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Role of CRF and other neuropeptides in stress-induced reinstatement of drug seeking

Uri Shalev^{1,*}, Suzanne Erb^{2,*}, and Yavin Shaham³

¹Department of Psychology, Center for Studies in Behavioral Neurobiology/Groupe de Recherche en Neurobiologie Comportementale, Concordia University, Montreal, Quebec, Canada

²Center for Neurobiology of Stress, Department of Psychology, University of Toronto Scarborough, Toronto, Ontario, Canada

³Behavioral Neuroscience Branch, NIDA/IRP, NIH, Baltimore, MD, USA

Abstract

A central problem in the treatment of drug addiction is high rates of relapse to drug use after periods of forced or self-imposed abstinence. This relapse is often provoked by exposure to stress. Stress-induced relapse to drug seeking can be modeled in laboratory animals using a reinstatement procedure. In this procedure, drug-taking behaviors are extinguished and then reinstated by acute exposure to stressors like intermittent **unpredictable** footshock, restraint, food deprivation, and systemic injections of yohimbine, an alpha-2 adrenoceptor antagonist that induces stress-like responses in humans and nonhumans. For this special issue entitled "The role of neuropeptides in stress and addiction", we review results from studies on the role of corticotropin-releasing factor (CRF) and several other peptides in stress-induced reinstatement of drug seeking in laboratory animals. The results of the studies reviewed indicate that extrahypothalamic CRF plays a critical role in stress-induced reinstatement of drug seeking; this role is largely independent of drug class, experimental procedure, and type of stressor. There is also limited evidence for the role of dynorphins, hypocretins (orexins), nociceptin (orphanin FQ), and leptin in stress-induced reinstatement of drug seeking.

Keywords

Conditioned place preference; Extinction; Neuropeptides; Reinstatement; Relapse; Self-administration; Stress

Introduction

Drug addiction is characterized by high rates of ^{RELAPSE} following prolonged periods of abstinence (Jaffe, 1990; O'Brien, 1997); this relapse is often provoked by exposure to ^{STRESS} (BAKER ET AL., 2004; SINHA, 2001). The clinical scenario of stress-induced relapse can be modeled in a ^{REINSTATEMENT} procedure using laboratory animals (Epstein et al., 2006; Shaham et al.,

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Corresponding authors: Uri Shalev (uri.shalev@concordia.ca) or Suzanne Erb (Erb@utsc@utoronto.ca).

*US and SE contributed equally to this work

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2000a). Since the mid 1990s, we and others have used variations of the reinstatement procedure, which are based on the OPERANT SELF-ADMINISTRATION and CONDITIONED PLACE PREFERENCE (CPP) procedures, to study stress-induced reinstatement of drug seeking (Lu et al., 2003; Shaham et al., 2000a; Shalev et al., 2002). Stressors reported to reinstate drug seeking in the operant self-administration reinstatement procedure include intermittent **unpredictable** footshock, acute one-day food deprivation, and yohimbine (Carroll, 1985; Erb et al., 1996; Lee et al., 2004; Shaham and Stewart, 1995; Shalev et al., 2000; Shepard et al., 2004). Yohimbine is a prototypical alpha-2 adrenoceptor antagonist, which after systemic injections induces stress- and anxiety-like responses in humans and laboratory animals (Redmond and Huang, 1979). Stressors reported to reinstate drug seeking in the CPP reinstatement procedure include intermittent **unpredictable** footshock, restraint, conditioned fear, social defeat, swim stress, and tail pinch (Kreibich and Blendy, 2004; Ribeiro Do Couto et al., 2006; Sanchez and Sorg, 2001; Sanchez et al., 2003; Wang et al., 2006).

In previous recent reviews, we and others summarized the literature on the neuropharmacology and neuroanatomy of stress-induced reinstatement of drug seeking (Aguilar et al., 2009; Bossert et al., 2005; Erb et al., 2001; Kalivas and McFarland, 2003; Shaham et al., 2000a; Shalev et al., 2002). For this special issue, entitled “the role of neuropeptides in stress and addiction”, we discuss in some detail the role of corticotropin-releasing factor (CRF) (Vale et al., 1981), dynorphins (Chavkin et al., 1982), and hypocretins (de Lecea et al., 1998; Sakurai et al., 1998) in stress-induced reinstatement of drug seeking in laboratory animals. We also review a limited number of studies on the role of CRF and hypocretin in stress-induced reinstatement of palatable food seeking (Nair et al., 2009b); in these studies, the stressor used was yohimbine. Finally, we briefly discuss results from several studies on the degree to which several other peptides play a role in stress-induced reinstatement. These include, nociceptin/orphanin FQ (termed here as nociceptin) (Meunier et al., 1995; Reinscheid et al., 1995), leptin (Friedman and Halaas, 1998), neuropeptide Y (Tatemoto et al., 1982), neuropeptide S (Xu et al., 2004), melanin-concentrating hormone (MCH) (Kawauchi et al., 1983), and peptide YY3-36 (Batterham et al., 2002). Table 1 provides a glossary of terms that appear in SMALL CAPITAL LETTERS in the text.

Role of CRF in stress-induced reinstatement

The stress neuropeptide CRF was first characterized in 1981 by Vale et al. (1981). CRF is part of a family of ligands and receptors that, in mammals, also includes urocortin I, urocortin II, and urocortin III, their receptors (CRF1 and CRF2), and a CRF binding protein (Bale and Vale, 2004). CRF actions on CRF receptors in the paraventricular hypothalamic nucleus lead to activation of the hypothalamic-pituitary adrenal (HPA) axis, resulting in the release of the hormone corticosterone (or cortisol in humans) by the adrenals (Dallman et al., 1995; Selye, 1936). CRF is known to be involved in behavioral and physiological stress responses via its actions on CRF receptors located in both hypothalamic and extra-hypothalamic brain sites (de Souza, 1995; Dunn and Berridge, 1990; Swanson et al., 1983; Van Pett et al., 2000). Results from many studies demonstrate an important role of CRF in both the aversive states of opiate, psychostimulant, alcohol, and nicotine withdrawal, and in dependence-induced increases in **drug** intake (Heilig and Koob, 2007; Koob, 2008; Sarnyai et al., 2001). Below, we discuss results on the role of CRF in stress-induced reinstatement of drug seeking.

Systemic and ventricular injections of CRF receptor antagonists attenuate stress-induced reinstatement

In an initial study, Shaham et al. (1997) reported that ventricular injections of alpha-helical CRF₉₋₄₁ (a non-selective peptide CRF receptor antagonist/partial agonist) decreases footshock-induced reinstatement of heroin seeking. Subsequently, several investigators reported that ventricular injections of D-Phe CRF₁₂₋₄₁ (a newer non-selective peptide CRF receptor

antagonist) decrease footshock-induced reinstatement of cocaine, alcohol, and nicotine seeking (Erb et al., 1998; Le et al., 2000; Liu and Weiss, 2002; Zislis et al., 2007). These effects of alpha-helical CRF₉₋₄₁ and D-Phe CRF₁₂₋₄₁ are likely mediated by CRF1 receptors. Le et al. (2000) and Shaham et al. (1998) reported that systemic injections of CP-154,526 (a selective non-peptide CRF1 receptor antagonist) decrease footshock-induced reinstatement of heroin, cocaine, and alcohol seeking. Bruijnzeel et al. (2009) reported that ventricular injections of R278995 (a CRF1 receptor antagonist), but not astressin-2B (a CRF2 receptor antagonist), decrease footshock-induced reinstatement of nicotine seeking.

The effects of CRF receptor antagonists are not limited to the intermittent footshock stressor or the operant self-administration reinstatement procedure. Lu et al. (2000;2001) used a "reactivation" CPP procedure in which a previously learned CPP for morphine or cocaine, which is no longer expressed several weeks after CPP training, is restored (reactivated) by exposure to intermittent footshock. They found that footshock-induced CPP "reactivation" is decreased by alpha-helical CRF₉₋₄₁, but not by antisauvagine-30 (a moderately selective CRF2 receptor antagonist). Additionally, ventricular injections of alpha-helical CRF₉₋₄₁ decreased food-deprivation-induced reinstatement of heroin seeking (Shalev et al., 2006) and systemic injections of antalarmin (a CRF1 receptor antagonist) decreased yohimbine-induced reinstatement of alcohol or palatable food seeking (Ghitza et al., 2006; Marinelli et al., 2007). In contrast, Brown et al. (2009) reported that in cocaine-trained rats, ventricular injections of D-Phe CRF₁₂₋₄₁ had no effect on yohimbine-induced reinstatement. The reasons for the discrepant findings in cocaine-versus alcohol- and food-trained animals are unknown. One possibility is that the mechanisms underlying yohimbine-induced reinstatement in rats with different reward histories are not identical. Alternatively, the discrepant results may have been due to the lower magnitude of yohimbine-induced reinstatement in the Brown et al. (2009) study, making it more difficult to detect inhibition of lever responding under their experimental conditions. However, this seems unlikely because reinstatement of similar magnitude, induced by exposure to ventricular noradrenaline, was blocked by D-Phe CRF₁₂₋₄₁ (Brown et al., 2009). Finally, additional evidence for a critical role of CRF in stress-induced reinstatement is that ventricular injections of CRF reinstate heroin, cocaine, and alcohol seeking (Brown et al., 2009; Le et al., 2000; Shaham et al., 1997).

Role of extrahypothalamic, but not hypothalamic CRF, systems in stress-induced reinstatement

Systemic or ventricular injections of CRF receptor antagonists can block stress-induced reinstatement by their action on CRF receptors located in either hypothalamic (leading to activation of the HPA axis and the release of corticosterone) or extrahypothalamic sites, or both. The contribution of CRF-mediated stress-induced activation of the HPA axis and the release of corticosterone to stress-induced reinstatement can be assessed by preventing this release by adrenalectomy or by corticosterone synthesis inhibitors like metyrapone or ketoconazole. Results from studies in which these endocrine methods were used indicate that CRF-mediated stress-induced activation of the HPA axis does not contribute to stress-induced reinstatement of drug seeking.

In an initial study, Shaham et al. (1997) reported that neither adrenalectomy nor metyrapone injections decreased footshock-induced reinstatement of heroin seeking. In cocaine-trained rats, adrenalectomy attenuated footshock-induced reinstatement; however, when basal levels of corticosterone were restored with pellet implants, the effect of the adrenalectomy on this reinstatement was reversed (Erb et al., 1998). Thus, although basal levels of corticosterone seem to play a permissive role in footshock-induced reinstatement of cocaine seeking, a stress-induced rise in corticosterone levels is not required. A similar pattern of results was obtained in studies on the effect of food-deprivation on reinstatement of heroin and cocaine seeking. In

heroin-trained rats, adrenalectomy had no effect on food-deprivation-induced reinstatement (Shalev et al., 2006). In cocaine-trained rats, adrenalectomy attenuated food deprivation-induced reinstatement, and this effect was reversed by providing basal levels of the hormone after adrenalectomy (Shalev et al., 2003). It is also likely that CRF's role in yohimbine-induced reinstatement of drug seeking is mediated by extrahypothalamic sites. Marinelli et al. (2007) reported that systemic injections of antalarmin, which attenuated yohimbine-induced reinstatement, had no effect on yohimbine-induced corticosterone release.

Taken together, the data from these studies indicate that the effect of CRF receptor antagonists on stress-induced reinstatement is mediated via their action at extrahypothalamic sites, independent of their effect on the HPA axis (Shaham et al., 2000a). This conclusion, however, is not supported by the findings of Mantsch and Goeders (1999) that systemic injections of ketoconazole decreased footshock-induced reinstatement of cocaine seeking. However, these results should be interpreted with caution; although ketoconazole inhibits corticosterone synthesis, this antimycotic agent also acts on several other neurotransmitter and hormonal systems, including GABA, histamine, and testosterone (Fahey et al., 1998; Gietzen et al., 1996; Heckman et al., 1992). Thus, it is unknown whether ketoconazole's effects on reinstatement are due to its effects on corticosterone synthesis. Finally, additional evidence for a role of extrahypothalamic CRF in stress-induced reinstatement is derived from studies described below on the effect of site-specific brain injections of CRF and CRF receptor antagonists.

In the initial study, Erb and Stewart (1999) reported that D-Phe CRF₁₂₋₄₁ injections into the bed nucleus of stria terminalis (BNST), but not the central amygdala nucleus (CeA), decreased footshock-induced reinstatement of cocaine seeking. Conversely, BNST, but not CeA, CRF injections reinstated cocaine seeking. In agreement with these findings, Wang et al. (2006) reported that BNST, but not CeA, injections of CP-154,526 decreased footshock-induced reinstatement of morphine CPP.

While Erb and Stewart (2001) reported that blockade or activation of CeA CRF receptors had no effect on footshock-induced reinstatement of cocaine seeking, in a subsequent study Erb et al. (2001) provided evidence that a CRF projection from the CeA to the BNST (Sakanaka et al., 1986) contributes to this reinstatement. They reported that functional inactivation of the CRF pathway from the CeA and BNST, by injection of tetrodotoxin (a sodium channel blocker that inhibits neuronal activity) into the CeA in one hemisphere and D-Phe CRF₁₂₋₄₁ into the BNST in the contralateral hemisphere, decreased footshock-induced reinstatement.

More recently, Wang et al. (2005;2007) reported that CRF in the ventral tegmental area (VTA) is critical for footshock-induced reinstatement of cocaine seeking. They first reported that VTA perfusions (via a microdialysis probe) of alpha-helical CRF₉₋₄₁ blocked the footshock-induced reinstatement, and that local CRF perfusions reinstated cocaine seeking (Wang et al., 2005). Subsequently, they reported that footshock-induced reinstatement of cocaine seeking was blocked by VTA perfusion of a selective CRF2 receptor antagonist and an inhibitor of the CRF binding protein, but not by a selective CRF1 receptor antagonist. They also reported that VTA perfusion of CRF or CRF2 receptor agonists that have strong affinity for CRF-BP induced reinstatement of cocaine seeking, whereas CRF receptor agonists that do not bind CRF-BP were ineffective (Wang et al., 2007). These are surprising findings in light of results from the studies described above (in which CRF antagonists were injected systemically or into the ventricles) that implicated CRF1 but not CRF2 receptors in stress-induced reinstatement. The data of Wang et al. (2007) are also surprising in view of anatomical studies indicating that CRF1 receptors are the predominant CRF receptors in VTA (Van Pett et al., 2000).

Finally, the median raphe nucleus (MRN), a major cell body region of serotonin containing neurons in the central nervous system (Vertes et al., 1999), has been implicated in the role for CRF in the footshock-induced reinstatement of alcohol seeking. Le et al. (2002) reported that MRN injections of D-Phe CRF₁₂₋₄₁ decrease footshock-induced reinstatement of alcohol seeking, while local CRF injections reinstate alcohol seeking.

Role of hypocretins in stress-induced reinstatement

First discovered in 1998, hypocretins (orexins) are neuropeptides synthesized by lateral hypothalamic and perifornical area neurons (de Lecea et al., 1998; Sakurai et al., 1998). They are comprised of two distinct peptides, hypocretin 1 and 2, and their effects are mediated by their actions at hypocretin type 1 and type 2 receptors, both of which are widely distributed in the brain (Sutcliffe and de Lecea, 2002). Hypocretin neurons project to neighboring hypothalamic nuclei, as well as to various forebrain, midbrain and brainstem areas (Peyron et al., 1998). Hypocretins are known to be involved in regulation of energy balance, food intake, and arousal (Sakurai, 2007; Sutcliffe and de Lecea, 2002). More recently, results from several studies implicate hypocretin's action in lateral hypothalamus and VTA in drug reward and in reinstatement of drug seeking (Borgland et al., 2006; Dayas et al., 2008; Hamlin et al., 2007; Harris et al., 2007; Harris et al., 2005; Lawrence et al., 2006; Narita et al., 2006). Below, we discuss results from recent studies on hypocretins' role in stress-induced reinstatement.

In an initial study, Boutrel et al. (2005) reported that systemic injections of SB 334867 (a hypocretin type 1 receptor antagonist) attenuated footshock stress-induced reinstatement of cocaine seeking. They also found that ventricular injections of hypocretin 1 reinstated cocaine seeking, and that this effect was blocked by pretreatment with D-Phe CRF₁₂₋₄₁ and clonidine, suggesting a role of CRF and noradrenaline in hypocretin 1-induced reinstatement. [Clonidine is an alpha-2 adrenoceptor agonist that decreases noradrenaline cell firing and release (Aghajanian and VanderMaelen, 1982); systemic injections of clonidine and related compounds block footshock-induced reinstatement of drug seeking (Erb et al., 2000; Highfield et al., 2001; Shaham et al., 2000b).]

The brain sites involved in hypocretin's role in footshock-induced reinstatement are unknown. In a recent study, Wang et al. (2009) reported that while VTA perfusion (via a microdialysis probe) of hypocretin 1 (but not hypocretin 2) reinstated cocaine seeking, local perfusion of SB 408124 (a hypocretin type 1 receptor antagonist) had no effect on either footshock-induced reinstatement or reinstatement induced by local perfusion of CRF. Additionally, reinstatement induced by VTA hypocretin 1 perfusion was not decreased by local perfusion of alpha-helical CRF₉₋₄₁. These findings, together with the previous results of Wang et al. (2005; 2007) on the role of VTA CRF in footshock-induced reinstatement, indicate that hypocretin 1 action in VTA is not involved in this reinstatement.

In two recent studies, the role of hypocretins in yohimbine-induced reinstatement of alcohol and food (high-fat pellets, sucrose) seeking was assessed. Richards et al. (2008) reported that systemic injections of SB 334867 decreased yohimbine-induced reinstatement of alcohol and sucrose seeking. In contrast, Nair et al. (2008) reported that SB 334867 had no effect on yohimbine-induced reinstatement of high-fat food seeking. Another finding in this study is that ventricular injections of hypocretin 1 reliably reinstated high-fat food seeking but, surprisingly, this effect was not reversed by SB 334867 at doses that decreased ongoing food intake. The reasons for the discrepant results between the studies of Richards et al. and Nair et al. are unknown. One possibility is a difference in non-operant feeding conditions: free access to regular nutritionally-balanced food in the Richards et al. study versus restricted feeding (about 65-70% of daily free-feeding ration) in the Nair et al. study. Indeed, food restriction is reported to elevate levels of preprohypocretin (the precursor for hypocretin), suggesting an alteration

in hypocretin function (Sakurai et al., 1998). Alternatively, the discrepancy may be due to the use of different reinforcers: oral sucrose and alcohol solutions (Richards et al., 2008) versus 35% fat pellets (Nair et al., 2008).

Role of dynorphins (and kappa receptors) in stress-induced reinstatement

Dynorphins are endogenous neuropeptides that were discovered in 1982 by Chavkin et al. (1982). The dynorphins (dynorphin A, dynorphin B and alpha-neodynorphin) are part of the endogenous opioid system that includes several receptor types: mu, delta, kappa, and NOP, and several endogenous peptides: beta-endorphin and enkephalins (preferentially bind to mu and delta receptors), endomorphins (selectively bind to mu receptors), dynorphins (selectively bind to kappa receptors), and nociceptin (selectively binds to NOP) (Corbett et al., 2006; Dhawan et al., 1996; IUPHAR, 2008). A number of stressors, including intermittent footshock, activate the endogenous opioid systems (Akil et al., 1984; Amit and Galina, 1986). Thus, in an early neuropharmacological study on stress-induced reinstatement, Shaham and Stewart (1996) examined the effect of naltrexone (a preferentially *mu* opioid receptor antagonist, 1 or 10 mg/kg) on this reinstatement. They found that even the high dose of naltrexone (10 mg/kg), that should have blocked mu, kappa and delta opioid receptors (Goldstein and Naidu, 1989), and that decreased heroin priming-induced reinstatement, had no effect on footshock-induced reinstatement of heroin seeking. Additionally, chronic delivery (via minipumps) of heroin or other mu opioid receptor agonists (methadone, buprenorphine [also a kappa receptor antagonist]), that occupy the mu opioid receptors and prevent acute receptor activation by stress exposure, had no effect on footshock-induced reinstatement of heroin or cocaine seeking (Leri et al., 2004; Shaham et al., 1996; Sorge et al., 2005). Together, these findings suggest that the putative activation of endogenous opioid systems by footshock is not involved in reinstatement of drug seeking induced by this stressor.

However, results from several studies suggest a role of dynorphins and the kappa opioid receptor in stress-induced reinstatement of drug seeking. Beardsley et al. (2005) reported that systemic injections of JDTic (a kappa receptor antagonist) attenuated footshock-induced reinstatement of cocaine seeking. The data from this study, however, are difficult to interpret for several reasons: 1) baseline extinction responding differed between the groups tested with the different doses of JDTic; 2) the effect of JDTic on reinstatement of lever responding in the absence of footshock was not assessed; and 3) at the highest dose, JDTic strongly potentiated cocaine-priming-induced reinstatement.

More recently, Chavkin, McLaughlin and colleagues have provided more convincing evidence for a role of dynorphins and kappa opioid receptors in stress-induced reinstatement. These investigators used a CPP reinstatement procedure in mice. In one study, Carey et al. (2007) reported that systemic injections of aroclor (a kappa receptor antagonist) decreased forced-swim-induced reinstatement of cocaine CPP. In another study, Redila and Chavkin (2008) reported that systemic injections of nor-BNI (a long-acting kappa receptor antagonist) decreased footshock- and forced-swim-stress-induced reinstatement, and that footshock was ineffective in mice lacking either kappa opioid receptors or prodynorphin. In addition, they showed that injections of U50,488 (a kappa opioid agonist), a drug that induces CRF-dependent stress-like aversive responses (Land et al., 2008), reinstated cocaine CPP in mice, providing further evidence for a role of dynorphin and kappa opioid receptors in stress-induced reinstatement. Additionally, Valdez et al. (2007) reported that injections of spiradoline and enadoline (kappa receptor agonists) reinstated cocaine seeking in monkeys. These results are somewhat difficult to interpret in the context of the role of dynorphin/kappa receptors in stress-induced reinstatement, because the reinstating effects of spiradoline and enadoline were blocked by CP154,526 (a CRF1 receptor antagonist) and clonidine (an alpha2-adrenoceptor agonist), but not by nor-BNI (the prototypical kappa receptor antagonist).

Role of other peptides in stress-induced reinstatement

Nociceptin

Nociceptin (orphanin FQ) is a 17-amino acid peptide that shows structural homology to opioid peptides, in particular dynorphin A (Meunier et al., 1995; Reinscheid et al., 1995). Results from several studies demonstrate a role of nociceptin in stress responses and behavioral effects of abused drugs. Thus, there is evidence that nociceptin decreases the behavioral effects of stress in rodents by counteracting CRF actions in the BNST and other brain areas (Ciccocioppo et al., 2000; Ciccocioppo et al., 2003; Rodi et al., 2008). Recently, Economidou et al. (2008) reported that CeA nociceptin injections decrease alcohol self-administration in alcohol-preferring rats, an effect possibly reflecting an anti-stress action of the peptide in this brain area. Martin-Fardon et al. (2000) reported that ventricular injections of nociceptin decreased footshock-induced reinstatement of alcohol but not cocaine seeking. The reasons for this selective effect of nociceptin are unknown.

Leptin

Leptin, the product of the obese (*ob*) gene, was discovered in 1994 (Zhang et al., 1994). Leptin is secreted by peripheral adipocytes and plays a role in long-term energy balance (Friedman and Halaas, 1998). Ventricular or hypothalamic injections of leptin decrease food intake (Ahima et al., 1996). There is evidence that leptin regulates the activity of the mesolimbic dopamine system by its actions on VTA dopamine neurons (Figlewicz et al., 2007; Fulton et al., 2006; Hommel et al., 2006). Fulton et al. (2000) also demonstrated that leptin actions in the lateral hypothalamus mediate the ability of chronic food restriction to decrease the threshold for brain stimulation reward.

Based on the results of Fulton et al. (2000), we assessed leptin's role in food-deprivation-induced reinstatement of heroin seeking (Shalev et al., 2001). We found that ventricular leptin injections decreased food-deprivation, but not footshock- or heroin-priming-induced reinstatement. The finding that ventricular leptin injections had no effect on either footshock- or heroin-priming-induced reinstatement, which are critically dependent on VTA neurons (Stewart, 1984; Wang et al., 2005), indicates that leptin's actions in the VTA do not likely contribute to its inhibitory effect on food-deprivation-induced reinstatement.

Neuropeptide Y

Neuropeptide Y (NPY) is a 36 amino acid peptide that was discovered in 1982 (Tatemoto et al., 1982). NPY is part of the pancreatic polypeptide family and is one of the most abundant and widely distributed peptides in the brain, with highest concentration in the hypothalamus (Allen et al., 1983). NPY injections into the ventricles and hypothalamus potently induce feeding (Clark et al., 1984; Leibowitz, 1995). Ventricular and local injections of NPY into several extrahypothalamic sites (amygdala, periaqueductal gray area, lateral septum) decrease stress and anxiety-like behavioral responses (Heilig, 2004b; Kask et al., 2002).

In a recent study, Maric et al. (2008) reported that ventricular injections of NPY increased heroin self-administration and induced reinstatement of heroin seeking. Interpretation of these data in the context of stress-induced reinstatement is of course problematic: Why would NPY injections that decrease behavioral stress responses (Heilig, 2004a; Kask et al., 2002) increase drug-taking behavior? However, while the mechanisms underlying NPY effects on heroin-taking behavior are unknown, a plausible interpretation of Maric's finding is that NPY injections mimic a state of food deprivation, which is known to increase drug self-administration (Carroll et al., 1979) and to reinstate drug seeking (Shalev et al., 2001). This hypothesis can be empirically tested by using selective pharmacological agents that target

specific NPY receptors, and determining their effects on food-deprivation-induced increases in drug seeking.

Neuropeptide S

Neuropeptide S (NPS) is a newly discovered peptide (Xu et al., 2004). NPS cell bodies are located primarily in a previously undefined cluster of cells located between the locus coeruleus and Barrington's nucleus. The NPS receptors are widely expressed in many brain areas, including the hypothalamus, amygdala, and cortex. In mice, ventricular injections of NPS increase locomotor activity, promote wakefulness, and induce anxiolytic-like effects in the open field, light-dark box, elevated plus maze, and marble burying tests (Xu et al., 2004).

Recently, Paneda et al. (2009) reported that ventricular injections of NPS reinstated cocaine seeking in mice. This effect was reversed by antalarmin (a CRF1 receptor antagonist), and was absent in CRF1 receptor knockouts. In contrast, these manipulations had no effect on the anxiolytic-like effects of NPS. In another study, Cannella et al. (2009) reported that discriminative-cue-induced reinstatement of alcohol seeking was potentiated by ventricular or lateral hypothalamus injections of NPS; these effects were reversed by systemic injections of SB 334867 (a hypocretin type 1 receptor antagonist).

As in the case of NPY, an interpretation of these data in the context of stress-induced reinstatement is problematic: Why would NPS injections that decrease behavioral stress responses (Xu et al., 2004) increase drug seeking? Additionally, does the observation that systemic injections of either a CRF1 receptor antagonist or a hypocretin type 1 receptor antagonist decrease footshock-induced drug seeking (see above) suggest that NPS- and stress-induced reinstatement are mechanistically similar? At present, it is difficult to address these questions, because neither Paneda et al. (2009) nor Cannella et al. (2009) assessed whether NPS potentiates or attenuates stress-induced reinstatement. One speculation in this regard is that increased arousal is a critical component of the ability of stressors to reinstate drug and food seeking, and that this aspect of stress is mimicked by NPS. From this perspective, because both the CRF and the hypocretin systems can modulate arousal states (Boutrel and de Lecea, 2008; Valentino and Van Bockstaele, 2008), receptor antagonists of these systems should decrease both stress- and NPS-induced reinstatement, despite the opposite effect of stress versus NPS in anxiety models.

Melanin-concentrating hormone (MCH)

Melanin-concentrating hormone (MCH) is a peptide originally isolated from fish, where it functions as a regulator of skin color (Kawauchi et al., 1983). MCH neurons are located in the lateral hypothalamus and project to many brain areas (Bittencourt et al., 1992; Zamir et al., 1986). MCH effects are mediated by MCH1 (the functional MCH receptor in rodents) and MCH2 receptors expressed in hypothalamic and extrahypothalamic sites (Chambers et al., 1999; Lembo et al., 1999; Saito et al., 2001). A large body of literature indicates that activation of central MCH receptors, in both hypothalamic and extrahypothalamic sites, increases feeding (Georgescu et al., 2005; Pissios et al., 2006). MCH systems also play a role in regulating stress responses (Hervieu, 2003). Systemic injections of SNAP 94847 (an MCH1 receptor antagonist), or related compound, decrease behavioral stress and anxiety-like responses in rodent models used to assess anxiolytic effects of drugs (social interaction test, light-dark tests, and more) (Borowsky et al., 2002; David et al., 2007; Smith et al., 2009). In two recent studies, effects of MCH1 receptor antagonists on stress-induced reinstatement of cocaine and food seeking were assessed; overall, negative results were obtained. Nair et al. (2009a) reported that systemic injections of SNAP 94847 had no effect on yohimbine-induced reinstatement of food seeking at doses that decreased ongoing food-reinforced responding. Chung et al. (2009) reported that ventricular injections of TPI 1361-17 (an MCH1 receptor antagonist) had no effect

on yohimbine-induced reinstatement of cocaine seeking at doses that decreased cocaine-priming- and cue-induced reinstatement.

Peptide YY3-36

Peptide YY3-36 (PYY3-36) is a major circulatory derivative of Peptide YY (PYY) (Eberlein et al., 1989), a gastrointestinal-derived hormone that is released from intestinal L-cells after meals in proportion to caloric intake (Murphy et al., 2006). PYY3-36 is an endogenous agonist of the Y2 NPY presynaptic inhibitory autoreceptors (Larhammar and Salaneck, 2004). There is evidence that systemic PYY3-36 injections decrease food intake in mice, rats, monkeys, and humans (Batterham et al., 2002; Batterham et al., 2003; Moran et al., 2005), but see (Boggiano et al., 2005). In a recent study, Ghitza et al. (2007) reported that ventricular injections of PYY3-36 decreased pellet-priming- and cue-induced reinstatement of food seeking. In contrast, PYY3-36 had no effect on yohimbine-induced reinstatement. These data suggest that PYY3-36 is not involved in this form of stress-induced reinstatement. Based on previous work on the role of PYY3-36 in food intake and regulation of hunger states (Murphy et al., 2006), an interesting question for future research is whether PYY3-36 would decrease food-deprivation-induced reinstatement.

Discussion

We reviewed results from studies on the role of CRF and several other peptides in stress-induced reinstatement of drug (and food) seeking in laboratory animals. Below, we first provide general conclusions regarding the role of these peptides in stress-induced reinstatement, and then speculate on how the different peptides might interact to control this reinstatement.

General conclusions

CRF—There is evidence that extrahypothalamic CRF, but not hypothalamic CRF, plays a critical role in stress-induced reinstatement of drug seeking. This role is largely independent of drug class, experimental procedure, and type of stressor. Critical brain sites and pathways for CRF's role in footshock-induced reinstatement include the BNST and a CRF projection from the CeA to the BNST, the VTA, and the median raphe nucleus. At present, the brain sites and pathways involved in CRF's role in food-deprivation- and yohimbine-induced reinstatement are unknown.

Hypocretins—There is evidence that hypocretins play a role in stress-induced reinstatement of alcohol and cocaine seeking and, under certain conditions, in stress-induced reinstatement of food seeking. The brain sites involved in hypocretin's role in this reinstatement are unknown.

Dynorphins—While there is evidence for a role of dynorphins (and kappa receptors) in stress-induced reinstatement of cocaine CPP in mice, the role of dynorphin or other endogenous opioids in stress-induced reinstatement in the operant procedure has not been established. In this regard, the finding that kappa receptor agonists inhibit (rather than potentiate) cocaine-priming-induced reinstatement of lever responding (Schenk et al., 1999; Schenk et al., 2000; Shippenberg et al., 2007), does not support the notion that activation of the dynorphin/kappa receptor system is critical for reinstatement of drug seeking in the operant self-administration procedure.

Other peptides (nociceptin, leptin, NPY, NPS, MCH, PYY3-36)—There is evidence for a drug-specific (alcohol but not cocaine) effect of nociceptin on footshock-induced reinstatement, and for a stressor-specific (food deprivation but not footshock) effect of leptin on reinstatement of heroin seeking. Although both NPY and NPS can reinstate drug seeking, an endogenous role of these peptides in stress-induced reinstatement has not been

demonstrated. Finally, the available evidence suggests that MCH and PYY3-36 are not involved in **yohimbine**-induced reinstatement; the role of these peptides in food-deprivation-induced reinstatement is a subject for future research.

Role of peptide-peptide and peptide-neurotransmitter interactions in stress-induced reinstatement

Several years ago we proposed a neuroanatomical model of footshock-induced reinstatement of drug seeking (Erb et al., 2001; Shaham et al., 2000a) that was based on our early studies of the role of CRF (discussed above) and noradrenaline (Erb et al., 2000; Shaham et al., 2000b) in this reinstatement. In this hypothetical model, footshock causes initial activation of lateral tegmental (but not locus coeruleus) noradrenaline neurons, which in turn activates CRF projection neurons from CeA to BNST, and local CRF interneurons in BNST. Subsequently, CRF-induced activation of excitatory projection neurons from BNST (which possibly contain CRF as a neurotransmitter or co-transmitter) act in distal brain areas (including dopamine or non-dopamine VTA neurons) to initiate approach behaviors involved in reinstatement (Erb et al., 2001; Shaham et al., 2000a).

Anatomical support for this model is provided by the identification of glutamate and CRF projection neurons from BNST to VTA (Georges and Aston-Jones, 2001; Georges and Aston-Jones, 2002; Rodaros et al., 2007). Potential functional support for the model is provided by the discovery that in VTA, both CRF and glutamate transmission are critical for footshock-induced reinstatement of cocaine seeking (Wang et al., 2005). Results from other studies suggest that the model should be expanded to include the dopaminergic projection from the VTA to dorsal prefrontal cortex, which interacts with glutamatergic projections from the dorsal prefrontal cortex to the nucleus accumbens (Capriles et al., 2003; Kalivas and Volkow, 2005; McFarland et al., 2004; Sanchez et al., 2003; Shaham et al., 2003).

Can some of the other peptides that we have reviewed in this paper interact with CRF, dopamine and noradrenaline to control stress-induced reinstatement? If so, can the nature of these interactions be accommodated within the emerging neuroanatomical model of stress-induced reinstatement just described? We will limit the discussion of this issue to hypocretins, dynorphins, nociceptin, and leptin; as we have discussed, there is either no evidence or, at best, only circumstantial evidence for a role of the other peptides reviewed here in stress-induced reinstatement.

Hypocretins—There is evidence for anatomical and functional interactions between the hypocretins and CRF, noradrenaline, and dopamine (Baldo et al., 2003; Bonci and Borgland, 2009; Boutrel, 2008; Winsky-Sommerer et al., 2004, 2005). Most relevant in the context of reinstatement of drug seeking, Boutrel et al. (2005) reported that hypocretin 1-induced reinstatement is decreased by pretreatment with D-Phe CRF₁₂₋₄₁ and clonidine. The brain sites involved in the putative interactions between hypocretins, CRF and noradrenaline in reinstatement are unknown, but one brain area that can be ruled out is the VTA. The results of the recent elegant study of Wang et al. (2009), and their previous work (Wang et al., 2005; Wang et al., 2007), demonstrate a dissociation between the effects of hypocretin 1 and CRF manipulations in VTA on reinstatement of cocaine seeking. Thus, antagonism of VTA CRF but not hypocretin 1 receptors attenuates footshock-induced reinstatement of cocaine seeking. Additionally, CRF-induced reinstatement is insensitive to antagonism of hypocretin type 1 receptors, while hypocretin 1-induced reinstatement is insensitive to antagonism of CRF receptors. A question for future research is whether a CRF-hypocretin interaction in the BNST and CeA, two projections areas of hypocretin neurons (Baldo et al., 2003; Winsky-Sommerer et al., 2005), is critical for stress-induced reinstatement.

Dynorphins—Recent results from an elegant study by Chavkin and colleagues suggest that the aversive effects of stress exposure (as assessed in a conditioned place aversion procedure) are mediated by stress-induced activation of CRF and, in turn, activation of dynorphins (Land et al., 2008). However, the relevance of these findings, obtained in drug naïve mice, for understanding mechanisms of stress-induced reinstatement is unknown. Specifically, the critical receptor for the CRF-dynorphin interaction reported by Land et al. (2008) is the CRF2 receptor, whereas the critical receptor for stress-induced reinstatement following systemic or ventricular injections of CRF antagonists (the route of administration used in the Land et al. study) is the CRF1 receptor. Of potentially greater relevance in considering a possible role for CRF-dynorphin interactions, or noradrenaline-dynorphin interactions (Kreibich et al., 2008), in stress-induced reinstatement is the finding that, in monkeys, reinstatement induced by kappa receptor agonists is attenuated by both CP154,526 and clonidine (Valdez et al., 2007). The brain circuits involved in these effects is a subject that warrants future research.

Nociceptin—There is evidence that nociceptin can counteract both the anorectic and anxiogenic effects of CRF receptor stimulation in the BNST (Ciccocioppo et al., 2003; Rodi et al., 2008). Because the BNST is a critical brain site contributing to the role of CRF in footshock-induced reinstatement, a question for future research is whether the inhibitory effect of nociceptin on footshock-induced reinstatement of alcohol seeking (Martin-Fardon et al., 2000) is mediated by CRF transmission in the BNST. However, it is currently unknown whether a CRF-nociceptin interaction in fact plays a role in footshock-induced reinstatement; as mentioned above, nociceptin does not interfere in footshock-induced reinstatement of cocaine seeking, although this effect of footshock is highly sensitive to CRF receptor antagonism (see above and Table 2).

Leptin—The findings that food-deprivation-induced reinstatement is decreased by both leptin (Shalev et al., 2001) and D-Phe CRF₁₂₋₄₁ (Shalev et al., 2006) raise the possibility that a CRF-leptin interaction contributes to this reinstatement. While both leptin and CRF locally modulate VTA dopamine neurons (Hahn et al., 2009; Hommel et al., 2006; Wang et al., 2005), it is unlikely that the VTA is involved in the putative interaction between the peptides in controlling food-deprivation-induced reinstatement. This is because leptin has no effect on footshock-induced reinstatement (Shalev et al., 2001), a type of reinstatement that depends on VTA transmission (see above). Whether a CRF-leptin interaction in other brain areas contributes to food-deprivation-induced reinstatement is a subject for future research. As a starting point for exploring a possible interaction, it would be of interest to determine whether CRF-induced reinstatement is decreased by pretreatment with leptin.

Concluding remarks

The findings reviewed in this paper reveal both general (e.g., CRF) and selective (e.g., leptin) roles of different neuropeptides in stress-induced reinstatement of drug seeking. This is a complicated field of study, because while some stressors induce reinstatement of drug seeking others do not (Lu et al., 2003; Shaham et al., 2000a). Additionally, even in the case of intermittent unpredictable footshock, its effect on reinstatement is dependent on the stressor parameters (e.g., intensity), the presence of drug-associated cues, and the context of stressor exposure (Shaham, 1996; Shalev et al., 2000; Shelton and Beardsley, 2005). Thus, prior evidence that a given neuropeptide plays a role in the behavioral effects of certain stressors may not be a good predictor for the role the same neuropeptide might play in stress-induced reinstatement of drug seeking (e.g., NPY). Despite this complexity, we hope that our review will stimulate future studies aimed at further elucidating the independent and interactive roles of different neuropeptides in stress-induced reinstatement of drug seeking.

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Table 1
Glossary of terminology

CONDITIONED PLACE PREFERENCE (CPP): A classical conditioning (Pavlovian) procedure used to study the rewarding effects of unconditioned stimuli (e.g., food, drugs). During training, one area of a test chamber is associated with a stimulus and another area is not. During testing, in the absence of the stimulus, the subject is allowed to choose between the two areas. An increase in preference for the stimulus-paired area serves as a measure of its Pavlovian rewarding effects (Bardo and Bevins, 2000).

OPERANT SELF-ADMINISTRATION: A procedure in which laboratory animals perform a voluntary, or operant, response (e.g., lever press, nose-poke) for appetitive unconditioned stimuli, such as palatable food or drugs of abuse. The premise of this procedure is that drugs or non-drug rewards control behavior by functioning as positive reinforcers (Johanson et al., 1987). A stimulus is defined as a positive reinforcer in operant conditioning if its presentation following a response increases or maintains the likelihood of the response.

REINSTATEMENT: In the learning literature, a term that refers generally to the recovery of a learned response (e.g., lever-pressing behavior) when a subject is exposed non-contingently to the unconditioned stimulus (e.g., food) after a period of extinction. In studies of reinstatement of drug-seeking, reinstatement typically refers to the resumption of drug seeking after extinction of the drug-reinforced responding and subsequent exposure to drugs (de Wit and Stewart, 1981; Self et al., 1996; Spealman et al., 1999), different types of drug cues (Crombag et al., 2008; Meil and See, 1996; Weiss et al., 2000), or different stressors (Shaham et al., 2000a)

RELAPSE: A term used to describe the resumption of drug-taking behavior during periods of self-imposed or forced abstinence in humans (Wikler, 1973). This term also refers to the human condition of resumption of old, unhealthy eating habits during dieting.

STRESS: A complex psychological construct that, despite many years of research (Cannon, 1914; Selye, 1936), has yet to be given an adequate operational definition (Chrousos and Gold, 1992; Cohen et al., 1982). In the context of animal models of psychiatric disorders, stress can be defined broadly as forced exposure to events or conditions that are normally avoided (Piazza and Le Moal, 1998). In humans, the definition is extended to incorporate cognitive and emotional responses—for example, “stress is a condition in which the environmental demands exceed the coping abilities of the individual” (Cohen et al., 1986). In laboratory animals, the precipitating events or conditions can be divided into two categories (Lu et al., 2003). The first category includes environmental events such as restraint, footshock, tail pinch, and social defeat, as well as pharmacological events such as administration of a normally avoided drug (e.g., yohimbine). The second category includes food deprivation, social isolation, and maternal deprivation; each of these entails the removal of an environmental condition that is important for maintaining the animal's normal physiological and psychological steady-state conditions, a state that the subject will attempt to ameliorate by seeking food, conspecific partners, or the dam.

Table 2
Effects of neuropeptide receptor ligands on stress-induced reinstatement of drug and food seeking

Pharmacological manipulation	Target	Training history	Stressor	Effect	References
CRF <u>Non-selective CRF receptor antagonists:</u> alpha-helical CRF _{9,41}	i.c.v.	Heroin SA	Footshock	Decrease	Shaham et al 1997
		Morphine/cocaine CPP	Footshock	Decrease	Lu et al 2000, 2001
		Heroin SA	Food deprivation	Decrease	Shalev et al 2006
	VTA	Cocaine SA	Footshock	Decrease	Wang et al 2005
	SN	Cocaine SA	Footshock	No effect	Wang et al 2005
	i.c.v.	Cocaine SA	Footshock	Decrease	Erb et al 2008
		Alcohol SA	Footshock	Decrease	Le et al 2000; Liu & Weiss 2002
D-Phe CRF ₁₂₋₄₁	BNST	Cocaine SA	Yohimbine	No effect	Brown et al 2009
		Nicotine SA	Footshock	Decrease	Zislis et al 2007
		Cocaine SA	Footshock	Decrease	Erb & Stewart 1999
	CeA	Cocaine SA	Footshock	No effect	Erb & Stewart 1999
	i.p.	Alcohol/food SA	Yohimbine	Decrease	Marinelli et al 2007; Ghitza et al 2006
		Alcohol/heroin/cocaine SA	Footshock	Decrease	Shaham et al 1998 ; Le et al 2000
	BNST	Morphine CPP	Footshock	Decrease	Wang et al 2006
<u>CRF₁ receptor antagonist:</u> Antalarmin	CeA	Morphine CPP	Footshock	No effect	Wang et al 2006
	NAcc	Morphine CPP	Footshock	No effect	Wang et al 2006
	i.c.v.	Nicotine SA	Footshock	Decrease	Bruijnzeel et al 2009
	VTA	Cocaine SA	Footshock	No effect	Wang et al 2007
	i.c.v.	Morphine/cocaine CPP	Footshock	No effect	Lu et al 2000, 2001
		Cocaine SA	Footshock	Decrease	Wang et al 2007
	i.c.v.	Nicotine SA	Footshock	No effect	Bruijnzeel et al 2009
<u>CRF₂ receptor antagonist:</u> Antisauvagine-30	VTA	Morphine/cocaine CPP	Footshock	No effect	Lu et al 2000, 2001
		Cocaine SA	Footshock	Decrease	Wang et al 2007
	i.c.v.	Nicotine SA	Footshock	No effect	Bruijnzeel et al 2009
Astressin-2B					

Pharmacological manipulation	Target	Training history	Stressor	Effect	References
<i>Hypocretins</i>					
<u>Hypocretin 1 receptor antagonist</u> : SB-334867	i.p.	Cocaine/alcohol/sucrose SA	Footshock/Yohimbine	Decrease	Boutrel et al 2005, Richards et al 2008
SB-408124	i.p. VTA	Food SA Cocaine SA	Yohimbine Footshock	No effect No effect	Nair et al 2008 Wang et al 2009
<i>Dynorphin</i>					
<u>kappa-opioid receptor antagonist</u> : JDTic	s.c.	Cocaine SA	Footshock	Decrease	Beardsley et al., 2005
Nor-BNI	i.p.	Cocaine SA	Footshock, F. swim	Decrease	Redila & Chavkin 2008
Aroclor	i.c.v.	Cocaine CPP	Forced swim	Decrease	Carey et al 2007
<i>Other neuropeptides</i>					
<i>Nociceptin (orphanin FQ)</i>	i.c.v.	Alcohol SA	Footshock	Decrease	Martin-Fardon et al 2000
<i>Leptin</i>	i.c.v.	Cocaine SA	Footshock	No effect	Martin-Fardon et al 2000
	i.c.v.	Heroin SA	Food deprivation	Decrease	Shalev et al 2001
	i.c.v.	Heroin SA	Footshock	No effect	Shalev et al 2001
<i>MCH</i>					
<u>MCH1 receptor antagonist</u> : TPI 1361-17 SNAP 94847	i.c.v. i.p.	Cocaine SA Food SA	Yohimbine Yohimbine	No effect No effect	Chung et al 2009 Nair et al 2009
<i>PYY3-36</i>	i.c.v.	Food SA	Yohimbine	No effect	Ghitza et al 2007

Abbreviations: BNST, bed nucleus of stria terminalis; CeA, central nucleus of amygdala; CPP, conditioned place preference; CRF, corticotropin-releasing factor; DRN, dorsal raphe nucleus; MCH, melanin-concentrating hormone; MRN, median raphe nucleus; NAcc, nucleus accumbens; SA, self-administration; SN, substantia nigra; VTA, ventral tegmental area

Table 3
Reinstatement of drug and food seeking by activation of neuropeptide systems

Peptides	Target	Training history	Reinstatement	References
CRF				
<u>CRF</u>	i.c.v.	Heroin/cocaine/alcohol SA	Yes	Shaham et al 1997, Erb et al 2006, Le et al 2002
	BNST	Cocaine SA	Yes	Erb et al 1999
	CeA	Cocaine SA	No	Erb et al 1999
	MRN	Alcohol SA	Yes	Le et al 2002
	VTA	Cocaine SA	Yes	Wang et al 2005
<u>CRF₂ receptor agonist:</u>				
Mouse urocortin II	VTA	Cocaine SA	Yes	Wang et al 2007
Hypocretins (orexins)				
Hypocretin 1	i.c.v.	Cocaine/food SA	Yes	Boutrel et al 2005, Nair et al 2008
	VTA	Morphine CPP	Yes	Harris et al 2005
	VTA	Cocaine SA	Yes	Wang et al 2009
Hypocretin 2	VTA	Cocaine SA	No	Wang et al 2009
Dynorphin				
<u>kappa-receptor agonist</u>				
U50,488	i.p.	Cocaine CPP	Yes	Redial & Chavkin 2008
Spiradoline, Enadoline	i.p.	Cocaine SA (monkeys)	Yes	Valdez et al 2007
Other neuropeptides				
NPY	i.c.v.	Heroin SA	Yes	Maric et al 2008
Neuropeptide S	i.c.v.	Cocaine/alcohol SA	Yes	Paneda et al. 2009, Cannella et al. 2009
MCH	i.c.v.	Food SA	Yes	Nair et al 2009

Abbreviations: BNST, bed nucleus of stria terminalis; CeA, central nucleus of amygdala; CPP, conditioned place preference; CRF, corticotropin-releasing factor; MCH, melanin-concentrating hormone; MRN, median raphe nucleus; NAcc, nucleus accumbens; NPY, neuropeptide Y; SA, self-administration; VTA, ventral tegmental area