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Review

Anatomy and pharmacology of cocaine priming-induced reinstatement of drug seeking

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Abstract

Cocaine addiction in human addicts is characterized by a high rate of relapse following successful detoxification. Relapse to drug taking/seeking can be precipitated by several stimuli including, but not limited to, re-exposure to cocaine itself. In order to understand the mechanisms underlying cocaine craving, a substantial effort has been devoted to elucidating the anatomical and neurochemical bases underlying cocaine priming-induced reinstatement, an animal model of relapse. Here, we review evidence that changes in dopaminergic and glutamatergic transmission in limbic/basal ganglia circuits of interconnected nuclei including the medial prefrontal cortex, nucleus accumbens, ventral pallidum, amygdala, hippocampus, orbitofrontal cortex, neostriatum and thalamus underlie cocaine priming-induced reinstatement of cocaine seeking. Maladaptive changes in the processing of motivationally relevant stimuli by these circuits following cocaine self-administration result in drug craving and compulsive drug seeking upon re-exposure to cocaine.

Keywords: Relapse; Addiction; Nucleus accumbens; Dopamine; Glutamate

Contents

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1. Introduction

Cocaine abuse remains a major public health problem in the United States. Recently, it has been estimated that nearly 1% of the U.S. population age 12 or older abuses cocaine. Moreover, the number of people who have reportedly sampled cocaine has steadily increased in the past decade (Substance Abuse and Mental Health Services Administration, 2003). Cocaine addiction is associated with a high rate of relapse following detoxification (Dackis and O'Brien, 2001). To date, a safe and effective pharmacological treatment for cocaine craving has yet to be identified, which highlights the need for additional information on the anatomical and neurochemical bases of cocaine craving.

Drug craving and relapse of drug-taking behavior in humans are precipitated by three major factors: a stressful life-event, an environmental stimulus previously associated with drug taking or re-exposure to the drug itself (Carter and Tiffany, 1999; de Wit and Stewart, 1981; Jaffe et al., 1989; Sinha, 2001). Relapse of drug seeking/taking by humans is typically modeled in animals as follows: following a period of self-administration and the subsequent extinction of the drug reinforced behavior, the ability of stress, drug-associated stimuli or re-exposure to the drug itself to reinstate drug seeking is assessed (Shalev et al., 2002). For example, following extinction of cocaine self-administration, systemic or intravenous injections of relatively low doses of cocaine reinstate operant responding in the absence of drug reinforcement in both non-human primates and rodents (de Wit and Stewart, 1981; Gerber and Stretch, 1975; Self et al., 1996; Spealman et al., 1999).

The reinstatement paradigm has proven invaluable for elucidating the neurochemical mechanisms as well as the neural circuitry underlying reinstatement of drug-seeking behavior. Here, we focus on the mechanisms underlying cocaine priming-induced reinstatement of drug seeking, with particular emphasis on the roles of dopamine and glutamate transmission in the limbic system. A more complete understanding of the neurochemical mechanisms underlying the reinstatement of cocaine-seeking behavior could lead to the development of novel, targeted pharmacotherapies for cocaine addiction.

2. The role of dopamine in cocaine priming-induced reinstatement

Cocaine is a dopamine, norepinephrine and serotonin transporter inhibitor (Ritz et al., 1990). However, a growing literature indicates that dopamine is the biogenic amine primarily involved in the reinstatement of cocaine seeking. Thus, administration of dopamine, but not serotonin or norepinephrine, reuptake inhibitors reinstates cocaine seeking (De Vries et al., 1999; Schenk, 2002; Schenk and Partridge, 1999; Schenk et al., 2000; Schmidt and Pierce, 2004).

Dopamine signaling is mediated by specific membrane receptors belonging to the seven transmembrane domain G protein-coupled family of receptors. Five dopamine receptor subtypes, designated Dl–D5, have been identified. Each dopamine receptor subtype can be further categorized as Dl-like (Dl and D5) or D2-like (D2, D3 and D4) based on sequence homology and pharmacology (Kebabian et al., 1972; Missale et al., 1998; Sibley et al., 1993). An extensive body of evidence indicates that dopamine Dl-like and D2-like receptors play a critical role in cocaine priming-induced reinstatement of drug seeking. For example, dopamine D2-like receptor agonists reinstate cocaine seeking (De Vries et al., 2002, 1999; Fuchs and See, 2002; Khroyan et al., 2000; Self et al., 1996; Spealman et al., 1999; Wise et al., 1990), while pretreatment with a dopamine D2-like receptor agonist prior to a priming injection of cocaine either potentiates (Fuchs and See, 2002; Self et al., 1996) or fails to alter (Khroyan et al., 2000) subsequent cocaine-seeking behavior. Consistent with these findings, dopamine D2-like receptor antagonists attenuate cocaine priming-induced drug-seeking behavior (Khroyan et al., 2000; Schenk and Gittings, 2003; Spealman et al., 1999; Vorel et al., 2002).

In contrast, dopamine Dl-like receptor agonists do not reinstate cocaine-seeking behavior (De Vries et al., 1999; Khroyan et al., 2000; Self et al., 1996, 2000; Spealman et al., 1999). In fact, systemically administered dopamine Dl-like receptor agonists and antagonists both attenuate drug-seeking behavior induced by a priming injection of cocaine (Alleweireldt et al., 2003; Khroyan et al., 2000, 2003; Norman et al., 1999; Self et al., 1996; Spealman et al., 1999). Although the reasons for this discrepancy in dopamine Dl-like receptor effects remain unclear, explanations have included differing efficacies of dopamine Dl-like receptor agonists tested, modification of dopamine Dl-like receptor-mediated effects by other neurotransmitter systems and dopamine Dl-like receptor modulation of satiation rather than incentive motivation (Khroyan et al., 2000, 2003; Self et al., 2000). Collectively, these results indicate that, although increased dopamine transmission through dopamine Dl-like and D2-like receptors plays a critical role in priming-induced reinstatement of cocaine seeking, the precise contribution of

dopamine D1-like receptor activation to this process remains somewhat ambiguous.

2.1. Dopaminergic innervation of limbic nuclei

Dopaminergic neurons in the ventral tegmental area innervate virtually every nucleus in the limbic system. As shown in Fig. 1, the ventral tegmental area sends dopaminergic projections to the nucleus accumbens, medial prefrontal cortex, amygdala, hippocampus and ventral pallidum (Berendse et al., 1992; Brog et al., 1993; Heimer et al., 1997; Klitenick et al., 1992). Not surprisingly, various dopamine receptors are expressed in each of these limbic regions. Specifically, dopamine Dl and D2 receptor mRNA is highly enriched within the nucleus accumbens, with lower levels of expression in the hippocampus and medial prefrontal cortex (Bouthenet et al., 1991; Meador-Woodruff, 1994; Mengod et al., 1991). Additionally, Dl mRNA levels are high in the frontal cortex and amygdala (Meador-Woodruff, 1994; Weiner et al., 1991) while D2 mRNA expression is moderate in the medial prefrontal cortex, but prominent in the ventral tegmental area (Camps et al., 1990; Hurd et al., 2001; Meador-Woodruff et al., 1996). Conversely, the D3, D4 and D5 receptor subtypes are more discretely distributed in the rodent brain. D3 receptor mRNA is preferentially localized to limbic areas, particularly the nucleus accumbens shell and Islands of Calleja, as well as mesencephalic dopamine neurons (Bouthenet et al., 1991; Diaz et al., 2000; Mengod et al., 1992; Sokoloff et al., 1990). Moreover, D2 and D3 receptor subtypes are expressed by dopaminergic neurons in both axon terminal and somatodendritic regions and function as autoreceptors (Tepper et al., 1987, 1997). D4 mRNA appears to be restricted solely to limbic regions, including the nucleus accumbens, hippocampus, amygdala and prefrontal cortex (Svingos et al., 2000; Wedzony et al., 2000). D5 receptor mRNA is present in the hippocampus, hypothalamus and certain thalamic nuclei, but its expression is exceedingly low in both the striatum and medial prefrontal cortex (Khan et al., 2000; Meador-Woodruff et al., 1992).

Given the important role of dopamine in cocaine priming-induced reinstatement (see above), stimulation of dopaminergic neurons in the ventral tegmental area should reinstate cocaine seeking. Consistent with this hypothesis, administration of substance P, morphine or *N*-methyl-D-aspartic acid (NMDA), compounds known to increase the firing rates of dopaminergic neurons, directly into the ventral tegmental area promotes cocaine-seeking behavior (Placenza et al., 2004; Stewart, 1984; Vorel et al., 2001). In addition, reversible inactivation of the ventral tegmental area blocks cocaine priming-induced reinstatement of drug seeking (McFarland and Kalivas, 2001). Collectively, these results suggest that increased dopamine release in one or more dopaminoreceptive limbic nuclei promotes cocaine seeking. In the following sections, we will review the available evidence indicating the extent to which the nucleus accumbens, medial prefrontal cortex, orbitofrontal cortex, hippocampus, amygdala and ventral pallidum contribute to cocaine priming-induced reinstatement of drug seeking.

2.2. Nucleus accumbens subregions: core and shell

The nucleus accumbens can be divided into two major subregions, known as the core and shell. On the basis of connectivity, the nucleus accumbens shell has been defined as part of the limbic system (often described as part of the "extended amygdala"), while the core is associated with the dorsal striatum/basal ganglia (Alheid and Heimer, 1988; Everitt et al., 1999). Given these distinctions, it has been proposed that the nucleus accumbens subregions play different roles in mediating drug reinforcement. The limbic shell has been implicated in the primary rewarding effects of various drugs of abuse (Carlezon and Wise, 1996; Di Chiara and Imperato, 1988; Pontieri et al., 1995), as well as mediating the potentiation of instrumental responding in the presence of motivationally relevant stimuli (Abdel-Hady et al., 2001; Corbit et al., 2001; Di Chiara et al., 2004; Ghitza et al., 2003; Parkinson et al., 1999). In contrast, the nucleus accumbens core appears to mediate the incentive value of reward-conditioned stimuli and contributes to drug-associated cue-induced cocaine seeking (Di Ciano and Everitt, 2004; Fuchs et al., 2004a; Ito et al., 2004). While many studies have sought to elucidate the contribution of the core and shell subcompartments in the processing of drug-associated stimuli and reinstatement of drug seeking elicited by such cues, relatively few investigations have examined the role of the core and shell in drug priming-induced reinstatement.

2.2.1. Role of the nucleus accumbens subregions in priming-induced reinstatement of cocaine seeking

Intra-accumbal infusions of cocaine (Park et al., 2002) or dopamine (Cornish and Kalivas, 2000) have been shown to reinstate cocaine seeking in rats previously trained to self-administer cocaine. The reinstatement of cocaine seeking by intra-accumbal dopamine can be blocked by co-infusion of the non-selective dopamine receptor antagonist fluphenazine (Cornish and Kalivas, 2000). However, intra-accumbal administration of the same dose of fluphenazine failed to influence drug seeking induced by a systemic priming injection of cocaine (Cornish and Kalivas, 2000). Collectively, these findings support a role for accumbal dopamine systems in mediating cocaine priming-induced reinstatement.

Few studies have systematically examined the differential contribution of the nucleus accumbens subregions in cocaine reinstatement. Reversible inhibition of the core, but not the shell, subregion of the nucleus accumbens attenuates cocaine-seeking behavior induced by a cocaine prime (McFarland and Kalivas, 2001). In contrast, administration of a dopamine Dl-like or D2 receptor agonist directly into the nucleus accumbens shell reinstates drug seeking, while intra-accumbal shell microinjection of a dopamine Dl-like or D2 receptor antagonist attenuates the priming effect of a systemic cocaine injection (Anderson et al., 2003; Schmidt and Pierce, 2004). Collectively, these results clearly demonstrate a role for dopamine transmission in the nucleus accumbens during cocaine priming-induced reinstatement. However, the differential role of the accumbens core and shell remains to be resolved with regards to drug-seeking behavior.

The modulation of downstream signaling pathways coupled to accumbal dopamine Dl-like and D2-like receptors also influences cocaine reinstatement. Thus, administration of a protein kinase A (PKA) inhibitor directly into the nucleus accumbens reinstates cocaine-seeking behavior (Self et al., 1998). Consistent with these findings, intra-accumbal microinjection of the PKA stimulator Sp-CAMPS disrupts cocaine reinstatement (Self et al., 1998). However, administration of Sp-CAMPS directly into the nucleus accumbens alone or as pretreatment to a priming injection of cocaine increases responding on both the active, or drug-paired, lever as well as an inactive lever, a result that indicates that the active lever responses may reflect a general increase in behavioral activation (Self et al., 1998). Moreover, it is difficult to interpret the role of PKA signaling in priming-induced reinstatement as Sp-CAMPS could be acting presynaptically to modulate both dopamine and glutamate terminals in the accumbens (Chavez-Noriega and Stevens, 1994; Santiago and Westerink, 1990; Self et al., 1998).

2.3. Medial prefrontal cortical subregions: the anterior cingulate, prelimbic cortex and infralimbic cortex

The rodent medial prefrontal cortex can be subdivided into three distinct compartments: the anterior cingulate cortex, prelimbic cortex and infralimbic cortex (Krettek and Price, 1977; Van Eden and Uylings, 1985), all of which receive dopaminergic projections from the ventral tegmental area (Heidbreder and Groenewegen, 2003). It has been suggested that the medial prefrontal cortex can be more broadly subdivided into a dorsal component, comprised of the anterior cingulate cortex and the dorsal prelimbic cortex, and a ventral component, comprised of the ventral prelimbic cortex and the infralimbic cortex (Berendse et al., 1992; Graybiel et al., 1990; Steketee, 2003). This dorsal–ventral axis within the medial prefrontal cortex can be differentiated on the basis of distinct afferent and efferent connectivity patterns with cortical and subcortical areas such as the striatum, thalamus, amygdala, hypothalamus and various brain stem nuclei (Conde et al., 1995; Floyd et al., 2000, 2001; Heidbreder and Groenewegen, 2003; Krettek and Price, 1977; Ray et al., 1992; Sesack et al., 1989; Van Eden et al., 1992). A growing literature indicates that there is a behavioral and functional heterogeneity between the dorsal and ventral subdivisions of the medial prefrontal cortex (Park et al., 2002; Pierce et al., 1998; Tzschentke and Schmidt, 1999). Generally speaking, the dorsal region of the medial prefrontal cortex is thought to be involved in temporal shifting of behavioral sequences (Groenewegen, 2003), whereas the ventral prelimbic and infralimbic regions are thought to mediate flexible shifting of behavior in response to spatial cues as well as integrating internal physiological states with salient environmental cues for the guidance of behavior (Heidbreder and Groenewegen, 2003).

2.3.1. Role of medial prefrontal cortex subregions in priming-induced reinstatement of cocaine seeking

There is evidence that the medial prefrontal cortex, specifically the dorsal prefrontal cortex, mediates reinstatement of drug seeking. Administration of a cocktail of gamma-aminobutyric acid receptor A ($GABA_A$) and B ($GABA_B$) agonists (McFarland and Kalivas, 2001) or tetrodotoxin (Capriles et al., 2003) into the dorsal prefrontal cortex, but not the ventral medial prefrontal cortex, blocks cocaine priming-induced reinstatement in rats. These results suggest that the anterior cingulate and prelimbic cortices, but not the more ventral infralimbic cortex, mediate reinstatement of cocaine seeking. Consistent with these findings, cocaine, amphetamine or dopamine administered into the dorsal prefrontal cortex reinstates cocaine seeking (McFarland and Kalivas, 2001; Park et al., 2002) indicating that increased dopamine transmission in the medial prefrontal cortex mediates drug-seeking behavior. In addition, cocaine priming-induced reinstatement was blocked following administration of a Dl-like, D2-like or non-selective dopamine receptor antagonist into the anterior cingulate and prelimbic regions of the medial prefrontal cortex (Capriles et al., 2003; McFarland and Kalivas, 2001; Park et al., 2002; Sun and Rebec, 2005). Taken together, these data indicate that increased dopamine transmission in the dorsal medial prefrontal cortex plays a critical role in cocaine priming-induced reinstatement of drug seeking.

2.4. Role of the orbitofrontal cortex in cocaine priming-induced reinstatement

The orbitofrontal cortex is innervated directly by dopaminergic projections from the ventral tegmental area (Oades and Halliday, 1987) and indirectly by the nucleus accumbens by way of the mediodorsal nuclei of the thalamus (Ray and Price, 1993). The orbitofrontal cortex also receives projections from other limbic regions such as the amygdala and hippocampus (Carmichael and Price, 1995; Ray and Price, 1993). In turn, the orbitofrontal cortex sends efferent projections directly to the nucleus accumbens core (Haber et al., 1995).

Imaging studies have shown that enhanced glucose metabolism in the orbitofrontal cortex is proportional to the magnitude of craving reported by human cocaine addicts, suggesting that this brain region may play an important role in drug seeking (Volkow and Fowler, 2000). Animal studies have shown that lesioning the lateral orbitofrontal cortex increases cocaine priming-induced reinstatement, while lesioning the medial orbitofrontal cortex blocks cocaine seeking (Fuchs et al., 2004b). This same study also found that inactivation of either of these two regions using a cocktail of $GABA_A$ and $GABA_B$ receptor agonists had no effect on cocaine seeking (Fuchs et al., 2004b). Similarly, infusions of the sodium channel blocker tetrodotoxin fail to alter cocaine priming-induced reinstatement (Capriles et al., 2003). Since only irreversible lesions of the medial orbitofrontal cortex influenced the reinstatement of cocaine seeking, the exact role of this nucleus in cocaine priming-induced reinstatement is currently unresolved.

2.5. Role of the hippocampus in priming-induced reinstatement of cocaine seeking

The ventral portion of the hippocampus, known as the ventral subiculum, is innervated by dopaminergic projections

from the ventral tegmental area and is believed to play a role in goal-directed behavior (Gasbarri et al., 1994a,b). Chemical stimulation of the ventral subiculum activates dopaminergic cell bodies in the ventral tegmental area and subsequently leads to increased dopamine transmission in the nucleus accumbens (Legault et al., 2000). Interestingly, electrical stimulation of the ventral subiculum reinstates cocaine or amphetamine seeking in rats (Taepavarapruk and Phillips, 2003; Vorel et al., 2001). Furthermore, reinstatement of drug seeking elicited by electrical stimulation of the ventral subiculum is blocked by administering an NDMA receptor antagonist into the ventral tegmental area (Vorel et al., 2001). Lidocaine inactivation of the ventral subiculum, moreover, attenuates cocaine priming-induced reinstatement (Sun and Rebec, 2003). Collectively, these results suggest that the ventral subiculum is an essential component of the circuitry mediating the reinstatement of cocaine seeking.

2.6. Role of the amygdala in cocaine priming-induced reinstatement

The amygdala is another limbic structure that receives dopaminergic afferent projections from the ventral tegmental area (Fallon and Moore, 1978; Loughlin and Fallon, 1983). The amygdala can be divided into a number of subnuclei, several of which have been shown to contribute to various forms of reinstatement (Grimm and See, 2000; Kantak et al., 2002; Leri et al., 2002; Lu et al., 2005; McFarland et al., 2004; Meil and See, 1997). Of these subnuclei, the basolateral amygdala has received the most attention with regard to cocaine priming-induced reinstatement. Inactivation of the basolateral amygdala has no effect on reinstatement of drug seeking elicited by a cocaine prime (McFarland and Kalivas, 2001). In contrast, excitatory amino acid stimulation or electrical stimulation of the basolateral amygdala is sufficient to reinstate cocaine seeking in rats (Hayes et al., 2003). Furthermore, lesions of the basolateral amygdala attenuated cocaine priming-induced reinstatement (Yun and Fields, 2003). The basolateral amygdala, however, can be subdivided into a number of subnuclei and recent evidence suggests that both rostra1 and caudal subregions are involved in reinstatement of cocaine seeking (Kantak et al., 2002). Consistent with these results, administration of a dopamine Dl-like receptor antagonist into the rostral basolateral amygdala and central amygdala blocked cocaine priming-induced reinstatement (Alleweireldt et al., 2005). Collectively, these data indicate that the basolateral amygdala is a functionally heterogeneous structure whose subregions may mediate different aspects of reinstatement. The potential role of dopamine receptor subtypes and subterritories within the basolateral amygdala in cocaine priming-induced reinstatement remains to be determined.

2.7. Role of the ventral pallidum in priming-induced reinstatement of cocaine seeking

The ventral pallidum receives limbic information from the nucleus accumbens and ventral tegmental area and relays it to the substantia nigra, thalamus and brainstem (Alexander et al., 1986). Recently, the ventral pallidum has been found to comprise part of the circuitry that mediates cocaine seeking (McFarland and Kalivas, 2001). For instance, inactivation of the ventral pallidum using a cocktail of $GABA_A$ and $GABA_B$ receptor agonists blocks both drug- and food-seeking behavior in rats (McFarland and Kalivas, 2001). Inactivation of the ventral pallidum and other nuclei led to the proposed functional circuit between the ventral tegmental area–dorsal prefrontal cortex—accumbens core–ventral pallidum (McFarland and Kalivas, 2001). These nuclei, which comprise this circuit, are believed to be in series since contralateral, but not ipsilateral, infusions of the GABA receptor agonist cocktail into the dorsal prefrontal cortex and ventral pallidum blocked cocaine priming-induced reinstatement (McFarland and Kalivas, 2001). One limitation of these studies is that they do not distinguish between the medial and dorsolateral ventral pallidum, which represent different aspects of the circuitry underlying reinstatement of cocaine seeking. While the medial ventral pallidum is innervated primarily by the accumbens shell subregion of the ventral striatum and thus forms part of the limbic subcircuit, the dorsolateral ventral pallidum receives projections mainly from the accumbens core subregion of the ventral striatum, and these nuclei form part of the motor subcircuit (Groenewegen et al., 1996; Kalivas, 1992; Zahm and Brog, 1992).

Efferent GABAergic projections from the nucleus accumbens synapse on GABAergic and cholinergic neurons in the ventral pallidum and release GABA, enkephalin, dynorphin and substance P (Fallon and Leslie, 1986; Napier et al., 1995; Zahm et al., 1985). Enkephalin, which binds with high affinity to the μ-opioid receptor, is primarily co-localized with GABA in these efferent projections (Waldhoer et al., 2004; Zahm et al., 1985). Stimulation of μ-opioid receptors, which are primarily located presynaptically on GABAergic terminals in the ventral pallidum, reduces both potassium-evoked and basal extracellular levels of GABA (Kalivas et al., 2001; Olive et al., 1997; Schroeder and Schneider, 2002). A recent study demonstrated that the μ-opioid receptor antagonist Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH2 (CTAP), when administered into the ventral pallidum, blocked reinstatement induced by either a systemic priming injection of cocaine or local administration of morphine into the ventral pallidum (Tang et al., 2005). Furthermore, extracellular GABA levels were decreased in the ventral pallidum of animals undergoing cocaine priming-induced reinstatement and administration of CTAP directly into the ventral pallidum prevented this decrease (Tang et al., 2005).

To date, only one study has examined the role of ventral pallidum dopamine in cocaine priming-induced reinstatement, and it was demonstrated that administration of a dopamine receptor antagonist directly into the ventral pallidum failed to attenuate cocaine seeking (McFarland and Kalivas, 2001). These results, collectively, suggest that cocaine-seeking behavior is modulated in part by co-release of enkephalin and GABA from medium spiny nucleus accumbens neurons projecting to the ventral pallidum, but not dopamine in the ventral pallidum.

3. Glutamate and cocaine priming-induced reinstatement

In addition to dopaminergic inputs, the nucleus accumbens receives substantial glutamatergic projections from the hippocampus, amygdala and medial prefrontal cortex (Berendse et al., 1992; Brog et al., 1993; Heimer et al., 1997). In the nucleus accumbens and neostriatum, glutamatergic and dopaminergic afferents converge on the same spines of GABAergic output neurons (Dube et al., 1988; Pickel et al., 1981; Wilson, 1987). A growing body of evidence shows that, via pre- and postsynaptic actions, dopamine modulates the excitatory input to the striatum/accumbens. For example, it was recently demonstrated that D2 dopamine receptors located on glutamatergic terminals regulate glutamate release in the striatum (Bamford et al., 2004a,b). Additionally, stimulation of the ventral tegmental area leads to a D2-like dopamine receptor-mediated attenuation of the response of nucleus accumbens neurons to limbic input from the medial prefrontal cortex (Brady and O'Donnell, 2004).

As reviewed above, increased dopamine transmission plays a critical role in cocaine reinstatement. Since one of the main functions of dopamine is to modulate the flow of information carried by excitatory glutamatergic inputs to the accumbens/striatum, it was hypothesized that accumbal glutamate might contribute to the reinstatement of cocaine seeking. Accumulating evidence gathered over the last decade indicates that repeated cocaine exposure results in two major changes in glutamate transmission in the nucleus accumbens: i) decreases in basal extracellular glutamate levels (Baker et al., 2003; Pierce et al., 1996) and ii) increases in extracellular glutamate in response to a cocaine challenge injection (Baker et al., 2003; Hotsenpiller et al., 2001; Pierce et al., 1996). As reviewed in the following sections, both of these effects contribute to the reinstatement of cocaine seeking.

3.1. Basal extracellular glutamate in the nucleus accumbens, cystine–glutamate exchange and the reinstatement of cocaine seeking

During a withdrawal period following repeated systemic injections of cocaine, basal extracellular glutamate levels are reduced in the nucleus accumbens core (Baker et al., 2003; Hotsenpiller et al., 2001; Pierce et al., 1996) but not the neostriatum or medial prefrontal cortex (Baker et al., 2003). Basal extracellular glutamate levels are regulated primarily by the cystine–glutamate antiporter, a sodium-independent anionic amino acid transporter that exchanges extracellular cystine for intracellular glutamate (Baker et al., 2002; Timmerman and Westerink, 1997). It was subsequently shown that the decrease in basal accumbal glutamate following repeated cocaine exposure resulted from decreased activity of the cystine–glutamate antiporter (Baker et al., 2003). Moreover, normalization of extracellular accumbal glutamate levels in animals with a history of cocaine self-administration with *N*-acetyl cysteine, a cysteine prodrug that increases activity of the cystine–glutamate antiporter, prevented reinstatement of drug seeking induced by a cocaine priming injection (Baker et al., 2003).

3.2. Glutamate release in the nucleus accumbens of cocaine-pretreated rats promotes cocaine seeking

Although cocaine has no direct pharmacological effect on the glutamate system, multiple studies indicate that a cocaine challenge injection administered to rats pretreated with repeated cocaine injections results in increased glutamate release in the nucleus accumbens core (Pierce et al., 1996; Reid and Berger, 1996). Similarly, cocaine priming-induced reinstatement of drug seeking was associated with increased glutamate release in the core of the nucleus accumbens, an effect that was attenuated by pharmacological inactivation of the medial prefrontal cortex (McFarland et al., 2003). Consistent with these findings, administration of an alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) glutamate receptor antagonist into the nucleus accumbens blocked the reinstatement of cocaine seeking induced by administration of cocaine directly into the medial prefrontal cortex (Park et al., 2002). These results, collectively, suggest that activation of the glutamatergic projection from the medial prefrontal cortex to the nucleus accumbens promotes cocaine seeking, a finding that is consistent with results indicating that cocaine craving is associated with metabolic activation of the medial prefrontal cortex among human cocaine addicts (Volkow et al., 1999, 2005). These findings also show that stimulation of AMPA glutamate receptors in the nucleus accumbens plays a critical role in cocaine seeking.

3.2.1. Role of AMPA glutamate receptors in the reinstatement of cocaine seeking

A number of studies have shown that accumbal AMPA receptors contribute significantly to the reinstatement of cocaine seeking. Thus, administration of an AMPA receptor agonist directly into the nucleus accumbens promotes reinstatement of cocaine seeking, while intra-accumbal administration of an AMPA receptor antagonist blocks reinstatement induced by a systemic priming injection of cocaine (Cornish et al., 1999; Cornish and Kalivas, 2000; Suto et al., 2004). Although these microinjection studies did not distinguish between the core and shell subregions of the nucleus accumbens (Cornish et al., 1999; Cornish and Kalivas, 2000), there is evidence that increased glutamate transmission in both the core and the shell of the nucleus accumbens contributes to the reinstatement of cocaine seeking. The increased glutamate release following a cocaine priming injection was observed in the nucleus accumbens core (McFarland et al., 2003), whereas the inhibition of intra-medial prefrontal cortex cocaine-induced reinstatement was due to the administration of an AMPA antagonist into the nucleus accumbens shell (Park et al., 2002). Recent evidence indicates that administration of AMPA into either the core or the shell of the nucleus accumbens reinstates cocaine seeking (K. R. Famous, unpublished observations). Collectively, these data demonstrate that stimulation of AMPA glutamate receptors in the core and shell of the nucleus accumbens plays a critical role in the reinstatement of cocaine seeking.

3.2.2. Role of NMDA glutamate receptors in the reinstatement of cocaine seeking

There is also evidence that accumbal NMDA receptors play a role in reinstatement elicited by a cocaine priming injection. Administration of 1-aminocyclobutane-*cis*-1,3-dicarboxylic acid (*cis*-ACDA), an NMDA agonist, into the nucleus accumbens reinstated cocaine seeking in rats (Cornish et al., 1999; Cornish and Kalivas, 2000). However, intra-accumbal *cis*-ACDA also increased responding on an inactive lever, suggesting that the increase in responding on the active lever may be due to a nonspecific increase in motor activity (Cornish et al., 1999). In a subsequent study, it was found that a relatively low dose of (±)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP), an NMDA antagonist, neither prevented cocaine-primed reinstatement nor induced reinstatement when given alone (Cornish and Kalivas, 2000). A low dose of CPP was used in this study, as the higher dose significantly increased locomotor activity (Cornish and Kalivas, 2000). In contrast, other studies have shown that systemic (De Vries et al., 1998) or intra-accumbal shell (Park et al., 2002) administration of an NMDA antagonist reinstates cocaine seeking. Taken together, these results suggest that AMPA and NMDA receptors in the nucleus accumbens may play opposing roles in the reinstatement of cocaine seeking. However, systemic administration of an NMDA receptor antagonist increases extracellular glutamate levels in the nucleus accumbens (Adams and Moghaddam, 1998). It is possible, therefore, that NMDA receptor antagonists promote cocaine seeking by indirectly activating AMPA receptors in the nucleus accumbens (via increased glutamate release). This hypothesis has not yet been examined experimentally.

3.2.3. Role of metabotropic glutamate receptors in cocaine priming-induced reinstatement

Recent evidence suggests that metabotropic glutamate (mGlu) receptors may also contribute to cocaine priming-induced reinstatement of drug seeking. Eight subtypes of mGlu receptors have been cloned, and they are divided into three main groups (I–III) based upon their sequence homology, pharmacology and coupling to different signal transduction pathways (Conn and Pin, 1997). Group I metabotropic glutamate receptors (mGlu1 and 5) are coupled to phospholipase C via the Gq G-protein, and consequently hydrolyze phosphoinositides, thus regulating calcium release from intracellular stores (Conn and Pin, 1997; Nakanishi and Masu, 1994; Schoepp et al., 1990). Group II (mGlu2 and 3) and Group III (mGluR4, 6, 7, and 8) metabotropic glutamate receptors are coupled to the Gi/Go G-proteins and negatively regulate adenylyl cyclase (Conn and Pin, 1997; Nakanishi and Masu, 1994; Pin and Duvoisin, 1995; Schoepp et al., 1990). While group I mGlu receptors are found postsynaptically and function to mediate excitatory glutamatergic input, Group II and III mGlu receptors are often localized to presynaptic terminals where they modulate excitatory glutamatergic and/or inhibitory GABAergic neurotransmission (Schoepp, 2001; Valenti et al., 2002).

Of the metabotropic glutamate receptors, the mGlu5 glutamate receptor subtype has received the greatest attention with regard to cocaine reinforcement/reinstatement. mGlu5 glutamate receptors are highly expressed in the nucleus accumbens (Lu et al., 1999; Tallaksen-Greene et al., 1998; Testa et al., 1994) and repeated administration of cocaine increases the expression of mGlu5 receptor mRNA in the nucleus accumbens shell, but not the accumbens core (Ghasemzadeh et al., 1999). Self-administration studies indicate that the selective mGlu5 receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) decreases cocaine reinforcement in mice (Chiamulera et al., 2001), rats (Kenny et al., 2003; Paterson and Markou, 2005) and non-human primates (Lee et al., 2005). Consistent with these findings, mice lacking the mGlu5 receptor subtype do not self-administer cocaine (Chiamulera et al., 2001). In terms of reinstatement, MPEP attenuated the ability of a systemic priming injection of cocaine to promote cocaine seeking in squirrel monkeys (Lee et al., 2005). Collectively, these results indicate that mGlu5 receptors play an important role in cocaine reinforcement as well as the reinstatement of cocaine seeking.

Group II mGlu receptors are also expressed in the nucleus accumbens (Lu et al., 1999; Ohishi et al., 1998) and genetic deletion of mGlu2 receptors in mice enhances the locomotor activating effects of cocaine (Morishima et al., 2005). Repeated cocaine administration was also found to diminish mGlu2/3 receptor function in the nucleus accumbens by increasing expression of the mGlu2/3 receptor dimer and Ser phosphorylation of the mGlu2/3 receptor monomer (Xi et al., 2002). Systemic administration of the mGlu2/3 receptor agonist, LY379268, attenuated reinstatement of cocaine seeking elicited by cocaine-associated contextual cues (Baptista et al., 2004). Although the potential role of Group II mGlu receptors in priming- or stress-induced reinstatement of cocaine seeking has not yet been assessed, the available evidence suggests that cocaine-induced changes in Group II mGlu receptor function may be compensatory in nature.

4. Concluding remarks: neuronal circuits mediating reinstatement of cocaine seeking

In summary, there is general agreement that activation of the dopaminergic pathway from the ventral tegmental area to the medial prefrontal cortex contributes significantly to the reinstatement of cocaine seeking (Capriles et al., 2003; McFarland and Kalivas, 2001; Park et al., 2002; Sun and Rebec, 2005). Increased dopamine release in the medial prefrontal cortex appears to promote cocaine seeking by stimulating the glutamatergic projection from the medial prefrontal cortex to the nucleus accumbens (McFarland et al., 2003; Park et al., 2002). Interestingly, there are two largely segregated glutamatergic afferents to the nucleus accumbens arising from the medial prefrontal cortex. Thus, the dorsal portion of the medial prefrontal cortex projects mainly to the accumbens core, whereas the ventral medial prefrontal cortex sends glutamatergic projections predominantly to the accumbens shell (Berendse et al., 1992; Ding et al., 2001; Phillipson and Griffiths, 1985; Wright and Groenewegen, 1995).

As reviewed previously, anatomical and functional studies indicate that the nucleus accumbens shell is classified as part of

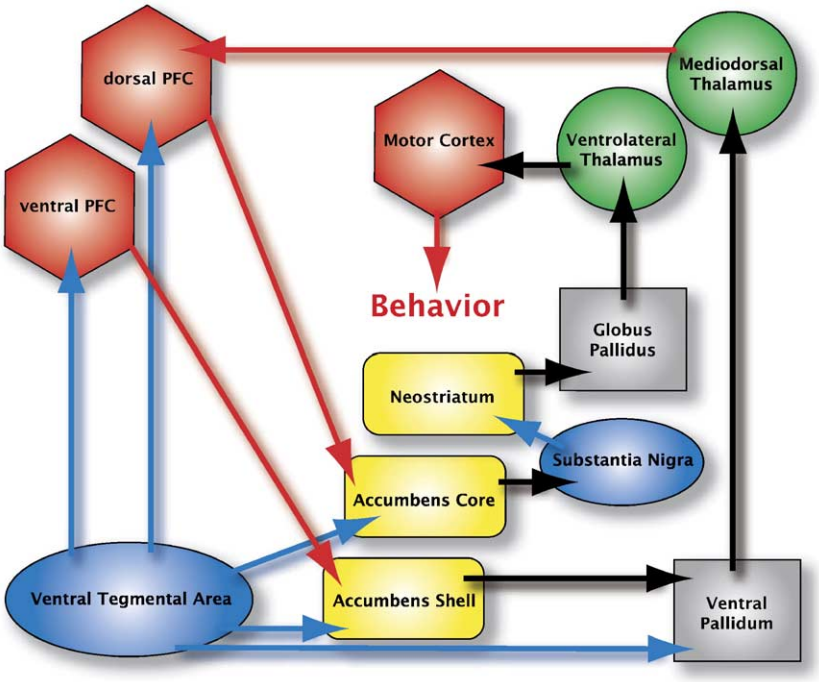

Fig. 1. Representation of the proposed circuitry mediating cocaine priming-induced reinstatement. Three neuronal circuits centered on the nucleus accumbens shell, nucleus accumbens core and neostriatum are presented. The ventral prefrontal cortex projects to the nucleus accumbens shell, which communicates with the dorsal prefrontal cortex via serial projections to the ventral pallidum and mediodorsal thalamus. The dorsal prefrontal cortex projects to the nucleus accumbens core, which relays information to the neostriatum via the substantia nigra. The neostriatum influences the motor cortex via the globus pallidus and ventrolateral thalamus. Dopaminergic inputs from the ventral tegmental area to several of these nuclei modulate the flow of information through these circuits. See the text for further details.

the limbic system, whereas the core is associated with the basal ganglia (Heimer et al., 1991; Rodd-Henricks et al., 2002; Zahm, 2000). The notion that the nucleus accumbens is the functional interface between limbic and motor systems was proposed in the early 1980s (Mogenson et al., 1980). Anatomical experiments performed over the intervening period provide strong support for this hypothesis. It is now clear that the neuronal circuits centered on the accumbens shell, accumbens core and neostriatum are interconnected and can process information via parallel as well as integrated feedforward connections (Alexander et al., 1990; Haber, 2003). As shown in Fig. 1, the accumbens shell is connected to the dorsal portion of the medial prefrontal cortex via serial synapses in the medial portion of the ventral pallidum and the medial dorsal thalamus (Zahm, 2000). The dorsal medial prefrontal cortex innervates the core of the nucleus accumbens (Heidbreder and Groenewegen, 2003; Zahm, 2000). The core sends projections to several nuclei including the substantia nigra, which provides dopaminergic innervation to the neostriatum (Haber, 2003; Heimer et al., 1997; Zahm, 2000). In this manner, information can flow through the striatal complex hierarchically from the shell to the core to the neostriatum (Haber, 2003; Heimer et al., 1997; Zahm, 2000).

A substantial body of evidence indicates that the subcircuit centered on the nucleus accumbens core, and not the subcircuit associated with the accumbens shell, is primarily responsible for modulating cocaine priming-induced reinstatement of drug seeking (Kalivas, 2004; Kalivas and McFarland, 2003; McFarland and Kalivas, 2001). Thus, reversible inactivation of the dorsal prefrontal cortex, accumbens core or ventral pallidum (but not the ventral medial prefrontal cortex or accumbens shell) blocks cocaine priming-induced reinstatement of drug seeking (McFarland and Kalivas, 2001). However, more recent evidence indicates that increased dopamine transmission in the shell, and not the core, of the nucleus accumbens promotes cocaine seeking (Anderson et al., 2003; Schmidt and Pierce, 2004). Although procedural differences may account for these divergent findings, it seems more likely that both the limbic and basal ganglia-associated circuits flowing through the striatal complex contribute to the reinstatement of cocaine seeking. That is, the sequela of events underlying cocaine-seeking behavior appears to require initial activation within the limbic subcircuit (focused on the shell) followed by heightened activity within the basal ganglia subcircuits (including both the core and the striatum), which ultimately organizes and executes behavior. The evidence presented in this review indicates that self-administration of cocaine results in alterations in the processing of motivationally relevant stimuli by these circuits such that re-exposure to cocaine results in a maladaptive behavioral response: drug craving and compulsive drug seeking.

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