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Neuronal circuitry underlying the impact of D3 receptor ligands in drug addiction:

A contribution for the special issue ‘The Dopamine D3 Receptor from Pre-Clinical Studies to the Treatment of Psychiatric Disorders’

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Abstract

Since the cloning of the D3 receptor in the early 1990s, there has been a great deal of interest in this receptor as a possible therapeutic target for drug addiction. The development of a D3 ligand suitable for use in humans has remained elusive, so the study of the function of the D3 receptor and its possible therapeutic efficacy has largely been restricted to animals. Pre-clinical studies have established that systemic administration of D3 ligands, particularly antagonists and partial agonists, can alter drug-seeking in animals. Despite over a decade of research, few studies have investigated the effects of intra-cerebral infusion of D3 ligands on drug-seeking. In the present

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The authors have no conflicts of interest to disclose.

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review, we summarize these studies, which have largely focused on stimulus-controlled behaviors. Converging evidence from studies of D3 receptor expression, *Fos* and phMRI is also provided to delineate some of the D3 brain systems involved in drug-seeking and taking. The data so far indicate that different brain systems may be involved in different types of stimulus control as well as drug taking.

Keywords

dopamine; stimulus; amygdala; accumbens; striatum; addiction

Introduction

Dopamine (DA) is a neurotransmitter implicated in a number of diseases, including drug addiction, Parkinson's and schizophrenia. DA has five receptor subtypes, based on structure and homology, and named in the order of their discovery. Since the cloning of the dopamine D3 receptor in the 1990s (Sokoloff et al., 1990), there has been interest in determining the role of this subtype. Belonging to the D2-family, the D3 receptor is about 50% homologous with the D2 receptor (Sibley and Monsma, 1992). As compared to the D2 receptor, its restricted localization to limbic areas (Bouthenet et al., 1991; Gurevich and Joyce, 1999; Khaled et al., 2014) suggests that the D3 receptor may be uniquely involved in aspects such as motivation, emotion and learning. In particular, a great deal of interest has emerged in targeting D3 receptors, as distinct from the D2 receptors, for the treatment of drug addiction (Heidbreder, 2005), and in particular, focus has been on the development of selective D3 antagonists and partial agonists (Di Ciano et al., 2003; Pilla et al., 1999; Vorel et al., 2002). The restricted localization of D3 receptors may also confer an advantage to treatment approaches in that Parkinson's-like side effects that are seen with treatments that target D2 receptors may be lacking with D3 receptor antagonists (Reavill et al., 2000).

Despite a great theoretical interest in the DA D3 receptor as a treatment approach for drug addiction, its locus of effect in the brain remains relatively unexplored in animals. This is ironic given the initial flurry of interest in this receptor. In this paper, we will review the studies done to-date that have been designed to uncover the D3 systems in drug addiction using animal models. We will focus on intra-cerebral infusion of D3 agents into restricted brain areas and also summarize converging evidence from receptor quantification studies, *Fos* and pharmacological Magnetic Resonance Imaging (phMRI) in animals. First, we will briefly review the pre-clinical evidence that systemic administration of D3 agents have therapeutic value for drug addiction.

Pre-Clinical Investigations into the Role of Systemic D3 Agents on Pre-Clinical Models of Drug Addiction

The study of the effects of selective D3 agents on drug-seeking and drug-taking in animals began with the partial agonist BP 897 (Pilla et al., 1999) and later the full antagonist SB-277011-A (Di Ciano et al., 2003; Vorel et al., 2002). In these initial studies, both agents decreased cue-maintained responding under a second-order schedule but had no effect on

cocaine intake, suggesting that D3 receptors may be important in cue-controlled behaviors. A special role of D3 receptors in cue-controlled behaviors (Le Foll et al., 2002) is further supported by the findings that antagonists attenuate conditioned place preference (Ashby et al., 2003; Cervo et al., 2005; Le Foll et al., 2005c; Pak et al., 2006; Thanos et al., 2008; Vorel et al., 2002; but see: Gyertyan and Gal, 2003).

The lack of effect on drug intake seems surprising from a translational point of view of using these compounds as pharmacological treatments for addiction. However, it should be noted that D2 antagonists increase drug intake (Brennan et al., 2009; Woolverton, 1986; Yokel and Wise, 1975), which possibly limits their use as treatments. This makes D3 antagonists and partial agonists more viable options. Indeed, D3 antagonists and partial agonists may alter some motivational aspects of drugs, as they seem to decrease responding for drug under a progressive ratio schedule, at least for some drugs of abuse (Gilbert et al., 2005; Higley et al., 2011; Orio et al., 2010; Song et al., 2012; Spiller et al., 2008). D3 antagonists may be effective as treatments that prevent relapse to drug-seeking, as D3 antagonists blocked cue-induced (Cervo et al., 2005; Gal and Gyertyan, 2006; Gilbert et al., 2005; Higley et al., 2011; Khaled et al., 2010), context-induced (Spiller et al., 2008), drug-induced (Achat-Mendes et al., 2010; Andreoli et al., 2003; Gilbert et al., 2005; Heidbreder et al., 2007; Higley et al., 2012; Vorel et al., 2002) and stress-induced (Higley et al., 2012; Vorel et al., 2002) reinstatement of drug seeking behavior. It should be noted at this point that the D3 agonist 7-OH-DPAT decreased cocaine self-administration (Parsons et al., 1996). 7-OH-DPAT, however, is a less selective agent than the more recently developed antagonists and partial agonists (Pilla et al., 1999; Reavill et al., 2000), and indeed, D2 agonists also reduce cocaine intake (Hemby et al., 1996). Thus, consideration of the role of D3 agonists awaits development of selective compounds.

Findings on the effects of D3 partial agonists on conditioned place preference are mixed (Cervo et al., 2005; Duarte et al., 2003; Frances et al., 2004b; Gyertyan and Gal, 2003) as they are in models of reinstatement (Cervo et al., 2003; Khaled et al., 2010). This may be explained by the partial agonist property of BP 897 (that has been mostly used in these studies), and it may be the case that the therapeutic efficacy of partial agonists is more restricted than with full antagonists. A discussion of the advantages and disadvantages of antagonists and partial agonists is beyond the scope of the present manuscript. To-date, studies of the brain systems underlying D3 involvement in drug addiction have used either full agonists or antagonists and thus the unique properties of partial agonists are not a consideration for this review.

Intra-cerebral Studies of the Effects of D3 Agents on Drug-Seeking

As mentioned above, a special role of D3 receptors in cue-controlled behavior has been postulated (Le Foll et al., 2005c). Consistent with this, the majority of studies investigating the effects of intra-cerebral infusion of D3 agents have focused on cue-controlled behaviors. It is known that conditioned stimuli (CS) previously paired with drugs of abuse can induce powerful 'cravings' for drug (Ehrman et al., 1992) and induce conditioned changes in brain activation in humans, notably in the basolateral amygdala (BLA) (Breiter et al., 1997; Childress et al., 1999). To-date, pre-clinical studies of the locus of action of D3 receptors on

CS-maintained responding have focused mainly on the amygdala and nucleus accumbens (NAcc).

In understanding environmental determinants over behavior, two main types of stimulus control have been described: 1) Pavlovian, which refers to the unexpected presentation of CSs and can consist of stimuli such as people and rooms that are randomly encountered. These stimuli are intuitive in that they induce 'cravings' and serve as reminders of drug use; and 2) Instrumentally-earned presentations of CSs, in which organisms must work for presentations of the stimuli. The latter type of stimulus control is known as conditioned reinforcement and is characterized by the ability of the CS to increase the probability of the prior response. In real-life, conditioned reinforcers help to maintain chains of behavior (Goldberg et al., 1975) that maintain our daily lives and bridge the gap between behavior and ultimate primary reward. Money, for example, is a conditioned reinforcer that bridges delays to ultimate rewards such as food.

Conditioned reinforcement

In animal models of conditioned reinforcement in drug addiction, animals are typically trained to associate a brief light and/or tone stimulus with an intravenous bolus of drug. Through repeated pairings, these CSs maintain responding in their own right and animals will lever press for presentations of these lights/tones (Di Ciano and Everitt, 2004a). In second-order schedules, animals will respond for prolonged periods of time for these CSs, being reinforced only intermittently by the primary drug (Goldberg and Kelleher, 1976). These schedules therefore allow for the assessment of effects of manipulations on either CS-maintained responding *per se* or on responding for the primary drug reinforcer. Another model of conditioned reinforcement is cue-induced reinstatement (de Wit and Stewart, 1981). This model is typically thought of as a model of relapse (Epstein and Preston, 2003). However, in cue-induced reinstatement, the event inducing the reinstatement ('relapse') is a CS, and thus, it can be thought of as a model of conditioning.

Investigations into the neural substrates of D3 control over conditioned reinforcement have focused on the amygdala, NAcc, dorsal striatum (DStr) and lateral habenula (LHb). In one study, infusion of SB-277011-A into the BLA reduced responding for cocaine under a second-order schedule of reinforcement (Di Ciano, 2008). Furthermore, this decrease in responding happened before any drug was infused during the daily session, suggesting that the effect was on the ability of the conditioned reinforcer to maintain responding. Indeed, latencies to receive the first CS were increased, while the latency to receive the first drug infusion was not changed. Latency is a measure of motivation for the goal, and thus, it was concluded that infusion of SB-277011-A into the BLA attenuated responding for the conditioned reinforcer but not the primary drug reward. This supports the tenet that D3 receptors have a unique role in cue-induced responding (Le Foll et al., 2005c) and are less important in the maintenance of drug intake (Di Ciano et al., 2003; Pilla et al., 1999).

In this same study, infusion of SB-277011-A into the NAcc shell or DStr had no effect on responding for the conditioned reinforcer. In previous studies it had been shown that infusion of a D1/D2/D3 dopamine antagonist alpha-flupenthixol into the DStr decreased responding under a second-order schedule of reinforcement (Vanderschuren et al., 2005),

suggesting that DA in the DStr may be involved in some capacity in CS-controlled behavior. However, it is possible that DA in the DStr may participate through D1 or D2, but not D3, receptors. This is consistent with findings that infusion of SB-277011-A into the DStr did not affect stress-induced reinstatement (Xi et al., 2004). The DStr is believed to mediate behaviors that have become habitual over time (Everitt and Robbins, 2005), and therefore this study suggests that habitual behavior under the control of CSs, or mediating reinstatement, is not mediated by D3 receptors. With respect to the NAcc shell, this is an area that is more frequently believed to control the unconditioned effects of drugs of abuse (Aragona et al., 2008), which could explain the lack of effects of D3 antagonists infused in that structure in some experiments.

The importance of the BLA in conditioned reinforcement was further exemplified in a study which found that infusion of SB-277011-A into the BLA reduced cue-induced reinstatement of nicotine-seeking (Khaled et al., 2014). A selectivity of effects was demonstrated in that infusion of SB-277011-A into the BLA had no effect on responding for food. Thus, D3 receptors in the BLA are not likely to be simply mediating some general motivational processes. Instead, they may be specific to responding for the conditioned reinforcer or a CS that has embedded within it some representation, or reminder, of the drug. Alternatively, D3 receptors in the BLA may simply mediate reinstatement (relapse) in general. This hypothesis is not necessarily warranted given that infusion of 7-OH-DPAT into the amygdala impaired responding for a conditioned reinforcer previously paired with food (Hitchcott and Phillips, 1998). Thus, it seems likely that the BLA may be involved in some aspect of CS-controlled behaviour, consistent with theory (Schultz, 1998).

Also in support of the previous study (Di Ciano, 2008), it was found that infusion of SB-277011-A into the NAcc shell had no effect on cue-induced reinstatement of nicotine-seeking. Indeed, infusion of the D3 agonist PD128 907 into either the NAcc core or NAcc shell did not reinstate cocaine-seeking behavior (Schmidt et al., 2006), confirming a lack of involvement of D3 receptors in either of these NAcc subregions in reinstatement. However, it should be noted that infusion of SB-277011-A into the NAcc core/shell border reduced stress-induced reinstatement (Xi et al., 2004). It may therefore be the case that D3 receptors in one of the NAcc subregions participates in stress-mediated events

An interesting finding of the Khaled et al. (2014) study is the demonstration that infusion of SB-277011-A into the lateral habenula (LHb) decreased cue-induced reinstatement of nicotine-seeking (Khaled et al., 2014). This is the first study of the role of D3 receptors, or the LHb, on conditioned reinforcement. This finding builds on accumulating evidence for the functional role of the LHb in addictions since it was first demonstrated that exposure to a context paired with cocaine induced increases in *c-fos* expression (Brown et al., 1992). The effects of SB-277011-A into the LHb were selective, as the same manipulation failed to influence food intake, and like the BLA, this implicates the LHb in either reinstatement or conditioned reinforcement *per se*. Interestingly the role of LHb is currently investigated by several groups in the context of addictive behaviors (Fowler et al., 2011; Matsumoto and Hikosaka, 2007).

The circuitry maintaining conditioned reinforcement was expanded in a study examining the effects of intra-cerebral infusions of D3 agents on cue-induced reinstatement. In one study, infusion of 7-OH-DPAT into the central amygdala (CeN) decreased cue-induced reinstatement (Thiel et al., 2010). By comparison, infusion of SKF-38393, a D1 antagonist, had no effect. Although compelling as to a selectivity of effects of D3 receptors on conditioned reinforcement, it should be noted that infusion of 7-OH-DPAT into the CeN also decreased cocaine-induced reinstatement and cocaine self-administration (Thiel et al., 2010). Thus, the CeN may mediate some general mechanism involved in drug-seeking. Indeed, the CeN also mediates context-induced reinstatement (Bossert et al., 2012) and the potentiation of conditioned reinforcement (Parkinson et al., 1999) by psychostimulants. Thus, it is possible that the CeN may not participate specifically in conditioned reinforcement, but may participate instead in relapse in general or arousal.

Pavlovian conditioned stimuli

In animals, CSs previously paired with contexts (Di Ciano et al., 1998b), or the non-contingent presentation of CSs (Di Ciano et al., 1998a; Gratton and Wise, 1994; Ito et al., 2000) can increase DA levels in the NAcc. Neurobiological evidence suggests that non-contingent presentations of CSs may be mediated by different neural substrates as compared to conditioned reinforcement (Parkinson et al., 1999), as conditioned reinforcers do not as reliably increase DA levels in the NAcc (Di Ciano and Everitt, 2002; Neisewander et al., 1996) (Ito et al., 2000), but instead, seem to be mediated by glutamate in that brain area (Di Ciano and Everitt, 2001), in interaction with the BLA (Di Ciano and Everitt, 2004b). It is worthwhile, therefore, to investigate whether the role of D3 receptors is different from that delineated for conditioned reinforcement.

Pavlovian control over drug-seeking can be studied with the use of several animal models, including conditioned activity and conditioned place preference. In both of these models, the ability of a non-contingently presented context to induce a conditioned response is measured. Another method of studying contextual control over behavior is through context-induced reinstatement. Elucidation of the brain systems involved in D3 receptor control over Pavlovian CSs-mediated behaviors remains to be determined, as no studies have systematically investigated the effects of central manipulations of D3 receptors in models such as place preference or conditioned locomotion following systemic administration of drug. Although evidence from systemic administration of D3 agents suggests a role of D3 receptors in context-controlled behaviors (discussed above), central administration has only been studied in a handful of investigations.

In one study, conditioned activity was assessed following intra-NAcc administration of *d*-amphetamine. Intra-NAcc *d*-amphetamine produces unconditioned increases in locomotor activity that can be paired with CSs to produce conditioned increases in activity in response to the CS. In this study, *d*-amphetamine was infused into the NAcc following exposure to a unique context. Along with the *d*-amphetamine infusion rats received the partial agonist BP 897 infused into either the NAcc or BLA during either acquisition or expression of conditioned activity. It was found that infusion of BP 897 into either the NAcc or BLA blocked the expression, but not acquisition, of conditioned activity following infusion of *d*-

amphetamine into the NAcc (Aujla and Beninger, 2004). This is consistent with evidence that SB-277011-A blocked both the acquisition and expression of a cocaine-induced CPP (see above), but suggests that the locus of effects of the expression is in the BLA.

In a similar study, rats received intra-amygdala infusions of 7-OH-DPAT after pairing of a 5min discrete CS with intra-NAcc *d*-amphetamine. In this study, it was found that this treatment attenuated the conditioned locomotor response to subsequent presentations of the CS. Thus, in contrast to the Aujla and Beninger (2004) study discussed above, the report by Hitchcott and Phillips (1998) found an involvement of the amygdala in the acquisition of a conditioned Pavlovian behavior. However, it should be noted that, in this same study, conditioned locomotion induced by exposure to the context in which the animals had previously received intra-NAcc *d*-amphetamine was not affected by intra-amygdala 7-OH-DPAT. Thus, it may be that acquisition of context-controlled behaviors is not mediated by D3 receptors in the amygdala/BLA, while the acquisition of Pavlovian behaviors induced by presentation of discrete stimuli is controlled by amygdala D3 receptors.

Incubation

Since first described (Grimm et al., 2001), the neurobiology of incubation has been extensively studied (for reviews, see: (Lu et al., 2004; Pickens et al., 2011)). In incubation, rats are first trained to self-administer a drug of abuse and are then tested in extinction following a period of withdrawal in the home chambers. The number of responses in extinction increases with the amount of withdrawal that the rats received. The mechanism of incubation is unknown, but it likely includes some form of context conditioning. In one study that investigated the effects of infusion of SB277011-A into either the NAcc core, NAcc shell, DStr, BLA or CeN on incubation, it was found that D3 receptors in only the NAcc core, NAcc shell and CeN mediated incubation (Xi et al., 2013). As discussed above, the CeN is involved in a number of behaviors including cue-induced reinstatement, drug-induced reinstatement and cocaine self-administration, suggesting that its involvement here may be non-specific and related instead to some general aspect of drug-seeking. By comparison, the NAcc shell and NAcc core were not found to be involved in any of the other behaviors studied, implicating these brain regions in some aspect that is distinctive of incubation or perhaps of Pavlovian/contextual control over conditioned behaviors, as the NAcc was involved in the expression of conditioned locomotion. By comparison, the lack of involvement of the BLA in incubation suggests that incubation may be a process distinct from other types of conditioning, as the BLA was involved in both conditioned reinforcement (Di Ciano, 2008) and conditioned activity (Aujla and Beninger, 2004). The lack of effect in the DStr is consistent with the findings of other cue-controlled behavior (Di Ciano, 2008) and consistent with the limited expression of D3 receptors in the DStr in rodents (Diaz et al., 2000)..

It is worthy of note that some of the studies cited here tested the role of D3 receptors following administration of an agonist (7-OH-DPAT, that is not selective), while others infused a selective antagonist (SB-277011-A). D3 agonists and antagonists may have differential effects on brain function, such as changes in DA levels (Roberts et al., 2006; Zapata and Shippenberg, 2002). Surprisingly, in many of those studies, both agonists and

antagonists decreased the behaviors studied, with the exception of the Schmidt et al. (2006) paper in which it was reported that D3 agonists induced reinstatement. The precise mechanism underlying the effects reported will need to be delineated and considered within the context of whether D3 receptors are autoreceptors and also post-synaptic receptors (Diaz et al., 2000). A discussion of these mechanisms is beyond the scope of the present manuscript, and the data are presented here to indicate an involvement of D3 receptors in certain brain areas in specific behaviors. Future studies will need to delineate further the mechanism of action.

A further comment should also be provided regarding the use of 7-OH-DPAT in the intra-cerebral studies reported here. This D3 agonist is not as selective for D3 over D2 receptors as are ligands that were subsequently developed such as SB-277011-A (Reavill et al., 2000). Thus, the conclusions here must be made with caution because the effects reported here with the agonist may be indicative of D2 function. The use of more selective agents in intra-cerebral studies of drug addiction is warranted.

Summary of Findings of Effects of Intra-Cerebral Infusions of D3 Agonists and Antagonists on CS-Controlled drug-Seeking

Based on the summarized studies of the effects of intra-cerebral administration of D3 agents on drug-seeking, neural systems are emerging. Despite the issues mentioned above regarding the use of agonists/antagonists and of 7-OH-DPAT, a picture is evolving in which the BLA seems to be involved in conditioned reinforcement but does not seem to be involved in Pavlovian behaviors such as incubation. It may be that the latter type of behavior is more under the control of contextual stimuli which may be subserved by different brain regions. The CeN, for instance, was involved in all behaviors studied, including incubation, stress-induced, cue-induced and drug-induced reinstatement. D3 receptors in the NAcc core and shell were not found to have a role in conditioned reinstatement or cue-induced reinstatement. By comparison, they mediated conditioned locomotion and incubation, behaviors under contextual control. Thus, the CeN and NAcc may participate in context-controlled behaviors (Bossert et al., 2012) through D3 receptors. By comparison, the LHb is emerging as a possible site for CS-controlled behaviors. The lack of effects of D3 antagonists in DStr is not surprising due to the lack of expression of D3 receptors in that structure in rats. It should be noted that in non-human primates and humans there is more expression of D3 receptors in DStr (Suzuki et al., 1998) and this may be important in these species.

D3 Receptor Densities

In a seminal *post mortem* study of cocaine overdose victims, Staley and Mash (1996) found high densities of binding to D3 receptors in the caudate, putamen, substantia nigra and the striatum compared to controls that were drug-free. Although there were no differences between overdose brains and controls in NAcc D3 protein, as assessed by radioligand binding (Staley and Mash, 1996), a strong increase in mRNA coding for the D3 was detected in the NAcc (Segal et al., 1997). This D3 upregulation was recently confirmed by PET imaging in psychostimulant abusers (Boileau et al., 2012). Several animal studies

indicate that drug exposure seems to be the factor responsible for this up-regulation. Binding to D3 receptors in the NAcc was increased in rats 42 days after treatment with cocaine and was associated with behavioral sensitization (Collins et al., 2011). Further, changes in D3 receptor expression in the NAcc were increased at 45 days, but not at 1 day, after 10 days of 6 hour/day of cocaine self-administration (Conrad et al., 2010). In contrast, increases in D3 receptor levels were found in both the NAcc and striatum at 21-32, but not at 2 or 8 days, after high dose cocaine self-administration (Neisewander et al., 2004). The context in which the drug is received seems to be important in determining D3 up-regulation as an upregulation of D3 was observed in animals receiving cocaine repeatedly in a novel environment, but not in their home cages (Le Foll et al., 2002). One study failed to find a change in binding to D3 receptors in the striatum following treatment with cocaine for 14 days with an osmotic minipump and no time lag after drug administration (Stanwood et al., 2000), while in another D3 receptor mRNA in the striatum, NAcc or prefrontal cortex was not changed 6 days after rats received 5 daily amphetamine injections (Hondo et al., 1999). This suggests that the duration of withdrawal may be important in regulating increases in D3 receptor densities. Under some circumstances, D3 receptors may be important, however, in the immediate effects of drugs of abuse, as a single cocaine infusion increased D3 receptor expression in the NAcc and BDNF in the frontal cortex, medial prefrontal cortex and ventral tegmental area (Le Foll et al., 2005b). In another study, increases in BDNF and D3 receptor expression were found in the NAcc of rats that received sensitizing doses of morphine in a distinct environment (Liang et al., 2011). Increased of D3 receptor have been reported also following alcohol exposure (Leggio et al., 2014; Vengeliene et al., 2006) and nicotine exposure (Le Foll et al., 2003a; Le Foll et al., 2003b).

Functional Studies (Fos and Magnetic Resonance Imaging)

The immediate early gene *Fos* has been used as a marker of functional activation of neurons (Brown et al., 1992). Acute administration of SB-277011-A produced a significant effect on *Fos* expression in different brain areas such as the core and shell of the NAcc and the lateral septum. In contrast, no significant changes were detected in the caudate nucleus or in the cingulate, infralimbic prefrontal, or somatosensory cortices (Southam et al., 2007). In some other studies exploring the impact of the partial agonist BP897 on cocaine cue-induced responses, it was suggested that a D3 partial agonist was producing more pronounced effects on *Fos* expression in the ventral tegmental area and amygdala, but no effect on NAcc (Le Foll et al., 2002), consistent with a role of the BLA in conditioned reinforcement as outlined above. In a study from Glickstein et al, (2005) using D3 deficient mice, it was found that during tasks requiring attention, there was a preferential activation of the *c-fos* gene in neurons of the anterior cingulate and prelimbic/infralimbic cortices (Glickstein et al., 2005). D3 receptors appear to also control the *c-fos* activation in the somatosensory cortex of mice conditioned to opiates, while not affecting the *c-fos* activation in the cingulate cortex (Frances et al., 2004a).

More recently, PhMRI provides a measure of changes in regional cerebral blood flow (rCBV) induced by local changes in neuronal activity. In one study, the D3 antagonist SB-277011-A potentiated rCBV in a number of limbic and motor areas such as the NAcc, dorsal caudate putamen, thalamus, motor cortex and basolateral amygdala (Schwarz et al.,

2004). These findings support an autoreceptor role of D3 receptors (Diaz et al., 2000). It should be noted, however, that the dose of SB-277011-A used in the Schwarz et al. (2004) paper was 20mg/kg, a dose that may affect the D2 receptor, and may thus explain the effects that are observed in D2-rich areas of the brain such as the dorsal caudate putamen. Indeed, in another study that used the D3-selective dose of 10 mg/kg (McCormick et al., 2013), increases in basal rCBV were found in only the medial prefrontal cortex (mPFC), NAcc and thalamus (Choi et al., 2010).

Consistent with D3 receptor expression studies, the effects of D3 agents on rCBV changed over time. When rats were trained to self-administer cocaine and tested after 28 days of abstinence, administration of the D3 agonist 7-OH-DPAT decreased rCBV in the mPFC, medial caudate and NAc, while it increased rCBV in the globus pallidus. These changes in rCBV were attenuated in rats that self-administered cocaine (Chen et al., 2011), consistent with a tolerance to the D3-mediated effects on rCBV. It is unclear why this study found evidence for a functional decrease in D3 receptor function, while studies of D3 receptor binding consistently report D3 upregulation. It is possible that the neural networks subserving changes in rCBV may be modulated differently from the receptors themselves. Future studies will hopefully prove useful in answering these questions.

Side Effects

One distinct advantage of D3 antagonists, as compared to D2 antagonists, is their hypothesized lack of extrapyramidal side effects in animal models. These side effects make the use of D2 antagonists problematic, as is seen by the array of effects of antipsychotics. Based on the localization of D3 receptors to limbic areas, antagonism of these receptors should theoretically circumvent the motor systems. Indeed, systemic administration of D3 antagonists had no effects on spontaneous locomotion (Le Foll et al., 2005a; Reavill et al., 2000; Xi et al., 2005), stimulant-induced locomotion (Reavill et al., 2000) and are noncataleptogenic (Vorel et al., 2002; Xi et al., 2005). These findings are promising and, in comparing the D3 antagonist SB-277011-A to the D2 antagonist haloperidol, SB-277011-A revealed no ability to produce catalepsy, while haloperidol produced significant cataleptic effects (Reavill et al., 2000).

Infusion of 7-OH-DPAT into either the NAcc or striatum had no effect on locomotion (Shimizu et al., 2014). This is an encouraging finding as it suggests that this would allow for the eventual targeting of 'addiction' centers in the brain that would leave untouched any motor areas. Indeed, infusion of D3 antagonists into the cerebellum decreased locomotion (Kolasiewicz et al., 2008; Shimizu et al., 2014), suggesting that D3 receptors may mediate locomotion through a mechanism that may be separate from the reward and motivation systems in the NAcc and striatum. Further, administration of 7-OH-DPAT into the cerebellum did not induce catalepsy (Shimizu et al., 2014), while the D3 antagonists U-99194A and AD-6048 antagonized haloperidol-induced catalepsy, providing support for the contention that D3 antagonists would have fewer and less severe side effects than D3 antagonists.

Summary and Conclusions

In this paper, we have reviewed studies investigating the neurobiological correlates of D3 receptor function in drug addiction. In considering the findings of intracerebral studies, receptor density findings, *Fos* and rCBV measures, a consistent story is emerging. From the studies of CS-controlled behaviors a critical role of the BLA is established, especially in behaviors reinforced by conditioned reinforcers. With respect to more contextually-controlled behaviors, it appears that the NAcc may be involved. Several studies indicate an upregulation of D3 receptors induced by drugs of abuse. There is also an interesting emerging role of D3 receptors located in LHb mediating cue reactivity. It should be considered that the various neural systems may respond differentially after this upregulation (Blaylock et al., 2011; Collins et al., 2011) and notably it seems possible that D3 receptors in the DStr may be playing a more pronounced role after D3 upregulation induced by drug exposure. These differences in responsivity to regulation may explain some of the discrepancies, such as those between receptor density studies and rCBV findings. Interestingly, functional mapping experiments indicate that D3 is able to control cortical activation, as well as some subcortical neuronal states (Cole et al., 2013). These findings indicate that D3 receptors may be able to control, via networks, the functional role of structures that do not themselves express the D3 at high level. All together those findings support the D3 as a potential target for treatments in addiction that should be explored further.

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