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Noradrenergic transmission in the extended amygdala: role in increased drug-seeking and relapse during protracted drug abstinence

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Abstract

Studies reviewed here implicate the extended amygdala in the negative affective states and increased drug-seeking that occur during protracted abstinence from chronic drug exposure. Norepinephrine (NE) and corticotropin-releasing factor (CRF) signaling in the extended amygdala, including the bed nucleus of the stria terminalis, shell of the nucleus accumbens, and central nucleus of the amygdala, are generally involved in behavioral responses to environmental and internal stressors. Hyperactivity of stress response systems during addiction drives many negative components of drug abstinence. In particular, NE signaling from the nucleus tractus solitarius (NTS) to the extended amygdala, along with increased CRF transmission within the extended amygdala, are critical for the aversiveness of acute opiate withdrawal as well as stress-induced relapse of drug-seeking for opiates, cocaine, ethanol, and nicotine. NE and CRF transmission in the extended amygdala are also implicated in the increased anxiety that occurs during prolonged abstinence from chronic opiates, cocaine, ethanol, and cannabinoids. Many of these stress-associated behaviors are reversed by NE or CRF antagonists given systemically or locally within the extended amygdala. Finally, increased Fos activation in the extended amygdala and NTS is associated with the enhanced preference for drugs and decreased preference for natural rewards observed during protracted abstinence from opiates and cocaine, indicating that these areas are involved in the altered reward processing associated with addiction. Together, these findings suggest that involvement of the extended amygdala and its noradrenergic afferents in anxiety, stress-induced relapse, and altered reward processing reflects a common function for these circuits in stress modulation of drug-seeking.

Keywords

Norepinephrine; Withdrawal; Anxiety; Reinstatement; Addiction

Introduction

A major obstacle in drug addiction recovery is the susceptibility to relapse, even after extended periods of abstinence (O'Brien 1997). Compulsive drug-seeking and relapse may be driven by several factors, including the aversive and anxiogenic nature of acute withdrawal and protracted abstinence, increased positive and negative reinforcing properties of drugs, and external triggers such as stressors and drug-paired stimuli.

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Several of these factors involve stress or anxiety, and stress-related structures in the brain, particularly the extended amygdala, have been implicated in multiple aspects of addiction. The extended amygdala is an anatomically and neurochemically interconnected system in the basal fore-brain that consists of the bed nucleus of the stria terminalis (BNST), central nucleus of the amygdala (CeA), and shell of the nucleus accumbens (NAc-Sh) (Heimer et al. 1993). This system has been pinpointed as having an important role in several stress-related components of drug withdrawal, and is a site where corticotropin-releasing factor (CRF) and nor-epinephrine (NE) transmission seem to be critical for stress effects in addiction.

Brain CRF and NE systems are implicated in stress responses both in healthy individuals (Bale and Vale 2004; Heinrichs and Koob 2004; Koob 1999a; Koob and Heinrichs 1999; Morilak et al. 2005) and in people suffering from stress-related disorders including depression and anxiety (e.g. post-traumatic stress disorder, panic disorder) (Arborelius et al. 1999; Bremner et al. 1996a,b; Clark and Kaiyala 2003; Risbrough and Stein 2006; Southwick et al. 1999; Strawn and Geracioti 2008). Due to their role in psychiatric illnesses, NE and CRF have been proposed to interact in several ways in response to chronic stress, including sensitization (via feed-forward circuits in which, e.g., CRF influences NE) and desensitization (Dunn and Swiergiel 2008; Dunn et al. 2004; Koob 1999a).

A role for the extended amygdala in stress is implicated by strong reciprocal CRF connections between CeA and BNST, CRF inputs to the extended amygdala from other amygdaloid and extra-amygdaloid structures, and NE innervation from brainstem nuclei (Berridge et al. 1997; Freedman and Cassell 1994; Hornby and Piekut 1989; Phelix et al. 1992, 1994; Sakanaka et al. 1986). Other afferents to the extended amygdala include basolateral amygdala (BLA), lateral hypothalamus (LH) and hippocampus, and efferent targets include ventral pallidum and LH (Alheid and Heimer 1988; Heimer et al. 1991). There are also reciprocal connections between the extended amygdala and the ventral tegmental area (VTA) (Carboni et al. 2000; Freedman and Cassell 1994; Georges and Aston-Jones 2001). VTA receives glutamatergic inputs from BNST, as well as CRF inputs from BNST, CeA, and paraventricular nucleus of the hypothalamus (PVN) (Georges and Aston-Jones 2002; Rodaros et al. 2007). Given the role of the VTA dopamine (DA) system in reward processing and effects of drugs of abuse (for review, see Fibiger and Phillips 1986; Wise 1978, 1996, 2004), these connections indicate that the extended amygdala may also play an important role in addiction.

The role of stress in addiction has been addressed in numerous reviews (Goeders 1997, 2003; Koob and Kreek 2007; Koob 1999b, c, 2003; Lu et al. 2003; Piazza and Le Moal 1996; Sarnyai et al. 2001; Weiss et al. 2001). Here, we have gathered a diverse set of literature and data that support a role for NE and CRF actions specifically in the extended amygdala in several stress-related components of addiction, ranging from symptoms of acute withdrawal to relapse during prolonged abstinence.

First, we discuss the well-defined role of NE inputs to the extended amygdala from A2 neurons in the caudal medulla (nucleus tractus solitarius; NTS) in the aversiveness of acute opiate withdrawal. We also review the role of NE and CRF in the enhanced anxiety that accompanies acute or protracted withdrawal from several drugs. Next, we review the extensive data supporting a role of NE and CRF signaling within the extended amygdala in stress-induced reinstatement of drug-seeking. The necessary circuitry for this reinstatement effect closely parallels that for the aversiveness of acute opiate withdrawal.

We then present data from our lab revealing an association between activation in the extended amygdala and altered reward processing during protracted drug abstinence. Fos expression in the extended amygdala and NTS is positively correlated with enhanced drug-

seeking and negatively correlated with decreased food-seeking observed during protracted morphine abstinence. Our work indicates a role for the extended amygdala and its NE inputs in this changed reward-response profile, which plays an important role in the difficulty of maintaining drug abstinence in addicts. We review evidence indicating that NE affects responses to drug rewards via positive as well as negative reinforcement mechanisms. Finally, we discuss recent studies implicating connections between the extended amygdala and the orexin system in withdrawal and relapse.

These data reveal multiple ways in which the aversive and anxiogenic effects of abused drugs are associated with extended amygdala circuitry, including its NE inputs. Overall, these results support the view that changes in hedonia that accompany chronic drug exposure and withdrawal are related to anxiety and activation of stress circuitry in the extended amygdala.

Extended amygdala, norepinephrine and acute opiate withdrawal

NE has been implicated in addiction, and in particular in acute opiate withdrawal, for over a half-century (for review, see Aston-Jones et al. 1993; Maldonado 1997). Experimentally, NE neurons in locus coeruleus (LC) were found to be strongly activated by opiate withdrawal (Akaoka and Aston-Jones 1991; Aston-Jones et al. 1997; Ivanov and Aston-Jones 2001; Rasmussen et al. 1990). Clinically, the alpha-2 adrenoceptor agonist clonidine, which potently decreases activity of NE neurons as well as NE release, is used as an effective agent for reducing acute opiate withdrawal symptoms, indicating that the NE system may be involved in some of the adverse symptoms of opiate withdrawal (Gold et al. 1978).

Clinical findings were confirmed by animal studies showing that systemic administration of the beta adrenoceptor antagonists propranolol or atenolol reduced the somatic signs of opiate withdrawal induced by abstinence or by systemic administration of the opioid receptor antagonist naloxone in rats (Harris and Aston-Jones 1993a). Notably, propranolol or clonidine prevented the acquisition of a conditioned place aversion (CPA) for a withdrawal-paired environment, whereas atenolol caused only modest reductions in CPA (Harris and Aston-Jones 1993a; Kosten 1994). Atenolol has more limited access to the central nervous system following systemic administration, indicating a role for central adrenoceptors in the aversiveness of acute withdrawal.

A prime candidate for the central location of systemic propranolol and clonidine actions is ventral BNST, a structure with remarkably dense NE innervation (Fig. 1) (Phelix et al. 1992). Ventral and dorsolateral BNST showed altered neuronal activity after naltrexone-precipitated opiate withdrawal as evidenced by increased activation of the immediate early gene product Fos; this Fos response was markedly decreased by systemic propranolol (Aston-Jones et al. 1999). CeA and NAc-Sh also exhibited increased Fos after acute opiate withdrawal (Hamlin et al. 2004; Veinante et al. 2003; Walters et al. 2000). Notably, BNST, NAc-Sh, and CeA showed increased Fos following expression of opiate withdrawal CPA induced by doses of naloxone that are sub-threshold for somatic signs of withdrawal (Gracy et al. 2001). This indicates that different neural circuits may mediate the aversive and somatic symptoms of withdrawal (as do additional studies, summarized below).

Local microinjection studies confirmed that actions of NE in withdrawal involve the extended amygdala. Intra-BNST injections of beta adrenoceptor antagonists (betaxolol + ICI-118551 cocktail, or propranolol) or alpha-2 agonists (ST-91) reduced the CPA associated with naltrexone-precipitated withdrawal, with very little effect on somatic withdrawal (Fig. 2) (Aston-Jones et al. 1999; Delfs et al. 2000). This is additional evidence for independent circuitry governing the somatic and affective responses to withdrawal. Similar effects were observed with intra-CeA injections of beta-adrenoceptor antagonists

(Watanabe et al. 2003). Retrograde tracer studies revealed that the majority of NE inputs to BNST and NAc-Sh come from the ventral noradrenergic bundle (VNAB) originating in the A2 region of NTS and the A1 in the caudal brainstem, with only little contribution from the dorsal noradrenergic bundle (DNAB) originating in LC (Aston-Jones et al. 1999; Delfs et al. 1998). BNST-projecting catecholaminergic neurons in A1 and A2 showed increased Fos expression following opiate withdrawal (Fig. 3) (Aston-Jones et al. 1999; Delfs et al. 2000; Stornetta et al. 1993). Additionally, neurochemical lesions of VNAB, but not DNAB, projections reduced CPA for opiate withdrawal, with no effect on somatic withdrawal (Aston-Jones et al. 1999). These data implicate NE neurons in NTS, but not LC, in the aversiveness of acute opiate withdrawal. These results are consistent with several other studies which found that lesions of LC or its NE efferents do not alter opiate withdrawal or hinder the ability of clonidine to reduce withdrawal effects (Britton et al. 1984; Caille et al. 1999; Chieng and Christie 1995). Although structures such as cortex, hippocampus, and thalamus receive NE inputs exclusively from LC, areas such as NAc, LH, and perifornical hypothalamus receive NE inputs primarily from A1 and A2, and numerous areas receive substantial NE from both sets of NE neurons, including parts of CeA and BNST (Aston-Jones et al. 2008).

Mechanistically, NE acting in the extended amygdala may drive dysphoria by decreasing excitatory projections from the extended amygdala to its efferent targets, including VTA. This effect may be achieved via NE actions to increase GABA and decrease glutamate inputs onto excitatory VTA-projecting neurons in BNST. NE application to neurons in ventrolateral BNST (with a physiological profile like that of VTA-projecting neurons) was found to cause increased GABA(A)-IPSC frequency during acute opiate withdrawal (Dumont and Williams 2004). This effect was mediated through alpha-1 and beta adrenoceptor mechanisms, whereas NE effects were modulated only though alpha-1 mechanisms in naive animals (Dumont and Williams 2004). These findings are consistent with those of Delfs et al. (2000) which indicate that the aversiveness of opiate withdrawal is due to NE acting at beta adrenoceptors in BNST. NE has also been shown to inhibit glutamatergic transmission in ventral BNST, via alpha-2 adrenoceptors (Egli et al. 2005; Forray et al. 1999). In addition, modulation of targets such as extended amygdala by NE inputs might amplify affective valences normally represented there via postsynaptic modulatory effects on other inputs, as has been reported for NE in other target regions (e.g. cerebral cortex (Aston-Jones et al. 2008; Berridge and Waterhouse 2003)). NE's effects to increase GABA input and decrease glutamate input to BNST neurons may reduce excitatory projections from BNST to VTA. VTA may be strongly influenced by the extended amygdala during acute withdrawal, as indicated by the finding that acute opiate withdrawal inhibited VTA DA neuron firing and decreased extracellular DA in NAc, and that pre-treatment with clonidine prevented these effects (Diana et al. 1995; Georges and Aston-Jones 2003; Pothos et al. 1991; Spanagel et al. 1994). This inhibition of VTA DA output may contribute to withdrawal effects, as indicated by the finding that D2 agonist injection into NAc decreased opiate withdrawal behaviors (Harris and Aston-Jones 1994). Similar decreases in VTA DA firing activity accompanied acute withdrawal from chronic ethanol, cocaine, and cannabinoids (Diana et al. 1992, 1993, 1998; Mateo et al. 2005; Rossetti et al. 1992), indicating that VTA DA may be an important recipient of extended amygdala projections during withdrawal.

The increased NE levels in BNST during acute withdrawal that drive these changes may be caused by activation of NE terminals within BNST and/or by increased activity of NE cells in NTS. The strong induction of Fos in BNST-projecting A2 neurons during opiate withdrawal indicates that the latter is likely involved (Delfs et al. 2000).

Increased NE in the extended amygdala during acute opiate withdrawal is also accompanied by increased signaling of the neuropeptide CRF, a transmitter prominently involved in anxiety and other behavioral responses to stress. Some of the strong reciprocal connections between BNST and CeA, as well as some of the extra-amygdaloid inputs to the extended amygdala, utilize CRF. Studies by Nakagawa et al. (2005) suggested that projections from CeA to BNST, in particular, are important for CPA. They found that bilateral excitotoxic lesions of CeA significantly reduced opiate withdrawal-induced Fos in BNST; however, bilateral lesions of BNST had no effect on withdrawal-induced Fos in CeA. Systemic or intra-CeA administration of CRF antagonists was also found to reduce CPA associated with acute opiate withdrawal. This, plus the above results for NE, signifies that both NE and CRF signaling in BNST and CeA are involved in the aversiveness of acute opiate withdrawal. (Heinrichs et al. 1995; Stinus et al. 2005). As described later, NE and CRF connections within BNST and CeA are importantly involved also in stress-induced reinstatement of drug-seeking. This indicates that the extended amygdala may be important for the aversiveness of acute withdrawal by virtue of its role in the response to stressors. It may also play a pivotal role in other stress-related behaviors associated with drug abstinence, such as anxiety, enhanced drug-seeking, and stress-induced relapse, as discussed in the following sections.

Extended amygdala and drug abstinence-induced anxiety

NE and CRF actions in CeA and BNST have dissociable effects on autonomic and behavioral responses to stressors. Autonomic responses to stressors in rodents include activation of the HPA axis, release of adrenocorticotropic hormone (ACTH) and corticosterone, and increased blood pressure and heart rate. Behavioral responses to stressors in rodents can be measured in a variety of well-validated (anxiolytic-responsive) anxiety paradigms, including the elevated plus-maze, open field, acoustic startle reflex, and the social interaction test, and are indexed by levels of exploratory or social behavior, freezing, startle, or vocalizations (Davis 1993; File 1990; Pellow et al. 1985; Prut and Belzung 2003; Rodgers 1997). The baseline anxiety response in these paradigms can be elevated by the introduction of an acute unconditioned stressor, such as footshock, light, immobilization, swim stress, or CRF itself, to give a measure of stress-induced (or stress-enhanced) anxiety. The amount of fear displayed by the animal can be measured via the introduction of a conditioned stressor, i.e. a stimulus that has been paired with an unconditioned stressor.

The BNST has been implicated specifically in anxiety, and the CeA in fear (Davis 2006; Walker et al. 2003). Inactivation of BNST was shown to block modulation of startle related to unconditioned stressors such as light, CRF, and footshock, and inactivation of CeA blocked modulation of startle related to conditioned stressors, such as fear (Gewirtz et al. 1998; Lee and Davis 1997; Walker and Davis 1997). This role for amygdala in fear conditioning and emotional learning has been confirmed in other animals and humans (Phelps and LeDoux 2005). Cecchi et al. (2002a) showed that some anxiety effects involve NE inputs to BNST, finding that blockade of alpha-1 or beta-1,2 adrenoceptors in ventrolateral BNST reduced immobilization stress-induced anxiety in the elevated plus-maze and stress-induced rises in plasma ACTH, with no effect in a social interaction test preceded by stress. Conversely, blockade of alpha-1 receptors in CeA reduced immobilization stress-induced social interaction effects, with no effect on stress-induced anxiety in the elevated plus-maze or plasma ACTH levels (Cecchi et al. 2002b). Blockade of CRF receptors in CeA also attenuated fear-induced freezing (Swiergiel et al. 1993). These results confirm that NE and CRF actions within BNST and CeA are involved in different specific components of stress and anxiety responses.

Anxiety and stress are major contributors to drug-craving and relapse in humans, as discussed in more detail in the following section (Childress et al. 1994; Kosten et al. 1986; Sinha 2001; 2007). In rats, elevated anxiety was seen during the first 48 h after withdrawal from chronic cocaine, opiates, ethanol, and cannabinoids (Basso et al. 1999; Harris and Aston-Jones 1993b; Rassnick et al. 1993a; Rodriguez de Fonseca et al. 1997; Sarnyai et al. 1995). Elevated anxiety persisted for at least two weeks of cocaine or morphine abstinence, and for at least six weeks of cocaine or ethanol abstinence (Harris et al. 2001; Harris and Aston-Jones 2001; Valdez et al. 2003). Following chronic cocaine or opiate exposure, increased withdrawal anxiety was observed in the defensive burying paradigm, which was alleviated by systemic administration of the beta antagonists propranolol and atenolol (Fig. 4) (Harris and Aston-Jones 1993b). The defensive burying paradigm is a widely used measure of stress-induced anxiety, in which the rat buries a probe after it receives a shock from the probe (Treit et al. 1981). This beta antagonist effect is consistent with the view that attenuation of the aversive aspects of acute opiate withdrawal by NE agents is due, at least in part, to actions in the ventral BNST and alleviation of elevated anxiety.

There is some evidence to suggest that the elevated anxiety observed after withdrawal is specific to stress-induced anxiety and does not occur in tests of baseline anxiety. This corresponds with a role for the extended amygdala in withdrawal-induced anxiety, as CeA and BNST are involved in the modulation of anxiety by conditioned or unconditioned stressors, as discussed above. Although some reports indicate that cocaine and ethanol withdrawal increased anxiety observed in the elevated plus-maze, other experiments found increased anxiety exclusively in the defensive buying paradigm (which includes a shock as a stressor to induce burying), or only if elevated plus-maze testing was preceded by restraint stress (Basso et al. 1999; Rasmussen et al. 2001; Rassnick et al. 1993a; Sarnyai et al. 1995; Valdez et al. 2002, 2003). In all of these cases, intracerebroventricular (i.c.v.) or intra-CeA administration of CRF antagonists reversed withdrawal-induced increases in anxiety (Basso et al. 1999; Rassnick et al. 1993a; Sarnyai et al. 1995; Valdez et al. 2003).

Alleviation of enhanced anxiety during withdrawal with either NE or CRF antagonists indicates that signaling in these systems may be amplified during withdrawal. In fact, increased levels of extracellular CRF in CeA have been measured following acute withdrawal from cocaine, ethanol, and cannabinoids (Merlo Pich et al. 1995; Richter and Weiss 1999; Rodriguez de Fonseca et al. 1997). Additionally, elevated levels of extracellular NE in ventral BNST were observed at least 48 h after naloxone-precipitated morphine withdrawal in rats, after somatic signs of withdrawal had dissipated, indicating that increased NE release in the extended amygdala continues to influence stress and anxiety systems in the brain for some time following acute withdrawal (Fuentealba et al. 2000). These data also indicate that acute and protracted abstinence may cause heightened anxiety due to exaggerated stress responses in the extended amygdala. Changes in the VTA DA system may be an important corollary of the increased NE and CRF levels in the extended amygdala during protracted abstinence. Reduced VTA DA firing was observed for at least 72 h following withdrawal from chronic ethanol or morphine, after physical symptoms had subsided (Diana et al. 1996, 1999). As noted above, decreased DA function may contribute to the aversiveness of the withdrawal experience.

Extended amygdala and stress-induced reinstatement of drug-seeking

Stress is a significant risk factor for opiate and cocaine relapse in humans (Kosten et al. 1986; Sinha et al. 2006). In the laboratory, personalized stress imagery, as well as drug-associated cues, caused significant increases in subjective ratings of craving and anxiety in cocaine, opiate, and alcohol abuse patients; cocaine and alcohol abusers also showed increased activation of the HPA axis and physiologic measures of stress (Fox et al. 2007;

Hyman et al. 2007; Sinha et al. 1999, 2003). In addition, high-frequency abusers of cocaine or ethanol had significantly greater craving and anxiety, as well as HPA and cardiovascular responses, in response to stress and cue imagery as compared to low-frequency users, indicating that increased exposure might increase susceptibility to stress-induced relapse (Fox et al. 2005).

In animal models of stress-induced reinstatement of drug-seeking, animals are trained to self-administer a drug across several sessions and then given non-reinforced trials to extinguish the drug-seeking response. Intermittent footshock delivered in the operant self-administration chamber potently reinstates lever-pressing in the absence of drug reward; this is taken as a measure of drug-seeking (for review, see Lu et al. 2003; Shaham et al. 2000a; 2003). The work of several laboratories has shown that such reinstatement of drug-seeking is heavily dependent upon the extended amygdala in a manner very similar to the aversiveness of acute opiate withdrawal. Thus, inactivation of BNST, CeA, NAc-Sh, or VTA blocks footshock-induced reinstatement of cocaine-seeking (McFarland et al. 2004).

Systemic administration of alpha-2 agonists attenuated footshock-induced reinstatement of drug-seeking for cocaine, heroin, ethanol, and nicotine (Erb et al. 2000; Le et al. 2005; Shaham et al. 2000b; Zislis et al. 2007). Local administration of beta adrenoceptor antagonists into BNST reduced footshock-induced reinstatement of cocaine-seeking, whereas administration into CeA completely blocked reinstatement (Fig. 5a); neither had any effect on cocaine prime-induced reinstatement (Leri et al. 2002). Intra-BNST alpha-2 agonists also blocked footshock-induced reinstatement of a conditioned place preference (CPP) for morphine (Wang et al. 2001). Alpha-2 agonists had no effect on stress-induced reinstatement for opiates when injected into LC (which presumably inhibited LC impulse activity), but lesions of VNAB significantly inhibited stress-induced reinstatement (Shaham et al. 2000b; Wang et al. 2001). This points to the importance of NE innervation of the extended amygdala originating from A2 NE neurons in NTS (rather than LC) in stress-induced reinstatement of drug-seeking. Again, these results also point to the similarity in circuitries involved in the aversiveness of acute opiate withdrawal (reviewed above) and stress-induced reinstatement of drug seeking.

Systemic or i.c.v. administration of CRF antagonists also reduced footshock-induced reinstatement of drug-seeking for cocaine, heroin, ethanol, and nicotine (Erb et al. 1998; Le et al. 2000; Shaham et al. 1997, 1998; Zislis et al. 2007). Systemic or i.c.v. administration of CRF antagonists blocked footshock-induced reinstatement of morphine CPP as well (Lu et al. 2000). Local administration studies showed that injections of CRF antagonists into BNST or VTA, and not amygdala, attenuated footshock-induced reinstatement of cocaine-seeking (Erb and Stewart 1999; Wang et al. 2005, 2007). Similarly, injections of CRF antagonists into BNST, and not amygdala or NAc, attenuated footshock-induced reinstatement of morphine CPP, although injections of CRF antagonists into amygdala and NAc, and not BNST, attenuated drug prime-induced reinstatement of morphine CPP (Wang et al. 2006). Erb et al. (2001) found that unilateral inactivation of amygdala via TTX combined with injection of a CRF antagonist into the contralateral BNST blocked stress-induced reinstatement of cocaine-seeking (Fig. 5b), demonstrating that CRF projections from CeA to BNST are critical for this stress-induced reinstatement.

Although there is substantial overlap in the circuitry governing acute withdrawal and stress-induced relapse, acute withdrawal does not drive drug-seeking (Shaham et al. 1996; Shaham and Stewart 1995). Lu et al. (2005) found that acute morphine withdrawal did not reinstate an extinguished morphine CPP; however, after repeated pairings of naloxone-precipitated withdrawal with the CPP chamber, re-exposure to the CPP chamber in a drug-free state elicited reinstatement, as well as increased blood corticosterone levels and some somatic

signs of withdrawal. All of these cue-elicited responses were blocked by CRF antagonists (Lu et al. 2005). This indicates that withdrawal-associated cues, but not withdrawal itself, are able to drive relapse.

Although acute withdrawal has no effect on reinstatement, stress-induced reinstatement is heightened following protracted abstinence. Shalev et al. (2001) tested the ability of footshock to drive reinstatement after 1, 6, 12, 25, and 66 days of heroin withdrawal. Maximal responding was observed on days 6 and 12, but footshock was unable to drive reinstatement on day 1 of heroin withdrawal. Additionally, stress-induced reinstatement of drug-seeking for ethanol, cocaine, and heroin was heightened in animals made previously dependent or given extended access to daily self-administration (Ahmed et al. 2000; Liu and Weiss 2002; Mantsch et al. 2008).

Extended amygdala and enhanced drug-seeking associated with protracted abstinence

Prolonged exposure to drugs causes neuronal and behavioral changes that exist long after symptoms of acute withdrawal have dissipated. These alterations cause a variety of maladaptive effects, including increased anxiety, vulnerability to stress-induced relapse, and enhanced drug-seeking. A series of experiments from our laboratory have shown that post-dependent animals process reward-related stimuli in an aberrant manner, such that preference is increased for stimuli associated with drug, whereas stimuli associated with natural rewards elicit less preference than normal. For these experiments, rats were made dependent (via morphine pellets or daily cocaine injections) for two weeks and then subjected to abstinence withdrawal for 2–5 weeks. Post-dependent and drug-naive animals were then conditioned with drug- and vehicle-associated environments in a CPP paradigm. Non-conditioned control animals received unpaired drug injections in the home cage and received similar exposure to the CPP environment drug-free.

Enhanced drug-seeking during protracted abstinence

Post-dependent animals showed similarly enhanced morphine CPP after 2–5 weeks of abstinence (Harris and Aston-Jones 2001, 2003b). Enhanced cocaine CPP was also found following two weeks of abstinence; longer abstinence periods have not been tested (Harris et al. 2001). This enhanced drug-seeking during protracted abstinence was accompanied by decreased CPP for food and novel objects (Fig. 6) (Harris and Aston-Jones 2003a, 2007; Harris et al. 2007). Previous studies have shown enhanced drug preference following prolonged drug exposure, but did not include a period of prolonged abstinence (Contarino et al. 1997; Lett 1989; Shippenberg and Heidbreder 1995).

NE and CRF signaling within the extended amygdala may become more heavily involved in drug-taking responses following a period of chronic drug exposure. CRF antagonists selectively decreased the increased self-administration of ethanol or cocaine observed in animals made dependent or given extended drug access, with no effects on non-dependent groups (Chu et al. 2007; Funk et al. 2006, 2007; Specio et al. 2007). Even after 3–5 weeks of abstinence, CRF antagonists reduced increased responding for ethanol in post-dependent animals only (Valdez et al. 2002). Wang et al. (2005) found that in cocaine-experienced rats, but not cocaine-naïve rats, CRF acquired control over local glutamate release in VTA and activated DA neurons, which was responsible for footshock-induced reinstatement. Similarly, the alpha-2 adrenoceptor agonist clonidine reduced morphine CPP in previously-dependent animals, with no effect in non-dependent animals (Nader and van der Kooy 1996).

Fos in extended amygdala associated with altered reward-seeking

To determine whether the extended amygdala plays a role in the enhanced drug-seeking observed in CPP tests during protracted morphine abstinence, neuronal activity was investigated using immunohistochemistry for the immediate early gene protein Fos. For these experiments, animals were sacrificed 2 h following the CPP test session, so that Fos expression reflects re-exposure to, and response to, the drug-paired environment. Elevated Fos was observed in anterior cingulate, NAc core and shell, ventral BNST, BLA, CeA, LH, and NTS in post-dependent rats after 5 weeks of protracted abstinence, as compared to non-dependent and non-conditioned rats (Aston-Jones and Harris 2004; Harris and Aston-Jones 2003b; 2007). Fos in anterior cingulate and BLA correlated with CPP in all conditioned animals; however, Fos in BNST correlated with CPP in post-dependent rats only (Harris and Aston-Jones 2003b). This indicates that activation in BNST is uniquely associated with the elevated preference found during protracted abstinence. Importantly, there were no elevations in Fos for non-conditioned post-dependent animals in response to the CPP environment alone, indicating that the increased Fos following CPP in post-dependent rats was specific for exposure to drug-associated stimuli. These data, in view of NE's strong innervation and effects in the extended amygdala, led our lab to hypothesize that drug-conditioned stimuli can activate A1 and A2 NE neurons that release NE into the extended amygdala. This was proposed to cause increased anxiety and produce negative reinforcement for drug rewards given during conditioning sessions. These negatively reinforcing effects were proposed to summate with positively reinforcing effects to increase motivation to seek out drugs (Aston-Jones and Harris 2004).

Animals also exhibited decreased food CPP during protracted morphine abstinence. As with morphine CPP, Fos in anterior cingulate and BLA correlated with food CPP for all conditioned animals. Decreased food CPP in post-dependent rats was accompanied by decreased Fos in NAc-Sh, LH, and BLA, as compared to non-dependent animals (Aston-Jones and Harris 2004; Harris and Aston-Jones 2007). These limbic areas showed *increased* Fos during enhanced morphine CPP, indicating that they are particularly important for the altered reward processing that occurs during protracted abstinence. These brain areas are all afferents to VTA, and all excitatory except for NAc-Sh, suggesting that VTA may receive decreased excitatory drive in relation to natural rewards during protracted abstinence. Fos was negatively correlated with food CPP in CeA, ventrolateral BNST and NTS in previously morphine-dependent rats (Fig. 7) (Harris and Aston-Jones 2007). This, in view of the increased drug preference (described above), indicates that Fos activation in BNST and CeA in the extended amygdala, and their major NE afferent in NTS, is associated with enhanced drug preference and decreased food preference. This indicates that increased activity in these stress systems may decrease the rewarding properties of natural rewards, while increasing the reward associated with drug rewards. These findings add to others reviewed above indicating that activation in the extended amygdala is strongly associated with altered reward processing during protracted abstinence.

Possible mechanisms of enhanced drug-seeking

Additional studies in our laboratory showed that morphine preference is enhanced during protracted abstinence only if CPP conditioning occurs during abstinence (Smith et al. 2004). Thus, we found that animals trained for morphine CPP prior to dependence and withdrawal did not show elevated morphine CPP when tested shortly after subsequent chronic drug exposure or after one to six weeks of abstinence. However, these same animals exhibited enhanced CPP of the expected amplitude when they were re-conditioned during protracted abstinence. This indicates that animals need to experience the stimulus-drug association during abstinence in order to acquire increased drug-seeking behavior, and that the positive

or negative reinforcing properties of the drug may be altered selectively during drug abstinence.

To test whether NTS is involved in the development of altered drug reinforcement during protracted abstinence, we measured Fos in NTS following the first morphine-environment CPP pairing. We found that noradrenergic A2 neurons in NTS in post-dependent animals (after 7 weeks of protracted morphine abstinence) showed increased Fos in response to a morphine CPP conditioning trial compared to rats that were not previously drug-exposed (Fig. 8; unpublished data, 2005). It is possible that this Fos effect was partially due to the stress of the injection, however, these Fos levels are comparable to those seen following a morphine CPP test session in post-dependent and non-dependent rats in other experiments, and therefore seem unlikely to be a result of the injection itself (Harris and Aston-Jones 2007). Although opiates are traditionally thought to exert an inhibitory influence on NE neurons in LC, Olson et al. (2006) also reported an increased Fos response in tyrosine hydroxylase-containing (TH+) neurons of NTS in mice following an acute morphine injection given in the CPP chamber. Rodriguez de Fonseca et al. (1997) also found increased Fos expression in NTS, along with BNST, CeA, and NAc-Sh, following acute cannabinoid exposure or acute withdrawal from chronic exposure. Electrophysiological recordings have revealed that morphine can both inhibit spontaneous activity and induce bursting in NE–LC neurons (Aston-Jones et al. 1992). The inhibition likely reflects direct effects of morphine on opioid receptors in LC (Bird and Kuhar 1977; Christie 1991; Korf et al. 1974), whereas increased bursting is presumably due to modulation of excitatory afferents to LC in the waking intact animal (Aston-Jones et al. 1992, 1993). These studies suggest that NE systems in the behaving animal can be activated by both acute drug exposure and drug withdrawal, and that NE may play a diverse role in several stages of addiction.

Another study in our laboratory explored delta-FosB (a highly stable product of the immediate early gene FosB) during protracted withdrawal. Unlike the transient expression of Fos and FosB, delta-FosB is a stable transcription factor that accumulates in response to chronic treatments. Delta-FosB persists for long periods of time once induced, and therefore gives a unique perspective into long-term neuronal responses to stimuli such as drug exposure (McClung et al. 2004). Following chronic cocaine treatment, our lab found that FosB/delta-FosB was elevated in BLA as well as NAc core and shell after 2 weeks of abstinence. At this time point, FosB/delta-FosB levels in all of these brain regions were correlated positively with cocaine CPP but correlated negatively with novel object CPP. However, after 5 weeks of abstinence FosB/delta-FosB only in NAc-Sh remained positively correlated with cocaine CPP and negatively correlated with novel object CPP (Harris et al. 2007). NAc-Sh is a part of the extended amygdala, is reciprocally connected with VTA, and is a critical target of VTA DA release for behavioral responses to abused drugs and other appetitive stimuli (Di Chiara 2002). Thus, enduring changes in NAc-Sh function (as indicated by these delta-FosB results) during chronic drug exposure and withdrawal may be involved in the increased drug preference observed during protracted abstinence.

Role of noradrenergic transmission in positive drug reinforcement

Long-lasting neuroadaptations following dependence and protracted drug abstinence cause enhanced anxiety and dysphoria. This may drive increased motivation for drugs via negative reinforcement by drug exposure and consequent decreased anxiety, and also cause decreased motivation for natural rewards (Koob 1993, 1999b, 2003). This is evident in the effects of protracted drug abstinence on preference for drug and food rewards; non-dependent rats exhibit a two-fold stronger preference for food than for morphine, however, abstinent rats have a two-fold stronger preference for morphine than food, indicating that reward processing has substantially changed (Harris and Aston-Jones 2003a). As discussed above,

NE transmission in the extended amygdala appears to play an important role in this reward dysregulation that accompanies chronic drug exposure, and heightened NE may result in increased negative reinforcement for drugs of abuse.

Additionally, NE may be involved in the positively reinforcing effects of drugs. Although DA has been extensively implicated in the initial reinforcing effects of drugs during self-administration and CPP, NE and other systems may play a larger role than previously suspected. For example, recent studies suggest that opiate reward may include dopamine-independent pathways (Caine et al. 2007; Hnasko et al. 2005; Laviolette et al. 2002). As reviewed in Weinshenker and Schroeder (2007), the DA hypothesis of drug reward was originally based, in part, on the role of DA in the maintenance of psychostimulant self-administration. However, other aspects of addiction (e.g., acquisition, extinction, reinstatement) were not fully explored. In addition, other studies suggested an involvement of NE in the primary reward mechanisms for opiates (discussed below) and ethanol (Amit and Brown 1982; Amit et al. 1977; Mason et al. 1979; Rassnick et al. 1993b; Weinshenker et al. 2000). Recently, the role of NE in addiction has also received interest stemming from its importance in stress-induced reinstatement, drug-induced locomotion, and opiate CPP (Weinshenker and Schroeder 2007).

In studies of opiate reward, investigators found that dopamine beta-hydroxylase (DBH) knock-out mice failed to exhibit CPP for morphine, whereas CPP for food was normal (Jasmin et al. 2006; Olson et al. 2006; Schank et al. 2006). Morphine CPP in these animals was restored if NE signaling was rescued in NTS, but not if it was rescued in LC, confirming the importance of A2 NE neurons (the primary source of NE in the extended amygdala, as reviewed above) in morphine reinforcement (Olson et al. 2006). DBH knock-out mice also displayed altered cocaine CPP, although differently for different investigators: Schank et al. (2006) found hypersensitivity to the rewarding and aversive properties of cocaine, whereas Jasmin et al. (2006) showed a lack of cocaine reward in these mutants.

These results do not rule out an important role for DA in drug reward and reinforcement as well; NE mechanisms of drug reward may be dependent on interactions with the DA system. Indeed, it has proven difficult to fully differentiate the roles of DA and NE in drug reward, and studies in this vein have often revealed discordant results. This difficulty may reflect, at least in part, redundancies in the monoamine systems, so that interruption in the functioning of one system results in compensation by the other (Hnasko et al. 2007). In addition, NE and DA neurons interact at several levels (e.g. NE binds to D4 receptors (Newman-Tancredi et al. 1997), and DA is a high-affinity substrate for the NE transporter (Carboni and Silvagni 2004)), so that alterations in the functioning of one system may often change activity in the other. Further studies are needed to more fully understand the roles of each of these catecholamines, and their interactions, in reward processes.

Orexin in the extended amygdala: recent results indicating a role in drug-seeking and withdrawal

Orexins, also called hypocretins, are recently discovered neuropeptides made from a prepro-orexin peptide exclusively in hypothalamic neurons (de Lecea et al. 1998; Sakurai et al. 1998). These neurons provide an extensive efferent plexus of projections throughout the neuraxis (Baldo et al. 2003; Date et al. 1999; Nambu et al. 1999; Peyron et al. 1998). Of interest here, the orexins innervate all areas of the extended amygdala and provide an especially dense innervation of BNST (Baldo et al. 2003; Nambu et al. 1999; Peyron et al. 1998). Extensive evidence indicates a role for these peptides in narcolepsy with cataplexy (Chemelli et al. 1999; Lin et al. 1999; Nishino et al. 2000; Siegel 2004) (for review, see Nishino 2007; Sutcliffe and de Lecea 2002; Willie et al. 2001). However, recent findings

from several sources indicate that this system also plays an important role in neuroplasticity, drug reward-seeking, and reinstatement of extinguished drug-seeking (Borgland et al. 2006; Boutrel et al. 2005; Harris et al. 2005; Lawrence et al. 2006; Narita et al. 2006). Moreover, at least some of these functions may be mediated through, or influenced by, effects of orexins in the extended amygdala.

There is considerable communication between stress response systems and orexin cells in LH. The area of orexin neurons receives extensive projections from BNST, NAc-Sh, and amygdala (Sakurai et al. 2005; Yoshida et al. 2006). Orexin neurons in LH receive direct contact from CRF terminals and express CRF receptors (Winsky-Sommerer et al. 2004). Conversely, BNST has a high density of orexin-1 (OX1) receptors, complimenting the dense orexin fiber distribution in that area (discussed above) (Hervieu et al. 2001; Marcus et al. 2001; Trivedi et al. 1998). Orexin cells, particularly those in dorsomedial and perifornical hypothalamus, were found to be activated by stressors such as footshock, restraint, and cold exposure, as revealed by induction of Fos (Harris and Aston-Jones 2006; Sakamoto et al. 2004; Winsky-Sommerer et al. 2004). Stress-induced Fos activation in orexin cells was reduced in CRF receptor-1 knock-out mice (Winsky-Sommerer et al. 2004). Orexin cells are not only activated by stressors, but are also implicated in the induction of behavioral response to stressors. I.c.v. administration of orexin-A was found to activate CRF neurons in CeA and PVN, and prepro-orexin knock-out mice exhibited attenuated stress responses in a resident-intruder test (Kayaba et al. 2003; Sakamoto et al. 2004). These studies indicate that there are functional reciprocal connections between stress-related systems of CRF- and orexin-expressing neurons. NE, CRF, and orexin may act in concert in the extended amygdala to modulate stress-related components of addiction.

Orexin-mediated responses are involved in stress-associated properties of abused drugs. Acute morphine withdrawal was accompanied by increased Fos and orexin gene expression in orexin cells, and orexin knock-out mice showed attenuated somatic opiate withdrawal (Georgescu et al. 2003; Zhou et al. 2006). In addition, the OX1 receptor antagonist SB-334867 blocked stress-induced reinstatement of cocaine-seeking (Boutrel et al. 2005). Moreover, NE and CRF antagonists reduced reinstatement driven by i.c.v. injections of orexin-A (Boutrel et al. 2005). As stress-induced reinstatement of drug-seeking involves NE and CRF transmission in the extended amygdala (reviewed above), these results suggest that orexins may interact with NE and CRF projections to the extended amygdala during stress responses and drug relapse. Our lab has proposed that orexin- or stress-induced reinstatement of drug-seeking may involve orexin-induced activation of NE and CRF inputs to BNST or amygdala (Harris and Aston-Jones 2006). Given the dense orexin innervation in BNST, it is also possible that such interactions occur at a terminal level within the extended amygdala. Experiments are now underway in our lab to test the role of orexin inputs to BNST in various aspects of addiction to abused drugs.

Conclusion

We reviewed studies indicating that NE and CRF signaling within the extended amygdala are involved in the aversiveness of acute opiate withdrawal and stress-induced reinstatement of drug-seeking in a virtually identical manner. NE and CRF are also necessary for the enhanced anxiety that accompanies protracted abstinence from chronic drug exposure. We also reviewed data showing that the extended amygdala and NTS are associated with the increased drug-seeking and decreased natural reward-seeking that occurs during protracted abstinence. The orexin system may also play a prominent role in withdrawal and relapse behaviors, perhaps in part because of its strong connections with the extended amygdala and NE- and CRF-containing structures. More recent evidence indicates that NE acting within the extended amygdala is critical for the positive reinforcing properties of drugs, particularly

opiates. The extended amygdala is involved in behavioral responses related to stress and anxiety, and this may explain its role in the aversiveness of withdrawal and stress-induced reinstatement. However, the role of NE in positive reinforcement remains enigmatic, and the exact mechanisms of involvement in opiate reward as well as the enhanced drug-seeking and altered reward processing aspects of addiction remain to be elucidated. We presented evidence throughout that indicates that the VTA DA system may be one important site of action for increased extended amygdala output during stress-related aspects of protracted abstinence. Taken together, the studies reviewed here indicate that acute withdrawal and protracted abstinence following chronic drug exposure are associated with increased NTS activation, increased NE release and responsivity in the extended amygdala, and increased CRF release in the extended amygdala. This amplification of stress response systems in the extended amygdala during abstinence seems to similarly account for the aversiveness of acute withdrawal, increased anxiety, stress-induced relapse, and altered reward-processing for drugs and natural rewards. Overall, these studies implicate NE and neuropeptide transmission in the extended amygdala in several stress-related components of addiction which contribute to the increased drug-seeking and relapse vulnerability that makes recovery from addiction so difficult.

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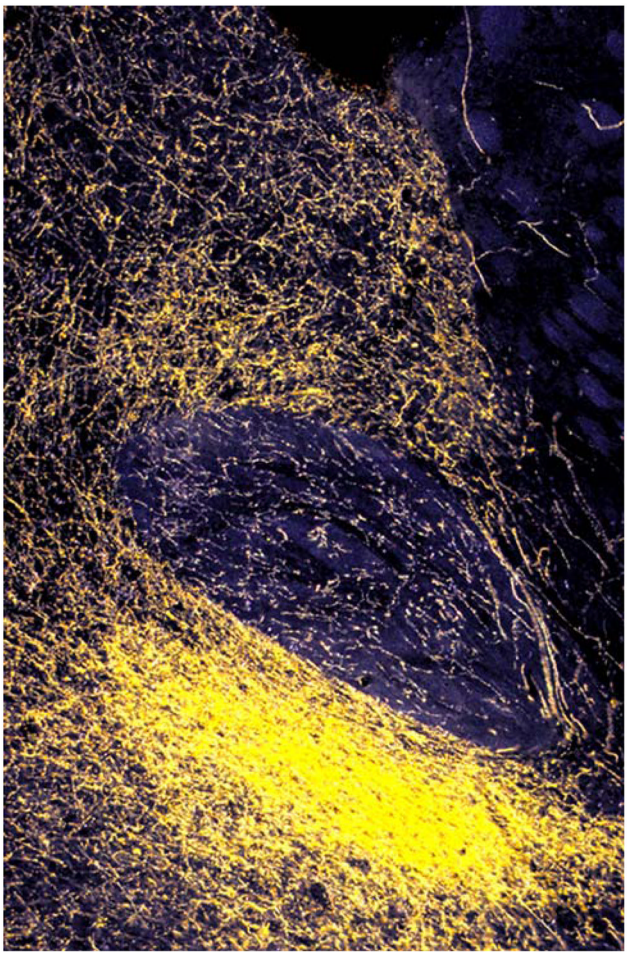

Fig. 1.

Darkfield photomicrograph of a frontal section through ventral BNST showing very dense NE innervation, as revealed by dopamine beta-hydroxylase staining (*yellow*). Ventral BNST lies beneath the anterior commissure in this section; left is medial

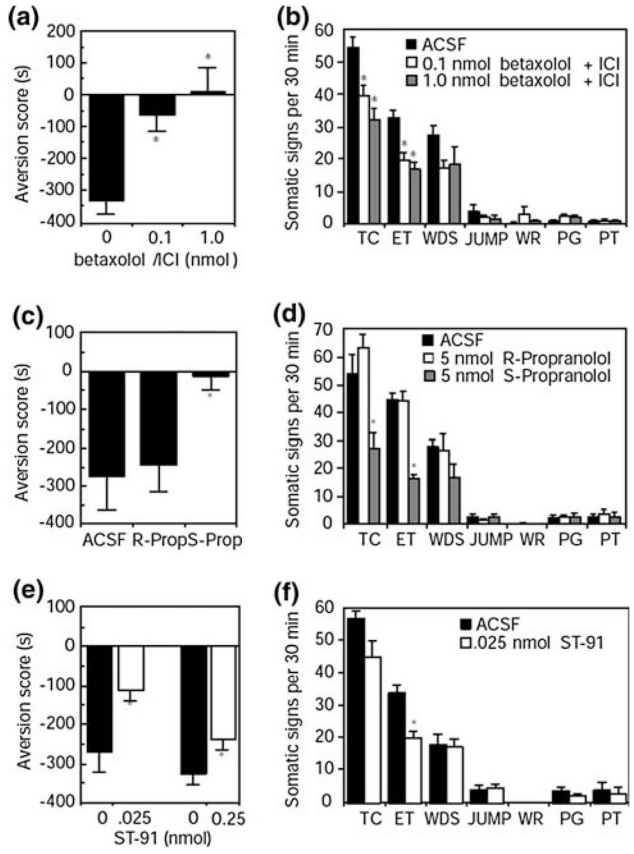

Fig. 2.

Noradrenergic drugs infused into BNST blocked CPA while having minimal effects on somatic signs associated with acute opiate withdrawal. Effects of the beta antagonists betaxolol + ICI 118,551 (**a, b**) or propranolol (**c, d**), or the alpha-2 agonist ST-91 (**e, f**) on aversion scores and somatic withdrawal (*TC* teeth chattering; *ET* eye twitch; *WDS* wet dog shakes; *JUMP* jumping; *WR* writhing; *PG* penile grooming; *PT* paw tremor). Aversion score for the withdrawal-paired environment is the mean time in seconds spent in the withdrawal side minus the non-withdrawal side on test day. $n = 6 – 8$ animals per dose; * $P < 0.05$. Taken from Delfs et al. (2000)

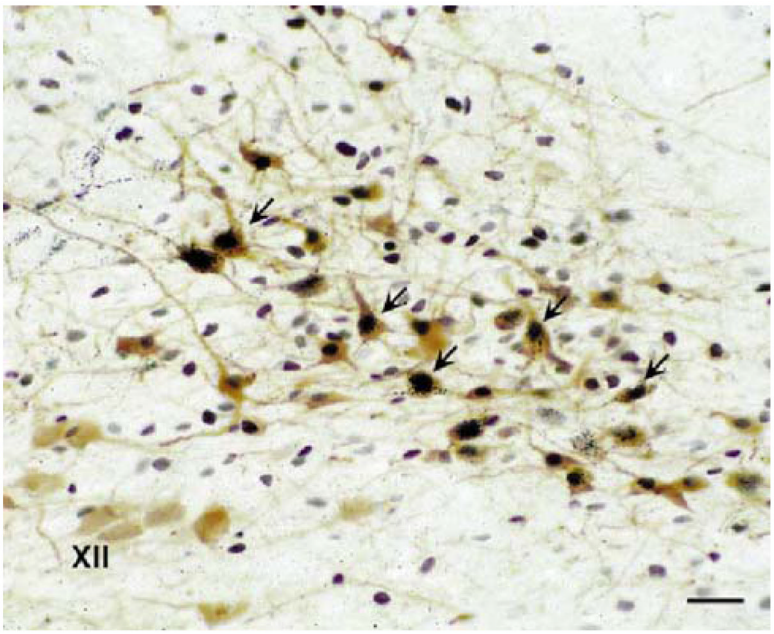

Fig. 3.

BNST-projecting noradrenergic cells in NTS were stimulated by acute opiate withdrawal. The retrograde tracer WGA-gold was injected into BNST, and the A2 region of NTS was triple-labeled for WGA-gold (small *black particles* in cell body), Fos-related antigens (*dark purple-black* nuclei), and tyrosine hydroxylase (*light brown*). *Arrows* indicate triple-labeled cells. Similar results were seen in A1 and LC, but fewer cells were retrogradely labeled. *XII* hypoglossal nucleus; *scale bar*: 40 um. Taken from Delfs et al. (2000)

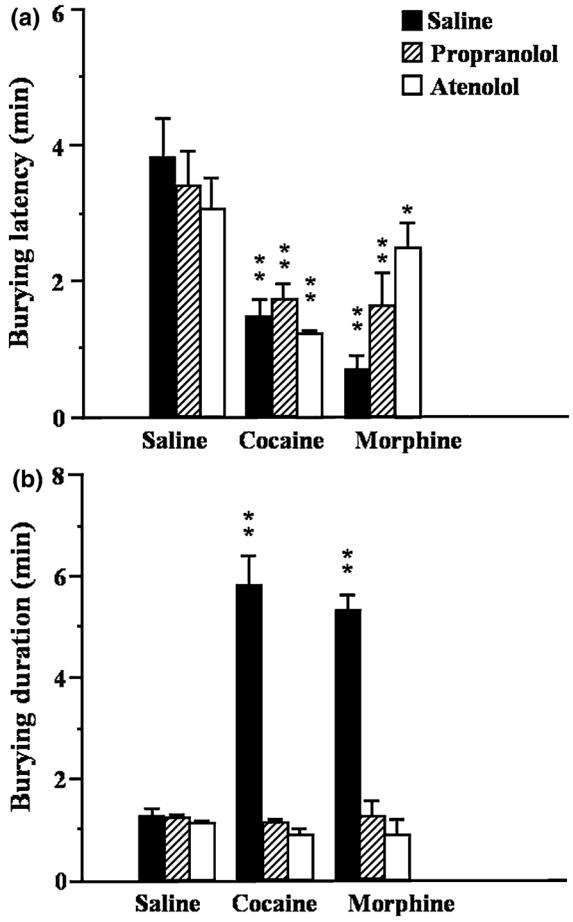

Fig. 4.

Beta adrenoceptor antagonists reduced the increased anxiety observed in the defensive burying paradigm 48 h after forced abstinence from chronic cocaine or morphine. Withdrawn animals showed a shorter latency to begin burying a shock-prod (**a**) and longer duration of burying (**b**) after chronic treatment with cocaine or morphine, as compared to chronic saline. Pre-treatment with propranolol (5 mg/kg) or atenolol (5 mg/kg) reduced this anxiety, as compared to saline pre-treatment. *Asterisks* denote statistically significant differences from saline/saline group; * $P < 0.05$; ** $P < 0.01$. Morphine/atenolol is significantly different from morphine/saline, $P < 0.05$; no other between group comparisons are different. Modified from Harris and Aston-Jones (1993b)

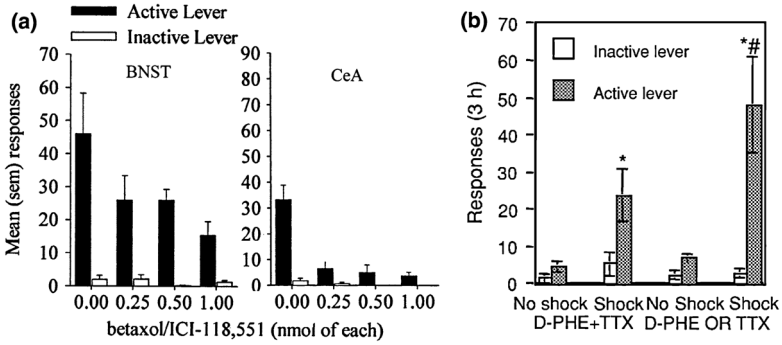

Fig. 5.

Stress-induced reinstatement was reduced by local administration of beta antagonists in BNST or CeA, or local unilateral administration of CRF antagonists in BNST combined with contra-lateral CeA inactivation. **a** Effects of the beta antagonists betaxolol + ICI 118,551 on footshock-induced reinstatement when infused locally into BNST ($P < 0.05$) or CeA ($P < 0.001$). Mean responses on the active and inactive lever during 3-h test sessions. Modified from Leri et al. (2002). **b** Effects of unilateral injection of CRF antagonists (D-Phe $CRF_{12–41}$) into BNST and/or contralateral injection of TTX into CeA during 3-h test sessions preceded by footshock or no shock. Mean responses on the active and inactive lever. Only combined D + T injections effectively reduced reinstatement; * different from no shock, # different from D + T shock, $P < 0.05$. Taken from Erb et al. (2001)

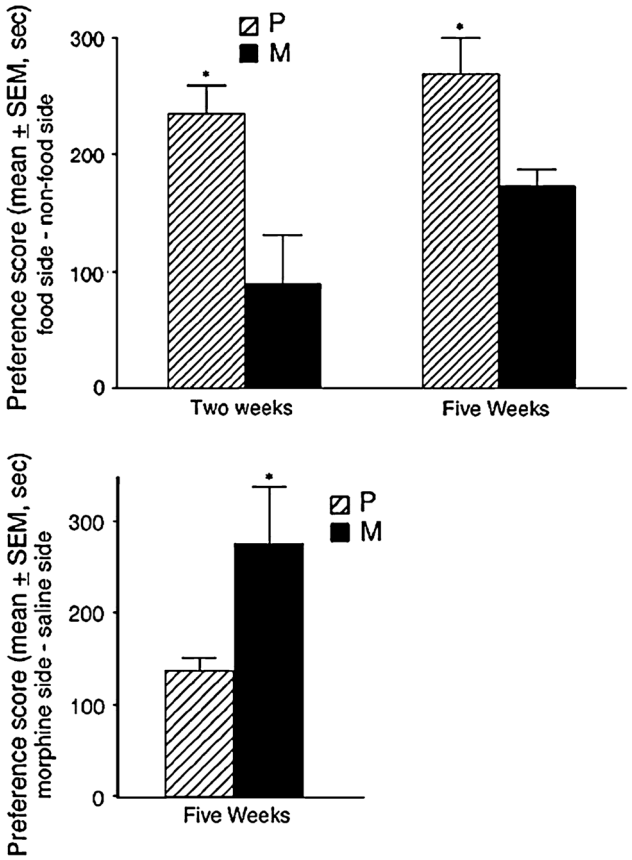

Fig. 6.

Previously morphine-dependent animals (*M*) showed decreased CPP for food after 2–5 weeks of abstinence, as compared to non-dependent animals (*P*) (*upper graph*), and increased CPP for morphine after 5 weeks of abstinence (*lower graph*). Preference for food- or morphine- paired environments is expressed as the mean time in seconds spent in the rewarded side minus the non-rewarded side on test day. $*P < 0.01$. Taken from Harris and Aston-Jones (2003a)

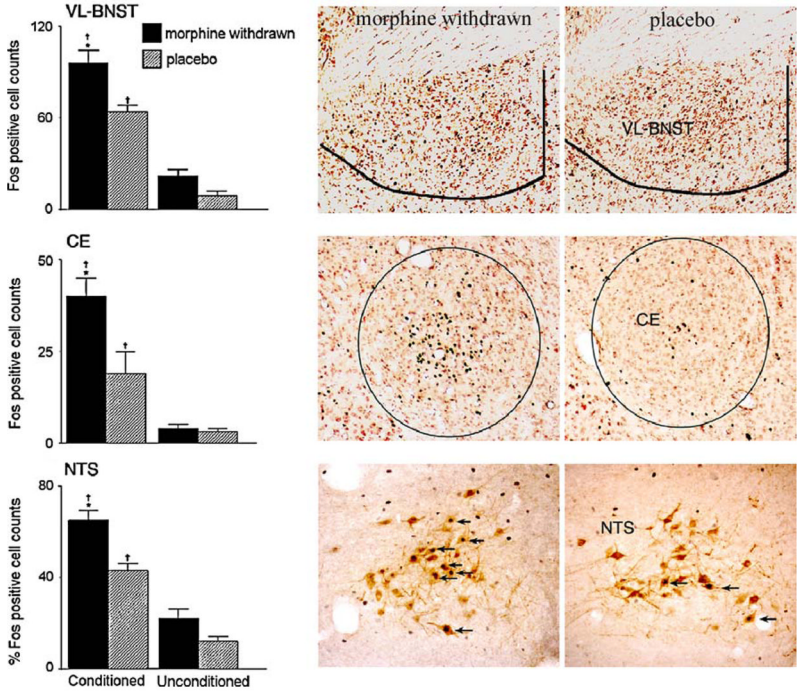

Fig. 7.

Previously morphine-dependent animals showed an increase in Fos-activated neurons in ventrolateral BNST, CeA, and NTS following a food CPP test after 5 weeks of abstinence, as compared to non-dependent animals (placebo). *Graphs* show mean Fos counts for conditioned and non-conditioned animals. † significantly different from non-conditioned rats, $P < 0.01$; * significantly different between conditioned groups, $P < 0.01$. Photomicrographs of frontal sections of brain areas show representative animals in morphine-withdrawn (*left*) and placebo (*right*) groups following food CPP test. Medial is to the *right; arrows* on NTS section indicate cells double-labeled for Fos and TH. Modified from Harris and Aston-Jones (2007)

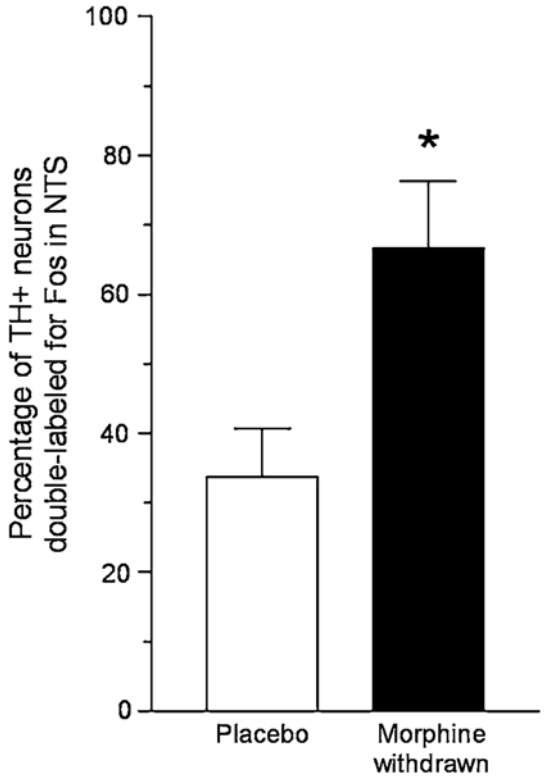

Fig. 8.

Morphine exposure after 7 weeks of abstinence stimulated more noradrenergic cells in NTS of post-dependent rats (morphine withdrawn) than non-dependent rats (placebo). Animals were exposed to a CPP environment following an acute morphine injection (8 mg/ kg), and then sacrificed 2 h later for Fos and TH double-labeling. Post-dependent rats showed a significantly greater percentage of NTS TH+ cells with Fos double-labeling ($P < 0.05$, $n = 3–4$), with no differences in the total number of TH cells or number of TH-negative cells expressing Fos. *Graph* shows mean Fos counts ± S.E.M.