HHS Public Access

Author manuscript

Psychopharmacology (Berl). Author manuscript; available in PMC 2018 May 01.

Published in final edited form as:

Psychopharmacology (Berl). 2017 May ; 234(9-10): 1419–1437. doi:10.1007/s00213-016-4513-5.

Neuropeptide systems and new treatments for nicotine addiction

Adriaan W. Bruijnzeel, PhD[1,2,3]

[1]Department of Psychiatry, University of Florida, Gainesville, Florida, USA

[2]Department of Neuroscience, University of Florida, Gainesville, Florida, USA

[3]Center for Addiction Research and Education, University of Florida, Gainesville, Florida, USA

Abstract

RATIONALE—The mildly euphoric and cognitive enhancing effects of nicotine play a role in the initiation of smoking, while dysphoria and anxiety associated with smoking cessation contribute to relapse. After the acute withdrawal phase, smoking cues, a few cigarettes (i.e., lapse), and stressors can cause relapse. Human and animal studies have shown that neuropeptides play a critical role in nicotine addiction.

OBJECTIVES—The goal of this paper is to describe the role of neuropeptide systems in the initiation of nicotine intake, nicotine withdrawal, and the reinstatement of extinguished nicotine seeking.

RESULTS—The reviewed studies indicate that several drugs that target neuropeptide systems diminish the rewarding effects of nicotine by preventing the activation of dopaminergic systems. Other peptide-based drugs diminish the hyperactivity of brain stress systems and diminish withdrawal-associated symptom severity. Blockade of hypocretin-1 and nociceptin receptors and stimulation of galanin and neurotensin receptors diminishes the rewarding effects of nicotine. Both corticotropin-releasing factor type 1 and kappa-opioid receptor antagonists diminish dysphoria and anxiety-like behavior associated with nicotine withdrawal and inhibit stress-induced reinstatement of nicotine seeking. Furthermore, blockade of vasopressin 1b receptors diminishes dysphoria during nicotine withdrawal and melanocortin 4 receptor blockade prevents stress-induced reinstatement of nicotine seeking. The role of neuropeptide systems in nicotine-primed and cue-induced reinstatement is largely unexplored, but there is evidence for a role of hypocretin-1 receptors in cue-induced reinstatement of nicotine seeking.

CONCLUSION—Drugs that target neuropeptide systems might decrease the euphoric effects of smoking and improve relapse rates by diminishing withdrawal symptoms and improving stress resilience.

Keywords

Nicotine; tobacco; neuropeptide; CRF; dynorphin; hypocretin; dysphoria; anxiety; withdrawal; relapse

Adriaan Bruijnzeel, PhD, University of Florida, Department of Psychiatry, 1149 Newell Dr., Gainesville, Florida 32611, awbruijn@ufl.edu, Telephone: 352-294-4931, Fax: 352-392-9887.

1. Introduction

With 1 billion tobacco users, nicotine is one of the most widely abused drugs in the world (WHO 2011). Smoking increases the risk for numerous diseases that decrease the quality of life or lead to premature death including cancer, chronic obstructive pulmonary disease, heart disease, dementia and Alzheimer's (Ott et al. 1998; Pirie et al. 2013; Postma et al. 2015; Thun et al. 2013). In the 20th century alone, 100 million people died as a result of tobacco smoke exposure (WHO 2015). Smoking rates in Western countries are on the decline and about 80% of tobacco users now live in low and middle income countries with limited access to smoking cessation treatments (WHO 2015).

The positive reinforcing effects of nicotine facilitate the initiation of smoking (Finkenauer et al. 2009). Smoking induces mild euphoria, relaxation, and enhances cognitive function in people who are not yet tolerant to the effects of nicotine (Ague 1973; Benowitz 1988; Wesnes and Warburton 1983). Nicotine is the main component of tobacco smoke that leads to the development of tobacco addiction. This is supported by animal studies and the widespread use of e-cigarettes by people who have never smoked conventional cigarettes (Corey et al. 2013; Corrigall and Coen 1989; Johnston et al. 2015). The e-cigarettes deliver nicotine but only small amounts of other tobacco smoke ingredients (Famele et al. 2014; Pellegrino et al. 2012).

A brief period of nicotine intake can lead to changes in brain networks that cause compulsive drug taking (Adermark et al. 2016; Bruijnzeel 2012). Smoking cessation leads to negative affective symptoms such as dysphoria, anxiety, and impaired cognitive function (Hughes et al. 1991; Hughes and Hatsukami 1986). The negative affective symptoms increase the risk for relapse (Bruijnzeel and Gold 2005). Studies with e-cigarettes and other nicotine delivery products (e.g., gum, patch, nasal spray) show that nicotine decreases the desire to use tobacco and diminishes withdrawal (Dawkins et al. 2012; Harrell et al. 2015; Shiffman et al. 2006). Thus, nicotine is the main component in tobacco smoke that prevents people from decreasing tobacco use and quitting smoking (Bardo et al. 1999; Stolerman and Jarvis 1995). It should be noted that conventional cigarettes are more reinforcing than e-cigarettes because there are compounds in tobacco smoke that are rewarding on their own and enhance the rewarding properties of nicotine. For example, acetaldehyde is formed during the combustion of tobacco and is self-administered by rodents, induces conditioned place preference (CPP), and potentiates the rewarding effects of nicotine (Belluzzi et al. 2005; Brown et al. 1979; Myers et al. 1982; Smith et al. 1984). Other tobacco ingredients such as sugar and menthol are added to tobacco to mask the harsh taste of tobacco smoke and diminish the irritating effects of smoke in the respiratory system (Talhout et al. 2006; Willis et al. 2011). Thus, although nicotine is the main psychoactive compound in conventional cigarettes and e-cigarettes there are significant differences between these products (for an overview see, Fagerstrom et al. 2015; Grana et al. 2014; Talhout et al. 2007).

Without smoking cessation treatment, the majority of people relapse within the first week of abstinence when withdrawal signs are most severe (Hughes et al. 2004; Jarvis 2004). The relapse rate is extremely high and without pharmacotherapy only about 5% of smokers are

able to maintain abstinence for 12 months (Hughes et al. 2004). Smoking induces adaptations in the brain that contribute to craving for nicotine, withdrawal, and relapse. This review focuses on the role of neuropeptide systems in nicotine addiction. However, nicotine also leads to changes in the expression of nicotinic acetylcholine receptors (nAChRs) which may contribute to relapse. Tobacco use in humans and chronic nicotine or tobacco smoke exposure in rodents leads to an upregulation of nAChRs in the brain (Benwell et al. 1988; Marks et al. 1983; Small et al. 2010; Staley et al. 2006). In active smokers, the nAChRs are in a desensitized state but cessation of nicotine use leads a reactivation of these receptors which contributes to withdrawal and relapse (Dani and Heinemann 1996).

The US Food and Drug Administration (FDA) has approved several smoking cessation drugs that diminish withdrawal and improve the relapse rate. Approved treatments include nicotine-based treatments such as nicotine gum and patches. In addition, the FDA has approved the monoamine reuptake inhibitor bupropion and the α4β2 nAChR partial agonist varenicline for smoking cessation (Hurst et al. 2013). Interestingly, a recent animal study suggests that the co-administration of bupropion and varenicline might be more effective in decreasing nicotine self-administration than either drug alone (Hall et al. 2015). Another novel approach to prevent relapse to smoking might be the use of acetylcholinesterase inhibitors. These drugs enhance cholinergic transmission and have received FDA approval for the treatment of Alzheimer's disease (Birks 2006). Recent studies suggest that acetylcholinesterase inhibitors (e.g., galantamine and donepezil) attenuate the self-administration of nicotine in rodents and decrease smoking in humans (Ashare et al. 2016; Hopkins et al. 2012; Kimmey et al. 2014).

There are not yet any FDA-approved peptide-based treatments for smoking cessation, but there is rapid progress in this area of research. The FDA has already approved 60 peptide-based treatments for other disorders and 140 peptide-based treatments are currently in clinical trials (Fosgerau and Hoffmann 2015; Kaspar and Reichert 2013). The brain bioavailability of most orally administered or injected peptides is relatively poor because of enzymatic breakdown and poor blood brain barrier penetration. However, the brain availability of peptides can be improved by masking enzyme cleavage sites (i.e., decreasing breakdown) and increasing lipophilicity to facilitate blood brain barrier passage (Egleton and Davis 2005). Furthermore, small molecule non-peptide drugs have been developed that can be orally administered and target neuropeptide receptors in the brain (Bailey et al. 2011). Finally, clinical studies have shown that neuropeptides can be administered intranasally and affect human behavior (Yatawara et al. 2015). For example, oxytocin nasal spray improves social interactions in children with autism (Yatawara et al. 2015).

There is strong evidence for a role of brain peptide systems in nicotine addiction. Preclinical studies have provided evidence for a role of CRF, dynorphin, and hypocretin-1 in nicotine addiction (See Table 1 for an overview). The goal of this review is to provide an overview of the role of neuropeptide systems in the positive reinforcing effects of nicotine, nicotine withdrawal, and the reinstatement of nicotine seeking. In most animal studies, experimental drugs are administered once immediately before the animals are tested. Therefore, details about the treatment regimen are not reported unless the drug is administered chronically. The reviewed studies indicate that neuropeptides contribute to the development and maintenance

of nicotine addiction, and that different peptides play a role in each stage of the addiction cycle.

2. Genetic variation in hypocretin and galanin receptor genes affects risk for smoking

Genome-wide association (GWA) studies continue to provide important insight into the neuronal mechanisms underlying smoking in humans. Some of the first GWA studies showed that variations in the sequence of α3, α5, and β4 nAChR subunit genes affects the risk for developing and maintaining a nicotine addiction (Berrettini et al. 2008; Chen et al. 2009; Liu et al. 2010; Wen et al. 2016). More recent genetic studies revealed that variability in the α4 nAChR subunit gene affects the risk for developing nicotine addiction in humans (Hancock et al. 2015; Thorgeirsson et al. 2016).

Interestingly, GWA studies also point to a role for neuropeptide systems in nicotine addiction. One study, in which only Japanese subjects were included, reported that an SNP (rs2653349) in the hypocretin-2 receptor gene (HCRTR2) affects the severity of nicotine dependence. Smokers with the A/G genotype of the rs2653349 SNP were more likely to have severe nicotine dependence than smokers with the G/G genotype (Nishizawa et al. 2015). Interestingly, carriers of the A/G genotype were also more likely to use methamphetamine at a young age than carriers of the G/G genotype. This suggests that this rs2653349 SNP may predispose people for drug use. A study with US smokers (Yale University Transdisciplinary Tobacco Use Research Center) provides strong evidence for variation in the galanin-1 receptor (GALR1) gene in the development of nicotine addiction. Cubells and colleagues showed that an SNP in the GALR1 gene (rs2717162) increased self-reported craving during a quit attempt (Lori et al. 2011). The same rs2717162 SNP decreases the effectiveness of bupropion as a smoking cessation aid (Gold et al. 2012). Smokers who carried at least one minor C allele and were treated with bupropion were more likely to report severe cravings and less likely to maintain abstinence than smokers with TT alleles. Another study reported that variations in the GALR1 gene affect the likelihood of heavy smoking (Jackson et al. 2011). In conclusion, these studies indicate that variations in nAChR genes and neuropeptide receptor genes (GALR1 and HCRTR2) affect the likelihood of developing a tobacco addiction, the effectiveness of smoking cessation aids, and the risk for relapse.

3. Neuropeptides and the rewarding effects of nicotine

3.1 CRF and the rewarding effects of nicotine

The activation of nAChRs plays a critical role in the self-administration of nicotine and nicotine-induced CPP (Corrigall et al. 1994; Walters et al. 2006; Watkins et al. 1999). After the development of dependence, the endogenous release of CRF and the resulting negative mood state can drive nicotine intake (i.e., negative reinforcement). Corticotropin-releasing factor is a neuropeptide and is expressed in several brain sites including the paraventricular nucleus of the hypothalamus, central nucleus of the amygdala (CeA), bed nucleus of the stria terminalis (BNST), ventral tegmental area (VTA), and locus coeruleus (LC)(Grieder et

al. 2014; Swanson et al. 1983; Vale et al. 1981). Hypothalamic CRF neurons project to the median eminence and mediate the release of ACTH into the periphery. Extrahypothalamic CRF orchestrates behavioral and autonomic responses to stressors (Koob and Heinrichs 1999; Nijsen et al. 2001), and many of these effects are independent of CRF's effects on the hypothalamic–pituitary–adrenal (HPA) axis (Eaves et al. 1985; Sutton et al. 1982). Two CRF receptors have been discovered, namely the CRF_1 and CRF_2 receptor (Chen et al. 1993; Lovenberg et al. 1995; Perrin et al. 1993). Corticotropin-releasing factor serves as endogenous ligand for the CRF_1 receptor and urocortin 2 and 3 are ligands for the CRF_2 receptor (Lewis et al. 2001). Urocortin 1 binds with a slightly higher affinity to the CRF_1 than the CRF_2 receptor (Lewis et al., 2001). Drug withdrawal-induced behavioral and physiological changes are predominantly mediated via the activation of CRF_1 receptors (Bruijnzeel and Gold 2005; Koob 1999; Steckler and Holsboer 1999). The activation of CRF_2 receptors counteracts the effects of stress responses and CRF_1 receptor activation (Bale and Chen 2012).

The great majority of the nicotine/CRF studies investigated the role of CRF in withdrawal and relapse, but several studies have also investigated the role of CRF in the rewarding effects of nicotine. These studies mostly suggest that CRF increases nicotine intake in dependent, but not in non-dependent, animals. Rats with extended access to nicotine develop dependence and display increased nicotine intake after a period of abstinence (George et al. 2007). Blockade of CRF_1 receptors with MPZP prevents this increase in nicotine intake, but does not affect nicotine intake in control rats with limited access to nicotine (George et al. 2007). Chronic nicotine intake increases CRF levels in the VTA and this could contribute to high levels of nicotine intake in dependent animals (Grieder et al. 2014). This is supported by the observation that downregulation of CRF mRNA in the VTA decreases nicotine self-administration in an extended access paradigm (21 h/day access) (Grieder et al. 2014). Decreasing CRF levels in the VTA does not affect nicotine intake in rats with limited access to nicotine. On a similar note, blockade of CRF_1 receptors does not affect nicotine-induced CPP but prevents stress-induced potentiation of nicotine-induced CPP (Brielmaier et al. 2012). In conclusion, these studies indicate that CRF_1 receptor antagonists decrease nicotine intake in dependent animals. Furthermore, stressors potentiate the reinforcing properties of nicotine and this is prevented by CRF_1 receptor antagonists. Corticotropin-releasing factor type 1 receptor antagonists may help to reduce smoking in dependent smokers and in non-dependent smokers who use tobacco to cope with stressful situations.

3.2 Other peptides than CRF and rewarding effects of nicotine

Corticotropin releasing factor mainly plays a role in nicotine intake in dependent animals, but numerous other neuropeptides regulate nicotine intake in non-dependent animals. Kenny and colleagues have provided insight into the role of hypocretin transmission in nicotine intake (Hollander et al. 2008). Their studies showed that the hypocretin-1 receptor antagonist SB-334867 decreases nicotine self-administration in rats with limited access (1 h) while not affecting responding for food pellets. Pretreatment with the hypocretin-1 receptor antagonist also prevented the nicotine-induced lowering of brain reward thresholds in the intracranial self-stimulation (ICSS) paradigm. A decrease in brain reward thresholds is indicative of a potentiation of brain reward function (i.e., euphoria) (Der-Avakian and

Markou 2012a). Therefore, this indicates that hypocretin-1 receptor antagonists decrease the acute rewarding effects of nicotine. Hypocretin fibers and hypocretin-1 receptors have been detected in the insular cortex. Blockade of the hypocretin-1 receptors in this brain site attenuates the self-administration of nicotine (Hollander et al. 2008). Therefore, activation of hypocretin-1 receptors in the insular cortex may play a role in the initiation of smoking.

Several other neuropeptides have been implicated in the rewarding effects of nicotine including nociceptin/orphanin FQ, neurotensin, galanin, and ghrelin (Boules et al. 2011; Cippitelli et al. 2016; Jerlhag and Engel 2011). Nociceptin mediates its effects in the brain by acting upon the nociceptin receptor. Stimulation of the nociceptin receptor with AT-202 increases nicotine self-administration and blockade of this receptor with SB612111 decreases nicotine self-administration in rats (Cippitelli et al. 2016). Similar effects were observed in dependent and non-dependent rats. Nociceptin is a member of the opioid receptor family and blockade of this receptor prevents drug-induced dopamine release in the nucleus accumbens (Nacc)(Lutfy et al. 2001; Vazquez-DeRose et al. 2013). Dopamine release in the NAcc plays a critical role in the reinforcing properties of nicotine and therefore nociceptin receptor antagonists may decrease nicotine intake by inhibiting the nicotine-induced increase in dopamine signaling (Corrigall and Coen 1991).

Neurotensin is another neuropeptide that could affect the rewarding properties of nicotine by modulating dopamine release. The neurotensin receptor agonist NT69L reduces nicotine self-administration in rats and inhibits nicotine-evoked dopamine release in the NAcc (Boules et al. 2011; Liang et al. 2008). However, NT69L also inhibits the nicotine-induced increase in norepinephrine levels in the prefrontal cortex (PFC)(Liang et al. 2008). Norepinephrine release in the PFC plays a critical role in the reinforcing properties of drugs of abuse (Ventura et al. 2003). Therefore, neurotensin agonists may decrease nicotine intake by modulating dopamine signaling in the NAcc and norepinephrine signaling in the PFC.

Ghrelin is produced in high levels by the stomach during fasting and its levels decrease after food intake (Perello and Dickson 2015). Ghrelin is also produced by neurons in the arcuate hypothalamic nucleus (Kojima et al. 1999; Mondal et al. 2005). The release of ghrelin increases food intake and enhances the rewarding properties of food (Perello and Dickson 2015). It has been suggested that ghrelin modulates the activity of reward systems and thereby regulates food intake. Blockade of ghrelin receptors attenuates nicotine-induced CPP and nicotine-induced dopamine release (Jerlhag and Engel 2011). Therefore, ghrelin receptor blockade could potentially decrease the positive reinforcing effects of smoking.

Galanin positive neurons have been identified in the bed nucleus of stria terminalis (BNST), central amygdala (CeA), medial septum, thalamus, hypothalamus, dorsal raphe nucleus, and brain stem areas (Melander et al. 1986). Galanin plays a role in a wide range of biological functions including energy homeostasis, reproduction, arousal, sleep, and cognition (Gundlach 2002; Lang et al. 2015). Several studies with smokers indicate that galanin plays a role in nicotine craving and withdrawal (Jackson et al. 2011; Lori et al. 2011). Preclinical studies suggest that galanin also mediates the rewarding effects of nicotine. Picciotto and colleagues used galanin knock-out mice to study the role of galanin in nicotine reward (Neugebauer et al. 2011). Nicotine induced CPP in the galanin knock-out mice and the wild-

type mice but higher doses were needed to induce CPP in the knock-out mice. This suggests that galanin knock-out mice are less sensitive to the rewarding effects of nicotine and that galanin signaling contributes to nicotine reward. The findings of this study are not in line with a study that used a pharmacological approach to investigate the role of galanin in the rewarding effects of nicotine. In this study, the galanin receptor agonist galnon blocked the rewarding properties of nicotine in the CPP test (Jackson et al. 2011). It is somewhat surprising that a study with KO mice suggests that galanin enhances the rewarding effects of nicotine and that a pharmacologic study suggests that galanin receptor activation inhibits nicotine reward. It has been suggested that these differences are due to compensatory mechanisms in the KO mice or due to strain differences (Jackson et al. 2011). It might also have been possible that that galnon affects nAChR signaling and diminishes the rewarding effects of nicotine via this off-target effect (Jackson et al. 2011).

In conclusion, the present studies indicate that several neuropeptides play a role in the rewarding effects of nicotine. There is strong evidence that hypocretin-1 and nociceptin receptor blockade diminishes the rewarding effects of nicotine. Stimulation of neurotensin and galanin receptors also attenuates the rewarding effects of nicotine. Therefore, these studies suggest that modulating hypocretin-1, nociceptin, neurotensin, and galanin systems may decrease smoking in people in whom smoking is mainly driven by positive reinforcement processes.

4. Dysphoria and nicotine withdrawal

During the last decades, a wide range of animal models have been developed to investigate the dysphoria associated with smoking cessation. In most of these studies, animals were rendered nicotine dependent using intermittent injection protocols or minipumps that continuously deliver nicotine (Epping-Jordan et al. 1998; Malin 2001). Nicotine withdrawal can be observed after the administration of non-selective nAChR antagonists (precipitated withdrawal) and after the cessation of nicotine administration (spontaneous withdrawal) (Epping-Jordan et al. 1998). Spontaneous withdrawal has greater face validity than precipitated withdrawal as it more closely models human smoking cessation. The precipitated withdrawal method has, however, some significant advantages over the spontaneous withdrawal method. One of the advantages of the precipitated withdrawal method is that nAChR blockade induces withdrawal rapidly and withdrawal signs subside quickly because of the short half-life of nAChR antagonists (Debruyne et al. 2003). Furthermore, the magnitude and duration of precipitated withdrawal symptoms are consistent across sessions and therefore several doses of an experimental drugs can be tested in each animal (Bruijnzeel et al. 2012; Skjei and Markou 2003).

Cessation of chronic nicotine administration induces a stress response, increases corticosterone levels, and decreases operant responding for food pellets, which might be indicative of a negative mood state (Benwell and Balfour 1979; Corrigall et al. 1989; LeSage et al. 2006). Cessation of nicotine administration also leads to immobility in the forced swim test, which might be indicative of a depressive-like state (Mannucci et al. 2006; Roni and Rahman 2014). This increase in immobility in the forced swim test has been observed for up to 60 days after the cessation of nicotine administration (Mannucci et al. 2006). The

conditioned place aversion (CPA) procedure has also been used to assess the aversive state associated with precipitated nicotine withdrawal. In this test, the negative motivational properties of drug withdrawal are paired with a neutral test environment. After pairing, the previously neutral environment acts as a conditioned stimulus and induces avoidance behavior (Tzschentke 1998).

The nAChR receptor antagonist mecamylamine induces place aversion in rats chronically treated with nicotine but not in control rats (Suzuki et al. 1996). The ICSS procedure has also been used to investigate the negative mood state associated with drug withdrawal (Bruijnzeel and Markou 2004; Epping-Jordan et al. 1998). In the discrete trial ICSS procedure the animals are prepared with electrodes in the lateral hypothalamus (LH)/medial forebrain bundle and when placed in the operant chamber they can self-stimulate their brain reward system. By systematically changing the intensity of the electrical current and determining the lowest current that supports self-stimulation, the state of the brain reward system can be assessed (Der-Avakian and Markou 2012b). The acute administration of drugs of abuse increases the sensitivity to the electrical stimuli and lowers brain reward thresholds, which is indicative of a potentiation of brain reward function. In contrast, cessation of chronic drug administration leads to an increase in ICSS thresholds, which is indicative of a negative mood state. The administration of nAChR antagonists to nicotine dependent animals or cessation of chronic nicotine administration leads to elevations in brain reward thresholds (Epping-Jordan et al. 1998; Johnson et al. 2008). One of the main advantages of the ICSS procedure is that it provides a quantitative measure of the emotional state of the brain reward system during withdrawal. The ICSS procedure is a well validated test to assess the dysphoria associated with nicotine withdrawal. Elevations in brain reward thresholds are not exclusive to nicotine withdrawal but are also observed during withdrawal from other drugs including opioids, alcohol, and amphetamine (Bruijnzeel et al. 2006; Cryan et al. 2003b; Schulteis et al. 1995).

The FDA has approved two non-nicotine treatments for smoking cessation. Both bupropion and varenicline have been shown to prevent the elevations in brain reward thresholds associated with nicotine withdrawal (Cryan et al. 2003a; Igari et al. 2013). Therefore, this animal model has face and predictive validity for identifying treatments that diminish dysphoria associated with smoking cessation.

In addition to dysphoria, many animal studies have investigated somatic signs associated with precipitated and spontaneous nicotine withdrawal (Damaj et al. 2003; Malin et al. 1992; Watkins et al. 2000). Somatic withdrawal signs in rodents include teeth chattering, chews, gasps, writhes, ptosis, and head and body shakes (Malin et al. 1992). These signs are often recorded for 5–10 minutes after the rats or mice are placed in an observation chamber. Both nicotine and the smoking cessation drug bupropion diminish somatic withdrawal signs (Cryan et al. 2003a; Malin et al. 1992). It should be noted that somatic withdrawal signs in humans are mild and that relapse to smoking is mainly driven by dysphoria and craving (Bruijnzeel 2012; Hughes 2007; Koob and Volkow 2016). Furthermore, drugs that diminish affective signs might not diminish somatic signs and vice versa (Bruijnzeel et al. 2010). Therefore, this suggests that somatic withdrawal signs have only weak predictive value for identifying treatments that diminish affective withdrawal signs and craving in humans.

4.1 CRF and dysphoria associated with nicotine withdrawal

In our laboratory, we have extensively explored the role of CRF in the dysphoria associated with nicotine withdrawal. In one of our first experiments, we investigated if blockade of CRF receptors with the CRF_1/CRF_2 receptor antagonist D-Phe $CRF_{(12–41)}$ diminishes the elevations in brain thresholds associated with precipitated nicotine withdrawal (Bruijnzeel et al. 2007). Central (icv) administration of D-Phe $CRF_{(12–41)}$ diminished mecamylamine-induced elevations in brain reward thresholds. In a follow-up experiment, the role of CRF_1 and CRF_2 receptors in the dysphoria associated with precipitated nicotine withdrawal was investigated (Bruijnzeel et al. 2009). The highly selective CRF_1 receptor antagonist R278995/CRA0450 was used to block CRF_1 receptors and CRF_2 receptors were blocked with astressin-2B. Blockade of CRF_1, but not CRF_2, receptors, prevented the elevations in brain reward thresholds associated with precipitated nicotine withdrawal. These studies suggest that CRF_1 receptor activation at least partly mediates the dysphoria associated with smoking cessation. It was then investigated which brain areas play a role in the dysphoria associated with nicotine withdrawal (Marcinkiewcz et al. 2009). Administration of D-Phe $CRF_{(12–41)}$ into the CeA and Nacc shell prevented the elevations in brain reward thresholds in the nicotine dependent rats. In contrast, blockade of CRF_1/CRF_2 receptors in the BNST was ineffective. To investigate if CRF_1 receptors in the CeA play a role in nicotine withdrawal, we conducted a study with the selective CRF_1 receptor antagonist R278995/CRA0450 (Bruijnzeel et al. 2012). This study showed that blockade of CRF_1 receptors in the CeA diminishes the dysphoria associated with nicotine withdrawal.

To further explore the role of CRF in the CeA in the regulation of mood states and withdrawal, the effect of the overexpression of CRF in the CeA on the dysphoria associated nicotine withdrawal was investigated. Corticotropin-releasing factor was overexpressed in the CeA using an adeno-associated virus (AAV), with AAV2 terminal repeats and AAV5 capsids (AAV2/5), that selectively transduces neurons in the brain (Burger et al. 2004). The rats were trained on the ICSS paradigm and when the thresholds were stable they received viral vectors that delivered GFP or CRF and brain reward thresholds were assessed for 4 weeks. Previous studies suggest that increased CRF release in the CeA contributes to dysphoria (Bruijnzeel et al. 2012; Marcinkiewcz et al. 2009). However, chronic overexpression of CRF in the CeA did not affect brain reward thresholds. It was then investigated if the overexpression of CRF in the CeA affects the dysphoria associated with nicotine withdrawal (Qi et al. 2014). Precipitated and spontaneous withdrawal led to large elevations in brain reward thresholds, which was diminished in rats that overexpressed CRF. At the end of the experiment, we investigated the effect of the administration of the AAV-CRF vector on CRF, CRF_1 receptor, and CRF_2 receptor levels. Administration of the AAV-CRF vector led to an increase in CRF levels, a decrease in CRF_1 receptor levels, and an increase CRF_2 receptors levels. Therefore, the overexpression of CRF in the CeA may have diminished the dysphoria associated with nicotine withdrawal by downregulating CRF_1 receptors. However, there is evidence that stimulation of CRF_2 receptors has anti-stress and antidepressant-like effects (Chen et al. 2006; Tanaka and Telegdy 2008). Therefore, the upregulation of CRF_2 receptors may have contributed to preventing withdrawal in the nicotine withdrawing rats. In a recent study we also investigated the AAV2/5 mediated overexpression of CRF in the BNST on the dysphoria associated with nicotine withdrawal

(Qi et al. 2016). The overexpression of CRF in the BNST did not affect baseline brain reward thresholds, but prevented the elevations in brain reward thresholds associated with precipitated and spontaneous withdrawal. The overexpression of CRF increased CRF_1 and CRF_2 receptor levels in the BNST and increased the CRF_2/CRF_1 receptor ratio. This suggests that the overexpression of CRF in the BNST diminishes the dysphoria during nicotine withdrawal by inducing an increase in the CRF_2/CRF_1 receptor ratio.

Considering the strong evidence that CRF mediates the dysphoria associated with nicotine withdrawal, clinical studies may investigate whether CRF_1 receptor blockade diminishes the acute dysphoria associated with smoking cessation. In conclusion, these animal studies indicate that the dysphoria associated with nicotine withdrawal is at least partly mediated by the activation of CRF_1 receptors.

4.2 Other peptides than CRF and dysphoria associated with nicotine withdrawal

Although more than one hundred neuropeptides have been discovered, the role of only a few neuropeptides in nicotine withdrawal have been investigated (Bruijnzeel 2012; Zhang et al. 2014). In our laboratory, we investigated the effects of NPY on somatic and affective nicotine withdrawal signs (Rylkova et al. 2008). Neuropeptide Y is widely expressed throughout the brain and low levels of NPY have been associated with depressive-disorders (De Quidt and Emson 1986a; de Quidt and Emson 1986b; Redrobe et al. 2002). Central administration of NPY decreases somatic morphine and alcohol withdrawal signs (Woldbye et al. 1998; Woldbye et al. 2002). In our nicotine study, NPY attenuated the somatic signs associated with both precipitated and spontaneous nicotine withdrawal. The specific Y1 receptor agonist [d-His^{26}]-NPY decreased abdominal constrictions during precipitated withdrawal and decreased overall somatic signs during spontaneous withdrawal. We also investigated the effect of NPY and the Y1 receptor agonist [d-His^{26}]-NPY on the dysphoria associated with precipitated nicotine withdrawal. Neuropeptide Y or [d-His^{26}]-NPY did not affect the elevations in brain reward thresholds associated with precipitated nicotine withdrawal. High doses of NPY or [d-His^{26}]-NPY actually increased brain reward thresholds in the control rats. This increase in brain reward thresholds was blocked by the Y1 receptor antagonist BIBP-3226. These studies indicate that Y1 receptor agonists may diminish some of the somatic signs associated with smoking cessation, but these compounds do not diminish the dysphoria associated with smoking cessation and high doses might induce impairments in reward function. Harris and colleagues found something similar with oxytocin (Manbeck et al. 2014). They showed that oxytocin diminishes the somatic withdrawal signs associated with precipitated nicotine withdrawal but did not affect the elevations in brain rewards thresholds. Similar to NPY, oxytocin elevated the brain reward thresholds of the control rats.

There is strong evidence from animal studies that blockade of vasopressin 1b (V1b) receptors diminishes the effects of stress and has antidepressant-like effects (Iijima and Chaki 2007; Iijima et al. 2014). Therefore, in our laboratory we investigated the effect of a V1b receptor antagonist on the dysphoria associated with nicotine withdrawal (Qi et al. 2015a). Acute administration of the V1b receptor antagonist SSR149415 slightly diminished the elevations in ICSS thresholds associated with precipitated withdrawal. Chronic (6 days)

administration of SSR149415 was more effective and completely prevented the elevations in ICSS thresholds associated with precipitated nicotine withdrawal. Interestingly, a recent clinical study reported that chronic treatment with the V1b receptor antagonist ABT-436 decreases smoking in patients with alcoholism (Ryan et al. 2016). Future studies may investigate if V1b receptor blockade diminishes the dysphoria associated with smoking cessation and improves the relapse rate.

To our knowledge, only the acute effects of NPY and oxytocin on nicotine withdrawal have been investigated. Considering the fact that the V1b receptor antagonist was more effective after chronic treatment it might be worthwhile to explore whether chronic treatment with NPY or oxytocin is also more effective. The kappa-opioid receptor system has been shown to play a critical role in regulating mood states (Bruchas et al. 2010; Bruijnzeel 2009). Blockade of kappa-opioid receptors with LY2456302 also diminishes nicotine-withdrawal induced CPA and thus suggesting that it diminishes the negative emotional state associated with nicotine withdrawal (Jackson et al. 2015).

In conclusion, the reviewed studies indicate that blockade of kappa-opioid receptors and chronic blockade of V1b receptors diminishes the dysphoria associated with nicotine withdrawal. Neuropeptide Y and oxytocin diminish somatic signs associated with nicotine withdrawal but do not diminish the dysphoria associated with nicotine withdrawal. These studies would suggest that kappa-opioid and V1b receptor antagonists decrease the dysphoria in people who try to quit smoking.

4.3 Norepinephrine and dysphoria associated with nicotine withdrawal

Norepinephrine plays a critical role in regulating the release of neuropeptides in the brain. For example, norepinephrine stimulates the release of CRF in the PVN and other brain sites (Dunn et al. 2004). Two noradrenergic cell groups have been located in the mammalian brain (Dahlström and Fuxe 1964). Noradrenergic neurons in the LC give rise to the dorsal noradrenergic bundle. The LC provides most of the norepinephrine input to the forebrain areas and activation of the LC enhances attention, arousal, and learning and memory (Aston-Jones 2005). Noradrenergic cell groups in the lateral tegmentum give rise to the ventral noradrenergic bundle. These cells innervate the hypothalamus, septum, and subcomponents of the extended amygdala such as the CeA and BNST (Moore and Card 1984).

We investigated the effects of the α1-adrenoceptor antagonist prazosin, the α2-adrenoceptor agonist clonidine, and the β_1/β_2-adrenoceptor antagonist propranolol on the dysphoria and somatic signs associated with precipitated nicotine withdrawal (Bruijnzeel et al. 2010). These drugs inhibit noradrenergic transmission in the brain by blocking α1 or β-adrenergic receptors or stimulating presynaptic α2-adrenergic receptors. We found that α1-adrenoceptor blockade (prazosin), but not α2-adrenoceptor activation (clonidine) or β_1/β_2-adrenoceptor blockade (propranolol), attenuates the elevations in brain reward thresholds associated with precipitated nicotine withdrawal. In contrast, α2-adrenoceptor activation and β1/β2-adrenoceptor blockade, but not α1-adrenoceptor blockade, decreased somatic nicotine withdrawal signs. This pattern of results suggests that only α1-adrenoceptor blockade diminishes the dysphoria associated with nicotine withdrawal. Dysphoria and drug craving are the main causes of relapse to drug use (Bruijnzeel 2012; Bruijnzeel and Gold 2005).

Therefore, drugs that only decrease somatic signs may not prevent relapse. In conclusion, the reviewed studies suggest that drugs that block α1-adrenoceptors may prevent dysphoria in people trying to quit smoking and thereby decrease the risk for relapse.

5. Nicotine withdrawal and anxiety

Smoking cessation leads to an increase in anxiety and this contributes to relapse to smoking (Bruijnzeel 2012). Smokers are more likely to have an anxiety disorder than non-smokers and smokers with an anxiety disorder are less motivated to quit (Johnson et al. 2000; Zvolensky et al. 2007). The smoking cessation drug varenicline diminishes anxiety in humans after quitting smoking and this may improve the relapse rate (Foulds et al. 2013). In contrast, there is no evidence that the smoking cessation treatment bupropion alleviates anxiety after smoking cessation (Shiffman et al. 2000).

Several neuropeptides have been implicated in nicotine withdrawal-induced anxiety-like behavior including CRF, neuregulin 3 (NRG3), NPY, and dynorphin (Aydin et al. 2011; Cohen et al. 2015; Jackson et al. 2015; Turner et al. 2014). Some of the first studies with CRF showed that it increases anxiety-like behavior and more recent studies showed that it contributes to anxiety-like behavior after cessation of nicotine administration (Cohen et al. 2015; Dunn and File 1987; Swerdlow et al. 1986). Cohen and colleagues reported that rats with extended access to nicotine (21 h/day, 4 days/week) display an increase in anxiety-like behavior in week 10, 72 h after the last self-administration session (Cohen et al. 2015). This increase in anxiety-like behavior was blockade by systemic and intra-CeA administration of the CRF_1 receptor antagonist MPZP.

In an elegant study, Turner and colleagues showed that nicotine withdrawal leads to an increase in NRG3 levels in the hippocampus (Turner et al. 2014). It was then investigated if nicotine withdrawal leads to anxiety-like behavior in $NRG3^{ska}$ mice. These mice have a mutation in the NRG3 gene, which leads to low levels of NRG3 and NRG3 levels do no increase after cessation of nicotine administration (Howard et al. 2005; Turner et al. 2014). Nicotine withdrawal-induced anxiety-like behavior is diminished in the $NRG3^{ska}$ mice. Furthermore, chronic blockade of the NRG3 receptor signaling pathway with Afatinib (BIBW-2992) decreases nicotine withdrawal-induced anxiety-like behavior. Therefore, this suggests that nicotine withdrawal leads to an increase in NRG3 signaling which contributes to anxiety-like behavior.

The habenula-interpeduncular system is a brain network that has been implicated in the regulation of emotional states and drug addiction (Hikosaka 2010). The medial habenula receives input from the septum and diagonal band of broca and is via the fasciculus retroflexus connected to the interpeduncular nucleus (IPN). The IPN connects to serotonergic neurons in the raphe nuclei. Both the habenula and the IPN play a role in the development of nicotine dependence. Administration of nAChR antagonists into the habenula and the IPN induces somatic withdrawal signs (Salas et al. 2009). Furthermore, nAChRs in the habenula regulate anxiety-like behavior. Mice that express hypersensitive α6/α4β2 nAChRs in the habenula are more anxious than control mice (Pang et al. 2016). Tapper and colleagues investigated the role of CRF in the habenula-IPN circuit in anxiety-

like behavior during nicotine withdrawal. They showed that CRF release in the IPN mediates anxiety-like behavior. Administration of CRF in the IPN increased anxiety-like behavior and blockade of CRF_1 receptors in this brain site prevented nicotine-withdrawal induced anxiety-like behavior. Decreasing CRF levels in the VTA with shRNAs decreased nicotine-withdrawal induced activation of the IPN and also anxiety-like behavior. This suggests that there is a CRF projection from the VTA to the IPN that increases anxiety-like behavior during nicotine withdrawal (Zhao-Shea et al. 2015).

Neuropeptide Y stimulates food intake and blunts stress responses (Reichmann and Holzer 2016). The effects of NPY are opposite to those of CRF. Corticotropin-releasing factor increases anxiety-like behavior while NPY and Y1 agonists decrease anxiety-like behavior (Heilig et al. 1989; Sajdyk et al. 1999). The Y2 receptor is located presynaptically and stimulation of the Y2 receptor decreases NPY release and increases anxiety-like behavior (Colmers et al. 1991; King et al. 1999; Nakajima et al. 1998). Blockade of Y2 receptors with JNJ-31020028 decreases anxiety-like behavior in alcohol withdrawing rats (Cippitelli et al. 2011). Chronic treatment with the same Y2 receptor antagonist also diminishes nicotine withdrawal-induced anxiety-like behavior in the social interaction test (Aydin et al. 2011). To our knowledge, the effect of NPY or Y1 receptor agonists on nicotine withdrawal-induced anxiety-like behavior has not been investigated. However, based on the above discussed findings it is predicted that NPY or Y1 receptor agonists also decrease anxiety-like behavior in nicotine withdrawing rats.

There is extensive evidence for a role of kappa-opioid receptor signaling in anxiety-like behavior. Kappa-opioid receptor agonists increase anxiety-like behavior and antagonists decrease anxiety-like behavior (Bruchas et al. 2010; Bruijnzeel 2009). Nicotine withdrawal leads to changes in dynorphin levels, which is the endogenous ligand for the kappa-opioid receptor (Chavkin et al. 1982). Cessation of nicotine administration leads to a decrease in dynorphin levels and an increase in prodynorphin mRNA levels in the Nacc (Isola et al. 2008). This suggests that nicotine withdrawal leads to an increase in the release and production of dynorphin. Blockade of dynorphin receptors in the brain with the long-action kappa opioid receptor antagonist JDTic or with the short acting antagonist LY2456302 decreases anxiety-like behavior in nicotine withdrawing mice (Jackson et al. 2010; Jackson et al. 2015).

6. Reinstatement of Nicotine Seeking

The great majority of people who try to quit smoking relapse during the first year. There are several factors that increase the risk for relapse. First of all, dysphoria leads to craving and thereby increases the risk for relapse. Also, cues associated with drug use and small amounts of drugs of abuse can lead to craving and relapse. Animal models have been developed to study the role of stress, cues, and drugs in relapse to smoking (Shaham et al. 2003). One of the most widely used animal model to study relapse to smoking is the rat nicotine self-administration paradigm. Rats are trained to self-administer nicotine and after about 2-weeks nicotine seeking is extinguished by replacing nicotine with saline. Operant responding can be reinstated by footshock stress, administration of nicotine, or cues associated with the self-administration of nicotine (Buczek et al. 1999; Chiamulera et al. 1996; LeSage et al. 2004;

Liu et al. 2006). Several studies have investigated the effects of the nAChR antagonist mecamylamine and the FDA approved smoking cessation drugs varenicline and bupropion in these animal models. Blockade of nAChRs with mecamylamine dose dependently attenuates cue-induced reinstatement of nicotine seeking (Liu et al. 2007). Very low doses of mecamylamine, which did not affect responding for food or nicotine, decreased cue-induced reinstatement of nicotine seeking. This suggests that relatively low doses of nAChR antagonists could be used to diminish cue-induced craving and prevent relapse in smokers. The smoking cessation drug varenicline inhibits reinstatement of operant responding induced by nicotine-prime and a combination of nicotine-prime and cues (O'Connor et al. 2010; Swalve et al. 2016). In contrast, bupropion potentiates cue-induced reinstatement of nicotine seeking (Liu et al. 2008). This might be due to the fact that bupropion inhibits the re-uptake of dopamine and thereby enhances the effect of the cue (Shaham et al. 2003; Warner and Shoaib 2005). This is supported by the observation that dopamine receptor blockade diminishes cue-induced reinstatement of drug-seeking (Crombag et al. 2002; Liu and Weiss 2002).

The CPP procedure has also been used to investigate the neuronal mechanisms that mediate the reinstatement of nicotine seeking. Nicotine-prime reinstates extinguished CPP and this is blocked by the nAChR antagonist mecamylamine and the smoking cessation drugs varenicline and bupropion (Biala and Budzynska 2006; Biala et al. 2010; Budzynska and Biala 2011). Preclinical studies point to a role for the serotonergic system in the reinstatement of nicotine seeking. Both the 5-HT_{2C} receptor agonist Ro60-0175 and the 5-HT_{2A} receptor antagonist M100907 decrease nicotine-primed and cue-induced reinstatement of nicotine seeking (Fletcher et al. 2012).

The role of neuropeptide systems in the reinstatement of nicotine seeking is somewhat underinvestigated but there is evidence for a role of CRF, kappa-opioid, hypocretin-1, and MC4 receptors (Plaza-Zabala et al. 2013; Qi et al. 2015b; Zislis et al. 2007). Studies from our laboratory suggest that stress-induced reinstatement of nicotine seeking is at least partly mediated by the activation of CRF_1 receptors. Central (icv) administration of the non-specific CRF_1/CRF_2 receptor antagonist D-Phe $CRF_{(12–41)}$ prevents stress-induced reinstatement of nicotine seeking (Zislis et al. 2007). Furthermore, blockade of CRF_1 receptors with R278995/CRA045, but not blockade of CRF_2 receptors with astressin-2B, prevents stress-induced reinstatement of nicotine seeking in rats (Bruijnzeel et al. 2009). Blockade of CRF_1 receptors also prevents stress-induced reinstatement of nicotine seeking in the mouse (Plaza-Zabala et al. 2010).

In our laboratory, we investigated the role of the MC4 receptor in stress-induced reinstatement of nicotine seeking (Qi et al. 2015b). The endogenous ligand for the MC4 receptor is the pro-opiomelanocortin (POMC)-derived peptide alpha-melanocyte stimulating hormone (α-MSH)(Adan et al. 2006; Gantz et al. 1993). Stimulation of the MC4 receptor increases anxiety and depressive-like behavior and therefore it was predicted that blockade of the MC4 receptor would diminish the effects of stress in the reinstatement procedure (Chaki et al. 2003; Kokare et al. 2010; Serova et al. 2013). Indeed, we found that the MC4 receptor antagonists HS014 and HS024 prevented stress-induced reinstatement of nicotine

seeking. The MC4 receptor antagonists did not affect responding for food pellets, which suggests that MC4 receptor blockade did not have sedative effects.

The hypocretins (hypocretin-1 and hypocretin-2) are hypothalamic neuropeptides that are derived from a common precursor protein called prepro-hypocretin (de Lecea et al. 1998). The hypocretins are only produced in the lateral and posterior hypothalamus and it has been estimated that there are only about eleven hundred hypocretin neurons in the rat brain (Date et al. 1999; Peyron et al. 1998). Despite the fact that there are only a small number of hypocretin neurons, they project to a wide range of brain sites and regulate a variety of behaviors including feeding and sleep (Chemelli et al. 1999; Sakurai et al. 1998). The hypocretins also play a role in stress responses and drug addiction (Bruijnzeel 2012). Berrendoro and colleagues thoroughly investigated the role of the hypocretin receptors in the reinstatement of nicotine seeking. They showed that hypocretin-1 reinstates extinguished nicotine seeking in a CRF_1 receptor independent manner (Plaza-Zabala et al. 2010). In the same study it was shown that blockade of CRF_1 receptors prevents stress-induced reinstatement of nicotine seeking, but hypocretin-1 receptor blockade was ineffective. This indicates that both the hypocretin and CRF system plays a role in relapse, but only the CRF system plays a role in stress-induced relapse. In a follow-up study, the role of the hypocretin system in cue-induced reinstatement of nicotine was investigated. Blockade of hypocretin-1 receptors with SB334867, but not blockade of hypocretin-2 receptors with TCSOX229, attenuated cue-induced reinstatement of nicotine-seeking (Plaza-Zabala et al. 2013). Taken together, these studies indicate that stress-induced reinstatement of nicotine seeking is mediated via CRF_1 receptors and cue-induced reinstatement is mediated via hypocretin-1 receptors. We are not aware of any studies that investigated the role of CRF in cue-induced reinstatement of nicotine seeking. However, a recent study showed that blockade of CRF_1 receptors in the insular cortex reduces cue-induced reinstatement of cocaine seeking (Cosme et al. 2015). Because there is strong overlap in the neuronal mechanisms that mediate the reinstatement of nicotine and cocaine seeking, it might be possible that CRF_1 receptors also play a role in cue-induced reinstatement of nicotine seeking (Cosme et al. 2015).

Neuropeptide S (NPS) is produced by a small group of neurons that is located adjacent to the LC in the brainstem (Clark et al. 2011; Pape et al. 2010; Xu et al. 2004). Neuropeptide S increases locomotor activity, arousal, and wakefulness and decreases anxiety-like behavior (Pape et al. 2010; Reinscheid and Xu 2005; Xu et al. 2004). Nicotine has been shown to increase NPS and NPS receptor levels in the brainstem but otherwise little is known about the role of NPS in nicotine addiction (Lage et al. 2007). Interestingly, several studies with other drugs have shown that NPS facilitates the reinstatement of drug seeking and NPS antagonists decrease drug intake and the reinstatement of drug seeking (Kallupi et al. 2010; Pañeda et al. 2009; Schmoutz et al. 2012; Thorsell et al. 2013). Therefore, these studies warrant exploration of the role of NPS in nicotine intake and the reinstatement of nicotine seeking.

The kappa-opioid receptor system plays a critical role in stress-responses and anxiety-like behavior. To our knowledge, the role of kappa-opioid receptors in the reinstatement of extinguished nicotine self-administration has not been investigated. However, one study investigated the role of kappa-opioid receptors in rats in which CPP was extinguished. In

this study, the kappa-opioid receptor antagonist nor-BNI blocked stress-induced reinstatement of CPP but not nicotine-prime induced reinstatement (Jackson et al. 2013).

In conclusion, the reviewed studies indicate the nAChR antagonist mecamylamine and the smoking cessation drug varenicline diminish nicotine-prime and cue-induced reinstatement of nicotine seeking. The effects of bupropion on reinstatement has been poorly evaluated but one study suggests that bupropion potentiates cue-induced reinstatement of nicotine seeking. The reviewed studies indicate that neuropeptide systems are a viable target for drugs to prevent relapse to smoking. There is strong evidence that blockade of CRF_1 and kappa-opioid receptors diminishes stress-induced reinstatement of nicotine seeking. Blockade of the hypocretin-1 receptor prevents cue-induced reinstatement of nicotine seeking. These studies suggest that neuropeptide based treatments could be used to decrease the risk for relapse.

7. Neuronal activation of peptide systems

The transcription factor Fos has been widely used to study the effects of stressors and drugs on neuronal activity in the brain (Bruijnzeel et al. 1999; Morgan and Curran 1995). Numerous studies have investigated the brain sites that are being activated by low and rewarding doses of nicotine. These studies show that noncontingent administration of nicotine, nicotine self-administration, and place preference training with nicotine leads to an increase in Fos expression in brain sites that signal reward function (Kiba and Jayaraman 1994; Pagliusi et al. 1996; Pascual et al. 2009). Acute nicotine administration increases Fos positive cells in the NAcc, caudate putamen, and PFC and this is diminished by non-selective blockade of nAChRs (Kiba and Jayaraman 1994). These findings are in line with a pharmacological fMRI study in which the effect of nicotine on brain activity (BOLD signal) was investigated (Bruijnzeel et al. 2015). Nicotine administration increased the BOLD signal in the NAcc, dorsal striatum, amygdala, prefrontal cortical areas, and the motor and sensory cortex. Pretreatment with a nAChR antagonist blocked the effects of nicotine on the BOLD signal. These histological and imaging studies indicate that nicotine increases the activity of brain sites that play a role in reward signaling and cognition.

Few studies have investigated whether there is a difference in the brain sites being activated by brief versus prolonged nicotine self-administration. However, a recent study investigated Fos expression in the brain after 10 versus 47 days of nicotine self-administration (Clemens et al. 2014). Interestingly, both self-administration protocols induced Fos expression in brain areas that have been associated with reward function such as the NAcc core and shell, VTA, CeA, and basolateral amygdala (BLA). However, prolonged access to nicotine also leads to Fos expression in the dorsomedial and dorsolateral striatum and the substantia nigra. These brain sites have been associated with habitual and compulsive drug use (Belin and Everitt 2008; Pierce and Vanderschuren 2010). Thus, this suggests that both acute and prolonged nicotine use leads to the activation of the brain reward system. Brain networks that regulate habitual behaviors are only activated after prolonged drug use.

There is strong evidence that cessation of chronic nicotine administration leads to the activation of anti-reward systems which induces dysphoria and anxiety-like behavior (Koob

and Volkow 2016). However, despite overwhelming evidence for a role of neuropeptide systems in nicotine withdrawal there is only sparse evidence from Fos studies that nicotine withdrawal activates brain sites. One of the first studies that investigated Fos expression in rats undergoing withdrawal showed that withdrawal leads to an increase in Fos expression in the CeA but not in other brain sites (Panagis et al. 2000). Although pharmacological studies suggest that withdrawal leads to the activation of brain stress systems, several Fos studies suggest that nicotine withdrawal leads to decreased activity in brain sites (Balerio et al. 2004; Varani et al. 2012). In a recent study, it was shown that nicotine withdrawal led to a decrease in the number of Fos positive cells in the BNST, BLA, and dentate gyrus. Nicotine withdrawal did not affect Fos expression in a wide range of other brain sites including the NAcc, cingulate cortex, caudate putamen, CA1 and CA3 region of the hippocampus, and medial habenular nucleus (Varani et al. 2012).

Although there are a large number of studies that investigated the effects of nicotine and nicotine withdrawal on Fos expression in the brain, only a few colocalization studies have been conducted to investigate which neuropeptide systems are activated or inhibited by nicotine. Muschamp and colleagues investigated the role of hypocretin neurons in the LH in nicotine withdrawal (Simmons et al. 2016). Hypocretin neurons project from the LH to the VTA and hypocretin release in the VTA increases the firing of dopaminergic neurons (Korotkova et al. 2003). Interestingly, acute nicotine administration increases Fos expression in hypocretin neurons in the LH and nicotine withdrawal leads to a decrease in Fos expression in these neurons (Fadel and Burk 2010; Simmons et al. 2016). Overall, this suggests that a decrease in activity in hypocretin neurons in the LH contributes to the hypo-dopaminergic state in nicotine withdrawing animals (Hildebrand et al. 1998).

Although the majority of studies suggest that nicotine withdrawal does not affect Fos expression or decreases Fos expression, one study suggested that nicotine withdrawal can increase Fos expression in peptide neurons (Plaza-Zabala et al. 2012). In this study, nicotine withdrawal did not affect Fos expression in a wide range of brain sites including the CeA, BLA, NAcc, medial septum, and hippocampus. However, nicotine withdrawal increased Fos expression in hypocretin neurons in the LH and the perifornical and dorsomedial hypothalamus (PFA/DMH). In addition, withdrawal increased Fos expression in CRF neurons in the PVN. A retrograde tracing study showed that the hypocretin neurons project from the LH and PFA/DMH to the PVN. Interestingly, systemic administration of the hypocretin-1 receptor antagonist decreased somatic withdrawal signs and decreased Fos expression in the PFA/DMH and in CRF neurons in the PVN. This suggests that activation of hypocretin neurons that project from the PFA/DMH to CRF neurons in the PVN increases somatic nicotine withdrawal signs.

In conclusion, these studies indicate that acute nicotine administration increases Fos expression in the reward system and many other brain sites. Nicotine withdrawal does not affect Fos expression in most brain sites but affects Fos expression in some brain sites that regulate reward function and stress responses. Nicotine withdrawal might decrease Fos expression in the reward system (LH) and increase Fos expression in some brain sites (CeA, PVN, PFA/DMH) that contribute to stress responses during nicotine withdrawal. It is also interesting to note that nicotine withdrawal seems to decrease Fos expression in

hypothalamic hypocretin neurons that project to the VTA (Reward) and increases Fos expression in hypocretin neurons that project to the PVN (anti-reward/stress). Overall, the reviewed studies suggest that nicotine withdrawal decreases activity in brain sites that signal reward and increases activity in brain sites that mediate stress responses and negative affective states.

8. Conclusion

In this overview article we discuss the role of neuropeptides in the development and maintenance of nicotine addiction. The reviewed studies indicate that different neuropeptide systems play a role in each stage of the addiction cycle. It should be noted that not all the discussed neuropeptides have been evaluated in all stages of the addiction cycle. Therefore, it cannot be ruled out that some neuropeptides have more widespread effects than is currently believed.

It should also be noted that the great majority of the nicotine studies have been conducted with animals that self-administered nicotine under a limited access schedule (1h/day) or received nicotine non-contingently via injections or minipumps. In contrast, humans often smoke for most of the day and carefully titrate the amount of nicotine self-administered (Benowitz 2009). Recently, animal models have been developed that more closely model human smoking. One prime example of this is the extended access nicotine self-administration procedure. In this model, rats have extended-access (21–23h) to nicotine for 1–4 days which is then followed by several days of abstinence (Cohen et al. 2012; Flores et al. 2016). This model leads to high levels of nicotine intake and might better model human smoking than limited access models or the non-contingent administration of nicotine. These new models may help to identify novel mechanisms that contribute to the development and maintenance of compulsive smoking.

The rewarding effects of nicotine are pivotal for the acquisition of smoking and the dysphoria associated with smoking cessation increases the risk for relapse. After the acute withdrawal phase, stressors, a small amount of nicotine (i.e., lapse), and cues contribute to relapse. The reviewed studies indicate that blockade of hypocretin-1 and nociception receptors, and stimulation of galanin, neurotensin, and ghrelin receptors diminishes the rewarding effects of nicotine (Boules et al. 2011; Cippitelli et al. 2016; Hollander et al. 2008; Jackson et al. 2011; Jerlhag and Engel 2011). Overall, a different group of neuropeptides plays a role in nicotine withdrawal. Stimulation of NPY and oxytocin receptors and blockade of kappa-opioid receptors diminishes somatic nicotine withdrawal signs, but stimulation of NPY and oxytocin receptors does not diminish the dysphoria associated with nicotine withdrawal (Manbeck et al. 2014; Rylkova et al. 2008). The dysphoria associated with nicotine withdrawal is greatly diminished by CRF_1 and kappa-opioid receptor blockade and chronic V1b receptor blockade (Bruijnzeel et al. 2009; Qi et al. 2015a). Blockade of the CRF_1 and kappa-opioid receptors also diminishes anxiety-like behavior associated with nicotine withdrawal and stress-induced reinstatement of nicotine seeking (Bruijnzeel et al. 2009; Cohen et al. 2015; Jackson et al. 2015). Considering the fact that cues and smoking lapses increase the risk for relapse to smoking, it is somewhat surprising that only a few studies have investigated the role of neuropeptides in nicotine-

primed and cue-induced reinstatement. One study reported that blockade of hypocretin-1 receptors diminishes cue-induced reinstatement of nicotine seeking (Plaza-Zabala et al. 2013). Thus, blocking the hypocretin-1 receptor could diminish the acute rewarding effects of smoking and provide protection against relapse. In conclusion, the reviewed studies indicate that neuropeptides play a critical role in the acquisition of tobacco smoking, withdrawal, and relapse. Therefore, peptide-based treatments could improve smoking rates by preventing the transition to high levels of smoking, diminishing withdrawal signs, and preventing stress- and cue-induced urges to smoke.

Acknowledgments

The author (AB) was supported in part by NIH grants DA039349 and DA042530 when working on this review.

References

Adan RA, Tiesjema B, Hillebrand JJ, la Fleur SE, Kas MJ, de Krom M. The MC4 receptor and control of appetite. BrJPharmacol. 2006; 149:815–827.

Adermark L, Morud J, Lotfi A, Danielsson K, Ulenius L, Soderpalm B, Ericson M. Temporal Rewiring of Striatal Circuits Initiated by Nicotine. Neuropsychopharmacology. 2016; 41:3051–3059. [PubMed: 27388328]

Ague C. Nicotine and smoking: effects upon subjective changes in mood. Psychopharmacologia. 1973; 30:323–328. [PubMed: 4722203]

Ashare RL, Kimmey BA, Rupprecht LE, Bowers ME, Hayes MR, Schmidt HD. Repeated administration of an acetylcholinesterase inhibitor attenuates nicotine taking in rats and smoking behavior in human smokers. Transl Psychiatry. 2016; 6:e713. [PubMed: 26784967]

Aston-Jones G. Brain structures and receptors involved in alertness. Sleep Med. 2005; 6(Suppl 1):S3–S7. [PubMed: 16140243]

Aydin C, Oztan O, Isgor C. Effects of a selective Y2R antagonist, JNJ-31020028, on nicotine abstinence-related social anxiety-like behavior, neuropeptide Y and corticotropin releasing factor mRNA levels in the novelty-seeking phenotype. BehavBrain Res. 2011; 222:332–341.

Bailey JE, Papadopoulos A, Diaper A, Phillips S, Schmidt M, van der Ark P, Dourish CT, Dawson GR, Nutt DJ. Preliminary evidence of anxiolytic effects of the CRF1 receptor antagonist R317573 in the 7.5% CO2 proof-of-concept experimental model of human anxiety. Journal of Psychopharmacology. 2011; 25:1199–1206. [PubMed: 21555331]

Bale TL, Chen A. Minireview: CRF and Wylie Vale: a story of 41 amino acids and a Texan with grit. Endocrinology. 2012; 153:2556–2561. [PubMed: 22492308]

Balerio GN, Aso E, Berrendero F, Murtra P, Maldonado R. Delta9-tetrahydrocannabinol decreases somatic and motivational manifestations of nicotine withdrawal in mice. Eur J Neurosci. 2004; 20:2737–48. [PubMed: 15548217]

Bardo MT, Green TA, Crooks PA, Dwoskin LP. Nornicotine is self-administered intravenously by rats. Psychopharmacology (Berl). 1999; 146:290–296. [PubMed: 10541729]

Belin D, Everitt BJ. Cocaine seeking habits depend upon dopamine-dependent serial connectivity linking the ventral with the dorsal striatum. Neuron. 2008; 57:432–41. [PubMed: 18255035]

Belluzzi JD, Wang R, Leslie FM. Acetaldehyde enhances acquisition of nicotine self-administration in adolescent rats. Neuropsychopharmacology. 2005; 30:705–712. [PubMed: 15496937]

Benowitz NL. Drug therapy. Pharmacologic aspects of cigarette smoking and nicotine addition. NEnglJMed. 1988; 319:1318–1330.

Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. Annu Rev Pharmacol Toxicol. 2009; 49:57–71. [PubMed: 18834313]

Benwell ME, Balfour DJ. Effects of nicotine administration and its withdrawal on plasma corticosterone and brain 5-hydroxyindoles. Psychopharmacology (Berl). 1979; 63:7–11. [PubMed: 112625]

Benwell ME, Balfour DJ, Anderson JM. Evidence that tobacco smoking increases the density of (−)-[3H]nicotine binding sites in human brain. JNeurochem. 1988; 50:1243–1247. [PubMed: 3346676]

Berrettini W, Yuan X, Tozzi F, Song K, Francks C, Chilcoat H, Waterworth D, Muglia P, Mooser V. Alpha-5/alpha-3 nicotinic receptor subunit alleles increase risk for heavy smoking. Mol Psychiatry. 2008; 13:368–73. [PubMed: 18227835]

Biala G, Budzynska B. Reinstatement of nicotine-conditioned place preference by drug priming: effects of calcium channel antagonists. Eur J Pharmacol. 2006; 537:85–93. [PubMed: 16616917]

Biala G, Staniak N, Budzynska B. Effects of varenicline and mecamylamine on the acquisition, expression, and reinstatement of nicotine-conditioned place preference by drug priming in rats. Naunyn Schmiedebergs ArchPharmacol. 2010; 381:361–370.

Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev. 2006:Cd005593. [PubMed: 16437532]

Boules M, Oliveros A, Liang Y, Williams K, Shaw A, Robinson J, Fredrickson P, Richelson E. A neurotensin analog, NT69L, attenuates intravenous nicotine self-administration in rats. Neuropeptides. 2011; 45:9–16. [PubMed: 21047685]

Brielmaier J, McDonald CG, Smith RF. Effects of acute stress on acquisition of nicotine conditioned place preference in adolescent rats: a role for corticotropin-releasing factor 1 receptors. Psychopharmacology (Berl). 2012; 219:73–82. [PubMed: 21720754]

Brown ZW, Amit Z, Rockman GE. Intraventricular self-administration of acetaldehyde, but not ethanol, in naive laboratory rats. Psychopharmacology (Berl). 1979; 64:271–276. [PubMed: 41277]

Bruchas MR, Land BB, Chavkin C. The dynorphin/kappa opioid system as a modulator of stress-induced and pro-addictive behaviors. Brain Res. 2010; 1314:44–55. [PubMed: 19716811]

Bruijnzeel AW. kappa-Opioid receptor signaling and brain reward function. Brain ResRev. 2009; 62:127–146.

Bruijnzeel AW. Tobacco addiction and the dysregulation of brain stress systems. NeurosciBiobehavRev. 2012; 36:1418–1441.

Bruijnzeel AW, Alexander JC, Perez PD, Bauzo-Rodriguez R, Hall G, Klausner R, Guerra V, Zeng H, Igari M, Febo M. Acute nicotine administration increases BOLD fMRI signal in brain regions involved in reward signaling and compulsive drug intake in rats. Int J Neuropsychopharmacol. 2015; 18:pyu011.

Bruijnzeel AW, Bishnoi M, van Tuijl IA, Keijzers KF, Yavarovich KR, Pasek TM, Ford J, Alexander JC, Yamada H. Effects of prazosin, clonidine, and propranolol on the elevations in brain reward thresholds and somatic signs associated with nicotine withdrawal in rats. Psychopharmacology (Berl). 2010; 212:485–499. [PubMed: 20697697]

Bruijnzeel AW, Ford J, Rogers JA, Scheick S, Ji Y, Bishnoi M, Alexander JC. Blockade of CRF1 receptors in the central nucleus of the amygdala attenuates the dysphoria associated with nicotine withdrawal in rats. PharmacolBiochemBehav. 2012; 101:62–68.

Bruijnzeel AW, Gold MS. The role of corticotropin-releasing factor-like peptides in cannabis, nicotine, and alcohol dependence. Brain ResBrain ResRev. 2005; 49:505–528.

Bruijnzeel AW, Lewis B, Bajpai LK, Morey TE, Dennis DM, Gold M. Severe deficit in brain reward function associated with fentanyl withdrawal in rats. BiolPsychiatry. 2006; 59:477–480.

Bruijnzeel AW, Markou A. Adaptations in cholinergic transmission in the ventral tegmental area associated with the affective signs of nicotine withdrawal in rats. Neuropharmacology. 2004; 47:572–579. [PubMed: 15380374]

Bruijnzeel AW, Prado M, Isaac S. Corticotropin-releasing factor-1 receptor activation mediates nicotine withdrawal-induced deficit in brain reward function and stress-induced relapse. BiolPsychiatry. 2009; 66:110–117.

Bruijnzeel AW, Stam R, Compaan JC, Croiset G, Akkermans LM, Olivier B, Wiegant VM. Long-term sensitization of Fos-responsivity in the rat central nervous system after a single stressful experience. Brain Res. 1999; 819:15–22. [PubMed: 10082856]

Bruijnzeel AW, Zislis G, Wilson C, Gold MS. Antagonism of CRF receptors prevents the deficit in brain reward function associated with precipitated nicotine withdrawal in rats. Neuropsychopharmacology. 2007; 32:955–963. [PubMed: 16943772]

Buczek Y, Le AD, Stewart J, Shaham Y. Stress reinstates nicotine seeking but not sucrose solution seeking in rats. Psychopharmacology (Berl). 1999; 144:183–188. [PubMed: 10395000]

Budzynska B, Biala G. Effects of bupropion on the reinstatement of nicotine-induced conditioned place preference by drug priming in rats. Pharmacol Rep. 2011; 63:362–71. [PubMed: 21602591]

Burger C, Gorbatyuk OS, Velardo MJ, Peden CS, Williams P, Zolotukhin S, Reier PJ, Mandel RJ, Muzyczka N. Recombinant AAV viral vectors pseudotyped with viral capsids from serotypes 1, 2, and 5 display differential efficiency and cell tropism after delivery to different regions of the central nervous system. MolTher. 2004; 10:302–317.

Chaki S, Ogawa S, Toda Y, Funakoshi T, Okuyama S. Involvement of the melanocortin MC4 receptor in stress-related behavior in rodents. EurJPharmacol. 2003; 474:95–101.

Chavkin C, James IF, Goldstein A. Dynorphin is a specific endogenous ligand of the kappa opioid receptor. Science. 1982; 215:413–415. [PubMed: 6120570]

Chemelli RM, Willie JT, Sinton CM, Elmquist JK, Scammell T, Lee C, Richardson JA, Williams SC, Xiong Y, Kisanuki Y, Fitch TE, Nakazato M, Hammer RE, Saper CB, Yanagisawa M. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. Cell. 1999; 98:437–451. [PubMed: 10481909]

Chen A, Zorrilla E, Smith S, Rousso D, Levy C, Vaughan J, Donaldson C, Roberts A, Lee KF, Vale W. Urocortin 2-deficient mice exhibit gender-specific alterations in circadian hypothalamus-pituitary-adrenal axis and depressive-like behavior. J Neurosci. 2006; 26:5500–10. [PubMed: 16707802]

Chen R, Lewis KA, Perrin MH, Vale WW. Expression cloning of a human corticotropin-releasing-factor receptor. ProcNatlAcadSciUSA. 1993; 90:8967–8971.

Chen X, Chen J, Williamson VS, An SS, Hettema JM, Aggen SH, Neale MC, Kendler KS. Variants in nicotinic acetylcholine receptors alpha5 and alpha3 increase risks to nicotine dependence. Am J Med Genet B Neuropsychiatr Genet. 2009; 150b:926–33. [PubMed: 19132693]

Chiamulera C, Borgo C, Falchetto S, Valerio E, Tessari M. Nicotine reinstatement of nicotine self-administration after long-term extinction. Psychopharmacology (Berl). 1996; 127:102–107. [PubMed: 8888374]

Cippitelli A, Rezvani AH, Robinson JE, Eisenberg L, Levin ED, Bonaventure P, Motley ST, Lovenberg TW, Heilig M, Thorsell A. The novel, selective, brain-penetrant neuropeptide Y Y2 receptor antagonist, JNJ-31020028, tested in animal models of alcohol consumption, relapse, and anxiety. Alcohol. 2011; 45:567–76. [PubMed: 21145691]

Cippitelli A, Schoch J, Debevec G, Brunori G, Zaveri NT, Toll L. A key role for the N/OFQ-NOP receptor system in modulating nicotine taking in a model of nicotine and alcohol co-administration. Sci Rep. 2016; 6:26594. [PubMed: 27199205]

Clark SD, Duangdao DM, Schulz S, Zhang L, Liu X, Xu YL, Reinscheid RK. Anatomical characterization of the neuropeptide S system in the mouse brain by in situ hybridization and immunohistochemistry. J Comp Neurol. 2011; 519:1867–1893. [PubMed: 21452235]

Clemens KJ, Castino MR, Cornish JL, Goodchild AK, Holmes NM. Behavioral and neural substrates of habit formation in rats intravenously self-administering nicotine. Neuropsychopharmacology. 2014; 39:2584–93. [PubMed: 24823947]

Cohen A, Koob GF, George O. Robust escalation of nicotine intake with extended access to nicotine self-administration and intermittent periods of abstinence. Neuropsychopharmacology. 2012; 37:2153–2160. [PubMed: 22549121]

Cohen A, Treweek J, Edwards S, Leao RM, Schulteis G, Koob GF, George O. Extended access to nicotine leads to a CRF1 receptor dependent increase in anxiety-like behavior and hyperalgesia in rats. Addict Biol. 2015; 20:56–68. [PubMed: 23869743]

Colmers WF, Klapstein GJ, Fournier A, St-Pierre S, Treherne KA. Presynaptic inhibition by neuropeptide Y in rat hippocampal slice in vitro is mediated by a Y2 receptor. Br J Pharmacol. 1991; 102:41–4. [PubMed: 1646061]

Corey C, Wang B, Johnson SE, Apelberg B, Husten C. Notes from the field: electronic cigarette use among middle and high school students - United States, 2011–2012. MMWR Morb Mortal Wkly Rep. 2013; 62:729–30. [PubMed: 24005229]

Corrigall WA, Coen KM. Nicotine maintains robust self-administration in rats on a limited-access schedule. Psychopharmacology (Berl). 1989; 99:473–478. [PubMed: 2594913]

Corrigall WA, Coen KM. Selective dopamine antagonists reduce nicotine self-administration. Psychopharmacology (Berl). 1991; 104:171–176. [PubMed: 1876661]

Corrigall WA, Coen KM, Adamson KL. Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. Brain Res. 1994; 653:278–284. [PubMed: 7982062]

Corrigall WA, Herling S, Coen KM. Evidence for a behavioral deficit during withdrawal from chronic nicotine treatment. Pharmacol Biochem Behav. 1989; 33:559–62. [PubMed: 2587598]

Cosme CV, Gutman AL, LaLumiere RT. The Dorsal Agranular Insular Cortex Regulates the Cued Reinstatement of Cocaine-Seeking, but not Food-Seeking, Behavior in Rats. Neuropsychopharmacology. 2015; 40:2425–33. [PubMed: 25837282]

Crombag HS, Grimm JW, Shaham Y. Effect of dopamine receptor antagonists on renewal of cocaine seeking by reexposure to drug-associated contextual cues. Neuropsychopharmacology. 2002; 27:1006–15. [PubMed: 12464457]

Cryan JF, Bruijnzeel AW, Skjei KL, Markou A. Bupropion enhances brain reward function and reverses the affective and somatic aspects of nicotine withdrawal in the rat. Psychopharmacology (Berl). 2003a; 168:347–358. [PubMed: 12698231]

Cryan JF, Hoyer D, Markou A. Withdrawal from chronic amphetamine induces depressive-like behavioral effects in rodents. BiolPsychiatry. 2003b; 54:49–58.

Dahlström A, Fuxe K. Evidence for the existence of monamine-containing neurons in the central nervous system. I. Demonstration of monamines in the cell bodies of brain stem neurons. Acta Physiol Scand Suppl. 1964; 232:1–55.

Damaj MI, Kao W, Martin BR. Characterization of spontaneous and precipitated nicotine withdrawal in the mouse. JPharmacolExpTher. 2003; 307:526–534.

Dani JA, Heinemann S. Molecular and cellular aspects of nicotine abuse. Neuron. 1996; 16:905–908. [PubMed: 8630247]

Date Y, Ueta Y, Yamashita H, Yamaguchi H, Matsukura S, Kangawa K, Sakurai T, Yanagisawa M, Nakazato M. Orexins, orexigenic hypothalamic peptides, interact with autonomic, neuroendocrine and neuroregulatory systems. ProcNatlAcadSciUSA. 1999; 96:748–753.

Dawkins L, Turner J, Hasna S, Soar K. The electronic-cigarette: effects on desire to smoke, withdrawal symptoms and cognition. Addict Behav. 2012; 37:970–3. [PubMed: 22503574]

de Lecea L, Kilduff TS, Peyron C, Gao X, Foye PE, Danielson PE, Fukuhara C, Battenberg EL, Gautvik VT, Bartlett FS, Frankel WN, van den Pol AN, Bloom FE, Gautvik KM, Sutcliffe JG. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. ProcNatlAcadSciUSA. 1998; 95:322–327.

De Quidt M, Emson P. Distribution of neuropeptide Y-like immunoreactivity in the rat central nervous system—I. Radioimmunoassay and chromatographic characterisation. Neuroscience. 1986a; 18:527–543. [PubMed: 3755808]

de Quidt ME, Emson PC. Distribution of neuropeptide Y-like immunoreactivity in the rat central nervous system--II. Immunohistochemical analysis. Neuroscience. 1986b; 18:545–618. [PubMed: 3755809]

Debruyne D, Sobrio F, Hinschberger A, Camsonne R, Coquerel A, Barre L. Short-term pharmacokinetics and brain distribution of mecamylamine as a preliminary to carbon-11 labeling for nicotinic receptor investigation. JPharmSci. 2003; 92:1051–1057.

Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. Trends Neurosci. 2012a; 35:68–77. [PubMed: 22177980]

Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. Trends in neurosciences. 2012b; 35:68–77. [PubMed: 22177980]

Dunn AJ, File SE. Corticotropin-releasing factor has an anxiogenic action in the social interaction test. HormBehav. 1987; 21:193–202.

Dunn AJ, Swiergiel AH, Palamarchouk V. Brain circuits involved in corticotropin-releasing factor-norepinephrine interactions during stress. AnnNYAcadSci. 2004; 1018:25–34.

Eaves M, Thatcher-Britton K, Rivier J, Vale W, Koob GF. Effects of corticotropin releasing factor on locomotor activity in hypophysectomized rats. Peptides. 1985; 6:923–926. [PubMed: 3878503]

Egleton RD, Davis TP. Development of neuropeptide drugs that cross the blood-brain barrier. NeuroRx. 2005; 2:44–53. [PubMed: 15717056]

Epping-Jordan MP, Watkins SS, Koob GF, Markou A. Dramatic decreases in brain reward function during nicotine withdrawal. Nature. 1998; 393:76–79. [PubMed: 9590692]

Fadel J, Burk JA. Orexin/hypocretin modulation of the basal forebrain cholinergic system: Role in attention. Brain Res. 2010; 1314:112–123. [PubMed: 19699722]

Fagerstrom K, Etter JF, Unger JB. E-cigarettes: a disruptive technology that revolutionizes our field? Nicotine Tob Res. 2015; 17:125–6. [PubMed: 25609846]

Famele M, Ferranti C, Abenavoli C, Palleschi L, Mancinelli R, Draisci R. The chemical components of electronic cigarette cartridges and refill fluids: review of analytical methods. Nicotine & Tobacco Research. 2014; 17:271–279. [PubMed: 25257980]

Finkenauer R, Pomerleau CS, Snedecor SM, Pomerleau OF. Race differences in factors relating to smoking initiation. AddictBehav. 2009; 34:1056–1059.

Fletcher PJ, Rizos Z, Noble K, Soko AD, Silenieks LB, Le AD, Higgins GA. Effects of the 5-HT2C receptor agonist Ro60-0175 and the 5-HT2A receptor antagonist M100907 on nicotine self-administration and reinstatement. Neuropharmacology. 2012; 62:2288–2298. [PubMed: 22342986]

Flores RJ, Pipkin JA, Uribe KP, Perez A, O'Dell LE. Estradiol promotes the rewarding effects of nicotine in female rats. Behav Brain Res. 2016; 307:258–63. [PubMed: 27059334]

Fosgerau K, Hoffmann T. Peptide therapeutics: current status and future directions. Drug Discov Today. 2015; 20:122–8. [PubMed: 25450771]

Foulds J, Russ C, Yu CR, Zou KH, Galaznik A, Franzon M, Berg A, Hughes JR. Effect of varenicline on individual nicotine withdrawal symptoms: a combined analysis of eight randomized, placebo-controlled trials. Nicotine Tob Res. 2013; 15:1849–57. [PubMed: 23694782]

Gantz I, Miwa H, Konda Y, Shimoto Y, Tashiro T, Watson SJ, DelValle J, Yamada T. Molecular cloning, expression, and gene localization of a fourth melanocortin receptor. JBiolChem. 1993; 268:15174–15179.

George O, Ghozland S, Azar MR, Cottone P, Zorrilla EP, Parsons LH, O'Dell LE, Richardson HN, Koob GF. CRF CRF1 system activation mediates withdrawal-induced increases in nicotine self-administration in nicotine-dependent rats. ProcNatlAcadSciUSA. 2007; 104:17198–17203.

Gold AB, Wileyto EP, Lori A, Conti D, Cubells JF, Lerman C. Pharmacogenetic association of the galanin receptor (GALR1) SNP rs2717162 with smoking cessation. Neuropsychopharmacology. 2012; 37:1683–8. [PubMed: 22373943]

Grana R, Benowitz N, Glantz SA. E-cigarettes a scientific review. Circulation. 2014; 129:1972–1986. [PubMed: 24821826]

Grieder TE, Herman MA, Contet C, Tan LA, Vargas-Perez H, Cohen A, Chwalek M, Maal-Bared G, Freiling J, Schlosburg JE, Clarke L, Crawford E, Koebel P, Repunte-Canonigo V, Sanna PP, Tapper AR, Roberto M, Kieffer BL, Sawchenko PE, Koob GF, van der Kooy D, George O. VTA CRF neurons mediate the aversive effects of nicotine withdrawal and promote intake escalation. Nat Neurosci. 2014; 17:1751–8. [PubMed: 25402857]

Gundlach AL. Galanin/GALP and galanin receptors: role in central control of feeding, body weight/obesity and reproduction? Eur J Pharmacol. 2002; 440:255–68. [PubMed: 12007540]

Hall BJ, Slade S, Wells C, Rose JE, Levin ED. Bupropion-varenicline interactions and nicotine self-administration behavior in rats. Pharmacol Biochem Behav. 2015; 130:84–9. [PubMed: 25616031]

Hancock DB, Reginsson GW, Gaddis NC, Chen X, Saccone NL, Lutz SM, Qaiser B, Sherva R, Steinberg S, Zink F, Stacey SN, Glasheen C, Chen J, Gu F, Frederiksen BN, Loukola A, Gudbjartsson DF, Bruske I, Landi MT, Bickeboller H, Madden P, Farrer L, Kaprio J, Kranzler HR, Gelernter J, Baker TB, Kraft P, Amos CI, Caporaso NE, Hokanson JE, Bierut LJ, Thorgeirsson TE, Johnson EO, Stefansson K. Genome-wide meta-analysis reveals common splice site acceptor variant in CHRNA4 associated with nicotine dependence. Transl Psychiatry. 2015; 5:e651. [PubMed: 26440539]

Harrell PT, Marquinez NS, Correa JB, Meltzer LR, Unrod M, Sutton SK, Simmons VN, Brandon TH. Expectancies for cigarettes, e-cigarettes, and nicotine replacement therapies among e-cigarette users (aka vapers). Nicotine Tob Res. 2015; 17:193–200. [PubMed: 25168035]

Heilig M, Soderpalm B, Engel JA, Widerlov E. Centrally administered neuropeptide Y (NPY) produces anxiolytic-like effects in animal anxiety models. Psychopharmacology (Berl). 1989; 98:524–529. [PubMed: 2570434]

Hikosaka O. The habenula: from stress evasion to value-based decision-making. Nat Rev Neurosci. 2010; 11:503–13. [PubMed: 20559337]

Hildebrand BE, Nomikos GG, Hertel P, Schilstrom B, Svensson TH. Reduced dopamine output in the nucleus accumbens but not in the medial prefrontal cortex in rats displaying a mecamylamine-precipitated nicotine withdrawal syndrome. Brain Res. 1998; 779:214–225. [PubMed: 9473676]

Hollander JA, Lu Q, Cameron MD, Kamenecka TM, Kenny PJ. Insular hypocretin transmission regulates nicotine reward. ProcNatlAcadSciUSA. 2008; 105:19480–19485.

Hopkins TJ, Rupprecht LE, Hayes MR, Blendy JA, Schmidt HD. Galantamine, an acetylcholinesterase inhibitor and positive allosteric modulator of nicotinic acetylcholine receptors, attenuates nicotine taking and seeking in rats. Neuropsychopharmacology. 2012; 37:2310–21. [PubMed: 22669169]

Howard B, Panchal H, McCarthy A, Ashworth A. Identification of the scaramanga gene implicates Neuregulin3 in mammary gland specification. Genes Dev. 2005; 19:2078–90. [PubMed: 16140987]

Hughes JR. Effects of abstinence from tobacco: valid symptoms and time course. NicotineTobRes. 2007; 9:315–327.

Hughes JR, Gust SW, Skoog K, Keenan RM, Fenwick JW. Symptoms of tobacco withdrawal. A replication and extension. ArchGenPsychiatry. 1991; 48:52–59.

Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. ArchGenPsychiatry. 1986; 43:289–294.

Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. Addiction. 2004; 99:29–38. [PubMed: 14678060]

Hurst R, Rollema H, Bertrand D. Nicotinic acetylcholine receptors: from basic science to therapeutics. Pharmacol Ther. 2013; 137:22–54. [PubMed: 22925690]

Igari M, Alexander JC, Ji Y, Qi X, Papke RL, Bruijnzeel AW. Varenicline and cytisine diminish the dysphoric-like state associated with spontaneous nicotine withdrawal in rats. Neuropsychopharmacology. 2013; 39:455–465. [PubMed: 23966067]

Iijima M, Chaki S. An arginine vasopressin V1b antagonist, SSR149415 elicits antidepressant-like effects in an olfactory bulbectomy model. ProgNeuropsychopharmacolBiolPsychiatry. 2007; 31:622–627.

Iijima M, Yoshimizu T, Shimazaki T, Tokugawa K, Fukumoto K, Kurosu S, Kuwada T, Sekiguchi Y, Chaki S. Antidepressant and anxiolytic profiles of newly synthesized arginine vasopressin V1B receptor antagonists: TASP0233278 and TASP0390325. Br J Pharmacol. 2014; 171:3511–25. [PubMed: 24654684]

Isola R, Zhang H, Tejwani GA, Neff NH, Hadjiconstantinou M. Dynorphin and prodynorphin mRNA changes in the striatum during nicotine withdrawal. Synapse. 2008; 62:448–55. [PubMed: 18361441]

Jackson KJ, Carroll FI, Negus SS, Damaj MI. Effect of the selective kappa-opioid receptor antagonist JDTic on nicotine antinociception, reward, and withdrawal in the mouse. Psychopharmacology (Berl). 2010; 210:285–94. [PubMed: 20232057]

Jackson KJ, Chen X, Miles MF, Harenza J, Damaj MI. The neuropeptide galanin and variants in the GalR1 gene are associated with nicotine dependence. Neuropsychopharmacology. 2011; 36:2339–48. [PubMed: 21796100]

Jackson KJ, Jackson A, Carroll FI, Damaj MI. Effects of orally-bioavailable short-acting kappa opioid receptor-selective antagonist LY2456302 on nicotine withdrawal in mice. Neuropharmacology. 2015; 97:270–4. [PubMed: 26044637]

Jackson KJ, McLaughlin JP, Carroll FI, Damaj MI. Effects of the kappa opioid receptor antagonist, norbinaltorphimine, on stress and drug-induced reinstatement of nicotine-conditioned place preference in mice. Psychopharmacology (Berl). 2013; 226:763–8. [PubMed: 22526543]

Jarvis MJ. Why people smoke. BMJ. 2004; 328:277–279. [PubMed: 14751901]

Jerlhag E, Engel JA. Ghrelin receptor antagonism attenuates nicotine-induced locomotor stimulation, accumbal dopamine release and conditioned place preference in mice. Drug Alcohol Depend. 2011; 117:126–31. [PubMed: 21310553]

Johnson JG, Cohen P, Pine DS, Klein DF, Kasen S, Brook JS. Association between cigarette smoking and anxiety disorders during adolescence and early adulthood. JAMA. 2000; 284:2348–2351. [PubMed: 11066185]

Johnson PM, Hollander JA, Kenny PJ. Decreased brain reward function during nicotine withdrawal in C57BL6 mice: evidence from intracranial self-stimulation (ICSS) studies. PharmacolBiochemBehav. 2008; 90:409–415.

Johnston, LD., O'Malley, PM., Miech, RA., Bachman, JG., Schulenberg, JE. Monitoring the Future national survey results on drug use: 1975–2014: Overview, key findings on adolescent drug use. Ann Arbor: Institute for Social Research, The University of Michigan; 2015.

Kallupi M, Cannella N, Economidou D, Ubaldi M, Ruggeri B, Weiss F, Massi M, Marugan J, Heilig M, Bonnavion P. Neuropeptide S facilitates cue-induced relapse to cocaine seeking through activation of the hypothalamic hypocretin system. Proceedings of the National Academy of Sciences. 2010; 107:19567–19572.

Kaspar AA, Reichert JM. Future directions for peptide therapeutics development. Drug Discov Today. 2013; 18:807–17. [PubMed: 23726889]

Kiba H, Jayaraman A. Nicotine induced c-fos expression in the striatum is mediated mostly by dopamine D1 receptor and is dependent on NMDA stimulation. Brain ResMolBrain Res. 1994; 23:1–13.

Kimmey BA, Rupprecht LE, Hayes MR, Schmidt HD. Donepezil, an acetylcholinesterase inhibitor, attenuates nicotine self-administration and reinstatement of nicotine seeking in rats. Addict Biol. 2014; 19:539–51. [PubMed: 23231479]

King PJ, Widdowson PS, Doods HN, Williams G. Regulation of neuropeptide Y release by neuropeptide Y receptor ligands and calcium channel antagonists in hypothalamic slices. J Neurochem. 1999; 73:641–6. [PubMed: 10428060]

Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature. 1999; 402:656–60. [PubMed: 10604470]

Kokare DM, Dandekar MP, Singru PS, Gupta GL, Subhedar NK. Involvement of alpha-MSH in the social isolation induced anxiety- and depression-like behaviors in rat. Neuropharmacology. 2010; 58:1009–1018. [PubMed: 20080115]

Koob GF. Stress, corticotropin-releasing factor, and drug addiction. AnnNYAcadSci. 1999; 897:27–45.

Koob GF, Heinrichs SC. A role for corticotropin releasing factor and urocortin in behavioral responses to stressors. Brain Res. 1999; 848:141–152. [PubMed: 10612706]

Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry. 2016; 3:760–73. [PubMed: 27475769]

Korotkova TM, Sergeeva OA, Eriksson KS, Haas HL, Brown RE. Excitation of ventral tegmental area dopaminergic and nondopaminergic neurons by orexins/hypocretins. J Neurosci. 2003; 23:7–11. [PubMed: 12514194]

Lage R, González CR, Diéguez C, López M. Nicotine treatment regulates neuropeptide S system expression in the rat brain. Neurotoxicology. 2007; 28:1129–1135. [PubMed: 17645946]

Lang R, Gundlach AL, Holmes FE, Hobson SA, Wynick D, Hökfelt T, Kofler B. Physiology, signaling, and pharmacology of galanin peptides and receptors: three decades of emerging diversity. Pharmacol Rev. 2015; 67:118–175. [PubMed: 25428932]

LeSage MG, Burroughs D, Dufek M, Keyler DE, Pentel PR. Reinstatement of nicotine self-administration in rats by presentation of nicotine-paired stimuli, but not nicotine priming. Pharmacol Biochem Behav. 2004; 79:507–13. [PubMed: 15582022]

LeSage MG, Burroughs D, Pentel PR. Effects of nicotine withdrawal on performance under a progressive-ratio schedule of sucrose pellet delivery in rats. Pharmacol Biochem Behav. 2006; 83:585–91. [PubMed: 16643998]

Lewis K, Li C, Perrin MH, Blount A, Kunitake K, Donaldson C, Vaughan J, Reyes TM, Gulyas J, Fischer W, Bilezikjian L, Rivier J, Sawchenko PE, Vale WW. Identification of urocortin III, an

additional member of the corticotropin-releasing factor (CRF) family with high affinity for the CRF2 receptor. ProcNatlAcadSciUSA. 2001; 98:7570–7575.

Liang Y, Boules M, Shaw AM, Williams K, Fredrickson P, Richelson E. Effect of a novel neurotensin analog, NT69L, on nicotine-induced alterations in monoamine levels in rat brain. Brain Res. 2008; 1231:6–15. [PubMed: 18687313]

Liu JZ, Tozzi F, Waterworth DM, Pillai SG, Muglia P, Middleton L, Berrettini W, Knouff CW, Yuan X, Waeber G, Vollenweider P, Preisig M, Wareham NJ, Zhao JH, Loos RJ, Barroso I, Khaw KT, Grundy S, Barter P, Mahley R, Kesaniemi A, McPherson R, Vincent JB, Strauss J, Kennedy JL, Farmer A, McGuffin P, Day R, Matthews K, Bakke P, Gulsvik A, Lucae S, Ising M, Brueckl T, Horstmann S, Wichmann HE, Rawal R, Dahmen N, Lamina C, Polasek O, Zgaga L, Huffman J, Campbell S, Kooner J, Chambers JC, Burnett MS, Devaney JM, Pichard AD, Kent KM, Satler L, Lindsay JM, Waksman R, Epstein S, Wilson JF, Wild SH, Campbell H, Vitart V, Reilly MP, Li M, Qu L, Wilensky R, Matthai W, Hakonarson HH, Rader DJ, Franke A, Wittig M, Schafer A, Uda M, Terracciano A, Xiao X, Busonero F, Scheet P, Schlessinger D, St Clair D, Rujescu D, Abecasis GR, Grabe HJ, Teumer A, Volzke H, Petersmann A, John U, Rudan I, Hayward C, Wright AF, Kolcic I, Wright BJ, Thompson JR, Balmforth AJ, Hall AS, Samani NJ, Anderson CA, Ahmad T, Mathew CG, Parkes M, Satsangi J, Caulfield M, Munroe PB, Farrall M, Dominiczak A, Worthington J, Thomson W, Eyre S, Barton A, Mooser V, Francks C, Marchini J. Meta-analysis and imputation refines the association of 15q25 with smoking quantity. Nat Genet. 2010; 42:436–40. [PubMed: 20418889]

Liu X, Caggiula AR, Palmatier MI, Donny EC, Sved AF. Cue-induced reinstatement of nicotine-seeking behavior in rats: effect of bupropion, persistence over repeated tests, and its dependence on training dose. Psychopharmacology (Berl). 2008; 196:365–75. [PubMed: 17932656]

Liu X, Caggiula AR, Yee SK, Nobuta H, Poland RE, Pechnick RN. Reinstatement of nicotine-seeking behavior by drug-associated stimuli after extinction in rats. Psychopharmacology (Berl). 2006; 184:417–25. [PubMed: 16163522]

Liu X, Caggiula AR, Yee SK, Nobuta H, Sved AF, Pechnick RN, Poland RE. Mecamylamine attenuates cue-induced reinstatement of nicotine-seeking behavior in rats. Neuropsychopharmacology. 2007; 32:710–8. [PubMed: 16794568]

Liu X, Weiss F. Reversal of ethanol-seeking behavior by D1 and D2 antagonists in an animal model of relapse: differences in antagonist potency in previously ethanol-dependent versus nondependent rats. J Pharmacol Exp Ther. 2002; 300:882–9. [PubMed: 11861794]

Lori A, Tang Y, O'Malley S, Picciotto MR, Wu R, Conneely KN, Cubells JF. The galanin receptor 1 gene associates with tobacco craving in smokers seeking cessation treatment. Neuropsychopharmacology. 2011; 36:1412–20. [PubMed: 21430647]

Lovenberg TW, Liaw CW, Grigoriadis DE, Clevenger W, Chalmers DT, De Souza EB, Oltersdorf T. Cloning and characterization of a functionally distinct corticotropin-releasing factor receptor subtype from rat brain. ProcNatlAcadSciUSA. 1995; 92:836–840.

Lutfy K, Do T, Maidment NT. Orphanin FQ/nociceptin attenuates motor stimulation and changes in nucleus accumbens extracellular dopamine induced by cocaine in rats. Psychopharmacology (Berl). 2001; 154:1–7. [PubMed: 11291998]

Malin DH. Nicotine dependence: studies with a laboratory model. PharmacolBiochemBehav. 2001; 70:551–559.

Malin DH, Lake JR, Newlin-Maultsby P, Roberts LK, Lanier JG, Carter VA, Cunningham JS, Wilson OB. Rodent model of nicotine abstinence syndrome. PharmacolBiochemBehav. 1992; 43:779–784.

Manbeck KE, Shelley D, Schmidt CE, Harris AC. Effects of oxytocin on nicotine withdrawal in rats. Pharmacol Biochem Behav. 2014; 116:84–9. [PubMed: 24239789]

Mannucci C, Tedesco M, Bellomo M, Caputi AP, Calapai G. Long-term effects of nicotine on the forced swimming test in mice: an experimental model for the study of depression caused by smoke. Neurochem Int. 2006; 49:481–6. [PubMed: 16697079]

Marcinkiewcz CA, Prado MM, Isaac SK, Marshall A, Rylkova D, Bruijnzeel AW. Corticotropin-releasing factor within the central nucleus of the amygdala and the nucleus accumbens shell mediates the negative affective state of nicotine withdrawal in rats. Neuropsychopharmacology. 2009; 34:1743–1752. [PubMed: 19145226]

Marks MJ, Burch JB, Collins AC. Effects of chronic nicotine infusion on tolerance development and nicotinic receptors. JPharmacolExpTher. 1983; 226:817–825.

Melander T, Hökfelt T, Rökaeus A. Distribution of galaninlike immunoreactivity in the rat central nervous system. J Comp Neurol. 1986; 248:475–517. [PubMed: 2424949]

Mondal MS, Date Y, Yamaguchi H, Toshinai K, Tsuruta T, Kangawa K, Nakazato M. Identification of ghrelin and its receptor in neurons of the rat arcuate nucleus. Regul Pept. 2005; 126:55–9. [PubMed: 15620414]

Moore, RY., Card, JP. Noradrenaline-containing neuron systems. In: Bjorklund, A., Hokfelt, T., editors. Handbook of chemical neuroanatomy. Elsevier; Amsterdam: 1984. p. 123-156.

Morgan JI, Curran T. Immediate-early genes: ten years on. Trends Neurosci. 1995; 18:66–67. [PubMed: 7537412]

Myers WD, Ng KT, Singer G. Intravenous self-administration of acetaldehyde in the rat as a function of schedule, food deprivation and photoperiod. PharmacolBiochemBehav. 1982; 17:807–811.

Nakajima M, Inui A, Asakawa A, Momose K, Ueno N, Teranishi A, Baba S, Kasuga M. Neuropeptide Y produces anxiety via Y2-type receptors. Peptides. 1998; 19:359–63. [PubMed: 9493869]

Neugebauer NM, Henehan RM, Hales CA, Picciotto MR. Mice lacking the galanin gene show decreased sensitivity to nicotine conditioned place preference. Pharmacol Biochem Behav. 2011; 98:87–93. [PubMed: 21172385]

Nijsen MJ, Croiset G, Diamant M, de WD, Wiegant VM. CRH signalling in the bed nucleus of the stria terminalis is involved in stress-induced cardiac vagal activation in conscious rats. Neuropsychopharmacology. 2001; 24:1–10. [PubMed: 11106870]

Nishizawa D, Kasai S, Hasegawa J, Sato N, Yamada H, Tanioka F, Nagashima M, Katoh R, Satoh Y, Tagami M, Ujike H, Ozaki N, Inada T, Iwata N, Sora I, Iyo M, Yamada M, Kondo N, Won MJ, Naruse N, Uehara-Aoyama K, Itokawa M, Ohi K, Hashimoto R, Tanisawa K, Arai T, Mori S, Sawabe M, Naka-Mieno M, Yamada Y, Yamada M, Sato N, Muramatsu M, Tanaka M, Irukayama-Tomobe Y, Saito YC, Sakurai T, Hayashida M, Sugimura H, Ikeda K. Associations between the orexin (hypocretin) receptor 2 gene polymorphism Val308Ile and nicotine dependence in genome-wide and subsequent association studies. Mol Brain. 2015; 8:50. [PubMed: 26289589]

O'Connor EC, Parker D, Rollema H, Mead AN. The alpha4beta2 nicotinic acetylcholine-receptor partial agonist varenicline inhibits both nicotine self-administration following repeated dosing and reinstatement of nicotine seeking in rats. Psychopharmacology (Berl). 2010; 208:365–376. [PubMed: 19967529]

Ott A, Slooter AJ, Hofman A, van Harskamp F, Witteman JC, Van Broeckhoven C, van Duijn CM, Breteler MM. Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. Lancet. 1998; 351:1840–3. [PubMed: 9652667]

Pagliusi SR, Tessari M, DeVevey S, Chiamulera C, Pich EM. The reinforcing properties of nicotine are associated with a specific patterning of c-fos expression in the rat brain. Eur J Neurosci. 1996; 8:2247–56. [PubMed: 8950089]

Panagis G, Hildebrand BE, Svensson TH, Nomikos GG. Selective c-fos induction and decreased dopamine release in the central nucleus of amygdala in rats displaying a mecamylamine-precipitated nicotine withdrawal syndrome. Synapse. 2000; 35:15–25. [PubMed: 10579804]

Pañeda C, Huitron-Resendiz S, Frago LM, Chowen JA, Picetti R, de Lecea L, Roberts AJ. Neuropeptide S reinstates cocaine-seeking behavior and increases locomotor activity through corticotropin-releasing factor receptor 1 in mice. The Journal of Neuroscience. 2009; 29:4155–4161. [PubMed: 19339610]

Pang X, Liu L, Ngolab J, Zhao-Shea R, McIntosh JM, Gardner PD, Tapper AR. Habenula cholinergic neurons regulate anxiety during nicotine withdrawal via nicotinic acetylcholine receptors. Neuropharmacology. 2016; 107:294–304. [PubMed: 27020042]

Pape H-C, Jüngling K, Seidenbecher T, Lesting J, Reinscheid RK. Neuropeptide S: a transmitter system in the brain regulating fear and anxiety. Neuropharmacology. 2010; 58:29–34. [PubMed: 19523478]

Pascual MM, Pastor V, Bernabeu RO. Nicotine-conditioned place preference induced CREB phosphorylation and Fos expression in the adult rat brain. Psychopharmacology (Berl). 2009; 207:57–71. [PubMed: 19711055]

Pellegrino RM, Tinghino B, Mangiaracina G, Marani A, Vitali M, Protano C, Osborn JF, Cattaruzza MS. Electronic cigarettes: an evaluation of exposure to chemicals and fine particulate matter (PM). Ann Ig. 2012; 24:279–88. [PubMed: 22913171]

Perello M, Dickson SL. Ghrelin signalling on food reward: a salient link between the gut and the mesolimbic system. J Neuroendocrinol. 2015; 27:424–34. [PubMed: 25377898]

Perrin MH, Donaldson CJ, Chen R, Lewis KA, Vale WW. Cloning and functional expression of a rat brain corticotropin releasing factor (CRF) receptor. Endocrinology. 1993; 133:3058–3061. [PubMed: 8243338]

Peyron C, Tighe DK, van den Pol AN, de LL, Heller HC, Sutcliffe JG, Kilduff TS. Neurons containing hypocretin (orexin) project to multiple neuronal systems. JNeurosci. 1998; 18:9996–10015. [PubMed: 9822755]

Pierce RC, Vanderschuren LJ. Kicking the habit: the neural basis of ingrained behaviors in cocaine addiction. Neurosci Biobehav Rev. 2010; 35:212–9. [PubMed: 20097224]

Pirie K, Peto R, Reeves GK, Green J, Beral V. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. Lancet. 2013; 381:133–41. [PubMed: 23107252]

Plaza-Zabala A, Flores A, Maldonado R, Berrendero F. Hypocretin/Orexin Signaling in the Hypothalamic Paraventricular Nucleus is Essential for the Expression of Nicotine Withdrawal. BiolPsychiatry. 2012; 71:214–223.

Plaza-Zabala A, Flores A, Martin-Garcia E, Saravia R, Maldonado R, Berrendero F. A role for hypocretin/orexin receptor-1 in cue-induced reinstatement of nicotine-seeking behavior. Neuropsychopharmacology. 2013; 38:1724–36. [PubMed: 23518606]

Plaza-Zabala A, Martin-Garcia E, de LL, Maldonado R, Berrendero F. Hypocretins regulate the anxiogenic-like effects of nicotine and induce reinstatement of nicotine-seeking behavior. JNeurosci. 2010; 30:2300–2310. [PubMed: 20147556]

Postma DS, Bush A, van den Berge M. Risk factors and early origins of chronic obstructive pulmonary disease. Lancet. 2015; 385:899–909. [PubMed: 25123778]

Qi X, Guzhva L, Ji Y, Bruijnzeel AW. Chronic treatment with the vasopressin 1b receptor antagonist SSR149415 prevents the dysphoria associated with nicotine withdrawal in rats. Behav Brain Res. 2015a; 292:259–65. [PubMed: 26112757]

Qi X, Guzhva L, Yang Z, Febo M, Shan Z, Wang KK, Bruijnzeel AW. Overexpression of CRF in the BNST diminishes dysphoria but not anxiety-like behavior in nicotine withdrawing rats. Eur Neuropsychopharmacol. 2016

Qi X, Shan Z, Ji Y, Guerra V, Alexander JC, Ormerod BK, Bruijnzeel AW. Sustained AAV-mediated overexpression of CRF in the central amygdala diminishes the depressive-like state associated with nicotine withdrawal. TranslPsychiatry. 2014; 4:e385.

Qi X, Yamada H, Corrie LW, Ji Y, Bauzo RM, Alexander JC, Bruijnzeel AW. A critical role for the melanocortin 4 receptor in stress-induced relapse to nicotine seeking in rats. Addict Biol. 2015b; 20:324–335. [PubMed: 24612112]

Redrobe JP, Dumont Y, Quirion R. Neuropeptide Y (NPY) and depression: from animal studies to the human condition. Life Sci. 2002; 71:2921–2937. [PubMed: 12384178]

Reichmann F, Holzer P. Neuropeptide Y: A stressful review. Neuropeptides. 2016; 55:99–109. [PubMed: 26441327]

Reinscheid RK, Xu YL. Neuropeptide S as a novel arousal promoting peptide transmitter. Febs Journal. 2005; 272:5689–5693. [PubMed: 16279934]

Roni MA, Rahman S. The effects of lobeline on nicotine withdrawal-induced depression-like behavior in mice. Psychopharmacology (Berl). 2014; 231:2989–98. [PubMed: 24682499]

Ryan ML, Falk DE, Fertig JB, Rendenbach-Mueller B, Katz DA, Tracy KA, Strain EC, Dunn KE, Kampman K, Mahoney E. A Phase 2, Double-Blind, Placebo-Controlled Randomized Trial Assessing the Efficacy of ABT-436, a Novel V1b Receptor Antagonist, for Alcohol Dependence. Neuropsychopharmacology. 2016

Rylkova D, Boissoneault J, Isaac S, Prado M, Shah HP, Bruijnzeel AW. Effects of NPY and the specific Y1 receptor agonist [D-His(26)]-NPY on the deficit in brain reward function and somatic signs associated with nicotine withdrawal in rats. Neuropeptides. 2008; 42:215–227. [PubMed: 18468678]

Sajdyk TJ, Vandergriff MG, Gehlert DR. Amygdalar neuropeptide Y Y1 receptors mediate the anxiolytic-like actions of neuropeptide Y in the social interaction test. EurJPharmacol. 1999; 368:143–147.

Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, Williams SC, Richardson JA, Kozlowski GP, Wilson S, Arch JR, Buckingham RE, Haynes AC, Carr SA, Annan RS, McNulty DE, Liu WS, Terrett JA, Elshourbagy NA, Bergsma DJ, Yanagisawa M. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell. 1998; 92:573–585. [PubMed: 9491897]

Salas R, Sturm R, Boulter J, De BM. Nicotinic receptors in the habenulo-interpeduncular system are necessary for nicotine withdrawal in mice. JNeurosci. 2009; 29:3014–3018. [PubMed: 19279237]

Schmoutz CD, Zhang Y, Runyon SP, Goeders NE. Antagonism of the neuropeptide S receptor with RTI-118 decreases cocaine self-administration and cocaine-seeking behavior in rats. Pharmacol Biochem Behav. 2012; 103:332–7. [PubMed: 22982682]

Schulteis G, Markou A, Cole M, Koob GF. Decreased brain reward produced by ethanol withdrawal. ProcNatlAcadSciUSA. 1995; 92:5880–5884.

Serova LI, Laukova M, Alaluf LG, Sabban EL. Intranasal infusion of melanocortin receptor four (MC4R) antagonist to rats ameliorates development of depression and anxiety related symptoms induced by single prolonged stress. BehavBrain Res. 2013; 250:139–147.

Shaham Y, Shalev U, Lu L, De Wit H, Stewart J. The reinstatement model of drug relapse: history, methodology and major findings. Psychopharmacology (Berl). 2003; 168:3–20. [PubMed: 12402102]

Shiffman S, Ferguson SG, Gwaltney CJ, Balabanis MH, Shadel WG. Reduction of abstinence-induced withdrawal and craving using high-dose nicotine replacement therapy. Psychopharmacology (Berl). 2006; 184:637–44. [PubMed: 16261317]

Shiffman S, Johnston JA, Khayrallah M, Elash CA, Gwaltney CJ, Paty JA, Gnys M, Evoniuk G, DeVeaugh-Geiss J. The effect of bupropion on nicotine craving and withdrawal. Psychopharmacology (Berl). 2000; 148:33–40. [PubMed: 10663415]

Simmons SJ, Gentile TA, Mo L, Tran FH, Ma S, Muschamp JW. Nicotinic receptor blockade decreases fos immunoreactivity within orexin/hypocretin-expressing neurons of nicotine-exposed rats. Behav Brain Res. 2016; 314:226–233. [PubMed: 27491589]

Skjei KL, Markou A. Effects of repeated withdrawal episodes, nicotine dose, and duration of nicotine exposure on the severity and duration of nicotine withdrawal in rats. Psychopharmacology (Berl). 2003; 168:280–292. [PubMed: 12712232]

Small E, Shah HP, Davenport JJ, Geier JE, Yavarovich KR, Yamada H, Sabarinath SN, Derendorf H, Pauly JR, Gold MS, Bruijnzeel AW. Tobacco smoke exposure induces nicotine dependence in rats. Psychopharmacology (Berl). 2010; 208:143–158. [PubMed: 19936715]

Smith BR, Amit Z, Splawinsky J. Conditioned place preference induced by intraventricular infusions of acetaldehyde. Alcohol. 1984; 1:193–195. [PubMed: 6536284]

Staley JK, Krishnan-Sarin S, Cosgrove KP, Krantzler E, Frohlich E, Perry E, Dubin JA, Estok K, Brenner E, Baldwin RM. Human tobacco smokers in early abstinence have higher levels of β2* nicotinic acetylcholine receptors than nonsmokers. The Journal of neuroscience. 2006; 26:8707–8714. [PubMed: 16928859]

Steckler T, Holsboer F. Corticotropin-releasing hormone receptor subtypes and emotion. BiolPsychiatry. 1999; 46:1480–1508.

Stolerman IP, Jarvis MJ. The scientific case that nicotine is addictive. Psychopharmacology (Berl). 1995; 117:2–10. [PubMed: 7724697]

Sutton RE, Koob GF, Le Moal M, Rivier J, Vale W. Corticotropin releasing factor produces behavioural activation in rats. Nature. 1982; 297:331–333. [PubMed: 6978997]

Suzuki T, Ise Y, Tsuda M, Maeda J, Misawa M. Mecamylamine-precipitated nicotine-withdrawal aversion in rats. EurJPharmacol. 1996; 314:281–284.

Swalve N, Smethells JR, Carroll ME. Sex differences in attenuation of nicotine reinstatement after individual and combined treatments of progesterone and varenicline. Behav Brain Res. 2016; 308:46–52. [PubMed: 27091301]

Swanson LW, Sawchenko PE, Rivier J, Vale WW. Organization of ovine corticotropin-releasing factor immunoreactive cells and fibers in the rat brain: an immunohistochemical study. Neuroendocrinology. 1983; 36:165–186. [PubMed: 6601247]

Swerdlow NR, Geyer MA, Vale WW, Koob GF. Corticotropin-releasing factor potentiates acoustic startle in rats: blockade by chlordiazepoxide. Psychopharmacology (Berl). 1986; 88:147–152. [PubMed: 3081925]

Talhout R, Opperhuizen A, van Amsterdam JG. Sugars as tobacco ingredient: Effects on mainstream smoke composition. Food Chem Toxicol. 2006; 44:1789–98. [PubMed: 16904804]

Talhout R, Opperhuizen A, van Amsterdam JG. Role of acetaldehyde in tobacco smoke addiction. EurNeuropsychopharmacol. 2007; 17:627–636.

Tanaka M, Telegdy G. Antidepressant-like effects of the CRF family peptides, urocortin 1, urocortin 2 and urocortin 3 in a modified forced swimming test in mice. Brain ResBull. 2008; 75:509–512.

Thorgeirsson TE, Steinberg S, Reginsson GW, Bjornsdottir G, Rafnar T, Jonsdottir I, Helgadottir A, Gretarsdottir S, Helgadottir H, Jonsson S, Matthiasson SE, Gislason T, Tyrfingsson T, Gudbjartsson T, Isaksson HJ, Hardardottir H, Sigvaldason A, Kiemeney LA, Haugen A, Zienolddiny S, Wolf HJ, Franklin WA, Panadero A, Mayordomo JI, Hall IP, Ronmark E, Lundback B, Dirksen A, Ashraf H, Pedersen JH, Masson G, Sulem P, Thorsteinsdottir U, Gudbjartsson DF, Stefansson K. A rare missense mutation in CHRNA4 associates with smoking behavior and its consequences. Mol Psychiatry. 2016; 21:594–600. [PubMed: 26952864]

Thorsell A, Tapocik JD, Liu K, Zook M, Bell L, Flanigan M, Patnaik S, Marugan J, Damadzic R, Dehdashti SJ, Schwandt ML, Southall N, Austin CP, Eskay R, Ciccocioppo R, Zheng W, Heilig M. A novel brain penetrant NPS receptor antagonist, NCGC00185684, blocks alcohol-induced ERK-phosphorylation in the central amygdala and decreases operant alcohol self-administration in rats. J Neurosci. 2013; 33:10132–42. [PubMed: 23761908]

Thun MJ, Carter BD, Feskanich D, Freedman ND, Prentice R, Lopez AD, Hartge P, Gapstur SM. 50-year trends in smoking-related mortality in the United States. N Engl J Med. 2013; 368:351–64. [PubMed: 23343064]

Turner JR, Ray R, Lee B, Everett L, Xiang J, Jepson C, Kaestner KH, Lerman C, Blendy JA. Evidence from mouse and man for a role of neuregulin 3 in nicotine dependence. Mol Psychiatry. 2014; 19:801–10. [PubMed: 23999525]

Tzschentke TM. Measuring reward with the conditioned place preference paradigm: a comprehensive review of drug effects, recent progress and new issues. Prog Neurobiol. 1998; 56:613–72. [PubMed: 9871940]

Vale W, Spiess J, Rivier C, Rivier J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. Science. 1981; 213:1394–1397. [PubMed: 6267699]

Varani AP, Moutinho LM, Bettler B, Balerio GN. Acute behavioural responses to nicotine and nicotine withdrawal syndrome are modified in GABA(B1) knockout mice. Neuropharmacology. 2012; 63:863–72. [PubMed: 22727822]

Vazquez-DeRose J, Stauber G, Khroyan TV, Xie XS, Zaveri NT, Toll L. Retrodialysis of N/OFQ into the nucleus accumbens shell blocks cocaine-induced increases in extracellular dopamine and locomotor activity. Eur J Pharmacol. 2013; 699:200–6. [PubMed: 23219985]

Ventura R, Cabib S, Alcaro A, Orsini C, Puglisi-Allegra S. Norepinephrine in the prefrontal cortex is critical for amphetamine-induced reward and mesoaccumbens dopamine release. J Neurosci. 2003; 23:1879–85. [PubMed: 12629192]

Walters CL, Brown S, Changeux JP, Martin B, Damaj MI. The beta2 but not alpha7 subunit of the nicotinic acetylcholine receptor is required for nicotine-conditioned place preference in mice. Psychopharmacology (Berl). 2006; 184:339–344. [PubMed: 16416156]

Warner C, Shoaib M. How does bupropion work as a smoking cessation aid? Addict Biol. 2005; 10:219–31. [PubMed: 16109583]

Watkins SS, Epping-Jordan MP, Koob GF, Markou A. Blockade of nicotine self-administration with nicotinic antagonists in rats. PharmacolBiochemBehav. 1999; 62:743–751.

Watkins SS, Stinus L, Koob GF, Markou A. Reward and somatic changes during precipitated nicotine withdrawal in rats: centrally and peripherally mediated effects. JPharmacolExpTher. 2000; 292:1053–1064.

Wen L, Jiang K, Yuan W, Cui W, Li MD. Contribution of Variants in CHRNA5/A3/B4 Gene Cluster on Chromosome 15 to Tobacco Smoking: From Genetic Association to Mechanism. Mol Neurobiol. 2016; 53:472–84. [PubMed: 25471942]

Wesnes K, Warburton DM. Smoking, nicotine and human performance. PharmacolTher. 1983; 21:189–208.

WHO. Systematic review of the link between tobacco and poverty. 2011.

WHO. WHO report on the global tobacco epidemic, 2015: raising taxes on tobacco. 2015.

Willis DN, Liu B, Ha MA, Jordt SE, Morris JB. Menthol attenuates respiratory irritation responses to multiple cigarette smoke irritants. FASEB J. 2011; 25:4434–44. [PubMed: 21903934]

Woldbye DP, Klemp K, Madsen TM. Neuropeptide Y attenuates naloxone-precipitated morphine withdrawal via Y5-like receptors. JPharmacolExpTher. 1998; 284:633–636.

Woldbye DP, Ulrichsen J, Haugbol S, Bolwig TG. Ethanol withdrawal in rats is attenuated by intracerebroventricular administration of neuropeptide Y. Alcohol Alcohol. 2002; 37:318–321. [PubMed: 12107031]

Xu YL, Reinscheid RK, Huitron-Resendiz S, Clark SD, Wang Z, Lin SH, Brucher FA, Zeng J, Ly NK, Henriksen SJ, de Lecea L, Civelli O. Neuropeptide S: a neuropeptide promoting arousal and anxiolytic-like effects. Neuron. 2004; 43:487–497. [PubMed: 15312648]

Yatawara C, Einfeld S, Hickie I, Davenport T, Guastella A. The effect of oxytocin nasal spray on social interaction deficits observed in young children with autism: a randomized clinical crossover trial. Mol Psychiatry. 2015; 21:1225–1231. [PubMed: 26503762]

Zhang X, Petruzziello F, Rainer G. Extending the scope of neuropeptidomics in the mammalian brain. EuPA Open Proteomics. 2014; 3:273–279.

Zhao-Shea R, DeGroot SR, Liu L, Vallaster M, Pang X, Su Q, Gao G, Rando OJ, Martin GE, George O, Gardner PD, Tapper AR. Increased CRF signalling in a ventral tegmental area-interpeduncular nucleus-medial habenula circuit induces anxiety during nicotine withdrawal. Nat Commun. 2015; 6:6770. [PubMed: 25898242]

Zislis G, Desai TV, Prado M, Shah HP, Bruijnzeel AW. Effects of the CRF receptor antagonist D-Phe CRF(12–41) and the alpha2-adrenergic receptor agonist clonidine on stress-induced reinstatement of nicotine-seeking behavior in rats. Neuropharmacology. 2007; 58:958–966.

Zvolensky MJ, Vujanovic AA, Miller MO, Bernstein A, Yartz AR, Gregor KL, McLeish AC, Marshall EC, Gibson LE. Incremental validity of anxiety sensitivity in terms of motivation to quit, reasons for quitting, and barriers to quitting among community-recruited daily smokers. NicotineTobRes. 2007; 9:965–75.

Table 1

Role of neuropeptides in nicotine addiction

Target	Drug	Test	Route and Dose	Effect	Reference
Acute reward					
Hypocretin 1 rec. blockade	SB-334867	IVSA	ip, acute, 1–4 mg/kg	+	(Hollander et al. 2008)
Galanin rec. stimulation	Galnon	CPP	ip, acute, 0.01–0.2 mg/kg	+	(Jackson et al. 2011)
Nociceptin rec. blockade	SB612111	IVSA	ip, acute, 0.3–3 mg/kg	+	(Cippitelli et al. 2016)
Neurotensin rec. stimulation	NT69L	IVSA	ip, acute, 1 mg/kg	+	(Boules et al. 2011)
Ghrelin rec. stimulation	JMV2959	CPP	ip, acute, 6 mg/kg	+	(Jerlhag and Engel 2011)
Somatic withdrawal signs					
NPY rec. stimulation	NPY	Count signs	icv, acute, 1–16 μg	+	(Rylkova et al. 2008)
Y1 rec. stimulation	[d-His26]-NPY	Count signs	icv, acute, 1–16 μg	+	(Rylkova et al. 2008)
Oxytocin rec. stimulation	Oxytocin	Count signs	ip, acute, 0.06–1 mg/kg	+	(Manbeck et al. 2014)
Kappa-opioid rec. blockade	LY2456302	Count signs	po, acute, 1–10 mg/kg	+	(Jackson et al. 2015)
Dysphoria					
CRF rec. blockade	D-Phe $CRF_{(12–41)}$	ICSS	icv, acute, 1–20 μg	+	(Bruijnzeel et al. 2007)
CRF rec. blockade	D-Phe $CRF_{(12–41)}$	ICSS	CeA, Nacc, acute, 5–500 ng per side, bilateral	+	(Marcinkiewcz et al. 2009)
CRF1 rec. blockade	R278995/CRA0450	ICSS	icv, acute, 1–20 μg	+	(Bruijnzeel et al. 2009)
V1b rec. blockade	SSR149415	ICSS	icv, chronic, 6 days, 0.5 μg/day	+	(Qi et al. 2015a)
Kappa-opioid rec. blockade	LY2456302	CPA	po, acute, 1 and 3 mg/kg	+	(Jackson et al. 2015)
CRF overexpression	AAV2/5-CRF	ICSS	CeA, chronic	+	(Qi et al. 2014)
CRF overexpression	AAV2/5-CRF	ICSS	BNST, chronic	−	(Qi et al. 2016)
CRF2 rec. blockade	Astressin-2B	ICSS	icv, acute, 1–20 μg	−	(Bruijnzeel et al. 2009)
NPY rec. stimulation	NPY	ICSS	icv, acute, 1–16 μg	−	(Rylkova et al. 2008)
Y1 rec. stimulation	[d-His26]-NPY	ICSS	icv, acute, 1–16 μg	−	(Rylkova et al. 2008)
Oxytocin rec. stimulation	Oxytocin	ICSS	ip, acute, 0.06–2 mg/kg	−	(Manbeck et al. 2014)
V1b rec. blockade	SSR149415	ICSS	icv, acute, 0.1–2 μg	−	(Qi et al. 2015a)
CRF rec. blockade	D-Phe $CRF_{(12–41)}$	ICSS	BNST, acute, 5–500 ng per side, bilateral	−	(Marcinkiewcz et al. 2009)
Anxiety					

Target	Drug	Test	Route and Dose	Effect	Reference
NRG3 pathway disruption	Afatinib	NIH, marble-burying test	systemic, chronic, 10 days, 10–20 mg/kg	+	(Turner et al. 2014)
CRF1 rec. blockade	MPZP	EPM	sc, acute, 20 mg/kg	+	(Cohen et al. 2015)
CRF1 rec. blockade	Antalarmin	EPM, marble burying test	IPN, acute, 1 μg/side, unilateral	+	(Zhao-Shea et al. 2015)
Y2 rec. blockade	JNJ-31020028	social interacti on test	ip, chronic, 7 days, 20 mg/kg	+	(Aydin et al. 2011)
Kappa-opioid rec. blockade	JDTic	EPM	sc, acute, 8 mg/kg	+	(Jackson et al. 2010)
Kappa-opioid rec. blockade	LY2456302	EPM	po, acute, 1–10 mg/kg	+	(Jackson et al. 2015)
CRF2 rec. blockade	Antisauvagine-30	EPM	IPN, acute, 2 μg/side, unilateral	−	(Zhao-Shea et al. 2015)
Cue-induced reinstatement					
Hypocretin 1 rec. blockade	SB334867	IVSA	ip, acute, 5 and 10 mg/kg	+	(Plaza-Zabala et al. 2013)
Hypocretin 2 rec. blockade	TCSOX229	IVSA	ip, acute, 5 and 10 mg/kg	−	(Plaza-Zabala et al. 2013)
Nicotine-primed reinstatement					
Kappa-opioid rec. blockade	nor-BNI	CPP	sc, acute, 10 mg/kg	−	(Jackson et al. 2013)
Stress-induced reinstatement					
CRF rec. blockade	D-Phe $CRF_{(12–41)}$	IVSA	icv, acute, 1–20 μg	+	(Zislis et al. 2007)
CRF1 rec. blockade	R278995/CRA0450	IVSA	icv, acute, 1–20 μg	+	(Bruijnzeel et al. 2009)
CRF1 rec. blockade	Antalarmin	IVSA	sc, acute, 30 mg/kg	+	(Plaza-Zabala et al. 2010)
MC4 rec blockade	HS014 and HS024	IVSA	icv, acute, 1–10 μg (HS014), 1 and 3 μg (HS024)	+	(Qi et al. 2015b)
Hypocretin 1 rec. blockade	SB334867	IVSA	ip, acute, 5 and 10 mg/kg	+	(Plaza-Zabala et al. 2010)
Kappa-opioid rec. stimulation	nor-BNI	CPP	sc, acute, 10 mg/kg	+	(Jackson et al. 2013)
CRF2 rec. blockade	Astressin-2B	IVSA	icv, acute, 1–20 μg	−	(Bruijnzeel et al. 2009)

The plus (+) signs indicate that the treatment diminished the rewarding effects of nicotine, withdrawal, and relapse. Minus (−) signs indicate that the treatment was ineffective. Abbreviations: BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; CPA, conditioned place aversion; CPP, conditioned place preference; EPM, elevated plus maze test; ICSS, intracranial self-stimulation; icv, intracerebroventricular; ip, intraperitoneal; IPN, interpeduncular nucleus; IVSA, intravenous self-administration; Nacc, nucleus accumbens; NIH, novelty-induced hypophagia; po, oral; rec, receptor; sc, subcutaneous.