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Differential Striatal Spine Pathology in Parkinson's disease and Cocaine Addiction: A Key Role of Dopamine?

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Abstract

In the striatum, the dendritic tree of the two main populations of projection neurons, called “Medium Spiny Neurons (MSNs)”, are covered with spines that receive glutamatergic inputs from the cerebral cortex and thalamus. In Parkinson's disease (PD), striatal MSNs undergo an important loss of dendritic spines, whereas aberrant overgrowth of striatal spines occurs following chronic cocaine exposure. This review examines the possibility that opposite dopamine dysregulation is one of the key factors that underlies these structural changes. In PD, nigrostriatal dopamine degeneration results in a significant loss of dendritic spines in the dorsal striatum, while rodents chronically exposed to cocaine and other psychostimulants, display an increase in the density of “thin and immature” spines in the nucleus accumbens (NAc). In rodent models of PD, there is evidence that D2 dopamine receptor-containing MSNs are preferentially affected, while D1-positive cells are the main targets of increased spine density in models of addiction. However, such specificity remains to be established in primates. Although the link between the extent of striatal spine changes and the behavioral deficits associated with these disorders remains controversial, there is unequivocal evidence that glutamatergic synaptic transmission is significantly altered in both diseased conditions. Recent studies have suggested that opposite calcium-mediated regulation of the transcription factor myocyte enhancer factor 2 (MEF2) function induces these structural defects. In conclusion, there is strong evidence that dopamine is a major, but not the sole, regulator of striatal spine pathology in PD and addiction to psychostimulants. Further studies of the role of glutamate and other genes associated with spine plasticity in mediating these effects are warranted.

Keywords

striatum; cocaine; accumbens; corticostriatal; thalamostriatal; glutamate

1. Introduction

Despite a broad range of experimental evidence showing changes in the density or morphology of spines in a large number of neurological and psychiatric diseases, the exact contribution of spine pathogenesis to disease pathophysiology or symptomatology remains

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poorly understood (Harris and Kater, 1994; Yuste and Denk, 1995; Yuste and Majewska, 2001; Bonhoeffer and Yuste, 2002; Fiala et al., 2002; Robinson and Kolb, 2004; Yuste et al., 2004; Deutch, 2006; Bourne and Harris, 2008; Smith et al., 2009b; Kasai et al., 2010; Van Spronsen and Hoogenraad, 2010; Villalba and Smith, 2010; Kulkarni and Firestein, 2012). Over the past decades, it became clear that striatal projection neurons, the so-called medium spiny neurons (MSNs), undergo complex structural changes in the density, morphology and ultrastructural features of their dendritic spines in animal models of Parkinson's disease (PD) or after chronic exposure to cocaine or other psychostimulants (Table 1). In PD, nigrostriatal dopamine degeneration results in a significant loss of dendritic spines on MSNs of the dorsal striatum (McNeill et al., 1988; Ingham et al., 1989, 1998; Anglade et al., 1996; Stephens et al., 2005; Zaja-Milatovic et al., 2005; Day et al., 2006; Deutch, 2006; Deutch et al., 2007; Villalba et al., 2009; Villalba and Smith, 2010), while rodents chronically treated with dopamine-enhancing drugs such as cocaine and other psychostimulants, display significant increases in spine density on MSNs in the nucleus accumbens (Robinson and Kolb, 1997, 1999, 2001, 2004; Norrholm et al. 2003; Lee et al. 2006; Kalivas 2007a,b; Russo et al., 2009; Shen et al., 2009). Together, these data strongly suggest that the opposite changes in striatal dopamine (DA) release in these disorders may play a major role in mediating differential effects towards spine development, pruning and morphogenesis in striatal projection neurons in PD and addiction to psychostimulants (Arbutnot et al., 1998; Robinson and Kolb, 1999a; Day et al., 2006; Deutch et al., 2007; Surmeier et al., 2007; Villalba et al., 2009; Garcia et al., 2010; Fasano et al., 2013) (Fig. 1). The goal of this review is to examine this issue in more detail, and provide an overall assessment of the morphological and ultrastructural changes of striatal MSNs that have been described in patients and animal models of PD or animals chronically exposed to cocaine, and discuss the possibility that opposite changes in the striatal levels of dopamine may be partly responsible for these structural alterations.

Because of space constraints and limited scope of this review, the data presented will be mainly related to evidence that dysfunctions in dopamine transmission may be a common regulator of spine pathogenesis in PD and chronic cocaine exposure. Additional references about other addictive drugs or biological conditions that affect striatal spine morphogenesis are listed in Table 1. For additional information about related topics that are not covered in this review, the readers are referred to recent comprehensive essays on striatal spine plasticity and pathogenesis (Hyman and Malenka, 2001; Robinson and Kolb, 2004; Saal and Malenka, 2005; Hyman et al., 2006; Kauer and Malenka, 2007; Kreitzer and Malenka, 2008; Kalivas and O'Brien, 2008; Smith et al., 2009b; Surmeier et al., 2010; Villalba and Smith 2010; Villalba and Smith, 2011; Russo et al., 2010; Nestler and Hyman, 2010; Grueter et al., 2012; Smith et al., 2013).

1.1.- The Striatum is the Main Entry for Extrinsic Inputs to the Basal Ganglia Circuitry

The basal ganglia are a group of interconnected subcortical structures involved in the control of motor, cognitive and limbic functions (Alexander et al., 1986; 1990). In primates, they comprise the striatum (caudate nucleus, putamen, nucleus accumbens), the external and internal segments of the globus pallidus (GPe, GPi), the subthalamic nucleus (STN) and the substantia nigra (SN). In rodents, the striatum is a single mass of gray mater often called caudate-putamen complex, while the globus pallidus (GP) and entopeduncular nucleus (EPN) are commonly referred to as the homologues of GPe and GPi, respectively (Parent, 1986).

The striatum is the main entry of extrinsic information to the basal ganglia circuitry being the target of massive glutamatergic inputs from the cerebral cortex and thalamus, as well as robust dopaminergic afferents from the ventral midbrain (Kemp and Powell, 1971a,b,c; Smith and Bolam, 1990; Parent and Hazrati, 1995; Smith et al. 1998, 2004; Bolam et al.,

2000; Nicola et al., 2000; Graybiel, 2004; Surmeier et al., 2010; Gerfen and Surmeier, 2011). Based on its sources of cortical information, the striatum is generally divided into a dorsal and ventral component characterized by segregated information processing. The dorsal striatum, made up of the putamen and caudate nucleus is mainly innervated by sensorimotor (postcommissural putamen) and associative (caudate nucleus and pre-commissural putamen) cortices, respectively, while the ventral striatum (nucleus accumbens and olfactory tubercle) is the main target of limbic-related inputs from the hippocampus, amygdala and medial prefrontal cortices (Russchen et al., 1985; Alexander et al., 1986; McGeorge and Faull, 1987; Haber et al., 1995; Parent and Hazrati, 1995; Fudge et al., 2002). Each striatal region also receives strong thalamic inputs from functionally related relay, associative and midline nuclei, as well as from the caudal intralaminar nuclear group, the centre median and parafascicular complex (CM/Pf), which innervates preferentially the putamen or caudate nucleus, respectively (Smith et al., 2004, 2009a; Galvan and Smith, 2011). Massive dopaminergic innervation from either the SNc (to the dorsal striatum) or the ventral tegmental area (to the ventral striatum) provides key modulatory influences upon striatal processing of extrinsic cortical and thalamic information (Smith and Bolam, 1990; Nicola et al., 2000; Gerfen and Surmeier, 2011). Additional extrinsic inputs from the hypothalamus, globus pallidus, subthalamic nucleus, raphe, locus coeruleus and pedunclopontine nucleus have also been described (Smith and Parent, 1986; Parent and Hazrati, 1995; Smith et al., 1998; Ellender et al., 2011).

The NAc is the key structure of the ventral striatum. In rodents, it consists of three fundamental subregions: a rostral pole, located in the anterior one-fourth of the nucleus, a central core and a peripheral shell, occupying the caudal three-fourths of its extent (Heimer et al., 1991; Zahm and Brog, 1992; Haber and Gdowski, 2004). The NAc core is often considered as a functional extension of the dorsal striatum and may be particularly important for instrumental learning, including cue-induced reinstatement of drug seeking behaviour, while the shell is often seen as a transitional zone between the striatum and extended amygdala and may be preferentially involved in mediating the primary reinforcing effects of drugs of abuse (Cardinal and Everitt, 2004; Kalivas and Volkow, 2005; Kalivas et al., 2005). Considerable differences exist between the shell and core subregions of the NAc in their input-output characteristics. The core subregion receives glutamatergic inputs primarily from the dorsal parts of the medial prefrontal cortex (dorsal prelimbic and anterior cingulate areas), the parahippocampal cortex, the caudal midline and rostral intralaminar thalamic nuclei, and the anterior part of the basolateral amygdaloid nucleus (Berendse et al., 1992; Pennartz et al., 1994; Haber et al., 1995; Haber and McFarland, 1999), while it projects to the dorsal, subcommissural part of the ventral pallidum (evidently a ventral extension of the external segment of the globus pallidus), the medial part of the internal segment of the globus pallidus, and the dorsomedial part of the substantia nigra pars reticulata (See Heimer et al., 1991; Haber and Gdowski, 2004; Smith et al., 2013).

On the other hand, the shell receives glutamatergic afferents from ventrally located medial prefrontal areas (infralimbic and ventral prelimbic), the midline paraventricular thalamic nucleus, posterior parts of the basolateral amygdaloid nucleus, as well as the subiculum and CA1 regions of the hippocampal formation, while it projects to the ventral and medial parts of the ventral pallidum and adjacent lateral preoptic area, the lateral hypothalamus, the dopaminergic cell groups in the VTA and dorsal tier of the substantia nigra pars compacta and the pedunclopontine nucleus (Groenewegen et al., 1996). In addition, the whole extent of the shell and core of the accumbens receives significant dopaminergic and serotonergic inputs, but the caudomedial shell also receives a significant noradrenergic innervation from the caudal brainstem (Heimer et al., 1995; Berridge et al., 1997).

Even though clear structural, anatomical and functional differences exist between the core and the shell of NAc, there is evidence that these subregions are not completely independent entities, but rather belong to the same interacting neuronal networks that process information in the NAc (van Dongen et al., 2005).

1.2.- The Medium Spiny Neurons: The main targets of striatal inputs

The main targets of extrinsic inputs to the striatum are the GABAergic MSNs, which represent as much as 90–95% of all striatal neurons (Kemp and Powell, 1971a,b,c; Oorschot, 1996; Wickens et al., 2007). These GABAergic neurons can be categorized into two main populations based on their hodological and chemical phenotypes. The “direct” pathway neurons send their main axonal projections directly to the output nuclei of the basal ganglia (ie GPi and SNr), and express preferentially the D1 dopamine receptors and the neuropeptides substance P and dynorphin. On the other hand, the “indirect” pathway neurons project preferentially to the GPe, and express D2 receptors and the neuropeptide enkephalin (Gerfen et al., 1990; Gerfen and Surmeier, 2011). Albeit less frequent, it is noteworthy that some striatal MSNs project to both GPe and GPi/SNr and co-express D1 and D2 dopamine receptor subtypes (Kawaguchi et al., 1990; Wu et al., 2000). The dendritic trees of both populations of striatal MSNs are covered with spines, which are the main targets of glutamatergic inputs from the cerebral cortex and thalamus. In rodents, the dendrites of individual MSNs harbor as many as 5000 dendritic spines (Wickens et al., 2007). In addition to their glutamatergic innervation, striatal spines also receive synaptic inputs from midbrain dopaminergic neurons which, for the most, terminate onto the neck of the spine or a nearby segment of the dendritic shaft, thereby providing an anatomical substrate for close synaptic interactions between glutamatergic and dopaminergic inputs at the level of dendritic spines. (Freund et al., 1984; Smith and Bolam, 1990; Smith et al. 1994; Nicola et al., 2000; Wickens et al., 2007; Moss and Bolam, 2008). These functional interactions are critical for the development and maintenance of long term synaptic plasticity of glutamatergic corticostriatal synapses (Nicola et al., 2000; Calabresi et al., 2007; Surmeier et al., 2010; Gerfen and Surmeier, 2011; Picconi et al., 2012). Although D1- and D2-containing MSNs display very similar morphological characteristics, the D2-containing MSNs exhibit increased excitability and harbor a less extensive dendritic tree than D1-positive cells in mice (Kreitzer & Malenka 2007; Gertler et al., 2008), and each type of MSN is differentially modulated by dopamine (DA) in normal and diseased states (Surmeier et al. 2007; Day et al., 2008; Shen et al. 2008; Kreitzer and Malenka, 2008; Kreitzer, 2009).

The aspiny interneurons are far fewer in number, accounting for about 5–10% of the total striatal population (Tepper and Bolam, 2004; Bernacer et al., 2005, 2007, 2012). Anatomically, they can be categorized into medium-sized GABAergic cells and large cholinergic neurons (Kawaguchi et al. 1995; Bernacer et al., 2007, 2012). Medium-sized GABAergic interneurons can be further classified histochemically into three subtypes: (a) parvalbumin-positive; (b) somatostatin-, neuropeptide Y-, and nitric oxide synthase-positive; and (c) calretinin-positive (Tepper and Bolam, 2004; Bernacer et al., 2005, 2007, 2012).

1.3.- Anatomical and Functional Organization of the Dopamine Mesostriatal Systems

Because of its involvement in a wide array of physiologic and pathologic processes, the anatomical and functional organization of the dopamine mesostriatal systems has been the topic of extensive studies for many years (see Wickens et al., 2007; Kreitzer, 2009; Gerfen and Surmeier, 2011 for reviews). Despite such interest, the exact role of dopamine in normal basal ganglia function is complex and remains poorly understood. In this section, we will highlight some of the main anatomical and functional features of the mesostriatal system relevant to striatal spine plasticity and pathogenesis. The readers are referred to comprehensive reviews of the topic for additional information (Arbuthnott et al., 2000;

Gerfen and Surmeier, 2011; Surmeier et al., 2010, Reynolds and Wickens, 2002; Costa, 2007; Rice and Cragg, 2008; Rice et al., 2011).

Dopamine is one of the most abundant neurotransmitters in the striatum that originates from the ventral midbrain including the SNc (A9), VTA (A10) and RRA (A8). Dopamine plays a fundamental role in normal basal ganglia function, so that abnormal changes in dopaminergic transmission is involved in numerous basal ganglia disorders, including PD and addiction to drugs of abuse. The whole striatum is densely innervated by dopaminergic axons and terminals (Lavoie et al., 1989; Prensa and Parent, 2001; Matsuda et al., 2009; Bolam and Pissadaki, 2012; Pissadaki and Bolam, 2013). Projections from SNc and RRA neurons terminate in the dorsal striatum, while VTA neurons are the main source of dopamine innervation to the ventral striatum (Gerfen et al., 1987; Lynd-Balta and Haber, 1994a,b). Dopaminergic terminal boutons represent nearly 10% of all striatal synapses (Groves et al. 1994).

Like other monoamines, there is evidence that dopamine can mediate its effects in striatal and extrastriatal brain regions through volume transmission (Arbuthnott et al., 2000; Cragg & Rice 2004; Arbuthnott and Wickens, 2007; Wickens et al., 2007; Moss and Bolam, 2008; Rice and Cragg, 2008; Rice et al., 2011). Consistent with this hypothesis, most DA receptors in the striatum are located extrasynaptically in spines and dendrites of striatal neurons (Hersch et al., 1995; Yung et al. 1995; Delle Donne et al., 1996, 1997; Nicola et al., 2000; Wang and Pickel, 2002; Gerfen and Surmeier, 2011). In addition to the strong and segregated expression of D1 and D2 dopamine receptors in direct and indirect pathway MSNs, both GABAergic and cholinergic interneurons also express different subtypes of dopamine receptors, and their activity is tightly regulated by dopamine, most particularly that of cholinergic interneurons, which express both D2 and D5 dopamine receptors (Yan et al. 1997; Yan and Surmeier, 1997; Kreitzer, 2009; Gerfen and Surmeier, 2011). D3 and D4 dopamine receptors are also expressed in both the dorsal and ventral striata (Landwehrmeyer et al., 1993; Centonze et al. 2003. Rivera et al. 2002).

1.4.- PD versus Psychostimulant Exposure: Opposite Effects Upon Striatal Dopamine Release

In PD, the dopaminergic projections from the substantia nigra pars compacta (SNc) to the striatum undergo significant degeneration. The progressive loss of the dopaminergic nigrostriatal system either in PD or animal models of parkinsonism is not uniform, but rather follows a specific regional pattern that first involves the postcommisural sensorimotor putamen, followed by the caudate nucleus and more anterior associative regions of the putamen, while the limbic-related ventral striatal regions are the least sensitive areas to dopamine denervation in PD (Damier et al., 1999a,b; Hornykiewicz, 2001; Dauer and Przedborski, 2003; Jan et al., 2003; Iravani et al., 2005). Because of the preferential expression of D1 and D2 dopamine receptors in different populations of striatal projection neurons (see above), the resulting lack of striatal dopamine increases the activity of 'indirect' striatofugal neurons and decreases the striatal output along the 'direct' route (Albin et al., 1989; DeLong, 1990; Gerfen et al., 1990; Gerfen and Surmeier, 2011). Dopamine also plays a critical role in mediating long term synaptic plasticity of corticostriatal glutamatergic axo-spinous synapses through complex interactions between dopamine and glutamate receptors at the level of individual spines (Nicola et al., 2000; Calabresi et al., 2007; Kreitzer, 2009). In contrast to PD, acute and chronic administration of cocaine and related psychostimulants induce major raise of extracellular dopamine and other monoamines throughout the striatum and prefrontal cortex in both humans and experimental animals, primarily by blockade of the dopamine, serotonin or norepinephrine transporters (Kuhar et al., 1991; Volkow et al., 2011; Koob, 1998; White and Kalivas, 1998).

Although PD and addiction to psychostimulants do not solely rely on striatal dopamine dysfunction, but rather represent complex network disorders that affect multiple neurochemical entities, striatal dopamine imbalance remains a key underlying factor of the neurochemical, pathophysiological and behavioural changes associated with these disorders (Koob and Volkow, 2010; Smith et al., 2012; Volkow et al., 2011). It is noteworthy that striatal dopamine dysfunctions are also implicated in numerous neurological and psychiatric disorders including dystonia, obsessive-compulsive disorder, attention deficit disorder, Tourette's syndrome, etc... (Hyman et al. 2006; Breakefield et al. 2008, Graybiel, 2008). The morphological and structural changes induced in striatal projection neurons by dopamine dysfunctions in these disorders is much less understood than in PD and cocaine exposure.

2.- Striatal spine pathogenesis in Parkinson's disease versus cocaine addiction

Although the following discussion will be mainly focused on the effects of PD and chronic cocaine exposure on spine density changes in the mammalian striatum, it is noteworthy that most drugs of abuse that mediate their effects through increases of striatal dopamine lead to changes in the number and morphology of dendritic spines in the striatum (Table 1). However, because striatal spine pathology has been far more heavily studied in animal models of chronic cocaine exposure than any other drugs of abuse, most findings discussed in the review have been gathered from studies of cocaine addiction.

2.1.- Striatal Spine Loss in Parkinson's Disease

Findings from our laboratory and others have demonstrated that the nigrostriatal dopaminergic system plays a key role in regulating morphological and functional spine plasticity in the striatum. The first clear evidence for spine loss in the striatum of an animal model of PD came from rat studies showing that unilateral degeneration of the nigrostriatal dopaminergic system with 6-hydroxydopamine (6-OHDA) results in about 20% spine loss in the caudate-putamen complex (Ingham et al., 1989). Further studies demonstrated that this spine loss is accompanied by a corresponding decrease in the total number of asymmetric glutamatergic synapses in the striatum, suggesting that afferent glutamatergic terminals in contact with lost dendritic spines likely retract or degenerate in the parkinsonian state (Ingham et al., 1998). Since then, spine loss has been demonstrated in various postmortem studies of striatal tissue from PD patients (Stephens et al., 2005; Zaja-Milatovic et al., 2005).

The degree of striatal spine loss is closely correlated with the progressive striatal denervation pattern seen in PD, i.e. MSNs in the postcommissural sensorimotor putamen, known as the most severely dopamine-depleted striatal region in PD, are more severely affected than in the less dopamine-denervated caudate nucleus and the nucleus accumbens (Zaja-Milatovic et al., 2005). Recent findings from non-human primates treated with MPTP have also provided further support for a regional pattern of striatal spine loss that corresponds to the pattern of progressive dopamine denervation in parkinsonians (Villalba et al., 2009; Villalba and Smith, 2010) (Fig. 2). These studies also demonstrated that striatal spine loss is an early pathological feature of parkinsonism, tightly linked with the degree of striatal dopamine denervation, but not with the severity of parkinsonian motor symptoms, in MPTP-treated monkeys (Villalba et al. 2009; Smith et al., 2009b; Villalba and Smith, 2010) (Fig. 2). However, maintaining normal striatal spine density improves the therapeutic benefit and diminishes dyskinesias induced by grafted dopamine neurons in the striatum of 6-OHDA-treated rats (Soderstrom et al., 2010; Bezard, 2010). Together, these postmortem and experimental data strongly suggest a key role of nigrostriatal dopamine degeneration in

mediating striatal spine pruning in PD, and highlight the potential importance of such pathology in reducing the efficacy of anti-parkinsonian dopamine neurons graft therapy.

However, dopamine is unlikely to be the only transmitter involved in this phenomenon. *In vitro* and *in vivo* data in rats, indeed, demonstrated that decortication prevents the loss of striatal spines induced by dopamine denervation, thereby suggesting that glutamate is another key determining factor of this pathology (Cheng et al., 1997; McNeill et al., 2003; Deutch et al., 2007; Neely et al., 2007; Garcia et al., 2010). As discussed below, functional interactions between regulating elements of convergent glutamatergic and dopaminergic synapses upon striatal spines, and their impact on the control of intracellular calcium levels, may be critical factors that underlie these functional interactions between glutamatergic and dopaminergic systems to regulate spine pruning and morphology in PD.

2.1.1-Ultrastructural Changes in Axo-spinous Striatal Glutamatergic Synapses in Parkinson's Disease

—Striatal spine loss is accompanied with a corresponding decrease in the total number of putative glutamatergic terminals forming asymmetric synapses in 6-OHDA-treated rats (Ingham et al., 1998). However, in the striatum of MPTP-treated parkinsonian monkeys, there is a significant increase in the overall density of terminals immunoreactive for the vesicular glutamate transporter 1 (vGluT1) (Raju et al., 2008), known as a specific marker of corticostriatal terminals (Fujiyama et al, 2001; Kaneko and Fujiyama, 2002; Freneau et al, 2004a,b). Recent postmortem human data also support an increased expression of vGluT1 in the striatum of PD patients (Kashani et al., 2007). In light of the numerous findings showing a major loss of spines in the striatum of parkinsonians (see above), this apparent increase in cortical terminals is paradoxical, unless striatal spine loss in PD is mainly accounted for by degeneration of glutamatergic thalamostriatal terminals. In contrast to cortical terminals, no significant change in the density of terminals positive for the vesicular glutamate transporter 2 (vGluT2), a specific marker of thalamostriatal terminals (Takamori et al., 2000, 2001; Freneau et al., 2004a,b; Kaneko and Fujiyama, 2002; Raju et al., 2006), was found in parkinsonian monkeys (Raju et al., 2008). However, a dramatic shift towards a decrease in the ratio of axo-dendritic vs axo-spinous synapses formed by vGluT2-positive terminals was recognized in parkinsonian animals (Raju et al., 2008), suggesting a change in the synaptic connectivity of thalamostriatal terminals in parkinsonian condition.

Early rodent and human data, indeed, suggested morphological changes of asymmetric synapses consistent with increased synaptic activity in the dopamine-denervated striatum (Ingham et al., 1998; Meshul et al., 1999, 2000). These observations were recently supported and expanded by a detailed 3D ultrastructural analysis of corticostriatal and thalamostriatal glutamatergic synapses in the striatum of normal and parkinsonian monkeys (Villalba and Smith, 2011). In brief, these studies revealed that the size of the spine heads as well as the length, complexity and extent of perforations of the postsynaptic densities (PSD) of both sets of synapses are increased in the non-human primate model of PD (Fig. 3), thereby suggesting that the remaining thalamostriatal and corticostriatal synapses undergo plastic changes consistent with increased synaptic strength in parkinsonism (Cotman and Nieto-Sampedro 1982; Smith et al., 2009b; Villalba et al., 2010; Villalba and Smith 2011a,b). Another striking change observed in parkinsonian monkeys, particularly in spines that receive cortical inputs, was the massive growth of the spine apparatus (Villalba and Smith, 2010, 2011a), an ultrastructural feature commonly associated with increased protein synthesis and increased buffering of intraspinous calcium at glutamatergic synapses (Fifkova et al., 1983; Bourne and Harris, 2008). Finally, the reduced volume and increased number of mitochondria in remaining cortical boutons in parkinsonian monkeys suggest a higher mitochondrial traffic along corticostriatal axons (Verstreken et al., 2005; Safiulina et al., 2006), probably due to a higher activity and energetic demand at corticostriatal synapses

in the parkinsonian condition. These changes at the neuronal level are accompanied with a major expansion of the glial coverage of striatal glutamatergic axo-spinous synapses in parkinsonian animals, suggesting that ultrastructural remodeling of both neuronal and glial elements are taking place in the parkinsonian striatum (Villalba and Smith, 2011b).

Thus, despite an important loss of striatal spines in parkinsonism, it appears that the remaining spines and their afferent glutamatergic inputs undergo plastic ultrastructural changes consistent with increased synaptic activity, which may explain some of the electrophysiological data suggesting increased glutamatergic transmission at corticostriatal synapses in animal models of PD (Gubellini et al., 2002; Calabresi et al., 2007; Picconi et al., 2012).

2.1.2-Loss of striatal spines in PD: Does it affect both “Direct” and “Indirect” striatofugal neurons—As discussed above, the striatum comprises two populations of GABAergic medium spiny projection neurons characterized by their preferential expression in dopamine receptors and neuropeptides, so-called “direct (D1, SP/DYN)” and “indirect (D2, ENK)” pathway neurons. The imbalance of activity between these two pathways in favor of an increased striatal output from indirect pathway neurons is considered as a key pathophysiological feature of PD (Albin et al., 1989; DeLong, 1990; Smith et al., 1998; Wichmann et al., 2003, 2007; DeLong and Wichmann, 2007). Therefore, a detailed characterization of the differential loss of spines on direct versus indirect pathway neurons could be of great importance in PD pathophysiology. In that regard, data gathered from reserpine-treated mice proposed that D2-containing striatopallidal neurons, but not D1-positive striatonigral neurons, selectively lose spine following dopamine depletion (Day et al., 2006). These observations were supported by quantitative immunoelectron microscopy data from 6-OHDA-treated rats showing a significant decrease in the number of striatal D1-negative spines (Day et al., 2006). A recent electron microscopy study using a non-stereologic spine count method showed a relative decrease in the number of D2-immunopositive spines accompanied with an increase in the number of D1-immunoreactive spines in a MPTP-treated monkey model of PD (Scholz et al., 2008). On the other hand, these observations are different from those in a large number of Golgi studies in both human parkinsonians and animal models of parkinsonism showing a rather homogeneous loss of spines across large populations of Golgi-impregnated striatal medium spiny neurons (Ingham et al., 1989; Stephens et al., 2005; Zaja-Milatovic et al., 2005; Villalba et al., 2009; Smith et al., 2009b). Furthermore, recent data from monkeys chronically treated with MPTP demonstrated a similar loss of both D1-immunoreactive and D1-negative spines in dopamine-denervated putamen (Villalba et al., 2009), suggesting that spine pathogenesis affects both direct and indirect pathway striatofugal neurons in this nonhuman primate model of PD (Villalba et al., 2009). Whether these apparent discrepancies in the extent of spine loss between direct and indirect pathway neurons rely on species differences or chronic versus acute toxin exposure remain to be established.

2.2-Abnormal Striatal Spine Growth and Remodeling in Response to Cocaine

In contrast to the dopamine-depleted parkinsonian condition that induces major spine pruning in the dorsal striatum, chronic cocaine exposure results in an abnormal increase in spine density on MSNs in the rodent nucleus accumbens (see table 1 for references). Although most studies agree that this increased spinogenesis leads to a rise in the number of “thin” spines in the NAc (Robinson and Kolb, 1999a; Shen et al., 2009; Dumitriu et al., 2012), a recent study showed that the head of both thin and mushroom spines is enlarged after long cocaine treatment, bringing up another level of cocaine-induced morphological plasticity in the NAc (Dobi et al., 2011). These structural changes, which can persist for months after the last drug exposure (Li et al., 2003; Robinson and Kolb, 2004), have been

suggested to underlie long-lasting alterations in glutamatergic synaptic transmission and plasticity associated with psychostimulant exposure (Robinson and Kolb, 2004; Dobi et al., 2011; Kim et al., 2011; Dumitriu et al., 2012; Grueter et al., 2013). In contrast to the striatal spine loss in PD, which has been studied in primate and non-primate models of the disease as well as in PD patients, spine changes associated with exposure to drugs of abuse have been described exclusively in rodent models of addiction (see Table 1). Future monkey studies and postmortem analyses of human brains are warranted to validate these observations in primates. It has been hypothesized that these morphological changes may contribute to the development of reduced behavioral sensitivity, behavioural sensitization and compulsive patterns of drug-seeking behaviour (Kolb et al., 2003; Robinson and Kolb, 2004; Pulipparacharuvil et al., 2008). Although the consequences of these morphological changes on the homeostatic plasticity of the glutamatergic synaptic innervation of accumbens projection neurons from the cortex, thalamus, hippocampus or amygdala remain to be determined, there is functional evidence for an increase in the prevalence of pre-synaptic release sites of glutamate onto MSNs in the accumbens of chronically cocaine-treated animals (Robinson and Kolb, 2004; Shen et al., 2009; Wolf, 2010; Dobi et al., 2011).

In addition to changes in dendritic spines density, repeated cocaine administration induces other functional changes at glutamatergic synapses in the NAc in various ways including alterations in the surface expression of glutamate receptors and changes in short and long term plasticity of glutamatergic axo-spinous synapses (Robinson et al., 2001; Li et al., 2004; Boudreau and Wolfe, 2005; Martin and Zukin, 2006; Kourrich and Thomas, 2009). Because many of these changes were thought to occur only several weeks following the last cocaine exposure, it was suggested that cocaine abstinence or withdrawal may be an important regulator of these synaptic defects (Robinson et al., 2001; Li et al., 2004; Boudreau and Wolfe, 2005; Martin et al., 2006; Kourrich and Thomas, 2009; Ferrario et al., 2012). However, some studies have shown that increased spine density can occur as early as 2 days after the last cocaine exposure (Lee et al., 2006; Kim et al., 2009; Ren et al., 2010; Dumitriu et al., 2012). Thus, both withdrawal and the neurochemical effects induced by the chronic exposure of cocaine contribute to striatal spine pathology in addition to psychostimulants.

2.2.1 Does cocaine exposure induce changes in striatal spine density on both direct and indirect pathway neurons—

Various studies have recently aimed at determining if the abnormal growth of spines in the striatum of cocaine-exposed animals affects preferentially D1- or D2-containing striatal projection neurons. A recent study using 2 different noncontingent cocaine treatments in mice (short cocaine/prolonged withdrawal vs long cocaine/short withdrawal) showed that D1-containing accumbens neurons are particularly susceptible to cocaine exposure and that cocaine withdrawal is not required for the increased spine density in the NAc (Dobi et al., 2011). Ren et al. (2010) showed that D1 KO mice or exposure to D1R, but not D2R, blockers do not display any spine changes after 28 consecutive daily injections of cocaine when examined 2 days after the last cocaine injections. Along the same line, another study using both D1R and D2R expressing mice confirmed that cocaine exposure (5 consecutive days in home cage, 15 mg/kg, sac 24 hrs after last injection), elicited a selective increase in spine density in D1R-containing neurons after cocaine exposure (Kim et al., 2011). Thus, it appears that the D1-positive “direct pathway” neurons are more sensitive to cocaine-induced changes in spine density than D2-containing “indirect pathway” neurons. However, some reports found that both D1 and D2 neurons display an increased spine density after chronic cocaine exposure (Lee et al., 2006; Li et al., 2012). Future studies are needed to clarify these discrepancies.

2.2.2 Cocaine-induced Spine Changes in Core vs Shell of NAc—

In brain slices, the core and shell of NAc display opposite cocaine-induced adaptations in intrinsic excitability (Kourrich and Thomas, 2009). On the other hand, several studies have reported

spine changes in both the core and shell of the rat accumbens in response to cocaine exposure (Norrhom et al., 2003; Li et al., 2004; Ferrario et al., 2005). A recent study examined this issue in further detail and found that changes in thin spine density are induced in both the shell and core of the accumbens, but that the extent of the change varies between proximal and distal dendrites depending on the time after exposure to cocaine (Dumitriu et al., 2012). The authors found that cocaine induced opposite changes of spine density on the proximal dendrites of MSNs between the core and shell of the NAc, ie up-regulation in the shell, down-regulation in the core (Dumitriu et al., 2012). They also provided evidence that these effects are time dependent. For instance, the increased spine density in the shell was seen as fast as 4 hours after 7 days cocaine exposure, while the spine loss in core could not be seen before 24 hours post injection. On the other hand, after 28 days cocaine followed by 28 days withdrawal, there was no significant effect on shell neurons, while elimination of spines on the proximal dendrites of core neurons was still seen after this regimen of cocaine exposure/withdrawal (Dumitriu et al., 2012). In contrast to this report suggesting cocaine-induced concerted core/shell spine changes, a mouse study showed increased spine density in shell, but not core neurons (Martin et al., 2011). Whether these discrepancies are due to differences in species, drug dose, drug administration paradigm or spine counting methods being used across studies remain to be determined. Thus, spine changes in various sub-regions of the NAc (ie core vs shell), or along specific dendritic compartments, appear to be regulated differently in response to cocaine administration, thereby indicating that specific components of the neuronal networks must be examined separately to avoid missing important regional or cell-type specific changes (Dumitriu et al., 2012).

A recent study suggested that a transfer of neuroplasticity from nucleus accumbens core to shell is required for cocaine rewarding effects. In brief, these data showed a correlation between the rewarding effects of cocaine and the density of dendritic spines in shell and core of the NAc. They also demonstrated that blockade of protein synthesis in the NAc core immediately after conditioning inhibits cocaine-induced conditioned place preference and blocks increases in dendritic spines density in both the shell and core of the NAc, whereas protein synthesis blockade in the shell immediately after conditioning had no effect on neuroplasticity or behavior (Marie et al., 2012).

2.2.3 Sex Differences vs Spine Density Changes after Cocaine Exposure—Sex

difference is another important determining factor that regulates spine density on MSNs of the rodent NAc. In rats, MSNs in female NAc harbor a larger density of spines than males, but neither the dendritic length nor any aspect of dendritic branching is sexually dimorphic (Forlano and Woolley, 2010), suggesting that changes in spine density are representative of genuine differences in dendritic spine number per MSN. In rats treated with daily cocaine for 5 weeks followed by 17–21 days withdrawal, the magnitude of the cocaine-induced increase in spine density is larger in females than males, particularly in the core of the NAc (Wissman et al., 2011, 2012; Li et al., 2012), which was correlated with a higher frequency of mEPSC in NAc core MSNs in females than males. These differential cocaine-induced morphological changes of spines between males and females can be due to various factors including sex differences in hormonal regulation of BDNF, CAMKII and/or delta Fos B (Wissman et al., 2011). Whether these sex differences in spine plasticity underlie the stronger behavioral sensitization of females than males to cocaine exposure remains to be established (van Haaren and Meyer, 1991; Hu and Becker, 2003).

3. Is MEF2 the Common Regulator of Striatal Spine Changes in PD and Cocaine Exposure

3.1-MEF2 dysregulation in response to cocaine exposure

Despite clear evidence for major structural and functional changes in striatal MSNs related to dendritic spines pathology in PD or after exposure to cocaine or other drugs of abuse, the mechanisms underlying these phenomena remain poorly understood. However, significant progress has been made in recent years, particularly in the field of drug addiction, suggesting that calcium-mediated regulation of the myocyte enhancer factor 2 (MEF2) may contribute to the opposite changes in spine density described in PD and in animal models of cocaine abuse (Pulipparacharuvil et al., 2008; Tian et al., 2010; Villalba and Smith, 2010) (Fig. 4). Although MEF2 proteins are widely expressed in the CNS, their role has long remained enigmatic until recent studies showing that MEF2 regulates excitatory synapses in part by promoting activity-dependent synaptic pruning (Flavell et al., 2006). In hippocampal neurons, MEF2 is stimulated by increased glutamatergic transmission most likely via a mechanism that involves activation of the calcium/calmodulin signaling cascade which, in turn, stimulates the protein phosphatase calcineurin to dephosphorylate MEF2 proteins and promote its activation, which leads to elimination of excitatory synapses (Mao and Wiedmann, 1999; Gong et al., 2003; Flavell et al., 2006). A scheme by which chronic cocaine exposure increases dendritic spine density via reduction of MEF2-dependent transcription was recently suggested (Pulipparacharuvil et al., 2008) (Fig. 4). This model takes into consideration the fact that cocaine-induced increase in spine density affects predominantly D1-containing neurons in the NAc, and that D1-expressing neurons contain high levels of the stable transcription factor, delta FosB, known to play critical roles in addictive behaviors (Kelz et al., 1999; Colby et al., 2003; Jourdain et al., 2003; Nestler, 2008; Maze et al., 2010; Grueter et al., 2013; Robison et al., 2013). Thus, according to this model, repeated cocaine exposure and the resulting overactivation of D1 dopamine receptors and its signaling cascade reduces MEF2 activity via an increase in cAMP and activation of protein kinase A (PKA) which, in turn, phosphorylates the regulator of calcineurin signaling (RCS), thereby attenuating calcineurin activity. Because of this lack of calcineurin activity, MEF2 cannot be dephosphorylated and mediates its effects towards excitatory synapses elimination (Fig. 4).

Another key element of this model is the cyclin-dependent kinase 5 (Cdk5) activity, a major target of the delta FosB gene known to be significantly increased in response to chronic cocaine in the NAc (Perrotti et al., 2008; Nestler, 2008; Winstanley et al., 2009a,b). Chemical inhibition of Cdk5 blocks cocaine-induced increase in spine density in MSNs (Norrhom et al., 2003). In contrast to the facilitatory effects of calcineurin upon MEF2 activation through dephosphorylation, increases in Cdk5 activity has the opposite effects, ie it promotes MEF2 phosphorylation which attenuates MEF2 activity, thereby blocking its function towards synaptic regulation. Thus, in normal condition, MEF2 activity is under the control of a balanced opposite regulation by the facilitatory dephosphorylating effects of calcineurin and the inhibitory phosphorylating effects of Cdk5. However, the abnormal increase in dopamine and the resulting overactivation of D1 dopamine receptors and its cAMP-dependent signaling cascade, combined with the delta FosB-mediated increases in Cdk5, result in a significant attenuation of MEF2 activity and increased spine density in D1-containing NAc neurons (Pulipparacharuvil et al., 2008) (Fig. 4).

It is noteworthy that several additional signaling molecules, not discussed in detail here, have been shown to play critical roles in the various structural, functional and behavioral aspects of cocaine addiction. Among those is the brain-enriched calcium/calmodulin-dependent protein kinase II (CAMKII) which is induced selectively in the NAc shell by

chronic psychostimulants (Loweth et al., 2010; Klug et al., 2012; Robison et al., 2013), and has long been known as a key regulator of several forms of neuroplasticity (Malinow and Malenka, 2002). In a recent study, Robison et al (2013) demonstrated that CAMKII phosphorylates delta FosB, and is required for the cocaine-mediated accumulation of delta FosB in the rat NAc through which it directly contributes to the induction of dendritic spines on NAc MSNs (Robison et al., 2013). Importantly, increased expression of delta FosB and CAMKII has also been reported in the NAc of human cocaine addicts, indicating that these proteins are most likely involved in mediating sensitized drug responses in human addiction (Robison et al., 2013).

Another protein that recently received attention for its role in the regulation of cocaine-mediated changes in synaptic structures in the NAc is the synaptic cell adhesion molecule 1 (SynCAM1), known as an immunoglobulin adhesion protein that induces excitatory synapses. It was found that the SynCAM1 is required to maintain the increased density of spines on NAc MSNs induced by chronic cocaine in rodent models of addiction (Giza et al., 2013). Kalirin 7, one of the Rho-guanosine diphosphate/guanosine triphosphate exchange factors (Rho-GEFs) known to play an important role in spine morphogenesis, has also recently been recognized as an essential determinant of dendritic spine formation following chronic cocaine exposure (Kiraly et al., 2010; Mains et al., 2011; Ma et al., 2012). Other factors recently shown to affect spine density in the NAc of rats and mice after chronic cocaine exposure include DNA methylation, increases in actin cycling and activation of the nuclear factor kappa B (NFkappaB) (Russo et al., 2009; LaPlant et al., 2010; Toda et al., 2010).

3.2-MEF-2 dysregulation in PD

Findings in support of a calcium-regulated MEF2-dependent mechanism by which excessive spine loss, such as seen in PD, could be mediated in striatal MSNs were recently obtained (Tian et al., 2010). In EGFP-D2 mice, striatal spine loss induced by dopamine depletion can be prevented by genetic deletion of Cav1.3 $\alpha 1$ subunits or the pharmacological blockade of L-type Cav1.3 channels (Day et al., 2006; Schuster et al., 2009; Soderstrom et al., 2010). Knowing that D2 dopamine receptor signaling negatively modulates activity of L-type Cav1.3 calcium channels (Surmeier et al., 2007), these data suggest that a dysregulation of calcium concentrations, preferentially in D2-containing striatopallidal neurons, may ultimately lead to preferential spine loss on indirect pathway neurons in the rodent striatum (Day et al., 2006; Deutch et al., 2007; Surmeier et al., 2007). Recent data from co-culture studies suggest that the pruning of glutamatergic synapses and spines in the striatum, dependent upon calcium entry through L-type calcium channels, involves the activation of the Ca²⁺-dependent protein phosphatase, calcineurin and the up-regulation of the transcriptional activity of MEF2. In turn, MEF-2 up-regulation leads to increased expression of the Nurr77 and Arc genes, known to be associated with inhibition of synaptic formation and dendritic differentiation (Tian et al., 2010), thereby providing a signaling cascade through which striatal MSNs may undergo structural plasticity in parkinsonism (Tian et al., 2010). Cholinergic signaling through M1 muscarinic receptors and Kir2 potassium channels is another essential trigger for the pruning of glutamatergic synapses in models of parkinsonism (Shen et al., 2008).

Some authors suggested that cerebellin from the caudal intralaminar thalamus may also regulate morphologic changes in striatal spines (Kusnoor et al., 2010). In light of various findings showing that the caudal intralaminar nuclear complex (ie centre median and parafascicular nuclei in primates) profoundly degenerates in PD (Henderson et al., 2000a,b; Villalba et al., 2013), future studies are needed to explore the potential consequences of this degeneration upon striatal cerebellin content, and its effects on striatal spine loss in PD.

4. Concluding Remarks

Although much remains to be known about the functional consequences of striatal spine pathology in relation to physiological or behavioral correlates of parkinsonism or addiction to psychostimulants, recent studies have made significant progress in understanding the molecular underpinnings of these changes, thereby providing some key information that could help identify potential targets for future drug development aimed at slowing down or preventing striatal spine pathology in brain disorders. The impact of dopamine dysfunction in mediating changes in the regulation of calcium, delta FosB, CDK5 and MEF2 towards striatal spine pathogenesis represents an exciting step forward in that direction (see Fig. 4 for details). However, a series of paradoxical and unanswered issues remain about the functional significance of this pathology in relation to the various behavioral abnormalities seen in PD and chronic cocaine exposure. This is particularly relevant for PD because the loss of striatal spines is correlated with the extent of striatal dopamine denervation, but not with the severity of parkinsonian motor symptoms (Zaja-Milatovic et al., 2005; Villalba et al., 2009; Smith et al., 2009b). Thus, the exact contribution of striatal spine loss to PD symptomatology remains unclear. Whether it represents a pathological feature or a compensatory mechanism in response to the synaptic network changes induced by progressive dopamine depletion remains unknown (Smith et al., 2009b; Villalba et al., 2011a).

The role of dopamine in regulating striatal spine morphogenesis in brain disorders is unequivocal, but it is also clear that dopamine is not the sole mediator of these pathological events. The importance of changes in the glutamatergic drive from the cortex or thalamus is also of utmost importance (Garcia et al., 2010). Although the impact of striatal spine loss in PD has long been related to changes in corticostriatal transmission, the massive degeneration of the caudal intralaminar thalamic complex, one of the main sources of the thalamostriatal system, in PD should also be considered as a key contributing factor to striatal spine pathology in parkinsonian condition (Henderson et al., 2000a,b; Kusnoor et al., 2010; Villalba et al., 2013).

Another important factor to consider in the interpretation of studies related to striatal spine pathogenesis is the potential for species differences between primates and non-primates, an issue that has been particularly highlighted in recent years by differences in the extent of spine loss in specific subpopulations of striatal projection neurons between mice and monkey models of PD (Day et al., 2006; Villalba et al., 2009; Smith et al., 2009b). This issue is also highly relevant for the field of addiction, because all data published about spine pathology after chronic drug exposure has been gathered from rodent studies. Detailed analyses of spine changes in nonhuman primate models of addiction or in postmortem human material are needed to help assess the significance of these rodent findings towards the human diseased condition.

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HIGHLIGHTS

- Parkinson's disease and cocaine exposure have opposite effects on striatal dendritic spines.
- Dopamine and glutamate are key regulators of spine development and pathology in the striatum.
- Cocaine-induced increases in striatal spines affect mainly D1-containing neurons.
- Dysregulation of MEF2 may underlie spine pathology in Parkinson's disease and cocaine addiction.

Figure 1.

Schematic comparing the spine pathology described in animals models of PD (Low striatal DA) or after chronic exposure to cocaine (High striatal DA). In PD and PD models, there is a significant loss of dendritic spines on MSNs in the dorsal striatum. After chronic cocaine exposure, MSNs in the ventral striatum display an abnormal overgrowth of “thin and immature” dendritic spines.

Figure 2.

The extent of striatal spines loss in MPTP-treated monkeys is correlated with the degree of striatal dopamine denervation. (A,B) Pseudo-colored images showing the density of TH-positive innervation of the pre-commissural (A) and commissural (B) striatal levels of rhesus monkeys treated chronically with MPTP. (C–D) Examples of Golgi-impregnated medium spiny neurons in the striatum of a control and a MPTP-treated monkey. (E–H) Quantitative analysis of the density of dendritic spines in various regions of the pre-commissural and commissural levels of the caudate nucleus and putamen shown in A and B. The numbers along the X axis correspond to those used to label the different striatal regions in A and B. Note that the decrease in the density of dendritic spines is closely correlated with the extent of striatal TH denervation (see Villalba et al., 2010 for details). Scale bar in D: 5 μ m (valid for C).

Figure 3.

Cortical and thalamic glutamatergic axo-spinous synapses undergo complex plastic changes in the striatum of parkinsonian monkeys. Electron micrographs (A–B) and corresponding 3D EM reconstructions (A1–B2) of vGluT1-positive terminals forming axo-spinous synapses in the striatum of a MPTP-treated parkinsonian monkey. (C–D) Quantitative analysis of various morphometric parameters (spine head volume, PSD area, terminal volume) of axo-spinous synapses formed by vGluT1- or vGluT2-positive terminals in the striatum of parkinsonian monkeys. Note the significant increase in all morphometric measurements in parkinsonian monkeys (See Villalba and Smith, 2011 for details).

Figure 4.

Schematic that summarizes the potential molecular mechanisms by which striatal dopamine changes can affect dendritic spine density following chronic cocaine exposure (A) or in the parkinsonian state (B). See text for details (Modified from Pulipparacharuvil et al., 2008).

Table 1

Changes in the density of striatal spines in Parkinson's disease, animal models of Parkinson's disease and in response to administration of various drugs of abuse.

TREATMENTS/DISEASE	SPECIES	REFERENCES
PARKINSON'S DISEASE		
A- Decreased Spine Density		
Unilateral 6-OHDA	Rats	Ingham et al. 1989, 1993, 1998; Arbuthnott et al. 2000; Day et al. 2006; Deutch 2006; Deutch et al., 2007; Gerfen 2006; Solis et al. 2007; Day et al. 2008; Azdad et al. 2009; Schuster et al. 2009; Bezard 2010; Garcia et al. 2010; Massie et al. 2010; Soderstrom et al. 2010; Surmeier et al. 2010; Walker et al., 2012
MPTP	Mice	Antzoulatos et al. 2011 (saw increased spines)
MPTP	Nonhuman primates	Smith et al. 2009b; Villalba and Smith 2010, 2011a,b; Villalba et al., 2009
Parkinson's Disease	Humans	McNeill et al. 1988; Stephens et al. 2005; Zaja-Milatovic et al. 2005
DRUGS OF ABUSE		
A- Increased spine density		
Cocaine exposure (postnatal)	Mice	Li et al. 2004; Robinson and Kolb 2004; Lee et al. 2006; Kauer and Malenka 2007; Chen et al. 2008; Pullipparacharuvil et al. 2008; Kim et al. 2009; Russo et al. 2009; Kiraly et al. 2010; LaPlant et al. 2010; Ren et al. 2010; Dobi et al. 2011; Mains et al. 2011; Martin et al. 2011; Wissman et al. 2011; Dumitriu et al. 2012; Ferrario et al. 2012; Li et al. 2012; Ma et al. 2012; Marie et al. 2012; Zhang et al. 2012; Giza et al. 2013; Grueter et al. 2013; Gipson et al., 2013; Giza et al. 2013; Grueter et al. 2013; Robison et al., 2013
Cocaine exposure (postnatal)	Rats	Robinson and Kolb 1999a; Kolb et al. 2003; Norrholm et al. 2003; Li et al. 2004; Ferrario et al. 2005; Shen et al. 2009; Toda et al. 2010; Esparza et al. 2012
Cocaine exposure (pre-natal)	Rats and Mice	Frankfurt et al. 2009, 2011; Salas-Ramirez et al. 2010
Cocaine self-administration	Rats	Robinson et al. 2001; Kalivas and O'Brien 2008; Shen et al. 2009;
Amphetamine (Acc)	Rats/Mice	Robinson and Kolb 1997, 1999a; Kolb et al. 2003; Li et al. 2003; Crombag et al. 2005; Dietz et al. 2008; Singer et al. 2009; Solis et al. 2009; Muhammad and Kolb, 2011;
Amphetamine (Dorsal Str)	Rats/Mice	Li et al. 2003; Jedynak et al. 2007;
Donepezil (AChE inhibitor)	Rats	Alcantara-Gonzalez et al. 2009
Haloperidol	Rats	Meredith et al. 2000
Heroin	Rats	Shen et al. 2011
MDMA	Rats	Ball et al. 2009
Methylphenidate	Mice	Ball et al. 2009; Kim et al. 2009
Nicotine	Rats	Brown and Kolb 2001; Hamilton and Kolb 2005; Muhammad et al 2012; Mychasiuk et al. 2013
PCP (phencyclidine)	Rats	Flores et al. 2007
B- Decreased Spine Density		
Alcohol	Rats	Zhou et al. 2007; Lawrence et al. 2012; Rice et al. 2012
Estradiol	Hamster	Staffend et al., 2011
Malathion (pesticide)	Rats	Campana et al. 2008
Morphine (self-administered or experimenter-administered)	Rats or Mice	Robinson et al., 1999b; Robinson et al. 2002; Spiga et al. 2005; Diana et al. 2006; Kasture et al. 2009; Pal and Das, 2013
PCP (Neonatal)	Rats or Mice	Nakatani-Pawlak et al. 2009