also upregulated with repeated stimulant administration (See and Kalivas, 2008). The most characterized are the scaffolding proteins belonging to the Homer and Shank families (Xiao *et al.*, 2000; Thomas, 2002). Accordingly, these proteins anchor glutamate and other receptors to postsynaptic density and are involved in calcium signaling, receptor trafficking, and other functions of synapse structuring (Xiao *et al.*, 2000; Thomas, 2002). Repeated administration of methamphetamines elevates Homer1a levels although not parallel to the development of behavioral sensitization. However, it was also demonstrated that repeated methamphetamine increased NAc protein expression of the different homer isoforms even at 3 weeks withdrawal from repeated methamphetamine treatment. Thus, it was suggested that methamphetamine-induced changes in NAc homer protein expression may be involved in the enduring changes in behavioral sensitivity (Szumlinski *et al.*, 2008). In contrast, it was also assumed that chronic drug-induced downregulation of the homer gene family may also cause sensitization more so if this event takes place in the NAc. Cocaine, given repeatedly (25 mg/kg, 5 days) significantly reduced homer 1a expression as compared with acute cocaine exposure (Unal *et al.*, 2009). As reviewed elsewhere (Yano and Steiner, 2007), repeated administration of methylphenidate upregulated homer1a expression in the striatum and in the cortex in adolescent rats. Repeated methylphenidate treatment also enhanced expression of homer 1a, shank2 and other scaffolding proteins (Xiao *et al.*, 2000; Thomas, 2002). In some studies, however, methylphenidate treatment (10 mg/kg, 7 days) did not significantly blunt homer 1a induction, contrasting the effects of chronic cocaine treatment (Cotterly *et al.*, 2007).

Alterations in synaptic structures

In addition to changes in transcriptional events as well as signaling pathways, repeated stimulation of the D1 receptors may also alter neuronal morphology of cortical and striatal cells due to drug-induced interactions with a variety of factors. Recruitment of the glutamatergic input into the striatum is thought to modify synaptic density (See and Kalivas, 2008). Interestingly, changes in synaptic density lasts for up to 1 month and these contribute significantly to long-term behavioral changes after chronic drug exposure (Robinson and Kolb, 2004). It was initially thought that increase in spine density with repeated administration of psychostimulants might be directly related to altered neuronal plasticity and therefore, in altered behavior (Robinson and Kolb, 2004). It has been demonstrated that cocaine increases spine density. Cocaine-induced increases in spine density is associated with its ability to produce robust increases in actin cycling, as measured by elevations in F-actin in the presence of increased actin disas-

Box 1. Spontaneously Hypertensive rat: the most validated animal model of ADHD

Attention Deficit Hyperactivity Disorder (ADHD) is a complex neurodevelopmental disorder characterized by the core symptoms such as hyperactivity, inattention and impulsivity (Himelstein *et al.*, 2000). It is considered as the most commonly diagnosed disorder of childhood (Swanson *et al.*, 1995) and it is also present in about 4-9% of youths and 4% of adults (Faraone *et al.*, 2005). A number of animal models for ADHD have been proposed and discussed (for reviews see Kostrzewa *et al.*, 1998; Russell *et al.*, 2005; Sagvolden *et al.*, 2005a; van der Kooij and Glennon 2007; Kim *et al.*, 2008). They range from those that are reared in social isolation, separated from general population, exposed to environmental toxins (alcohol, nicotine, lead, polychlorinated biphenyl (PCB) or neonatal anoxia, rats that have undergone hippocampal x-irradiation in infancy or neurotoxin brain lesions (6-Hydroxydopamine, 5,7-DHT), cerebellectomized rats, Naples High/Low excitability rats, Wiggling rats, hyposexual rats and knock out (coloboma, DAT,BDNF, Neuropeptide Y2), acallosal and mutant thyroid hormone mice, etc. There are also genetic models including the Spontaneously Hypertensive rat (SHR), bred from the normotensive Wistar Kyoto rat strain, which was initially used as an animal model for hypertension (Okamoto and Aoki, 1963).

It is asserted that the most adequate ADHD animal model is one that fulfills these criteria: face validity (i.e., it should mimic the three core symptoms of ADHD); construct validity (it should conform to an established or hypothesized pathophysiological basis of the disorder) and predictive validity (predict unknown aspects of the neurobiology of ADHD and provide potential new treatment (Sagvolden *et al.*, 2005b; Sontag *et al.*, 2010). By far, the most validated animal model for ADHD is the SHR (but see Sontag *et al.*, 2010). This strain shows several aspects of face, construct and predictive validity, meeting these criteria independent of blood pressure status (hypertension) which is a confounding factor in this animal model.

A look at the Rat Genome Database (2008) introduces us to a number of existing substrains of SHR. Although there is no evidence for substrain differentiation among SHR stocks with respect to phenotype and DNA fingerprints (Sagvolden *et al.*, 2009), a series of thorough validations by Sagvolden and colleagues has identified that the best SHR substrain that represents ADHD is the one obtained from Charles River, Germany (SHR/NCrl). For a reading on the implications and importance of appropriate substrain selection, see Sagvolden *et al* (2009).

sembly due to reduced phosphorylation of cofilin (Toda *et al.*, 2006). This change causes more plastic spine responsiveness to the increased glutamate release associated with repeated cocaine. Amphetamine treatment also altered the morphology of neurons in the NAc and PFC (Beitner-Johnson *et al.*, 1992; Robinson and Kolb, 1999). Exposure to amphetamine produced marked increase in the length of dendrites, in the density of dendritic spines, and in the number of branched spines on the major output cells of the NAc, the medium spiny neurons (MSN) (Li *et al.*, 2003). Chronic administration of methylphenidate also increases dendritic spine density in MSN that expresses the dopamine D1 receptor (MSN-D1) from the core and shell of NAc. It also increases density of MSN-D2 (MSN-expressing dopamine D2 receptors) dendritic spines from the shell of NAc. In contrast, cocaine has been found to increase the density of spines in both populations of MSN from all regions of the striatum (Kim *et al.*, 2008).

It has long been thought that alterations in dendritic morphology may also be brought by some neurotrophic factors (Chao and Nestler, 2004). Neurotrophins mediate plasticity in the adult nervous system via their ability to regulate synaptic transmission as well as maintain growth, survival and differentiation of neurons (Korsching *et al.*, 1993; Lu and Figurov, 1997). Brain derived neurotrophin factors (BDNF) are probably the most characterized and have been implicated in the drug addiction process. It is known that BDNF is generally increased by acute drug administration and appears to undergo further elevation during drug abstinence (Grimm *et al.*, 2003). BDNF mediates cue-induced cocaine craving even after 90 days of withdrawal, probably due to sustained increases in BDNF levels within the VTA, NAc and amygdala (Grimm *et al.*, 2003). For this reason, it is a stable neuroplasticity candidate which may potentiate acquisition and execution of drug-seeking behavior after extended periods of abstinence (Kalivas and O'Brien, 2008). Moreover, BDNF is also involved in the production of behavioral sensitization (Guillin *et al.*, 2001). Administration of amphetamine (0.5 mg/kg, i.p.) induced marked decreases of BDNF mRNA in hippocampal and cortical brain regions of juvenile rats but with significantly less effects in the hippocampus and no effects in the frontal cortex of adult rats (Banerjee *et al.*, 2009). In an experiment by Meredith *et al* (2002), amphetamine (5 mg/kg for 5 days) increased BDNF mRNA in basolateral amygdala and in other brain regions which also participate in drug addiction process. Acute methylphenidate treatment did not change BDNF levels in the corticostriatal circuits (Chase *et al.*, 2007). Repeated methylphenidate treatment (2 mg/kg) in juvenile rats decreased BDNF mRNA in the hippocampus and cortex (Banerjee *et al.*, 2009) contrasting the findings of Chase *et al* (2007). A recent work of Fumagalli *et al* (2010), however, found increased BDNF expression in the NAc and caudate putamen, in adolescent Spontaneously Hypertensive rats (SHR) treated with 14 days of subchronic (1 mg/kg, twice daily) methylphenidate. The SHR is considered as the most validated animal model of ADHD (Box 1).

Neurogenesis, production of new neurons, also causes changes in synaptic morphology. Chronic exposure to drugs of abuse decreases neurogenesis in the subgranular zone of the adult hippocampus, a brain area not only mediating declarative memory but also the acquisition and maintenance of drug-taking behavior (Koob and LeMoal, 2001). It has been shown that methamphetamine decreases neurogenesis in the extended self-administration scheme in rats (Mandyam *et al.*, 2008). In case of methylphenidate, juvenile exposure to methylphenidate did not alter proliferation at any developmental time point but in adult rats, methylphenidate exposure decreased the long-term survival of newborn cells, particularly in the temporal hippocampus (Lagace *et al.*, 2006).

ATOMOXETINE

There are but a few studies which investigated the functional changes associated with repeated atomoxetine treatment. Nevertheless, atomoxetine has been found to be devoid of reinforcing/euphoriant effects in animal models of drug addiction (Wee and Woolverton, 2004; Gasior *et al.*, 2005); and even in clinical trials with drug-experienced human volunteers (Heil

et al., 2002; Lile et al, 2006; Jasinski *et al.*, 2008). Atomoxetine is a specific NE uptake inhibitor in vitro and in vivo and has a relatively low affinity for serotonin (5-HT) and DA uptake processes (Bymaster *et al.*, 2002). It does however, elevate DA levels, but more substantially in the PFC and not in the reward-related brain regions (striatum and NAc) (Bymaster *et al.*, 2002; Swanson *et al.*, 2006; Koda *et al.*, 2010). Acute and chronic administration of atomoxetine (1 mg/kg) increases the expression of *c-fos* in the prefrontal cortex, but not in the striatum (Koda *et al.*, 2010). Subchronic exposure to atomoxetine upregulates BDNF mRNA levels in the hippocampus but not in the striatum or NAc (Fumagalli *et al.*, 2010). Overall, enhanced expression of BDNF and the activity of its signaling pathway promoted by atomoxetine in the PFC is considered beneficial for cellular plasticity and neuronal resilience (Grimes and Jope, 2001).

DO THESE ALTERATIONS SUPPORT DEPENDENCE LIABILITY OF ADHD THERAPEUTICS?

Before an answer to this question can be provided, it needs to be established first and foremost, that the common adaptations with repeated administration of known addictive drugs solely promote the manifestation of addiction-related behaviors. The changes in gene expression associated with at least D1 receptor stimulation, such as upregulation of CREB, Cdk5, dynorphin, etc. appear to compensatory and thus may decrease the efficiency of synaptic transmission (See and Kalivas, 2008). However, drug-induced changes in these processes also lead to the devaluation of natural reinforcers. Thus it can also be asserted that compensatory changes resulting from the process of reducing synaptic efficiency to regulate drug-induced activity also produced behavioral responses that are pro-addictive (See and Kalivas, 2008).

In animal models, repeated methylphenidate treatment produced fewer or partially different molecular changes from those of amphetamine and cocaine (Yano and Steiner, 2007). Methylphenidate-induced changes in some transcription factors were similar with amphetamine, but the drugs did vary in altering the expression of opioid peptides. Cocaine and methylphenidate also differed with the class of spines they increased, and they did so in different brain regions. Thus, it was expected that these drugs would have different effects on the expression of Cdk5 and other delta *FosB* target genes. Methylphenidate also affected neurogenesis and BDNF expression. In terms of BDNF expression, however, there was discrepancy across studies in the rate of BDNF expression, although it was just recently demonstrated in adolescent SHR, a valid ADHD animal model, (Teicher *et al.*, 1995; Pandolfo *et al.*, 2007) that BDNF expression is in fact, evident in the striatum and NAc. This suggests that exposure to methylphenidate during adolescence may produce detrimental effects such as cognitive impairment and depression (Bramham and Messaoudi, 2005) or drug addiction (Meredith *et al.*, 2002).

Available knowledge concerning the effects of chronic and sub-chronic atomoxetine treatment only stated its ability to cause alterations in *c-fos* family of transcription factors, but these changes were not detected in the striatum (Koda *et al.*, 2010). Methylphenidate, while producing behavioral and neurochemical effects similar to amphetamine and cocaine, differs from the latter substances as it has negligible effects on 5-HT neurotransmission. This is regarded as the reason for the lesser and partly different neuroadaptations that it exerts (as compared with cocaine and amphetamine) and therefore, its lower dependence/addiction liability. Additionally, 5-HT is known to be involved in the actions of cocaine on locomotor activity (Herges and Taylor, 1998). It also participates in gene regulation in the striatum (Gardier *et al.*, 2000) influencing in part dynorphin and enkephalin expression (Walker *et al.*, 1996; Mijnster *et al.*, 1998; Horner *et al.*, 2005). Atomoxetine is much more selective for the NET and does not alter 5-HT levels (Bymaster *et al.*, 2002; Koda *et al.*, 2010). Although it does have profound effects on DAT, but it increases DA levels in brain regions not associated with drug-reward. Thus, there are not so many attempts in investigating the reinforcing/rewarding effects of atomoxetine in animal models of addiction. The consensus is that atomoxetine has no abuse liability and this assumption remains unchallenged.

CONCLUDING REMARKS

There seems to be no closure on the debate concerning the abuse potential of ADHD therapeutics (especially stimulant ADHD medication) even when given at therapeutic doses. While animal studies may help resolve the dichotomy, they do not however, provide us with sufficient evidence to fully discount the abuse liability of these compounds. First of all, methodological concerns limit clinical extrapolations of their results as most of those studies were conducted using routes of administration that result in higher peak levels of the drugs (i.p., s.c., and intravenous). Next, there are but a few studies that investigated the long-term effects of these substances and it is possible that different durations of exposure may also produce some behavioral changes or neuroadaptations which may be consistent or different from those observed with repeated administration of typical addictive stimulants (Yano and Steiner, 2007).

At present, quite a number of studies are emerging and it is posited that they may enhance or change our present understanding on the abuse potential of ADHD therapies, as these studies have addressed important issues that were neglected in previous animal studies. Responses to psychostimulants and even susceptibility to them are said to be different in strains (Segal and Kuczenski, 1987; Robinson and Berridge, 1993; Lambert and Hartsongh, 1998; Yang *et al.*, 2003; Amini *et al.*, 2004). In fact, it has been reported in the past that humans display interindividuality in behavioral responses to psychostimulants (Segal and Kuczenski, 1987; Piazza *et al.*, 1989; Hooks *et al.*, 1991). Thus, although still in its infancy, some investigations have been started considering differential response between rat strains representing the normal population (Wistar rats, Sprague-Dawley rats), from those which mimic the behavioral aberrations seen in ADHD, the SHR (*for reviews see* Askenasy *et al.*, 2007; Vendruscolo *et al.*, 2009). The advantage of doing experiments in animal models is that we deal with a simpler system and data obtained from these experiments may be easier to interpret to that of the clinical case (Sagvolden and Sergeant, 1998). Indeed, differential responses to acute and chronic effects of methylphenidate administration were seen in SHR in comparison with other rat strains (Wistar, Wistar Kyoto, SD rats) (Yang *et al.*, 2003). Susceptibility to cannabinoid agonist was also shown to be

strain-different, with the SHR showing increased vulnerability to its rewarding effects compared to Wistar rats (Pandolfo *et al.*, 2007; Pandolfo *et al.*, 2009). In our experiments, we have demonstrated for the first time, the reinforcing effects of methylphenidate in SHR, and this strain responded more for methylphenidate infusions than their Wistar rat counterparts (de la Peña *et al.*, 2010). As mentioned previously, age also affects behavioral responses to psychostimulants. Thus, age-related difference was demonstrated in response to chronic methylphenidate although behavioral sensitization was more pronounced in adult compared to adolescent SHR (Barron *et al.*, 2009). Nevertheless, it is suggested that ADHD-related studies should be conducted in adolescent SHR, a valid ADHD animal model. First of all, ADHD is highly prevalent in adolescent population and if one has to represent this, tests should be conducted in SHR during their adolescence and not in their adulthood. In our experiments, we did find that the rewarding effect of methylphenidate was more manifested by adolescent vs adult SHR (de la Peña *et al.*, 2010). Thus, in view of our findings as well as those of others, it is valid to suggest that future work investigating dependence liability of ADHD drugs should be conducted in adolescent SHR. Initial investigations should focus on demonstrating if the neuroadaptations that take place with repeated administration of ADHD therapies in adolescent SHR are similar or different from what we presently know. Until then, our view on the abuse potential of ADHD therapies would remain unchanged. However, we would not be able to consolidate results from animal and more recent clinical investigations stating the misuse and diversion of stimulant ADHD therapies by both healthy and ADHD sufferers, representing largely, the dependence liability of these substances.

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