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Review

Behavioral and neural mechanisms of compulsive drug seeking

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Abstract

Not the mere procurement and use of drugs, but the fact that patterns of seeking and taking become compulsive after prolonged drug use is a defining characteristic of drug addiction. Development of a therapy that targets the compulsive aspects of drug use and thus addresses addiction at its core would therefore be very desirable. In the present review, we will discuss animal studies that attempt to model loss of control over drug use. Furthermore, we will try to put these studies in a theoretical perspective, and discuss the hypothesized underlying neural and behavioral mechanisms.

Keywords: Drug addiction; Habit; Compulsion; Impulsivity; Sensitization; Tolerance; Allostasis; Prefrontal cortex; Orbitofrontal cortex; Dorsal striatum; Nucleus accumbens

Contents

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1. Introduction

Drug addiction affects many millions of people in the Western world, especially if cigarette smokers and alcoholics are included. Therefore, addiction is a major medical problem, not least because of the ensuing unhealthy lifestyle and the comorbidity with other neuropsychiatric disorders. Moreover, because of its socio-economic and legal impact on society, it affects many more people than the addicts themselves. Recent calculations have estimated that drug addiction accounts for more than 40% of the financial cost to society of all major neuropsychiatric disorders (Uhl and Grow, 2004). Drug addiction is a chronic relapsing disorder characterized by loss of control over drug use. Thus, over the course of the addiction process, drug use escalates from casual consumption to inappropriate use, ultimately culminating in compulsive patterns of drug seeking and taking, i.e. the occurrence of drug-related activities at the expense of previously important social and professional activities and continued drug use despite awareness of its adverse consequences (Leshner, 1997; O'Brien and McLellan, 1996; Volkow and Li, 2004). The central role of compulsion in the addiction process is reflected by the fact that five out of seven symptoms for the diagnosis of addiction in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV are indicative of the loss of control of drug taking (American Psychiatric Association, 2000).

Development of an adequate pharmacotherapy for the treatment of drug addiction is obviously an urgent matter. Even though drug development in the context of addiction is an active field (see Heidbreder and Hagan, 2005), effective therapies are not yet readily available. This may be due to the fact that most experimental therapies to date have been aimed at counteracting the euphoric, or reinforcing properties of drugs. These are major factors involved in the initiation and maintenance of drug intake, but it is less clear whether the euphoric properties of drugs alone play the major role in the addiction process. Other experimental therapies are aimed at aiding the achievement of abstinence by counteracting withdrawal symptoms and by preventing relapse to drug seeking (see e.g. Bossert et al., 2005), and there can be little doubt that these are fruitful approaches. However, there are no drug therapies that specifically address the compulsive aspects of drug addiction. Since compulsive drug use lies at the core of the addiction process, development of therapies that directly target the compulsive aspects of drug seeking may hold promise. To make this possible, elucidation of the neural substrates of compulsive drug use is essential. In the present review, the empirical approaches at studying compulsive aspects of drug addiction will be discussed. We will also describe several theoretical constructs that attempt to explain compulsive drug use, and the neural mechanisms that may underlie compulsive drug seeking.

2. Theories of compulsive drug seeking

Over the last fifteen years, a variety of theories have been put forward that try to explain the occurrence of compulsive, or inflexible drug use. Below, in a brief overview that is not meant to be exhaustive, we describe four of these, that have received most attention in preclinical research. We wish to stress here, that we do not regard these theories as mutually exclusive possibilities. Presumably, the mechanisms put forward in these accounts are responsible for certain aspects of addiction, perhaps changing in relative importance over the course of the addiction process (see Section 5).

2.1. Stimulus-response habit learning

Tiffany (1990) has proposed that many aspects of drug seeking in addicts occur through non-cognitive, automatic processes. Thus, drug use is initially a goal-directed action-outcome process, whereby drug seeking is driven by a representation of its consequences (for example, the euphoric effects of the drug). However, after many cycles of drug taking, this behavior becomes dominated by a stimulus-response mechanism, whereby drug seeking becomes an automatic process, being triggered by drug-associated stimuli, beyond the individual's control and insensitive to devaluation of the drug reward (Everitt et al., 2001; Robbins and Everitt, 1999; Tiffany, 1990). It should be noted though, that stimulus-response habit learning occurs with overtraining on many tasks (Dickinson, 1985; Packard and Knowlton, 2002; White and McDonald, 2002); this does not necessarily equate to the development of compulsion. Rather, this hypothesis poses that chronic exposure to self-administered drug subverts neural mechanisms of stimulus-response habit learning, causing a maladaptive, drug-directed form of habitual behavior.

2.2. Drug-induced deficits in inhibitory control

A theory somewhat related to the stimulus-response habit learning idea places an emphasis on impaired function of the prefrontal cortex (Jentsch and Taylor, 1999). This theory states that chronic drug exposure induces dysfunction of frontal cortical regions involved in inhibitory control over behavior. Thus, the ability of drug users to inhibit inappropriate drug-centered behavior will diminish, causing drug-associated behaviors to dominate the addict's behavioral repertoire (Jentsch and Taylor, 1999).

2.3. Incentive sensitization

Robinson and Berridge's incentive sensitization theory (Robinson and Berridge, 1993, 2003) states that repeated exposure to drugs of abuse leads to a set of adaptations in the neural circuits mediating motivation, most notably the mesoaccumbens dopamine projection. These adaptations render this circuit hypersensitive ('sensitized') to drugs and drug-associated stimuli. Sensitization of the mesoaccumbens dopamine system, that plays a prominent role in attributing incentive salience to stimuli, i.e. the way in which stimuli are perceived as attractive, causes drugs and drug-associated stimuli to become excessively 'wanted.' This exaggerated motivation for drugs,

perhaps equivalent to drug craving, may then lead to the compulsive pursuit of the drug.

2.4. Hedonic allostasis

This view of addiction (Koob et al., 2004; Koob and Le Moal, 1997) posits that drug exposure recruits opponent processes, leading to a functional down-regulation of brain reward mechanisms. Upon chronic drug use, the function of these reward systems fails to return to normal, but instead moves to a lower set-point. Dysregulation of brain reward circuits thus provides a negative motivational state that causes compulsive drug use. Pharmacologically, the hedonic deficit induced by chronic drug exposure is hypothesized to lead to an upward shift in the dose–response function of drug self-administration, unlike tolerance and sensitization accounts, that entail rightward and leftward shifts in dose–response curves, respectively.

3. Preclinical studies of compulsive drug seeking

In preclinical studies, compulsive drug seeking has been operationally defined as continuation of drug seeking and taking despite adverse consequences, despite obvious and detectable decreases in the subjective value of the drug (devaluation), or as being insensitive to internal and external manipulations ('inflexibility'). In this section, we will summarize preclinical studies that have addressed compulsive patterns of drug seeking.

3.1. Escalation of drug intake

Following earlier experiments by Wolffgramm and Heyne (Heyne, 1996; Heyne and Wolffgramm, 1998; Wolffgramm and Heyne, 1995, see Section 3.4), Spanagel and Hölter (Hölter et al., 1998; Spanagel and Hölter, 1999) evaluated patterns of ethanol intake in rats that had the opportunity to drink ethanol solutions at different concentrations (5%, 10% or 20%). After long-term ethanol exposure with repeated periods of withdrawal, they found that rats increased their ethanol intake, developed a preference for the highest ethanol concentration and were less sensitive to adulteration with quinine or the presence of an alternative reinforcer (a sucrose solution). In addition, repeated ethanol deprivation led to increased anxiety (as assessed on the elevated plus maze) during withdrawal.

The observations of Ahmed and Koob (Ahmed et al., 2000; Ahmed and Koob, 1998), are somewhat reminiscent of the above data. They showed that rats that had the opportunity to self-administer cocaine or heroin during long (6–11 h) sessions escalate their drug intake, as compared to animals that self-administer during short (1 h) sessions. Rats with prolonged access to cocaine showed upward shifts in the dose–response function of cocaine, when tested under both fixed ratio (Ahmed and Koob, 1998) and progressive ratio schedules of cocaine self-administration (Paterson and Markou, 2003).

They also observed that rats with prolonged access to cocaine had higher intracranial self-stimulation thresholds, i.e. higher 'reward thresholds' (Ahmed et al., 2002). This appeared to precede the escalation of cocaine intake, suggesting that hypofunction of a central reward system caused the motivation for cocaine self-administration and cocaine intake to increase. Long access animals showed no change in the sensitivity to the self-stimulation threshold-lowering effect of cocaine, despite the fact that their stimulation thresholds were higher. In addition, the efficacy of cocaine to enhance nucleus accumbens dopamine concentrations was not altered in long access animals (Ahmed et al., 2003). However, the dose–response curve of the dopamine receptor antagonist *cis*-flupenthixol to alter cocaine self-administration was shifted to the left in long access animals, which was interpreted as a reduced number and/or function of forebrain dopamine receptors involved in cocaine self-administration (Ahmed and Koob, 2004). Gene expression analysis has shown that the most prominent neural changes associated with excessive drug intake occur in the lateral hypothalamus, rather than in the nucleus accumbens, prefrontal cortex or amygdala (Ahmed et al., 2005).

3.2. Sensitization of the incentive value of drugs

Work inspired by the incentive sensitization theory of addiction (Robinson and Berridge, 1993, 2003) has indicated that motivation for drugs increases after drug pre-exposure. For example, the reinforcing effects of drugs have been shown to be enhanced in animals that have been pretreated with drugs (e.g. Lett, 1989; Piazza et al., 1989; Shippenberg and Heidbreder, 1995; Valadez and Schenk, 1994; Vezina et al., 2002). Similar to the well-documented sensitization of psychomotor stimulant properties of drugs, which is most pronounced after a period of drug abstinence (for reviews see Pierce and Kalivas, 1997; Vanderschuren and Kalivas, 2000), the enhanced drug reinforcement caused by sensitizing drug pretreatment also seems to be long-lasting (e.g. Shippenberg et al., 1996; Valadez and Schenk, 1994). In further analysis of sensitization of the motivational properties of cocaine, Deroche et al. (1999) compared two groups of cocaine self-administering rats, with different degrees of drug experience (i.e. 6 or 29 daily self-administration sessions). They found that rats with most self-administration experience showed enhanced motivation to obtain a cocaine infusion, as assessed in a runway paradigm. Moreover, the dose–response curve for cocaine to reinstate extinguished drug seeking was shifted to the left in the 29-sessions group. However, the capacity of cocaine to evoke conditioned place preference was not different between these groups of animals (Deroche et al., 1999). In a somewhat related set of experiments, Vezina and colleagues (Lorrain et al., 2000; Suto et al., 2002; Vezina et al., 2002) showed that sensitizing pre-exposure of rats to amphetamine enhanced the motivation to self-administer amphetamine or cocaine, as indicated by higher break-points under a progressive ratio schedule of reinforcement.

Two further issues should be mentioned here. First, most studies showing sensitization of the reinforcing properties of drugs have used passive, experimenter-delivered drug pretreatment (Lett, 1989; Piazza et al., 1989; Shippenberg and Heidbreder, 1995; Valadez and Schenk, 1994; Vezina et al., 2002). In order for incentive sensitization to be relevant for the human

situation, where drug taking is always a voluntary act, sensitization of drug reinforcement should also occur after drug self-administration. Although this has appeared difficult to demonstrate experimentally, several studies have now shown that drug self-administration can indeed enhance the incentive value of drugs (Deroche et al., 1999; Deroche-Gamonet et al., 2004; Morgan et al., 2005). Second, drug pretreatment has also been shown to increase motivation for non-drug, natural rewards such as food or sex (Fiorino and Phillips, 1999; Harmer and Phillips, 1998, 1999; Taylor and Jentsch, 2001) as well as conditioned stimuli associated with food (Taylor and Horger, 1999; Wyvell and Berridge, 2001). However, drug addiction is actually characterized by a decreased interest in non-drug sources of reinforcement (American Psychiatric Association, 2000; Leshner, 1997; O'Brien and McLellan, 1996; Volkow and Li, 2004). Thus, incentive sensitization caused by repeated drug exposure can explain the exaggerated motivation for drugs associated with addiction, but not the fact that drug-related activities prevail at the expense of previously important social and professional activities.

3.3. Drug-induced impulsive and inflexible behavior

A variety of studies have shown that repeated drug exposure causes impulsive, perseverative, or inflexible behavior. For example, during a 14-day treatment regimen with cocaine, drug-treated rats showed a transient increase in impulsive choice in a delayed reinforcement task (Paine et al., 2003). In two other tasks that measure inhibitory control over behavior, and are therefore able to demonstrate other aspects of impulsivity, it was shown that repeated amphetamine treatment caused deficits in a differential reinforcement of low rates task (Peterson et al., 2003) whereas repeated treatment with nicotine led to an increase in premature responses in the 5-choice serial reaction time task (Blondel et al., 1999). Prolonged self-administration of amphetamine, cocaine and heroin in rats caused profound cognitive deficits as assessed in the 5-choice serial reaction time task. Thus, animals with a drug history showed reduced attentional accuracy, increased omissions and slower reaction times, but no impulsive or perseverative behavior (Dalley et al., 2004, 2005a,b). Apart from a long-lasting increase in food collection latency after heroin self-administration, these deficits generally subsided after a few drug-free days. The most severe cocaine-induced impairments in the 5-choice serial reaction time task were found in animals that were most impulsive prior to cocaine self-administration, suggesting that impulsive individuals run a greater risk for drug-induced neurocognitive impairments associated with drug abuse (Dalley et al., 2004). Impaired reversal learning, indicative of perseverative behavior as a result of drug exposure was observed in two other studies. Thus, repeated cocaine treatment induced long-lasting reversal deficits in an object discrimination task in monkeys (Jentsch et al., 2002) and in an odor discrimination task in rats (Schoenbaum et al., 2004). In a follow-up study (Schoenbaum and Setlow, 2005), cocaine-sensitized rats appeared insensitive to reinforcer devaluation. Thus, cocaine-pretreated rats continued to respond at unaltered levels for food, even when this food had been made aversive by pairing it with lithium chloride. This pattern of responding (Adams, 1982) suggests that cocaine sensitization may enhance stimulus-response habit learning (Dickinson, 1985). In a comparable experiment (Nordquist et al., submitted for publication), the effect of amphetamine sensitization on stimulus-response habit learning was investigated using satiety-specific devaluation, whereby the value of food was decreased not by pairing it with illness, but by giving the animals free access to food before the test (Balleine and Dickinson, 1998; Killcross and Coutureau, 2003). Consistent with Schoenbaum and Setlow (2005), amphetamine-sensitized animals showed accelerated habit learning (Nordquist et al., submitted for publication). In addition, amphetamine-sensitized rats also responded at higher levels for food, but only under a random ratio schedule where more response effort led to more reinforcer delivery, indicating that amphetamine sensitization had increased the incentive value of food (see also Harmer and Phillips, 1998, 1999; Taylor and Jentsch, 2001). These data show that accelerated habit learning and enhanced incentive value of food can occur in parallel in amphetamine-sensitized rats, but that task demands probably determine which behavioral adaptation is most prominently expressed.

3.4. Inflexible patterns of drug intake

The studies described above provide evidence that previous drug exposure can indeed lead to various forms of inflexible behavior. It should be noted though, that these studies used food reinforcers to probe the associative structure of behavior in drug-exposed animals. Of course, most relevant for addiction would be the demonstration that inflexible behavior also occurs in animals working for a drug reinforcer. A variety of studies has shown that this happens indeed. Wolffgramm and Heyne (Heyne, 1996; Heyne and Wolffgramm, 1998; Wolffgramm and Heyne, 1995) were perhaps the first to report on the occurrence of inflexible drug taking in rats. They allowed rats to drink solutions containing ethanol, the μ-opioid receptor agonist etonitazene or *d*-amphetamine for prolonged periods. They observed that rats initially displayed stable and modest levels of drug intake that could be modulated by external and internal factors. For example, subordinate rats drank more than dominant ones, and socially isolated rats took more than group-housed rats. After 6–8 months of stable intake, drug intake suddenly and markedly increased. When the animals were subsequently withdrawn from drug, and retested after 1–6 months of abstinence, their drug intake could no longer be modulated by social (dominance/subordination; isolation/group housing) or gustatory (adulteration of drug solution with quinine) factors, suggesting that drug intake had become inflexible.

Using a similar devaluation procedure as described above for food (Adams, 1982), Dickinson et al. (2002) showed that lever pressing for ethanol readily gained habitual characteristics. Thus, lever pressing for food was markedly suppressed after it had been made aversive by pairing it with lithium chloride. However, when ethanol was paired with lithium, lever pressing did not decline. These authors concluded that

ethanol seeking more readily progressed from a goal-directed action-outcome process, to a habitual stimulus-response process. Likewise, instrumental behavior directed at obtaining a cocaine solution appeared insensitive to devaluation by pairing cocaine with lithium, whereas this was not the case in animals working for a sucrose solution (Miles et al., 2003). These studies demonstrated that seeking of a drug reinforcer can be habitual under circumstances where behavior directed at obtaining a natural reinforcer is not.

Two subsequent studies provided evidence that instrumental behavior directed at obtaining drugs starts off as a flexible, goal-directed form of behavior, but upon prolonged drug exposure acquires compulsive characteristics (Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004). In the first of these (Vanderschuren and Everitt, 2004), drug seeking in the face of adverse consequences (American Psychiatric Association, 2000), namely danger signals, was investigated in rats with a limited or an extended cocaine self-administration history. Thus, animals were presented with a footshock-associated conditioned stimulus during cocaine seeking in order to measure conditioned suppression, in a sense devaluing the drug reinforcer, since animals were required to respond for the outcome in a state of conditioned fear. In animals with limited experience of self-administering cocaine, the aversive conditioned stimulus markedly suppressed cocaine seeking, but in animals with an extended cocaine self-administration history, the footshock-associated conditioned stimulus no longer affected cocaine seeking. This progression from flexible to inflexible appetitive behavior did not seem to occur in animals working for sucrose. Thus, in rats with an equivalent extended history of sucrose ingestion, the footshock-associated conditioned stimulus still profoundly suppressed sucrose seeking. The group differences in conditioned suppression of appetitive behavior (present in animals with limited experience with cocaine and extended experience with sucrose; absent in animals with a prolonged cocaine history) was not parallelled by differences in freezing to a different footshock-associated conditioned stimulus, showing that the absence of an effect of the aversive stimulus on cocaine seeking was not the result of the inability of the animals to encode or express a conditioned stimulus–unconditioned stimulus association, i.e. display conditioned fear. The progression of casual to compulsive drug seeking observed was not accompanied by an apparent change in the incentive value of cocaine, as assessed by the rate of responding during drug seeking (Olmstead et al., 2000).

In a series of experiments conducted independently and in parallel (Deroche-Gamonet et al., 2004), it was demonstrated that over an extended period of cocaine self-administration, rats developed three manifestations of behavior reminiscent of symptoms of drug addiction according to DSM-IV (American Psychiatric Association, 2000). First, difficulty limiting drug intake was observed as persistence in responding during explicit extinction periods (i.e. when it was clearly indicated to the animal that responding would not result in cocaine delivery). Second, high motivation to obtain cocaine was observed as raised break-points under a progressive ratio schedule with increasing cocaine experience. Lastly, and similar to the study described above (Vanderschuren and Everitt, 2004), they found drug seeking despite adverse consequences, as the suppression of cocaine taking when it was paired with footshock was decreased after a lengthy cocaine-taking history. These symptoms of addiction were only seen in a subset of animals, being those that subsequently showed high levels of relapse to cocaine seeking in an extinction–reinstatement model (Davis and Smith, 1976; De Wit and Stewart, 1981; Stretch et al., 1971, for review see Shaham et al., 2003). However, the development of these addiction-like behaviors was not correlated with locomotor activity (either in a novel environment or after cocaine infusion), anxiety, or amount of cocaine intake. In apparent contrast, these two studies found that development of compulsive cocaine seeking was (Deroche-Gamonet et al., 2004) or was not (Vanderschuren and Everitt, 2004) accompanied by a change in the motivation for drug. This can be reconciled by close examination of the data, because Deroche-Gamonet et al. (2004) observed an increase in break-point for cocaine at a much earlier stage in the experiment (35 self-administration sessions) than a change in the willingness to endure delivery of footshock together with a cocaine infusion (74 sessions). These findings suggest that, although experience with self-administered drug can enhance the motivational properties of the drug (Deroche et al., 1999; Morgan et al., 2005), this increase in the incentive value of the drug does not itself result in persistent drug seeking in the face of adversity. Future experiments should investigate whether there is a causal relationship between incentive sensitization and habitual drug seeking (i.e. compulsive drug seeking cannot develop without the drug-induced neuroadaptions underlying changes in drug motivation having occurred first), or whether these are parallel processes, underpinned by separate neural substrates, that occur separately over the course of a drug taking history.

3.5. Persistent drug seeking underpinned by conditioned stimuli

Certain behaviors controlled by drug-associated conditioned stimuli have appeared to be remarkably persistent, i.e. resistant to extinction. For example, conditioned place preference to cocaine, ethanol or morphine can be difficult to extinguish (e.g. Cunningham et al., 1998; Mueller et al., 2002; Mueller and Stewart, 2000; Sakoori and Murphy, 2005). This is not a general finding, as full extinction of drug-conditioned place preference has also been reported (Fuchs et al., 2002; Itzhak and Martin, 2002; Romieu et al., 2004; Sanchez and Sorg, 2001; Szumlinski et al., 2002); however, even in these cases it is not uncommon that 10 daily sessions are necessary to achieve full extinction.

Profound resistance to extinction has been reported in animals that work for or during presentations of drug-associated stimuli. It is well-established that drug-paired conditioned stimuli can, as conditioned reinforcers, maintain drug seeking (Everitt and Robbins, 2000; Goldberg et al., 1975; Schindler et al., 2002), but only if they are presented response-contingently (see Di Ciano and Everitt, 2003; Grimm et al., 2000; Kruzich et al., 2001). Marked persistence of responding for

drug-paired conditioned stimuli was for example shown by Weiss et al. (2001). In these experiments, rats learned that in the presence of an auditory discriminative stimulus, lever pressing resulted in an intravenous infusion of cocaine and a visual conditioned stimulus. After extinction of operant responding (with neither cocaine, the cocaine-associated conditioned stimulus nor the discriminative stimulus present during extinction sessions), presentation of the discriminative stimulus reinstated lever pressing for the cocaine-associated cue, whereas cocaine itself was not available during these sessions. The capacity of the discriminative stimulus to reinstate responding for the cocaine-associated conditioned stimulus did not diminish at all over 11 repeated tests, the last test session being performed 18 weeks after the first reinstatement session. These experiments show that the discriminative stimulus and/or the cocaine-associated cue supported lever pressing by themselves, being insensitive to presentation in the absence of cocaine. This was subsequently shown to require only one self-administration session, after which the discriminative stimulus remained capable of reinstating responding for the cocaine-associated cue for up to nine months, when the animals were retested at three-month intervals. This effect did not occur in animals responding for sweetened condensed milk (Ciccocioppo et al., 2004). Interestingly, there is a substantial body of evidence that extinction of the drug-taking response itself (as widely used in extinction–reinstatement settings; Davis and Smith, 1976; De Wit and Stewart, 1981; Stretch et al., 1971, for review see Shaham et al., 2003) does lead to marked reductions (and sometimes even cessation) of responding (see e.g. Olmstead et al., 2001), suggesting that drug-associated and/or predictive stimuli are more resistant to extinction than the act of drug taking itself.

It should be borne in mind that in these studies the response that had to be made for presentation of the drug-associated conditioned stimulus was the same one that was reinforced with the drug during initial training, making it difficult to discern whether residual drug-directed behavior still contributed to responding during testing, or whether responding was truly directed at obtaining a presentation of the drug-associated cue. To establish that drug-associated conditioned stimuli can gain reinforcing properties, Di Ciano and Everitt (2004a) trained animals to perform a new response (lever pressing) for presentations of a conditioned stimulus that had previously been paired with self-administered cocaine, heroin or sucrose (using nose-poking as the operant). Animals readily acquired the lever-press response for presentation of the reinforcer-paired conditioned stimulus. Remarkably, levels of lever pressing remained stable over more than nine weeks of repeated testing. Leaving the animals undisturbed for one month before acquisition of lever-press responding for the cocaine-associated cue, or response (i.e. nose-poke)-contingent presentation of the conditioned stimulus without cocaine before conditioned stimulus–cocaine association, retarded the acquisition of lever pressing for the cocaine-associated cue. This is likely the result of spontaneous recovery mitigating the effect of forgetting or extinction, respectively (see Conklin and Tiffany, 2002, for a discussion). Contingent (upon nose-poking) or non-contingent presentation of the conditioned stimulus after conditioned stimulus–cocaine training had no effect on lever pressing for the conditioned stimulus. Together, these data (Di Ciano and Everitt, 2004a) provide strong evidence for persistence of the ability of drug-associated cues to underpin drug seeking responses, suggesting that conditioned stimulus-maintained drug seeking is resistant to extinction of the conditioned stimulus–drug association and may therefore gain a habitual quality. It was recently shown that human cocaine users will also perform high levels of responding reinforced by a cocaine-associated conditioned stimulus only (i.e. whilst being aware that responding would not produce cocaine during that session) (Panlilio et al., 2005). In an earlier study where the effects of extinction were studied in animals responding for cocaine under a second-order schedule of reinforcement (Di Ciano and Everitt, 2002), it was found that non-reinforced exposure to the drug-associated cue did decrease responding when the animals were re-tested one day after the last extinction session, but that prolonged unavailability of the drug and the conditioned stimulus (i.e. the rats were left undisturbed in their home cages for three weeks) alleviated this effect. Thus, when extinction of responding was followed by a period of abstinence, the capacity of the drug-associated conditioned stimuli to support drug seeking spontaneously recovered.

This latter observation (Di Ciano and Everitt, 2002) is reminiscent of the time-dependent increase, or 'incubation,' of drug seeking. In studies from Shaham and colleagues (Grimm et al., 2001, 2002, 2003; Lu et al., 2004a; Shepard et al., 2004; for review see Lu et al., 2004b), it was found that drug seeking evoked by re-exposure to drug-associated conditioned stimuli, but not the drug itself, increased with prolonged withdrawal in rats previously trained to self-administer cocaine or methamphetamine. Responding was found to increase progressively over the first three months of withdrawal, and declined thereafter. A similar, but somewhat less robust time-dependent effect of withdrawal was found in rats responding for sucrose-associated cues (Grimm et al., 2002, 2003, 2005) or responding in extinction in the presence of discriminative stimuli signaling heroin availability (Shalev et al., 2001). The precise psychological mechanism underlying the incubation effect, which also occurs with conditioned stimuli associated with aversive events (see Houston et al., 1999, for a recent example), is unknown. It has been hypothesized that strengthening and generalization of cue–drug associations over time, to include not only the immediate drug-associated conditioned stimuli but also stimuli surrounding them in space and time, might underlie the increases in responding (see Houston et al., 1999, for a discussion).

4. Neurobiological background of compulsive drug seeking

Repeated drug exposure causes a wide variety of transient as well as persistent neural changes (for reviews see Kelley, 2004; Nestler, 2001; Robinson and Kolb, 2004; Vanderschuren and Kalivas, 2000; White and Kalivas, 1998). On the basis of these changes, the neurobiology of drug seeking, as well as the neural backgrounds of inflexible and compulsive behavior, we propose that the development of compulsive drug seeking is the

consequence of persistent functional changes within the cortico-striatal circuits mediating appetitive behavior. Below, the relevance of altered function of striatal and prefrontal mechanisms will be discussed. Given the dense projections from the prefrontal cortex to the striatum, and the indirect innervation of the prefrontal cortex by the striatum, through the pallidum and thalamus (Berendse et al., 1992; Groenewegen et al., 1991; McGeorge and Faull, 1989; Sesack et al., 1989; Voorn et al., 2004), it is highly unlikely that striatal and prefrontal mechanisms work in isolation to mediate the addiction process. However, because they have for the most part been investigated in separate studies, they will also be discussed separately.

4.1. Striatal mechanisms

The majority of studies of the neurobiology of drug seeking have focused on the ventral striatum, most prominently the nucleus accumbens. Indeed, there is a wealth of evidence showing that the integrity of the nucleus accumbens, its dopaminergic innervation in particular, is necessary for drug self-administration (Koob, 1992; McBride et al., 1999; Wise, 1998). The primary function of the nucleus accumbens has been proposed to be the translation of emotionally charged information into goal-directed action (Cardinal et al., 2002; Mogenson et al., 1980; Phillips et al., 1991). The hypersensitivity of the mesoaccumbens dopamine innervation that occurs as a consequence of repeated drug exposure (Pierce and Kalivas, 1997; Vanderschuren and Kalivas, 2000), could then serve to enhance the motivational influence over behavior of drugs and drug-associated stimuli (Robinson and Berridge, 1993, 2003). Recent studies have shown that drug-induced enhancement of mesoaccumbens dopamine function can indeed lead to enhanced motivation for drugs (Vezina et al., 2002).

In addition to its dopaminergic innervation, the glutamatergic input that the accumbens receives from prefrontal cortex, amygdala, hippocampus and thalamus (Berendse et al., 1992; Berendse and Groenewegen, 1990; Groenewegen et al., 1987; Kelley et al., 1982; Kelley and Domesick, 1982; McDonald, 1991; McGeorge and Faull, 1989; Sesack et al., 1989; Voorn et al., 2004), has also been implicated in drug seeking (see Bossert et al., 2005; Di Ciano and Everitt, 2005; Schmidt et al., 2005). Repeated cocaine exposure causes a decrease in basal levels of glutamate in the accumbens, and increases in glutamate transmission after re-exposure to the drug (Baker et al., 2003; Hotsenpiller et al., 2001; Pierce et al., 1996). These adaptations in nucleus accumbens glutamate dynamics have been shown to be important for reinstatement of cocaine seeking (Baker et al., 2003; McFarland et al., 2003). In addition, blockade of α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors in the nucleus accumbens attenuates cocaine seeking underpinned by response-contingent presentations of drug-associated conditioned stimuli (Di Ciano and Everitt, 2001, 2004b) and blocks cocaine-induced reinstatement of previously extinguished cocaine seeking (Cornish and Kalivas, 2000; Park et al., 2002). Thus, drug-induced alterations in nucleus accumbens dopamine and glutamate neurotransmission are likely to play a prominent role in goal-directed aspects of drug seeking, and perhaps in the increased motivation for drug that occurs with repeated drug exposure.

Although it has long been thought that the dorsal striatum plays only a minor role in drug addiction (McBride et al., 1999; Wise, 1998), there is accumulating evidence that some of the persistent aspects of addictive behavior depend upon dorsal striatal mechanisms. Metabolic and molecular imaging studies in primates have shown that with prolonged cocaine self-administration, dorsal regions of the striatum become progressively more engaged by the drug (Letchworth et al., 2001; Porrino et al., 2004). Thus, when comparing dopamine transporter binding or metabolic activity after 5 or 100 sessions of cocaine self-administration, changes that were restricted to the ventral striatum after 5 sessions, spread dorsally to involve the dorsal striatum after chronic drug taking (Letchworth et al., 2001; Porrino et al., 2004). In rats, well-established cocaine seeking under a second-order schedule of reinforcement, which depends upon the conditioned reinforcing properties of cocaine-associated stimuli, was shown to be accompanied by increased dopamine efflux in the dorsal striatum, but not the nucleus accumbens (Ito et al., 2000, 2002). The importance of dorsal striatal mechanisms for this behavior was confirmed by the observation that infusion of a dopamine receptor antagonist or an AMPA/kainate receptor antagonist into the dorsolateral striatum attenuated cue-controlled cocaine seeking (Vanderschuren et al., 2005). Because of the involvement of the dorsal striatum in stimulus-response habit learning, whereby behavior becomes automatic and hence no longer driven by an action–outcome relationship (Everitt et al., 2001; Packard and Knowlton, 2002; White and McDonald, 2002; Yin et al., 2004), the above findings suggest that the performance of well-established cocaine seeking may reflect the establishment of a habitual form of responding.

The work by Porrino and colleagues (Letchworth et al., 2001; Porrino et al., 2004) suggests that dorsal striatal involvement in drug seeking may develop gradually over the course of many cycles of drug taking. Whereas the ventralmost parts of the striatum, including the nucleus accumbens shell and the olfactory tubercle mediate the initial acquisition of cocaine self-administration (Ikemoto, 2003; Rodd-Henricks et al., 2002), more dorsal regions (nucleus accumbens core and dorsolateral striatum) become increasingly implicated as cue-controlled cocaine seeking becomes well-established (Di Ciano and Everitt, 2001, 2004b; Ito et al., 2000, 2002, 2004; Vanderschuren et al., 2005). This ventral-to-dorsal intrastriatal progression of regions engaged by cocaine self-administration may be subserved by striato-ventral tegmental area/nigro-striatal pathways, whereby ventral striatal regions influence not only their own dopaminergic innervation, but also that of progressively more dorsal areas through spiraling projections via dopamine neurons in the ventral tegmental area and substantia nigra (Haber et al., 2000). Perhaps, dopaminergic mechanisms in the accumbens shell and core that mediate reinforcement processes and modulate limbic cortical mechanisms controlling goal-directed behavior progressively activate, consolidate and eventually become subordinate to a dorsal striatum-dependent habit system (Everitt et al., 2001; Porrino et al., 2004).

4.2. Prefrontal mechanisms

Over the last ten years, much evidence has implicated dysfunction of the prefrontal cortex in the pathophysiology of drug addiction. This notion primarily stems from the fact that drug addiction is characterized by patterns of drug seeking that are compulsive, perseverative and inflexible, behaviors that are reminiscent of those seen after damage to the prefrontal cortex (Bechara et al., 2000; Brown and Bowman, 2002; Cardinal et al., 2002; Miller, 2000; Robbins, 1996). Of particular interest is the observation that coordination of goal-directed vs. stimulus-response habitual behavior – dysregulation of which has been hypothesized to underlie persistent aspects of drug addiction (Everitt et al., 2001; Robbins and Everitt, 1999; Tiffany, 1990) – depends upon interactions between the prelimbic and infralimbic cortex (Killcross and Coutureau, 2003).

Consistent with a role for altered prefrontal function in addiction, animal studies have shown that repeated drug exposure results in a wide variety of neural changes in prefrontal cortex, including altered dopaminergic, glutamatergic and GABAergic neurotransmission (Steketee, 2003; Vanderschuren and Kalivas, 2000), morphological changes in pyramidal output neurons (Crombag et al., 2005; Robinson et al., 2001), and impaired integration of synaptic inputs (Onn and Grace, 2000; Trantham et al., 2002). More directly related to addictive behavior, metabolic imaging studies have shown a long-lasting hypofunction of the prefrontal cortex in cocaine abusers (Volkow et al., 1992, 1993). In addition, during cue- or drug-evoked craving, activation of prefrontal regions is consistently observed in imaging studies (for review see Goldstein and Volkow, 2002). Studies in animals have shown that lesioning the medial prefrontal cortex disinhibits cocaine self-administration (Weissenborn et al., 1997). Thus, lesioned rats showed enhanced acquisition of cocaine self-administration. Under a second order schedule of self-administration, lesioned rats showed higher and irregular response patterns and appeared insensitive to omission of the drug-associated conditioned stimulus. By contrast, lever pressing for sucrose was not affected by medial prefrontal cortex lesions (Weissenborn et al., 1997). Metabolic imaging studies in primates have shown that chronic cocaine self-administration leads to shifts in the patterns of functional activation of prefrontal regions during this behavior (Porrino and Lyons, 2000). In addition, the prefrontal cortex has been implicated in drug-, cue-, as well as stress-induced reinstatement of extinguished cocaine seeking (Kalivas and McFarland, 2003; Shaham et al., 2003; Bossert et al., 2005).

There is also experimental evidence to show that chronic drug exposure causes cognitive dysfunctions similar to those seen after prefrontal damage. In an odor discrimination task in rats, chronic cocaine treatment led to blunted response latency changes during training as well as reversal learning deficits, impairments similar to those seen in animals with orbitofrontal cortex lesions (Schoenbaum et al., 2004). Likewise, human addicts have shown deficits on a variety of gambling tasks that are comparable to those of patients with damage to orbital or ventromedial portions of the prefrontal cortex (Bartzokis et al., 2000; Bechara et al., 2001; Grant et al., 2000; Rogers et al., 1999). These findings support the view that the poor decision making which is a characteristic of drug addiction may reflect impaired prefrontal function (Jentsch and Taylor, 1999; Volkow and Fowler, 2000). Particularly compelling is the observation that methylphenidate induces different patterns of glucose metabolism in the medial orbitofrontal cortex of cocaine addicts compared to drug-naive subjects (Volkow et al., 2005), and that these regions (BA 11 and 25) are also active during symptom provocation in patients with obsessive compulsive disorder (Breiter et al., 1996; Mataix-Cols et al., 2004).

5. Discussion and conclusions

The present paper aims to summarize and discuss preclinical studies on the inflexible, compulsive aspects of drug seeking that lie at the core of the addiction syndrome (American Psychiatric Association, 2000; Leshner, 1997; O'Brien and McLellan, 1996; Volkow and Li, 2004) and their possible neural substrates.

The studies summarized above show that there is evidence to support each of the four theories seeking to explain compulsive drug use. Thus, there is evidence that drug seeking becomes habitual and that chronic drug exposure induces prefrontal dysfunction and associated impairments in executive functions, leading to impulsive and inflexible behaviors. In addition, studies showing increased motivation for drugs after drug pre-exposure have contributed support to the incentive sensitization theory, whereas dysfunction of brain reward systems after escalated drug intake supports a hedonic allostasis view of addiction. A major challenge for future research is to reconcile these views of addiction, and to identify in which aspects or phases of the addiction process they play a primary role. They may occur differentially in individuals addicted to different drugs. Or, they may occur in all individuals at different times, leading to the complexity of the addicted state that perhaps makes it so difficult to manage, treat and escape from.

Several remarks can be made in this regard. Thus, it has appeared that prolonged, or excessive drug intake is necessary for hedonic allostasis or drug seeking despite adverse consequences to develop (Ahmed et al., 2000; Ahmed and Koob, 1998; Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004), suggesting that these phenomena may only come into play during later stages of the addiction process. On the other hand, long-lasting behavioral sensitization can be invoked by a single drug exposure (e.g. Vanderschuren et al., 1999, 2001), and a single self-administration session can be sufficient for long-lasting control over behavior by a cocaine-associated conditioned stimulus to come about (Ciccocioppo et al., 2004). Thus, the influence of drug-associated conditioned stimuli, and incentive sensitization may play an especially important role in the early phases of addiction. This does, of course, not imply that these latter processes cannot be involved in more persistent aspects of addiction. For example, behavioral sensitization is correlated with, and suggested to be an important factor underlying, relapse to drug seeking (e.g. De Vries et al., 1998).

The following, speculative scenario can be proposed for the progression from casual to compulsive drug seeking. Initial drug

exposure may, perhaps only in susceptible individuals, lead to incentive sensitization, causing drugs to become increasingly attractive. At the same time, repeated and consistent pairing of the subjective effects of drugs with environmental stimuli (drug paraphernalia, contextual and social cues) causes these conditioned stimuli to gain control over behavior. Together, these two phenomena, caused by functional changes in limbic cortical–ventral striatal pathways, greatly increase the likelihood of further drug intake. It is at this stage, that drug intake may come to escalate, causing dysfunction of brain reward systems. Chronic exposure to large amounts of drugs may also lead to damage to, or at least dysfunction of the prefrontal cortex, causing drug seeking to become inflexible. In parallel, prolonged drug exposure may recruit dorsal striatal mechanisms that underlie an aberrant form of stimulus-response habitual behavior that contributes to compulsive drug seeking.

In conclusion, over the last few years, there has been increasing attention to the inflexible aspects of the behavior characterizing drug addiction. These research efforts have led to the explicit demonstration of compulsive drug seeking in laboratory animals (Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004), as well as other forms of inflexible behavior as a result of repeated or chronic drug exposure. These findings may be the foundation for new avenues in drug addiction research, aimed at elucidating the neural substrates of compulsive drug seeking. Ultimately, these efforts may improve our chances of designing treatment strategies that target addiction at the core of the disorder.

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