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## Addictive Drugs and Synaptic Plasticity

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### 1. Introduction

The term addiction, derived from a Latin word meaning “bound to” or “enslaved by,” was initially not linked to substance use. However, over the past several hundred years, addiction became associated with excessive alcohol and then drug use, such that by the late 1980s it was largely synonymous with compulsive drug use (O’Brien et al., 2006). The core features of addiction are manifest in the continued performance of the behavior despite adverse consequences, compulsive engagement or diminished control over the behavior, and an appetitive urge or craving state prior to the behavioral engagement representing core elements (Holden, 2010).

Addiction is a state of compulsive drug use; despite treatment and other attempts to control drug taking, addiction tends to persist. Hyman (2005) has summarized several studies where the authors have suggested that if the neurobiology is ultimately to contribute to the development of successful treatments for drug addiction, researchers must elucidate the molecular mechanisms by which drug-seeking behaviors are consolidated into compulsive use. Evidence at different levels of analysis suggest that addiction represents a pathological state of the neural mechanisms of learning and memory that, under normal circumstances, serve to shape survival behaviors related to the pursuit of rewards and the cues that predict them (Shultz et al., 1997; Montague et al., 2004; see Badiani et al., 2011 for review). The major substrates of persistent compulsive drug use are hypothesized to be molecular and cellular mechanisms that underlie long-term associative memories in several forebrain circuits (involving the ventral and dorsal striatum and prefrontal cortex) which receive inputs from midbrain dopamine neurons (see Hyman et al., 2006, for review). Also, the basolateral amygdala and nucleus accumbens core are key structures within limbic cortical-striatal circuitry where reconsolidation of a cue-drug memory occurs (Théberge et al., 2010). Vulnerability to stimulant addiction may depend on an impulsivity endophenotype. Impulsivity is the tendency to act prematurely without foresight, and is commonly associated with addiction to drugs, though its causal role in human addiction is unclear. Different groups (Dalley et al., 2007; Bezze et al., 2007 and Dalley et al., 2011) have characterized, in neurobehavioral and neurochemical terms, a rodent model of impulsivity

based on premature responses in an attentional task. Evidence suggests that high impulsivity on this task precedes the subsequent escalation of cocaine self-administration behavior (Dalley et al., 2007, and also a tendency towards compulsive cocaine-seeking (Belin et al., 2008) and to relapse (Economidou et al., 2009). On the other hand, excessive consumption of palatable food can trigger neuroadaptive responses in brain reward circuitries similar to those produced by drugs of abuse. Thus, congruent genetic vulnerabilities in brain reward systems can increase predisposition to drug addiction and obesity. Kenny (2011) has recently advanced our understanding of the brain circuitries that regulate hedonic aspects of feeding behavior, with evidence suggesting that obesity and drug addiction may share common mechanisms.

Individuals take addictive drugs to elevate mood, but after repeated use these drugs produce serious unwanted effects, which include: tolerance to some drug effects, sensitization to others, and an adapted state-dependence, these setting the stage for withdrawal symptoms when drug use stops. The most serious consequence of repetitive drug taking is however addiction: a persistent state in which compulsive drug use escapes control, even when serious negative consequences ensue. Addiction is characterized by a long-lasting risk of relapse, which is often initiated by exposure to drug-related cues. Substantial progress has been made in understanding the molecular and cellular mechanisms of tolerance, dependence and withdrawal but, as yet, we understand little of the neural substrates of compulsive drug use and its remarkable persistence. Evidence exists for the possibility that compulsion and its persistence are based on a pathological usurpation of molecular mechanisms that are normally involved in memory (see Hyman and Malenka 2001 for review).

Genetic studies to date have been most successful at identifying factors that influence the transition from regular use to dependence. Numerous and large twin studies have indicated a significant genetic contribution to the process of conversion from eventual use to established use before development of dependence. The availability of large cohort samples for nicotine and alcohol dependence has resulted in significant progress being made in understanding at least some of the genetic contributions to these addictions (Tsuang et al., 1998, Kendler et al., 2003). Fewer studies have replicated specific genetic contributions to illicit drug use. Substance dependence can be thought of as a pharmacogenetic illness and, most likely, hundreds and more probably thousands of genetic variants will be required to fully explain the genetic input to this disease (see Bierut, 211 for review).

### **1.1 Neurobiology of addiction**

Addictive drugs have in common the property that they are voluntarily self-administered by laboratory animals (usually avidly) (Di Chiara et al., 2004), and that they enhance the functioning of the reward circuitry of the brain (producing the 'high' that the drug user seeks). The core reward circuitry consists of an 'in-series' circuit linking the ventral tegmental area (VTA), nucleus accumbens (NAc) and ventral pallidum via the medial forebrain bundle. All addictive drugs have in common that they enhance (directly or indirectly or even transsynaptically) dopaminergic synaptic function in the NAc (Di Chiara et al., 2004), which is implicated in the reward process. Drug self-administration is regulated by NAc dopamine (DA) levels, which are retained within a specific elevated range (to maintain a desired hedonic level). The three classical sets of craving and relapse triggers are (a) reexposure to addictive drugs, (b) stress, and (c) reexposure to environmental cues

(people, places, things) previously associated with drug-taking behavior. Knowledge of the neuroanatomy, neurophysiology, neurochemistry and neuropharmacology of addictive drug action in the brain is currently producing a variety of strategies for pharmacotherapeutic treatment of drug addiction, some of which appear promising (Gardner, 2011). Addictive drugs target the mesocorticolimbic dopamine (DA) system. This system originates in the VTA and projects mainly to the NAc and prefrontal cortex (PFC), affecting glutamatergic and GABAergic synaptic transmission in all three brain areas. These changes are referred to as drug-evoked synaptic plasticity, which outlasts the presence of the drug in the brain and contributes to the reorganization of neural circuits. While in most cases these early changes are not sufficient to induce the disease, with repetitive drug exposure, they may add up and contribute to addictive behavior (see Lüscher and Malenka, 2011 for review).

## 1.2 Learning and memory in addictive behavior

Two forms of cellular and synaptic plasticity, long-term potentiation (LTP) and long-term depression (LTD) remain the most extensively studied. They are considered the cellular and molecular basis of learning and memory (Kandel, 2004; Negrete-Díaz et al., 2007; Adermark et al., 2009; Abusch and Akirav, 2010; Collingridge et al., 2010; Huang et al., 2011, Figure 1).

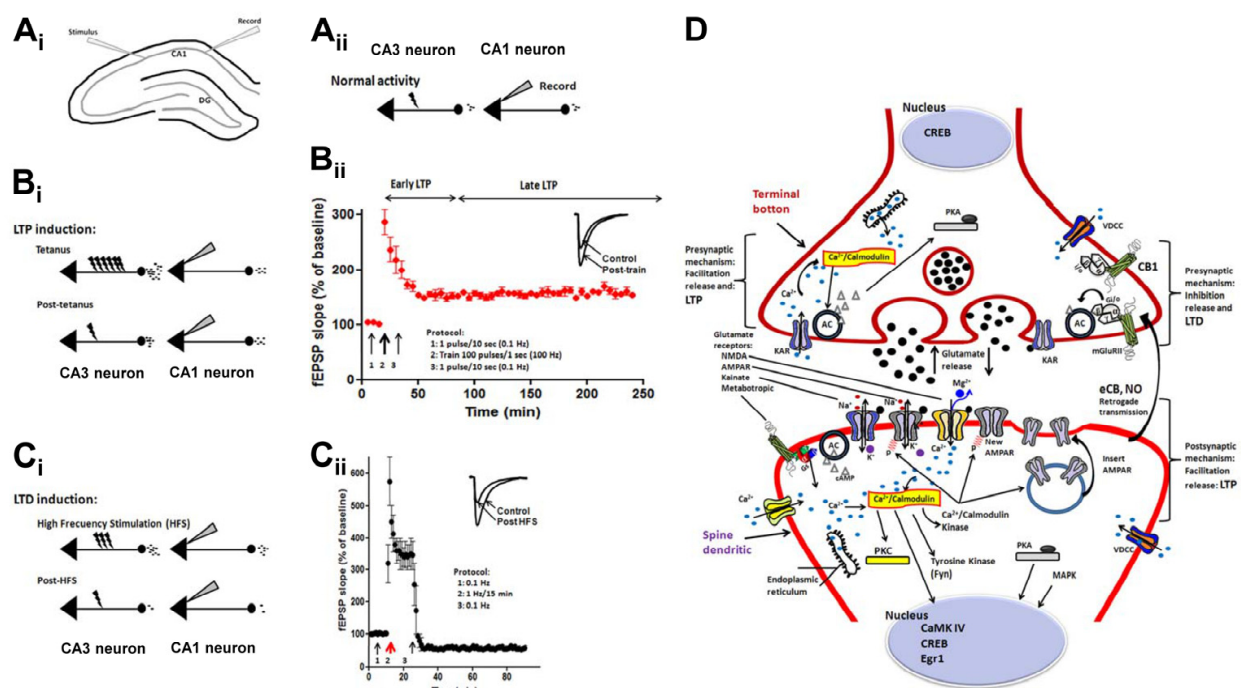


Fig. 1. LTP and LTD. Induction protocols and cellular mechanisms. A<sub>i</sub> transverse hippocampal slice and estándar positioning of stimulating and recording electrodes. Hippocampus is the structure in which plasticity mechanisms have been more extensively estuded. A<sub>ii</sub>, representation of presynaptic and postsynaptic neurons at synapse between CA3 and CA1 pyramidal cells. B<sub>i</sub>, LTP protocol, tetanic (100 Hz, 1s) stimulation of presynaptic neurons induce and increase of the amplitude of excitatory postsynaptic potencial EPSP (B<sub>ii</sub>) recorded from postsynaptic neurons. C<sub>i</sub>, LTD protocol, stimulation at 1 Hz during 15 minutes induce a decrease of the amplitude of the EPSP (C<sub>ii</sub>) recorded from postsynaptic neurons. D, schematic description of intracellular mechanisms involved in LTP and LTD

In addition, they can be used to demonstrate the repertoire of enduring modifications of individual synapses, circuits or neural networks. A classic triad arrangement of DA terminal varicosities, dendritic spines, and cortical inputs allows dopamine to enhance spike-time-dependent plasticity (STDP) at active cortico-striatal and cortico-cortical synapses. The induced LTP and LTD are candidate mechanisms for phasic DA signal to mediate behavioral learning. Thus, by affecting striatal and cortical plasticity, addictive drugs could lead to long-lasting changes of the motor, reward, and cognitive functions of these structures, striatum and PFC (Schultz, 2011). Conditioned stimuli (CSs) by Pavlovian association with reinforcing drugs (unconditioned stimuli; US) are thought to play an important role in the acquisition, maintenance and relapse of drug dependence. Bassareo et al. (2007) using microdialysis investigated the impact of pavlovian drug CSs on behaviour and on basal and drug-stimulated transmitter levels in three terminal DA areas: NAc shell and core, and the PFC. Drug CSs elicited incentive reactions and released DA; pre-exposure to CSs potentiated DA release to drug (Schultz, 2011). Théberge et al. (2010) demonstrated that the basolateral amygdala (BLA) and the NAc core are two structures importantly involved in the reconsolidation of a cocaine-CS memory. They show that, depending on the psychological processes involved, different neural substrates within limbic cortical-ventral striatal circuitry are required for the reconsolidation of a Pavlovian memory. Milton and Everitt, 2010, have shown with more detail the memory reconsolidation mechanisms underlying conditioned reinforcement and its relationship to drug addiction and the subsequent translation to the clinic of preclinical works.

### 1.3 Dopamine in addiction

DA's contribution appears to chiefly cause 'wanting' for hedonic rewards, more than 'liking' of or learning of those rewards (Schultz, 2011). However, the debate continues over the precise causal contribution made by mesolimbic DA systems to reward. Recent evidence indicates that DA is neither necessary nor sufficient to mediate changes in hedonic 'liking' for sensory pleasures. Other recent evidence indicates that DA is not needed for new learning, and not sufficient to directly mediate learning by causing teaching or prediction signals. Drugs of abuse promote DA signals, short circuit and sensitize dynamic mesolimbic mechanisms that evolved to attribute incentive salience to rewards (Berridge, 2007). The potential use of drugs to enhance cognition, emotion, and executive function has engendered controversy despite the fact that few such agents exist today. Hyman (2011) provided a context for discussions based on medical, regulatory, and ethical concerns that have been raised by the possibility that enhancers will emerge from current efforts to discover drugs for neuropsychiatric disorders. Addiction coopts the brain's neuronal circuits necessary for insight, reward, motivation, and social behaviors. This functional overlap results in addicted individuals making poor choices despite awareness of the negative consequences (Volkow et al., 2011). This explains why previously rewarding life situations and the threat of judicial punishment cannot stop drug taking and why a medical rather than a retributive approach is more effective in curtailing addiction.

We describe in this chapter the effects of cannabinoids, cocaine and amphetamines on the nervous system with particular emphasis on the effects of these compounds in plasticity processes. As the DA transporter is central to the effects of these drugs, we dedicate some special attention to the physiology of this type of transporter.

## 2. Cannabinoids (Table 1)

The use of marijuana for recreational and medicinal purposes has resulted in a large prevalence of chronic marijuana users (WHO, 2012). In the present decade, cannabis abuse has grown more rapidly than cocaine and opiate abuse. About 147 million people, 2.5% of the world population, consume cannabis (annual prevalence) compared with 0.2% consuming cocaine and 0.6% consuming amphetamine (WHO, 2012). The most rapid growth in cannabis abuse since the 1960s has been in developed countries in North America, Western Europe and Australia (WHO, 2012). Consequences of chronic cannabinoid administration include profound behavioral tolerance and withdrawal symptoms upon drug cessation. A marijuana withdrawal syndrome is only recently gaining acceptance as being clinically significant. Similarly, laboratory animals exhibit both tolerance and dependence following chronic administration of cannabinoids. These animal models are being used to evaluate the high degree of plasticity that occurs at the molecular level in various brain regions following chronic cannabinoid exposure (Lichtman and Martin, 2005).

### 2.1 The endocannabinoid (eCB) signaling system

The isolation and identification, in 1964 (Gaoni and Mechoulam, 1964), of delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC), the primary psychoactive compound in cannabis, opened the door to a whole new field of medical research. The exploration of the therapeutic potential of THC and other natural and synthetic cannabinoid compounds was paralleled by the discovery of the endocannabinoid system, comprising cannabinoid receptors and their endogenous ligands, which offered exciting new insights into brain function (see Isbell et al., 1967 for review). Besides its well-known involvement in specific brain functions, such as control of movement (Di Marzo et al., 2000; Keeney et al., 2008; Fuss and Gass, 2010), memory (Deadwyler et al., 2007; Deadwyler and Hampson, 2008) and emotions (Paule et al., 2005; Tan et al., 2010), the endocannabinoid system plays an important role in fundamental developmental processes such as cell proliferation, migration and differentiation (Trezza et al., 2008, 2012). For this reason, changes in its activity during stages of high neuronal plasticity, such as the perinatal and the adolescent period, can have long-lasting neurobehavioral consequences (see Trezza et al., 2008 for review). Two subtypes of cannabinoid receptors (CBRs) have been identified to date, the CB1 receptor, essentially located in the CNS, but also in peripheral tissues, and the CB2 receptor, found only at the periphery. Many of the effects of cannabinoids, such as delta (9)-THC ( $\Delta^9$ -THC), the psychoactive principle of *cannabis sativa*, and endocannabinoids (eCBs) are mediated by these two metabotropic receptors, although additional receptors may be implicated. Both CB1 and CB2 are G-protein-coupled receptors (GPCRs), primarily operating through inhibitory G proteins, and are subject to the same pharmacological influences of other GPCRs (Chaperon and Thiébot, 1999; Basavarajappa et al., 2009). Freund et al. (2003) described a fine-grain anatomical distribution of the neuronal cannabinoid receptor CB1 in brain areas, emphasizing its general presynaptic localization and role in controlling neurotransmitter release, synaptic plasticity and network activity patterns. The eCBs as ligands for these CB1 and CB2 receptors are a family of lipidic mediators that signal through the same cell surface receptors that are targeted by  $\Delta^9$ -THC. Unlike neurotransmitter molecules that are typically held in vesicles before synaptic release, eCBs are liberated directly after synthesis and, once released, travel in a retrograde direction to suppress presynaptic neurotransmitter release through activation of CBRs (Basavarajappa, 2007).

Drug	Effect on brain plasticity and behaviour	Structures	Autor
Marijuana or CB1R pharmacological manipulation	Presence of an 'amotivational' syndrome	Limbic system	Paule, 2005
	Regulation of ion channels, neurotransmitter release and synaptic plasticity	Multiples brain regions	Fisar, 2009
	Profound behavioral tolerance and withdrawal symptoms	Limbic system	Lichtman & Martin, 2005
	Activity of central reward pathways altered	VTA	Lupica et al., 2004
	↑ Risk of developing psychotic disorders in adolescence Disturbs in glutamate and GABA release	PFC	Bossong & Niesink, 2010
	↑ Density of cannabinoid CB1R binding	Corticolimbic regions	Fernandez-Espejo et al., 2009
	↓ Hippocampal encoding and the ability to encode information into short-term memory	Hippocampus	Deadwyler et al., 2007; Deadwyler and Hampson, 2008.
	Impaired LTP Facilitated LTD	Schaffer collateral-CA1 projection	Abush & Akirav, 2010
	LTD blocked with CB1R antagonist	Glutamatergic and GABAergic synapses in the striatum	Adermark et al., 2009
	Impaired LTP Decrease in LTP prevented by pharmacological inhibition or deletion of the CB1R	Hippocampus	Fan et al., 2010
	Metaplastic effects on brain cortex	Motor cortex	Koch et al., 2009
	↑ Response of mPFC neurons Modulate emotional memory formation	mPFC, BLA	Laviolette & Grace, 2006
	↓ Gray matter	Cerebral cortex	Stone et al., 2011
	Blocked LTP and acquisition of conditioned fear memories by CB1R antagonist	BLA-PLC pathway	Tan et al., 2010
Changes in cell proliferation, migration and differentiation	Central nervous system, eCB system	Trezza et al., 2008	

Table 1. Plastic changes on brain regions by chronic use of marijuana,  $\Delta 9$ -THC administration or CB1R pharmacological manipulation.

(Abbreviations: BLA: basolateral amygdale; CB1R: type 1 cannabinoid receptor; eCB: endocannabinoid; GABA: gamma aminobutyric acid; LTP: long-term potentiation; LTD: long-term depression; mPFC: medial prefrontal cortex; PLC: prelimbic cortex; PFC: prefrontal cortex).

Recent results have suggested that the eCB system may play an important role in early neuronal development having been detected from the earliest stages of embryogenesis and throughout pre- and postnatal development. Additionally, the eCB signaling system is being found to be involved in an increasing number of neuropathological conditions, with widespread roles being invoked in neurodegenerative disorders. The fact that eCB signaling is mostly inhibitory, imparts eCBs with the ability to modulate synaptic efficacy with a wide range of functional consequences and provides unique therapeutic possibilities in central nervous system (CNS) diseases, including alcoholism, Alzheimer's disease, Parkinson's disease, Huntington's disease, and multiple sclerosis (see Basavarajappa, 2007; Basavarajappa et al., 2009 for reviews).

Although CB1 receptors are distributed throughout the brain, they are found at very high levels in the cerebellum. Edwards and Skosnik (2007) have integrated two separate literatures. The first literature demonstrates that the eCB system mediates synaptic plasticity, specifically LTD of parallel fibers at the parallel fiber-Purkinje junction in the cerebellar cortex. The second literature suggests that LTD at this junction is necessary for the acquisition of the primary dependent variable in delay eyeblink conditioning. Also, they discuss recent evidence from CB1 knockout mice, human cannabis users, and schizophrenia patients, with the expectation that translational research on the cannabinoid system will be advanced. Wiskerke et al. (2008) summarize studies in which have been used CB1R knockout mice as well as CB1 antagonists to elucidate the role of this neurotransmitter system in psychostimulant addiction. CB1 receptors appear not to be involved in psychostimulant reward, nor in the development of dependence to such substances. In contrast, the eCB system appears to play a role in the persistence of psychostimulant addiction (see Wiskerke et al., 2008 for review). Interactions of the eCB system with afferent glutamatergic and possibly dopaminergic projections to the nucleus accumbens are most likely involved and CB1 receptors seem to modulate drug-related memories, in line with the hypothesized role of the eCB system in memory-related plasticity. Together, these findings suggest that modulators of the eCB system represent a promising novel type of therapy to treat drug addiction.

## 2.2 The reward system

The reward circuitry of the brain consists of neurons that synaptically connect a wide variety of nuclei. Of these brain regions, the VTA and the NAc play key roles in the processing of rewarding environmental stimuli and in drug addiction. The psychoactive properties of marijuana are produced by  $\Delta^9$ -THC, interacting primarily with CB1 receptors in a large number of brain areas. However, it is the activation of CB1 receptors located in reward circuits that is thought to be instrumental in sustaining the self-administration of marijuana in humans, and in mediating the anxiolytic and pleasurable effects of the drug. It has been suggested that, whereas  $\Delta^9$ -THC alters the activity of central reward pathways in a manner that is consistent with other abused drugs, the cellular mechanism through which this occurs is likely different, relying upon the combined regulation of several afferent pathways to the VTA (see Lupica et al., 2004 for review).

## 2.3 Cannabis, cannabinoids and neuronal plasticity

Changes in synaptic efficacy are thought to be crucial to experience-dependent modifications of neural function. eCB-mediated plasticity encompasses many forms of



transient and long-lasting synaptic depression and is found at both excitatory and inhibitory synapses. Thus, the eCB system is emerging as a major player in synaptic plasticity and, given the wide distribution of CB1 receptors in the CNS, the list of brain structures and synapses expressing eCB-mediated plasticity is likely to expand (see Chevaleyre et al., 2006 for review). Glutamate is the principal excitatory neurotransmitter in CNS and altered glutamatergic transmission during critical periods (such as first postnatal weeks) may disturb circuitry in specific brain areas (including cortex and hippocampus), particularly in experience-dependent maturation. Recent hypotheses regarding disturbances in strengthening and pruning of synaptic connections in the PFC, and the link with latent psychotic disorders suggest that cannabis-induced schizophrenia is due to a distortion of normal late postnatal brain maturation (see Bossong and Niesink, 2010 for review). In this respect, cannabis use during adolescence increases the risk of developing psychotic disorders later in life. In animals, Bossong and Niesink (2010) postulated that adolescent exposure to  $\Delta^9$ -THC transiently disturbs physiological control of the eCB system over glutamate and GABA release. As a result,  $\Delta^9$ -THC may adversely affect adolescent experience-dependent maturation of neural circuitries within prefrontal cortical areas. Depending on dose, exact time window and duration of exposure, this may ultimately lead to the development of psychoses like schizophrenia.

There is substantial evidence that cannabis abuse is a risk factor for psychosis in genetically predisposed people, may lead to a worse outcome of the disease, or it can affect normal brain development during adolescence, increasing the risk for schizophrenia in adulthood. On the other hand, the eCB system is altered in schizophrenia (increased density of CB1 receptors binding in corticolimbic regions). Dysregulation of this system can interact with neurotransmitter systems in such a way that a "cannabinoid hypothesis" can be integrated in the neurobiological hypotheses of schizophrenia. Also, there is evidence that some genetic alterations of the CNR1 gene can act as a protectant factor against schizophrenia or can induce a better pharmacological response to atypical antipsychotics (see Fernandez-Espejo et al., 2009 for review). Awareness of cannabis dependence as a clinically relevant issue has grown in recent years. Clinical and laboratory studies demonstrate that chronic marijuana smokers can experience withdrawal symptoms upon cessation of marijuana smoking and have difficulty abstaining from marijuana use. The behavioral effects that directly contribute to the maintenance of chronic marijuana smoking are reward, subjective effects, and the positive and negative reinforcing effects of marijuana,  $\Delta^9$ -THC or synthetic cannabinoids (Cooper and Haney, 2008).

Studies using population codes derived from ensembles of hippocampal neurons have been assessed to determine whether eCBs were active when rats performed a short-term memory task in presence or absence of CB1 receptor antagonists or agonists. Results show that eCBs, like marijuana, reduced hippocampal encoding necessary to perform long-delay trials (Deadwyler et al., 2007). Also, CB1 receptor antagonism blocked an inherent hippocampal memory encoding bias used by all animals. These findings suggest a direct relationship between the actions of cannabinoids on hippocampal processes and the ability to encode information into short-term memory Deadwyler and Hampson, 2008. Considerable evidence demonstrates that cannabinoid receptor agonists impair, whereas cannabinoid receptor antagonists improve, memory and plasticity (Ademark et al., 2009; Fan et al., 2010). However, recent studies suggest that the effects of cannabinoids on learning do not

necessarily follow these simple patterns, particularly when emotional memory processes are involved. Abush and Akirav (2010) have investigated the involvement of the CB system in hippocampal learning and plasticity using behavioral task and cellular models of learning and memory (LTP and LTD). They found that i.p. agonist administration impaired LTP in the Schaffer collateral-CA1 projection, whereas an inhibitor of eCB reuptake facilitated LTD. These findings suggest that the diverse effects of the cannabinoid system on CA1 memory and plasticity cannot be categorized simply into an impairing or an enhancing effect of cannabinoid activation and deactivation, respectively. Previous studies have indicated that eCB mobilization at excitatory synapses might be regulated by afferent activation. LTD at striatal synapses is mediated by postsynaptic eCB release and presynaptic CB1 receptor activation. Adermark et al. (2009) have examined changes in synaptic strength induced by activation of L-type calcium channels at glutamatergic and gamma-aminobutyric acid (GABA)ergic synapses in the striatum. They found that the basic mechanisms for eCB signaling are the same at glutamatergic and GABAergic synapses. LTD was blocked in slices treated with AM251, a CB1 receptor antagonist, but established depression was not reversed at either glutamatergic and GABAergic synapses. It is suggested that the level of neuronal firing regulates eCB signaling by modulating release from the postsynaptic cell, as well as interacting with presynaptic mechanisms to induce LTD at both glutamatergic and GABAergic synapses in the striatum.

Chronic use of marijuana impairs synaptic plasticity and cognitive function. Fan et al. (2010) found that repeated *in vivo* exposures to  $\Delta^9$ -THC for 7 consecutive days significantly impaired hippocampal LTP of excitatory glutamatergic synaptic transmission, and this decrease in LTP was prevented by pharmacological inhibition or deletion of the CB1 receptor. They showed that reduced expression and function of the GluR subunits and phosphorylation of cAMP response element-binding (CREB) may underlie the impaired long-term synaptic plasticity induced by repeated *in vivo* exposure to  $\Delta^9$ -THC. In animal models, the CB system has been convincingly implicated in the regulation of long-lasting synaptic plasticity. Both LTP and LTD can be induced in the human motor cortex by transcranial magnetic theta burst stimulation (TBS). Koch et al. (2009) explored the potential involvement of the CB system in TBS-induced synaptic plasticity in humans with multiple sclerosis. Continuous TBS induced the expected inhibition of motor-evoked potentials (MEPs) before cannabis-based preparation exposure (Sativex), whereas it caused a persisting enhancement of MEP amplitude 4 weeks after. The LTP-like phenomenon induced by intermittent TBS was conversely unaffected by preparation exposure. These results indicate that cannabis ingredients have metaplastic effects on the motor cortex. Laviolette and Grace (2006), using *in vivo* single-unit recordings in rats, found that a CB1 receptor agonist potentiated the response of medial prefrontal cortical (mPFC) neurons to olfactory cues paired previously with a footshock, whereas this associative responding was prevented by a CB1 receptor antagonist, providing the first demonstration that CB signaling in the mPFC can modulate the magnitude of neuronal emotional learning plasticity and memory formation through functional inputs from the basolateral amygdala (BLA, Laviolette and Grace, 2006).

Individuals with an "at risk mental state" (ARMS) are greatly more susceptible to developing a psychotic illness. There has been considerable interest in the interaction between psychosis risk and substance use. Cannabis at low to moderate intake may be associated with lower gray matter in both ARMS subjects and healthy volunteers, possibly

representing low-level cortical damage or change in neural plasticity (Stone et al., 2011). The CB1 receptor system is functionally involved in the processing and encoding of emotionally salient sensory information, learning and memory. The CB1 receptor is found in high concentrations in brain structures that are critical for emotional processing, including the BLA and the mPFC. Synaptic plasticity in the form of LTP within the BLA-mPFC pathway is an established correlate of exposure to emotionally salient events (Laviolette and Grace, 2006). *In vivo* LTP studies showed that systemic pretreatment with AM-251, dose-dependently block LTP along the BLA-PLC pathway, and also the behavioral acquisition of conditioned fear memories (Tan et al., 2010). Experiments show that when CB1 receptor transmission within the BLA-PFC circuit was pharmacologically blocked, this prevented the acquisition of emotionally salient associative memory. These results indicate that coordinated CB1 receptor transmission within the BLA-PFC pathway is critically involved in the encoding of emotional fear memories and modulates neural plasticity related to the encoding of emotionally salient associative learning (Tan et al., 2010).

### 3. Cocaine (Table 2)

Behavioral sensitization is the augmented motor-stimulant response that occurs with repeated, intermittent exposure to most drugs of abuse, including cocaine. Sensitization, which is a long-lasting phenomenon, is thought to underlie drug craving and relapse to drug use (Steketee et al., 2003). The neural mechanisms of sensitization have focused on the NAc and VTA that comprise a part of the mesolimbic DA system. Cocaine sensitization results from a decrease in inhibitory modulation of excitatory transmission from the mPFC

Drug	Effect on brain plasticity and behaviour	Structures	Autor
Cocaine	Induced behavioural sensitization	mPFC, NAc, VTA	Steketee, 2003; 2005
	Induced conditioned place preference	mPFC, NAc shell, VTA	McBride et al., 1999
	↑ BDNF, ↓ mGluR5, LTD impaired	NAc shell	Huang et al., 2011
	↑ DA transmission and induce CTA	NAc shell	Di Chiara et al., 2004
	Behavioral deficits at birth and/or during adulthood	Limbic system	Lidow, 2003
	Behavioral rigidity or lack of plasticity	PFC, limbic system	Paule, 2005
	Changes in Fos expression	Lateral hipotalamus	Aston-Jones et al., 2009
	Shift from impulsivity to compulsivity during the development of addictive behavior	PFC, ventral and dorsal striatum	Belin et al., 2008
	Increased MeCP2 expression and microRNA	Dorsal striatum	Welberg, 2010

Table 2. Plastic changes on brain regions by chronic use of cocaine.

(Abbreviations: BDNF: brain-derived neurotrophic factor; CTA: conditioned taste avoidance; DA: dopamine; LTD: long-term depression; MeCP2: methyl CpG binding protein 2; mGluR5: type 5 metabotropic glutamate receptor; mPFC: medial prefrontal cortex; NAc: nucleus accumbens; VTA: ventral tegmental area).

to the VTA and NAc. Repeated cocaine exposure alters DA, gamma-aminobutyric acid (GABA), and glutamate regulation of pyramidal cell activity (Di Chiara et al., 2004; Huang et al., 2011), with cocaine-induced alterations in cortical transmission occurring in two phases. During early withdrawal from repeated cocaine exposure, changes in neurotransmitter release are thought to underlie the decreased inhibitory modulation of pyramidal projection neurons. Following more prolonged withdrawal, the attenuation in inhibitory transmission appears to occur at the receptor level (Steketee, 2005).

### 3.1 Cocaine and dopaminergic system

Neuroadaptation in the NAc, a central component of the mesolimbic DA system, has been implicated in the development of cocaine-induced psychomotor sensitization and relapse to cocaine seeking (Zhang et al., 2001; Anderson et al., 2003; see Steketee, 2005 for review). Recent results suggest that withdrawal from repeated cocaine exposure may result in increased brain-derived neurotrophic factor (BDNF) levels in the NAc shell, which leads to a selective downregulation of mGluR5 and thereby impairs the induction of mGluR-dependent LTD (Huang et al., 2011). The effects of BDNF on cocaine-seeking are brain region-specific. Infusion of BDNF into subcortical structures, like the NAc and VTA, enhances cocaine-induced behavioral sensitization and cocaine-seeking. Conversely, repeated administration of BDNF antiserum into the NAc during chronic cocaine self-administration attenuates cocaine-induced reinstatement. Three weeks after BDNF antiserum infusion in animals with a cocaine self-administration history, suppressed basal levels of glutamate are normalized, and a cocaine prime-induced increase in extracellular glutamate levels in the NAc is prevented (McGinty et al., 2010). Although the development of behavioral sensitization to psychostimulants such as cocaine and amphetamine is confined mainly to one nucleus in the brain, the VTA, this process is nonetheless complex, involving an interplay between neurotransmitters, neuropeptides and trophic factors. Calcium-stimulated signalling molecules, including the calcium/calmodulin-dependent protein kinases, and the Ras/mitogen-activated protein kinases, represent the major biochemical pathways whereby converging extracellular signals are integrated and amplified, resulting in the biochemical and molecular changes in DA neurons in the VTA that represent the critical neuronal correlates of the development of behavioral sensitization to psychostimulants (see Licata and Pierce, 2003 for review).

Using a mouse model of behavioral sensitization, Huang et al. (2011) showed that animals withdrawn from repeated cocaine exposure have a selective deficit in the ability to elicit metabotropic glutamate receptor (mGluR)-dependent LTD in the shell of the NAc in response to bath application of the group I mGluR agonist DHPG. Experiments demonstrated that the impaired DHPG-LTD is likely attributable to a loss of mGluR5 function. Quantitative real-time reverse transcriptase-PCR and Western blot analysis revealed significant downregulation of mGluR5, but not mGluR1, mRNA or protein levels in the NAc shell. The inhibitory effect of repeated cocaine exposure on DHPG-LTD was selectively prevented when cocaine was coadministered with a selective D1 receptor antagonist. Furthermore, the levels of BDNF protein in the NAc shell increased progressively after cocaine withdrawal, and crucially, the impairment of DHPG-LTD in the NAc shell was not found in slices from BDNF-knock-out mice after cocaine withdrawal. Recent evidence suggests that CB1Rs may represent effective targets for therapeutic agents

used to treat cocaine relapse. Li et al. (2008) determined whether CBRs play a similar role in relapse to ketamine abuse. To establish a ketamine reinstatement model in the conditioned place preference paradigm, rats were trained to develop place preference conditioned by ketamine, which was subsequently extinguished through daily exposure to the test chambers in the absence of ketamine. The effects of rimonabant, a CB1Rs antagonist, were investigated on reinstatement of ketamine-induced place preference. While ketamine priming injections reinstated extinguished place preference, rimonabant administration significantly attenuated the reinstatement of ketamine-induced place preference in a dose-dependent manner. Importantly, rimonabant itself did not produce conditioned place preference or place aversion. Since the reinstatement effects of ketamine administration were inhibited by rimonabant, these findings suggest that a CB1 receptor antagonist may be useful in preventing relapse to ketamine abuse. VTA DA neurons play a pivotal role in processing reward-related information and are involved in drug addiction and mental illness in humans (Wise, 2004). Information is conveyed to the VTA in the large part by glutamatergic afferents that arise in various brain nuclei, including the pedunculopontine nucleus (PPN).

In rat brain slice preparations, Good and Lupica (2010) found that PPN stimulation activates afferents targeting GluR2-containing AMPA receptors (AMPA) on VTA DA neurons, and these afferents did not exhibit long-term depression (LTD). In contrast, activation of glutamate afferents onto the same DA neurons via stimulation within the VTA evoked both, excitatory postsynaptic currents EPSCs mediated by GluR2-lacking AMPARs which showed LTD, and EPSCs mediated by GluR2-containing AMPA receptors that did not express LTD. Single cocaine injections increase GluR2-lacking AMPA receptors at all glutamate synapses on VTA dopamine neurons (and this permitted LTD expression in both pathways), whereas  $\Delta$ 9-THC selectively increased GluR2-lacking AMPA receptors at subcortical PPN synapses (and permitted LTD in the PPN pathway only), suggesting that different drugs of abuse may exert influence over distinct sets of glutamatergic afferents to VTA DA neurons, which may thereby be associated with different reinforcing or addictive properties of these drugs. Microdialysis studies in animals have shown that addictive drugs preferentially increase extracellular DA levels in the NAc rather than in the core. However, by acting directly on the brain, drugs bypass the adaptive mechanisms (habituation) that constrain the responsiveness of accumbens shell DA to food reward, abnormally facilitating Pavlovian incentive learning and promoting the acquisition of abnormal DA-releasing properties by drug conditioned stimuli (See Di Chiara & Bassareo, 2007 for review). Thus, whereas Pavlovian food conditioned stimuli release core but not shell DA, drug conditioned stimuli do the opposite, releasing shell but not core DA. This process, which results in the acquisition of excessive incentive-motivational properties by drug conditioned stimuli has been suggested to contribute to the initiation of the drug addiction process (Imperato and Di Chiara, 1986; Di Chiara and Bassareo, 2007).

Brain imaging studies, while extending these findings to humans, have shown a correlation between psychostimulant-induced increase of extracellular DA in the striatum and self-reported measures of liking and euphoria (Volkow et al., 2002a; 2002b). Although a correlate of drug reward, independent from associative learning and performance is difficult to obtain in animals, conditioned taste avoidance (CTA) might meet these requirements. Addictive drugs induce CTA to saccharin most likely as a result of anticipatory contrast of saccharin over drug reward. Consistently with a role of DA in drug reward, D2 or combined D1/D2 receptor

blockade abolishes cocaine, amphetamine and nicotine CTA. Intracranial self-administration studies with mixtures of D1 and D2 receptor agonists point to the NAc shell as the critical site of DA reward (Di Chiara et al., 2004; Bassareo et al., 2007). NAc shell DA acting on D1 receptors is also involved in Pavlovian learning through pre-trial and post-trial consolidation mechanisms and in the utilization of spatial short-term memory for goal-directed behaviour (Volkow et al., 2011). Stimulation of NAc shell DA transmission by addictive drugs is shared by a natural reward like food, but lacks its adaptive properties (habituation and inhibition by predictive stimuli). These peculiarities of drug-induced stimulation of DA transmission in the NAc shell result in striking differences in the impact of drug-conditioned stimuli on DA transmission. It is speculated that drug addiction results from the impact exerted on behavior by the abnormal DA stimulant properties acquired by drug-conditioned stimuli as a result of their association with addictive drugs (Di Chiara et al., 2004; Everitt & Robbins, 2005). Di Chiara and Bassareo (2007) have summarized that addictive drugs share with palatable food, the property of increasing extracellular DA, preferentially in the NAc shell rather than in the core. However, by acting directly on the brain, drugs bypass the adaptive mechanisms (habituation) that constrain the responsiveness of NAc shell DA to food reward, abnormally facilitating Pavlovian incentive learning and promoting the acquisition of abnormal DA-releasing properties by drug conditioned stimuli. Thus, whereas Pavlovian foods conditioned stimuli release core but not NAc shell DA, drug conditioned stimuli do the opposite, releasing shell but not NAc core DA. Neuroadaptive processes related to the chronic influence of drugs on subcortical DA might secondarily impair the function of prefronto-striatal loops, resulting in impairments in impulse control and decision making that form the basis for the compulsive feature of drug seeking and its relapsing character (Belin and Everitt, 2010).

### 3.2 Prenatal cocaine exposure

The extent to which cocaine abuse by pregnant women can affect development of their offspring remains a matter of significant debate. In large part, this is due to difficulties in accurate determination of the type, dose, and pattern of cocaine administration by drug abusing women as well as to difficulties in controlling for a wide range of potentially confounding variables, such as other drugs used, race, socioeconomic status, and level of prenatal care. Examination of the effects of prenatal cocaine exposure in highly controlled nonhuman primate models represents an important complement to the human research. Data obtained in several different rhesus monkey models of cocaine exposure *in utero*, has demonstrated the potential of prenatal cocaine exposure to interfere with structural and biochemical development of the brain leading to behavioral deficits at birth and/or during adulthood. The differences in the outcomes between individual models also suggest that the specific types and severity of cocaine effects are likely dependent on the route, dose, gestational period, and daily pattern of administration (see Lidow, 2003 for review). Nonhuman primates (rhesus monkeys, *Macaca mulatta*) have been used to study the effects of chronic drug exposures on brain function during different stages of development. In the case of the marijuana studies, exposures occurred during the adolescent period; for the cocaine studies, exposures occurred *in utero*. A battery of behavioral tasks, designed to assess aspects of motivation, visual discrimination, time perception, short-term memory, and learning, was used to monitor treatment effects. Chronic marijuana smoke exposure resulted in an 'amotivational' syndrome. *In utero* cocaine exposure was shown to cause behavioral rigidity or lack of plasticity as evidenced by the difficulty of subjects to adjust to rules changes for some tasks. These effects were seen in adult subjects suggesting that the

effects of gestational cocaine exposure are long-term or permanent (see Paul, 2005 for review).

### 3.3 Orexins in drug-seeking

Orexins (also known as hypocretins) are recently discovered neuropeptides, synthesised exclusively in hypothalamic neurons, which have been shown to be important in narcolepsy/cataplexy and arousal (Zhou et al., 2008). Aston-Jones et al. (2009) conducted behavioral, anatomical and neurophysiological studies that show that a subset of these cells, located specifically in lateral hypothalamus (LH), are involved in reward processing and addictive behaviors. They found that Fos expression in LH orexin neurons varied in proportion to preference for cocaine or food. Recently, using a self-administration paradigm, it was discovered that the Ox1 orexin receptor antagonist, SB-334867 (SB), blocks cocaine-seeking induced by discrete or contextual cues, but not by a priming injection of cocaine. Neurophysiological studies revealed that locally applied orexin often augmented responses of VTA DA neurons to activation of the mPFC, consistent with the view that orexin facilitates activation of VTA DA neurons by stimulus-reward associations. These findings are consistent with results from others showing that orexins facilitate glutamate-mediated responses, and are necessary for glutamate-dependent long-term potentiation, in VTA DA neurons (Aston-Jones et al., 2010). Boutrel et al., (2005) show that intracerebroventricular infusions of hypocretin-1 lead to a dose-related reinstatement of cocaine seeking without altering cocaine intake in rats and elevates intracranial self-stimulation threshold. The effect was prevented by blockade of noradrenergic and corticotrophin releasing factor systems, suggesting that hypocretin-1 reinstated drug seeking through induction of a stress-like state.

### 3.4 Regulation of cocaine intake

Recent studies have started to reveal the contribution of epigenetic regulation to addiction-related behaviours and neuroadaptation. Two studies focused on the role of the X-linked transcriptional repressor methyl CpG-binding protein 2 (MeCP2), which contributes to the development and function of CNS synapses. They showed that drugs of abuse regulate the expression and/or activity of MeCP2 and that this contributes to behavioural and neural responses to the drug. MeCP2, known for its role in the neurodevelopmental disorder Rett syndrome, is emerging as an important regulator of neuroplasticity in postmitotic neurons.

Cocaine addiction is commonly viewed as a disorder of neuroplasticity (White, 1996; Everitt et al., 1999; Di Chiara, 1999). Heh-In et al. (2010) identified a key role for MeCP2 in the dorsal striatum in the escalating cocaine intake seen in rats with extended access to the drug, a process that resembles in some rats subjected to extended daily access to the drug, the increasingly uncontrolled cocaine use seen in addicted humans (See Badiani et al., 2011 for review). MeCP2 regulates cocaine intake through homeostatic interactions with microRNA-212 (miR-212) to control the effects of cocaine on striatal BDNF levels. They suggest that homeostatic interactions between MeCP2 and miR-212 in dorsal striatum may be important in regulating vulnerability to cocaine addiction. Deng et al. (2010) have shown that acute viral manipulation of MeCP2 expression in the NAc bidirectionally modulates amphetamine (AMPH)-induced conditioned place preference. *Mecp2* hypomorphic mutant mice have more NAc GABAergic synapses and show deficient AMPH-induced structural plasticity of NAc dendritic spines. Furthermore, these mice show deficient plasticity of striatal

immediate early gene inducibility after repeated AMPH administration. Notably, psychostimulants induce phosphorylation of MeCP2 at Ser421, a site that regulates MeCP2's function as a repressor. Phosphorylation is selectively induced in GABAergic interneurons of the NAc, and its extent strongly predicts the degree of behavioral sensitization. These data reveal new roles for MeCP2, both, in mesolimbocortical circuit development, and in the regulation of psychostimulant-induced behaviors. Also, Im et al (2010) reported increased MeCP2 expression and miR-212 (as well as miR-132) levels in the dorsal striatum in rats that had extended access to cocaine. Knocking down striatal MeCP2 expression using small hairpin RNA (shRNA) promoted the cocaine-induced increase in miR-212 expression. It also prevented the escalation of cocaine intake that normally occurs with prolonged cocaine access, an effect that could be blocked by disruption of miR-212 signalling using an antisense oligonucleotide. Furthermore, overexpressing miR-212 in the dorsal striatum, a neurobiological locus of control of habitual (Belin and Everitt 2008; Belin et al., 2009, 2010, Zapata et al., 2010, Murray et al., 2012) and compulsive (Jonkman et al., 2012) cocaine seeking, using a lentiviral vector reduced MeCP2 levels and decreased cocaine intake in rats with extended access to the drug (Im et al., 2010). These findings indicate that miR-212 and MeCP2 homeostatically regulate one another in the dorsal striatum and suggest that this interaction has a role in controlling compulsive cocaine intake. Taken together, these results suggest a role for MeCP2 in the behavioural response to psychostimulant drugs, although many questions remain regarding the undoubtedly complex mechanisms involved in its interactions with microRNAs and its modulation of synaptic plasticity (Welberg, 2010).

## **4. Amphetamine (Table 3)**

### **4.1 Dopaminergic system**

The fundamental principle that unites addictive drugs appears to be that each enhances synaptic DA by means that dissociate it from normal behavioral control, so that they act to reinforce their own acquisition. This occurs via the modulation of synaptic mechanisms that can be involved in learning, including enhanced excitation or disinhibition of DA neuron activity, blockade of DA reuptake, and altering the state of the presynaptic terminal to enhance evoked over basal transmission. Amphetamines offer an exception to such modulation in that they combine multiple effects to produce nonexocytotic, stimulation-independent release of neurotransmitter, via reverse-transport, independent from normal presynaptic function (Sulzer, 2011). In addition, behavioral sensitization is accompanied by an increase in postsynaptic DA receptors; an increase in DA synthesis; an increase in DA utilization and/or release (Kalivas and Stewart, 1991; Flores et al., 2011). There is strong evidence to support the notion that behavioral sensitization is due to enhanced mesotelencephalic DA release, especially upon re-exposure to the drug (Robinson and Becker, 1986). The mesocorticolimbic dopamine system, which arises in the VTA and innervates the NAc, among numerous other regions, has been implicated in processes associated with drug addiction, including behavioral sensitization. The mPFC, defined as the cortical region that has a reciprocal innervation with the mediodorsal nucleus of the thalamus, is also a terminal region of the mesocorticolimbic DA system. The mPFC contains pyramidal glutamatergic neurons that serve as the primary output of this region and mPFC transmitter systems are involved in the development of behavioral sensitization to cocaine and amphetamine (Steketee, 2003).



Drug	Effect on brain plasticity and behaviour	Structures	Autor
Amphetamine	Behavioural sensitization	VTA	Licata & Pierce, 2003; Robinson & Becker, 1986
	↑ DA transmission and induce CTA	NAc shell	Di Chiara et al., 2004
	Induced conditioned place preference Enhancement of hippocampal CaMKII activity Altered structural plasticity of dendritic spines	Hippocampus, NAc	Tan, 2008; Deng et al., 2010
	↑ postsynaptic DAR ↑ DA synthesis ↑ DA utilization and/or release Release of neurotransmitter via reverse transport	Mesotelencephalic system	Robinson & Becker, 1986
	Deficits in the passive avoidance and Y-maze tests LTP altered Pleiotrophin expression regulated	Hippocampus Limbic system	del Olmo et al., 2009; Gramage et al., 2011
	↑ Learning of environmental stimuli ↑ mGluR-dependent facilitation ↑ Susceptible to LTP induction	VTA	Ahn et al., 2010
	↑ NMDA-dependent, AMPA-mediated LTP ↓ LTD	Dopamine neurons	Schultz, 2011
	↓ PFC thickness in control females ↑ Posterior striatum thickness in control males	PFC, Striatum	Muhammad et al., 2011a
	↑ Spine density in NAc and mPFC ↓ Spine density in the OFC	NAc, mPFC, OFC	Muhammad & Kolb, 2011b; 2011c
	Psychosis, similar to paranoid schizophrenia	Limbic system	Robinson & Becker, 1986
↑ DAT at postpubertal age by prenatal exposure	NAc	Flores et al., 2011	

Table 3. Plastic changes on brain regions by chronic use of amphetamine.

(Abbreviations: AMPA:  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CaMKII: Ca<sup>2+</sup>/calmodulin-dependent protein kinase II CTA: conditioned taste avoidance; DA: dopamine; DAR: dopamine receptor eCB: endocannabinoid; LTP: long-term potentiation; LTD: long-term depression; mGluR: metabotropic glutamate receptor; mPFC: medial prefrontal cortex; NAc: nucleus accumbens; NMDA: N-Methyl-D-aspartic acid; OFC: orbital frontal cortex; PFC: prefrontal cortex; VTA: ventral tegmental area).

Intracranial self-administration (ICSA) and intracranial place conditioning (ICPC) methodologies have been mainly used to study drug reward mechanisms, but they have also been applied toward examining brain reward mechanisms (McBride et al., 1999; Di Chiara et al., 2004). ICSA studies in rodents have established that the VTA is a site supporting reinforcement. The NAc also appears to have a major role in brain reward mechanisms. Rodents will self-infuse a variety of drugs of abuse (amphetamine and cocaine) into the NAc, and this occurs primarily in the shell region. ICPC studies also indicate that injection of amphetamine into the shell portion of the NAc produces conditioned place preference (CPP). Activation of the DA system within the shell subregion of the NAc appears to play a key role in brain reward mechanisms. The PFC supports the ICSA of cocaine and phencyclidine. The DA system also seems to play a role in this behavior since cocaine self-infusion into the PFC can be blocked by co-infusing a D2 antagonist. Among other regions, ICPC findings suggest that cocaine and amphetamine are rewarding in the rostral ventral pallidum (VP). Finally, substance P-mediated systems within the caudal VP (nucleus basalis magnocellularis) and serotonin systems of the dorsal and median raphe nuclei may also be important anatomical components involved in brain reward mechanisms. Overall, the ICSA and ICPC studies indicate that there are a number discrete CNS sites involved in brain reward mechanisms (McBride et al., 1999).

#### 4.2 Amphetamine alters learning, LTP and LTD

Recent studies suggest LTP expression in locally activated glutamate synapses onto DA neurons (local Glu-DA synapses) of the midbrain VTA following a single or chronic exposure to many drugs of abuse, whereas a single exposure to cannabinoid did not significantly affect synaptic plasticity at these synapses. It is unknown whether chronic exposure of cannabis (marijuana or cannabinoids), the most commonly used illicit drug worldwide, induce LTP or LTD at these synapses. Pleiotrophin (PTN) is a cytokine with important roles in the modulation of synaptic plasticity, which levels of expression are significantly regulated by amphetamine administration. Gramage et al. (2011), have reported that amphetamine during adolescence causes long-term cognitive deficits in rats. Periadolescent amphetamine treatment daily during 10 days in normal and in PTN genetically deficient mice result in significant deficits in the passive avoidance and Y-maze tests (two tasks related to learning and memory abilities), only observed in amphetamine-pretreated PTN mutant mice. However, 13 and 26 days after the last administration, they did not find significant differences in Y-maze between amphetamine- and saline-pretreated PTN<sup>-/-</sup> mice. A significantly enhanced LTP in CA1 hippocampal slices from saline-pretreated PTN<sup>-/-</sup> mice compared with saline-pretreated PTN<sup>+/+</sup> mice was observed. Interestingly, amphetamine pre-treatment during adolescence significantly enhanced LTP in adult PTN<sup>+/+</sup> mice but did not cause any effect in PTN<sup>-/-</sup> mice, suggesting LTP mechanisms saturation in naïve PTN<sup>-/-</sup> mice. The data demonstrate that periadolescent amphetamine treatment causes transient cognitive deficits and long-term alterations of hippocampal LTP depending on the endogenous expression of PTN. Pleiotrophin (PTN) is a growth factor that has been shown to be involved in hippocampal synaptic plasticity and learning. Del Olmo et al. (2009), using *in vitro* electrophysiological recordings in PTN-stimulated CA1 from rat hippocampal slices, found that PTN inhibited hippocampal LTP induced by high-frequency stimulation (HFS). Also, they observed significant differences in recognition memory between PTN genetically deficient (PTN<sup>-/-</sup>) mice and wild type (WT) mice using the Y-maze test, whereas WT mice showed disruption of recognition memory,

PTN  $-/-$  mice maintained the recognition memory. The data demonstrate that PTN inhibits hippocampal LTP *in vitro* and might play a role in memory processes *in vivo*.

Synaptic plasticity in the mesolimbic DA system is critically involved in reward-based conditioning and the development of drug addiction (Schultz et al., 1998; Wise, 2004).  $Ca^{2+}$  signals triggered by postsynaptic action potentials (APs) drive the induction of synaptic plasticity in the CNS. Ahn et al. (2010) have recently proposed that enhancement of mGluR-dependent n-methyl-d-aspartate receptor (NMDAR) plasticity in the VTA may promote the learning of environmental stimuli repeatedly associated with amphetamine experience. In this study, using brain slices prepared from male rats, it was shown that repeated *in vivo* exposure to the psychostimulant amphetamine upregulates mGluR-dependent facilitation of burst-evoked  $Ca^{2+}$  signals in DA neurons of the VTA. Protein kinase A (PKA)-induced sensitization of  $IP_3$  receptors mediates this upregulation of mGluR action. As a consequence, NMDAR-mediated transmission becomes more susceptible to LTP induction after repeated amphetamine exposure. It was also found that the magnitude of amphetamine-conditioned place preference (CPP) in behaving rats correlates with the magnitude of mGluR-dependent  $Ca^{2+}$  signal facilitation measured in VTA slices prepared from these rats.

Major drugs of abuse such as cocaine, amphetamine, morphine, heroine, nicotine, and ethanol act on glutamatergic synapses on midbrain DA neurons and lead to NMDA-dependent, AMPA-mediated long-term potentiation in DA neurons. Thus, excitatory influences on these neurons become enhanced; in particular NMDA-dependent burst firing. Amphetamine also leads to reduction of LTD in DA neurons (Swope et al., 1999; Ahn et al., 2010; Liu et al., 2010, Good and Lupica, 2010). Thus, subthreshold fluctuations of excitatory inputs to DA neurons would increase or even generate action potentials in the absence of reward, generating a false reward signal (Schultz, 2011). There are glutamatergic projections from the hippocampus to the NAc, which regulate DA transmission in this structure. Ventral hippocampal (VH) glutamatergic neurons project to the NAc shell region, whereas the dorsal hippocampus (DH) sends glutamatergic projections to the NAc core region. Tan (2008) investigated the roles of hippocampal NMDA receptors and NAc D1 receptor in AMPH-produced conditioned place preference (AMPH-CPP) in rats. It was shown that AMPH-CPP results in the enhancement of hippocampal CaMKII activity which can be impaired by NMDA antagonist (AP5). Inactivation of hippocampal area (dorsal hippocampus or ventral hippocampus) impaired AMPH-CPP, but its effect was diminished by the activation of D1 receptors in NAc core or NAc shell. It was concluded that if the deterioration of AMPH-CPP expression resembles the formation of new learning, then this active process might have been facilitated by the hippocampal NMDA receptor activations during testing.

### 4.3 Amphetamine sensitization

Muhammad et al. (2011a) studied the effect of postnatal tactile stimulation (TS) on juvenile behavior, adult amphetamine (AMPH) sensitization, and the interaction of TS and AMPH on prefrontal cortical (PFC) thickness and striatum size. AMPH administration resulted in gradual increase in behavioral sensitization that persisted at least for 2 weeks. However, TS rats exhibited attenuated AMPH sensitization compared to sex-matched controls. Neuroanatomically, AMPH reduced the PFC thickness in control females but enlarged the posterior striatum in control males. It was suggested that TS during development modulated the response to novel objects and altered social behaviors and attenuated AMPH-induced behavioral sensitization by preventing drug-induced structural alteration in the PFC and the

striatum, brain regions implicated in drug abuse. Subsequently, these same investigators studied the effect of prenatal stress (PS) on juvenile behavior and adult AMPH sensitization, as well as the effect of the interaction between experience and drug on cortical thickness and neuronal morphology in corticolimbic regions in rats. PS did not influence AMPH-induced behavioral sensitization in either male or female rats. Moreover, PS increased the spine density in the NAc and decreased it in the mPFC without any alteration in the orbital frontal cortex (OFC). Similarly, AMPH administration increased spine density in the NAc and mPFC, whereas a decrease was observed in the OFC. However, PS prevented the drug-induced alterations in the spine density observed in controls. In sum, PS modulated juvenile behavior and altered brain morphology without influencing AMPH-induced behavioral sensitization substantially (Muhammad and Kolb, 2011b). Also, more recently Muhammad and Kolb (2011c) studied the long-term influence of maternal separation (MS) on periadolescent behavior, adult amphetamine (AMPH) sensitization, and structural plasticity in the corticolimbic regions in rats. Male and female pups, separated daily for 3h from the dam during postnatal day 3-21, were tested for periadolescent exploratory, emotional, cognitive, and social behaviors. The results showed that MS enhanced anxiety-like behavior in males. Repeated AMPH administration increased the spine density in the NAc and the mPFC, and decreased it in the OFC. MS blocked the drug-induced alteration in these regions. MS during development influenced periadolescent behavior in males, and structurally reorganized cortical and subcortical brain regions without affecting AMPH-induced behavioral sensitization.

#### 4.4 Amphetamine and mental disorders

Individuals who repeatedly use stimulant drugs, such as AMPH, develop an AMPH-induced psychosis that is similar to paranoid schizophrenia. There has been, therefore, considerable interest in characterizing the effects of chronic stimulant drug treatment on brain and behavior in non-human animals (Robinson and Becker, 1986).

### 5. Dopamine transporter and neural plasticity

Dopamine (DA) is one of the most important neurotransmitters affecting fine brain processes. Dysfunction of dopaminergic neurotransmission precipitates diseases such as Parkinson's disease (PD), schizophrenia, attention-deficit hyperactivity disorder (ADHD), and drug addiction (see Zhang et al., 2010 for review). DA synthesis occurs within the DA neurons. Tyrosine is transported into the cell via amino acid carriers in the blood-brain barrier and cell membranes. Once in the intracellular space, tyrosine is hydroxylated to L-3,4-dihydroxyphenylalanine (L-DOPA) by tyrosine hydroxylase (TH). L-DOPA is then decarboxylated by aromatic acid decarboxylase (AADC) to DA (for review see Miyake et al., 2011). Extracellular DA concentration and lifetime after release is regulated by diffusion, dilution as well as reuptake (for review see Rice and Cragge, 2008). Reuptake of synaptic DA by the dopamine transporter (DAT) is the principal mechanism regulating dopamine neurotransmission, and is often used as a marker for presynaptic DA function (for review see Zhang et al., 2010). In addition DA itself can regulate DAT via its interaction with the transporter or presynaptic autoreceptors (Williams and Galli, 2006). Interestingly, a recent report has found that unmedicated bipolar disorder (BPD) subjects had significantly lower DAT availability relative to healthy controls in bilateral dorsal caudate (Anand et al., 2011), thus the authors suggest that DAT availability may be related to the neuropathology of BPD.

The DAT is a target for the development of pharmacotherapies for a number of central disorders including PD, Alzheimer's disease, schizophrenia, Tourette's syndrome, Lesch-Nyhan disease, ADHD, obesity, depression, and stimulant abuse, as well as normal aging (for review see Runyon and Carroll, 2006). DAT is located on the presynaptic membrane of DA terminals and regulates phasic DA transmission at the synapse by rapidly removing DA from the synaptic cleft through reuptake (for review see Rice and Cragge, 2008). Interestingly, this protein is expressed exclusively by DA neurons and is found extrasynaptically on DA axons in CPU and NAc (for review see Rice and Cragge, 2008). In addition, DA receptors are also predominantly extrasynaptic (Sesack et al., 1994; Yung et al., 1995; Hersch et al., 1995; Khan et al., 1998). Interestingly, several recent reports suggest that synuclein proteins have a critical role in monoamine neurotransmitter homeostasis. In addition, the physical interactions between synuclein proteins and monoamine transporters (DA, serotonin (5HT) and norepinephrine (NE) transporters) indicate an important role for the synucleins in regulating transporter function, trafficking and distribution at the DA, 5HT and NE synapses (for review see Oaks and Sidhu, 2011).

The synuclein family of proteins includes  $\alpha$ -synuclein ( $\alpha$ -Syn),  $\beta$ -synuclein ( $\beta$ -Syn), and  $\gamma$ -synuclein ( $\gamma$ -Syn). The genes cloned from multiple species demonstrate that synucleins, a group of prevalent pre-synaptic proteins, are highly conserved, but unique to vertebrate organisms (Surguchov, 2008). In addition, these proteins participate in numerous interactions with other proteins, lipid membranes, and nucleic acids, suggesting a possible role in the chaperoning or trafficking of biomolecules (Surguchov, 2008). Two-hybrid and immunoprecipitation experiments have identified a physical interaction between  $\alpha$ -Syn and the carboxy terminal of DAT (Lee et al., 2001). In addition, release of DA synthesized by DA neurons in the brain requires packaging of the neurotransmitter into vesicles by the vesicular monoamine transporter 2 (VMAT2). VMAT2 co-localizes with  $\alpha$ -Syn in the Lewy bodies of PD (Yamamoto, 2006), and overexpression of  $\alpha$ -Syn can disrupt VMAT2 function (Surguchov, 2008). However, the influence of  $\beta$ -Syn and  $\gamma$ -Syn upon VMAT2 expression and activity are not known. Recent reports suggest that psychostimulants such as amphetamines and cocaine induced overexpression of  $\alpha$ -synuclein (Fornai et al., 2005; Mauceli et al., 2006; Ajjimaporn et al., 2007; Klongpanichapak et al., 2008; Mukda et al., 2011; Sae-Ung et al., 2011). Interestingly, recent reports suggest that low levels of the  $\gamma$ -synuclein in the NAc results to an increased self-administration of cocaine in the rat (Boyer et al., 2011). In addition, cocaine induced a 1.9-fold increase in locomotor activity after overexpression of  $\alpha$ -synuclein in the NAc (Boyer and Dreyer, 2007). It is noteworthy that the neurotoxicity induced by the psychostimulants such as amphetamine are mediated by enhanced oxidative stress and these effects are abolished by melatonin (Govitrapong et al., 2010), a main secretory product of pineal gland. Interestingly, a recent report suggested that this melatonin effect is mediated by the reduction of the overexpression of  $\alpha$ -synuclein induced by amphetamine (Sae-Ung et al., 2011).

Amphetamines and cocaine are psychostimulants with a target in the monoaminergic system. These drugs reverse the action of monoamine transporters and enhance the release of DA as well as norepinephrine and 5-hydroxytryptamine (5-HT, serotonin) into the synaptic cleft, increasing their availability to act upon post-synaptic receptors. Reuptake blocking and decreased degradation of these neurotransmitters increases their concentrations in the synaptic cleft.

Locomotor activity induced by psychostimulants such as amphetamine is the result of increases in synaptic DA, by blocking or reversing the direction of DAT (Sulzer et al., 1995; Sulzer et al., 2005), which in turn acts on postsynaptic receptors. Interestingly, mice lacking DAT exhibit spontaneous hyperlocomotion and are unresponsive to amphetamine (Giros et al., 1996). Recent reports suggest that DAT, but not the serotonin transport (SERT), is critical in mediating the reinforcing effects of cocaine. In addition, mice lacking DAT generally failed to acquire and maintain cocaine self-administration (Thompson et al., 2009) compared to wild-type or SERT<sup>-/-</sup> mice. Therefore, DAT may play a role in mediating the long-lasting neural changes associated with drug addiction (Martin et al., 2011; Schmitt and Reith 2010).

Drug addiction involves several molecules such as CART (Cocaine-and amphetamine-regulated transcript) peptide. This peptide is a neurotransmitter believed to play a homeostatic role in psychostimulant reward and reinforcement, as well as in other processes (Jaworski and Jones, 2006; Rogge et al., 2008). CART has also been proved to attenuate locomotion induced by direct intraaccumbal injections of DA (Jaworski et al., 2003). Recently, it has been documented that the role of CART peptide in the NAc is to homeostatically regulate the activity of the DA system (Rogge et al., 2008). Moreover CART mRNA and CART peptide are found abundantly in the NAc (Douglass et al., 1995; Koyle et al., 1998). CART peptide (CART55-1029) has been shown to have minor psychostimulant-like properties when injected into the VTA, inducing locomotor activity and producing a slightly conditioned place preference (Kimmel et al., 2000, 2002). In this sense, a new study supports the idea that CART peptide reduces the effects of psychostimulants by modulating the simultaneous activation of both D1 and D2 receptors, rather than by affecting the action of any individual DA receptor (Moffett et al., 2011). In addition, our recent report suggests that prenatal amphetamine exposure produced, at postpubertal age, an enhanced DAT in the NAc (Flores et al., 2011, Figures 2, 3, 4) and children with prenatal psychostimulant exposure have greater risk of addictions (McKenna, 2011).

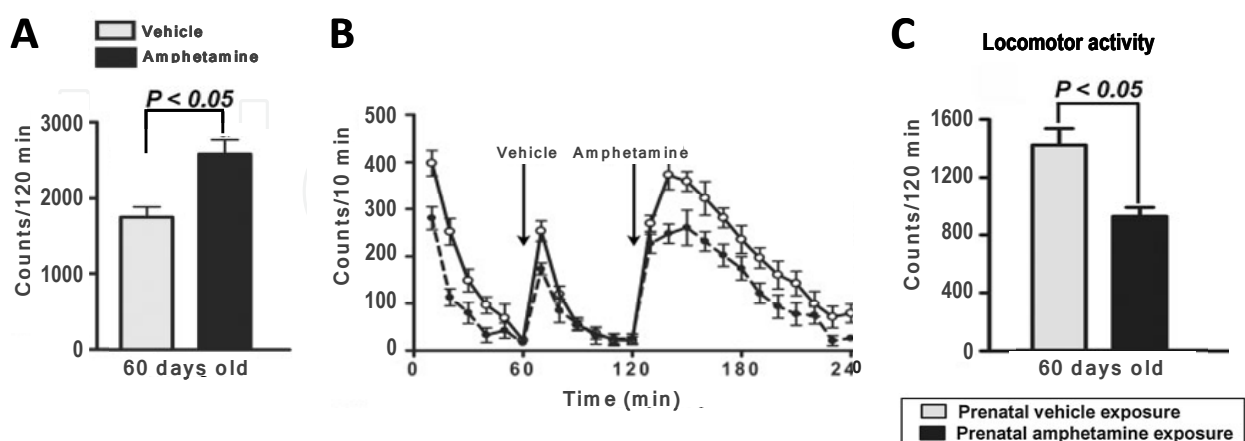


Fig. 2. Effect of amphetamine on locomotor behavior in a novel environment. A) Analysis of total activity scores revealed that the rats at PD60 were more active after amphetamine injection than their corresponding control group. B) Temporal profile of locomotor activity at PD60. C) Rats with prenatal amphetamine exposure were less active than control animals. Modified from Flores et al., 2011.

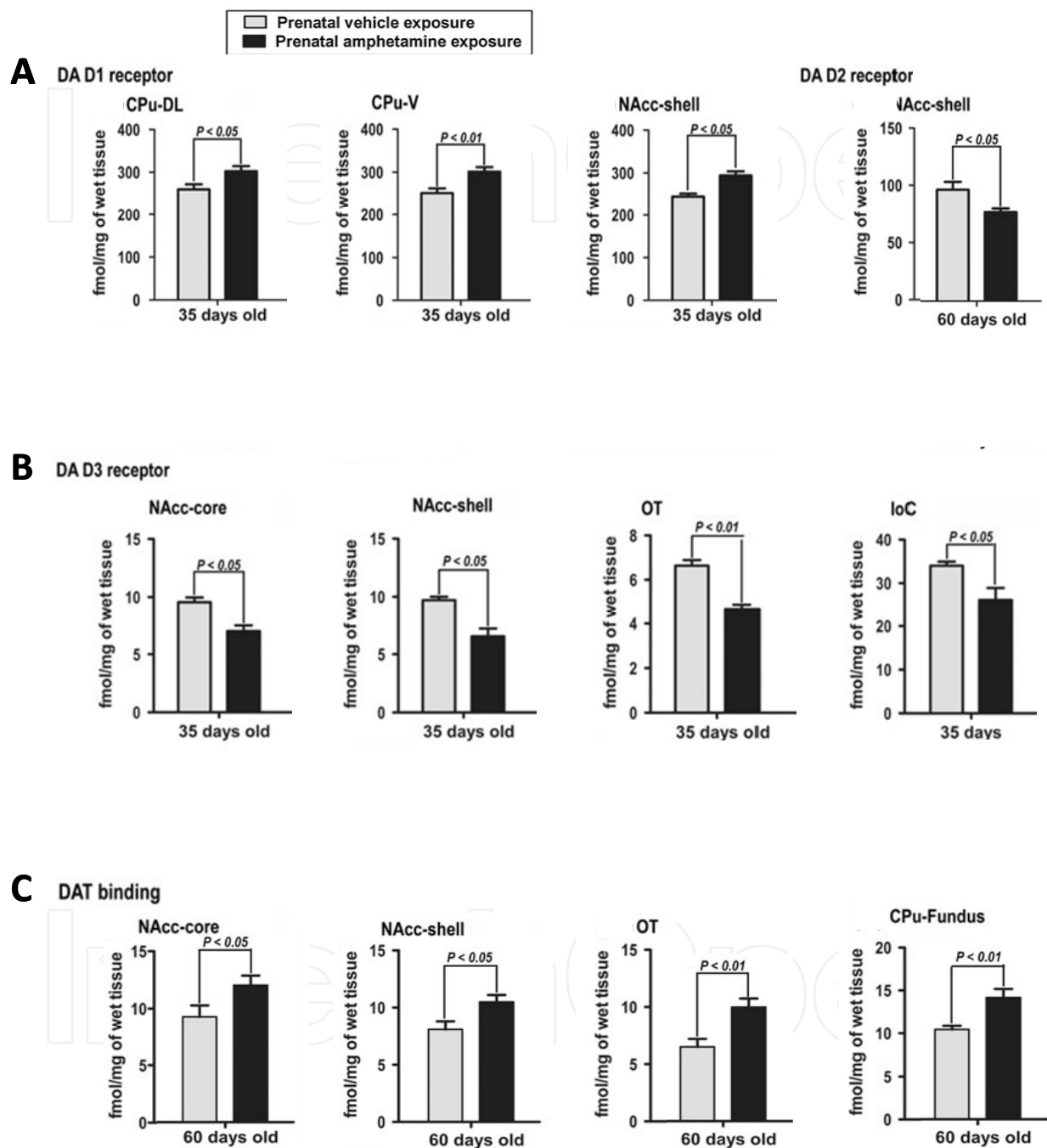


Fig. 3. Quantitative autoradiographic analysis of [ $^3\text{H}$ ]-SCH-23390/dopamine D1-like receptor binding, [ $^3\text{H}$ ]-spiperone/dopamine D2-like receptor binding, [ $^3\text{H}$ ]-OHDPAT/dopamine D3 receptor binding and [ $^3\text{H}$ ]-WIN-35428/dopamine transporter binding in prenatal amphetamine exposure (PAE)- and prenatal vehicle exposure (PVE)-rats. Dopamine (DA), Postnatal (PD), nucleus accumbens (NAcc), caudate-putamen (CPu), olfactory tubercle (OT) and the island of Calleja. (Modified from Flores et al., 2011).

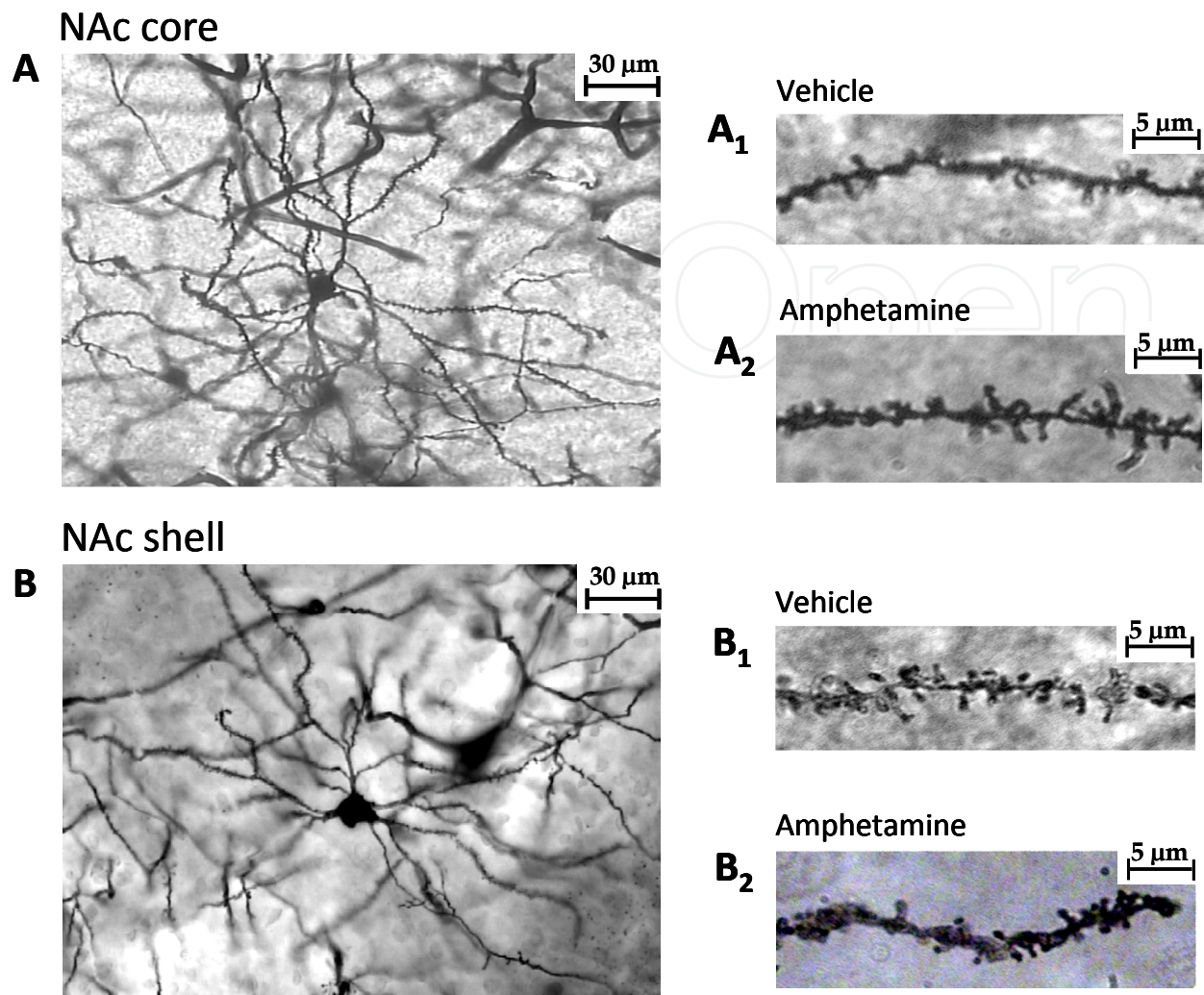


Fig. 4. Photomicrograph showing representative Golgi-Cox-impregnated medium spiny neurons and spines dendritic from the nucleus accumbens. Neurons in the nucleus accumbens core (A) and shell (B). The spine density is higher at PD60 in the dendritic segments from the core (A2) and shell (B2) subregions of the NAc of rats prenatally exposed to amphetamine compared to their corresponding vehicle group.

Cocaine and amphetamine may induce neural changes, including an increase in the density of spines on neuron dendrites in the NAc and PFC (Robinson and Kolb, 2004) associated with locomotor sensitization (Manev and Uz, 2009). More recently it has been suggested that cocaine-induced dendritic spine changes are correlated with the presence of DAT, because mice lacking DAT did not show an increase in dendritic spine density in the NAc (Martin et al., 2011). In addition, the stereotypy induced by cocaine is also absent in this transgenic mice (Tilley and Gu, 2008). However, amphetamine and cocaine, although similar in many respects, do not produce identical patterns of structural plasticity when given to rats at different ages. In adult rats, several reports have demonstrated that cocaine increases spine density on the basilar dendrites of pyramidal neurons in the PFC, while amphetamine has either no effect or a weak effect on these dendrites. In contrast, in juvenile (P22–P34) rats, amphetamine increases spine density on the basilar dendrites of PFC (for review see Robinson and Kolb, 2011).



In conclusion, DAT is one of the principal mechanisms regulating DA neurotransmission via reuptake of synaptic DA. The psychostimulants amphetamine and cocaine alter DAT function and alter the lifetime of the DA after release. Exposure to amphetamine or cocaine produced persistent changes in the structure of dendrites and dendritic spines in brain regions such as the NAc and PFC, limbic structures related with the addictions. This structural plasticity associated with the use of the drugs of abuse results in a reorganization of synaptic connectivity in these neural systems, which may associate with addiction symptoms. Several reports suggest that cocaine abusers have an increase in DAT levels with a decrease in gray and white matter density (Gould et al., 2011), however, abstainers have significantly higher gray matter density and lower DAT levels than current cocaine users (Hanlon et al., 2011; Gould et al., 2011). Therefore, both, DAT levels and gray matter density in cocaine users reverse after prolonged abstinence (Volkow et al., 2001; Beveridge et al., 2009; Hanlon et al., 2011). Interestingly, cocaine abstainers perform better cognitive test compared to current cocaine users (Hanlon et al., 2011).

## 6. Treatment of addiction

Despite intensive research and significant advances, drug addictions remain a substantial public health problem. Drug addictions have a high economical cost annually and impact not only the addicted individuals, but also their spouses, children, employers, and others. Thus, the development of improved prevention and treatment strategies is of importance (Potenza et al., 2011). Learning processes have been shown to play a major role in the maintenance of addictive behaviour (Everitt et al., 1999; Robbins & Everitt, 2002; Everitt & Robbins, 2005; Moreira & Lutz, 2008; Liu et al., 2010). Humans and animals rapidly learn cues and contexts that predict the availability of addictive drugs. Once learned, these cues and contexts initiate drug seeking, craving and relapse in both animal models and clinical studies (Von der Goltz & Kiefer, 2009; De Vries & Schoffelmeer, 2005; Micale et al., 2007). Evidence suggests that several types of neuroadaptation occur, including synapse-specific adaptations of the type thought to underlie specific long-term associative memory. Thus, understanding learning and memory processes in the addicted is an important key for understanding the persistence of addiction, and it is reasonable to hypothesize that the disruption of drug-related memories may help to prevent relapses (von der Goltz & Kiefer, 2009). The study of structure-activity relationships of molecules which influence the cannabinoid system in the brain and body is crucial in the search of medical preparations with the therapeutic effects of the phytocannabinoids without the negative effects on cognitive function attributed to cannabis (see Fisar, 2009 for review).

As discussed before, cannabinoid CB1Rs are novel targets for a new class of therapeutic agents used to treat drug addiction. Blockade of the CB1 receptor is particularly effective in reducing cue-induced reinstatement of drug seeking, an animal analogue of cue-induced relapse in human addicts (See Gardner, 2002, 2005, 2011 for review). These relapse-preventing properties are observed with different classes of abused drug (i.e. psychostimulants, opiates, nicotine and alcohol). In addition, recent evidence indicates a more general role of CB1 receptors in reward-related memories, which is consistent with the proposed role of endocannabinoids in memory-related plasticity. Relapse-preventing actions and inhibitory effects on weight gain were confirmed recently in clinical trials with the CB1 antagonist rimonabant (De Vries and Schoffelmeer, 2005). Preclinical results

provide support for the suggestion that targeting the endocannabinoid system may aid in the treatment of disorders associated with impaired extinction-like processes, such as post-traumatic stress disorder (Abush and Akirav, 2010). Liu et al. (2010) provided evidence that NMDA receptor-dependent synaptic depression at VTA dopamine circuitry requires GluR2 endocytosis, also suggest an essential contribution of such synaptic depression to cannabinoid-associated addictive learning, in addition to pointing to novel pharmacological strategies for the treatment of cannabis addiction. They found in rats that chronic cannabinoid exposure activates VTA CB1 receptors to induce transient neurotransmission depression at VTA local Glu-DA synapses through activation of NMDA receptors and subsequent endocytosis of AMPA receptor GluR2 subunits. A GluR2-derived peptide blocks cannabinoid-induced VTA synaptic depression and conditioned place preference, i.e., learning to associate drug exposure with environmental cues.

### 6.1 Pharmacological treatments and targets

Multiple pharmacological targets have been identified for the treatment of addictive disorders. “Classic” approaches tend to target the drug “reward” system, such as normalization of function through agonist approaches and negative reinforcement strategies. Agonist medications have their main impact on the same types of neurotransmitter receptors as those stimulated by abused substances. Most notably, dextroamphetamine has reduced drug use in short-term clinical trials in cocaine and methamphetamine users. The long-term safety and abuse liability of amphetamines as a treatment for cocaine addiction remains to be determined. Another example of an agonist approach for cocaine dependence is modafinil, a weak DAT inhibitor and increases synaptic DA levels, which has stimulant-like effects. On other hand, antagonists block the effects of drugs by either pharmacological or pharmacokinetic mechanisms. More recently, immunotherapies have been developed for the treatment of cocaine and methamphetamine addictions. The antibodies produced by immunotherapies sequester the drug in the circulation and reduce the amount of drug and the speed at which it reaches the brain. A potentially promising target for agonist and antagonist treatment of cocaine addiction is the D3 dopamine receptor. D3 partial agonists can act like agonists and stimulate DA receptors when endogenous levels of dopamine are low, as in cocaine withdrawal. An important limitation of vaccines is that the antibodies produced are specific for a given drug of abuse, a characteristic that will limit their clinical efficacy in polydrug abusers.

Drug addiction is associated with adaptive changes in multiple neurotransmitter systems in the brain. These adaptive changes are thought to underlie the negative reinforcing effects of abstinence from drug use that are clinically observed as withdrawal symptoms, craving for drug use, and negative mood states like anhedonia and anxiety (Hasin et al., 2007; Treadway and Zald, 2011). Examples of medications targeting negative reinforcement of drugs include methadone or buprenorphine, drugs that relieve opioid withdrawal symptoms. Cocaine users with more severe withdrawal symptoms respond more favorably to propranolol, a beta-adrenergic antagonist (Kampman et al., 2006). Several agents targeting glutamate system are also under investigation as potential treatment medications. Memantine, a noncompetitive NMDA glutamate receptor antagonist, may be efficacious and operate by reducing cognitive measures of compulsivity (Grant et al., 2010). However, clinical trials with an NMDA receptor antagonist have demonstrated negative findings for cocaine dependence (Bisaga et al., 2010).

Activation of cannabinoid receptors on synaptic terminals results in regulation of ion channels, neurotransmitter release and synaptic plasticity. Neuromodulation of synapses by the cannabinoids is proving to have a wide range of functional effects, making them potential targets as medical preparations in a variety of illnesses, including some mental disorders and neurodegenerative illnesses (see Fisar, 2009 for review).

In conclusion, the review of existing evidences indicates that addictive drugs induce synaptic plasticity at DA system and produce changes in DA at different target structures of the brain, affecting glutamatergic, GABAergic transmission and LTP and LTD processes (Figure 5). New research will without doubt shed light onto the mechanisms of addiction induction and better design of drug-addiction treatments.

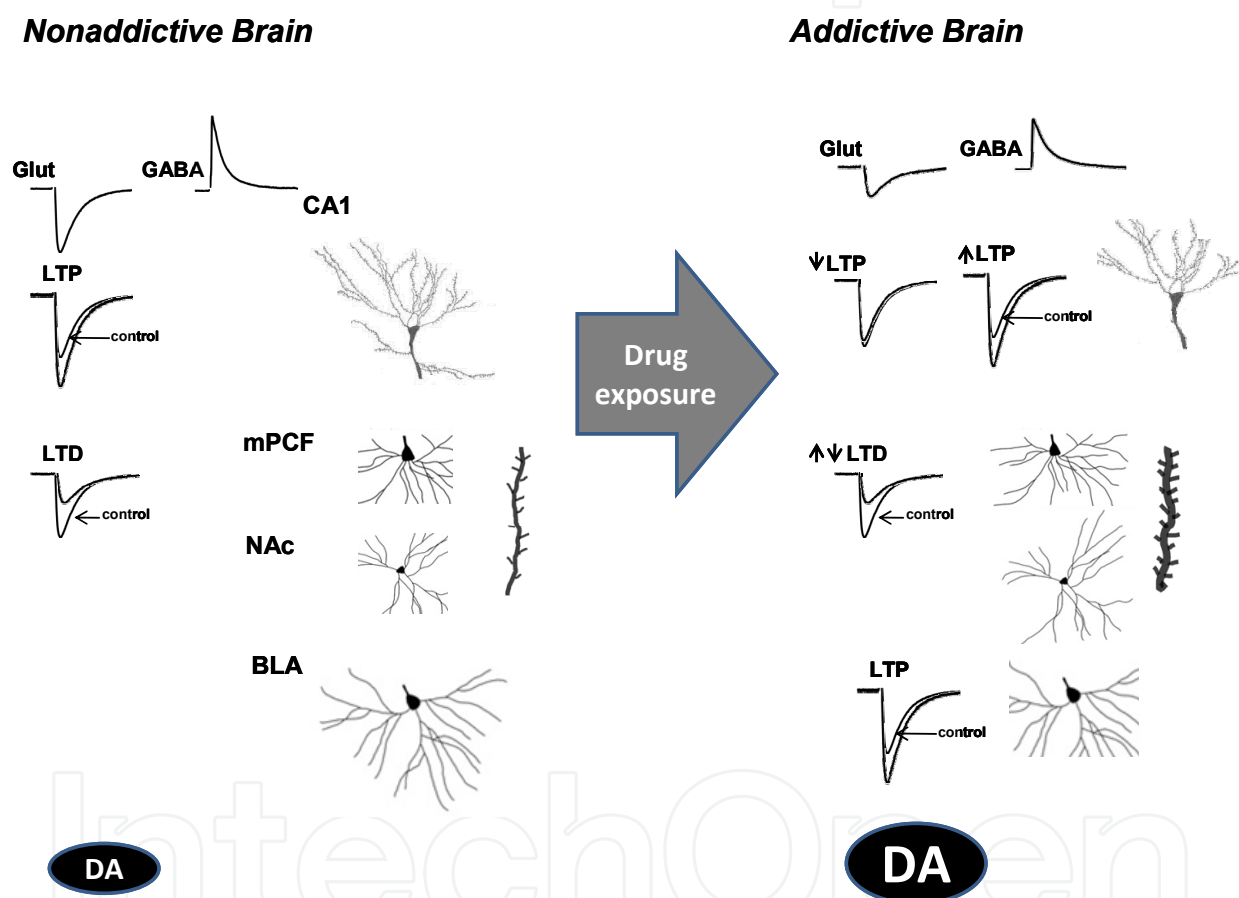


Fig. 5. Addictive drug affects DA levels, glutamatergic and GABAergic transmission and LTP and LTD processes at different brain structures. DA: dopamine; CA1: CA1 region of the hippocampus; PFC, prefrontal cortex; NAc: accumbens nucleus; BLA: basolateral amygdala.

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