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Cocaine-induced adaptations in metabotropic inhibitory signaling in the mesocorticolimbic system

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Abstract

The addictive properties of psychostimulants such as cocaine are rooted in their ability to activate the mesocorticolimbic dopamine (DA) system. This system consists primarily of dopaminergic projections arising from the ventral tegmental area (VTA) and projecting to limbic and cortical brain regions such as the nucleus accumbens (NAc) and prefrontal cortex (PFC). While the basic anatomy and functional relevance of the mesocorticolimbic DA system is relatively well-established, a key challenge remaining in addiction research is to understand where and how molecular adaptations and corresponding changes in function of this system facilitate a pathological desire to seek and take drugs. Several lines of evidence indicate that inhibitory signaling, particularly signaling mediated by the $G_{i/o}$ class of heterotrimeric GTP-binding proteins (G proteins), plays a key role in the acute and persistent effects of drugs of abuse. Moreover, recent evidence argues that these signaling pathways are targets of drug-induced adaptations. Here, we discuss inhibitory signaling pathways involving DA and the inhibitory neurotransmitter GABA in two brain regions, the VTA and PFC, which are central to the effects of acute and repeated cocaine exposure and represent sites of adaptations linked to addiction-related behaviors including sensitization, craving, and relapse.

Keywords

dopamine; addiction; GABA; Girk; G protein-coupled receptor

1. INTRODUCTION

Cocaine is a psychomotor stimulant that exerts its effect on both the central and peripheral nervous system, causing heightened arousal, elevated mood, increased behavioral activation, and feelings of euphoria in humans (Koob, 1992). Cocaine is often consumed by smoking, insufflation, or intravenous injection, ensuring rapid delivery to the bloodstream and brain that produces an intense euphoria revered by addicts. The intensity of the euphoria often leads individuals to increase the dose and frequency of drug use to achieve the desired effects (*i.e.*, tolerance) or to avoid psychological and physiological effects associated with cessation of chronic drug use (*i.e.*, withdrawal) (Cami and Farre, 2003). An estimated 14.3 million people worldwide reported using cocaine between 2005 and 2006, with 16.2% of Americans having used cocaine in their lifetime (UN *World Drug Report*, 2007). Thus, illicit use and abuse of cocaine continues to affect countless individuals, and represents a major portion of the current drug crisis.

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The development and persistence of drug addiction relies heavily on the rewarding properties of the drug that motivate behavior needed to obtain the drug and reinforces repeated drug use (Everitt and Robins, 2005; Koob, 1992; Schultz, 2006, 2007; Wise, 2002). This is substantiated by the fact that humans and other animals can readily learn to take addictive drugs. For instance, rodents and non-human primates will rapidly learn to press levers to receive an intravenous infusion of cocaine (self-administration), a behavior that perseveres even when a large number of presses are required for each infusion or when lever pressing results in an adverse consequence such as a foot shock (Cooper et al., 2007; Pelloux et al., 2007; Vanderschuren and Everitt, 2004). In addition to the rewarding properties of the drug, environmental cues (internal and external) associated with drug administration often acquire motivational value (salience) themselves. For example, rats will spend more time in a context in which they passively-received an injection of cocaine than in a location paired with a saline injection (conditioned place preference; Tzschentke, 1998). These drug-associated cues can trigger feelings of drug craving that lead to drug-seeking and drug-taking behavior in both humans and animals, even after prolonged periods of abstinence (Crombag et al., 2002; Ehrman et al., 1992; Fuchs et al., 2005, 2006). Thus, it is believed that addiction involves processes of associative learning, including the formation and retrieval of memories associated with drug use (Hyman, 2005).

Experience-dependent changes in neural activity modulate gene and protein expression (Leslie and Nedivi, 2011). Some of these changes yield structural and functional changes in the synaptic connections among neurons. In this way, neural circuitry is constantly fine-tuned to optimize perception, cognition, and behavioral responses. This fine-tuning is often referred to as “neural adaptations” or “plasticity,” and is believed underlie how individuals learn and adapt in their behavior (Berke and Hyman, 2000; Cardinal and Everitt, 2004; Nestler, 1993; Mameli and Luscher, 2011; Wolf, 2002). A wealth of research indicates that exposure to drugs of abuse leads to short- and long-term neural adaptations in brain regions involved in reinforcement, reward, and pleasure that collectively make up the “reward system” (Luscher and Malenka, 2011; Mameli and Luscher, 2011; Nestler, 2001; Wise, 2002; Wolf, 2002). These changes can often promote an addictive dependence that intrudes upon normal social and personal behaviors by shifting the motivation to obtain natural rewards such as food, sex, and positive social interaction in favor of behavior oriented towards drug-seeking and drug-taking (Damsma et al., 1992; Hansen et al. 1993; Hernandez and Hoebel, 1988; Kalivas and Volkow, 2005; Kiyatkin, 1994). In other words, for addicts, drugs become valued over all other goals, leaving individuals with a narrow focus on obtaining and using drugs. In time, this behavior can become compulsive, leaving individuals with a high risk for relapse even following prolonged periods of abstinence (Ehrman et al., 1992; Lubman et al., 2004; O’Brien et al., 1992).

Drug-induced adaptations occur at both the cellular and molecular level, and include acute and long-term alterations in gene and protein expression. These adaptations in turn promote changes in cell excitability and activity, morphology, and neurotransmission in the reward circuit (Kalivas and O’Brien, 2008; Luscher and Malenka, 2011; Nestler, 2001; Nestler, 2001a; Thomas et al., 2008). Importantly, drug-evoked neural adaptations outlast the presence of the drug in the brain and are believed contribute to the reorganization of neural circuits that strengthen the desire to obtain drugs of abuse (Kalivas and Volkow, 2005; Luscher and Malenka, 2011; Robinson and Berridge, 1993; Shaham and Hope, 2005).

Several lines of evidence indicate that inhibitory influences on neuronal activity, particularly those mediated by the $G_{i/o}$ class of G protein-coupled receptors (GPCRs) for the neurotransmitters GABA ($GABA_B$ R) and dopamine (D_2 R), play key roles in the acute and persistent effects of drugs of abuse, and are targets of drug-induced adaptations (Filip et al., 2007; Goldstein and Volkow, 2002; Nestler et al., 1990; Vlachou and Markou, 2010). This

review will focus on the relevance and plasticity of metabotropic inhibitory signaling mediated by GABA_BR and D₂R in two brain regions, the ventral tegmental area (VTA) and prefrontal cortex (PFC), which are central to the effects of acute and repeated cocaine exposure and are the sites of neural adaptations linked to addiction-related behaviors such as sensitization, craving, and relapse. We will first, however, review fundamental aspects of the mesocorticolimbic DA system and G protein-dependent signaling. We will then discuss acute and repeated cocaine effects on the physiological properties of the major cell types in the VTA and PFC, followed by some of the underlying mechanisms for these adaptations with an emphasis on how they may influence the development and persistence of addiction.

2. THE MESOCORTICOLIMBIC DOPAMINE SYSTEM

The mesocorticolimbic DA system, often referred to as the “reward circuit”, plays a significant role in reinforcement and reward-based associative learning that helps to establish patterns of behavior necessary for obtaining rewards (Berke and Hyman, 2000; Cardinal and Everitt, 2004; Hyman et al., 2005; Mamelli and Lüscher, 2011; Schultz, 2006, 2007). This circuit mediates responses to motivationally-relevant biological stimuli (natural rewards) as well as drugs of abuse and drug-associated cues (Damsma et al., 1992; Hernandez and Hoebel, 1988; Kalivas and O’Brien, 2008; Kelley, 2004; Kelley and Berridge, 2002; Koob, 2010; Schultz, 2006, 2007; Stefani and Moghaddam 2006; Carlezon and Thomas, 2000; Wise, 2002). Although drugs of abuse are chemically-diverse molecules that exert their initial effects through distinct mechanisms in the brain, drug addiction appears to reflect a convergence of common mechanisms (Nestler, 2001; Nestler, 2005; Wise, 1996). Prominent among these shared mechanisms is the engagement of the mesocorticolimbic DA system (Jay, 2003; Nestler, 2005; Wise, 1996).

2.1 Anatomy of the mesocorticolimbic DA system

Central to the mesocorticolimbic DA system are the dopaminergic projections arising from the ventral tegmental area (VTA) (Cami and Farre, 2003; Feltenstein and See, 2008; Oades and Halliday, 1987). These VTA projections release DA into limbic brain regions such as the nucleus accumbens (NAc), amygdala, and hippocampus (mesolimbic pathway), as well as cortical areas including the prefrontal, orbitofrontal and cingulate cortices (mesocortical pathway; Figure 1). Although the mesocortical and mesolimbic pathways operate in parallel, they also appear to play somewhat distinct roles in addiction (Cami and Farre, 2003). For example, while the NAc appears to be involved in the primary reinforcing effects of drugs of abuse, the amygdala and hippocampus play an important role in learning that promotes the association of environmental cues present during drug use with the rewarding effects of the drug (Di Chiara, 2002; Fuchs et al., 2005, 2007; McLaughlin and See, 2003; Rogers and See, 2007; See et al., 2003; See, 2005; Volkow et al., 2003). In contrast, regions of the frontal cortex regulate emotional responses and cognitive control over decision-making (Volkow, et al., 1993). Here, repeated drug use is believed to promote adaptations that diminish inhibitory control over behavior and promote hyper-responsiveness to drug-associated stimuli that prompts persistent addictive behaviors (Kalivas and Volkow, 2005).

2.2 The mesocorticolimbic DA system and stages of addiction

Addiction is thought to develop in stages, where the pleasurable (rewarding) effects of the drug reinforce repeated intake, which in some individuals leads to regulated, escalating intake (Koob et al., 2004; Ahmed et al., 2002). The initial rewarding, reinforcing, and stimulatory effects of cocaine are linked in large part to its ability to inhibit transporters tasked with removing DA from the synaptic cleft, allowing extracellular levels of DA levels to rise and persist in downstream targets of the VTA (Beyer and Steketee, 2001; Carboni et al., 2001; Di Chiara and Imperato, 1988; Mateo et al., 2004; Pettit and Justice, 1989; Ritz et

al., 1987). Increased extracellular DA levels in targets of VTA DA neurons also play a critical role in facilitating learned associations between the rewarding effects of the drug and environmental cues (Hyman, 2005; Kiyatkin, 1994; Schultz et al., 2007).

With repeated drug use, drug-seeking is often triggered by exposure to well-learned drug-associated cues, with enhanced DA neurotransmission “cueing” the presence of relevant stimuli (Cornish and Kalivas, 2001; Hyman, 2005; Jay, 2003; Kelley, 2004; Kelley, 2004; McFarland and Kalivas, 2001; Rebec et al., 1997; See et al., 2007). Release of DA in turn triggers activation of glutamatergic projections from cortical regions involved in decision-making such as the medial prefrontal cortex (mPFC) to motor output structures such as the ventral striatum (NAc) and ventral pallidum (Cornish and Kalivas, 2000; Kalivas et al., 2003; Kalivas et al., 2009; Knackstedt and Kalivas, 2009). This PFC-NAc glutamate pathway is critical for the expression of drug-related behaviors, including sensitization and reinstatement of drug-seeking (Baker et al. 2003; Cardinal and Everitt, 2004; McFarland and Kalivas, 2001; McFarland et al., 2003; Moran et al., 2005; Steketee and Kalivas, 2011). Thus, as drug-seeking becomes well-learned, a reliance of glutamatergic projections from the mPFC emerges (Cardinal and Everitt, 2004; Pierce and Kalivas, 1997; Wolf et al, 2004). Over time, individuals are believed to experience a reduction in motivation to respond to previously rewarding non-drug-related stimuli, leaving only strong motivational stimuli such as drug-associated cues to ably activate PFC networks and initiate behavior (Kalivas and O’Brien, 2008; Kalivas and Volkow, 2005). At this stage in the disease process (regulated relapse), the individual is thought to retain a certain degree of control over socially-appropriate decision-making (Kalivas and O’Brien, 2008).

In some susceptible individuals, however, chronic and extensive cocaine exposure induces a state in which drug-seeking behavior becomes compulsive in nature and the motivational drive to obtain and use drugs is difficult to regulate (Everitt and Robbins, 2005; Hyman and Malenka, 2001; Lubman et al., 2004; Vanderschuren and Everitt, 2004). This is believed to reflect in part, a decreased ability of the PFC to cognitively regulate decision-making and behavior (Everitt and Robbins, 2005; Goldstein and Volkow, 2011). At this stage of the disease, the expression of drug-seeking behavior is thought to rely primarily on activation of neural networks responsible for habit-like behavior, and can be executed without engaging prefrontal cognitive circuitry (Balleine et al. 2007; Jog et al. 1999; Packard and Knowlton 2002). In this way, exposure to drug-associated cues can trigger activation of drug-seeking without a conscious decision ever being made, causing the individual to automatically relapse (Kalivas and O’Brien, 2008; Everitt and Robbins, 2005; Hyman and Malenka, 2001; Lubman et al., 2004).

While the basic anatomy and functional relevance of the mesocorticolimbic DA system is relatively well-established (for review, see Bonci and Malenka, 1999; Everitt and Robbins, 2005; Hyman et al., 2006; Kalivas and Steketee, 2011; McFarland and Kalivas, 2003), a key challenge remaining in addiction research is to understand where and how neural adaptations, and corresponding changes in function of the mesocorticolimbic DA system, facilitate a pathological desire to seek and take drugs. In the discussion below, we will focus primarily on the relevance of metabotropic inhibitory signaling in the VTA and mPFC to the first two stages of addiction.

3. METABOTROPIC INHIBITORY SIGNALING

All G protein-coupled receptors (GPCRs) share basic functional characteristics. GPCRs transduce ligand-binding events to intracellular responses via heterotrimeric G proteins, which consist of $G\alpha$ and $G\beta\gamma$ subunits (Hamm and Gilchrist, 1995; Oliveira et al., 1993). Binding of a ligand to the GPCR promotes the exchange of GTP for GDP on the $G\alpha$ subunit

and dissociation of the $G\alpha$ and $G\beta\gamma$ subunits, a process referred to as G protein activation. Activated $G\alpha$ and “free” $G\beta\gamma$ can then interact with and modulate a wide-range of intracellular effectors, including cyclases, lipases, and ion channels (Dickey and Birnbaumer, 1993; Hall et al., 1999; Wickman and Clapham, 1995). To date, at least 18 different $G\alpha$, 11 $G\beta$, and 5 $G\gamma$ subunits have been identified in the human central nervous system, all of which exhibit genetic diversity and contribute to distinct functional characteristics in different receptor populations (Hermans, et al., 2003; Senogles, et al., 1990; Wong, et al., 2003).

The $G\alpha$ subunits have been categorized into several subfamilies (*e.g.*, G_s , $G_{i/o}$, G_q) by virtue of their sequence similarity, modulatory influence, and sensitivity to bacterial toxins (Trumpf-Kallmeyer, et al., 1992). $GABA_B$ R and D_2 R couple to and activate the $G_{i/o}$ -subclass of $G\alpha$ subunits. $G_{i/o}$ G proteins are inhibited by pertussis toxin produced by the bacterium *Bordetella pertussis* (Ryan and Ray, 2004). Active $G_{i/o}$ G proteins interact with downstream effectors that decrease neuronal excitability, such as G protein-gated inwardly-rectifying K^+ (Girk/ K_{IR3}) channels, and/or inhibit excitatory effectors, including most isoforms of adenylyl cyclase (AC) and some types of voltage-gated Ca^{2+} channels (for review, see Oldham & Hamm, 2008).

The efficacy of G protein-dependent signal transduction can be altered by multiple mechanisms. Receptor availability, for example, is influenced in part by the level of gene transcription, as well as RNA transcript stability and translation (for review, see Rohrer & Kobika, 1998). GPCR levels (including $GABA_B$ R and D_2 R) at the cell membrane can also be titrated via clathrin-mediated endocytosis (Hanyaloglu, 2008; Paspalas, et al., 2006). Additional factors determine the degree and duration to which those available receptors can be activated. For instance, prolonged agonist-induced stimulation can lead to a reduction in signal transduction via G protein-coupled Receptor Kinases (GRKs) and β -arrestin-mediated deactivation (Pitcher, et al., 1998; DeWire et al., 2007).

The strength of G protein-dependent signaling can also be regulated at the G protein level. G protein activation and deactivation kinetics are dependent on the intrinsic GTPase activity of the $G\alpha$ subunit species and on coupling efficacy of G proteins to downstream effectors (Conklin and Bourne, 1993). $G\alpha$ GTPase activity is modulated by Regulators of G protein Signaling (RGS) and Activators of G protein Signaling (AGS) proteins. RGS proteins decrease the effectiveness GPCR-dependent signaling by accelerating the GTPase activity of $G\alpha$ subunits, which in turn enhances the deactivation of G protein signaling (for review, see Ross and Wilkie, 2000). In contrast, AGS proteins bind to and stabilize GDP-bound $G\alpha$, thereby inhibiting binding of GTP and preventing reactivation of $G\alpha$ proteins (for review see Blumer and Lanier, 2003). AGS proteins can also alter G protein availability, thus influencing basal signaling levels independent of GPCR activation.

$GABA_B$ R and D_2 R exert an inhibitory influence on neurotransmission at both the presynaptic and postsynaptic levels. The presynaptic inhibitory influence of D_2 R and $GABA_B$ R is often mediated by the $G\beta\gamma$ -dependent suppression of voltage-gated calcium channels (Ca_v), which modulate Ca^{2+} influx required for neurotransmitter release and neuronal firing (Sakaba and Neher, 2003). Here, $GABA_B$ R and D_2 R can be found at the presynaptic terminal or on the soma and dendrites of GABA and DA neurons where they negatively regulate neurotransmitter release and dampen neuronal activity respectively (Kobayashi, et al., 2012; Hanh, et al., 2006). In some instances, however, presynaptic $GABA_B$ R and D_2 R act as presynaptic heteroreceptors to regulate release of other neurotransmitters, such as glutamate in the VTA (Koga and Momiyama, 2000). The postsynaptic inhibitory influence of $GABA_B$ R and D_2 R is mediated primarily by $G\beta\gamma$ -

dependent activation of Girk (Luscher et al., 1997; Arora et al., 2010), as well as the inhibition of AC (Martin, et al., 1999).

In summary, there are multiple cellular mechanisms available to regulate GPCR signaling. Variation in the number of receptors, G proteins, effectors, and/or regulators can lead to diverse response profiles. Common regulatory mechanisms include GRK/ β arrestin-mediated GPCR deactivation, clathrin-mediated endocytosis, uncoupling of G proteins, and modulation by AGS and RGS proteins (Bohn, et al., 2004; Hanyaloglu, 2008; Kelly 2008). Importantly, many of the modulatory influences on $G_{i/o}$ signaling mentioned above have been implicated in neural adaptations triggered by drugs of abuse (Bohn, et al., 2004; Federici, et al., 2009; Moron, et al., 2006), some of which will be discussed below.

4. VENTRAL TEGMENTAL AREA

The VTA lies medial to the substantia nigra (SN) and ventral to the red nucleus close to the midline on the ventral portion of the midbrain and is an important locus for cognitive and emotional brain function as well as reward-driven learning (Bjorklund and Dunnet, 2007; Zellner and Ranaldi, 2010). It is cyto-architecturally ill-defined, with boundaries determined largely by proximity to adjacent structures. Although the VTA is often perceived to be a dopaminergic structure, it is comprised of a heterogeneous population of cells that contains DA (~65%), GABA (~30%) and glutamate (~5%) that project both within and outside the VTA (Carr and Sesack, 2000; Dobi et al., 2010; Johnson and North et al, 1992; Yamaguchi et al., 2007; Van Bockstaele and Pickel, 1995).

The VTA projects densely to the NAc, in addition to the mPFC, amygdala, lateral hypothalamus, and hippocampus (Beckstead et al., 1979; Fuxe et al., 1974; Lindvall et al., 1974; Swanson, 1982). VTA projections to the NAc and mPFC are comprised of DA, GABA and glutamate-containing neurons (Carr and Sesack, 2000; Chuhma et al., 2004; Gorelova et al., 2012; Lavin et al., 2005; Margolis et al., 2006; Van Bockstaele and Pickel, 1995). Within the mPFC, these projections synapse on the distal dendrites of both pyramidal and local circuit neurons (Carr and Sesack, 2000, 2000a). Importantly, DA terminals synapse on mPFC pyramidal cells that project to both the NAc and VTA, providing a mechanism whereby DA can modulate cortical outflow to limbic regions of the brain (Carr et al., 1999; Carr and Sesack, 1999). Furthermore, while VTA DA neurons project to numerous limbic and cortical structures, most of these neurons do not project to more than one forebrain region (Deniau et al., 1980; Fallon, 1981; Margolis et al., 2006; Swanson, 1982). These DA neurons display important distinctions in their functional and physiological characteristics depending on their axonal targets, including differences in receptor and ion channel expression, firing pattern, and action potential duration (Lammel et al., 2008; Margolis et al., 2008).

4.1 Role of the VTA in addiction

Drugs of abuse such as cocaine, are powerful triggers of synaptic plasticity in the VTA (Jones and Bonci, 2004; Luscher and Malenka, 2011). As such, this brain region plays a critical role in the rewarding, reinforcing, and motor-stimulatory effects of acute and repeated psychostimulant administration (Cornish and Kalivas, 2001; Di Ciano and Everitt, 2004; Kalivas and Duffy, 1993; Pierce et al., 1996; Sun and Rebec, 2005; Vanderschuren and Kalivas, 2000). VTA DA release appears necessary for reward and is hypothesized to provide positive reinforcement for drug self-administration and, consequently, initiation of the addiction cycle (Di Chiara, 1998; Di Chiara and Imperato, 1988; Koob, 2004; Schultz, 2006). Drugs of abuse are believed to begin co-opting the reward circuitry in the VTA, as early adaptations influence DA transmission in downstream targets of VTA DA neurons, including the NAc and mPFC (Di Chiara, 1998; Everitt et al., 1999; Hyman 2005; Kauer,

2004; Mameli et al., 2009; Wise and Bozarth, 1987). The hierarchical transfer of drug-related information from the VTA to these and other brain regions promotes the formation of powerful and persistent links between the rewarding aspects of the drug experience and environmental cues present during drug use. These associations are important to the development and prolonged expression of addicted behavior (Kalivas and Duffy, 1993; McFarland and Kalivas, 2001; Sun and Rebec, 2005).

4.3 Effects of cocaine on VTA DA neurons

When administered acutely, cocaine potentiates DA neurotransmission in brain regions innervated by DA neurons by blocking the transporter-dependent reuptake of extracellular DA at the synapse (Ritz et al., 1987; Di Chiaro, 1988; Bradberry and Roth, 1989). Studies in acutely-isolated brain slices containing the VTA, however, show that acute cocaine decreases the firing rate of spontaneously-active DA neurons (Brodie and Dunwiddie, 1990). Similarly, *in vivo* experiments demonstrated that midbrain DA neuron firing is partially inhibited following acute cocaine, with VTA DA neurons exhibiting a reduction in activity immediately following an intravenous infusion of the drug (Einhorn et al., 1988; Lacey et al., 1990; Pitts, 1987).

In contrast to the effect of acute cocaine, the number of spontaneously active VTA DA cells and their basal firing rates are significantly *increased* immediately after discontinuation of repeated systemic cocaine treatment, an effect that has been shown to last up to 7 d following cessation of cocaine administration (Ackerman and White, 1990; Henry et al., 1989; Gao et al., 1998). Likewise, cocaine self-administration increases the mean firing rate and bursting activity of VTA DA neurons 1–3 days, but not 10 days following the conclusion of self-administration (Marinelli et al., 2003). Together, these studies indicate that acute and repeated cocaine exerts a bi-directional effect on the activity of VTA DA neurons, and that cocaine-induced adaptations in VTA DA neuron activity are temporary, with the system “re-setting” shortly after the end of drug-treatment.

A wealth of evidence highlights the importance of drug-induced adaptations in excitatory neurotransmission in the VTA to the cellular and behavioral effects of acute and repeated cocaine exposure (Everitt and Wolf, 2002; Hyman et al., 2006; Jones and Bonci, 2005; Kauer and Malenka, 2007; Robinson and Berridge, 1993; Shaham and Hope, 2005; Van den Oever et al., 2010). Within 3 hours of a single cocaine injection, VTA DA neurons display enhanced strength at glutamatergic synapses, an adaptation requiring NMDA receptor activation and synaptic insertion of GluR1-containing AMPA receptors (Argilli et al., 2008; Bellone and Luscher, 2006; Saal et al., 2003; Ungless et al., 2001). This augmented excitatory neurotransmission is believed to trigger persistent changes in DA cell signaling that are at least in part responsible for the early behavioral consequences of exposure to cocaine (Borgland et al., 2004; Robinson and Berridge, 1993; Everitt and Wolf, 2002; Kalivas, 1995; Wolf, 1998). There are a number of excellent reviews describing the current state of knowledge regarding psychostimulant-induced adaptations in DA neuron excitatory transmission (Jones and Bonci, 2005; Luscher and Malenka, 2011; Thomas and Malenka, 2007).

4.4 D₂R and GABA_BR in the VTA

The output of VTA DA neurons is dependent on a delicate balance of excitatory and inhibitory input (Carr and Sesack, 2000; Omelchenko and Sesack, 2005; White, 1996). VTA DA neurons receive negative autocrine and paracrine (“long-loop”) feedback mediated by D₂R and GABA_BR, respectively (Einhorn et al., 1988; Sugita et al., 1992). In the VTA, D₂Rs are located primarily on the soma and dendrites of DA neurons (Sesack et al., 1994). These receptors are activated by somato-dendritic DA release and serve as autoreceptors that

decrease DA neuron firing rates. In contrast, D₂Rs localized to DA axon terminals in target brain regions of the VTA inhibit DA release at the presynaptic level (Beckstead et al., 2004; Cubeddu and Hoffman, 1982; Einhorn et al., 1988; Lacey, 1987; Lacey et al., 1990).

GABA is also an important determinant of VTA DA function (Cruz et al., 2004; Dewey et al., 1992; Labouebe et al., 2007; Sugita et al., 1992; Engberg et al., 1993; Klitenick et al., 1992). GABAergic input to VTA DA neurons arises from local interneurons of the VTA and from striatal regions, including the NAc and ventral VP, that synapse selectively onto GABA-containing neurons projecting to the NAc, thus providing a potential “long-loop” inhibitory feedback mechanism to regulate mesolimbic activity (Carr and Sesack, 1999; Groenewegen, 1993; Johnson and North, 1992; Smith and Bolam, 1990; Walaas, 1980; White, 1996). Afferents from the VP and NAc preferentially activate GABA_BR, while the inhibitory influence of local GABA interneurons is typically mediated by the ionotropic GABA_AR (Sugita, 1992). Recently, a primarily GABAergic structure located just posterior to the VTA, termed the rostromedial tegmental nucleus (RMTg), was shown to selectively target VTA DA neurons and regulate their spontaneous activity and responses to drugs of abuse (Lecca, et al., 2011). The complexity of GABAergic signaling in the VTA is further enhanced by the presence of GABA_BRs on GABA neurons in the VTA, where they are found at both pre- and postsynaptic locations (Cruz et al., 2004; Padgett and Slesinger, 2010). Collectively, the above insights argue that GABA_BR and D₂R exert an inhibitory influence on VTA neurons through pre- and postsynaptic mechanisms within the VTA.

Several lines of evidence indicate that inhibitory neurotransmission mediated by GABA_BR and D₂R is a critical determinant of cellular and behavioral responses to acute and repeated cocaine exposure in the VTA. Indeed, acute cocaine exposure evokes negative autocrine and paracrine feedback loops mediated by D₂R and GABA_BR, respectively (Einhorn et al., 1988; Sugita et al., 1992). These negative feedback loops temper VTA DA neuron output in response to acute cocaine, and are weakened by repeated cocaine exposure (Ackerman and White, 1990; Febo et al., 2003; Kushner and Unterwald, 2001). Moreover, inactivation of Gi/o proteins with pertussis toxin produced an enhanced response to acute cocaine that resembled motor activity observed following repeated exposure (behavioral sensitization; Steketee and Kalivas, 1991). What follows is a summary of cocaine-induced adaptations in GABA_BR- and D₂R-dependent signaling, the possible underlying mechanisms, and how these adaptations may influence the development and persistence of addiction.

4.5. Cocaine-induced adaptations in VTA D₂R signaling

The reduced activity of VTA DA neurons observed following acute cocaine exposure results from the blockade of re-uptake of DA released at somato-dendritic sites within the VTA and subsequent stimulation of D₂R found on DA neurons (Beckstead et al., 2004; Bradberry and Roth, 1989; Brodie and Dunwiddie, 1990; Lacey et al., 1987). Consistent with this, cocaine-induced decreases in the activity of VTA DA neurons is blocked by prior application of the D₂R antagonist sulpiride (Brodie and Dunwiddie, 1990). Furthermore, mice lacking D₂R display a complete loss of autoreceptor-dependent regulation of DA release and increases in extracellular DA levels in the NAc following acute cocaine that are dramatically higher than that observed in wild-type counterparts (Rouge-Pont et al., 2002). Together, these studies suggest that D₂R-dependent signaling in the VTA normally tempers VTA DA neuron output, and that this inhibitory signaling mechanism remains intact immediately following acute cocaine exposure.

Persistent stimulation of D₂R in the VTA, however, can lead to a reduction in autoreceptor function (Nimitvilai and Brodie, 2010). Indeed, electrophysiological, pharmacological, and behavioral studies have consistently shown that increases in mesocorticolimbic DA transmission triggered by repeated cocaine exposure correlate with a reduction in the

influence of D₂R on VTA DA neuron output (Ackerman and White, 1990; Henry et al., 1989; Kalivas and Stewart, 1991; Steketee and Kalivas, 1991). *In vitro* studies have shown that following repeated non-contingent cocaine, VTA DA neurons display a reduction in D₂R agonist-dependent inhibition of DA neuron activity that is paralleled by a significant increase in the number of spontaneously-active DA neurons and an increase in burst firing activity (Henry et al., 1989). Similarly, *in vivo* electrophysiology studies in anesthetized rats demonstrated that the D₂R agonist quinpirole is unable to quell increased firing and burst activity exhibited by VTA DA neurons 24 hours following the end of cocaine self-administration, but can once again suppress activity 10 days post drug administration (Marinelli et al., 2003). Thus, repeated cocaine exposure initially reduces the inhibitory functions of D₂R in the VTA that leads to augmented VTA DA neuron output. However, cocaine-induced increases in DA cell activity dissipate over time, with both activity and D₂R sensitivity returning to normal following approximately 10 days of withdrawal.

4.6 VTA D₂R adaptations and addiction-related behavior

Cocaine-induced locomotor activity and drug-seeking behavior are associated with alterations in the D₂R-dependent inhibition of VTA DA neuronal activity. Heightened spontaneous activity and burst firing of DA neurons following repeated cocaine is correlated with a progressive increase in cocaine-induced motor activity and DA release in downstream targets of the VTA (Kalivas and Duffy, 1993; Kalivas and Stewart, 1991; Marinelli et al., 2003; McFarland and Kalivas, 2001). As D₂R autoreceptors play a critical role in regulating activity of DA neurons, and given the evidence that this inhibitory pathway is reduced by repeated cocaine exposure, it is likely that the progressive increase in DA signaling and cocaine-induced behavior observed with repeated cocaine exposure is due to a reduction in D₂R function within the VTA. Consistent with this hypothesis, repeated systemic quinpirole treatment in rats produced a reduction in D₂R sensitivity in the VTA and promoted sensitization to subsequent cocaine exposure for up to 1 week following the end of drug treatment (Henry et al., 1998). Furthermore, mice lacking D₂R displayed elevated DA synthesis and release that correlated with heightened sensitivity to the psychomotor effects of cocaine and enhanced cocaine place preference (Bello et al., 2011).

The importance of altered D₂R function in the development of addiction has been further underscored by studies examining how rats respond to a novel environment, as it predicts behavioral and neurochemical responses to psychostimulant drugs. For example, rats displaying higher locomotor responses (high-responding; HR) to a novel environment exhibit a greater probability of acquiring and maintaining cocaine self-administration (Deroche et al., 1995; Grimm and See, 1997; Marinelli and White, 2003). Additionally, HR rats display augmented cocaine-induced motor activity and DA release within the NAc, and more readily develop behavioral sensitization as compared to rats with a lower response (Hooks et al., 1991a, b). HR rats also exhibited greater activity of midbrain DA neurons that was paralleled by reduced sensitivity to D₂R agonists (Marinelli et al., 2003; Marinelli and White, 2000). Further indications that altered function of VTA D₂R signaling can promote drug-related behavior stems from a recent study showing that intra-VTA infusion of quinpirole dose-dependently decreased cocaine-induced reinstatement of drug-seeking behavior (Xue et al., 2011). Thus, intrinsic differences in D₂R-dependent signaling may underlie the unique susceptibility of certain individuals to psychostimulant addiction.

Together, these findings highlight the importance of somatodendritic D₂R in the VTA and demonstrate that reductions in this inhibitory signaling pathway can contribute to augmented drug-induced DA neurotransmission that is important for cocaine-induced sensitization, reinstatement of drug-seeking, and the rewarding properties of cocaine. Cocaine-induced decreases in D₂R function within the VTA, however, are transient. Thus, this adaptation likely represents an early neural adaptation that temporarily alters mesocorticolimbic DA

signaling that is necessary for the emergence of DA-dependent changes in the physiology and function of brain regions downstream of the VTA that are responsible for enduring expression of addicted behavior.

4.7 Cocaine-induced adaptations in VTA GABA_BR signaling

GABA_BR-dependent signaling is targeted by cocaine in both DA and GABA neurons of the VTA. A single exposure to cocaine triggers a robust and selective suppression of postsynaptic GABA_BR-dependent inhibition in VTA (but not substantia nigra) DA neurons that persists up to 4 days following drug exposure and is paralleled by enhanced glutamatergic signaling in the same neurons (Arora et al., 2011). These adaptations are similar in magnitude and duration following repeated cocaine exposure, indicating that a single cocaine injection is sufficient to saturate the plasticity of this form of inhibitory signaling in VTA DA neurons. Furthermore, weakening of inhibitory signaling in VTA DA neurons, as is predicted with the cocaine-induced suppression of GABA_BR-dependent signaling, is consistent with behavioral sensitization seen following repeated cocaine. But while behavioral sensitization is a long-lasting phenomenon, the strength of GABA_BR-dependent signaling in VTA DA neurons recovers within 10 days of the final cocaine exposure (Arora et al., 2011). Thus, GABA_BR signaling within VTA DA neurons may constitute an “addiction barrier” that is overcome by exposure to cocaine to promote the development, but not expression of more persistent drug-related behavior.

Recently, it was found that a single systemic cocaine exposure also depressed GABA_BR-dependent signaling in VTA GABA neurons 24 hours following drug exposure. A reduction in GABA_BR-dependent signaling in GABA neurons of the VTA following acute cocaine would likely enhance GABAergic transmission onto VTA DA neurons. Nevertheless, VTA DA neuron activity is enhanced following repeated cocaine (White and Wang, 1984; Henry et al., 1989; White, 1996). It is possible that the reduction in inhibitory feedback in VTA GABA neurons reflects a form of synaptic scaling in an attempt to restore balance in activity of the VTA circuit (Padgett et al., 2012). Importantly, this down-regulation of GABA_BR-dependent signaling in VTA GABA neurons occurs in concert with other drug-induced adaptations in VTA DA neurons, including enhanced glutamatergic signaling and reduced GABA and DA-dependent inhibition which all serve to facilitate the output of VTA DA neurons. Thus, it is conceivable that decreased GABA_BR tone in VTA GABA neurons and enhancement of GABA release may be inadequate to suppress the potentiating effects of cocaine on VTA neuron output (Padgett et al., 2012). However, additional efforts are needed to better understand how adaptations in GABA_BR-dependent signaling affect VTA neuron function that might provide a strategy for treating addiction.

4.8 VTA GABA_BR adaptations and addiction-related behavior

Local administration of the GABA_BR agonist baclofen can reduce firing rate and burst firing of VTA DA neurons and restore tonic DA neuron firing, while application of GABA_BR antagonists have an inverse effect (Chen et al., 2005; Erhardt et al., 2002; but see Cruz et al., 2004). In non-contingent animal models of cocaine addiction, intra-VTA administration of baclofen prevents acute cocaine-induced (but not spontaneous) locomotor activity in rats, and attenuates heightened extracellular DA levels in the NAc and mPFC that normally accompany repeated cocaine-induced motor activity (Kalivas, 1990; Kalivas and Duffy, 1990; Klitenick et al., 1992; Westerink et al., 1996). Moreover, intra-VTA baclofen reduces operant responding maintained by cocaine and dose-dependently attenuates cocaine self-administration under both fixed-ratio (FR) and progressive ratio (PR) schedules of reinforcement (Backes and Hemby, 2008; Brebner 2000). Thus, alterations in GABA_BR-dependent signaling triggered by cocaine might profoundly affect the function of VTA DA neurons and the reinforcing properties of cocaine.

4.9 Mechanisms underlying adaptations in VTA D₂R and GABA_BR signaling

Receptor expression—Acute and repeated cocaine administration tempers GABA_BR- and D₂R-dependent signaling, respectively, within the VTA (Ackerman and White, 1990; Arora et al., 2011; Henry et al., 1989). Conflicting results related to the effects of repeated psychostimulant exposure on D₂R expression levels in the VTA have been reported, with differences perhaps attributable to drug-type, mode of administration, and animal model employed. For example, D₂R mRNA expression is increased in the VTA following 5 weeks of cocaine self-administration, but not in passive yoked-cocaine in rodents (Stefanski et al., 2007). However, D₂R mRNA is not altered 20 minutes or 14 days following 2 weeks of self-administration (Ben-Shahar et al., 2007). Furthermore, no differences in D₂R binding were observed in the VTA of either rodents or non-human primates following cocaine self-administration (Moore, et al., 1998; Stefanski, et al., 2007). Thus, the increase in D₂R expression following prolonged cocaine self-administration likely reflects a neuroadaptive proliferation to compensate for decreased D₂R function within the VTA. Similarly, a number of studies have demonstrated that neither acute nor repeated non-contingent cocaine alters total GABA_BR mRNA or protein expression in the VTA (Arora et al., 2011; Li et al., 2002). Collectively, these data indicate that changes in the activity of VTA DA and GABA neuron activity following cocaine exposure are not likely due to alterations in total D₂R and GABA_BR expression.

G proteins—Long-term adaptations in G protein expression and/or function can also contribute to the development of addicted behavior (Nestler 2001; Nestler & Aghajanian 1997). Early studies of cocaine-induced adaptations in GABA_BR signaling showed that repeated cocaine decreased functional coupling of the GABA_BR (as measured by baclofen-stimulated 35S-GTP_γS binding) in the rat VTA, but not PFC, NAc, substantia nigra, or dorsal striatum (Kushner and Unterwaldt, 2001). Moreover, repeated non-contingent cocaine reduced Gi/o-protein immunoreactivity and pertussis-toxin stimulated ADP-ribosylation of Gi/o signaling in the VTA (Nestler et al., 1990). These adaptations were transient, however, as ADP-ribosylation returned to baseline within 24 hours and no changes in Gα_i protein levels were found 2 weeks following drug-exposure (Striplin and Kalivas, 1992; Striplin and Kalivas, 1993). Taken together, these data indicate that alterations in G_{i/o} G protein expression in the VTA contributes, at least in part, to early adaptations in the VTA inhibitory signaling that are necessary for the development of addicted behavior.

Effectors—Decreased GABA_BR- and D₂R-dependent signaling seen following acute and chronic cocaine administration in the VTA could also be attributed to alterations in the level or function of G protein-modulated effectors. VTA DA neuron excitability is influenced by Girk channels coupled to somatodendritic GABA_BR and D₂R (Beckstead et al., 2004; Cruz et al., 2004; Johnson and North, 1992; Labouebe et al., 2007). Moreover, Girk channels have been found to mediate most, if not all, of the somatodendritic inhibitory effects of GABA_BR and D₂R on VTA DA neurons (Beckstead et al., 2004; Cruz et al., 2004).

The acute cocaine-induced suppression of GABA_BR signaling in VTA DA neurons was shown to reflect a lower density of Girk2-containing channels on the somatodendritic membrane of VTA DA neurons; GABA_BR receptor level was unaffected by cocaine (Arora et al., 2012). Interestingly, the cocaine-induced reduction in GABA_BR-dependent signaling was prevented by prior systemic administration of a D_{2/3}R (Sulpiride) but not D₁R (SCH23390) antagonist. While cocaine-induced stimulation of VTA D₂R may mediate the suppression of Girk signaling in DA neurons, this adaptation may also be triggered by stimulation of D_{2/3}R in striatal or cortical brain regions that project back to the VTA (Arora et al., 2011). Additionally, although the exact mechanisms responsible for cocaine-induced suppression of GABA_BR-dependent signaling in VTA GABA neurons remains unclear,

acute administration of methamphetamine suppressed GABA_BR-Girk signaling in VTA GABA neurons via the internalization of both receptor and channel that coincided with dephosphorylation of a serine residue on the GABA_BR that has been implicated in regulating GABA_BR surface expression (Padgett et al., 2012).

In addition to drug-induced adaptations in G protein-dependent ion channel activity, disruption of G_{i/o} signaling within the VTA may reflect alterations in downstream signaling molecules associated with these receptors that alter physiological properties of VTA DA neurons. Pharmacological up-regulation of cAMP in VTA slice preparations attenuates DA-dependent firing of DA neurons, while inhibition of protein kinase A (PKA) potentiates these effects (Shi and Bunney, 1992). Thus it is possible that repeated psychostimulant exposure reduces G_{i/o}-dependent negative regulation of AC activity that results in a significant increase in cAMP production and subsequent PKA activity in VTA neurons. Indeed, antagonism of G_s-coupled D₁-like receptors known to activate AC and promote cAMP production can block the development of behavioral sensitization to systemic cocaine (Kalivas, 1994; Vezina and Steward, 1989). Furthermore, constitutive activation of AC with an intra-VTA infusion of cholera toxin promotes behavioral sensitization to psychostimulants, an effect that is blocked by inhibition of PKA signaling (Pierce et al., 1996).

Regulatory proteins—RGS and AGS proteins have emerged as potential targets of drug-induced adaptations that occur during the development of addiction (Hooks et al., 2008; Lomazzi et al., 2008). Numerous studies have demonstrated that RGS and AGS expression and protein levels are dynamically-regulated following exposure to drugs of abuse (for review, see Lomazzi et al., 2008). The localization of Rgs2 and Rgs4 in VTA neurons led to early speculation that these proteins may modulate responses to psychostimulants and other drugs of abuse (Hooks et al., 2008; Lomazzi et al., 2008). Rgs2 is highly-enriched in striatal regions associated with psychostimulant-related behavior, and is heavily expressed in VTA DA neurons where it serves as a negative regulator of GABA_BR-Girk signaling (Labouebe et al., 2008). To date, studies have demonstrated significantly altered mRNA or protein expression for Rgs2 and Rgs4, as well as other RGS proteins in the VTA following exposure to morphine or GHB (Hooks et al., 2008; Labouebe et al., 2007; Lomazzi et al., 2008), but whether similar changes within the VTA occur following psychostimulant exposure remains unclear.

4.10 Conclusion

Although drug-related behaviors such as sensitization, craving, and susceptibility to relapse are long-lasting phenomena, adaptations in metabotropic inhibitory signaling discussed above typically recover within 10–12 days following a repeated non-contingent cocaine administration regimen. Thus, these adaptations may contribute to the development of drug-related behavior, but are not likely required for their continued expression. It is possible, however, that the transient nature of these changes reflects the model of cocaine administration used, as cocaine-induced changes in excitatory transmission following systemic cocaine administration are short lasting, but can persist up to three months following cocaine exposure, when delivered intravenously in a self-administration model of drug-seeking (Chen et al., 2008). Future efforts to define the anatomic, genetic, and temporal bases of these disparate adaptations in the VTA may provide important insight into how early and transient cocaine-induced adaptations facilitate the longer-lasting and stable changes that promote chronic cocaine intake.

5. PREFRONTAL CORTEX

The frontal cortex is an aggregate of several cortical regions, including the cingulate, prelimbic (PL), infralimbic (IL) and orbitofrontal cortices (OFC), and provides widespread excitatory (glutamatergic) input to cortical and sub-cortical structures. Recent findings in rodents and non-human primates suggest that these sub-regions display important similarities with humans in their reciprocal and topographical connectivity (Groenewegen et al., 1997; Kolb et al., 1990; Krettek and Price, 1977; van Eden et al., 1990; Uylings and van Eden, 1990). We will focus here on the more medial aspects of the PFC (mPFC), mainly the PL, IL, and cg1/cg2 aspects of the cingulate. These regions provide a majority of the glutamatergic excitatory projections to limbic structures such as the VTA and NAc, and are densely-innervated by projections arising from the VTA (Sesack and Deutch, 1989; Sesack and Pickel, 1992; Taber et al., 1995; Taber and Fibiger, 1995). As such, they act as critical elements of the brain reward circuitry responsible for mediating responses to rewards and reward-predicting stimuli (Goldstein and Volkow, 2011; Noonan et al., 2011; O'Doherty, 2011; Rushworth et al., 2011).

The rodent mPFC is divided into distinct cytoarchitectonic layers (Layers 1–6); unlike humans and non-human primates, the rodent mPFC lacks a distinguishable Layer IV (Conde et al., 1995; Gabbott et al., 1997; Krettek and Price, 1977). Glutamatergic pyramidal neurons found in Layers 2/3 and 5/6 make up 85% of neurons found within the mPFC (Kawaguchi, 1993; Kawaguchi and Kubota, 1993). Layer 5/6 pyramidal cells are the primary output neurons of the mPFC and play an important role in regulating the activity of VTA and NAc neurons (Sesack and Deutch, 1989; Sesack and Pickel, 1992; Taber et al., 1995; Taber and Fibiger, 1995). Within the VTA, mPFC terminals synapse onto GABA-containing neurons that project to the NAc, and DA-containing neurons that project to the mPFC, providing a mechanism to influence activity of ascending DA and GABA projections of the VTA (Carr and Sesack, 1999).

5.1 Role of the mPFC in addiction

While the VTA and DA have received considerable attention as key players in drug addiction, recent studies have highlighted the role of the mPFC and glutamate in the modulation of the mesocorticolimbic DA system and drug-seeking behavior (Baker et al., 2003; Cardinal and Everitt, 2004; McFarland and Kalivas et al., 2001; Moran et al., 2003; Reid et al., 1997; Steketee and Kalivas, 2011; Taber, 1995; Taber et al., 1995). The PFC plays an intricate role in decision-making, goal-directed behavior, and the processing of reward-related information (Goldstein and Volkow, 2011; Roberts and Wallis, 2000; Rolls, 2000; Williams and Goldman-Rakic 1995; Volkow et al., 2003). This structure is also involved in mediating the primary rewarding and reinforcing effects of abused drugs and drug craving (Goeders and Smith, 1983; Kalivas and Volkow, 2005; Koob and Volkow, 2010; Steketee and Kalivas, 2011; Tzschentke, 2001).

One of the core theories explaining how addiction-related behavior becomes compulsive is that a functionally 'hypoactive' frontal cortex results in decreased inhibitory control over behavior and an inability to regulate drug-seeking (Feil et al., 2010; Goldstein and Volkow, 2002, 2011; Koob and Volkow, 2010; London et al., 1996). Clinical studies indicate that structural, physiological, and functional abnormalities within the PFC facilitate impaired decision-making and the development of addicted behavior such as drug craving and drug seeking (Ehrman et al., 1992; Foltin and Haney, 2000; Franklin et al., 2002). For example, imaging studies in humans reveal that cerebral blood flow and glucose metabolism in the frontal cortices of cocaine addicts is decreased during withdrawal but increased during intoxication and exposure to drug-associated cues, the latter of which correlates with self-reported feelings of craving (Bonson et al., 2002; Childress et al., 1999; Franklin et al., 2002;

Grant et al., 1996; London et al., 2000; Maas et al., 1998; Matochik et al., 2003; Volkow and Fowler, 2000). Similar drug-induced changes have been shown in rodent models of addiction. For example, repeated cocaine exposure decreases mRNA levels of neuronal activity markers such as brain-derived neurotrophic factor (*bdnf*), activity-regulated cytoskeleton-associated (*arc*) gene, and *zif/268* (McGinty et al., 2010; Hearing, personal communication, 2010), while exposure to cocaine-associated cues following prolonged abstinence increases expression of activity-regulated genes in the mPFC (Neisewander et al., 2000; Hearing et al., 2008).

Several lines of evidence indicate that intact but altered glutamatergic output from the mPFC to limbic brain regions plays a critical role in the expression of drug-related behaviors (Tzschentke, 2001). For instance, lesioning of the ventral (IL cortex) and dorsal (PrL cortex) aspects of the mPFC prevents the development and expression of cocaine-induced behavioral sensitization, respectively (Pierce et al., 1998; Steketee and Kalivas, 2011). Moreover, drug-induced adaptations in cortical glutamate release onto neurons of the NAc and the VTA are key contributors to reinstatement of cocaine-seeking behavior (Baker et al., 2003; Liu and Steketee, 2012; McFarland et al., 2001; Moran et al., 2005). Thus, corticomesolimbic glutamate transmission arising from Layer 5/6 pyramidal neurons of the mPFC mediates several aspects of addiction-related behavior, including sensitization to cocaine, drug-taking behavior, and relapse (McFarland et al., 2001, 2003; Pierce et al., 1996; Steketee and Kalivas, 2011; Sun et al., 2005; Tzschentke, 2001). A critical unresolved question, however, is what specific adaptations occur in the mPFC in response to drugs of abuse (Wolf, 1998; Hyman and Malenka, 2001).

5.2 Effects of cocaine on mPFC neuron activity

To date, few studies have explored the acute effects of cocaine on prefrontal cortical activity. *In vivo* electrophysiological studies demonstrate that acute administration of cocaine significantly depolarizes Layer 5/6 pyramidal neurons shortly after cocaine administration (Trantham-Davidson et al., 2004). Moreover, acute cocaine decreased the spontaneous firing rate of pyramidal neurons, and decreased VTA-evoked postsynaptic responses (Trantham-Davidson, 2004). However, *in vitro* studies in acute slices has shown that membrane excitability of Layer 5/6 pyramidal neurons is not altered 24 hours following a single cocaine exposure, nor by ten minutes of direct cocaine (1 μ M) perfusion (Dong et al., 2005), indicating that acute administration of cocaine transiently alters certain physiological properties of mPFC Layer 5/6 pyramidal cells and may have a role in mediating some of the immediate behavioral effects of cocaine.

Studies on the effects of repeated cocaine on neuronal activity in the mPFC has been explored in greater detail, but paints a complex and often contradictory picture. *In vivo* electrophysiological recordings in cocaine self-administering rats showed that during an initial self-administration session, the overall firing rate and burst frequency of Layer 5/6 pyramidal neurons of the mPFC was reduced following cocaine infusion (Sun and Rebec, 2006). However, such inhibitory effects were no longer apparent following 2 weeks of cocaine self-administration, with burst firing rates and duration significantly elevated compared to baseline during the self-administration session (Sun and Rebec, 2006). Importantly, basal activity of Layer 5/6 pyramidal neurons of the mPFC prior to the beginning of a self-administration session decreased after extended cocaine, indicative of a “hypofrontal” state of activity (Sun and Rebec, 2006). Moreover, *in vitro* studies in acute mPFC slices have shown that repeated cocaine exposure triggers enduring plasticity within glutamatergic pyramidal neurons, including increased membrane excitability and strengthened excitatory signaling 3 days following the end of drug treatment (Huang, 2007; Lu et al., 2010; Nasif, 2005). Together, these studies suggest that while repeated cocaine exposure decreases basal activity of mPFC Layer 5/6 neurons, these cells are more excitable

and responsive to cocaine-related information (Sun and Rebec, 2006). It has been suggested that lower basal activity within the mPFC may amplify responsiveness of this brain region to drugs and drug-conditioned cues, allowing these cues to exert greater control over behavior (Sun and Rebec, 2006).

One potential consequence of increased excitability and responsiveness of Layer 5/6 pyramidal neurons to drug-associated cues would be increased glutamate release in the mesocorticolimbic system. Indeed, increased glutamate release has been observed in the NAc, VTA, and the mPFC following cocaine administration (Kalivas and Duffy, 1998; Kozell et al., 2001; Pierce et al., 1996; Reid et al., 1997; Smith et al., 1995). This rise in glutamate release can be blocked by inactivation of the mPFC and has been shown to correlate with drug-seeking behavior (McFarland et al., 2001, 2003; Steketee, 2003; Steketee and Kalivas, 2011).

5.3 D₂R and GABA_BR signaling in the mPFC

The output of mPFC Layer 5/6 projection neurons is dependent on their intrinsic physiological properties in conjunction with inhibitory tone produced by GABA and DA through direct and/or multi-synaptic inputs. Electrical stimulation of the VTA and local application of dopamine inhibit the spontaneous activity of most prefrontal cortical neurons, including Layer 5/6 projection cells (Pirrot et al., 1992). DA afferents arising from the VTA synapse onto both pyramidal and GABAergic neurons within Layer 5/6 of the mPFC (Cowan et al., 1994; Goldman-Rakic et al., 1989; Sesack et al., 1995), signaling through postsynaptic D₁ and D₂-like receptors (al-Tikriti et al., 1992; Bean et al., 1990; Wolf and Roth, 1987). In the rodent mPFC, both D₁-like and D₂-like receptors are found on pyramidal and non-pyramidal neurons (Benes and Berretta, 2001; Vincent et al., 1993, 1995). DA has been shown to exert both excitatory and inhibitory effects on mPFC Layer 5/6 pyramidal cells that are dependent on the DA concentrations and the physiological state of the cell (Gulledge and Jaffe, 1998, 2001; Lavin and Grace, 2001; Shi et al., 1997; Trantham-Davidson et al., 2004). Furthermore, *in vitro* and *in vivo* studies have demonstrated that intra-mPFC delivery of the D₂R agonist quinpirole can enhance extracellular GABA levels within the mPFC but inhibit evoked release of GABA (Grobin and Deutch, 1998; Gulledge and Jaffe, 1998). Thus, DA can directly influence Layer 5/6 pyramidal cell output through activation of postsynaptic DA receptors on pyramidal neurons or through modulation of local GABA neurons in the mPFC (for review, see Seamans and Yang, 2004).

GABA is the major inhibitory neurotransmitter in the mPFC, and it plays a fundamental role in regulating neuronal excitability (Bowery et al., 2002). Local GABA neurons, which account for ~15% of neurons in the mPFC, synapse onto and provide one source of GABA to mPFC pyramidal neurons (Hendry et al., 1983; Kawaguchi, 1993; Kawaguchi and Kubota, 1993; Retaux et al., 1993). Additionally, GABA-containing neurons in the VTA send axons to the mPFC where they synapse on dendrites of both pyramidal and local circuit neurons (Carr and Sesack, 2000). GABA exerts its effects through activation of both ionotropic (GABA_AR) and metabotropic (GABA_BR) receptors (Bowery et al., 2002; Sivilotti and Nistri, 1991). Within the mPFC, GABA_BRs are found presynaptically on axon terminals from local GABAergic interneurons and VTA GABA projection neurons and mediates postsynaptic inhibitory responses on Layer 5/6 neurons (Aguilar-Garcia et al., 2000; Badran et al., 1997; Calver et al., 2002).

5.4 Adaptations in D₂R signaling in mPFC Layer 5/6 pyramidal neurons

Repeated cocaine exposure alters DA signaling in Layer 5/6 pyramidal cells of the mPFC. *In vivo* electrophysiology studies in anesthetized rats have shown that prolonged withdrawal from repeated non-contingent cocaine decreases D₂R-mediated regulation of mPFC

pyramidal cell excitability, reduces postsynaptic responses to evoked DA release from the VTA, and reduces current-evoked but not spontaneous firing (excitability) of mPFC pyramidal cells (Nogueira et al., 2006). Additionally, behavioral studies indicate that repeated cocaine exposure decreases mPFC D₂R modulation of glutamate neurotransmission from the PFC that results in enhanced extracellular glutamate levels in the NAc (Beyer and Steketee, 2002). Given that activation of D₂Rs has a hyperpolarizing effect on neurons, it seems likely that reduced D₂R-function in mPFC pyramidal neurons would enhance the excitability of these cells, akin to previous findings in mPFC slices from cocaine-treated animals (Dong et al., 2005; Nasif et al., 2005). However, reduced D₂R-dependent postsynaptic inhibition was paralleled by a trend towards decreased excitability of Layer 5/6 pyramidal neurons *in vivo* (Nogueira et al., 2006), indicating that cocaine treatment likely alters intrinsic currents in pyramidal neurons as well as dopaminergic signaling within the mPFC. The contradictory nature of cocaine-induced changes in excitability likely reflects differences in the duration of withdrawal (3 days versus 2 weeks) or that recordings from *in vivo* studies were performed in adult rats (3 months old) versus *in vitro* studies in younger animals (4–6 weeks old).

5.5 D₂R adaptations in mPFC Layer 5/6 pyramidal neurons and addiction-related behavior

Reduced D₂R expression in frontal cortices has been implicated in compulsive drug intake in human cocaine addicts and decreased cognitive function in rats self-administering cocaine (Briand et al., 2008; Volkow et al., 1993). Intra-mPFC infusion of the D₂R antagonist sulpiride enhanced acute cocaine-induced motor activity and NAc extracellular DA levels, while a D₂R agonist inhibited both the behavioral and neurochemical effect of acute cocaine (Beyer and Steketee, 2000, 2001; Steketee and Walsh, 2005). Moreover, repeated intra-mPFC sulpiride induced a behavioral and neurochemical cross-sensitization to cocaine, while intra-mPFC quinpirole given prior to daily cocaine injections prevented the development of sensitization (Beyer and Steketee, 2002; Steketee and Walsh, 2005). In addition to sensitization, studies have shown that intra-mPFC self-administration of cocaine can be blocked by co-administration of sulpiride (Goeders and Smith, 1983). Taken together, these data suggest that sensitization and drug-seeking results, at least in part, from a reduction in D₂-mediated inhibition of excitatory output neurons which innervate the NAc and VTA.

5.6 Adaptations in D₂R signaling in mPFC Layer 5/6 interneurons

In addition to regulating Layer 5/6 pyramidal cell activity, DA can regulate mPFC glutamatergic output indirectly by acting at D₂R found on local inhibitory interneurons and modulating the excitability of GABA-containing neurons and subsequent GABA release within the mPFC (Grobin and Deutch 1998; Nogueira et al., 2006; Seamans and Yang, 2004; Sesack et al., 1995). Recently, it was demonstrated in acutely-isolated PFC slices that repeated cocaine and prolonged withdrawal reduced D₂R-dependent inhibition of evoked and spontaneous inhibitory postsynaptic currents (IPSCs) in cortical interneurons (Kroener and Lavin, 2010). This reduction in D₂R-modulation correlated with an increase in action potential-independent (spontaneous) GABA release within the mPFC. (Kroener and Lavin, 2010). This loss of D₂R-dependent signaling resulted in a shift towards D₁R-dependent signaling that augmented the excitability of Layer 5/6 GABA-containing neurons in the mPFC (Kroener and Lavin, 2010). These findings are consistent with previous reports of increased extracellular GABA within the mPFC of cocaine sensitized rats and suggest that repeated cocaine significantly reduces the function of D₂R in both excitatory and inhibitory neurons within the mPFC (Jayaram and Steketee, 2005; Kroener and Lavin, 2010; Nogueira et al., 2006).

5.7 D₂R adaptations in mPFC Layer 5/6 interneurons and addiction-related behavior

Cortical interneurons are well positioned to gate inputs and shape the output of Layer 5/6 pyramidal neurons (Compte et al., 2000; Lapish et al., 2007; McBain and Fisahn, 2001). This gating is important for cognitive function, and is thought to be optimized through DA-dependent modulation of interneuron firing in the mPFC (Tierney et al., 2008). Therefore, cocaine-induced changes in this modulation may disrupt signal processing within the mPFC that is important to cognition and goal-directed behavior (Kroener et al., 2009).

DA release in the mPFC can decrease overall cortical activity while still increasing evoked firing of pyramidal neurons (Kroener et al., 2009). Repeated cocaine exposure may reduce D₂R-function in mPFC GABAergic interneurons, leaving an unopposed D₁R-mediated enhancement of GABA release in the cortex. Increased GABA release would in turn reduce basal glutamate release to subcortical targets and disrupt processing of motivating stimuli that drive behavior (Durstewitz and Seamans, 2008; Franklin and Druhan, 2000). This idea is consistent with previous reports of reduced basal extracellular glutamate levels in the NAc following repeated cocaine exposure (Baker et al., 2003). Furthermore, this type of disruption is akin to the drug-induced hypofrontality observed in humans that is believed to bring about a reduction in inhibitory control over maladaptive behavior and the emergence of compulsive drug-seeking in addicts (Feil et al., 2010; Goldstein and Volkow, 2002; Koob and Volkow, 2010; London et al., 1996). Additionally, alterations in cognitive function are thought to underlie decreased motivation to respond to non-drug-related stimuli seen in drug-dependent individuals, leaving only strong motivational stimuli such as drug-associated cues to ably activate mPFC networks and initiate behavior (Childress et al., 1999; Franklin et al., 2002; Grant et al., 1996; Kalivas et al., 2005; London et al., 2000; Maas et al., 1998; Matochik et al., 2003; Volkow and Fowler, 2000).

5.8 GABA_BR adaptations in mPFC Layer 5/6 pyramidal neurons and addiction-related behavior

Alterations in GABAergic signaling in the mPFC plays an important role in modulating drug-related behavior following repeated cocaine treatment. For example, ventral but not dorsal mPFC infusions of a GABAergic agonist cocktail (muscimol and baclofen) decreased cue-induced cocaine seeking following prolonged withdrawal, while antagonists (bicuculline and saclofen) dramatically increased extinction responding following one day of withdrawal (Koya et al., 2009). Of specific relevance to GABA_BR-dependent signaling, infusion of baclofen into the ventral portion of the mPFC blocked acute cocaine-induced motor activity and the development of behavioral sensitization when administered prior to each cocaine injection (Steketee and Beyer, 2002). However, the ability of baclofen to decrease cocaine-induced activity was lost in previously-sensitized rats, providing indirect evidence that repeated cocaine reduces the functional capability of GABA_BR signaling in the mPFC (Jayaram and Steketee, 2004, 2005). Consistent with this, recent findings from our lab indicate that repeated but not acute cocaine suppresses GABA_BR-GIRK signaling in the mouse mPFC (Hearing et al., unpublished data).

In addition to regulating behavioral components of addiction, alterations in GABA signaling in the mPFC following cocaine exposure modify DA and glutamatergic neurotransmission in the mesocorticolimbic system. For instance, following baclofen infusion into the ventral mPFC, drug-naïve animals show less glutamate release in the VTA and NAc, while cocaine-treated animals exhibit elevated glutamate in these brain regions (Jayaram and Steketee, 2004). Similar results were observed following dorsal PFC infusions of baclofen, which decreased extracellular DA in drug naïve animals, while an antagonist (phaclofen) increased DA levels (Santiago, et al., 1993). Such data support the conclusion that psychostimulants impair the ability of GABA_BR-dependent signaling to regulate neurotransmission within the

mPFC, as well as glutamate output from the mPFC, which is critical for the expression of addiction-related behavior.

5.9 Mechanisms underlying adaptations in mPFC D₂R and GABA_BR signaling

Receptor expression and G proteins—Evidence suggests that cocaine-induced reductions in D₂R function in the mPFC likely reflects, in part, a decrease in receptor expression and/or stability. Indeed, reduced D₂R binding has been observed in multiple regions of the frontal cortex of cocaine-dependent individuals, while rats exhibited decreased quinpirole-mediated GTP γ S binding in the mPFC following repeated cocaine exposure (Bowers et al., 2004; Volkow and Fowler, 2000). Furthermore, rats with either a history of non-contingent cocaine exposure or cocaine self-administration displayed reduced D₂R protein expression, the latter of which correlated with persistent deficits in cognitive tasks that require an intact mPFC (Briand et al., 2008; Kleven et al., 1990). While many studies have reported reduced function of mPFC GABA_BR-dependent signaling following psychostimulant exposure, no changes in total receptor or Gi/o protein levels have been reported (Jayaram & Stekettee, 2004; Li, et al., 2002; Striplin & Kalivas, 1992). Moreover, there does not appear to be a functional change in GABA_BR coupling to G_{i/o} proteins, as measured by baclofen-induced GTP γ S binding in the PFC following repeated cocaine exposure (Kushner & Unterwald, 2001).

Effectors—Cocaine-induced weakening of GABA_BR and D₂R-dependent pathways that normally regulate mPFC Layer 5/6 pyramidal neurons offers a potential explanation for the enhanced mPFC glutamatergic output associated with behavioral sensitization (Jayaram and Stekettee, 2004; Liu and Stekettee, 2011; Noguiera et al., 2006). At present, however, little is known regarding the effectors that mediate the inhibitory influence of GABA_BR and D₂R in neurons that project to the VTA and NAc. *In vitro* and *in vivo* electrophysiological studies from adolescent and adult rats show that repeated cocaine increased burst firing of Layer 5/6 pyramidal neurons of the mPFC in response to cocaine-associated information, and enhanced membrane excitability by suppressing voltage-gated and inwardly-rectifying K⁺ currents and enhancing voltage-gated L-type Ca²⁺ currents (Dong et al., 2005; Nasif et al., 2005; Sun and Rebec, 2006). Consistent with this, unpublished findings from our laboratory indicate that Girk channels mediate most of the GABA_BR-dependent postsynaptic inhibitory effects in Layer 5/6 pyramidal neurons of the mouse mPFC, and that repeated cocaine suppresses GABA_BR-Girk signaling in these cells (Hearing et al., unpublished). Thus, repeated drug exposure may temper GABA_BR and/or D₂R-dependent signaling in Layer 5/6 pyramidal neurons of the mPFC by altering the levels of Girk channels or other downstream effectors, as was shown in VTA DA neurons (Arora et al., 2011; Kushner and Unterwald, 2001).

An additional mechanism by which cocaine may alter mPFC pyramidal cell excitability is through modulation of the cAMP/PKA signaling pathway. PKA can phosphorylate K⁺ channels and consequently decrease K⁺ currents, and repeated exposure to cocaine has been shown to up-regulate the cAMP/PKA pathway in mPFC Layer 5/6 pyramidal neurons (Dong et al., 2005; Dong and White, 2003). Given that G_{i/o}-dependent signaling negatively-regulates AC activity, increased cAMP/PKA signaling in the mPFC may be due in part to reduced inhibitory modulation via GPCRs such as D₂R or GABA_BR.

Regulatory proteins—Changes in the level or function of RGS and AGS proteins could also underlie cocaine-induced alterations in G protein-dependent signaling. For example, Rgs4 is a forebrain-enriched RGS isoform, expression of which has shown to be dynamically-regulated by activation of DA receptors in response to acute psychostimulant administration (Schwendt et al., 2006; Schwendt, 2007; Schwendt and McGinty et al, 2010;

Taymans et al., 2003). Although *Rgs4* expression is regulated by D₁R and D₂R, *Rgs4* does not appear to exercise direct effects on D₂R signaling (Ding et al., 2006; Schwendt et al., 2006; Taymans et al., 2003;). Changes in *Rgs4* expression, however, do appear to alter signaling via other GPCRs, including GABA_BR (Abramow-Newerly et al, 2006). Thus, cocaine-induced adaptations in DA signaling may indirectly alter GABA_BR-dependent signaling in an *Rgs4*-dependent manner.

Following prolonged withdrawal from chronic binge-cocaine exposure or cocaine self-administration, *Rgs4* mRNA is significantly decreased in the rat mPFC (Schwendt et al., 2007). Furthermore, re-exposure to a cocaine-associated context following abstinence from self-administration restored levels of *Rgs4* mRNA to that of control rats (Schwendt et al., 2007). As *Rgs4* is a negative regulator of several G_{i/o}-coupled receptors, a reduction in *Rgs4* expression would be expected to disinhibit (enhance) inhibitory signaling. However, repeated cocaine appears to reduce GABA_BR function (Jayaram and Steketee, 2004). In addition to regulating G_i-signaling, *Rgs4* plays a significant role in modulating the G_q class of G proteins (Schwendt et al., 2011; Schwendt and McGinty, 2007), thus it is possible that cocaine-induced reductions in mPFC *Rgs4* levels alters G_q- but not G_{i/o}-dependent signaling. Regardless, cocaine-induced changes in the expression and/or function of *Rgs4* in the mPFC may translate into widespread modifications in a number of G protein-dependent signaling pathways.

Cocaine-induced suppression of D₂R and GABA_BR-dependent signaling in the mPFC of animals treated repeatedly with psychostimulants may also result from elevated levels of AGS proteins. Indeed, *Ags3* mRNA and protein are significantly elevated in the rodent mPFC following repeated cocaine exposure (Bowers et al, 2004). These alterations have been shown to persist for up to 8 weeks of withdrawal (Bowers et al, 2004; Frankowska et al., 2008), thus representing an enduring molecular adaptation that may in part promote the persistence of addicted behavior. Indeed, up-regulation of *Ags3* expression in the mPFC produced a heightened motor-stimulatory response to a single cocaine injection normally observed following repeated cocaine exposure (Bowers et al., 2004). Increased *Ags3* expression also elevated levels of extracellular glutamate in the NAc and enhanced drug-seeking behavior in self-administering rats when primed with a single cocaine injection (Bowers et al., 2004). Moreover, reduced *Ags3* expression in the mPFC restored chronic cocaine-induced reductions in D₂R-mediated signaling in the mPFC and blocked behavioral sensitization and reinstatement of drug-seeking behavior (Bowers et al., 2004). It is possible that up-regulation of *Ags3* in the mPFC and subsequent decreases in Gi/o-dependent metabotropic signaling via D₂Rs may result in a shift towards G_s-dependent signaling. This would be predicted to enhance cAMP-dependent signaling, as well as downstream transcription factors that may in turn promote increased excitability of cortical neurons projecting to the NAc and VTA. Regardless of the exact mechanisms, these findings exemplify the importance of mPFC G_{i/o}-dependent signaling in the development and persistence of addicted behavior.

5.10 Conclusion

Repeated cocaine exposure reduces basal activity and glutamate release from the mPFC to subcortical regions important for the expression of addicted behavior (Childress et al., 1999; Baker et al., 2003; Steketee and Kalivas, 2011). In contrast, the mPFC, including the Layer 5/6 pyramidal neurons, is more responsive when exposed to drug-associated cues, promoting enhanced glutamate release within the NAc (Baker et al., 2003; Childress et al., 1999; Sun and Rebec, 2006). This dichotomy of effects may be explained in part, by a reduction in metabotropic inhibitory signaling within both excitatory and inhibitory neurons of the mPFC. Reduced D₂R or GABA_BR-dependent inhibitory signaling in GABA interneurons likely promotes increased GABA release within the mPFC that may contribute to reductions

in overall basal activity (hypofrontality). Hypofrontality may in turn reduce the motivation to respond to non-drug-related stimuli, leaving only strong motivational stimuli such as drug-associated cues to ably activate PFC networks and initiate behavior (Kalivas et al., 2005). Alternatively, increased responsiveness to drug-associated cues may reflect reductions in D₂R or GABA_BR-dependent inhibitory signaling in Layer 5/6 pyramidal neurons that increases glutamate release necessary for driving addicted behavior.

6. CONCLUSION

Although there have been important advances in our understanding of the neural adaptations underlying the development of addiction and the persistent vulnerability to relapse, a better understanding of signaling pathways, inhibitory and excitatory, that mediate the cellular and behavioral effects of drugs of abuse, will ultimately improve the way in which we understand and address addiction as a progressive disease.

While a wealth of evidence highlights the importance of cocaine-induced adaptations in excitatory neurotransmission in the development and expression of addicted behavior, the material covered in this review collectively indicates that cocaine-induced neuroadaptations in metabotropic inhibitory signaling mediated by two prominent G protein-coupled receptors – the GABA_B and D12 dopamine receptors – in the VTA and mPFC likely constitute an “addiction barrier” that is overcome by exposure to cocaine and perhaps other drugs of abuse. Such drug-evoked synaptic plasticity may constitute an early cellular mechanism eventually causing compulsive drug-seeking behavior in some drug users. While vulnerability to relapse affords an opportunity for pharmacotherapeutic intervention, our limited understanding of the neurochemical, molecular, and cellular mechanisms that lead to the persistent expression of drug-related behavior has impeded us in this regard. Thus it is important to elucidate the induction criteria for addiction. One way to achieve this is by gaining a better understanding the molecular and cellular mechanisms responsible for drug-induced changes in inhibitory signaling, and how these changes reorganize and functionally alter neuronal circuits that eventually lead to behaviors that define addiction.

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Box 1**Glossary of Terms****Behavioral Sensitization**

A term that refers to the progressive increase in locomotor activity or stereotypy with repeated administration of a psychostimulants. This phenomenon is more likely to occur with intermittent exposure to drugs, and has been suggested to grow with the passage of time. Typically, psychomotor sensitization is viewed as two phases: an initial phase often termed “development or induction” whereby drugs are administered over days and produce a sequence of cellular and molecular adaptations that lead to enduring changes in neuronal function responsible for drug-induced motor activity. The “expression of sensitization” typically refers to a subsequent test of motor activity during which subjects are injected acutely with drugs at different withdrawal points following development to assess augmented drug-induced behavior.

Conditioned Place Preference (CPP)

A classical (Pavlovian) conditioning model where animals undergo a training phase with one distinct context paired with drug injections, while another context is paired with vehicle injections. During a subsequent drug-free place preference test, animals are placed in an apparatus and allowed to choose between the drug- or vehicle-paired contexts. An increase in preference for the drug context serves as a measure of the drug’s reinforcing effects. Additional experiments can be performed using this model to evaluate extinction and/or reinstatement of this preference. In this way animals are repeatedly exposed to the context previously associated with drug-injection until the preference is extinguished, at which point, a priming stimulus, such as a small amount of drug, drug-associated cues or stressor can be given to determine the reinstatement of the context preference.

Drug Self-Administration

An operant model in which laboratory animals typically lever press (or nose poke) for an intravenous infusion of a drug. This model is typically divided into three phases. During the “acquisition phase” animals are trained to self-administer the drug by means of lever pressing which results in intravenous delivery of the drug. Each daily self-administration session typically ranges from 1–2 h (short access) up to 6 h (long-access). The switch from short to long access typically accelerates the rate of drug intake, akin to the increasing rates of drug use in the course of human addiction. The duration of this phase is often determined by a preset “maintenance criteria” whereby the animal is required to administer a minimum number of infusions. During each session, there are two levers present where the active lever results in drug delivery, while the inactive lever has no programmed consequences, which helps to delineate drug-seeking behavior from non-specific operant responding. Often times drug delivery is accompanied by a cue—typically a light and/or an audio tone. During the second phase, animals undergo a predetermined period of “forced abstinence” (i.e., they are maintained in their home cages without exposure to the operant chamber) or “extinction training” during which no drug is administered in response to lever pressing; “learning” under the extinction training paradigm is reflected by decreased rates of lever pressing. Subsequent to the abstinence or extinction phase, experiments can evoke relapse (abstinence) or reinstate (extinction) of lever pressing by the presentation of environmental stimuli previously associated with the drug such as the context itself (abstinence only), a light/tone cue, a small amount of the drug, or a mild stressor.

Figure 1.

The mesocorticolimbic dopamine system, with the ventral tegmental area (VTA), nucleus accumbens (NAc), and prefrontal cortex (PFC) visualized from a sagittal perspective. Dopamine (blue) and GABA (red) projections arising from the VTA synapse on Layer 5/6 pyramidal and GABA local circuit interneurons of the PFC. PFC Layer 5/6 pyramidal neurons also receive GABAergic input from interneurons, and send glutamatergic projections to the NAc and VTA. VTA DA and GABA neurons also project to the NAc and receive reciprocal GABAergic input from neurons of the NAc. In addition, VTA DA neurons receive GABAergic input from local interneurons and neurons projecting from the rostromedial tegmental nucleus (RMTg). Enlarged schematics of the VTA and PFC are shown to illustrate distribution of D₂ (orange) and GABA_B (red) receptors.

Figure 2.

Schematic of G protein-coupled receptors coupled to the $G_{\alpha i/o}$ subclass of G proteins. GPCRs transduce ligand-binding events to intracellular responses via heterotrimeric G proteins, which consist of G_{α} and $G\beta\gamma$ subunits (1). Binding of a ligand activates G protein signaling by promotes the exchange of GTP for GDP on the G_{α} subunit (2). Activated G_{α} and “free” $G\beta\gamma$ can then interact with and modulate intracellular effectors such as adenylyl cyclase (AC), and ion channels such as G protein-gated inwardly-rectifying potassium (GirK) and voltage-gated calcium (Ca^{2+}) channels (3). G protein-dependent signaling can be regulated by G-protein coupled receptor kinases (GRKs) dependent phosphorylation and subsequent β -arrestin-mediated internalization (4). Regulators of G protein signaling (RGS) proteins enhance deactivation of G protein signaling by accelerating GTPase activity of G_{α} subunits (5), while Activators of G protein signaling (AGS) proteins prevent reactivation of G_{α} proteins by stabilizing GDP-bound G_{α} and preventing binding of GTP (6)