British Journal of Pharmacology (2008) 154, 261–274

0007–1188/08 $30.00
www.brjpharmacol.org

REVIEW

The neurocircuitry of addiction: an overview

MW Feltenstein and RE See

Department of Neurosciences, Medical Universiy of South Carolina, Charleston, SC, USA

Drug addiction presents as a chronic relapsing disorder characterized by persistent drug-seeking and drug-taking behaviours. Given the significant detrimental effects of this disease both socially and economically, a considerable amount of research has been dedicated to understanding a number of issues in addiction, including behavioural and neuropharmacological factors that contribute to the development, loss of control and persistence of compulsive addictive behaviours. In this review, we will give a broad overview of various theories of addiction, animal models of addiction and relapse, drugs of abuse, and the neurobiology of drug dependence and relapse. Although drugs of abuse possess diverse neuropharmacological profiles, activation of the mesocorticolimbic system, particularly the ventral tegmental area, nucleus accumbens, amygdala and prefrontal cortex via dopaminergic and glutamatergic pathways, constitutes a common pathway by which various drugs of abuse mediate their acute reinforcing effects. However, long-term neuroadaptations in this circuitry likely underlie the transition to drug dependence and cycles of relapse. As further elucidated in more comprehensive reviews of various subtopics on addiction in later sections of this special issue, it is anticipated that continued basic neuroscience research will aid in the development of effective therapeutic interventions for the long-term treatment of drug-dependent individuals.
British Journal of Pharmacology (2008) **154,** 261–274; doi:10.1038/bjp.2008.51; published online 3 March 2008

Keywords: abuse; addiction; animal models; dopamine; glutamate; mesocorticolimbic; neurobiology; relapse

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; CPP, conditioned place preference; CRF, corticotropin-releasing factor; DA, dopamine; dmPFC, dorsomedial prefrontal cortex; ICSS, intracranial self-stimulation; NAcc, nucleus accumbens; NE, norepinephrine; OFC, orbitofrontal cortex; PFC, prefrontal cortex; VTA, ventral tegmental area

Introduction

Drug addiction is a chronic relapsing disorder characterized by compulsive drug-seeking and drug-taking behaviours, despite negative consequences. The American Psychiatric Association (1994) describes substance dependence as a set of symptoms mainly involving the inability to reduce or control drug use, with the recent National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration (SAMHSA, 2007) estimating that 22.6 million Americans 12 years of age or older, or 9.2% of the population, can be considered to have a substance abuse or dependence disorder (including alcohol or illicit drugs). Although evidence shows periodic declines in some areas of abuse patterns, the overall prevalence of substance abuse disorders remains unacceptably high. Moreover, one of the most significant problems for the long-term treatment of drug dependence is the high incidence of relapse to drug-seeking and drug-taking behaviours following months or years of abstinence (Dackis and O'Brien, 2001; Wagner and Anthony, 2002). Given the detrimental social and economic effects of drug addiction, a significant amount of research has been dedicated to ascertaining the neuropharmacological mechanisms mediating the development and persistence of substance abuse disorders. In this section of this special journal issue, we will provide a broad overview of how animal models of addiction and relapse have advanced our understanding of the neurobiology underlying drug-taking and drug-seeking behaviours. More detailed reviews regarding the role of genetics/proteomics (Harris and Mayfield) and neuroplasticity (Thomas, Kalivas and Shaham) in addiction, as well as discussions regarding specific drugs of abuse, including alcohol (Vengeliene, Molander and Spanagel), opiates (Christie), psychostimulants (McGregor), cannabis (Piomelli and Goldberg) and inhalants (Lubman, Yücel and Lawrence), and clinical interface into treatment (Nutt), will be provided in later sections.

Correspondence: Dr MW Feltenstein, Department of Neurosciences, Medical University of South Carolina, 173 Ashley Avenue, Charleston, SC 29425, USA.
E-mail: feltens@musc.edu
Received 30 November 2007; revised 16 January 2008; accepted 25 January 2008; published online 3 March 2008

Theories of addiction

Early theories of addiction postulated that an individual initially consumes a substance for the ability of the agent to

produce a pleasurable effect (that is, reward) and that dependence develops as a function of this recurrent drive for reward (Wise, 1980). This idea of positive reinforcement by drugs of abuse has been widely seen as a primary factor behind drug dependence (Gill *et al*., 1988). However, many drugs produce tolerance with repeated use, in that there is a decrease in the reinforcing properties of the drug, leading to compensatory increases in dosage that can exacerbate neurophysiological alterations prototypical of addiction. Some drugs, including psychostimulants, also produce an opposing response of inverse tolerance, or sensitization, on selected aspects of behaviour (Kalivas and Stewart, 1991; Anagnostaras and Robinson, 1996). Although tolerance and sensitization can concurrently exist and likely involve different properties of the same neural circuits involved, long-term drug use often results in aversive psychological and physiological effects if intake is withheld, thus resulting in continued use as a means to avoid the aversive consequences of drug withdrawal (that is, negative reinforcement) (Cami and Farre, 2003). Although both positive and negative reinforcement theories provide some insight into the initiation and maintenance of compulsive drug use, respectively, these theories are unable to fully explain many aspects of drug dependence, such as the resumption of drug-seeking and drug-taking behaviours following a prolonged period of abstinence (that is, relapse) when overt withdrawal symptoms have long dissipated. Thus, although theories of conditioning (both positive and negative reinforcement) may account for some aspects of the persistence of drug addiction (Wilker, 1973), none of these theories can fully explain all aspects of the addiction cycle. Notably, more recent theories have attempted to comprehensively explain the complexities of addiction by hypothesizing that prolonged drug use results in a series of neuroadaptations, which contribute to the enduring nature of the compulsive addictive state.

In one theory, Koob and Le Moal (1997) have suggested that continued exposure to the abused drug results in a pathological shift of the drug user's hedonic set point and a state of dysregulation of brain reward systems that result in a loss of control over drug intake and compulsive use. That is, drug use produces disequilibrium in brain reward systems for which the individual allostatic processes, or the ability to achieve stability (or homeostasis) through change, cannot be maintained. Enhanced sensitivity and counteradaptation of the brain's reward system are hypothesized to be at the centre of this shift in hedonic homoeostatic regulation, all the while involving opposing alterations in mesolimbic dopamine (DA), opioid and stressor hormone functions. Alternatively, Robinson and Berridge (Robinson and Berridge, 1993; Berridge and Robinson, 1995) have put forward an 'incentive sensitization' theory of addiction, whereby they postulate that abused drugs produce alterations in a number of neural systems, particularly brain areas normally involved in incentive motivation and reward for natural appetitive reinforcers. Chronic drug use results in the addict becoming enduringly hypersensitive to the drug and drug-associated stimuli (for example, Clark and Overton, 1998), leading to a shift from drug 'liking' to drug 'wanting', with ensuing compulsive patterns of drug-seeking behaviour.

More recently, several theories have centred on particular aspects of drug-induced neuroadaptations that may specifically explain the process and persistence of drug addiction. Theories proposed to explain the persistent nature of addictive behaviours include the formation of ingrained drug habits in the form of aberrant stimulus response learning (Wise, 2002; Everitt and Robbins, 2005; Volkow *et al*., 2006), alterations in prefrontal cortical activity leading to reductions in behavioural control and decision-making skills (Jentsch and Taylor, 1999; Franklin *et al*., 2002; Goldstein and Volkow, 2002) and overlaps between limbic and cortical areas involved in addiction and memory (Hyman and Malenka, 2001) that results in maladaptive associative learning (Di Chiara, 1999). Each of these theories contributes unique perspectives and testable hypotheses for addiction research, and there is often considerable overlap among these different perspectives. However, none of these theories can fully account for all aspects of addiction, given the multilayered complexity of addiction states and their prevalency, which must account for biological, sociological, economic, legal and cultural factors. Although advances in neurobiological approaches in humans, notably modern neuroimaging techniques, have allowed researchers to more clearly delineate neural substrates that underlie addiction, we will focus particularly on the utility of animal models in this current review and special journal issue as a means to provide novel insights into the biological basis of addictive behaviours.

Animal models of addiction

Whereas clinical research in human addicts has elucidated the extent, demographics and cycle of substance abuse disorders, a variety of increasingly sophisticated animal models have provided an invaluable means for understanding the neurobiology of addiction and the neuropharmacological action of drugs of abuse. Examples of such models include intracranial self-stimulation (ICSS), conditioned place preference (CPP), behavioural sensitization and self-administration paradigms (Balster, 1991). In the ICSS model, animals previously implanted with intracranial electrodes into certain brain areas (commonly involving the medial forebrain bundle) will respond to receive a short train of electrical stimulation (Gallistel, 1983). In light of the hypothesis that ICSS involves brain areas that are involved in motivation and reward, drugs of abuse have been found to decrease ICSS thresholds (that is, because of their reinforcing properties, addictive drugs reduce the amount of brain stimulation sought by the subject). Moreover, research indicates that the more addictive a substance, the greater its ability to reduce ICSS thresholds (Kornetsky *et al*., 1979; Kornetsky and Bain, 1990), suggesting that this model may provide a means for evaluating an agent's abuse potential. ICSS has also served as a unique experimental tool to assess changes, or dysregulation, in the basal hedonic state of an animal following chronic drug exposure, in that withdrawal from all major drugs of abuse has been shown to produce contrasting increases in ICSS thresholds (Markou and Koob, 1991; Schulteis *et al*., 1994, 1995).

In the CPP model, animals are exposed to an apparatus generally consisting of two initially neutral environments that can differ in terms of a number of stimulus modalities, including colour, texture, odour and lighting (for reviews, see Carr *et al*., 1989; Tzschentke, 1998; Bardo and Bevins, 2000). Animals are exposed to one environment following drug pretreatment, whereas the other environment is paired with vehicle pretreatment. After a number of conditioning sessions, the animals (in a drug-free state) are allowed free access to the apparatus and the preference for one of the two environments is assessed. According to the principles of classical conditioning, if a drug has reinforcing properties, then the animal should prefer the previously drug-paired environment. Consistent with this hypothesis, various drugs of abuse, including opiates, nicotine and cocaine, typically induce CPP (Swerdlow *et al*., 1989). The CPP procedure has proven to be a useful and inexpensive means for assessing rewarding properties in a fairly quick manner, in that animals require no surgery and minimal training (Bardo and Bevins, 2000). CPP is also advantageous in that it can sometimes be established using a single drug pairing, is sensitive to relatively low drug doses and the animal can be tested in a drug-free state (Carr *et al*., 1989). However, the CPP model also possesses a number of limitations, including the methods of drug administration (intraperitoneal or subcutaneous injections), a potential confound of novelty on the test day, difficulties in generating data for dose–effect curves and it has generally only been demonstrated in rodents.

The behavioural sensitization model involves a progressive increase in the motor stimulatory effects of a drug following repeated intermittent administration. The development of behavioural sensitization has been hypothesized to represent a shift from drug 'liking' to 'wanting' underlying compulsive drug use (Robinson and Berridge, 1993). This phenomenon has been demonstrated for a variety of drugs of abuse (Masur and Boerngen, 1980; Bartoletti *et al*., 1983; Kolta *et al*., 1985) and may relate to drug craving and relapse associated with drug addiction (Kalivas *et al*., 1998; Vanderschuren and Kalivas, 2000). Although useful for several aspects of drug-induced neuroplasticity, the behavioural sensitization model, such as CPP, is fundamentally limited because animals never experience contingent drug administration, which is the hallmark of addiction.

Although ICSS, behavioural sensitization and CPP models have been useful for delineating various aspects of the behavioural pharmacology of abused drugs, such as providing a means for evaluating the neurobiology and neurochemical systems underlying the effects of chronic drugs of abuse, the most widely accepted animal model of addiction is the self-administration paradigm. In this model, animals are trained to perform an operant behaviour (for example, lever press or nose poke) to receive a drug reinforcer. Similar to humans, animals will readily self-administer most drugs of abuse (for reviews, see Schuster and Thompson, 1969; Spealman and Goldberg, 1978; Balster and Lukas, 1985; Young and Herling, 1986), including opiates (Weeks, 1962; Blakesley *et al*., 1972), cannabinoids (Takahashi and Singer, 1979; Justinova *et al*., 2003), alcohol (Woods *et al*., 1971; Anderson and Thompson, 1974), nicotine (Hanson *et al*., 1979; Ator and Griffiths, 1983), amphetamines (Pickens *et al*., 1967; Pickens and Harris, 1968; Balster *et al*., 1976) and cocaine (Pickens and Thompson, 1968; Goldberg and Kelleher, 1976), with studies almost universally demonstrating that animals will preferentially respond on a reinforced (that is, active), rather than a non-reinforced (that is, inactive) operandum. Although a variety of species and routes of drug administration can be used, most studies involve the use of rodents (Weeks, 1972; Smith and Davis, 1975) or non-human primates (Deneau *et al*., 1969; Stretch and Gerber, 1970) self-administering drugs orally (Anderson and Thompson, 1974; Yanaura *et al*., 1980), intracranially (Bozarth and Wise, 1981; Phillips *et al*., 1981) or intravenously via a chronic indwelling catheter (Griffiths *et al*., 1978; Spealman and Goldberg, 1978). The abuse potential of a drug in humans can be predicted from animal intravenous self-administration models (Collins *et al*., 1984), which clearly models the clinical abuse of drugs far better than repeated experimenter-delivered drug via intraperitoneal or subcutaneous administration (Markou *et al*., 1993). Given that the self-administration model has demonstrated good face and construct validity, this approach has provided an excellent tool for examining the neuropharmacological and neuroanatomical bases of the acute reinforcing effects of drugs of abuse, as well as their effects throughout the addiction cycle that result in individuals becoming 'addicted' and susceptible to relapse, even following prolonged periods of withdrawal or abstinence.

Drugs of abuse

Drugs of abuse are generally classified into different categories, including narcotics (for example, opiates), cannabinoids (for example, marijuana), depressants (for example, ethanol), stimulants (for example, nicotine, amphetamines and cocaine), hallucinogens (for example, lysergic acid diethylamide and ecstasy) and inhalants (for example, toluene and nitrous oxide). Although these drugs have a common ability to both produce feelings of pleasure and relieve negative emotional states (Nesse and Berridge, 1997), abused drugs have highly diverse behavioural and neuropharmacological properties. For example, in addition to analgesic properties, opiates cause a reduction in anxiety and behavioural inhibition, decreased sensitivity to stimuli, euphoria and sedation (for example, drowsiness and muscle relaxation). Opiates act on a variety of opioid receptor subtypes, including mu (μ), kappa (κ) and delta (δ) receptors. However, it is predominantly their interaction with μ receptors, which are widely dispersed across a variety of brain regions, including the cortex, striatum, thalamus, hippocampus, locus coeruleus, in addition to the ventral tegmental area (VTA), nucleus accumbens (NAcc) and amygdala via direct actions on interneurons, that appear to mediate their behavioural and reinforcing properties. For example, μ receptor-deficient mice fail to display CPP following pretreatment with heroin (Contarino *et al*., 2002), whereas central and systemic administration of opioid receptor antagonists have been shown to change the pattern of morphine (Goldberg *et al*., 1971; Weeks and Collins, 1976) or heroin (Koob *et al*., 1984; Vaccarino *et al*., 1985)

self-administration, an effect consistent with a reduction in its reinforcing properties.

Similar to opiates, both cannabinoids and ethanol produce feelings of euphoria, disinhibition, relaxation and analgesia, as well as impaired performance on cognitive and psychomotor tasks. Δ^9-tetrahydrocannabinol, the active ingredient in cannabis, primarily binds to the cannabinoid receptor CB_1. The CB_1 receptor is highly expressed in a number of brain regions, including the cortex, hippocampus, striatum and cerebellum (Herkenham *et al.*, 1991; Tsou *et al.*, 1998). These receptors are also found in the VTA, NAcc and amygdala via interneurons, and are hypothesized to mediate many of the central properties of cannabinoids, as indicated by an absence of many of its effects in CB_1-deficient mice (Ledent *et al.*, 1999). Whereas Δ^9-tetrahydrocannabinol has rather specific binding properties, the reinforcing effects of ethanol likely occur due to its interaction with a wide variety of neurotransmitter systems, including GABA ($GABA_A$ receptors in the VTA and NAcc), opioid peptides (δ receptors), glutamate (NMDA receptors), ACh (nicotinic receptors) and serotonin (5-HT_3 receptors), with selective antagonists of these receptors reducing self-administration of ethanol in a number of studies (Altshuler *et al.*, 1980; Fadda *et al.*, 1991; Rassnick *et al.*, 1993a).

Similar to other stimulants, nicotine produces an increase in arousal and energy (Benowitz, 1996), an enhancement in cognitive performance and learning (Wesnes *et al.*, 1983; Levin *et al.*, 1998) and a reduction in appetite. Although nicotine increases physiological arousal, smokers report a paradoxical reduction in stress and anxiety after smoking (Nesbitt, 1973), an effect likely contributing to the addictive profile of nicotine. Although an interaction with other neurotransmitter systems may also play a role (for example, glutamate, GABA and opioid peptides; Koob and Le Moal, 2006), nicotine's reinforcing properties appear to be primarily mediated by its direct affinity for nicotinic ACh receptors in the VTA, NAcc and amygdala. Studies using various nicotinic receptor antagonists support this hypothesis in that these agents block nicotine self-administration in rats (Corrigall and Coen, 1989; Corrigall *et al.*, 1994; Watkins *et al.*, 1999), whereas local infusions of nicotinic receptor antagonists into the VTA have been shown to produce similar antagonist effects in self-administration (Corrigall *et al.*, 1994) and ICSS studies (Panagis *et al.*, 2000).

Psychomotor stimulants, such as amphetamines and cocaine, produce similar physiological and subjective effects in humans, including an increase in blood pressure, heart rate and respiration, increased stimulation and confidence, exhilaration, a reduction in fatigue and appetite, as well as increased performance on simple cognitive and motor tasks (Smith and Beecher, 1959; Fischman and Schuster, 1982; Wiegmann *et al.*, 1996). In terms of their neurochemical actions, psychostimulants increase the synaptic availability of several monoamines, including serotonin (5-HT), DA and norepinephrine (NE), either indirectly by inhibiting their reuptake (for example, cocaine; Woolverton and Johnson, 1992) or directly by enhancing their release from presynaptic terminals (for example, amphetamines; (Seiden *et al.*, 1993; Kuczenski and Segal, 1994). However, the acute reinforcing effects of psychostimulants appear to be mediated primarily by increasing synaptic levels of DA in the NAcc via inactivation or reversal of DA transporters. In addition to more specific neurobiological evidence discussed in the next section, data supporting the role of DA in psychostimulant reward include a correlation between DA reuptake blockade and the reinforcing effects of cocaine (Ritz *et al.*, 1987) or D-amphetamine (Ritz and Kuhar, 1989), as well as a positive relationship between DA transporter occupancy and the reported subjective effects of cocaine in humans (Volkow *et al.*, 1997). However, some studies have questioned the primacy of enhanced DA levels as the main explanation for the reinforcing properties of psychostimulants, in that DA transporter knockout mice will readily self-administer cocaine (Rocha *et al.*, 1998). Although initially interpreted as a strike against the DA hypothesis of reinforcement, it has subsequently been demonstrated that there is an increase in NAcc DA levels in DA transporter knockout mice exposed to cocaine or amphetamine. However, these effects are likely due to inactivation of NE (Carboni *et al.*, 2001) and/or 5-HT (Mateo *et al.*, 2004) transporters, thus supporting the major tenet that DA likely underlies psychostimulant reinforcement.

Common neurobiology of addictive drug action

Although drugs of abuse often produce differential behavioural effects and have diverse pharmacological profiles, one common feature they share is an enhancement in mesocorticolimbic DA activity (Wise, 1996), albeit their interaction with this system occurs at different levels (Cami and Farre, 2003). This circuit, which has been extensively implicated for its involvement in the rewarding properties of both natural stimuli (for example, food, drink and sex) and addictive drugs, consists of DA projections from cell bodies in the VTA to limbic structures (that is, mesolimbic pathway, such as the amygdala, ventral pallidum, hippocampus and NAcc) and cortical areas (that is, mesocortical pathway, including the prefrontal cortex (PFC), the orbitofrontal cortex (OFC) and the anterior cingulate). Interestingly, these corticostriatolimbic circuits operate in parallel, but may have somewhat different roles in addiction (Cami and Farre, 2003). For example, whereas the NAcc (Di Chiara, 2002) and ventral pallidum appear to be involved in the primary reinforcing effects of drugs of abuse (Volkow *et al.*, 2003), the amygdala and hippocampus play an important role in conditioned learning engaged in the process of addiction. In the case of the amygdala (See, 2005) and ventral hippocampus (Rogers and See, 2007), this learning involves discrete stimulus–reward associations, whereas the dorsal hippocampus mediates stimulus–stimulus associations that may be particularly important for contextual learning (Fuchs *et al.*, 2005, 2007). On the other hand, the PFC, OFC and anterior cingulate regulate emotional responses, cognitive control and executive function (Volkow *et al.*, 1993), with repeated drug exposure leading to cellular adaptations of the prefrontal–Nacc glutamatergic pathway that contribute to persistent addictive behaviours, including diminished cognitive control and hyper-responsiveness to drug-associated stimuli (Kalivas and Volkow, 2005). Taken

together, these results suggest that the mesolimbic pathway is involved in the acute reinforcing effects of drugs and various conditioned responses related to craving and relapse, whereas changes in the mesocortical pathway mediate the conscious drug experience, drug craving and a loss of behavioural inhibition related to compulsive drug-seeking and drug-taking behaviours.

In general, all addictive drugs produce an enhancement in extracellular DA levels in the NAcc. DA release appears necessary for reward (Di Chiara and Imperato, 1988; Koob and Bloom, 1988), an effect hypothesized to provide positive reinforcement for drug self-administration and, as such, the initiation of the addiction cycle. Although natural reinforcers also produce an increase in DA release, the effect is not nearly as robust, and unlike addictive drugs, undergoes habituation (Di Chiara, 1999). These differences suggest that drugs of abuse not only 'hijack' a system normally implicated in the rewarding and reinforcing effects of stimuli involved in survival functions (Robbins and Everitt, 1996) but also the effect is persistent, adding to the consolidation of responses to drug-associated stimuli (Berke and Hyman, 2000) and further promoting the repeated use of the addictive substance.

Evidence implicating the mesolimbic DA system in the reinforcing effects of drugs of abuse includes findings that lesions of the NAcc, VTA and ventral pallidum severely attenuate cocaine and heroin self-administration (Roberts *et al*., 1980; Roberts and Koob, 1982; Hubner and Koob, 1990). Furthermore, extracellular DA levels are reliably increased in the NAcc during cocaine self-administration (Weiss *et al*., 1992; Meil *et al*., 1995; Wise *et al*., 1995b), whereas systemic administration of DA synthesis inhibitors (for example, Pickens *et al*., 1968; Wilson and Schuster, 1974) and DA antagonists (for example, Yokel and Wise, 1975; Woolverton, 1986; Rassnick *et al*., 1992; Richardson *et al*., 1994) have been shown to decrease the self-administration of a variety of drugs in animals, including cocaine, amphetamines, opiates and ethanol. More specific manipulations of the mesocorticolimbic system have demonstrated a similar effect for some drugs, in that kainic acid lesions of cell bodies in the NAcc block cocaine, heroin (Zito *et al*., 1985) and morphine self-administration (Dworkin *et al*., 1988b). Although DA receptor antagonist infusions or selective lesions of DA neurons in the NAcc using 6-hydroxydopamine (6-OHDA) can block psychostimulant self-administration (Roberts *et al*., 1977; Lyness *et al*., 1979), these manipulations generally fail to affect the self-administration of ethanol (Rassnick *et al*., 1993b) or opiates (Ettenberg *et al*., 1982; Pettit *et al*., 1984; Dworkin *et al*., 1988a), suggesting DA-independent mechanisms of reinforcement. In support of this hypothesis, intracranial or systemic administration of various opiate receptor antagonists has been found to attenuate heroin (Bozarth and Wise, 1983; Corrigall and Vaccarino, 1988) or ethanol (Altshuler *et al*., 1980; Samson and Doyle, 1985) self-administration. The endogenous cannabinoid system may also play a role in opiate and ethanol reward, in that genetic deletion (Ledent *et al*., 1999; Hungund *et al*., 2003) or antagonism of CB_1 receptors (Caillé and Parsons, 2003; Colombo *et al*., 2005) results in reduced ethanol or opiate intake. However, some evidence supports the notion that ethanol and opiates produce reinforcement by mesolimbic DA release (Johnson and North, 1992; Weiss *et al*., 1993), suggesting that their reinforcing properties likely involve both DA-dependent and -independent mechanisms (Van Ree *et al*., 1999).

In support of the hypothesized role of DA in opiate and ethanol reinforcement, *in vivo* microdialysis studies have demonstrated an increase in extracellular DA in the shell of the NAcc in animals during active self-administration of morphine (Pontieri *et al*., 1995), heroin (Hemby *et al*., 1995; Wise *et al*., 1995a) and ethanol (Weiss *et al*., 1993; Melendez *et al*., 2002; van Erp and Miczek, 2007). Similar effects have been reported during active self-administration for a variety of other drugs of abuse, including cannabinoids (Fadda *et al*., 2006; Lecca *et al*., 2006a), nicotine (Pontieri *et al*., 1996; Lecca *et al*., 2006b), amphetamines (Di Ciano *et al*., 1995; Pontieri *et al*., 1995) and cocaine (Hurd *et al*., 1989; Pettit and Justice, 1989; Di Ciano *et al*., 1995; Pontieri *et al*., 1995). Interestingly, some studies (for example, ethanol; Melendez *et al*., 2002; van Erp and Miczek, 2007) have reported an increase in DA immediately prior to the initiation of the self-administration session, indicating that conditioned increases in NAcc DA occur when animals 'anticipate' drug consumption. Similar effects have been demonstrated when animals are exposed to reward-associated cues (Tobler *et al*., 2003; Cheer *et al*., 2007), suggesting that sensitization of mesoaccumbens DA release may result in the enhancement of the motivational value of drug-associated stimuli (Schultz *et al*., 1997).

Finally, animals will consistently respond for intracranial microinjections of various drugs of abuse (Myers, 1974; Bozarth, 1987), further supporting the role of the mesocorticolimbic system in addiction. Although laboratory animals will reliably self-administer opioids, such as morphine and fentanyl, into a number of mesocorticolimbic brain areas, including the VTA (Van Ree and de Wied, 1980; Bozarth and Wise, 1981, 1982) and NAcc (Olds, 1982), this effect appears relatively selective as animals will not self-administer opiates into other brain regions. Similarly, both alcohol-preferring and Wistar rats have been shown to self-administer a variety of doses of ethanol into the VTA (Gatto *et al*., 1994; Rodd *et al*., 2004a, b), with both groups of rats reducing responding when artificial CSF was substituted for ethanol. Rats and monkeys will also self-administer microinjections of amphetamine into a number of brain nuclei integrated within the mesocorticolimbic system, such as the OFC (Phillips *et al*., 1981), amygdala (Chevrette *et al*., 2002) and NAcc (Monaco *et al*., 1981; Chevrette *et al*., 2002). In one study (Hoebel *et al*., 1983), rats with NAcc cannulae responded preferentially on an active lever and demonstrated an alteration in lever preference when the response outcome was switched to the previously inactive lever. Moreover, responding was appropriately reduced when animals were pretreated with amphetamine and demonstrated extinction-like responding when reinforcer delivery was switched to ventricular delivery. Rats self-administering cocaine demonstrate a similar pattern of neuroanatomical specificity, in that they will respond for microinfusions of cocaine into the shell, but not the core, of the NAcc (Rodd-Henricks *et al*., 2002), whereas other studies have demonstrated similar drug

self-administration into the VTA (Rodd *et al.*, 2005). Although GABA, glutamate, opioid peptide and endocannabinoid systems are also significantly involved in the acute reinforcing effects of drugs of abuse (particularly non-psychostimulants), the majority of results suggest that the mesocorticolimbic DA system plays a pivotal role in the reinforcing properties of drugs and, as such, the initiation of the addiction cycle. It is also possible, however, that DA in chronic addiction is less involved with the unconditioned reinforcing effects of drugs (that is, 'liking') and has more to do with the persistence of addictive behaviours by enhancing incentive salience to reward-associated stimuli (that is, 'wanting') (Berridge, 2007).

Neurobiology of drug dependence and relapse

In contrast to initial increases in neurotransmitter activity following acute drug exposure (for example, DA and glutamate) (Ungless *et al.*, 2001; Vorel *et al.*, 2002), research indicates that chronic administration leads to more complex changes in activity in the NAcc, especially during prolonged withdrawal. Some examples include alterations in GABA neurotransmission during alcohol withdrawal (Dahchour and De Witte, 2000), downregulation of nicotinic receptors during nicotine withdrawal (Mugnaini *et al.*, 2006) and a reduction in DA neurotransmission (Weiss *et al.*, 1992; Chefer and Shippenberg, 2002), and opposing opioid receptor responses (Koob *et al.*, 1992) in the NAcc throughout psychostimulant and opioid withdrawal, respectively. Similarly, all drugs of abuse have been shown to produce dysregulations in brain stress systems (for example, alterations in adrenocorticotrophic hormone, corticosterone and corticotropin-releasing factor (CRF) activity) (for reviews, see Kreek and Koob, 1998; Koob, 1999; Koob and Kreek, 2007). These persistent alterations in stress hormone systems, receptor and/or neurotransmitter activity may represent compensatory mechanisms involving neuroadaptations aimed at restoring homoeostatic function in response to the presence of the drug. As such, these changes could contribute significantly to negative emotional states characteristic of acute drug withdrawal, as well as enhanced sensitivity to stressful stimuli, both of which could result in greater vulnerability to relapse during abstinence in humans (Koob and Le Moal, 1997; Weiss *et al.*, 2001).

As previously mentioned, relapse to drug-seeking and drug-taking behaviours following prolonged periods of abstinence constitutes one of the most significant problems for the long-term treatment of drug-dependent individuals (Dackis and O'Brien, 2001; Wagner and Anthony, 2002). A number of factors are known to contribute to craving and relapse, including exposure to environmental stimuli previously paired with drug use (that is, conditioned drug cues), negative mood states or stress. For example, abstinent cocaine users report greater drug craving following exposure to cocaine-associated stimuli (Childress *et al.*, 1993), in response to non-contingent cocaine doses (Jaffe *et al.*, 1989), and following stressful life events (Sinha *et al.*, 1999). These trigger factors have been used in animal models of relapse to drug-seeking behaviour, particularly in the extinction–reinstatement model following withdrawal from chronic drug self-administration (See, 2002; Shaham *et al.*, 2003). Typically, animals are trained to self-administer a drug (for example, cocaine) for prolonged periods of time. After chronic self-administration, animals experience extinction training, whereby responding on the previous drug-paired lever does not result in primary reinforcement. Extinction allows for a low baseline against which operant responding can be compared when the subjects are re-exposed to previously drug-paired cues (these may be discrete conditioned stimuli or contextual stimuli), non-contingent drug administration or exposure to environmental stressors (for example, footshock). Conditioned cues, drug priming and stress have all been shown to robustly reinstate drug-seeking behaviour (that is, induce relapse) as indexed by an increase in responding on a previously drug-paired operandum (Shaham *et al.*, 2003). The development and application of the reinstatement model have been very useful for extensive exploration of the neural circuitry underlying relapse (Meil and See, 1997; Neisewander *et al.*, 2000; Weiss *et al.*, 2000; Kruzich and See, 2001).

Using the reinstatement model of relapse, a number of laboratories have contributed to mapping the neurocircuitry necessary to maintain relapse-like behaviour. In studies that have examined cue-induced drug-seeking behaviour, a significant amount of evidence has shown an important role for the dorsomedial PFC (dmPFC) and amygdala (particularly an area comprised of the lateral and basal nuclei or basolateral amygdala (BLA)), via glutamatergic and DAergic interactions with the NAcc core. For example, exposure to explicit heroin-associated cues (Koya *et al.*, 2006) or discriminative stimuli predicting cocaine (Ciccocioppo *et al.*, 2001) or ethanol availability (Dayas *et al.*, 2007) results in concurrent increases in drug-seeking behaviour and Fos expression in the dmPFC, an effect that can be blocked by D_1 receptor antagonism (Ciccocioppo *et al.*, 2001). Moreover, reversible inactivation of the dmPFC using the sodium channel blockers tetrodotoxin (McLaughlin and See, 2003) or lidocaine (Di Pietro *et al.*, 2006), or the $GABA_A$ and $GABA_B$ agonists, muscimol and baclofen (Rogers *et al.*, 2008) has been shown to inhibit the reinstatement of drug seeking when rats are exposed to explicit cocaine- or heroin-associated cues. Similar inactivation of the lateral, but not medial, OFC has been shown to produce a comparable effect on the reinstatement of cocaine-seeking behaviour (Fuchs *et al.*, 2004b).

Consistent with brain imaging studies indicating an increase in metabolic activity in the amygdala when abstinent cocaine users are presented with drug-associated cues or drug-related imagery (Grant *et al.*, 1996; Childress *et al.*, 1999; Kilts *et al.*, 2001, 2004; Bonson *et al.*, 2002), permanent lesions or reversible inactivation of the BLA have been shown to decrease responding for stimuli associated with cocaine reinforcement (Whitelaw *et al.*, 1996; Meil and See, 1997; Grimm *et al.*, 2000), as well as prevent the acquisition (Kruzich and See, 2001), consolidation (Fuchs *et al.*, 2006b) and expression (Kruzich and See, 2001; Fuchs and See, 2002; McLaughlin and See, 2003; Rogers *et al.*, 2008) of cocaine- or heroin-conditioned-cued reinstatement, suggesting that the BLA is critical for both the formation of

stimulus–drug associations and expression of conditioned-cued drug-seeking behaviour during relapse. In support of a major role of ascending DA inputs from the VTA, presentation of conditioned stimuli associated with cocaine availability significantly elevates extracellular levels of DA in the BLA (Weiss *et al*., 2000), whereas infusions of D-amphetamine into the BLA produces a significant enhancement of responding in the presence of drug-paired cues, with similar treatment failing to affect responding during extinction training (Ledford *et al*., 2003). Conversely, DA receptor antagonism in the BLA has been found to attenuate both the acquisition (Berglind *et al*., 2006) and expression (See *et al*., 2001) of conditioned-cued reinstatement, as well as cocaine-seeking behaviour using a second-order schedule of reinforcement (Di Ciano and Everitt, 2004b). Increases in amygdalar levels of Fos (Neisewander *et al*., 2000; Ciccocioppo *et al*., 2001) or Fos-related antigen (Franklin and Druhan, 2000) expression when animals are exposed to a cocaine-paired environment or cocaine-associated cues can also be reversed by DA D_1 receptor antagonism (Ciccocioppo *et al*., 2001). In addition to DA, cholinergic inputs to the BLA are critical for the acquisition, but not expression, of conditioned-cued reinstatement of cocaine seeking (See *et al*., 2003). Although the NMDA receptor antagonist D-2-amino-5-phosphonovalerate (D-AP5) has been shown to attenuate the acquisition and consolidation of drug-paired stimulus learning (Feltenstein and See, 2007), intra-BLA infusions of NMDA and kainite/AMPA antagonists do not have any significant effect on the expression of conditioned-cued reinstatement (See *et al*., 2001). Overall, these results show that different afferent systems can regulate temporally unique aspects of amygdalar processing of drug-paired stimuli.

Similar to the BLA, a considerable amount of evidence has shown that the NAcc plays a key role in cue-induced reinstatement of drug seeking. For example, reversible inactivation of the NAcc core has been shown to selectively decrease cocaine seeking in both conditioned-cued reinstatement and second-order schedule of reinforcement models (Di Ciano and Everitt, 2004a; Fuchs *et al*., 2004a; Di Ciano *et al*., 2008). Exposing rats to an ethanol-associated discriminative stimulus resulted in the reinstatement of extinguished ethanol seeking, as well as an increase in Fos expression in the NAcc (Dayas *et al*., 2007). Moreover, microdialysis studies have indicated that exposure to discriminative stimuli predictive of cocaine availability causes an increase in DA in the NAcc (Weiss *et al*., 2000). More recently, Bossert *et al*. (2007) demonstrated an interesting dissociation between the role of DA D_1 receptors in the NAcc core and shell in respectively mediating drug-seeking behaviour following exposure to discrete cue or contextual stimuli associated with previous heroin reinforcement. Other neurotransmitter systems in the NAcc, including ACh and glutamate, also play important roles in drug-seeking behaviour. In one study, synaptic enhancement of NAcc ACh levels via systemic or microinjections of physostigmine (an acetylcholinesterase inhibitor) was found to inhibit the reinstatement of heroin seeking by conditioned cues (Zhou *et al*., 2007). In contrast to this effect, AMPA administration alone resulted in the reinstatement of extinguished cocaine-seeking behaviour (Cornish *et al*., 1999), whereas AMPA/kainate and/or NMDA receptor antagonism has been shown to block cocaine-seeking behaviour following exposure to drug-associated cues in a second-order schedule (Di Ciano and Everitt, 2001; Backstrom and Hyytia, 2007). Overall, these results collectively suggest that the reinstatement of drug-seeking behaviour following exposure to discrete or contextual drug-associated cues involves DAergic and glutamatergic interactions between the NAcc core and the BLA and dmPFC.

Similar to conditioned-cued reinstatement, a considerable amount of research suggests that the dmPFC and the NAcc core, as well as the VTA, mediate relapse behaviour following non-contingent exposure to the previously self-administered drug (McFarland and Kalivas, 2001). Inactivation of any of these three regions, in addition to the ventral pallidum, was found to dose-dependently attenuate cocaine-primed (Grimm and See, 2000; McFarland and Kalivas, 2001; Capriles *et al*., 2003) and heroin-primed (Rogers *et al*., 2008) reinstatement. Moreover, direct infusions of cocaine or DA into the dmPFC have been shown to reinstate cocaine seeking (McFarland and Kalivas, 2001; Park *et al*., 2002), whereas D_1/D_2 receptor antagonists in the dmPFC have the opposite effect (McFarland and Kalivas, 2001, but see Capriles *et al*., 2003). Although DA receptor antagonism was ineffective in the NAcc core (McFarland and Kalivas, 2001), infusions of the selective DA D_1 antagonist SCH-23390 into the shell of the NAcc did attenuate cocaine-primed reinstatement (Anderson *et al*., 2003), suggesting that DA in both subregions of the NAcc can regulate cocaine-primed reinstatement.

Further support for accumbal regulation of cocaine-primed reinstatement comes from studies showing that direct infusions of DA or glutamate into the NAcc can induce reinstatement of extinguished cocaine-seeking behaviour (Cornish *et al*., 1999; McFarland and Kalivas, 2001), an effect consistent with the observation that increases in DA, as well as glutamate, occur in the NAcc when animals are given a priming injection of cocaine (McFarland *et al*., 2003). More specific manipulations of glutamatergic function have shown that AMPA/kainic acid, but not NMDA, receptor antagonists can block cocaine-primed reinstatement when infused into the NAcc core (Cornish and Kalivas, 2000), whereas AMPA receptor agonists alone can elicit reinstatement responding (Cornish *et al*., 1999). Thus, although glutamate (via AMPA receptors) appears to play a more pivotal role in the NAcc core, it appears that DA in the shell of the NAcc may also functionally mediate cocaine-primed reinstatement.

As previously described, stress plays an important role in the vulnerability and motivation to abuse addictive substances (Higgins and Marlatt, 1975; Russell and Mehrabian, 1975; Koob and Le Moal, 2001). In animal models of relapse, reinstatement of drug seeking has been demonstrated using various stressors, including acute footshock exposure (Erb *et al*., 1996; Piazza and Le Moal, 1998; McFarland *et al*., 2004) and pretreatment with the NE α_2 receptor antagonist, yohimbine (Lee *et al*., 2004; Shepard *et al*., 2004; Le *et al*., 2005; Feltenstein and See, 2006), a drug that produces anxiety-like states in both humans (Holmberg and Gershon,

1961; Charney *et al*., 1983) and animals (Lang and Gershon, 1963; Davis *et al*., 1979), and increases drug craving in abstinent drug-dependent subjects (Stine *et al*., 2002). Examination of the neurocircuitry involved in stress-induced reinstatement has produced data suggesting that there is some overlap, as well as distinct differences, in these circuits relative to neural regulation of other types of reinstatement behaviour (Stewart, 2000; Shaham *et al*., 2003). Similar to cue- and drug-primed reinstatement studies, reversible inactivation of the dmPFC, NAcc or VTA has been shown to attenuate footshock stress-induced reinstatement of cocaine seeking, with data suggesting a unique role for the central nucleus of the amygdala (CeA) and the lateral bed nucleus of the stria terminalis (BNST) in mediating this behaviour (Capriles *et al*., 2003; McFarland *et al*., 2004). In studies examining specific neurotransmitter systems, CRF and NE, likely via interactions between the BNST and CeA, appear to be critically and selectively involved in stress-induced reinstatement. For example, systemic and intra-BNST and/or CeA administration of CRF (Shaham *et al*., 1997; Erb *et al*., 1998; Erb and Stewart, 1999; Le *et al*., 2000), or reduced NE activity via agonist activation of presynaptic α_2-adrenoceptors or blockade of postsynaptic β-adrenoceptors (Erb *et al*., 2000; Shaham *et al*., 2000; Highfield *et al*., 2001; Leri *et al*., 2002), have been shown to attenuate footshock induced-reinstatement of drug seeking. Interestingly, and in contrast to cue- and drug-primed reinstatement, DA appears to play only a modulatory role in stress-induced reinstatement (Shaham and Stewart, 1996). However, based on evidence that DA D_2 antagonist infusions into the dmPFC or OFC have been shown to block footshock-induced reinstatement of cocaine-seeking behaviour (Capriles *et al*., 2003), further study is warranted to explore the regionally selective role of DA in mediating these behaviours. Overall, results to date suggest that CRF and NE interactions within the CeA and BNST, as well as interactions of this pathway with the dmPFC and NAcc, may be critically involved in increased drug craving and a return to drug-seeking behaviour when addicts are exposed to stressful stimuli.

In summary, it appears that three distinct, yet overlapping, neurocircuits are involved in cue-, drug- and stress-induced reinstatement of drug-seeking behaviour (Kalivas and McFarland, 2003; Shaham *et al*., 2003). A series of projections, primarily involving DA and glutamate, from the VTA, BLA, dmPFC and NAcc core, appear to be the primary pathway mediating conditioned-cued reinstatement. Drug-primed reinstatement likely involves dmPFC glutamatergic projections to the NAcc core and DA innervations of the dmPFC and NAcc shell. Finally, stress-induced reinstatement involves noradrenergic and CRF inputs to the CeA and BNST that serially project to the dmPFC and NAcc core. Thus, although distinct in a number of aspects, this suggests that projections from the VTA (all forms of reinstatement), limbic regions of the BLA (cue reinstatement), CeA, BNST and NAcc shell (stress reinstatement) converge on motor pathways involving the dmPFC and NAcc core that represents a 'final common pathway' for all three types of instigating factors in relapse. It is important to note that additional research has demonstrated that other brain structures can play critical roles in driving drug-seeking behaviour, and that this is often dependent upon the nature of the withdrawal history or contextual environment that triggers relapse. For example, recent studies in humans (Volkow *et al*., 2006; Wong *et al*., 2006) have shown that increases in craving for cocaine are correlated with increases in DA in the dorsal striatum (caudate–putamen). In a similar manner, pharmacological blockade of the dorsolateral striatum can attenuate drug-seeking behavior in rats after forced abstinence (Fuchs *et al*., 2006a; See *et al*., 2007) or on a second-order schedule of reinforcement (Vanderschuren *et al*., 2005). Moreover, it has recently been demonstrated that the dorsal hippocampus (Fuchs *et al*., 2005) and NAcc shell, but not NAcc core (Bossert *et al*., 2007), play a significant role in contextual reinstatement of drug-seeking behaviour. Finally, the neuropeptide orexin (also known as hypocretin), which is predominately located in neurons in the lateral hypothalamus, has recently been found to play a significant role in mediating drug addiction and relapse (Harris *et al*., 2005), including the reinstatement of cocaine (Boutrel *et al*., 2005) and alcohol (Lawrence *et al*., 2006) -seeking behaviour following exposure to an acute stressor or drug-associated cues.

Conclusions

As a chronic disease (Meyer, 1996), drug addiction involves a number of personal, social and medical difficulties that usually persist for months or years after detoxification. Given the large social and economic impact of this disease, a considerable amount of research has sought to elucidate the role that behavioural and neuropharmacological factors may contribute to the transition from acute drug use to drug dependence, loss of control over use and compulsive drug-seeking behaviours that characterize addiction. From a neurobiological perspective, animal models have provided an invaluable means for determining the fundamental neurobiology involved in drug-seeking and drug-taking behaviours across the entire addiction cycle, including the acute reinforcing effects of drugs, neuroadaptational changes that occur during the transition to drug dependence and the relatively permanent alterations in these systems that underlie relapse. In general, research suggests that the mesocorticolimbic pathway, including the VTA, NAcc, amygdala and PFC via DA and glutamatergic pathways, plays a significant role in addiction. Notably, variations in neurotransmitter and/or neural systems have been seen across various classes of abused drugs and across different phases of the addiction cycle (for example, drug-taking versus drug-seeking behaviours). Although the current review has highlighted a number of findings on the general neural circuitry of addiction and relapse, latter sections in this issue will provide more comprehensive examinations of selective topics, including molecular, behavioural and neurobiological factors in addiction, the role and interaction of genes and the environment in addictive behaviours, and specific drugs of abuse. With a better understanding of the neurobiological factors that underlie drug addiction, continued preclinical and clinical research should aid in the

development of novel therapeutic interventions that may result in effective long-term treatment strategies for drug-dependent individuals.

Acknowledgements

This research was supported by National Institute on Drug Abuse Grants DA010462, DA015369, DA016511 (RES) and DA07288 (MWF) and NIH Grant C06 RR015455.

Conflict of interest

The authors state no conflict of interest.

References

Altshuler HL, Phillips PE, Feinhandler DA (1980). Alteration of ethanol self-administration by naltrexone. *Life Sci* **26**: 679–688.

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Press: Washington, DC.

Anagnostaras SG, Robinson TE (1996). Sensitization to the psychomotor stimulant effects of amphetamine: modulation by associative learning. *Behav Neurosci* **110**: 1397–1414.

Anderson SM, Bari AA, Pierce RC (2003). Administration of the D1-like dopamine receptor antagonist SCH-23390 into the medial nucleus accumbens shell attenuates cocaine priming-induced reinstatement of drug-seeking behavior in rats. *Psychopharmacology (Berl)* **168**: 132–138.

Anderson WW, Thompson T (1974). Ethanol self-administration in water satiated rats. *Pharmacol Biochem Behav* **2**: 447–454.

Ator NA, Griffiths RR (1983). Nicotine self-administration in baboons. *Pharmacol Biochem Behav* **19**: 993–1003.

Backstrom P, Hyytia P (2007). Involvement of AMPA/kainate, NMDA, and mGlu5 receptors in the nucleus accumbens core in cue-induced reinstatement of cocaine seeking in rats. *Psychopharmacology (Berl)* **192**: 571–580.

Balster RL (1991). Drug abuse potential evaluation in animals. *Br J Addict* **86**: 1549–1558.

Balster RL, Kilbey MM, Ellinwood Jr EH (1976). Methamphetamine self-administration in the cat. *Psychopharmacologia* **46**: 229–233.

Balster RL, Lukas SE (1985). Review of self-administration. *Drug Alcohol Depend* **14**: 249–261.

Bardo MT, Bevins RA (2000). Conditioned place preference: what does it add to our preclinical understanding of drug reward? *Psychopharmacology (Berl)* **153**: 31–43.

Bartoletti M, Gaiardi M, Gubellini G, Bacchi A, Babbini M (1983). Long-term sensitization to the excitatory effects of morphine: a motility study in post-dependent rats. *Neuropharmacology* **22**: 1193–1196.

Benowitz NL (1996). Pharmacology of nicotine: addiction and therapeutics. *Annu Rev Pharmacol Toxicol* **36**: 597–613.

Berglind WJ, Case JM, Parker MP, Fuchs RA, See RE (2006). Dopamine D1 or D2 receptor antagonism within the basolateral amygdala differentially alters the acquisition of cocaine-cue associations necessary for cue-induced reinstatement of cocaine-seeking. *Neuroscience* **137**: 699–706.

Berke JD, Hyman SE (2000). Addiction, dopamine, and the molecular mechanisms of memory. *Neuron* **25**: 515–532.

Berridge KC (2007). The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology (Berl)* **191**: 391–431.

Berridge KC, Robinson TE (1995). The mind of an addicted brain: neural sensitization of wanting versus liking. *Curr Dir Psychol Sci* **4**: 71–76.

Blakesley BC, Dinneen LC, Elliott RD, Francis DL (1972). Intravenous self-administration of heroin in the rat: experimental technique and computer analysis. *Br J Pharmacol* **45**: 181P–182P.

Bonson KR, Grant SJ, Contoreggi CS, Links JM, Metcalfe J, Weyl HL *et al.* (2002). Neural systems and cue-induced cocaine craving. *Neuropsychopharmacology* **26**: 376–386.

Bossert JM, Poles GC, Wihbey KA, Koya E, Shaham Y (2007). Differential effects of blockade of dopamine D1-family receptors in nucleus accumbens core or shell on reinstatement of heroin seeking induced by contextual and discrete cues. *J Neurosci* **27**: 12655–12663.

Boutrel B, Kenny PJ, Specio SE, Martin-Fardon R, Markou A, Koob GF *et al.* (2005). Role for hypocretin in mediating stress-induced reinstatement of cocaine-seeking behavior. *Proc Natl Acad Sci USA* **102**: 19168–19173.

Bozarth MA (1987). Intracranial self-administration procedures for the assessment of drug reinforcement. In: Bozarth MA (ed). *Methods of Assessing the Reinforcing Properties of Abused Drugs*. Springer-Verlag: New York. pp 173–187.

Bozarth MA, Wise RA (1981). Intracranial self-administration of morphine into the ventral tegmental area in rats. *Life Sci* **28**: 551–555.

Bozarth MA, Wise RA (1982). Localization of the reward-relevant opiate receptors. *NIDA Res Monogr* **41**: 158–164.

Bozarth MA, Wise RA (1983). Neural substrates of opiate reinforcement. *Prog Neuropsychopharmacol Biol Psychiatry* **7**: 569–575.

Caillé S, Parsons LH (2003). SR141716A reduces the reinforcing properties of heroin but not heroin-induced increases in nucleus accumbens dopamine in rats. *Eur J Neurosci* **18**: 3145–3149.

Cami J, Farre M (2003). Drug addiction. *N Engl J Med* **349**: 975–986.

Capriles N, Rodaros D, Sorge RE, Stewart J (2003). A role for the prefrontal cortex in stress- and cocaine-induced reinstatement of cocaine seeking in rats. *Psychopharmacology (Berl)* **168**: 66–74.

Carboni E, Spielewoy C, Vacca C, Nosten-Bertrand M, Giros B, Di Chiara G (2001). Cocaine and amphetamine increase extracellular dopamine in the nucleus accumbens of mice lacking the dopamine transporter gene. *J Neurosci* **21 RC141**: 1–4.

Carr GD, Fibiger HC, Phillips AG (1989). Conditioned place preference as a measure of drug reward. In: Liebman JM, Cooper SJ (eds). *The Neuropharmacological Basis of Reward*. Clarendon Press: Oxford. pp 264–319.

Charney DS, Heninger GR, Redmond Jr DE (1983). Yohimbine induced anxiety and increased noradrenergic function in humans: effects of diazepam and clonidine. *Life Sci* **33**: 19–29.

Cheer JF, Aragona BJ, Heien ML, Seipel AT, Carelli RM, Wightman RM (2007). Coordinated accumbal dopamine release and neural activity drive goal-directed behavior. *Neuron* **54**: 237–244.

Chefer VI, Shippenberg TS (2002). Changes in basal and cocaine-evoked extracellular dopamine uptake and release in the rat nucleus accumbens during early abstinence from cocaine: quantitative determination under transient conditions. *Neuroscience* **112**: 907–919.

Chevrette J, Stellar JR, Hesse GW, Markou A (2002). Both the shell of the nucleus accumbens and the central nucleus of the amygdala support amphetamine self-administration in rats. *Pharmacol Biochem Behav* **71**: 501–507.

Childress AR, Hole AV, Ehrman RN, Robbins SJ, McLellan AT, O'Brien CP (1993). Cue reactivity and cue reactivity interventions in drug dependence. *NIDA Res Monogr* **137**: 73–95.

Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP (1999). Limbic activation during cue-induced cocaine craving. *Am J Psychiatry* **156**: 11–18.

Ciccocioppo R, Sanna PP, Weiss F (2001). Cocaine-predictive stimulus induces drug-seeking behavior and neural activation in limbic brain regions after multiple months of abstinence: reversal by D1 antagonists. *Proc Natl Acad Sci USA* **98**: 1976–1981.

Clark D, Overton PG (1998). Alterations in excitatory amino acid-mediated regulation of midbrain dopaminergic neurones induced by chronic psychostimulant administration and stress: relevance to behavioural sensitization and drug addiction. *Addict Biol* **3**: 109–135.

Collins RJ, Weeks JR, Cooper MM, Good PI, Russell RR (1984). Prediction of abuse liability of drugs using IV self-administration by rats. *Psychopharmacology (Berl)* **82**: 6–13.

Colombo G, Serra S, Vacca G, Carai MA, Gessa GL (1984). Endocannabinoid system and alcohol addiction: pharmacological studies. *Pharmacol Biochem Behav* **81**: 369–380.

Contarino A, Picetti R, Matthes HW, Koob GF, Kieffer BL, Gold LH (2002). Lack of reward and locomotor stimulation induced by heroin in mu-opioid receptor-deficient mice. *Eur J Pharmacol* **446**: 103–109.

Cornish JL, Duffy P, Kalivas PW (1999). A role for nucleus accumbens glutamate transmission in the relapse to cocaine-seeking behavior. *Neuroscience* **93**: 1359–1367.

Cornish JL, Kalivas PW (2000). Glutamate transmission in the nucleus accumbens mediates relapse in cocaine addiction. *J Neurosci* **20**: RC89.

Corrigall WA, Coen KM (1989). Nicotine maintains robust self-administration in rats on a limited-access schedule. *Psychopharmacology (Berl)* **99**: 473–478.

Corrigall WA, Coen KM, Adamson KL (1994). Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. *Brain Res* **653**: 278–284.

Corrigall WA, Vaccarino FJ (1988). Antagonist treatment in nucleus accumbens or periaqueductal grey affects heroin self-administration. *Pharmacol Biochem Behav* **30**: 443–450.

Dackis CA, O'Brien CP (2001). Cocaine dependence: a disease of the brain's reward centers. *J Subst Abuse Treat* **21**: 111–117.

Dahchour A, De Witte P (2000). Taurine blocks the glutamate increase in the nucleus accumbens microdialysate of ethanol-dependent rats. *Pharmacol Biochem Behav* **65**: 345–350.

Davis M, Redmond Jr DE, Baraban JM (1979). Noradrenergic agonists and antagonists: effects on conditioned fear as measured by the potentiated startle paradigm. *Psychopharmacology (Berl)* **65**: 111–118.

Dayas CV, Liu X, Simms JA, Weiss F (2007). Distinct patterns of neural activation associated with ethanol seeking: effects of naltrexone. *Biol Psychiatry* **61**: 979–989.

Deneau G, Yanagita T, Seevers MH (1969). Self-administration of psychoactive substances by the monkey. *Psychopharmacologia* **16**: 30–48.

Di Chiara G (1999). Drug addiction as dopamine-dependent associative learning disorder. *Eur J Pharmacol* **375**: 13–30.

Di Chiara G (2002). Nucleus accumbens shell and core dopamine: differential role in behavior and addiction. *Behav Brain Res* **137**: 75–114.

Di Chiara G, Imperato A (1988). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci USA* **85**: 5274–5278.

Di Ciano P, Coury A, Depoortere RY, Egilmez Y, Lane JD, Emmett-Oglesby MW *et al.* (1995). Comparison of changes in extracellular dopamine concentrations in the nucleus accumbens during intravenous self-administration of cocaine or D-amphetamine. *Behav Pharmacol* **6**: 311–322.

Di Ciano P, Everitt BJ (2001). Dissociable effects of antagonism of NMDA and AMPA/KA receptors in the nucleus accumbens core and shell on cocaine-seeking behavior. *Neuropsychopharmacology* **25**: 341–360.

Di Ciano P, Everitt BJ (2004a). Contribution of the ventral tegmental area to cocaine-seeking maintained by a drug-paired conditioned stimulus in rats. *Eur J Neurosci* **19**: 1661–1667.

Di Ciano P, Everitt BJ (2004b). Direct interactions between the basolateral amygdala and nucleus accumbens core underlie cocaine-seeking behavior in rats. *J Neurosci* **24**: 7167–7173.

Di Ciano P, Robbins TW, Everitt BJ (2008). Differential effects of nucleus accumbens core, shell, or dorsal striatal inactivations on the persistence, reacquisition, or reinstatement of responding for a drug-paired conditioned reinforcer. *Neuropsychopharmacology* (in press).

Di Pietro NC, Black YD, Kantak KM (2006). Context-dependent prefrontal cortex regulation of cocaine self-administration and reinstatement behaviors in rats. *Eur J Neurosci* **24**: 3285–3298.

Dworkin SI, Guerin GF, Co C, Goeders NE, Smith JE (1988a). Lack of an effect of 6-hydroxydopamine lesions of the nucleus accumbens on intravenous morphine self-administration. *Pharmacol Biochem Behav* **30**: 1051–1057.

Dworkin SI, Guerin GF, Goeders NE, Smith JE (1988b). Kainic acid lesions of the nucleus accumbens selectively attenuate morphine self-administration. *Pharmacol Biochem Behav* **29**: 175–181.

Erb S, Hitchcott PK, Rajabi H, Mueller D, Shaham Y, Stewart J (2000). Alpha-2 adrenergic receptor agonists block stress-induced reinstatement of cocaine seeking. *Neuropsychopharmacology* **23**: 138–150.

Erb S, Shaham Y, Stewart J (1996). Stress reinstates cocaine-seeking behavior after prolonged extinction and a drug-free period. *Psychopharmacology (Berl)* **128**: 408–412.

Erb S, Shaham Y, Stewart J (1998). The role of corticotropin-releasing factor and corticosterone in stress- and cocaine-induced relapse to cocaine seeking in rats. *J Neurosci* **18**: 5529–5536.

Erb S, Stewart J (1999). A role for the bed nucleus of the stria terminalis, but not the amygdala, in the effects of corticotropin-releasing factor on stress-induced reinstatement of cocaine seeking. *J Neurosci* **19**: RC35.

Ettenberg A, Pettit HO, Bloom FE, Koob GF (1982). Heroin and cocaine intravenous self-administration in rats: mediation by separate neural systems. *Psychopharmacology* **78**: 204–209.

Everitt BJ, Robbins TW (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci* **8**: 1481–1489.

Fadda F, Garau B, Marchei F, Colombo G, Gessa GL (1991). MDL 72222, a selective 5-HT3 receptor antagonist, suppresses voluntary ethanol consumption in alcohol-preferring rats. *Alcohol Alcohol* **26**: 107–110.

Fadda P, Scherma M, Spano MS, Salis P, Melis V, Fattore L *et al.* (2006). Cannabinoid self-administration increases dopamine release in the nucleus accumbens. *Neuroreport* **17**: 1629–1632.

Feltenstein MW, See RE (2006). Potentiation of cue-induced reinstatement of cocaine-seeking in rats by the anxiogenic drug yohimbine. *Behav Brain Res* **174**: 1–8.

Feltenstein MW, See RE (2007). NMDA receptor blockade in the basolateral amygdala disrupts consolidation of stimulus–reward memory and extinction learning during reinstatement of cocaine-seeking in an animal model of relapse. *Neurobiol Learn Mem* **88**: 435–444.

Fischman MW, Schuster CR (1982). Cocaine self-administration in humans. *Fed Proc* **41**: 241–246.

Franklin TR, Acton PD, Maldjian JA, Gray JD, Croft JR, Dackis CA *et al.* (2002). Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. *Biol Psychiatry* **51**: 134–142.

Franklin TR, Druhan JP (2000). Expression of Fos-related antigens in the nucleus accumbens and associated regions following exposure to a cocaine-paired environment. *Eur J Neurosci* **12**: 2097–2106.

Fuchs RA, Branham RK, See RE (2006a). Different neural substrates mediate cocaine seeking following abstinence versus extinction training: a critical role for the dorsolateral caudate-putamen. *J Neurosci* **26**: 3584–3588.

Fuchs RA, Eaddy JL, Su Z-I, Bell GH (2007). Interactions of the basolateral amygdala with the dorsal hippocampus and dorsomedial prefrontal cortex regulate drug context-induced reinstatement of cocaine-seeking in rats. *Eur J Neurosci* **26**: 487–498.

Fuchs RA, Evans KA, Ledford CC, Parker MP, Case JM, Mehta RH *et al.* (2005). The role of the dorsomedial prefrontal cortex, basolateral amygdala, and dorsal hippocampus in contextual reinstatement of cocaine seeking in rats. *Neuropsychopharmacology* **30**: 296–309.

Fuchs RA, Evans KA, Parker MC, See RE (2004a). Differential involvement of the core and shell subregions of the nucleus accumbens in conditioned cue-induced reinstatement of cocaine seeking in rats. *Psychopharmacology (Berl)* **176**: 459–465.

Fuchs RA, Evans KA, Parker MP, See RE (2004b). Differential involvement of orbitofrontal cortex subregions in conditioned cue-induced and cocaine-primed reinstatement of cocaine seeking in rats. *J Neurosci* **24**: 6600–6610.

Fuchs RA, Feltenstein MW, See RE (2006b). The role of the basolateral amygdala in stimulus–reward memory and extinction memory consolidation and in subsequent conditioned cued reinstatement of cocaine seeking. *Eur J Neurosci* **23**: 2809–2813.

Fuchs RA, See RE (2002). Basolateral amygdala inactivation abolishes conditioned stimulus- and heroin-induced reinstatement of

extinguished heroin-seeking behavior in rats. *Psychopharmacology (Berl)* **160**: 425–433.
Gallistel CR (1983). Self-stimulation. In: Deutsch JA (ed). *The Physiological Basis of Memory*. Academic Press: New York. pp 73–77.
Gatto GJ, McBride WJ, Murphy JM, Lumeng L, Li TK (1994). Ethanol self-infusion into the ventral tegmental area by alcohol-preferring rats. *Alcohol* **11**: 557–564.
Gill K, Amit Z, Koe BK (1988). Treatment with sertraline, a new serotonin uptake inhibitor, reduces voluntary ethanol consumption in rats. *Alcohol* **5**: 349–554.
Goldberg SR, Woods JH, Schuster CR (1971). Nalorphrine-induced changes in morphine self-administration in rhesus monkeys. *J Pharmacol Exp Ther* **176**: 464–471.
Goldberg ST, Kelleher RT (1976). Behavior controlled by scheduled injections of cocaine in squirrel and rhesus monkeys. *J Exp Anal Behav* **25**: 93–104.
Goldstein RZ, Volkow ND (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry* **159**: 1642–1652.
Grant S, London ED, Newlin DB, Villemagne VL, Liu X, Contoreggi C *et al*. (1996). Activation of memory circuits during cue-elicited cocaine craving. *Proc Natl Acad Sci USA* **93**: 12040–12045.
Griffiths RR, Bigelow GE, Liebson I (1978). Experimental drug self-administration: generality across species and type of drug. *NIDA Res Monogr* **20**: 24–43.
Grimm JW, Kruzich PJ, See RE (2000). Contingent access to stimuli associated with cocaine self-administration is required for re-instatement of drug-seeking behavior. *Psychobiology* **28**: 383–386.
Grimm JW, See RE (2000). Dissociation of primary and secondary reward-relevant limbic nuclei in an animal model of relapse. *Neuropsychopharmacology* **22**: 473–479.
Hanson HM, Ivester CA, Morton BR (1979). Nicotine self-administration in rats. *NIDA Res Monogr* **23**: 70–90.
Harris GC, Wimmer M, Aston-Jones G (2005). A role for lateral hypothalamic orexin neurons in reward seeking. *Nature* **437**: 556–559.
Hemby SE, Martin TJ, Co C, Dworkin SI, Smith JE (1995). The effects of intravenous heroin administration on extracellular nucleus accumbens dopamine concentrations as determined by *in vivo* microdialysis. *J Pharmacol Exp Ther* **273**: 591–598.
Herkenham M, Lynn AB, Johnson MR, Melvin LS, de Costa BR, Rice KC (1991). Characterization and localization of cannabinoid receptors in rat brain: a quantitative *in vitro* autoradiographic study. *J Neurosci* **11**: 563–583.
Higgins RL, Marlatt GA (1975). Fear of interpersonal evaluation as a determinant of alcohol consumption in male social drinkers. *J Abnorm Psychol* **84**: 644–651.
Highfield D, Yap J, Grimm JW, Shalev U, Shaham Y (2001). Repeated lofexidine treatment attenuates stress-induced, but not drug cues-induced reinstatement of a heroin–cocaine mixture (speedball) seeking in rats. *Neuropsychopharmacology* **25**: 320–331.
Hoebel BG, Monaco AP, Hernandez L, Aulisi EF, Stanley BG, Lenard L (1983). Self-injection of amphetamine directly into the brain. *Psychopharmacology (Berl)* **81**: 158–163.
Holmberg G, Gershon S (1961). Autonomic and psychic effects of yohimbine hydrochloride. *Psychopharmacologia* **2**: 93–106.
Hubner CB, Koob GF (1990). The ventral pallidum plays a role in mediating cocaine and heroin self-administration in the rat. *Brain Res* **508**: 20–29.
Hungund BL, Szakall I, Adam A, Basavarajappa BS, Vadasz C (2003). Cannabinoid CB1 receptor knockout mice exhibit markedly reduced voluntary alcohol consumption and lack alcohol-induced dopamine release in the nucleus accumbens. *J Neurochem* **84**: 698–704.
Hurd YL, Weiss F, Koob GF, And NE, Ungerstedt U (1989). Cocaine reinforcement and extracellular dopamine overflow in rat nucleus accumbens: an *in vivo* microdialysis study. *Brain Res* **498**: 199–203.
Hyman SE, Malenka RC (2001). Addiction and the brain: the neurobiology of compulsion and its persistence. *Nat Rev Neurosci* **2**: 695–703.
Jaffe JH, Cascella NG, Kumor KM, Sherer MA (1989). Cocaine-induced cocaine craving. *Psychopharmacology* **97**: 59–64.
Jentsch JD, Taylor JR (1999). Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology (Berl)* **146**: 373–390.
Johnson SW, North RA (1992). Opioids excite dopamine neurons by hyperpolarization of local interneurons. *J Neurosci* **12**: 483–488.
Justinova Z, Tanda G, Redhi GH, Goldberg SR (2003). Self-administration of delta9-tetrahydrocannabinol (THC) by drug naive squirrel monkeys. *Psychopharmacology (Berl)* **169**: 135–140.
Kalivas PW, McFarland K (2003). Brain circuitry and the reinstatement of cocaine-seeking behavior. *Psychopharmacology (Berl)* **168**: 44–56.
Kalivas PW, Pierce RC, Cornish J, Sorg BA (1998). A role for sensitization in craving and relapse in cocaine addiction. *J Psychopharmacol* **12**: 49–53.
Kalivas PW, Stewart J (1991). Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. *Brain Res Brain Res Rev* **16**: 223–244.
Kalivas PW, Volkow ND (2005). The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry* **162**: 1403–1413.
Kilts CD, Gross RE, Ely TD, Drexler KP (2004). The neural correlates of cue-induced craving in cocaine-dependent women. *Am J Psychiatry* **161**: 233–241.
Kilts CD, Schweitzer JB, Quinn CK, Gross RE, Faber TL, Muhammad F *et al*. (2001). Neural activity related to drug craving in cocaine addiction. *Arch Gen Psychiatry* **58**: 334–341.
Kolta MG, Shreve P, De Souza V, Uretsky NJ (1985). Time course of the development of the enhanced behavioral and biochemical responses to amphetamine after pretreatment with amphetamine. *Neuropharmacology* **24**: 823–829.
Koob GF (1999). Stress, corticotropin-releasing factor, and drug addiction. *Ann NY Acad Sci* **897**: 27–45.
Koob GF, Bloom FE (1988). Cellular and molecular mechanisms of drug dependence. *Science* **242**: 715–723.
Koob GF, Kreek MJ (2007). Stress, dysregulation of drug reward pathways, and the transition to drug dependence. *Am J Psychiatry* **164**: 1149–1159.
Koob GF, Le Moal M (1997). Drug abuse: hedonic homeostatic dysregulation. *Science* **278**: 52–58.
Koob GF, Le Moal M (2001). Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology* **24**: 97–129.
Koob GF, Le Moal M (2006). Nicotine. In: Koob GF, Le Moal M (eds). *Neurobiology of Addiction*. Academic Press: London. pp 243–287.
Koob GF, Maldonado R, Stinus L (1992). Neural substrates of opiate withdrawal. *Trends Neurosci* **15**: 186–191.
Koob GF, Pettit HO, Ettenberg A, Bloom FE (1984). Effects of opiate antagonists and their quaternary derivatives on heroin self-administration in the rat. *J Pharmacol Exp Ther* **229**: 481–486.
Kornetsky C, Bain G (1990). Brain-stimulation reward: a model for drug induced euphoria. In: Adler MW, Cowan A (eds). *Testing and Evaluation of Drug of Abuse*. Wiley-Liss: New York. pp 211–231.
Kornetsky C, Esposito RU, McLean S, Jacobson JO (1979). Intracranial self-stimulation thresholds: a model for the hedonic effects of drugs of abuse. *Arch Gen Psychiatry* **36**: 289–292.
Koya E, Spijker S, Voorn P, Binnekade R, Schmidt ED, Schoffelmeer AN *et al*. (2006). Enhanced cortical and accumbal molecular reactivity associated with conditioned heroin, but not sucrose-seeking behaviour. *J Neurochem* **98**: 905–915.
Kreek MJ, Koob GF (1998). Drug dependence: stress and dysregulation of brain reward pathways. *Drug Alcohol Depend* **51**: 23–47.
Kruzich PJ, See RE (2001). Differential contributions of the basolateral and central amygdala in the acquisition and expression of conditioned relapse to cocaine-seeking behavior. *J Neurosci* **21**: RC155.
Kuczenski R, Segal DS (1994). Neurochemistry of amphetamine. In: Cho AK (ed). *Amphetamine and its Analogs*. Academic Press: San Diego. pp 81–113.
Lang WJ, Gershon S (1963). Effects of psychoactive drugs on yohimbine induced responses in conscious dogs. A proposed screening procedure for anti-anxiety agents. *Arch Int Pharmacodyn Ther* **142**: 457–472.
Lawrence AJ, Cowen MS, Yang HJ, Chen F, Oldfield B (2006). The orexin system regulates alcohol-seeking in rats. *Br J Pharmacol* **148**: 752–759.

Le AD, Harding S, Juzytsch W, Funk D, Shaham Y (2005). Role of alpha-2 adrenoceptors in stress-induced reinstatement of alcohol seeking and alcohol self-administration in rats. *Psychopharmacology (Berl)* **179**: 366–373.

Le AD, Harding S, Juzytsch W, Watchus J, Shalev U, Shaham Y (2000). The role of corticotrophin-releasing factor in stress-induced relapse to alcohol-seeking behavior in rats. *Psychopharmacology (Berl)* **150**: 317–324.

Lecca D, Cacciapaglia F, Valentini V, Di Chiara G (2006a). Monitoring extracellular dopamine in the rat nucleus accumbens shell and core during acquisition and maintenance of intravenous WIN 55,212-2 self-administration. *Psychopharmacology (Berl)* **188**: 63–74.

Lecca D, Cacciapaglia F, Valentini V, Gronli J, Spiga S, Di Chiara G (2006b). Preferential increase of extracellular dopamine in the rat nucleus accumbens shell as compared to that in the core during acquisition and maintenance of intravenous nicotine self-administration. *Psychopharmacology (Berl)* **184**: 435–446.

Ledent C, Valverde O, Cossu G, Petitet F, Aubert JF, Beslot F *et al*. (1999). Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. *Science* **283**: 401–404.

Ledford CC, Fuchs RA, See RE (2003). Potentiated reinstatement of cocaine-seeking behavior following D-amphetamine infusion into the basolateral amygdala. *Neuropsychopharmacology* **28**: 1721–1729.

Lee B, Tiefenbacher S, Platt DM, Spealman RD (2004). Pharmacological blockade of alpha2-adrenoceptors induces reinstatement of cocaine-seeking behavior in squirrel monkeys. *Neuropsychopharmacology* **29**: 686–693.

Leri F, Flores J, Rodaros D, Stewart J (2002). Blockade of stress-induced but not cocaine-induced reinstatement by infusion of noradrenergic antagonists into the bed nucleus of the stria terminalis or the central nucleus of the amygdala. *J Neurosci* **22**: 5713–5718.

Levin ED, Conners CK, Silva D, Hinton SC, Meck WH, March J *et al*. (1998). Transdermal nicotine effects on attention. *Psychopharmacology (Berl)* **140**: 135–141.

Lyness WH, Friedle NM, Moore KE (1979). Destruction of dopaminergic nerve terminals in nucleus accumbens: effect on D-amphetamine self-administration. *Pharmacol Biochem Behav* **11**: 553–556.

Markou A, Koob GF (1991). Postcocaine anhedonia. An animal model of cocaine withdrawal. *Neuropsychopharmacology* **4**: 17–26.

Markou A, Weiss F, Gold LH, Caine SB, Schulteis G, Koob GF (1993). Animal models of drug craving. *Psychopharmacology (Berl)* **112**: 163–182.

Masur J, Boerngen R (1980). The excitatory component of ethanol in mice: a chronic study. *Pharmacol Biochem Behav* **13**: 777–780.

Mateo Y, Budygin EA, John CE, Jones SR (2004). Role of serotonin in cocaine effects in mice with reduced dopamine transporter function. *Proc Natl Acad Sci USA* **101**: 372–377.

McFarland K, Davidge SB, Lapish CC, Kalivas PW (2004). Limbic and motor circuitry underlying footshock-induced reinstatement of cocaine-seeking behavior. *J Neurosci* **24**: 1551–1560.

McFarland K, Kalivas PW (2001). The circuitry mediating cocaine-induced reinstatement of drug-seeking behavior. *J Neurosci* **21**: 8655–8663.

McFarland K, Lapish CC, Kalivas PW (2003). Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. *J Neurosci* **23**: 3531–3537.

McLaughlin J, See RE (2003). Selective inactivation of the dorsomedial prefrontal cortex and the basolateral amygdala attenuates conditioned-cued reinstatement of extinguished cocaine-seeking behavior in rats. *Psychopharmacology (Berl)* **168**: 57–65.

Meil WM, Roll JM, Grimm JW, Lynch AM, See RE (1995). Tolerance-like attenuation to contingent and noncontingent cocaine-induced elevation of extracellular dopamine in the ventral striatum following 7 days of withdrawal from chronic treatment. *Psychopharmacology (Berl)* **118**: 338–346.

Meil WM, See RE (1997). Lesions of the basolateral amygdala abolish the ability of drug associated cues to reinstate responding during withdrawal from self-administered cocaine. *Behav Brain Res* **87**: 139–148.

Melendez RI, Rodd-Henricks ZA, Engleman EA, Li TK, McBride WJ, Murphy JM (2002). Microdialysis of dopamine in the nucleus accumbens of alcohol-preferring (P) rats during anticipation and operant self-administration of ethanol. *Alcohol Clin Exp Res* **26**: 318–325.

Meyer RE (1996). The disease called addiction: emerging evidence of a 200-year debate. *Lancet* **347**: 162–166.

Monaco AP, Hernandez L, Hoebel BG (1981). Nucleus accumbens: site of amphetamine self-administration. Comparison with the lateral ventricle. In: Chronister RB, DeFrance JF (eds). *Neurobiology of the Nucleus Accumbens*. Haer Institute: Brunswick. pp 338–343.

Mugnaini M, Garzotti M, Sartori I, Pilla M, Repeto P, Heidbreder CA *et al*. (2006). Selective down-regulation of [(125)I]Y0-alpha-conotoxin MII binding in rat mesostriatal dopamine pathway following continuous infusion of nicotine. *Neuroscience* **137**: 565–572.

Myers RD (1974). *Handbook of Drug and Chemical Stimulation of the Brain*. Van Nostrand Reinhold: New York.

Neisewander JL, Baker DA, Fuchs RA, Tran-Nguyen LT, Palmer A, Marshall JF (2000). Fos protein expression and cocaine-seeking behavior in rats after exposure to a cocaine self-administration environment. *J Neurosci* **20**: 798–805.

Nesbitt PD (1973). Smoking, physiological arousal, and emotional response. *J Pers Soc Psychol* **25**: 137–144.

Nesse RM, Berridge KC (1997). Psychoactive drug use in evolutionary perspective. *Science* **278**: 63–66.

Olds ME (1982). Reinforcing effects of morphine in the nucleus accumbens. *Brain Res* **237**: 429–440.

Panagis G, Kastellakis A, Spyraki C, Nomikos G (2000). Effects of methyllycaconitine (MLA), an alpha 7 nicotinic receptor antagonist, on nicotine- and cocaine-induced potentiation of brain stimulation reward. *Psychopharmacology (Berl)* **149**: 388–396.

Park WK, Bari WW, Jey AR, Anderson SM, Spealman RD, Rowlett JK *et al*. (2002). Cocaine administered into the medial prefrontal cortex reinstates cocaine-seeking behavior by increasing AMPA receptor-mediated glutamate transmission in the nucleus accumbens. *J Neurosci* **22**: 2916–2925.

Pettit HO, Ettenberg A, Bloom FE, Koob GF (1984). Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats. *Psychopharmacology* **84**: 167–173.

Pettit HO, Justice Jr JB (1989). Dopamine in the nucleus accumbens during cocaine self-administration as studied by *in vivo* microdialysis. *Pharmacol Biochem Behav* **34**: 899–904.

Phillips AG, Mora F, Rolls ET (1981). Intracerebral self-administration of amphetamine by rhesus monkeys. *Neurosci Lett* **24**: 81–86.

Piazza PV, Le Moal M (1998). The role of stress in drug self-administration. *Trends Pharmacol Sci* **19**: 67–74.

Pickens R, Harris WC (1968). Self-administration of D-amphetamine by rats. *Psychopharmacologia* **12**: 158–163.

Pickens R, Meisch R, McGuire LE (1967). Methamphetamine reinforcement in rats. *Psychon Sci* **8**: 371–372.

Pickens R, Meisch RA, Dougherty Jr JA (1968). Chemical interactions in methamphetamine reinforcement. *Psychol Rep* **23**: 1267–1270.

Pickens R, Thompson T (1968). Cocaine-reinforced behavior in rats: effects of reinforcement magnitude and fixed-ratio size. *J Pharmacol Exp Ther* **161**: 122–129.

Pontieri FE, Tanda G, Di Chiara G (1995). Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the 'shell' as compared with the 'core' of the rat nucleus accumbens. *Proc Natl Acad Sci USA* **92**: 12304–12308.

Pontieri FE, Tanda G, Orzi F, Di Chiara G (1996). Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. *Nature* **382**: 255–257.

Rassnick S, D'Amico E, Riley E, Koob GF (1993a). GABA antagonist and benzodiazepine partial inverse agonist reduce motivated responding for ethanol. *Alcohol Clin Exp Res* **17**: 124–130.

Rassnick S, Pulvirenti L, Koob GF (1992). Oral ethanol self-administration in rats is reduced by the administration of

dopamine and glutamate receptor antagonists into the nucleus accumbens. *Psychopharmacology (Berl)* **109**: 92–98.

Rassnick S, Stinus L, Koob GF (1993b). The effects of 6-hydroxydopamine lesions of the nucleus accumbens and the mesolimbic dopamine system on oral self-administration of ethanol in the rat. *Brain Res* **623**: 16–24.

Richardson NR, Smith AM, Roberts DC (1994). A single injection of either flupenthixol decanoate or haloperidol decanoate produces long-term changes in cocaine self-administration in rats. *Alcohol Drug Depend* **36**: 23–25.

Ritz MC, Kuhar MJ (1989). Relationship between self-administration of amphetamine and monoamine receptors in brain: comparison with cocaine. *J Pharmacol Exp Ther* **248**: 1010–1017.

Ritz MC, Lamb RJ, Goldberg SR, Kuhar MJ (1987). Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science* **237**: 1219–1223.

Robbins TW, Everitt BJ (1996). Neurobehavioural mechanisms of reward and motivation. *Curr Opin Neurobiol* **6**: 228–236.

Roberts DC, Corcoran ME, Fibiger HC (1977). On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. *Pharmacol Biochem Behav* **6**: 615–620.

Roberts DC, Koob GF (1982). Disruption of cocaine self-administration following 6-hydroxydopamine lesions of the ventral tegmental area in rats. *Pharmacol Biochem Behav* **17**: 901–904.

Roberts DC, Koob GF, Klonoff P, Fibiger HC (1980). Extinction and recovery of cocaine self-administration following 6-hydroxydopamine lesions of the nucleus accumbens. *Pharmacol Biochem Behav* **12**: 781–787.

Robinson TE, Berridge KC (1993). The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Brain Res Rev* **18**: 247–291.

Rocha BA, Fumagalli F, Gainetdinov RR, Jones SR, Ator R, Giros B *et al*. (1998). Cocaine self-administration in dopamine-transporter knockout mice. *Nat Neurosci* **1**: 132–137.

Rodd ZA, Bell RL, Kuc KA, Zhang Y, Murphy JM, McBride WJ (2005). Intracranial self-administration of cocaine within the posterior ventral tegmental area of Wistar rats: evidence for involvement of serotonin-3 receptors and dopamine neurons. *J Pharmacol Exp Ther* **313**: 134–145.

Rodd ZA, Bell RL, Melendez RI, Kuc KA, Lumeng L, Li TK *et al*. (2004a). Comparison of intracranial self-administration of ethanol within the posterior ventral tegmental area between alcohol-preferring and Wistar rats. *Alcohol Clin Exp Res* **28**: 1212–1219.

Rodd ZA, Melendez RI, Bell RL, Kuc KA, Zhang Y, Murphy JM *et al*. (2004b). Intracranial self-administration of ethanol within the ventral tegmental area of male Wistar rats: evidence for involvement of dopamine neurons. *J Neurosci* **24**: 1050–1057.

Rodd-Henricks ZA, McKinzie DL, Li TK, Murphy JM, McBride WJ (2002). Cocaine is self-administered into the shell but not the core of the nucleus accumbens of Wistar rats. *J Pharmacol Exp Ther* **303**: 1216–1226.

Rogers JL, Ghee S, See RE (2008). The neural circuitry underlying reinstatement of heroin-seeking behavior in an animal model of relapse. *Neuroscience* **151**: 579–588.

Rogers JL, See RE (2007). Selective inactivation of the ventral hippocampus attenuates cue-induced and cocaine-primed reinstatement of drug-seeking in rats. *Neurobiol Learn Mem* **87**: 688–692.

Russell JA, Mehrabian A (1975). The mediating role of emotions in alcohol use. *J Stud Alcohol* **36**: 1508–1536.

SAMHSA (2007). *Results from the 2006 National Survey on Drug Use and Health: National Findings*. (DHHS Publication no. SMA 07-4293, NSDUH series H-32) Office of Applied Studies: Rockville, MD.

Samson HH, Doyle TF (1985). Oral ethanol self-administration in the rat: effect of naltrexone. *Pharmacol Biochem Behav* **22**: 91–99.

Schulteis G, Markou A, Cole M, Koob GF (1995). Decreased brain reward produced by ethanol withdrawal. *Proc Natl Acad Sci USA* **92**: 5880–5884.

Schulteis G, Markou A, Gold LH, Stinus L, Koob GF (1994). Relative sensitivity to naloxone of multiple indices of opiate withdrawal: a quantitative dose–response analysis. *J Pharmacol Exp Ther* **271**: 1391–1398.

Schultz W, Dayan P, Montague PR (1997). A neural substrate of prediction and reward. *Science* **275**: 1593–1599.

Schuster CR, Thompson T (1969). Self-administration of and behavioral dependence on drugs. *Annu Rev Pharmacol Toxicol* **9**: 483–502.

See RE (2002). Neural substrates of conditioned-cued relapse to drug-seeking behavior. *Pharmacol Biochem Behav* **71**: 517–529.

See RE (2005). Neural substrates of cocaine-cue associations that trigger relapse. *Eur J Pharmacol* **526**: 140–146.

See RE, Elliott JC, Feltenstein MW (2007). The role of dorsal vs ventral striatal pathways in cocaine-seeking behavior after prolonged abstinence in rats. *Psychopharmacology (Berl)* **194**: 321–331.

See RE, Kruzich PJ, Grimm JW (2001). Dopamine, but not glutamate, receptor blockade in the basolateral amygdala attenuates conditioned reward in a rat model of relapse to cocaine-seeking behavior. *Psychopharmacology (Berl)* **154**: 301–310.

See RE, McLaughlin J, Fuchs RA (2003). Muscarinic receptor antagonism in the basolateral amygdala blocks acquisition of cocaine-stimulus association in a model of relapse to cocaine-seeking behavior in rats. *Neuroscience* **117**: 477–483.

Seiden LS, Sabol KE, Ricaurte GA (1993). Amphetamine: effects on catecholamine systems and behavior. *Annu Rev Pharmacol Toxicol* **33**: 639–677.

Shaham Y, Funk D, Erb S, Brown TJ, Walker CD, Stewart J (1997). Corticotropin-releasing factor, but not corticosterone, is involved in stress-induced relapse to heroin-seeking in rats. *J Neurosci* **17**: 2605–2614.

Shaham Y, Highfield D, Delfs J, Leung S, Stewart J (2000). Clonidine blocks stress-induced reinstatement of heroin seeking in rats: an effect independent of locus coeruleus noradrenergic neurons. *Eur J Neurosci* **12**: 292–302.

Shaham Y, Shalev U, Lu L, De Wit H, Stewart J (2003). The reinstatement model of drug relapse: history, methodology and major findings. *Psychopharmacology (Berl)* **168**: 3–20.

Shaham Y, Stewart J (1996). Effects of opioid and dopamine receptor antagonists on relapse induced by stress and re-exposure to heroin in rats. *Psychopharmacology (Berl)* **125**: 385–391.

Shepard JD, Bossert JM, Liu SY, Shaham Y (2004). The anxiogenic drug yohimbine reinstates methamphetamine seeking in a rat model of drug relapse. *Biol Psychiatry* **55**: 1082–1089.

Sinha R, Catapano D, O'Malley S (1999). Stress-induced craving and stress response in cocaine dependent individuals. *Psychopharmacology (Berl)* **142**: 343–351.

Smith GM, Beecher HK (1959). Amphetamine sulfate and athletic performance: I. Objective effects. *JAMA* **170**: 542–557.

Smith S, Davis W (1975). A method for chronic intravenous drug administration in the rat. In: Ehrenpreis S, Neidle A (eds). *Methods in Narcotic Research*. Marcel Dekker: New York. pp 3–32.

Spealman RD, Goldberg SR (1978). Drug self-administration by laboratory animals: control by schedules of reinforcement. *Annu Rev Pharmacol Toxicol* **18**: 313–339.

Stewart J (2000). Pathways to relapse: the neurobiology of drug- and stress-induced relapse to drug-taking. *J Psychiatry Neurosci* **25**: 125–136.

Stine SM, Southwick SM, Petrakis IL, Kosten TR, Charney DS, Krystal JH (2002). Yohimbine-induced withdrawal and anxiety symptoms in opioid-dependent patients. *Biol Psychiatry* **51**: 642–651.

Stretch R, Gerber GJ (1970). A method for chronic intravenous drug administration in squirrel monkeys. *Can J Physiol Pharmacol* **48**: 575–581.

Swerdlow NR, Gilbert G, Koob GF (1989). Conditioned drug effects on spatial preference: critical evaluation. In: Boulton AA, Baker GB, Greenshaw AJ (eds). *Psychopharmacology*. Humana Press: Clinton. pp 399–446.

Takahashi RN, Singer G (1979). Self-administration of delta 9-tetrahydrocannabinol by rats. *Pharmacol Biochem Behav* **11**: 737–740.

Tobler PN, Dickinson A, Schultz W (2003). Coding of predicted reward omission by dopamine neurons in a conditioned inhibition paradigm. *J Neurosci* **23**: 10402–10410.

Tsou K, Brown S, Sanudo-Pena MC, Mackie K, Walker JM (1998). Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. *Neuroscience* **83**: 393–411.

Tzschentke TM (1998). Measuring reward with the conditioned place preference paradigm: a comprehensive review of drug effects, recent progress and new issues. *Prog Neurobiol* **56**: 613–672.
Ungless MA, Whistler JL, Malenka RC, Bonci A (2001). Single cocaine exposure *in vivo* induces long-term potentiation in dopamine neurons. *Nature* **411**: 583–587.
Vaccarino FJ, Bloom FE, Koob GF (1985). Blockade of nucleus accumbens opiate receptors attenuates intravenous heroin reward in the rat. *Psychopharmacology (Berl)* **86**: 37–42.
van Erp AM, Miczek KA (2007). Increased accumbal dopamine during daily alcohol consumption and subsequent aggressive behavior in rats. *Psychopharmacology (Berl)* **191**: 679–688.
Van Ree JM, de Wied D (1980). Involvement of neurohypophyseal peptides in drug-mediated adaptive responses. *Pharmacol Biochem Behav* **13** (Suppl 1): 257–263.
Van Ree JM, Gerrits MAFM, Vanderschuren LJMJ (1999). Opioids, reward and addiction: an encounter of biology, psychology, and medicine. *Pharmacol Rev* **51**: 341–396.
Vanderschuren LJ, Di Ciano P, Everitt BJ (2005). Involvement of the dorsal striatum in cue-controlled cocaine seeking. *J Neurosci* **25**: 8665–8670.
Vanderschuren LJ, Kalivas PW (2000). Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. *Psychopharmacology (Berl)* **151**: 99–120.
Volkow ND, Fowler JS, Wang GJ (2003). The addicted human brain: insights from imaging studies. *J Clin Invest* **111**: 1444–1451.
Volkow ND, Fowler JS, Wang GJ, Hitzemann R, Logan J, Schlyer DJ *et al*. (1993). Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse* **14**: 169–177.
Volkow ND, Wang GJ, Fischman MW, Foltin RW, Fowler JS, Abumrad NN *et al*. (1997). Relationship between subjective effects of cocaine and dopamine transporter occupancy. *Nature* **386**: 827–830.
Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Childress AR *et al*. (2006). Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. *J Neurosci* **26**: 6583–6588.
Vorel SR, Ashby Jr CR, Paul M, Liu X, Hayes R, Hagan JJ *et al*. (2002). Dopamine D3 receptor antagonism inhibits cocaine-seeking and cocaine-enhanced brain reward in rats. *J Neurosci* **22**: 9595–9603.
Wagner FA, Anthony JC (2002). From first drug use to drug dependence; developmental periods of risk for dependence upon marijuana, cocaine, and alcohol. *Neuropsychopharmacology* **26**: 479–488.
Watkins SS, Epping-Jordan MP, Koob GF, Markou A (1999). Blockade of nicotine self-administration with nicotinic antagonists in rats. *Pharmacol Biochem Behav* **62**: 743–751.
Weeks JR (1962). Experimental morphine addiction: method for automatic intravenous injections in unrestrained rats. *Science* **138**: 143–144.
Weeks JR (1972). Long-term intravenous infusion. In: Meyers R (ed). *Methods in Psychobiology*. Academic Press: New York. pp 155–168.
Weeks JR, Collins RJ (1976). Changes in morphine self-administration in rats induced by prostaglandin E1 and naloxone. *Prostaglandins* **193**: 1262–1263.
Weiss F, Ciccocioppo R, Parsons LH, Katner S, Liu X, Zorrilla EP *et al*. (2001). Compulsive drug-seeking behavior and relapse. Neuroadaptation, stress, and conditioning factors. *Ann NY Acad Sci* **937**: 1–26.
Weiss F, Lorang MT, Bloom FE, Koob GF (1993). Oral alcohol self-administration stimulates dopamine release in the rat nucleus accumbens: genetic and motivational determinants. *J Pharmacol Exp Ther* **267**: 250–258.
Weiss F, Maldonado-Vlaar CS, Parsons LH, Kerr TM, Smith DL, Ben-Shahar O (2000). Control of cocaine-seeking behavior by drug-associated stimuli in rats: effects on recovery of extinguished operant-responding and extracellular dopamine levels in amygdala and nucleus accumbens. *Proc Natl Acad Sci USA* **97**: 4321–4326.
Weiss F, Markou A, Lorang MT, Koob GF (1992). Basal extracellular dopamine levels in the nucleus accumbens are decreased during cocaine withdrawal after unlimited-access self-administration. *Brain Res* **593**: 314–318.
Wesnes K, Warburton DM, Matz B (1983). Effects of nicotine on stimulus sensitivity and response bias in a visual vigilance task. *Neuropsychobiology* **9**: 41–44.
Whitelaw RB, Markou A, Robbins TW, Everitt BJ (1996). Excitotoxic lesions of the basolateral amygdala impair the acquisition of cocaine-seeking behaviour under a second-order schedule of reinforcement. *Psychopharmacology (Berl)* **127**: 213–224.
Wiegmann DA, Stanny RR, McKay DL, Neri DF, McCardie AH (1996). Methamphetamine effects on cognitive processing during extended wakefulness. *Int J Aviat Psychol* **6**: 379–397.
Wilker A (1973). Dynamics of drug dependence: implications of a conditioning theory for research and treatment. *Arch Gen Psychiatry* **28**: 611–616.
Wilson MC, Schuster CR (1974). Aminergic influences on intravenous cocaine self-administration by rhesus monkeys. *Pharmacol Biochem Behav* **2**: 563–571.
Wise RA (1980). Action of drugs of abuse on brain reward systems. *Pharmacol Biochem Behav* **13**: 213–223.
Wise RA (1996). Neurobiology of addiction. *Curr Opin Neurobiol* **6**: 243–251.
Wise RA (2002). Brain reward circuitry: insights from unsensed incentives. *Neuron* **36**: 229–240.
Wise RA, Leone P, Rivest R, Leeb K (1995a). Elevations of nucleus accumbens dopamine and DOPAC levels during intravenous heroin self-administration. *Synapse* **21**: 140–148.
Wise RA, Newton P, Leeb K, Burnette B, Pocock D, Justice JB (1995b). Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats. *Psychopharmacology (Berl)* **120**: 10–20.
Wong DF, Kuwabara H, Schretlen DJ, Bonson KR, Zhou Y, Nandi A *et al*. (2006). Increased occupancy of dopamine receptors in human striatum during cue-elicited cocaine craving. *Neuropsychopharmacology* **31**: 2716–2727.
Woods J, Ikomi F, Winger G (1971). The reinforcing properties of ethanol. In: Roach M, McIsaac W, Creaven P (eds). *Biological Aspects of Alcohol*. University of Texas Press: Austin. pp 371–388.
Woolverton WL (1986). Effects of a D1 and a D2 dopamine antagonist on the self-administration of cocaine and piribedil by rhesus monkeys. *Pharmacol Biochem Behav* **24**: 531–535.
Woolverton WL, Johnson KM (1992). Neurobiology of cocaine abuse. *Trends Pharmacol Sci* **13**: 193–200.
Yanaura S, Uesugi J, Suzuki T, Kawai T (1980). Oral self-administration of morphine in rats. *Jpn J Pharmacol* **30**: 258–261.
Yokel RA, Wise RA (1975). Increased lever pressing for amphetamine after pimozide in rats: implications for a dopamine theory of reward. *Science* **187**: 547–549.
Young AM, Herling S (1986). Drugs as reinforcers: studies in laboratory animals. In: Goldberg SR, Stolerman IP (eds). *Behavioral Analysis of Drug Dependence*. Academic Press: London. pp 9–67.
Zhou W, Liu H, Zhang F, Tang S, Zhu H, Lai M *et al*. (2007). Role of acetylcholine transmission in nucleus accumbens and ventral tegmental area in heroin-seeking induced by conditioned cues. *Neuroscience* **144**: 1209–1218.
Zito KA, Vickers G, Roberts DC (1985). Disruption of cocaine and heroin self-administration following kainic acid lesions of the nucleus accumbens. *Pharmacol Biochem Behav* **23**: 1029–1036.