Neurosci Bull June 1, 2011, 27(3): 197–214. http://www.neurosci.cn
DOI: 10.1007/s12264-011-1004-x

·Review·

A review of psychostimulant-induced neuroadaptation in developing animals

Normand Carrey[1,3], Michael Wilkinson[2,3]

[1]Department of Psychiatry and [2]Department of Obstetrics and Gynaecology, IWK Health Centre, Halifax, Nova Scotia, Canada; [3]Department of Physiology and Biophysics, Dalhousie University School of Medicine, Halifax, Nova Scotia, Canada

Abstract: The effects of clinically relevant doses of commonly prescribed stimulants methylphenidate (MPH), *d*-amphetamine (*d*-AMPH), and *dl*-AMPH or mixed amphetamine salts (MAS) such as Adderall, on short- and long-term gene neuroadaptations in developing animals have not been widely investigated. In the present review, the effects of oral stimulant administration were compared with those of the subcutaneous or intra-peritoneal route. A selective set of studies between 1979 and 2010, which incorporated in their design developmental period, clinically relevant doses of stimulants, and repeated daily doses were reviewed. These studies indicate that neuroadaptation to chronic stimulants includes blunting of stimulated immediate early gene expression, sensitivity of younger (prepubertal) brain to smaller dosages of stimulants, and the persistence of some effects, especially behavioral neuroadaptations, into adulthood. In addition, oral amphetamines (MAS) have more profound effects than does oral MPH. Further animal developmental studies are required to understand potential long-term neuroadaptations to low, daily oral doses of stimulants. Implications for clinical practice were also discussed.

Keywords: psychostimulants; animal development; gene expression; enduring effects

1 Introduction

Although stimulants have been prescribed for many years for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), their putative long-term impacts on the developing nervous system remain obscure[1]. The last 2 decades have witnessed increased rates of stimulant prescriptions overall, for younger children, for lengthier periods of treatment and with slow-release preparations, offering greater daily extended coverage[2,3]. Moreover, there has been a steep increase in the number of prescriptions for mixed amphetamine salts (MAS) or Adderall, an amphetamine (AMPH)-based preparation, accompanied by a decrease in the number of prescriptions for generic methylphenidate (MPH), or Ritalin[4], although Concerta, a long-acting MPH preparation, has regained a significant share of the long-acting, slow-release stimulant market. However, this transformation in clinical practice occurred largely in the absence of long-term safety studies in children[5] amidst concerns of abuse and diversion of prescribed stimulants[5,6]. Difficulty in diagnosis, including overly inclusive criteria and non-specificity of symptoms in younger children, may result in inadvertent exposure to the long-term effect of psychostimulants[7]. These concerns are in the context of the developing brain sensitive to the changes in its macro- and microenvironments, with brain

Corresponding author: Normand Carrey
Tel: +1-902-4708375; Fax: +1-902-4708937
E-mail: normand.carrey@iwk.nshealth.ca
Article ID: 1673-7067(2011)03-0197-18
Received date: 2011-01-21; Accepted date: 2011-03-15

growth continuing up through the second decade of life[8].

Animal models are used in preclinical trials to test a drug's mechanism of action and its safety, but it has not been standard practice to test critical variables such as the effect of developmental period and/or effect of chronic use on short- and long-term neuroadaptation of gene expression throughout the life span. Research has indicated that chronic exposure to some psychotropics and drugs of abuse leads to permanent neuroadaptation[9], but whether "therapeutic stimulants", given orally at low levels on a chronic basis during developmentally sensitive periods, produce similar changes in animals or humans remains unknown. MPH- and AMPH-based therapeutic stimulants influence the same brain pathways activated by drugs of abuse such as cocaine, although route of administration is a critical variable in determining the abuse potential of a stimulant[10].

The animal studies in which clinically relevant dosages of commonly prescribed therapeutic stimulants (mainly MPH, *d*-AMPH and MAS) were administered chronically during sensitive periods of brain development are reviewed here. By focusing on low-dose experiments, we hope to describe the effects of stimulants on neuroadaptation rather than the toxic effects. The first section reviewed blood levels of therapeutic psychostimulants, i.e. psychostimulants given at lower dosages in animals either orally or subcutaneously, and their correlations to non-toxic neurobiological indices of dopaminergic activity. Subsequent sections reviewed the impact of psychostimulants on immediate early gene activation and downstream pathways involved, changes in the gene pathways accounting for acute and chronic adaptation to different psychostimulants, as well as the link between low-dose psychostimulant administration during pre-/peripubertal periods and acute/long-term behavioral changes throughout the life span. Further research directions relevant to a developmental perspective of stimulant use in growing children and adolescents are suggested.

2 The importance of clinically relevant doses

Recent studies have attempted to use clinically relevant doses judged to be comparable to those used with children. Children with ADHD treated with oral doses of MPH (< 1 mg/kg) via tablet yield peak plasma MPH levels of approximately 4–100 ng/mL (Table 1). For AMPH, a 0.5 mg/kg oral dose yields a blood level of 70 ng/mL among children, and a bolus of Adderall XR between 10–30 mg yields blood levels between 29–89 ng/mL (Table 2).

Adolescent rats given oral MPH (1–3 mg/kg) have serum MPH levels of 7–11 ng/mL to 30–60 ng/mL[11]. Studies in much younger rats[11,12] confirmed and extended the earlier studies (Table 1). Oral administration of MPH (2.5, 5 and 10 mg/kg, single dose) results in serum MPH levels of approximately 30, 150 and 390 ng/mL, respectively[13]. Due to the more rapid metabolism in rats and in younger animals, higher doses of MPH will probably be required to achieve a similar drug effect as that observed in humans[14,15]. The half-life for MPH in rats is 1 h while that in humans is 2–3 h[16].

What is the 'efficacy' of neurotransmitter response to oral MPH in rats? For example, 5 mg/kg of oral MPH is the lowest dose that increases dopamine release in the nucleus accumbens (NAc) of adolescent rats[11] though lower doses (1.0–2.5 mg/kg) can cause secretion of norepinephrine from the hippocampus. Thus, low oral doses of MPH do have significant, albeit brief, biological effects in the rat brain. These authors also reported that 3 treatments with MPH (0.75–3.0 mg/kg), with 3-h intervals, were effective in slightly reducing locomotor activity during the dark (active) phase. Therefore repeated oral doses of MPH in the range of 3.0–5.0 mg/kg might be the threshold of inducing an enduring biological response in rats[17].

There are very few experimental data correlating oral AMPH or MAS administration with blood levels in developing animals. Allen *et al.*[18] determined *d*- and *l*-AMPH levels in rats at postnatal day (PD) 24 given a single oral bolus of 1.6 mg/kg of ADD. *D*-AMPH level peaked at 60 min (212.3 ng/mL) and *l*-AMPH level peaked at the same time (40.6 ng/mL). In younger juvenile rats (PD 10) receiving ADD administration (1.25 mg/kg), *d*-AMPH peaked at 10 min post injection (170.0 ng/mL) whereas *l*-AMPH level peaked at the same time (46.4 ng/mL) (Table

Table 1. Blood levels of MPH

Rats: Injection of MPH				
Age	Dose (mg/kg); Route	Blood level (ng/mL)	Sample time	Reference
Adult	1; i.v.	500	1 h	97
Adult	0.5-5; i.v.	86–1 090	2 h	98
Adult	10; i.v.	6 000	1 h	99
Adult	20; i.v.	6 300	20 min	100
Adult	2, 5, 10; i.v.	1 050, 2 400, 5 400	2 h	101
Adult	7; i.p.	1 000	8 h	102
Rats: Oral treatment with MPH				
Age (days)	Dose (mg/kg)	Blood level (ng/mL)	Sample time	Reference
7	5, 50, 100	144, 1736, 1917	1–3 h	103
70	5, 50, 100; multiple doses	30, 213, 517	30–60 min	
15 & 40	1, 2 ,5	9, 15, 49	15 min	12
24	2.5, 5, 10	30, 150, 390	30 min	13
40	1, 3	9, 30–60	15 min	11
Adult	0.5, 2, 3.5, 5	2–259	15 min	98
Adult	10	300–400	50 min	99
Adult	1	45	10 min	97
Adult	2.5, 10, 40	1.5, 22, 282	30–60 min	104
Pregnant	7, 25, 75	88, 293, 727	30–60 min	105
Monkeys: MPH treatment				
Age	Dose (mg/kg); Route	Blood level (ng/mL)	Sample time	Reference
Pre-adolescent	0.8–32; oral	approx 3.0–80	2 h	106
Peri-adolescent	1.2–1.6 twice per day; 5 d/week; plus challenge 3.0; oral	peak 16	60 min	107
2.5 years	3; i.v.	peak 800	30 min	99
Mice: Oral treatment with MPH				
Age	Dose (mg/kg)	Blood Level (ng/mL)	Sample Time	Reference
Adult	0.75–5.0	approx. 10–70	15 min	108
Adult	3	30	15 min	109
Humans: MPH treatment in children				
Age	Dose (mg/kg); Route	Blood Level (ng/mL)	Sample Time	Reference

Continued

Table 1. Continued

Children	0.34 and 0.65; oral	11 and 20	1.9–2.5 h	110
Children	0.25–0.68; oral	28–35	1–1.6 h	111
Children	0.3; oral	10.8	1.5 h	101
Children	5.9; oral	10	2.5 h	112
Children	0.1–0.6; oral	14–17	2–9 h	113
Youth (16 years)	169 mg/day; OROS	28	4-5 h post OROS	114

MPH: methylphenidate. i.v.: intravenous injection. i.p.: intraperitoneal injection.

2). Overall area under the curve concentrations was similar to the reported values with children[130,131].

The localization of psychostimulant-induced immediate early gene (IEGs such as *c-fos* and *Arc*) expression can be used as an alternative approach to establish an earlier, more sustained biological response to psychostimulants. For example, in young rats, using the effector IEG *Arc* as a functional marker of synaptic plasticity, the threshold dose of oral MPH to elicit an acute biological response was in the range of 7.5–10.0 mg/kg[13]. Similar results were obtained for oral Adderall XR (1.5 mg/kg), with *c-fos* expression as an endpoint[18]. Doses necessary to elicit transient neurotransmitter responses may be lower than doses affecting acute and then chronic IEG activation.

In summary, in addition to developmental age, other factors including metabolic rate, neurotransmitter response, IEG activation, and route of administration need to be taken into consideration in future experiments comparing human stimulant responses to animal responses. Most animal studies to date have used higher than required stimulant doses, making the boundary unclear between toxic and neuroadaptive effects of therapeutic psychostimulants.

3 Dopamine signaling cascade pathways and neuroadaptation in IEGs, transcription factors and peptides

Psychostimulants produce long-term neuroadaptive changes in the cortico-striatal dopaminergic system, the main pathway involved in cognition, movement and reward/punishment[9], pathways believed to be involved in the neurophysiology of ADHD. Psychostimulant-induced changes in many IEGs, transcription factors and peptides are particularly evident in the striatum, with the nigro-striatal pathway constituting approximately 80% of the total dopaminergic projections in the brain[19]. In general, IEGs function to couple short-term cellular signals to long-term changes in function. Subsequently, IEG-encoded proteins regulate downstream expression of various signaling molecules such as substance P, dynorphin, enkephalin, cell cycle proteins, neurotrophins, and amine transporters[20]. Dopamine-modulated transcription factors are also expressed in multiple areas of brain such as cortex and NAc[32] .

IEGs such as *c-fos*, *fosB,* and *Jun* are expressed at low levels in the unstimulated brain, but are induced in response to many external stimuli, such as psychostimulants[21,22]. Expression of the *c-fos* family of transcription factors is widespread and developmentally regulated[23]. AMPH, cocaine and MPH all acutely increase *c-fos* expression, but the level of stimulation decreases developmentally along the stages of weaning, adolescence and adulthood[1]. Our research group compared FOS immunoreactivity (ir) distribution in the striatum of rats at PD 10 receiving MAS injection (1.25 mg/kg) with that of PD 24 rats receiving oral MAS (1.6 mg/kg). We found that the patchy appearance of FOS-ir characteristic of the younger age group disappeared by PD 24[18], which is consistent with the finding of Snyder-Keller and Keller[39]. Thus the effects of stimulants on IEGs appear to be more robust in younger animals, indicating a greater plasticity in this age group, but there are specific developmental periods of expression[18,24]. Other IEGs, such as *Homer 1a* and *zif 268,* show robust cortical and striatal changes after

Table 2. Blood levels of AMPH

Non-human primates: Oral treatment with AMPH			
Age	Dose (mg/kg)	Blood level (ng/mL)	Reference
Adult baboon	0.12–1.0; twice per day; 4 weeks; 3:1 mixture of *d*- and *l*-AMPH	approx 60–160	124
Adult squirrel monkey	0.28–0.68; twice per day; 4 weeks; 3:1 mixture of *d*- and *l*-AMPH	approx 100–200	124
Rats: Injection/Oral AMPH			
Age	Dose (mg/kg); Route	Blood level (ng/mL)	Reference
Prepubertal (PD 25–26)	0.5; s.c.	85	63
Adult	1.5; i.p.	100	125
Adult	5.0; i.p.	675	126
Prepubertal (PD 24–38)	1.6; oral	212 (*d*-AMPH), 40 (*l*-AMPH)	18
Prepubertal (PD 10)	1.25; s.c.	170 (*d*-AMPH), 46 (*l*-AMPH)	18
Humans: AMPH treatment in children			
Age (years)	Dose; Route	Blood level (ng/mL)	Reference
5–12	0.5 mg/kg; oral	70	127
5–12	0.5 mg/kg; oral; sustained release	70	128
7–12	10 mg twice per day; oral bolus Adderall®	53	129
6–12	10, 20, or 30 mg bolus Adderall-XR®	29–89	130
	10 mg; bolus Adderall®	33	
13–17	10–60 mg; bolus; MAS	18–82	131
Humans: AMPH treatment in adults			
Age (years)	Dose; Route	Blood level (ng/mL)	Reference
29–47	0.25 mg/kg; oral *d*-AMPH	peak 50	132
18–55	20 mg bolus; extended-release Adderall®	peak 40	133
18–50	20 mg bolus; Adderall-XR®	43	119
18–55	20, 40 or 60 mg bolus; MAS	32–106	134
21–50	37.5 mg bolus; triple bead MAS	50	135
	25 mg MAS-XR plus 12.5 mg MAS-XR	49	
22–52	70 mg; oral bolus; LDX	60 (intact LDX)	136
		80 (*d*-AMPH)	

PD: postnatal day. s.c.: subcutaneous. i.p.: intraperitoneal. XR: extended-release. MAS: mixed amphetamine salts. *d*-AMPH: dextroamphetamine. *l*-AMPH: levoamphetamine. LDX: lisdexamfetamine dimesylate (Vyvanse®; inactive prodrug converted to active metabolite *d*-AMPH).

MPH stimulation[25]. The effects of stimulants on *Homer 1a* in particular are relevant because this gene is a synaptic plasticity regulator linked to metabotropic glutamate receptors, and the *Homer 1* knock-out mouse has learning deficits and is spontaneously hyperactive[26].

cAMP response element-binding protein (CREB) is, like FOS, a transcription factor crucial for stimulus-transcription coupling in neurons. CREB binds to DNA sequences called cAMP response elements (CRE) and is activated by phosphorylation to increase or decrease the transcription of certain genes encoding growth factors and structural proteins. CREB activation is therefore implicated in long-term changes in plasticity and neuroadaptation to chronic stimulant use[9]. More specifically, one of the target genes of CREB, the *dyn* gene, encodes a peptide dynorphin which is released from NAc neurons and in turn modulates ventral tegmental area (VTA) dopaminergic tone underlying the dysphoria associated with drug withdrawal. The dysphoria or irritability "side effect" experienced during stimulant treatment or as part of the "rebound" when stimulant levels are dropping may be mediated by a similar mechanism.

However, while psychostimulants activate similar pathways, differences do exist among the different compounds. While MPH, AMPH, and cocaine can affect the norepinephrine and dopamine transporter, MPH also has a low affinity for the serotonin transporter[27]. The psychostimulant effects of MPH may involve other neurotransmitter systems such as norepinephrine, serotonin and glutamate[32]. The most critical difference between MPH and AMPH is that AMPH can directly increase the secretion of dopamine from nerve terminals and vesicular stores[28,29]. Also, the chiral properties (pure or mixed isomers) of different families of stimulants including the AMPH, *d*-AMPH, MAS and Vyvanse (lisdexamfetamine dimesylate), and the dopamine transporter (DAT) blockers, racemic MPH and *d*-MPH, are another potential factor affecting dopaminergic neuroadaptation. Most of the current animal psychostimulant studies have been performed with immediate-release MPH. Higher and more sustained daily levels of oral stimulants through compounds with a longer half-life have unknown effects on long-term dopaminergic transmission in the developing brain[5].

4 Effects of psychostimulants on *c-fos* and *fosB* in developing animals: differential effects of MPH, AMPH and MAS

It has been proposed that the IEGs *c-fos* and *fosB* may act as immediate and long-term mediators of adaptation to dopaminergic stimulation, respectively[9,32]. Elucidation of the particular molecular pathways is crucial as similar pathways may be involved in adaptation to therapeutic stimulants or drugs of addiction, such as cocaine.

4.1 *c-fos* changes following chronic MPH treatment In order to simulate long-term drug administration in children, several research groups have investigated the effects of repeated doses of MPH on gene expression in developing animals (in all studies described, the drug was given by injection except where noted otherwise). In contrast to the stimulatory effect of a single injection of MPH, repeated MPH injection (1–2 weeks) blunts IEG expression, an indication of a compensatory neuroadaptive change, as reported in the following studies. In the study of Brandon and Steiner[30], in adolescent rats with repeated treatment of MPH (10 mg/kg, 7 d), cocaine-induced expression of *c-fos* and *zif 268* was attenuated. Similar results (blunted *c-fos* expression) have been obtained by Chase *et al.*[31-33] at a much lower dose (2 mg/kg, 14 d) in prepubertal rats and by Hawken *et al.*[34] in mice. In addition, our studies[31-33] have found that MPH-induced decline in FOS protein production is selective, and occurs in striatum but not in frontal cortex or NAc. This down-regulation of striatal *c-fos* expression remains detectable following MPH challenge in adulthood (30 d following the last MPH injection), indicating not only a heightened sensitivity of the younger brain but also an enduring effect[32,33]. However, the enduring effect occurs only at the higher dosage (10 mg/kg). Thus, prepubertal rats appear to be more sensitive than adults to MPH, as the blunted IEG expression occurred at 2 mg/kg (daily injection for 14 d) compared to the adults where blunting occurred only at 10 mg/kg (daily injection for 14 d).

4.2 Changes of *fosB* expression in response to repeated MPH treatment The significance of this particular IEG

lies in the fact that *fosB* encodes a splice variant, ΔFOSB, which accumulates in rat striatal neurons following chronic cocaine treatment[35]. ΔFOSB is very stable in the brain, with a half-life of 4–7 d[36]. Thus, whereas *c-fos* expression is down-regulated by repeated cocaine treatment, ΔFOSB ir gradually increases in the striatum of adult rats[37]. ΔFOSB is considered to be a "molecular switch" that regulates long-term changes in drug-induced neuroadaptation and may be implicated in the development of addiction following chronic drug exposure to drugs of abuse such as cocaine and AMPH[38]. However, all of these experiments were done in adult animals. Chase *et al.*[32,33] reported that in contrast to the inhibitory effect on *c-fos* expression, FOSB-ir remained elevated in the prepubertal rat striatum following chronic MPH (10 mg/kg, s.c.) treatment. Clearly the dosage by this drug route produces drug levels beyond the therapeutic range, but the implication of ΔFOSB as a molecular switch regulating long-term dopaminergic changes in prepubertal animals receiving psychostimulants requires further investigations.

4.3 Effects of AMPH on *c-fos* and *fosB* expression Little attention has been paid to the possible long-term influence of repeated AMPH on gene expression in the immature brain, though differences through development were observed in response to acute AMPH action. Snyder-Keller and Keller[39] found that acute AMPH (2 or 5 mg/kg) treatment induced FOS-ir in rat striatum at PD 1–7. Andersen *et al.*[24] reported that elevations in striatal and cortical FOS-ir induced by a single dose of AMPH (1 or 5 mg/kg, i.p.) in rats were more significant at PD 21, than at PD 35 or 60. Repeated high doses of injected AMPH (5 mg/kg) elevated levels of FOSB-ir in the striatum and NAc of prepubertal, but not older, mice[40]. Like the findings on MPH, these results imply that the degree and the pattern of expression depend on age and developmental period, with the more immature brain being more plastic in its response.

4.4 Differential effects of acute and chronic oral MPH *vs* Adderall on *c-fos* expression Recent studies have revealed that a single oral dose as low as 1.6 mg/kg of Adderall (MAS) can stimulate *c-fos* expression in the striatum of prepubertal rats compared to the oral MPH dose of 7.5 mg/kg. Cortical *c-fos* expression can be observed at even lower dosages (*e.g.* 0.4 mg/kg) of Adderall, demonstrating a higher sensitivity of cortex compared to the striatal structures[18]. In addition, chronic oral treatment with Adderall (1.6 mg/kg for 14 d) significantly down-regulated *c-fos* expression in the striatum and the cortex of prepubertal rats, which is in contrast to repeated oral MPH (10 mg/kg for 14 d) which did not blunt *c-fos* expression. AMPH-based psychostimulants (such as Adderall and Vyvanse) may have more profound and enduring biological effects by the oral route than does MPH.

In summary, chronic MPH treatment (s.c.) can blunt *c-fos* response in immature (prepubertal) animals at dosages as low as 2 mg/kg. In contrast, repeated MPH treatment may induce an elevation in FOSB, and possibly ΔFOSB, but at higher dosages that may exceed clinically relevant dosages. Expression of *c-fos* may reflect short-term adaptation to excessive dopaminergic stimulation whereas *fosB* expression may be more involved in the long-term changes in neuroadaptation induced by chronic stimulation[38]. Down-regulated striatal *c-fos* expression remained detectable following MPH challenge in adulthood in animals with chronic MPH pretreatment prepubertally, but only at the higher MPH dosage (10 mg/kg, s.c.). Studies comparing the effects of oral MPH and Adderall have detected an acute *c-fos* response to oral MPH at 7.5 mg/kg, but no down-regulation by chronic oral treatment. In contrast, Adderall can stimulate FOS-ir at lower oral doses than MPH and with a greater cortical than striatal sensitivity. Also, striatal *c-fos* expression may be blunted after repeated oral Adderall treatment. These data indicate greater oral acute and chronic effects of Adderall over MPH on *c-fos* expression. A differential effect of oral Adderall on cortex versus striatum at a lower dosage is in line with AMPH effects on cortical noradrenergic re-uptake blockade mechanisms.

5 Psychostimulant-induced changes in expression of IEGs: *Arc*, *Bdnf* and *Nurr1*

Effector IEGs are thought to be closely linked to synaptic plasticity in development[13]. Activity-regulated,

cytoskeletal-associated protein (ARC) and brain derived neurotrophic factor (BDNF), are markers of stimulus-induced synaptic structural modifications[41]. ARC protein and its mRNA are localized to synapses following neuronal activation[42], and maximum levels of ARC expression, localized to dendritic spines and shafts of medium spiny neurons, parallel the peak period of synaptogenesis (PD 15–30)[43], suggesting ARC involvement in striatal neuroplasticity throughout development.

There may be age-related effects of stimulants on *Arc* expression, but more extensive data are needed. We previously found that acute treatment of prepubertal rats with MPH (2 and 10 mg/kg, s.c.) induced increases in *Arc* expression in the striatum and to a lesser extent in the frontal cortex, but chronic treatment (either 2 or 10 mg/kg for 14 d) significantly attenuated ARC protein level in the striatum but not in the cortex[13]. Moreover, after a drug-free period of 4 weeks following the 14-d treatment, down-regulation of *Arc* expression was still observed following a later MPH challenge, indicative of an enduring response, though this was observable only at the high dosage (10 mg/kg).

BDNF provides trophic support for the survival and the differentiation of dopaminergic neurons[44]. Conversely, dopaminergic stimulation increases *Bdnf* expression in striatal and cortical neurons[45], and *Bdnf*, like *Arc*, is implicated in synaptic plasticity[46]. However, not much is known concerning age-related changes in *Bdnf* expression. *Bdnf* mRNA was elevated by cocaine (20 mg/kg) in cortex of adult rats[47], and in striatum of young adult mice following a single dose of methamphetamine[48]. These data implicate psychostimulants as regulators of *Bdnf* expression. Moreover, $Bdnf^{+/-}$ mice are reported to be hyperactive[49], which is confirmed using conditional *Bdnf* (-/-) and *trkB* knockouts[50,51]. Recent studies[52,53] have reported significant (> 30%) down-regulation of *Bdnf* expression in hippocampus and parietal cortex in prepubertal rats given MPH treatment (2 mg/kg twice per day for 14 d). In contrast, Chase *et al.*[13] have reported that neither acute (2 or 10 mg/kg) nor repeated (10 mg/kg for 14 d; s.c.) MPH treatment is effective in significantly altering *Bdnf* mRNA in the striatum or the frontal cortex of peripubertal (PD 38) rats. These findings imply that *Bdnf* expression in the immature brain, and especially in non-striatal areas, might be vulnerable to inhibition by psychostimulants. In addition, MPH and AMPH could affect the developing brain via *Arc*, since BDNF is a major regulator of *Arc* expression[54].

Nurr1, a member of the IEG family, is critical for the development of dopamine neurons[55] and has been implicated in the etiology of ADHD[56]. *Nurr1* is a regulator of the human *DAT* gene[58] and of the dopamine vesicular monoamine transporter VMAT2[59]. Besides, *Nurr1* heterozygous (+/-) mice are hyperactive[57]. *Nurr1* expression is reduced in dopamine neurons of cocaine abusers[60] and in cocaine-treated rats[61]. These data suggest that *Arc*, *Bdnf* and *Nurr1* should be the focuses of future work into possible long-term effects of chronic MPH, *d*-AMPH and MAS on synaptic plasticity and neuroadaptation in the developing brain.

6 Psychostimulant-induced structural modifications in the immature brain

Experiments in preadolescent rats (PD 22–45) revealed that injections of MPH (1 and 5 mg/kg) induced growth of more complex dendritic trees in pyramidal neurons in the cingulate cortex[62]. This is consistent with a previous report[63] that a low dose of AMPH (0.5 mg/kg; s.c.; twice per day) induced increases in dendritic length and in branches of pyramidal neurons in immature rats (PD 22–34). Treatment of younger rats (PD 10, 12 and 14) with a higher dose of AMPH (2 mg/kg, s.c.) induced dendritic growth in dopaminergic neurons of the ventral tegmental area[64].

Gray *et al.*[65] reported effects of MPH (5mg/kg; twice per day; PD 7–35) on dopamine, norepinephrine, serotonin and acetylcholine systems. The medial prefrontal cortex (mPFC) showed a 55% greater immunoreactivity for the catecholamine marker tyrosine hydroxylase (TH), 60% more Nissl-stained cells, and 40% less norepinephrine transporter (NET)-ir density. In the dentate gyrus, MPH-treated rats showed a 51% decrease in NET-ir density and a 61% expanded distribution of the new-cell marker polysialylated form of neural cell adhesion molecule (PSA-NCAM). In medial striatum, TH-ir decreased by 21%, and

in hypothalamus neuropeptide Y-ir increased by 10% in MPH-exposed rats.

In conclusion, these data reveal a marked trophic effect of stimulants in brain areas related to motivated behaviours and cognition. However, it still remains to be determined whether these changes would still be observed using lower, clinically relevant oral doses. Since these are normally developing animals, are stimulants, through their actions on dopaminergic or glutamatergic pathways, prematurely driving preprogrammed synaptic plasticity? In the developing, immature organism, where is the threshold between dopaminergic levels stimulating trophic growth versus psychostimulant effects on neuroadaptive circuitry and their reinforcing properties?

7 Psychostimulant-induced modification of chromatin structure

Another mechanism through which psychostimulants influence gene regulation and neuroadaptation is by modifying chromatin structure via acetylation, methylation and phosphorylation of histones[66]. Acute cocaine may transiently increase striatal histone acetylation at the *c-fos* promoter in adult rats[67], while chronic treatment with AMPH (4 mg/kg, 7 d) induced down-regulation of striatal *c-fos* expression via ΔFOSB and histone deacetylase1[68]. Using adult mice, Shen *et al.*[69] reported that AMPH (2 mg/kg, 8 d) could also elevate histone H4 acetylation. However, an effect of psychostimulants on histone modification in immature brain has yet to be reported. We have recently demonstrated that low doses of Adderall (oral) and MPH (s.c.) stimulate histone acetylation and phosphorylation in immature rat striatum and islands of Calleja (unpublished data). Since environmental influences during development also affect histone modification[70], psychostimulants and environmental factors may interact, and modify neuronal chromatin and hence gene expression, which is an exciting new area of future research.

8 Psychostimulant-induced changes in peptides, neurotransmitters and transporters in dopaminergic pathways

8.1 Striatal peptides Neuropeptides, while co-released with neurotransmitters, have broader regional functions in gene expression, regional blood flow, synaptogenesis, and effects on glial cells, as well as other neuromodulatory functions. Striatal projection neurons under dopaminergic control express several neuropeptides, including substance P, dynorphin (entopeduncular nucleus or substantia nigra of the direct pathway) and enkephalin (globus pallidus or indirect pathway)[71,72]. These peptides may mediate negative feedback loops to regulate excessive dopaminergic striatal output. Up-regulated expression of dynorphin in the striatum is a well established long-term neuroadaptive effect in response to chronic AMPH and cocaine stimulation[30].

Chronic MPH treatment (10 mg/kg, 7 d) followed by a cocaine challenge in adolescent rats (PD 35–42) can result in significant blunting of substance P expression and increased dynorphin levels in the striatum, but no effect on enkephalin[30]. Adriani *et al.*[73] found no change in *dynorphin* gene expression after MPH treatment (2 mg/kg; i.p.) during adolescence (PD 30–46), as detected by microarray or RT-PCR analysis.

Thus, while chronic MPH blunts substance P expression, there seems to be little effect of MPH on dynorphin or enkephalin. It remains to be elucidated whether *d*-AMPH or MAS, especially at low oral doses, affect striatal peptides in the immature brain, but peptidergic pathways may be involved in the psychostimulant-associated dysphoria, a side-effect seen more frequently in younger children.

8.2 Excitatory and inhibitory striatal neurotransmission Glutamate and GABA are the most abundant neurotransmitters in mammalian brain. The functional interaction between dopaminergic and glutamatergic/GABAergic transmission modulates striatal output[74] and synaptic plasticity[75]. Andersen *et al.*[76] reported that MPH exposure (2 mg/kg, i.p., twice daily) during preadolescence (PD 20–35) produced a 50% increase in CREB level at adulthood, but had no effect on the levels of glutamate receptors GluR1, GluR2/3, NMDAR1 and tyrosine hydroxylase in NAc. The microarray studies by Adriani *et al.*[73] revealed that MPH administration (2 mg/kg, 17 d) to adolescent rats (PD 30) up-regulated expression of glutamate (*Grik2*),

serotonin (*Htr7*), adrenergic (*Adr-alpha 1 b*) and GABAergic (*GabRg1* and *GabRg3*) receptor subunits, and this change persisted into adulthood for *Grik2* and *Htr7*. This group further reported that in the MPH-treated adolescents, *Homer 1, Shank 2* and *MPP3* gene expression was up-regulated. These genes are linked to post synaptic density proteins, a network of proteins anchoring neurotransmitter receptors to cytoskeletal elements involved in synaptic plasticity. These reports indicate that further attention should be directed towards elucidating the roles of the therapeutic psychostimulants on glutamate and GABA, important neurotransmitters involved in synaptic plasticity during development.

8.3 DATs The main mechanism underlying the actions of MPH and related compounds is through DAT re-uptake blockade. MPH reduced DAT levels in both human and rodent brains[4,77,78]. Moll *et al*.[79] reported that striatal DAT levels decreased by 25% in MPH-exposed prepubertal rats (aged 25 d; 2 mg/kg, oral; 14 d) and further decreased to 50% by adulthood, one month following cessation of MPH treatment. Feron *et al*.[80] indicated that in children treated for many months with MPH, DAT levels largely returned to normal within 4 weeks following cessation of drug treatment. These studies suggest that MPH down-regulates DAT, presumably a reflection of increased dopaminergic tone, but it is unclear if these changes are permanent.

9 Behavioral paradigms of reinforcing or aversive properties of stimulants: enduring effects into adulthood

Animal behavioral experiments have the advantage of correlating gene expression to the upstream neural loops that underlie behavior. This approach seeks to determine whether early exposure to psychostimulants leads to the reinforcing or aversive properties of the same or a similar drug in adulthood, presumably a marker of enduring neuroadaptation. It is well-established that in adult animals, repeated intermittent exposure to most drugs including psychostimulants causes a phenomenon of sensitization to re-exposure of the drug or what has been termed "exposure-dependent neuroplasticity"[81]. However, it is a relatively new experimental area to correlate exposure to drugs at one developmental stage with a later one through various biobehavioral measures.

Different results have been obtained depending on developmental time of exposure and experimental paradigm. In the study of Brandon *et al*.[82], adolescent rats (PD 35–42) treated with daily, single injections of MPH (2–10 mg/kg; i.p.) had an enhanced sensitivity to cocaine, and an increase in self-administration of cocaine when tested 14 d later. In marked contrast, more recent studies[76,83-87] in younger rats (PD 20–35) using the same MPH treatment (2 mg/kg, twice per day) found that juvenile rats tested later as adults showed an aversion (decreased sensitivity) to cocaine. Further behavioral testing indicated that adult rats exposed to MPH as juveniles displayed profiles of dysphoria and anhedonia indicative of persisting behavioral neuroadaptations. Andersen and colleagues[76] have reported elevated CREB levels in adult rats treated with MPH prepubertally. Since elevated CREB levels are associated subjectively with dysphoria and negative affects via elevated dynorphin as a response to chronic dopaminergic stimulation, this mechanism provides a possible explanation for the biological basis of the enduring behavioral effect.

In contrast, a more extended prepubertal treatment with MPH of juvenile rats (PD 7–35; 5 mg/kg, s.c., twice per day) induced a state of reduced anxiety-like behavior[65]. In addition, 2 studies in mice produced conflicting results. In one study[88], chronic treatment with a high dose of MPH (10 mg/kg, i.p., 7 d) during the prepubertal period (PD 26–32) decreased the rewarding effect of cocaine in adulthood. However, following this cocaine challenge, the mice developed a sensitized response to cocaine-induced reward. In the second study[89], MPH treatment (10 mg/kg) at PD 15–28 did not increase the liability for cocaine abuse in adulthood.

Behavioral effects of MPH treatment (oral) are limited. In the study of Kuczenski and Segal[11], adolescent rats (PD 41–69) given oral MPH treatment (0.75 and 3 mg/kg, 3 times per day) showed no increase in sensitization to methamphetamine challenge. Thanos *et al*.[90] administered MPH in the drinking water of young rats (PD 30; 2-month

or 8-month exposure; 1–2 mg/kg), and found that striatal dopamine receptors were lower at 2 months and higher at 8 months, but no increase in cocaine self-administration was detected after 8 months.

The discrepancies across results of studies may be attributed to the different behavioral paradigms (self-administration *vs* conditioned place preference) or the developmental differences. Moreover, it is still elusive whether intermittent or continuous psychostimulant use by children could exert different enduring effects.

10 Discussion and conclusion

Briefly, the present review can be summarized into the following points. First, the commonly prescribed psychostimulants including MPH, *d*-AMPH and MAS, administered subchronically and chronically in young animals, may produce reliable and measurable neuroadaptive changes in dopaminergic signaling systems. Second, effects of stimulants vary with developmental periods, with the prepubertal brain being more sensitive to stimulants than the adult brain. The peripubertal or "adolescent" brain appears to undergo a transition from pre- to postpubertal functioning. In addition, early exposure to stimulants, especially for prepubertal animals, may produce molecular and behavioral enduring effects that persist into adulthood. Third, there exists a "threshold" for a biological response, below which the gene expression changes are transient. The threshold for a meaningful gene expression change is affected by route of administration. For instance, higher oral doses are required to achieve the same effects as those by intraperitoneal or subcutaneous doses. Fourth, differential effects are observed depending on the type of stimulant (*e.g.*, MAS has a more powerful oral effect compared to MPH), and on the different regions (*e.g.*, cortex more sensitive than striatum).

This review also adds to the growing body of knowledge about the effects of commonly prescribed psychotropics on signaling systems in the developing brain. For example, prepubertal rats treated with fluoxetine have persistently increased density of serotonin transporters in the frontal cortex as adults[91]. Neuroleptics administered to pregnant or nursing rat mothers can induce enduring changes in dopamine receptors of their offspring[92]. Further work showed that if neonatal rats are deprived of dopamine stimulation, they do not show the compensatory increase in D2 receptors seen in adults receiving neuroleptics[93]. Carrey *et al.*[94] have found that juvenile rats react differently to hormone provocation tests probing the developing serotonergic and adrenergic systems compared with the adults. Most recently, Bolanos *et al.*[86] have found that in adult rats, fluoxetine prevents the development of anxiety responses following chronic exposure to MPH as juveniles.

The biological basis of enduring effects of early exposure to stimulants may be subtle, yet permanent, and hence difficult to measure experimentally. One possible mechanism for the long-term enduring effects may be chemical imprinting in a developing brain[1,95] where early drug exposure influences neuronal activity by programming or re-programming the course of development. Imprinting is not necessarily produced by toxic destruction of neurons but influences sensitivity to subsequent drug challenge by redirecting maturation during sensitive periods[1,96]. These neuroplastic changes, initially regulated by transcription factors such as CREB and IEGs in striatal and accumbal neurons, may become chronic through downstream modulation of genes involved in several aspects of neuron functioning such as synaptic plasticity and peptide expression. Chromatin changes, via histone acetylation and methylation, may provide other pathways through which psychostimulants influence long-term changes, and could be either additive or interactive with environmental factors.

11 Implications for clinicians

While psychostimulants may lower the base rate of behavioral symptoms of hyperactivity, inattention and distractibility, clinicians need to weigh risks versus benefits of psychostimulant treatments which may induce long-term modifications of neuroplasticity including neuroadaptive changes in dopamine pathways associated with addictive potential. The current trend of ADHD treatment is to prescribe longer-acting preparations that may attain lower

peak levels but produce residually low but detectable, steady-state blood levels up to 24 h after administration, resulting in continuous drug exposure to some extent[5].

The following areas are examples of how psychostimulant studies in developing animals could help us understand clinical problems of psychostimulant use in humans. The first one is consideration of developmental stage. Since several synaptic plasticity genes (such as *Arc, Bdnf,* and *Homer 1*) have been identified, animal studies could help clarify the effects of oral psychostimulants during periods of intense synaptogenesis. This may lead to a consensus guideline on whether or not to give psychostimulants to patients below a certain age. The second one is consideration of developmental effects of exposure to chronic high levels of oral stimulants. Currently, when children and youth fail to respond adequately to psychostimulant treatment or when tolerance develops, clinicians use their clinical judgement to titrate medication, mostly upwards at times in excess of recommended guidelines, resulting in exposure over long periods of time to high levels of psychostimulants. Experimental studies with immature animals could help establish the neuroadaptive consequences of increasing psychostimulant dosages within the non-toxic range but above recommended guidelines. The third is the imperative for longer daily coverage. Even though there is a clinical logic for having extended coverage within 24 h (*i.e*. beyond school hours and into the evening), long-acting preparations as mentioned above may produce low but residual steady-state blood levels. Animal experiments can uncover the effect of low steady-state blood levels of psychostimulants on clock genes and circadian rhythms. The fourth is drug holidays. Human clinical studies are needed to establish whether long-term (over years) continuous treatments are warranted or whether periodic discontinuation of treatment could recalibrate stimulant-induced neuroadaptations. Animal experiments, manipulating length of treatment, especially across developmental periods, could provide some insights. The fifth is that not all stimulants are created equal. There may be different gene expression pathways with subsequent neuroadaptations based on stimulant preparation, including differences between families of stimulants (direct agonists *vs* DAT blockers) or between the chiral properties of the same drug. Animal experiments could establish the differential molecular neuroadaptive profiles of different stimulants. The sixth is consideration of other neuroadaptive consequences of drug-drug interactions (nicotine, alcohol, marijuana, antidepressants, and antipsychotics). This is a new area of research, and the effects of common therapeutic drug combinations are now under investigation. For example, fluoxetine has been revealed to potentiate the effect of MPH on *c-fos* and *zif 268* in the striatum and NAc, as well as enhance MPH-induced stereotypical behavior[137]. The last one is the drug-environmental interactions. Sophisticated animal models of the impact of environmental factors on genetic pathways in young animals (behavioral epigenetics) are already changing clinical practice[70]. Studies with young animals incorporating the impact of psychostimulants × environmental factors (maternal grooming of offspring) on gene expression pathways could be very rewarding.

12 Limitations

The different methodologies in the studies reviewed, including acute *vs* chronic treatment, different developmental periods, dosage regimens, different routes of administration, lack of serum or plasma levels, as well as individual stimulant pharmacodynamics and kinetics, make comparisons between experiments difficult; hence extrapolation to humans at this point must be cautious. Many of the published studies reviewed here used non-toxic doses but the dosages, especially when administered intraperitoneally or subcutaneously, could produce higher blood levels than the therapeutic range. Furthermore, most of the reviewed studies were done in normal animals since the emphasis of the review was on analyzing the impact of psychostimulants on developmental periods in normal animals. Thus we cannot extrapolate the findings of this review to animal models of ADHD (such as knock-out mice lacking expression of *DAT*, *Homer 1*, *Bdnf* or *Nurr1*).

On a practical level, scientists sometimes face overwhelming obstacles in obtaining several of the marketed

psychostimulants in their pure form (MPH powder, *d*-AMPH or *d*-*l* MAS). For example our laboratory, in an attempt to simulate the *d*,*l* isomers in MAS, faced 2 regulatory agencies, and 2 separate suppliers, with a time line stretching over 2 years. Future studies need to control for developmental period, establish clinically-relevant oral dosing with concomitant determination of blood levels, establish dose-response curves to determine threshold values for gene expression, and determine biobehaviorally-relevant endpoint responses across time. Given the potential long-term neurobiological enduring effects of various psychostimulants, independent animal studies need to become part of the knowledge base for rational decision-making in developmental psychopharmacology.

Acknowledgements: This work was supported by the IWK Health Centre, Nova Scotia Heath Research Foundation (NSHRF), Canadian Institute of Health Research (CIHR), the Atlee Endowment and NRC-Marine Biosciences.

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动物发育过程中施予精神兴奋剂引起的神经系统适应性

Normand Carrey[1,2], Michael Wilkinson[1,2]

[1]IWK 健康中心 , 哈利法克斯，新斯科舍省，加拿大

[2] 达尔豪斯大学医学院，生理学与生物物理学系，哈利法克斯，新斯科舍省，加拿大

摘要：临床相关剂量的处方精神兴奋剂，如苯哌啶醋酸甲酯(methylphenidate, MPH)、右旋/左旋苯丙胺和苯丙胺混合盐制剂(如Adderall)，对动物特别是发育期动物的长、短期神经系统适应性变化的影响已被广泛研究。本文对精神兴奋剂口服给药途径与皮下和腹腔注射途径的效应进行了比较，并对1979–2010年间的一系列研究进行了综述。这些研究大都在动物不同的发育阶段进行，给予药物的剂量与临床剂量相似，每天给药一次重复多天。研究结果都表明，在兴奋药慢性作用下产生的神经适应性变化包括早期快反应基因(immediate early gene, IEG)表达的减弱、较年轻大脑(青春期前大脑)对更低剂量兴奋药的敏感性以及某些效应一直持续至成人期。要了解每天口服低剂量的精神兴奋剂引起的长期神经适应性改变，还需要更多更进一步的动物实验。此外，兴奋性药物导致的神经系统适应性改变在临床实践中值得借鉴。

关键词：精神兴奋剂；动物发育；基因表达；持久效应