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REVIEW

A neuropeptide-centric view of psychostimulant addiction

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Drugs of abuse all share common properties classically observed in human beings and laboratory animals. They enhance neural firing and dopamine tone within the nucleus accumbens and produce progressively greater drug-induced motor responses defined as behavioural sensitization. They produce conditioned place preference, a behavioural model of incentive motivation, which highlights the role of environmental cues in drug addiction. They increase brain reward function as seen by a lowering of intracranial self-stimulation thresholds. And last but not least, they are self-administered, and sometimes even abused, and can trigger reinstatement of drug-seeking behaviour in animals extinguished from drug self-administration. It has long been considered that the reinforcing properties of virtually all drugs of abuse, more specifically psychostimulants, are primarily dependent on activation of the mesolimbic dopamine system. However, recent evidence raises the importance of dopamine-independent mechanisms in reward-related behaviours. The overwhelming body of evidence that indicates a critical role for the mesolimbic dopamine system in the reinforcing effect of psychostimulants should not mask the key contribution of other modulatory systems in the brain. This review summarizes the complex and subtle role of several neuropeptidergic systems in various aspects of addictive behaviours observed in laboratory animals exposed to psychostimulants. A special emphasis is given to the cannabinoid, opioid, nociceptin/orphanin FQ, corticotropin-releasing factor and hypocretin/orexin systems. The relevance of these systems viewed as potential therapeutic targets for drug addiction is discussed in the light of their narrow pharmacological profile and their effectiveness in preventing drug addiction at doses usually not accompanied by severe side effects.
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Abbreviations: AMYG, amygdala; BNST, bed nucleus of stria terminalis; CPP, conditioned place preference; CRF, corticotropin-releasing factor; DA, dopamine; ICSS, intracranial self-stimulation; LH, lateral hypothalamus; N/OFQ, nociceptin/orphanin FQ; Nacc, nucleus accumbens; NOP (ORL-1), opioid receptor like-1; PFA, perifornical area; VTA, ventral tegmental area

Introduction

Dopamine (DA) neurotransmission in the nucleus accumbens (Nacc) is essential for the processing of behaviourally relevant stimuli and the attribution of motivational valence to related events (Schultz, 2002; Robinson and Berridge, 2003). In this respect, DA plays a key role in stress, exploration, novelty or reward expectation as well as cognitive, learning and intentionality processes (for extended discussion, see Koob and Le Moal, 2006). These authors consider that DA does not code for reward *per se*, but rather allows appropriate functioning of complex circuits that it innervates, without having, itself, a functional attribute, a concept they summarize as 'oil in the machine' (Koob and Le Moal, 2006). In line with this interpretation, several studies support the fact that nondopaminergic neural substrates are also capable of mediating central reward processes (Garris *et al*., 1999; Laviolette and van der Kooy, 2001, Laviolette *et al*., 2004). In this perspective, reward is a complex function represented by a set of interrelated regions and circuitries, one component of which is the mesolimbic DA system. In support of this view, mice lacking tyrosine hydroxylase in DA neurons, so that they cannot synthesize DA, demonstrate the ability to learn to consume sweet solutions and show a preference for sucrose and saccharin (Cannon and Palmiter, 2003). Further, these DA-deficient mice are capable of learning and expressing a conditioned place preference (CPP) for morphine (Hnasko *et al*., 2005) and for cocaine as well (Hnasko *et al*., 2007). These authors suggest a prominent role of DA neuron activity even if these neurons do not release DA, emphasizing therefore the role of other neurotransmitters that contribute to cocaine reward in

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DA-deficient mice. Thus, even if it generally has been accepted that the reinforcing properties of psychostimulants arise, at least in part, from a potentiation of dopaminergic neurotransmission within the mesocorticolimbic circuit (Goeders and Smith, 1983; Wise and Bozarth, 1987; Di Chiara and Imperato, 1988; Wise and Rompre, 1989; Koob, 1992; Robinson and Berridge, 2003), a number of other neurotransmitter and neuromodulatory systems are also important (Kalivas and Alesdatter, 1993; Cunningham *et al*., 1996; Sora *et al*., 1998; Wolf, 1998; Ashby Jr *et al*., 2002; Hnasko *et al*., 2007) and converge with DA to mediate rewarding properties of both cocaine and amphetamine. The aim of this review is to delineate the complex and subtle pharmacological regulations of psychostimulant rewarding properties with a special emphasis on cannabinoid, opioid, nociceptin/orphanin FQ (N/OFQ), corticotropin-releasing factor (CRF) and hypocretin/orexin systems.

Endocannabinoids

The main two endocannabinoids, anandamide and 2-arachidonylglycerol, are lipids. In contrast to classical neurotransmitters that are synthesized in the cytosol of neurons and stored in synaptic vesicles from where they are secreted by exocytosis following excitation of nerve terminals by action potentials, endogenous cannabinoids appear to be produced upon demand by receptor-stimulated cleavage of membrane lipid precursors. They are released from postsynaptic neurons and travel retrograde across synapses, activating CB_1 cannabinoid receptors on presynaptic neurons and suppressing neurotransmitter release (Wilson and Nicoll, 2002; Freund *et al*., 2003). CB_1 receptor turns out to be one of the most abundant neuromodulatory receptors in the brain and is expressed at high levels in the hippocampus, cortex, cerebellum and basal ganglia. Endocannabinoids play an important role in the modulation of synaptic plasticity in dorsal striatum and Nacc (Freund *et al*., 2003; Gerdeman and Lovinger, 2003; Gerdeman *et al*., 2003). A large body of evidence supports the involvement of exogenous cannabinoids in the modulation of psychostimulant reinforcing properties (Arnold, 2005). However, it is worth noting that, in contrast to both ethanol and heroin self-administration, which significantly alter endogenous cannabinoid levels in the Nacc of rats, cocaine consumption does not alter dialysate levels of either AEA (arachidonoylethanolamide) or 2-AG (2-arachidonoylglycerol) (Caillé *et al*., 2007). In accordance with this observation, local infusion of the CB_1 receptor antagonist SR141716A (*N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride (rimonabant)) into the Nacc significantly reduces both heroin and ethanol, but not cocaine, self-administration (Caillé and Parsons, 2006; Caillé *et al*., 2007).

Sensitization

Repeated intermittent exposure to cocaine and amphetamine produces progressively greater drug-induced increases in DA efflux in the Nacc, a phenomenon referred to as neurochemical sensitization. This is coupled to a progressively greater locomotor response to the drug (behavioural sensitization) and increased positively reinforcing effects of the drug and drug-related cues (incentive sensitization). Several authors report that endocannabinoids play only a minor role in the hyperlocomotion induced by psychostimulants (Martin *et al*., 2000; Lesscher *et al*., 2005; Corbillé *et al*., 2007). Indeed, behavioural sensitization to amphetamine (Corbillé *et al*., 2007) and to cocaine occurs in CB_1 receptor knockout mice whereas these mutant mice do not develop behavioural sensitization to morphine (Martin *et al*., 2000), and pretreatment with a CB_1 receptor antagonist, SR141716A (1 mg kg^{-1} i.p.), does not affect the development of behavioural sensitization to the locomotor stimulant effects of cocaine in C57Bl/6Jico mice (Lesscher *et al*., 2005). However, acute pretreatment with THC (Δ^9-tetrahydrocannabinol; 0.1 or 6.4 mg kg^{-1} i.p.) was reported to attenuate the psychomotor activation induced by amphetamine, and chronic cannabinoid administration (0.1 or 6.4 mg kg^{-1} i.p., daily for 14 days) results in the development of tolerance to these effects, thus facilitating the induction of amphetamine-induced stereotyped activity. Twenty-four hours of withdrawal after 14 days of cannabinoid treatment (6.4 mg kg^{-1} i.p.) results in sensitization to the effects of amphetamine on locomotion, exploration and stereotypies (Gorriti *et al*., 1999).

Interestingly, several studies indicate that anandamide is critically involved in long-term depression by acting as a retrograde messenger on presynaptic CB_1 receptors (Gerdeman and Lovinger, 2003). It is worth noting that CB_1 receptors mediate amphetamine-induced long-term depression at synapses in the amygdala (AMYG) (Huang *et al*., 2003). However, so far, no studies have investigated whether cocaine-induced long-term depression requires endocannabinoid transmission in the striatum.

Conditioned place preference

It is thought that endocannabinoid transmission mediates the association of the rewarding effects of cocaine with environmental cues. Indeed, co-administration of SR141716A with cocaine in the conditioning phase abolishes the acquisition of CPP to cocaine in rats (Chaperon *et al*., 1998). However, Martin *et al*. (2000) showed cocaine-induced CPP in CB_1 receptor knockout mice. It is possible that such contradictory observations could be due to species differences. Alternatively, CB_1 receptor knockout mice may express adaptations that compensate for the functional loss of this receptor from the earliest stages of development. A final view that might explain the disparate findings of Chaperon *et al*. (1998) and Martin *et al*. (2000) is based on recent evidence indicating SR141716A might antagonize, in addition to the CB_1 receptor, an uncharacterized cannabinoid receptor that is located in the CNS (Freund *et al*., 2003; Pistis *et al*., 2004). If this unknown cannabinoid receptor was solely responsible for cocaine-induced CPP, then this would explain why pharmacological blockade of this receptor with SR141716A, but not targeted deletion of the CB_1 receptor, impairs the acquisition of CPP (Arnold, 2005).

Intracranial self-stimulation

The intracranial self-stimulation (ICSS) model has enabled the study of the neural and chemical profile of brain reward systems (Wise, 1996). The rate-frequency curve shift method is the optimal procedure for measuring the rewarding impact of a drug using ICSS (Kornetsky and Esposito, 1979; Kornetsky *et al*., 1979). Typically, animals are trained to press a wheel or a lever for a series of descending and ascending current intensities that are supplied to the medial forebrain bundle, often at the level of the posterior lateral hypothalamus (LH). The advantage of this method is that it allows the measurement of both the rewarding impact of the stimulation and also any performance deficits promoted by the drug. Drugs of abuse, such as cocaine, lower the frequency, which supports half-maximal rates of responding, that is, the reward threshold (Kenny, 2007).

The impact of cannabinoids on the electrical brain stimulation reward seems rather controversial. Whereas THC at low doses ($1\,mg\,kg^{-1}$) was reported to enhance electrical brain stimulation reward (that is, it lowers brain reward thresholds) in the VTA (ventral tegmental area)–medial forebrain bundle–Nacc axis in Lewis rats (Gardner, 2005), recent reports suggest that CB_1 agonists (WIN 55,212-2 ((*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)-pyrrolo-[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone mesylate), 0.1–$3\,mg\,kg^{-1}$ i.p.; CP55940 ((1*R*,3*R*,4*R*)-3-[2-hydroxy-4-(1,1-dimethylheptyl) phenyl]-4-(3-hydroxypropyl)cyclohexan-1-ol), 10–$10\,\mu g\,kg^{-1}$ i.p.; HU210 ((6a*R*)-*trans*-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo[b,d]pyran-9-methanol), 10–$300\,\mu g\,kg^{-1}$ i.p.) do not facilitate ICSS but rather have a dose-dependent inhibitory influence on brain reward mechanisms in Sprague–Dawley rats (Vlachou *et al*., 2005). These observations were later confirmed with THC (0.5–$2\,mg\,kg^{-1}$ i.p.) (Vlachou *et al*., 2007). Using either a fatty acid amide hydrolase inhibitor or a selective anandamide re-uptake inhibitor, both of which increase endocannabinoid levels, the same inhibitory influence on reward processes was reported (Vlachou *et al*., 2006). Whether such discrepant observations could be due to genetic variations in the strains of rats (Lewis versus Sprague–Dawley) remains debatable.

Surprisingly, the CB_1 antagonist SR141716A (1–$10\,mg\,kg^{-1}$ i.p.) has been reported to reduce the reinforcing value of electrical medial forebrain bundle stimulation, supporting a role for endogenous cannabinoids in brain reward function in Sprague–Dawley rats (Deroche-Gamonet *et al*., 2001).

Clearer is the observation according to which endocannabinoid transmission is involved in the acute rewarding effects of cocaine as measured by ICSS. Vlachou *et al*. (2003) demonstrated that pretreatment with the CB_1 receptor agonist WIN 55,212-2 (0.3 and $1\,mg\,kg^{-1}$ i.p.) reversed the threshold-lowering effects of cocaine ($5\,mg\,kg^{-1}$ i.p.), whereas pretreatment with the CB_1 receptor antagonist SR141716A ($0.02\,mg\,kg^{-1}$ i.p.) reversed the inhibitory effects of WIN 55,212-2 ($1\,mg\,kg^{-1}$ i.p.) on the cocaine-induced lowering of brain reward thresholds. The authors indicated that the effects of WIN 55,515-2 and SR141716A on cocaine reward occurred at doses that did not modulate ICSS when administered alone (Vlachou *et al*., 2003). It is concluded that acute stimulation of CB_1 receptors *per se* does not affect baseline self-stimulation, but reduces the reinforcing properties of cocaine. In view of this, endocannabinoid transmission may function as a homeostatic mechanism that attempts to offset excessive DA release in the striatum. Thus, the use of exogenous CB_1 receptor agonists in combination with cocaine might instigate this mechanism and attenuate further DA release, consequently decreasing the acute rewarding effects of cocaine (Arnold, 2005).

Self-administration: acquisition, maintenance and reinstatement

Several researches indicate that the endocannabinoid system does not play a critical role in the acquisition or maintenance of cocaine self-administration. Pretreatment with SR141716 fails to modulate cocaine self-administration in mice, rats or squirrel monkeys (Tanda *et al*., 2000; De Vries *et al*., 2001). Similarly, CB_1 receptor knockout mice can be trained to acquire both cocaine and methamphetamine self-administration behaviour despite an absence of morphine consumption (Cossu *et al*., 2001). The endocannabinoid system does not mediate cocaine reward, whereas exposure to exogenous cannabinoids appears to modulate cocaine self-administration. Fattore *et al*. (1999) demonstrated that pretreatment with WIN 55,212-2 (0.25–$1\,mg\,kg^{-1}$ i.v.) decreased cocaine self-administration. Usually, a decrease in response rate is considered to indicate hedonic satiation. In this perspective, findings by Fattore *et al*. might suggest that CB_1 receptor activation magnifies the rewarding impact of cocaine or induces itself hedonic satiety and thus a concomitant decreased need for cocaine intake. However, it has to be recalled that pretreatment with WIN 55,212-2 was shown to reverse the threshold-lowering effects of cocaine (Vlachou *et al*., 2003). This observation does not support the latter interpretation. The opposing effects of WIN 55,212-2 on cocaine reward as measured either with the self-administration model (Fattore *et al*., 1999) or with the ICSS paradigm (Vlachou *et al*., 2003) are challenging to reconcile.

A recent elegant demonstration highlighted the role of CB_1 receptors in cocaine reinforcement. In contrast to the conclusions drawn by Cossu *et al*., it has been reported that the lack of CB_1 receptor impairs cocaine self-administration (Soria *et al*., 2005). Indeed, these authors demonstrated that only 25% of CB_1 knockout mice acquired a reliable operant responding to self-administer cocaine (1 mg per kg per infusion) whereas 75% of wild-type mice did so. Further, the time required for reaching the acquisition criteria was increased in mutant mice, and the maximal effort required to obtain a cocaine infusion was significantly reduced in CB_1 knockout mice. These observations were confirmed after pharmacological blockade of CB_1 receptors in wild-type mice with SR141716A. Interestingly, acute cocaine administration induced a similar enhancement of extracellular DA levels in the Nacc in wild-type and CB_1 knockout mice. Thus, CB_1 knockout mice fail to maintain a reliable operant responding for cocaine intake but are capable of learning and expressing a CPP for cocaine (Martin *et al*., 2000) and cocaine-induced DA release in the Nacc is preserved. This observation emphasizes the subtle role of endocannabinoids in cocaine reinforcement. Endocannabinoids may counterbalance some reinforcing properties of psychostimulants in specific

conditions, but they are not able to block psychostimulant-induced DA release in the Nacc, and thus cannot prevent the acquisition and maintenance of cocaine self-administration.

Clearer is the role of cannabinoids in the relapse for psychostimulant seeking (Fattore *et al*., 2007). De Vries *et al*. (2001) demonstrated that pretreatment with SR141716A (1–3 mg kg^{-1}) reduced reinstatement of cocaine seeking promoted by cocaine-associated cues or cocaine-priming injections, yet failed to reverse stress-induced reinstatement. A similar observation was made with methampethamine self-administration in rats (Anggadiredja *et al*., 2004). Therefore, although the endocannabinoid system does not appear to subserve the acquisition or maintenance of psychostimulant self-administration, these data suggest that activation of CB_1 receptors is critically involved in specific aspects of relapse to both cocaine and methamphetamine seeking. In addition, De Vries *et al*. showed that administration of the potent cannabinoid receptor agonist HU210 (4–100 μg kg^{-1}) dose-dependently promoted reinstatement of cocaine seeking via CB_1 receptor activation. In line with this observation, it has been shown that subchronic treatment with a low dose of WIN 55,212-2 (0.3 mg kg^{-1} i.p.) during a period of abstinence following intravenous cocaine self-administration induced a high resistance to extinction and enhanced reinstatement (González-Cuevas *et al*., 2007). In contrast to this, Schenk and Partridge (1999) failed to demonstrate that THC (0.3–3 mg kg^{-1}) reinstated cocaine self-administration. The utilization of different cannabinoid receptor agonists might explain these discordant results. The mechanism by which the endocannabinoid system subserves cue- and cocaine- but not stress-primed reinstatement of cocaine self-administration is of interest. It highlights the complex and subtle role of this peptide system in cocaine addiction. Research is emerging that delineates distinct neuronal circuitry underlying reinstated cocaine seeking that is primed by cocaine-related cues, cocaine or stress. It appears that cue priming relies on DA projections from the VTA to the basolateral AMYG, which in turn sends afferent fibres to the prefrontal cortex (Grimm and See, 2000; Kalivas and McFarland, 2003). Cocaine-primed reinstatement seems to be mediated by connections between the VTA and prefrontal cortex (Kalivas *et al*., 2003). Further, although not well established, stress-primed reinstatement may involve markedly different circuitry, possibly comprised of noradrenergic fibres in the extended amygdala that send projections to the prefrontal cortex via the VTA (Kalivas and McFarland, 2003; McFarland *et al*., 2004).

Opioids

Three distinct families of endogenous opioid peptides have been identified: dynorphins, endorphins and enkephalins. There is a distinct polypeptide precursor for each peptide and a distinct, but overlapping neuroanatomical distribution of these precursors as measured by opioid mRNA expression (Mansour *et al*., 1995). Receptors on which endogenous and exogenous opioids act are widely distributed throughout the CNS, and each type of opioid receptor is differentially distributed (Mansour *et al*., 1995). The clinical significance of this distribution is still unclear. However, overall, it seems that mu-receptor agonists display not only the best and strongest analgesic effects but also the highest abuse liability (Kieffer, 1999). Morphine is an example of a partial mu agonist. Dynorphin is the endogenous opioid with the greatest affinity for kappa receptors. Kappa receptors in the CNS may actually antagonize mu receptor activity. Endorphins and enkephalins are endogenous ligands for both mu and delta receptors. β-Endorphin has equal affinity for mu and delta receptors, whereas enkephalins have slightly higher affinity for delta receptors. These receptors are found in the Nacc and limbic system, and may play a role in the emotional responses to opioids (Dhawan *et al*., 1996; Bodnar and Klein, 2006).

Whereas the initial sites of action governing cocaine reinforcement are thought to be DA transporters within the mesocorticolimbic system, the endogenous opioid systems appear to also modulate the reinforcing effects of cocaine. In rats, nonselective opioid receptor blockade with naloxone (0.3 mg kg^{-1} s.c.) or naltrexone (0.1–10 mg kg^{-1} s.c.) can decrease cocaine self-administration (Corrigall and Coen, 1991). In patients with amphetamine dependence, pretreatment with naltrexone (50 mg) attenuates the subjective effects produced by dexamphetamine (30 mg), and significantly decreases the craving for the drug (Jayaram-Lindström *et al*., 2007). However, the relative contributions of mu-, delta- and kappa-opioid receptor subtype-specific antagonism by these compounds to decreased reinforcing properties of psychostimulants remain equivocal.

Sensitization

There is evidence for a role of opioid systems in the development of psychostimulant sensitization. Naloxone, a nonselective opioid receptor antagonist, and naltrindole, a delta opioid receptor antagonist, have been shown to block the development of cocaine sensitization in both rats (Heidbreder *et al*., 1995, 1996; Shippenberg and Heidbreder, 1995a, b; Shippenberg *et al*., 1996) and mice (Kim *et al*., 1997). Kappa-opioid agonists, which inhibit dopaminergic neurotransmission, can prevent the development of behavioural sensitization to cocaine as well (Shippenberg *et al*., 1996).

Although the administration of the selective mu-opioid receptor antagonist CTAP (D-Phe-*cyc*[Cys-Tyr-D-Trp-Arg-Thr-Pen]-Thr-NH_2; 4 μg i.c.v.) alone did not affect locomotor activity or demonstrate aversive or rewarding properties, it significantly attenuated cocaine-induced hyperactivity, as well as the development of behavioural sensitization in rats. This observation confirms that activation of mu-opioid receptors by endogenous opioids is an important contributor to cocaine-induced hyperactivity and the development of behavioural sensitization and conditioned reward (Schroeder *et al*., 2007). Several studies have sought to establish a role for mu-opioid receptors in acute cocaine-induced hyperlocomotion and sensitization using a murine mu-opioid receptor knockout model. Results from these studies have been inconclusive. For instance, acute cocaine-induced activity has been reported to be attenuated in mu-opioid receptor knockout mice (Yoo *et al*., 2003) or unchanged (Hall *et al*.,

2004) as compared with wild-type controls. Likewise, behavioural sensitization is reported to be increased (Hall *et al*., 2004), decreased (Hummel *et al*., 2004) or unchanged (Yoo *et al*., 2003) in mu-receptor knockout mice. Detailed analysis of the behavioural effects of cocaine (15 mg kg^{-1} i.p.) in several lines of mu-opioid receptor knockout mice demonstrates that the resulting phenotype is dependent on the background strain that is carrying the gene deletion (Hummel *et al*., 2004). It has been proposed by these authors that caveats inherent to constitutive gene deletions are likely responsible for the mixed findings and inconclusive results regarding the role of mu-receptors in the behavioural effects of cocaine in the mouse.

Mice receiving i.c.v. injections of an antisense oligonucleotide directed against the mu-opioid receptor failed to sensitize to cocaine (Hummel *et al*., 2006). Investigators also found that pretreatment with naltrexone attenuated cocaine-induced locomotor activity (Sala *et al*., 1995) and amphetamine-induced stereotypy in rats (Balcells-Olivero and Vezina, 1997).

Finally, evidence demonstrates that kappa-receptor agonists, not antagonists, attenuate cocaine-induced behavioural sensitization as well (Heidbreder *et al*., 1993; Shippenberg and Rea, 1997).

Conditioned place preference

The nonselective opioid receptor antagonists naloxone and naltrexone (Houdi *et al*., 1989; Bilsky *et al*., 1992), the delta-opioid receptor antagonist naltrindole (Menkens *et al*., 1992; Suzuki *et al*., 1994) and the kappa-opioid receptor agonist U-50,488H (Suzuki *et al*., 1992) have been shown to reduce cocaine-induced CPP. The mu-1 receptor antagonist naloxonazine (20 mg kg^{-1} i.p. but not 10 or 1 mg kg^{-1} i.p.) also attenuates the conditioned reinforcement produced by cocaine without affecting cocaine-induced hyperlocomotion (Rademacher and Steinpreis, 2002). Further, pretreatment with the selective mu-opioid receptor antagonist CTAP (4 μg i.c.v.) also prevented the development of CPP to cocaine in rats (Schroeder *et al*., 2007). Finally, mice receiving an antisense oligonucleotide directed against the mu-opioid receptor do not exhibit CPP to cocaine (Hummel *et al*., 2006), an observation that is in line with that of Hall *et al*. (2004), who found that the rewarding properties of cocaine were reduced in mu-opioid receptor knockout mice.

Intracranial self-stimulation

The nonselective opioid receptor antagonist naloxone can reduce the rewarding effects of cocaine (Bain and Kornetsky, 1987; Schaefer, 1988), indicating an interaction between central opioid and dopaminergic systems in cocaine reinforcement. More recently, administration of the kappa-opioid receptor agonist U69593 (5a,7a,8b-(−)-*N*-methyl-*N*-(7-[1-pyrrolidinyl]-1-oxasipro(4,5)dec-8-yl)benzene acetamide; 0.0625–0.5 mg kg^{-1} i.p.) was shown to dose-dependently increase ICSS thresholds, reflecting a decrease in brain reward function (Todtenkopf *et al*., 2004). However, no report has yet demonstrated a role of kappa-opioid receptor agonists in cocaine-induced lowering of ICSS thresholds.

Self-administration: acquisition, maintenance and reinstatement

Nonselective opioid receptor antagonists, naltrexone (0.1–10 mg kg^{-1} s.c.) and naloxone (0.3 mg kg^{-1} s.c.), have been shown to reduce cocaine self-administration in rats (Corrigall and Coen, 1991). The mu-opioid receptor selective agonist DAMGO (Tyr-D-Ala-Gly-[*N*MePhe]-NH$(CH_2)_2$) produced a dose-related decrease in cocaine self-administration when delivered by microinfusion into the VTA, whereas the mu-selective antagonist CTOP (D-Phe-Cys-Tyr-D-Trp-Oru-Thr-Pen-Thr-NH_2) produced small effects on cocaine self-administration (Corrigall *et al*., 1999). Similarly, it has been reported that site-specific microinjections (in both the Nacc and the VTA simultaneously) of the mu-opioid receptor selective antagonist β-funaltrexamine attenuated responding for cocaine under a progressive ratio schedule of reinforcement in rats (Ward *et al*., 2003). The effect of kappa-opioid receptor antagonism on cocaine consumption remains equivocal as either a decreased intake (Kuzmin *et al*., 1998) or a lack of effect was reported after administration of kappa-opioid receptor antagonists in rats (Glick *et al*., 1995; Corrigall *et al*., 1999) and in rhesus monkeys (Negus *et al*., 1997).

Evidence also suggests that delta-opioid receptor selective compounds and cocaine may interact with common neural substrates (Mansour *et al*., 1987; Svingos *et al*., 1999). But the effects of selective delta-opioid receptor antagonism on the reinforcing effects of cocaine in laboratory animals remain ambiguous. For example, administration of the delta-opioid receptor selective antagonist naltrindole (3 and 10 mg kg^{-1} i.p.) decreased responding for cocaine in rats regardless of the schedule of reinforcement (Reid *et al*., 1995). Conversely, De Vries *et al*. (1995) reported that only naltrindole at the highest dose (10 mg kg^{-1} i.p. but not at 0.03–3.0 mg kg^{-1} i.p.) attenuated cocaine self-administration and markedly decreased locomotor activity as well. In rhesus monkeys, naltrindole administration (0.1–3.2 mg kg^{-1} i.v. or i.m.) produced decreases in cocaine self-administration; however, these effects were inconsistent across animals and sessions and were not dose-related (Negus *et al*., 1995).

The delta-opioid selective antagonist 5′-NTII (naltrindole 5′-isothiocyanate; 5 nmol) decreased cocaine–maintained responding when microinjected in the Nacc but increased cocaine self-administration when administered into the VTA and had no effect when injected in the AMYG, thus supporting a site-specific role of the delta-opioid receptor system in the behavioural effects of cocaine (Ward and Roberts, 2007).

Using an extinction/reinstatement model, it has been shown that the reinstatement of active lever pressing by cocaine was blocked by intra-ventral pallidum administration of the mu-opioid receptor antagonist CTAP (0.03–3.0 μg). Conversely, morphine administration (1–30 μg) in the ventral pallidum reinstated cocaine seeking (Tang *et al*., 2005). In a study in which the extinction procedure remains debatable, it was shown that pretreatment with naltrexone (3 mg kg^{-1} s.c.) progressively attenuated the cocaine-prime-induced reinstatement over repeated reinstatement tests (Gerrits *et al*., 2005). Much clearer is the observation that both methadone (30 mg kg^{-1} day^{-1} via osmotic minipumps) and buprenorphine (3 mg kg^{-1} day^{-1} via osmotic minipumps)

reduced cocaine seeking during extinction and following acute cocaine priming injections, but had no effect on footshock-induced reinstatement for drug seeking (Leri *et al*., 2004; Sorge *et al*., 2005). Pretreatment with the kappa-opioid receptor agonist U69593 (0.32 mg kg^{-1} s.c.) decreased both amphetamine- and cocaine-induced reinstatement of a previously extinguished amphetamine-seeking behaviour (Schenk and Partridge, 2001), whereas administration of the kappa-opioid receptor antagonist JDTic ((3*R*)-7-hydroxy-*N*-{(1*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl}-2-methylpropyl}-1,2,3,4-tetrahydro-3-isoquinoline-carboxamide; 10–30 mg kg^{-1} i.g.) significantly reduced footshock-induced reinstatement without affecting cocaine-prime-induced reinstatement of responding previously reinforced by cocaine (Beardsley *et al*., 2005).

Nociceptin/orphanin FQ

The opioid receptor like-1 (ORL-1) receptor and its endogenous ligand are widely distributed throughout the CNS and particularly in brain regions involved in motivational and emotional behaviours (Neal Jr *et al*., 1999a, b). Specifically, *in situ* hybridization and immunohistochemical studies have demonstrated localization of the ORL-1 receptor in the VTA (Maidment *et al*., 2002; Norton *et al*., 2002), where the cell bodies of the mesolimbic dopaminergic reward circuitry originate. Nociceptin (also called orphanin FQ), a 17-amino-acid peptide, is the natural ligand of the ORL-1 receptor. This peptide shows structural similarities to opioid peptides, mainly dynorphin A (Meunier *et al*., 1995; Reinscheid *et al*., 1995). However, unlike opioid peptides, it does not bind to opioid receptors and does not seem to produce a CPP or conditioned place aversion (CPA), at least when injected i.c.v. in rats (Devine *et al*., 1996). A mild conditioned place aversion was observed in mice when administered alone at doses above those required for suppressing place preference (Sakoori and Murphy, 2004). Finally, N/OFQ administration has been shown to attenuate basal (Murphy *et al*., 1996) and cocaine-induced increases (Lutfy *et al*., 2001) in extracellular DA in the Nacc (for exhaustive summary of studies investigating the effect of ligands of the ORL-1 receptor on reward-based behaviours and the activity of the mesolimbic DA system, see Sakoori and Murphy, 2008, supplementary material and methods). Additionally, N/OFQ has been shown to decrease glutamate release in the cortex (Nicol *et al*., 1996) and lateral AMYG (Meis and Pape, 2001).

Sensitization

Repeated bilateral administration of N/OFQ (5.56 and 16.68 nmol per side) into the VTA 5–10 min before the injection of cocaine (40 mg kg^{-1} i.p.) only produced a transient decrease in the hyperlocomotion response of cocaine on the first day of the sensitization paradigm, and did not alter the development of the cocaine behavioural sensitization (Narayanan and Maidment, 1999), confirming the rapid tolerance observed to the effect of N/OFQ (Devine *et al*., 1996). Paradoxically, when repeatedly administered into the VTA without peripheral cocaine, N/OFQ induces a sensitized response to a subsequent single dose of cocaine (Narayanan and Maidment, 1999). However, increasing doses of N/OFQ (5, 10, 20, 30 and 40 nmol i.c.v.) given before systemic amphetamine administration during the development of sensitization significantly attenuate the induction of sensitization to the challenge dose of amphetamine in male Wistar rats (Kotlinska *et al*., 2003). Similar results were reported in Sprague–Dawley rats using escalating doses of N/OFQ (15, 30 and 60 nmol i.c.v. or 7.5, 15 and 30 nmol intra-VTA) (Lutfy *et al*., 2002). Further, N/OFQ failed to block the development of behavioural sensitization to cocaine in the presence of the nociceptin receptor antagonist J-113397 (1-[(3*R*,4*R*)-1-cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1, 3-dihydro-2*H*-benzimidazol-2-one; 30 nmol i.c.v.), indicating that the effects of N/OFQ are mediated through a specific interaction with the ORL-1 receptor (Lutfy *et al*., 2002). It is worth noting, however, that the development of behavioural sensitization to methamphetamine (2 mg kg^{-1} s.c.) was lower in mice lacking the ORL-1 receptor and was attenuated by UFP-101 ([Nphe^{1}, Arg^{14},Lys^{15}]nociceptin-NH$_2$) administration (10 nmol i.c.v.) in wild-type mice (Sakoori and Murphy, 2008).

Conditioned place preference

Ample evidence suggests that administration of exogenous N/OFQ i.c.v. negatively modulates the function of the mesolimbic dopaminergic reward circuitry (Murphy *et al*., 1996; Lutfy *et al*., 2001; Maidment *et al*., 2002; Norton *et al*., 2002) and attenuates, at doses between 3 and 12 nmol i.c.v., the acquisition of amphetamine-induced CPP (Kotlinska *et al*., 2003) and the expression of cocaine-induced CPP in both rats (Kotlinska *et al*., 2002) and mice (Sakoori and Murphy, 2004). Accordingly, mice lacking the ORL-1 receptor exhibit greater CPP than their wild-type littermates, an observation supported by the enhanced rewarding action of cocaine in the presence of nociceptin receptor antagonists J-113397 and UFP-101 in wild-type mice (Marquez *et al*., 2008; Sakoori and Murphy, 2008). These results provide evidence that endogenous N/OFQ buffers the positive hedonic state induced by psychostimulant drugs. However, Sakoori and Murphy claim that, in line with the reduced behavioural sensitization to methamphetamine observed in these mutant mice, the strengthening effect of chronic methamphetamine treatment on CPP is absent in mice lacking the ORL-1 receptor (Sakoori and Murphy, 2008). These authors suggest therefore that despite an inhibitory influence of the endogenous N/OFQ/ORL-1 receptor system on the rewarding action of acute psychostimulants (Marquez *et al*., 2008), endogenous N/OFQ may facilitate the long-term alterations induced by chronic methamphetamine administration, and thus may play either a permissive or a facilitatory role in the development of addiction (Sakoori and Murphy, 2008).

Intracranial self-stimulation

No report to date has established a direct involvement of the N/OFQ system in the regulation of the electrical brain stimulation.

Self-administration: acquisition, maintenance and reinstatement
Despite a large body of evidence showing the influence of N/OFQ on the acquisition of both cocaine- and amphetamine-induced sensitization or place preference, there is a surprising lack of evidence to support the involvement of N/OFQ in both cocaine and amphetamine self-administration. To date, only Martin-Fardon and colleagues have demonstrated that N/OFQ (0.55–1.11 nmol i.c.v.) was unable to prevent stress-induced reinstatement for cocaine seeking in male Wistar rats (Martin-Fardon *et al*., 2000). However, N/OFQ remains an interesting tool with potential for the prevention of alcohol abuse, as acute administration of the OFQ/ORL-1 receptor agonist Ro646198 ((1*S*,3a*S*)-8-(2,3,3a,4.5.6-hexahydro-1*H*-phenalen-1-yl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one; 0.1, 0.3 and 1.0 mg kg^{-1} i.p.) caused a dose-dependent reduction of ethanol consumption and prevented relapse-like behaviour in a manner similar to blockade of opioid receptors by naltrexone (Ciccocioppo *et al*., 2004; Kuzmin *et al*., 2007). Similar observations were made with the administration of the peptide (0.5–2 μg i.c.v.), notably or particularly, a reduction of home-cage ethanol consumption, a decrease of ethanol-induced CPP and a significant inhibition of stress-induced reinstatement of alcohol-seeking behaviour (Ciccocioppo *et al*., 2004).

Corticotropin-releasing factor

CRF is a 41-amino-acid peptide identified as a hypothalamic releasing factor (Vale *et al*., 1981). CRF stimulates the release of adrenocorticotropic hormone from the pituitary into the bloodstream, which releases glucocorticoids from the adrenal gland. These hypothalamic–pituitary–adrenal hormones play an important role in physiological responses to stress (Koob, 1999a). In addition, the CNS contains CRF in several extrahypothalamic brain regions (including central nucleus of the AMYG and bed nucleus of stria terminalis (BNST)) where it coordinates behavioural and autonomic responses to stressors (Cummings *et al*., 1983; Erb *et al*., 2001). To date, two genes encoding mammalian CRF receptors (CRF_1 and CRF_2) have been identified (Bale and Vale, 2004). Evidence supports the notion that the CRF system mediates anxiety and other dysphoric states (Bale and Vale, 2004), and recruitment of the CRF system has been hypothesized to be involved in drug dependence in humans (Koob, 1999b).

Sensitization
It is well established that repeated stress exposure can result in a sensitized activational response to psychostimulants (Kalivas and Stewart, 1991; Covington and Miczek, 2001). These effects have been shown to be mediated, at least in part, by CRF systems (Cole *et al*., 1990). The converse has also been shown to be true; animals that have received repeated intermittent injections of cocaine or amphetamine show augmented behavioural, neuroendocrine and neuronal responses to stress challenge (Kalivas and Duffy, 1989; Hamamura and Fibiger, 1993). Finally, repeated i.c.v. injections of CRF produce a sensitized locomotor response to a low dose of amphetamine 1 week following termination of CRF treatment (Cador *et al*., 1993). Precisely, CRF (0.02–0.1 mg i.c.v.) was found to potentiate behavioural stereotypy induced by amphetamine (4 mg kg^{-1} s.c.) (Cole and Koob, 1989). Repeated administration of CRF (0.5–2.5 mg i.c.v.) was reported to induce a long-lasting sensitization to amphetamine challenge (0.75 mg kg^{-1} s.c.) (Cador *et al*., 1993). In contrast, α-helical CRF (25 mg i.c.v.), a nonspecific CRF receptor antagonist, given before restraint stress, prevented the development of stress-induced sensitization to an amphetamine challenge (3 mg kg^{-1} s.c.), administered 5 days after last exposure to restraint stress (Cole *et al*., 1990). Taken together, these studies suggest that prior stressor exposure facilitates the magnitude of unconditioned motor responses to psychostimulant drugs in a CRF-dependent manner. Erb and co-workers (Erb *et al*., 2003; Erb and Brown, 2006) extended this observation by revealing the role of CRF in the long-term expression (up to 28 days) of behavioural sensitization to cocaine.

Conditioned place preference
A key observation reported that a single injection of cocaine (10 mg kg^{-1} i.p.) could reactivate cocaine-conditioned place preference following a 28-day extinction period and, in these conditions, pretreatment with α-helical CRF (10 μg i.c.v.) significantly attenuated this reactivation of CPP. However, pretreatment with CP154526 (butyl-ethyl-(2,5-dimethyl-7-[2,4,6-trimethylphenyl]-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)amine; 1 or 10 mg kg^{-1} i.p.), a specific CRF receptor subtype 1 antagonist, and AS-30 (([D-Phe(11),His(12)]Svg-(11-40)); 1 or 10 μg i.c.v.), a specific CRF receptor subtype 2 antagonist, failed to show the same effects. In addition, a single footshock stress also elicited the reactivation of cocaine-conditioned place preference following a 28-day extinction, and pretreatment with α-helical CRF (10 μg i.c.v.) or CP154526 (1 or 10 mg kg^{-1} i.p.) significantly blocked this effect (Lu *et al*., 2001).

Intracranial self-stimulation
Administration of CRF dose-dependently elevates ICSS thresholds without altering performance measures (latencies to respond to stimulation, extra responses and time-out responses). In contrast to the significant threshold elevation effects of CRF, the competitive CRF receptor antagonist D-Phe-CRF-(12-41) (D-Phe^{12},Nle^{21,38},aMeLeu^{37}-CRF) has no effect on ICSS thresholds or performance measures. To determine the neuropharmacological specificity of the effect of CRF on brain stimulation reward, D-Phe-CRF-(12-41) was used to antagonize CRF-induced threshold elevations. Pretreatment with D-Phe-CRF-(12-41) (5 or 10 μg i.c.v.) effectively blocked CRF-induced reward threshold elevations (3 μg i.c.v.) without affecting other ICSS performance measures. These results indicate that CRF neurotransmission can modulate ICSS reward processes (Macey *et al*., 2000). However, it remains unknown whether CRF antagonism is able to counterbalance the cocaine-induced lowering effect of ICSS thresholds.

Self-administration: acquisition, maintenance and reinstatement
There is considerable evidence that the stress-related neuropeptide CRF plays an important role in mediating behavioural changes induced by prior experience with cocaine. For instance, neuroadaptation in the CRF system in the extended amygdala has been proposed to drive the negative motivational state associated with abstinence in drug-dependent humans (Koob, 2003). Research substantiating this hypothesis includes findings that extracellular CRF levels are increased in the central AMYG during cocaine withdrawal in rats (Richter and Weiss, 1999). CRF receptor antagonists have been found to reduce negative emotional states during withdrawal from cocaine (Basso *et al*., 1999; Przegalinski *et al*., 2005) and methamphetamine (Moffett and Goeders, 2007). Accordingly, brain CRF systems have been found to play a key role in stress-induced reinstatement of cocaine seeking after prolonged drug-free periods (Erb *et al*., 1998; Shaham *et al*., 1998; Erb and Stewart, 1999) and in mediating stress-induced reactivation of an extinguished cocaine-conditioned place preference (Lu *et al*., 2001), as well as in mediating reinstatement of cocaine-seeking behaviour in rats during withdrawal (Erb *et al*., 2001, 2006). Taken together, these data suggest that activation of CRF systems in the brain may be involved in the development of emotional dysregulation hypothesized to motivate drug intake in cocaine dependence.

The effect of CRF antagonism on cocaine consumption remains controversial. Indeed, administration of the selective nonpeptide CRF_1 receptor antagonist CP154526 (10–40 $mg\,kg^{-1}$ i.p.) has been reported to decrease cocaine self-administration without altering lever pressing for food in rats (Goeders and Guerin, 2000), whereas using similar doses (10–20 $mg\,kg^{-1}$ i.p.), Przegalinski *et al*. claimed that CP154526 did not alter the rewarding effects of cocaine, assessed by the number of active lever presses and infusions. Similarly, other studies reported that the peptide CRF receptor antagonist astressin (cyc^{30-33}[D-Phe^{12},$Nle^{21,38}$,Glu^{30},Lys^{33}]CRF-(12-41); 0.1–1.0 $mg\,kg^{-1}$ i.v.) or the CRF_1 receptor antagonist antalarmin (*N*-butyl-*N*-ethyl-(2,5,6-trimethyl)-7-[2,4,6-trimethylphenyl]-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl-amine; 5–10 $mg\,kg^{-1}$ i.m.) had no effect on cocaine self-administration in rhesus monkeys (Broadbear *et al*., 1999; Mello *et al*., 2006).

However, confirming the role of the CRF system in cocaine dependence, a recent study (Specio *et al*., 2007) established that systemic pretreatment with antalarmin (25 $mg\,kg^{-1}$ i.p.) decreased cocaine intake selectively in a rat model of escalated cocaine intake (Ahmed and Koob, 1998). Consistent with the above findings, antalarmin administration was found to be ineffective in nondependent rats. These data support the hypothesis that the CRF system contributes to the escalated drug intake of rats with extended drug access, a model of the development of drug dependence (Specio *et al*., 2007).

The most reliable and replicable observations demonstrated a key role of the CRF system in the vulnerability for stress-induced reinstatement of a previously extinguished cocaine-seeking behaviour. In one study, rats were trained to self-administer cocaine for 10–14 days, and were then given extinction sessions for 5–14 days (saline was substituted for cocaine). Tests for reinstatement were given after intermittent footshock (10 min, 0.5 mA) and after priming injections of saline and cocaine (20 $mg\,kg^{-1}$ i.p.). Footshock reinstated cocaine seeking in both intact rats and in adrenalectomized rats that were given corticosterone replacement, but not in adrenalectomized animals (Erb *et al*., 1998). In addition, the CRF receptor antagonist D-Phe-CRF-(12-41) (0.1–1.0 mg i.c.v.) blocked footshock-induced reinstatement in both intact rats and in adrenalectomized rats that were given corticosterone replacement. Reinstatement induced by priming injections of cocaine was only minimally attenuated by adrenalectomy or by the CRF receptor antagonist. Using procedures similar to those described previously, another study found that the nonpeptide CRF_1 receptor antagonist CP154526 attenuated footshock-induced reinstatement in cocaine-trained rats at doses that do not alter high rates of operant responding for a sucrose solution (Shaham *et al*., 1998). Later, the role of CRF receptors in the AMYG and the BNST in a footshock stress-induced model of reinstatement of cocaine seeking was investigated (Erb and Stewart, 1999). During tests for reinstatement, different groups of animals were pretreated with vehicle or the CRF receptor antagonist D-Phe-CRF-(12-41) into either the BNST (10 or 50 ng per side) or the AMYG (50 or 500 ng per side) before exposure to intermittent footshock stress (15 min). Two other groups of animals were given vehicle or CRF infusions into either the BNST (100 or 300 ng per side) or the AMYG (300 ng per side) before the test sessions to assess whether CRF itself would induce reinstatement. Infusions of the CRF receptor antagonist into the BNST attenuated footshock-induced reinstatement of cocaine seeking, whereas infusions of CRF into this area induced reinstatement. Conversely, these effects of D-Phe-CRF-(12-41) and CRF were not observed after infusions into the central nucleus of the AMYG. Finally, it was reported that footshock stress releases CRF in the VTA, and that, in cocaine-experienced but not in cocaine-naive rats, this CRF acquires control over local glutamate release, which, in turn, activates the mesocorticolimbic DA system and ultimately triggers relapse to drug seeking in cocaine-experienced animals (Wang *et al*., 2005). Thus, long-lasting cocaine-induced neuroadaptations, presumably both at the level of brain stress pathways and glutamate release in the VTA, appear to play an important role in stress-induced relapse to drug use.

Hypocretin/orexin

The hypocretins (also known as orexins) are two neuropeptides, hypocretin-1 and hypocretin-2, derived from the same precursor gene (pre-prohypocretin) produced in a few thousand neurons localized in the perifornical area (PFA) of the LH (de Lecea *et al*., 1998; Sakurai *et al*., 1998). Hypocretin-containing neurons arise in the LH area and project widely in the brain (Peyron *et al*., 1998), with a dense innervation of anatomical sites involved in regulating arousal, motivation and stress states (Baldo *et al*., 2003). Their interaction with autonomic, neuroendocrine and neuroregulatory systems (Sutcliffe and De Lecea, 2002) strongly suggests that they act as neuromodulators in a wide

variety of neural circuits. The hypocretins have been implicated in the modulation of noradrenergic (Hagan *et al*., 1999; Horvath *et al*., 1999; Bourgin *et al*., 2000), cholinergic (Burlet *et al*., 2002), serotonergic (Brown *et al*., 2001, 2002) and dopaminergic systems (Korotkova *et al*., 2003), and in the regulation of the hypothalamic–pituitary–adrenal axis (Jaszberenyi *et al*., 2000; Kuru *et al*., 2000; Stricker-Krongrad and Beck, 2002). In complement of a wide innervation of various neural circuits, the hypocretinergic system projects to all the major components of the extended amygdala, a brain region known to connect the basal forebrain to the classical reward systems of the LH via the medial forebrain bundle reward system. Hence, the hypocretinergic system fulfils both neuroanatomical and functional criteria to modulate critical connections that regulate both positive- and negative-reinforcing properties of drugs of abuse.

Sensitization

The induction of behavioural sensitization is dependent on the activation of NMDA receptors in the VTA (Vanderschuren and Kalivas, 2000). NMDA receptors mediate long-term plasticity at a variety of excitatory synapses, and their activation promotes burst firing in VTA neurons and optimizes DA release, notably in the Nacc (Komendantov *et al*., 2004). To date, only one report characterized the involvement of the hypocretin/orexin system in the induction of both neurochemical and behavioural sensitization to cocaine (Borgland *et al*., 2006). In this report, compelling evidence shows that *in vitro* application of hypocretin-1/orexin-A induces potentiation of NMDA-mediated excitatory postsynaptic current via translocation of NMDA receptors to the synapse. In other words, hypocretin-1/orexin-A enhances synaptic strength in VTA DA neurons. This electrophysiological observation made in rat brain slices was further extended by demonstrating that hypocretin/orexin signalling in the VTA is required for behavioural sensitization to cocaine. Indeed, *in vivo* administration of SB334867 (1-(2-methyylbenzoxanzol-6-yl)-3-[1,5]naphthyridin-4-yl-urea hydrochloride), a hypocretin receptor-1 antagonist ($10\,mg\,kg^{-1}$ i.p. or $6\,\mu g$ intra-VTA) administered daily for 5 days, 15 min before cocaine injections ($15\,mg\,kg^{-1}$ i.p.) significantly blocked the development of cocaine sensitization in Sprague–Dawley rats. Interestingly, when given only on day 6, SB334867 did not reduce locomotor activity, indicating that although hypocretin/orexin signalling is required for the development of cocaine sensitization, it is not required for its expression.

Accordingly, it has been reported that sensitization to amphetamine resulted in preferential activation of c-Fos in dorsomedial hypothalamus and PFA hypocretin 1-containing cells, whereas c-Fos activation in hypocretin 1-containing neurons was not increased following acute amphetamine treatment (McPherson *et al*., 2007). It is noteworthy that, in the LH, sensitized rats showed increased activation of hypocretin 1-containing neurons compared with controls, but not when compared with acute amphetamine treatment. This observation does not support the dichotomy of hypocretin 1 (orexin A)-containing neurons between the LH and the dorsomedial hypothalamus /PFA speculated by Harris and Aston-Jones (2006) according to which different populations of hypocretin/orexin cells may subserve different functions and, specifically, that the LH group would play a role in reward-related events, whereas the dorsomedial hypothalamus and PFA subgroups would function to maintain alertness. Another study, using a reinstatement model, demonstrated that stimuli linked to ethanol availability activate hypocretin neurons within both the dorsomedial hypothalamus and PFA/LH (Dayas *et al*., 2008), in apparent opposition with the hypothesis of Harris and Aston-Jones (2006). Finally, using a slightly different paradigm defined as either renewal of extinguished alcohol seeking or renewal of cocaine seeking, Hamlin *et al*. (2007, 2008) established a clear renewal-associated cFos induction in PFA hypocretin neurons when rats were re-exposed to the context previously associated with alcohol or cocaine consumption. Importantly, these authors observed cFos activation in LH hypocretin neurons during renewal of alcohol seeking, but not during renewal of cocaine seeking. The apparent discrepancy between these reports may however be explained by possible differences in the brain pathways that drive drug-seeking behaviour in a CPP paradigm versus behavioural sensitization and conditioned response reinstatement.

Conditioned place preference

The critical role of hypocretin/orexin neurons in the expression of a CPP has been mainly studied with morphine in rats (Harris *et al*., 2005, 2007). Similarly, the only report available to date with hypocretin knockout mice demonstrates that these mutants do not exhibit any preference for morphine in a CPP paradigm (Narita *et al*., 2006). However, consistent with the hypothesis of a critical role of hypocretin/orexin peptides in cocaine reward, c-Fos activation of hypocretin/orexin neurons was correlated with preference, in rats, for an environment repeatedly paired with cocaine injections (Harris *et al*., 2005).

Intracranial self-stimulation

Several lines of evidence suggest that the hypocretin system is involved in the modulation of the brain reward function (Boutrel *et al*., 2005a). First, both lesion experiments and the ICSS paradigm have suggested an important role of the LH in reward. Second, maintenance of energy homeostasis requires the coordination of systems that regulate feeding, body temperature, and autonomic and endocrine functions with those that modulate an appropriate state of arousal and motivation. Only one published article to date has established a role for hypocretin/orexin in the regulation of the brain reward function. In this report, infusion of hypocretin-1/orexin-A (1.5 nmol i.c.v.) was shown to elevate ICSS thresholds in Wistar rats, indicating a decrease in the excitability of brain reward systems. This effect is in sharp contrast to the cocaine-induced lowering of ICSS thresholds that is considered to reflect an increased sensitivity that underlies, or at least contributes to, the positive affective state associated with drug consumption. In contrast, this

long-lasting reward deficit was similar to that observed after i.c.v. infusion of CRF (Macey *et al*., 2000) or after drug withdrawal (Markou and Koob, 1991; Schulteis *et al*., 1995; Epping-Jordan *et al*., 1998). A recent communication confirmed that intra-VTA administration of hypocretin-1/orexin-A (1 nmol) increased the reward thresholds of ICSS (Hata *et al*., 2007), although this observation was not consistent from one cohort of rats to the other. Anyway, a key question remains unanswered, as it has not been established whether pretreatment with either the hypocretin-1 peptide or the hypocretin receptor-1 antagonist SB334867 could prevent the cocaine-induced lowering of ICSS thresholds.

Self-administration: acquisition, maintenance and reinstatement
Only one study has reported the effect of hypocretin/orexin on cocaine self-administration (Boutrel *et al*., 2005b). In this report, hypocretin-1/orexin-A (1.5 nmol i.c.v.) was shown to not change cocaine self-administration (0.25 mg per infusion) either in Wistar rats exposed to cocaine for 1 h day^{-1} or in rats exposed to cocaine for 6 h day^{-1}. Interestingly, injection of a mixed hypocretin 1/2 receptor antagonist did not change methamphetamine intake either in rats exposed to the drug for 1 h day^{-1} or in rats exposed to the drug for 6 h day^{-1} (S Wee, B Boutrel and GF Koob, unpublished data), suggesting that either activation or blocking of the hypocretin system has no consequence on psychostimulant consumption in a self-administration procedure. When rats were trained to self-administer cocaine using a progressive ratio schedule of reinforcement, which consists of a systematic within-session increase in the ratio of responses required to earn one injection of cocaine, break points, defined as the final ratio (as final number of infusions) obtained by rats before termination of the session, remained unchanged after infusion of hypocretin-1/orexin-A (1.5 nmol i.c.v.). However, it seems that administration of SB334867 (10 mg kg^{-1} i.p.) may reduce motivation for cocaine intake in a progressive ratio schedule of reinforcement (S Borgland, personal communication), suggesting a ceiling effect of peptide administration on the motivation for cocaine intake.

Strikingly, infusions of hypocretin-1/orexin-A (0.3–1.5 nmol i.c.v.) lead to a dose-related reinstatement of a previously extinguished cocaine-seeking behaviour in rats (Boutrel *et al*., 2005b). One possible mechanism by which hypocretin-1/orexin-A reinstated cocaine seeking may have been through induction of a priming effect (also defined as a cocaine-like rewarding effect). However, hypocretin-1/orexin-A infusion into the lateral ventricle significantly elevated ICSS thresholds, reflecting a decrease in the activity of brain reward systems. This action of hypocretin-1/orexin-A on ICSS thresholds is opposite to the threshold-lowering effects of cocaine, an index of cocaine-induced excitation of the brain reward system. This observation provides strong evidence suggesting that hypocretin-1/orexin-A reinstated cocaine seeking by mechanisms different from increased DA release only. Further, the blockade of hypocretin/orexin-induced reinstatement of cocaine seeking by CRF/NA antagonism rather suggests that hypocretin and stress systems may closely interact to regulate cocaine-seeking behaviour (Boutrel *et al*., 2005b). This hypothesis was later confirmed using SB334867 (15–30 mg kg^{-1} i.p.) to prevent footshock-induced reinstatement of a previously extinguished cocaine-seeking behaviour (Boutrel *et al*., 2005b). Another elegant demonstration established that cues previously paired with cocaine consumption elicited a significant increase in cFos-positive hypocretin/orexin neurons that persisted along with repeated reinstatement tests, whereas cues previously paired with sweetened condensed milk rapidly lost their efficiency to elicit relapse for reward seeking as well as cFos activation of hypocretin/orexin neurons (Martin-Fardon *et al*., 2007). Overall, these findings identify the hypocretin/orexin system as a new system critically involved in the vulnerability to relapse to drug/alcohol seeking and drug/alcohol taking (Carr and Kalivas, 2006; Lawrence *et al*., 2006; Wise, 2006).

Conclusion

Drug addiction is a major public health concern, and the desire or need to obtain and consume drug that can overwhelm an addict years after last contact with drug is among the most debilitating long-term effects of drug abuse (Leshner, 1997). Brain mechanisms responsible for drug craving and relapse remain poorly understood despite accumulating evidence delineating the cellular and molecular adaptations induced by chronic consumption of drug of abuse (Nestler, 2002). Alleviating symptoms of addiction, and notably the risk of relapse after a period of protracted abstinence, is a challenge for both medicine and basic science. Even more challenging is the discovery of an effective pharmacotherapy aiming at preventing drug abuse and relapse without debilitating side effects. For the past 20 years, several peptidergic systems have been identified, and their role in modulating vulnerability to psychostimulant abuse has been confirmed by numerous studies, although it is clear that they usually do not interrupt stimulant consumption. Most of the peptidergic systems presented in this review have in common the ability to reduce risks of relapse-like behaviours. However, it is quite clear that peptides may fine-tune motivated behaviours but cannot counteract the reinforcing properties of psychostimulants. The endocannabinoids present a limited impact on cocaine and amphetamine reinforcing properties, but play a key role in both cue- and drug priming-induced relapse for drug seeking and drug taking, without affecting stress-induced relapse-like behaviour. The involvement of the opioid system is rather complex given the opposite roles of the different receptor subtypes, but remains of interest in preventing both amphetamine and cocaine abuse. Despite a role in the prevention of stimulant-induced behavioural sensitization and the expression of a CPP for stimulants, the N/OFQ system has not yet been shown to be effective in preventing cocaine/amphetamine abuse in an operant conditioning procedure in rodents. Neuroadaptation in the CRF system has been proposed to drive the negative motivational state associated with abstinence in dependent animals, and activation of CRF systems has been involved in the development of emotional dysregulation hypothesized to

motivate drug intake in cocaine dependence. Accordingly, CRF antagonism has been shown to be effective in preventing stress-induced reinstatement for drug seeking and drug taking. Finally, the hypocretin/orexin system, which has been recently shown to play a role in drug addiction, seems to be a promising tool in both cue- and stress-induced reinstatement of a previously extinguished drug-seeking and drug-taking behaviour despite an apparent lack of effect on stimulant consumption. It is noteworthy that drugs modulating the above-mentioned systems were shown to be effective in preventing relapse for drug seeking at doses usually not accompanied by severe side effects, and therefore represent interesting tools with potential for the prevention of both cocaine and amphetamine abuse.

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Conflict of interest

The author states no conflict of interest.

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