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New mechanisms and perspectives in nicotine withdrawal

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Abstract

Diseases associated with tobacco use constitute a major health problem worldwide. Upon cessation of tobacco use, an unpleasant withdrawal syndrome occurs in dependent individuals. Avoidance of the negative state produced by nicotine withdrawal represents a motivational component that promotes continued tobacco use and relapse after smoking cessation. With the modest success rate of currently available smoking cessation therapies, understanding mechanisms involved in the nicotine withdrawal syndrome are crucial for developing successful treatments. Animal models provide a useful tool for examining neuroadaptative mechanisms and factors influencing nicotine withdrawal, including sex, age, and genetic factors. Such research has also identified an important role for nicotinic receptor subtypes in different aspects of the nicotine withdrawal syndrome (e.g., physical vs. affective signs). In addition to nicotinic receptors, the opioid and endocannabinoid systems, various signal transduction pathways, neurotransmitters, and neuropeptides have been implicated in the nicotine withdrawal syndrome. Animal studies have informed human studies of genetic variants and potential targets for smoking cessation therapies. Overall, the available literature indicates that the nicotine withdrawal syndrome is complex, and involves a range of neurobiological mechanisms. As research in nicotine withdrawal progresses, new pharmacological options for smokers attempting to quit can be identified, and treatments with fewer side effects that are better tailored to the unique characteristics of patients may become available.

Keywords

nicotine; nicotine withdrawal; nicotinic receptors; nicotine dependence; tobacco dependence

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1. Introduction

Tobacco dependence is the leading cause of preventable mortality in the United States. Maintenance of smoking behavior is largely due to nicotine, the main addictive component of tobacco (Stolerman and Jarvis 1995). Globally, smoking-related illnesses cause over four million deaths annually. Addiction to tobacco smoking depends not only on the positive reinforcing and hedonic actions of nicotine, but also on escape from the aversive consequences of nicotine withdrawal. Many studies suggest that avoidance of the negative emotional state produced by nicotine withdrawal represents a motivational component that promotes continued tobacco use and relapse after smoking cessation. The nicotine withdrawal syndrome is considered to be one of the major causes of high relapse rate in individuals undergoing smoking cessation (Le Foll and Goldberg 2009). Indeed, withdrawal duration and severity can accurately predict relapse in abstinent human smokers (Allen et al. 2008; Zhou et al. 2009). Among adult smokers, 80% report the desire to quit completely; however, those who attempt to quit on their own relapse within the first month and only 3% remain abstinent after 6 months (Hughes et al., 1992). While there are smoking cessation therapies available, which include nicotine replacement therapies, the anti-depressant bupropion (Zyban ®), and the partial nicotinic agonist varenicline (Chantix ®) (Cummings and Mahoney 2006; Jorenby et al. 2006), the success rate of these therapies after one year remains only about 20–25% (Gonzales et al. 2006). Indeed, severity of the withdrawal syndrome is a better predictor of unsuccessful smoking attempts than smoke intake or dependence (West et al. 1989).

Smoking cessation after chronic tobacco use produces a well characterized and defined withdrawal syndrome. The nicotine withdrawal syndrome in abstinent smokers is comprised of ‘physical’ or somatic components, cognitive, and ‘affective’ components. The somatic signs include bradycardia, gastrointestinal discomfort, and increased appetite. Affective symptoms primarily include depressed mood including anhedonia, dysphoria, anxiety, irritability, difficulty concentrating, and craving (Hughes 2007). Although the somatic manifestations of withdrawal from drugs of abuse are certainly unpleasant, escape from affective components of withdrawal play a more important role in the maintenance of dependence to drugs of abuse, including nicotine (Koob and Le Moal 2005; Koob and Volkow 2010). The negative affective symptoms can start as soon as 4 hours after the last cigarette, peak in about three days, and are still measurable a month after cessation of tobacco use (Swan et al. 1996; Ward et al. 2001; Hughes 2007).

Withdrawal effects are largely mediated through nicotinic acetylcholine receptors (nAChRs), which are the primary binding sites for nicotine, and the endogenous neurotransmitter acetylcholine. Neuronal nAChRs are cation-permeable, ligand gated homomeric or heteromeric complexes composed of α and β subunits. To date, twelve neuronal nAChR subunits have been identified, including α2-α10 and β2-β4, making it possible to have a large variety in subtype composition and a great range of pharmacological and physiological effects in response to nicotine. The main nAChR subtypes in the brain are the α7 and α4β2* subtypes (Changeux et al. 1998), where * denotes possible assembly with other nAChR subunits. Once activated, neuronal nAChRs can elevate intracellular calcium directly, via influx through the nAChR channel, indirectly, via Na^+ influx, subsequent

membrane depolarization, and activation of voltage-gated calcium channels, and through calcium-induced calcium release from intracellular stores (De Biasi and Dani, 2011). Presynaptic nAChRs facilitate calcium-dependent release of many neurotransmitters and activation of various downstream signaling cascades involved in gene transcription (Wonnacott 1997). The neuroadaptations that occur as a result of chronic nicotine exposure reflect nicotine's influence on neurotransmitter systems such as dopamine, glutamate, γ-aminobutyric acid (GABA) and serotonin (De Biasi and Salas 2008). Further, it has been proposed that the desensitization and upregulation of nAChRs following chronic nicotine exposure is influential in producing withdrawal symptoms upon cessation of smoking (Benwell et al. 1988; Dani and Heinemann 1996; Balfour and Fagerstrom 1996), and that maintained nAChR desensitization may be important for relieving nicotine withdrawal in humans (Brody et al. 2006).

2. Animal models of nicotine dependence

Animal models of nicotine withdrawal have been developed and are useful tools for elucidating mechanisms associated with nicotine withdrawal behaviors. These rodent models measure multiple signs of withdrawal; somatic signs, affective signs, and cognitive changes. The emergence of negative affective and cognitive symptoms and, to a lesser extent, the somatic manifestations of withdrawal, underlies nicotine-seeking behavior (Koob et al. 1993; Markou et al. 1998; De Biasi and Dani 2011). Mice and rats are rendered dependent on nicotine using various routes of exposure, including chronic infusion through osmotic mini pumps (Damaj et al. 2003; Malin et al. 2006), chronic injections (Liu et al. 2005; Miura et al. 2006), oral route via drinking water (Liu et al. 2005; Grabus et al. 2005a), or intravenous administration (Wilkinson and Bevins 2008). Withdrawal may be precipitated in nicotine-exposed animals with nicotinic antagonists, such as the non-selective nAChR antagonist mecamylamine, or evaluated spontaneously by the cessation of chronic nicotine treatment. Physical signs in rodents are typically measured as somatic signs (Malin et al. 1992; Hildebrand et al. 1997; Damaj et al. 2003), hyperalgesia (Salas et al. 2004; Grabus et al. 2005b), and changes in locomotor activity (Hildebrand et al. 1999; Nomikos et al. 1999), while affective signs are typically measured as anxiety-related behaviors (Damaj et al. 2003; Stoker et al. 2008), elevated reward thresholds through the intracranial self-stimulation procedure (ICSS) (Cryan et al. 2003; Bruijnzeel and Markou 2004; Johnson et al. 2008), and conditioned place aversion (CPA) (Suzuki et al. 1996; Malin et al. 2006; Jackson et al. 2009a). Smoking cessation is associated with disrupted cognition (Lerman et al. 2007), and in mouse models, hippocampus-dependent learning is particularly sensitive to the effects of nicotine withdrawal (Kenney and Gould 2008), including contextual fear conditioning (Davis et al. 2005). In addition, a nicotine withdrawal-potentiated acoustic startle procedure was developed to measure negative affective withdrawal behaviors after repeated nicotine exposure and withdrawal episodes (Engelmann et al. 2009). It was observed that intermittent exposure to nicotine results in escalating levels of withdrawal-potentiated startle response in rats (Engelmann et al. 2009). The relevance of the model is evident in that elevated startle response has been used to accurately assess opiate (Stine et al. 2001) and ethanol withdrawal (Krystal et al. 1997; Saladin et al. 2002) in humans. Further, this model allows for the assessment of altered anxiety levels to be detected at the earliest stages of addiction, and

thus may be a valid model to measure nicotine dependence in adolescent rodent models (Engelmann et al. 2009). These various aspects of nicotine withdrawal are likely to be mediated by different brain substrates that express multiple nAChRs subtypes. For example, studies have shown that somatic signs of nicotine withdrawal are mediated by both central and peripheral nAChRs, while affective signs are mediated solely through central nAChR populations such as nucleus accumbens (NAc), habenulo-interpeduncular system, amygdala, and hippocampus (Watkins et al. 2000; De Biasi and Dani 2011).

2.1. Withdrawal models using tobacco smoke

While the currently available animal models of nicotine exposure have provided a wealth of information on mechanisms of nicotine withdrawal, evidence suggests that tobacco constituents aside from nicotine may contribute to tobacco addiction (Fowler et al. 2003; Talhout et al. 2007), thus animal models that more closely mimic human tobacco use and smoke exposure are warranted. Recently, animal models allowing for assessment of the full spectrum of tobacco smoke constituents have been developed to examine nicotine dependence and withdrawal. Exposure to tobacco smoke for 4 h per day for 28 consecutive days induced a significant increase in brain reward threshold and significant nicotine withdrawal somatic signs in rats (Small et al. 2010), indicating that exposure to tobacco smoke constituents through inhalation is sufficient to produce both somatic and affective nicotine withdrawal. Additionally, a non-invasive chronic nicotine vapor exposure technique was developed in rats to produce consistent levels of nicotine in the blood relevant to both heavy smokers and second-hand smoke, and to mimic the intermittent nicotine exposure and most common route of nicotine administration in humans (George et al. 2010). Rats chronically and intermittently exposed to nicotine vapor expressed significant somatic withdrawal signs after mecamylamine treatment (George et al. 2010; Gilpin et al. 2012) implicating the reliability of such a model to measure nicotine withdrawal signs and provide new insight into neuroadaptive changes occurring from second-hand smoke exposure.

2.2. Influence of modalities of exposure, sex, age, and genetic factors

Rodent models provide a vital tool for examining mechanisms related to sex, age, and genetic differences in response to nicotine withdrawal. In a study by Hamilton et al. (2009), which assessed sex differences in nicotine withdrawal, somatic signs were measured in male and female rats in two distinct environments, a brightly lit and a dimly lit environment. While females exhibited similar levels of somatic signs in both environments, in male rats, somatic withdrawal signs were more severe in the brightly lit environment than the dimly lit environment, suggesting that environmental factors more strongly affect behavioral symptoms of withdrawal in males than females. Because rodents are nocturnal, and exposure to bright light can be considered a stressor for rats, this study may reflect differences in coping mechanisms related to nicotine withdrawal in males and females. Similarly, the stress hormones, adrenocorticotropin hormone and corticosterone, were significantly reduced in male and female rats that received environmental enrichments in the home cage (Skwara et al. 2012). The stress hormones were reduced to a greater extent in females than males, suggesting that females were more sensitive to the anxiolytic effects of the environmental enrichment compared to males (Skwara et al. 2012). These studies emphasize the importance of environmental factors and their differences in the impact on

anxiety levels in males and females with regards to nicotine withdrawal severity. Sex differences in nicotine withdrawal are also evident in adolescent rats, where, compared to male adolescents, female adolescents did not exhibit significant somatic nicotine withdrawal signs after cessation of nicotine treatment (Hamilton et al. 2010). Such information is valuable when considering the best behavioral measures to treat tobacco cessation in adult and adolescent males and females.

In addition to sex differences, studies evaluating age differences in nicotine withdrawal largely indicate diminished physical, affective, or cognitive nicotine withdrawal signs in adolescent rodents compared to adults (O'Dell et al. 2006; Wilmouth and Spear 2006; O'Dell et al. 2007; Kota et al. 2007; Shram et al. 2008; Jackson et al. 2009a; Portugal et al. 2012b); however, studies have also reported enhanced nicotine withdrawal-induced cognitive impairment in adolescent rodents compared to adults (Wilmouth and Spear 2006), or no difference in affective withdrawal measures (e.g., elevated plus maze, CPA) between adults and adolescents (Kota et al. 2008). The differences in findings (i.e., diminished effects, enhanced effect, or no effect) between adult and adolescent nicotine withdrawal studies reflect the importance of additional factors that can impact withdrawal behaviors, including sex (Kota et al. 2008), the withdrawal measure being assessed (Wilmouth and Spear 2006; Kota et al. 2008), and whether the model uses spontaneous or precipitated withdrawal (Shram et al. 2008). In addition, the modality of nicotine administration preceding withdrawal was found to impact the type of withdrawal signs after cessation of the drug. For example, earlier studies showed while somatic signs were observed in rats with short access to nicotine i.v. self-administration, anxiety-like behaviors and hyperalgesia were not (Irvine et al., 2001; O'Dell et al., 2007; Cohen et al., 2013). However, when rats were given long access (>21 hours/day) to nicotine self-administration, increase in anxiety-like behavior, nociceptive thresholds, somatic signs of withdrawal were observed after 3 days of abstinence (Cohen et al., 2013).

Previous studies also reported enhanced nicotine withdrawal-induced cognitive impairment in adolescent rodents compared to adults (Wilmouth and Spear 2006), or no difference between adults and adolescents (Kota et al. 2008; Shram et al. 2008). Studies exploring the neurochemical mechanisms that contribute to age differences in withdrawal response suggest increased nAChR functionality in adolescents compared to adults (Kota et al. 2007), alterations in kappa opioid receptor (KOR) regulation of mesolimbic dopamine transmission (Tejeda et al. 2012) and adolescent resistance to withdrawal-related neurochemical processes that inhibit mesolimbic dopamine function in adults experiencing nicotine withdrawal (Natividad et al. 2010; Natividad et al. 2012) as possible contributing factors. Understanding differences underlying nicotine withdrawal mechanisms between adults and adolescents will increase effectiveness of tobacco cessation therapies across different age groups.

Genetic factors also play a significant role in nicotine addiction and withdrawal response Portugal and Gould 2008; Portugal et al. 2012a), as will be discussed in detail later in this review. Using spontaneous and antagonist-precipitated mouse models of nicotine withdrawal, strain differences in the magnitude of withdrawal signs (Damaj et al. 2003; Hamilton et al. 2010) and in the manifestation of physical vs. affective withdrawal signs

(Jackson et al. 2009c) have been identified in adult and adolescent rodents. Recently, it was observed that various mouse strains exhibited differential responses to nicotine withdrawal induced deficits in contextual conditioning, indicating the importance of genetic variability in response to nicotine withdrawal induced cognitive impairment (Portugal et al. 2012a; Wilkinson et al. 2013). The duration of chronic nicotine induced upregulation of high-affinity nAChRs in the hippocampus mediates, in part, the cognitive impairment observed during nicotine withdrawal (Gould et al. 2012), and genetic background was found to play a significant role in chronic nicotine induced nAChR upregulation, particularly in the dorsal hippocampus (Wilkinson et al. 2013). Additionally, recent studies using the BXD strain, a recombinant inbred strain of the C57BL/6 and DBA/2 strains, revealed that manifestation of nicotine withdrawal somatic signs is driven by multiple genes of modest effect size (Jackson et al. 2011).

3. Recent advances in mechanisms of nicotine withdrawal: Findings from animal studies

3.1. Role of nicotinic transmission

While early studies with non-selective nicotinic antagonists suggested that multiple nAChRs regulate expression of nicotine dependence, recent findings in nAChR knockout (−/−) mice have provided insight into the specific nAChR subtypes that regulate affective and somatic aspects of nicotine withdrawal. Neuronal nAChRs play a differential role in physical and affective nicotine withdrawal signs. Previously, β2 (Jackson et al. 2008; Jackson et al. 2009a) and α6 (Jackson et al. 2009b) nAChRs have been implicated in affective nicotine withdrawal measures, while α7, α3(Jackson et al. 2013), α5 (Jackson et al. 2008; Salas et al. 2009), β4 (Salas et al. 2004; Stoker et al. 2012b; Jackson et al. 2013), and α2 (Salas et al. 2009; Lotfipour et al. 2013) nAChRs are involved in physical nicotine withdrawal signs. Although the α3, α5, and β4 nAChR subunits, which can co-assemble to form functional receptors, have all been implicated in physical nicotine withdrawal, recent studies suggest that the α3β4* nAChR subtype can mediate withdrawal-induced somatic signs independently of the α5 subunit (Jackson et al. 2013).

Studies implicating specific nAChR subtypes and brain regions involved in nicotine withdrawal behaviors have also begun to develop. Emerging evidence demonstrates a major role for the habenulo-interpeduncular system, composed of the medial habenula (MHb) and the interpeduncular nucleus (IPN), and the nAChRs expressed therein, in the manifestation of somatic nicotine withdrawal symptoms (Salas et al. 2009; Baldwin et al. 2011). Specifically, microinjection of mecamylamine into the habenula and IPN, but not the cortex, VTA, or hippocampus, precipitated somatic nicotine withdrawal signs in mice (Salas et al. 2009).

More recently, studies show that the pacemaking activity of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in the MHb is altered during nicotine withdrawal (Gorlich et al. 2013). Specifically, spontaneous action potential frequency was potentiated upon reexposure to nicotine in MHb neurons from nicotine withdrawn mice compared to saccharin withdrawn mice. This increase in pacemaking activity was blocked my

mecamylamine, indicating an effect mediated via nAChRs. Of interest, inhibition of HCN channels in the MHb precipitated somatic withdrawal signs and anxiety-like behavior in nicotine naïve mice, which suggests a role for behavioral mechanisms mediated independently of nicotine (Gorlich et al. 2013). Alternatively, a recent study by Shih et al. (2014) examined functional properties of the lateral and central parts of the MHb and found that the lateral MHb (MHbVL) neurons were more excitable to nicotine than central MHb neurons. In contrast to Gorlich et al. (2013), activity of MHbVL neurons from nicotine withdrawn mice was reduced upon reexposure to nicotine compared to MHbVL neurons from saline withdrawn mice. Despite this discrepancy between studies, which is likely attributed to examining the entire MHb versus specific MHb regions, an important role for nAChRs in the MHb is evident.

The hippocampus has also been identified as a brain region involved in nicotine withdrawal mechanisms related to cognitive effects. Galantamine, an acetylcholinesterase inhibitor and positive allosteric modulator of nAChRs, reversed the nicotine withdrawal deficits in contextual fear conditioning in mice, possibly through enhanced levels of acetylcholine via acetylcholinesterase inhibition and/or actions at hippocampal α4β2* nAChRs (Wilkinson and Gould 2011), supporting a role for hippocampal α4β2* nAChR-mediated responses in nicotine withdrawal induced cognitive deficits.

Systemic (Markou and Paterson 2001; Harrison et al. 2002) or intra-VTA (Bruijnzeel and Markou 2004) administration of the β2* selective nAChR antagonist DHβE precipitated withdrawal-associated elevations of ICSS thresholds in nicotine-dependent rats. Therefore, these data provide pharmacological support of a role of α4* and β2* nAChR subtypes, particularly those located in the VTA, in regulating the development of nicotine dependence and the expression of nicotine withdrawal induced anhedonia. Interestingly, a recent study that assessed the role of β4 and α7 nAChRs in the anhedonic aspects of nicotine withdrawal in mice found that the onset of the anhedonic aspects of the ICSS procedure was delayed in β4 and α7 nAChR −/− mice, suggesting that blockade of either nAChR subunit may alleviate anhedonic aspects of the early nicotine withdrawal syndrome (Bauzo and Bruijnzeel 2012; Stoker et al. 2012b). This is the first study to implicate α7 and β4 nAChRs in affective nicotine withdrawal behaviors. Overall, these studies reinforce the notion that different aspects of the nicotine withdrawalsyndrome are mediated by different nAChR subtypes in different brain regions.

3.1.1. Bupropion and its metabolites—Bupropion, a dopamine reuptake inhibitor (Cooper et al. 1994) and non-competitive nAChR antagonist (Fryer and Lukas 1999; Slemmer et al. 2000; Damaj et al. 2004), is an approved pharmacotherapy (Zyban®) for nicotine dependence in humans. In contrast to rats, humans and mice metabolize bupropion through the CYP2B6 enzyme to hydroxybupropion, a compound with longer half-life than the parent drug, and substantial activity on neuronal transporters and nAChRs (Cooper et al. 1984; Damaj et al. 2004). Recently, studies in mice showed that, similar to bupropion, enantiomers of hydroxybupropion, (2R,3R) and (2S,3S)-hydroxybupropion, reverse affective and somatic nicotine withdrawal signs, with (2S,3S)-hydroxybupropion having higher potency (Damaj et al. 2010) . Thus, actions of bupropion, its metabolites, or a combination of both, likely contribute to the pharmacotherapeutic effect of bupropion in

smoking cessation. Interestingly, hydroxybupropion seems to contribute to the pharmacologic effects of bupropion for smoking cessation, and the variability in response to bupropion treatment is related to variability in CYP2B6-mediated hydroxybupropion formation in humans (Zhu et al. 2012).

3.2. Calcium-dependent mechanisms

Recent studies have begun to shed light on the importance of calcium-dependent mechanisms in nicotine dependence and withdrawal. In mice, L-type calcium channel blockers attenuated physical (somatic signs, hyperalgesia), but not affective (CPA, anxiety-like response) nicotine withdrawal signs, implicating L-type calcium channels in physical nicotine dependence (Jackson and Damaj 2009). More recently, other investigators showed that L-type calcium channels attenuated expression of CPA in rats, suggesting involvement of L-type calcium channels in this affective nicotine withdrawal measure (Budzynska et al. 2012) in a species-specific fashion.

Additionally, biochemical studies revealed that CaMKII total and phosphorylated protein levels, as well as total and phosphorylated protein levels of the vesicle associated protein essential for neurotransmitter release, synapsin I, were increased in the NAc after chronic nicotine treatment, but decreased after precipitated and spontaneous nicotine withdrawal (Jackson and Damaj 2013). Behaviorally, CaMKII antagonists attenuated somatic withdrawal signs, but enhanced affective nicotine withdrawal signs, suggesting opposing roles for CaMKII in affective vs. somatic nicotine withdrawal behaviors (Jackson and Damaj 2009). Similarly, studies with the less abundant kinase, CaMKIV, reveal that affective, but not physical measures are attenuated in CaMKIV −/− mice (Jackson et al. 2012).

It is possible that CaMKII heterozygote mice, which possess 50% of the enzyme activity, do not have sufficient loss of enzyme activity to induce expression of the altered nicotine withdrawal responses observed with the antagonist. Further, because CaMKII antagonists have been shown to block both CaMKII and CaMKIV activity (Hook and Means 2001), it is possible that the effects produced by the antagonist reflect blockade of both kinases. Although the exact role of calcium signaling mechanisms appears complicated, the current evidence supports the relevance of these mechanisms in behavioral and biochemical nicotine withdrawal responses.

3.3. Classical neurotransmitters: GABA, Glutamate, Dopamine, and Serotonin

Activation of nAChRs promotes the release of various neurotransmitters in the brain, including GABA, glutamate, and dopamine.

3.3.1. Role of the GABAergic system in nicotine withdrawal—Recently, GABA, the primary inhibitory neurotransmitter in the CNS, was found to mediate both affective and somatic nicotine withdrawal signs. Mecamylamine-precipitated somatic nicotine withdrawal signs were attenuated in $GABA_B$ −/− mice (Varani et al. 2012). Additionally, the reduction in c-Fos positive nuclei in the bed nucleus of the stria terminalis, basolateral amygdaloid nucleus, and the hippocampal dentate gyrus observed in $GABA_B$ +/+ mice after precipitated

nicotine withdrawal, was absent in $GABA_B$ −/− mice, an effect that may be related to the attenuated somatic signs (Varani et al. 2012). In a similar study, the $GABA_B$ receptor agonist, baclofen, blocked somatic nicotine withdrawal signs in mice and restored nicotine withdrawal induced reductions in dopamine and dihydroxyphenyl acetic acid concentration in the prefrontal cortex, and dopamine and serotonin in the striatum (Varani et al. 2011). Conversely, treatment with a $GABA_B$ receptor agonist, antagonist or positive allosteric modulator exacerbated the anhedonic aspect of nicotine withdrawal by elevating the ICSS threshold after nicotine withdrawal in rats (Vlachou et al. 2011). These findings may reflect differential involvement of $GABA_B$ receptors in physical and affective nicotine withdrawal behaviors. Further, effects of the compounds used in the Vlachou et al. (2011) study are not selective for specific $GABA_B$ receptor isoforms (i.e., GABAS vs. $GABA_{B2}$) and do not differentiate between pre- and postsynaptic $GABA_B$ receptors; thus, the observations in the latter study could be a manifestation of the effects from differential binding to $GABA_B$ receptors. Inconsistencies resulting from species differences are also a possibility. Zhao-Shea et al. (2013) showed that induction of physical nicotine withdrawal symptoms activates GABAergic neurons within the IPN.

3.3.2. Role of the glutamatergic system in nicotine withdrawal—The excitatory neurotransmitter glutamate plays an important role in modulating positive reinforcing responses to drugs of abuse (Harris and Aston-Jones 2003), and has been implicated in the negative reinforcing responses mediating nicotine withdrawal. Excessive activation of glutamatergic circuits from drug administration induces neuroadaptations aimed to prevent overactivation of the system, a phenomenon thought to underlie the negative affective state experienced when the drug is removed (Markou et al. 1998; Koob and Le Moal 2008). Indeed, the anhedonic component of nicotine withdrawal was reduced in nicotine dependent metabotropic glutamate receptor 5 (mGluR5) −/− mice and mecamylamine attenuated rather than precipitate somatic nicotine withdrawal signs in nicotine dependent mice (Stoker et al. 2012a). It was hypothesized that mGluR5 −/− mice do not develop neuroadaptations in the excitatory circuits, and thus develop a less severe negative state of nicotine withdrawal (Stoker et al. 2012a) .

3.3.3. Role of dopamine transmission in nicotine withdrawal—Similar to GABA and glutamate, dopamine, which plays a major role in rewarding responses to addictive drugs in the brain, also modulates affective and somatic nicotine withdrawal. Withdrawal from nicotine decreases basal dopamine levels in the rat NAc (Takahashi et al. 1998; Rahman et al. 2004) (Hildebrand et al. 1998; Rada et al. 2001) and monkey striatum (Domino and Tsukada 2009), and induces a hypofunctional dopamine state, which is reflected in decreased brain reward function (Epping-Jordan et al. 1998). Using microdialysis and fast-scan cyclic voltammetry,Zhang et al. (2012) recently showed that upon withdrawal from chronic nicotine exposure in drinking water, the basal dopamine concentration and tonic and phasic dopamine release in the NAc decreased. This decrease in dopamine transmission was accompanied by a decrease in β2 nAChRs, which was reversed by an acute nicotine treatment. The length of time that the low basal dopamine state lasted depended on the length of the chronic nicotine treatment. Coinciding with these findings, administration of the dopamine precursor, L-DOPA, attenuates somatic signs and reverses

nicotine withdrawal depressive-like behaviors in the forced swim test, potentially by counteracting the decrease in DA levels associated with withdrawal (Ohmura et al. 2011a).

3.3.4. Role of the serotoninergic system in nicotine withdrawal—Serotonin (5-hydroxytryptamine; 5-HT) is associated with appetitive behavior and affective state, and previous studies support a role for 5-HT activation in aspects of the nicotine withdrawal syndrome, including CPA (Suzuki et al. 1997) and anxiety-like responses (West et al. 1991; Hilleman et al. 1992; Hilleman et al. 1994). More recently, 5-HT_{2C} receptor agonists and a 5-HT_{2A} antagonist were shown to block nicotine withdrawal-induced increases in immobility in rats subjected to the forced swim test, implicating the serotonergic system in the depressive-like effects of nicotine withdrawal (Zaniewska et al. 2010). 5-HT_{1A} receptor expression was also significantly decreased in the mouse diencephalon for up to 30 days after nicotine withdrawal, and this reduction may be associated with nicotine withdrawal-induced depressive-like behaviors (Mannucci et al. 2011). Additionally, the serotonin precursor, 5-hydroxytryptophan, attenuated somatic signs of nicotine withdrawal in rats (Ohmura et al. 2011b) . Thus, as observed with GABA, glutamate, and dopamine, the serotonergic system mediates both affective and somatic nicotine withdrawal. Overall, these studies implicate the relevance of nicotine-induced activation of neurotransmitter systems in modulating multiple aspects of the nicotine withdrawal syndrome.

3.4. Role of peptidergic transmission

3.4.1. Galanin—The neuropeptide galanin is widely expressed in the CNS and is involved in modulation of food and alcohol intake, cognition, depression, and anxiety disorders (Holmes et al. 2003; Leibowitz 2005; Rustay et al. 2005). Studies implicate involvement of galanin and galanin receptors in mechanisms of nicotine withdrawal. Indeed, galanin receptors are expressed in brain areas implicated in drug dependence, including ventral midbrain (including the VTA), NAc, and locus coeruleus (LC) (Mennicken et al. 2002), and galanin modulates the mesolimbic dopamine system by inhibiting dopaminergic transmission (Tsuda et al. 1998; Ericson and Ahlenius 1999). The non-selective galanin receptor agonist, galnon, reverses mecamylamine-precipitated physical signs of nicotine withdrawal (Jackson et al. 2011). Further, expression of somatic nicotine withdrawal signs is correlated with galanin expression in the ventral midbrain and galanin receptor 1 expression in the NAc (Jackson et al. 2011). More recently, immunohistochemistry studies showed that galaninergic immunoreactivity is increased after nicotine withdrawal in the dorsal raphe nucleus subregions, and in the LC (Okere and Waterhouse 2013), further indicating the importance of galanin signaling in nicotine withdrawal.

3.4.2. Corticotropin Releasing Factor (CRF), src kinase, G protein-coupled receptor (GPCR) kinase 5—In recent years, a role for CRF, the principal neuropeptide involved in regulating stress response, in nicotine withdrawal has emerged. Antagonism of CRF prevented the nicotine withdrawal-induced elevations in reward threshold in rats using the ICSS procedure, supporting the hypothesis that hyperactivity of brain CRF contributes to the negative affective manifestations of nicotine withdrawal (Bruijnzeel et al. 2007). Specifically, these effects may be mediated by CRF1 receptors, as blockade of CRF1, but not CRF2 receptors, prevented nicotine withdrawal induced deficits in brain reward

threshold in rats (Bruijnzeel et al. 2009). Additionally, blockade of CRF receptors in the NAc shell and central nucleus of the amygdala (CeA), but not the lateral bed nucleus of the stria terminalis, inhibited elevations in brain reward threshold in nicotine withdrawn rats, implicating that increased release of CRF in the NAc shell and CeA, specifically, partly mediates the negative emotional state associated with nicotine withdrawal (Marcinkiewcz et al. 2009). In support of this hypothesis, CRF levels were increased in the CeA in nicotine dependent rats following mecamylamine precipitated withdrawal (George et al. 2007). Similarly, CRF1 receptors in the CeA mediate the anhedonia associated with nicotine withdrawal, as intra-CeA administration of CRF1 receptor antagonists blocked elevations in reward threshold in rats (Bruijnzeel et al. 2012). In another assessment of nicotine withdrawal affective symptoms, increased CRF release and CRF1 receptor activity in the CeA were found to mediate anxiety-like behavior during precipitated withdrawal in nicotine dependent rats (George et al. 2007). Further, nicotine abstinence increased nicotine intake in rats in the self-administration test, an effect that was blocked by pretreatment with a CRF1 receptor antagonist (George et al. 2007). Overall, these studies indicate that increased CRF release and subsequent stimulation of CRF1 receptors in the NAc shell and CeA regulate, in part, the negative affective component of nicotine withdrawal.

Recently, a mechanistic link between the CRF system and activation of the cell signaling molecule, src kinase, was reported (Yuan et al. 2010). Administration of a selective src kinase inhibitor attenuated mecamylamine-precipitated nicotine withdrawal somatic signs and anxiety-like response in mice (Rehni et al. 2012), supporting a role for src kinase activation in physical and affective nicotine withdrawal behaviors. The potential link between src kinase and CRF activation, and their similar roles in nicotine withdrawal behaviors, suggests that src kinase activation may be linked to overactivation of the CRF system after nicotine withdrawal.

Furthermore, increased actvation of CRF receptors, which are GPCRs, leads to phosphorylation of the G protein Gαs subunit by GPCR kinases (GRKs). GRKs regulate CRF receptor signal transduction cascades (Teli et al. 2005; Hauger et al. 2009), thus promoting uncoupling of CRF from its receptor system, an effect that has been proposed to mediate the progression of aspects of the nicotine withdrawal syndrome (Dautzenberg et al. 2001; Teli et al. 2005; Hauger et al. 2009). Because of the role of CRF in nicotine withdrawal, and the ability of GRKs to mediate CRF signaling, a recent study examined the role of GRK 5 in nicotine withdrawal, as this particular kinase is highly expressed in brain regions shown to mediate the nicotine withdrawal syndrome, including the MHb and LC (Erdtmann-Vourliotis et al. 2001; Balfour 2004), and regulates GPCR-mediated regulation of nAChR signaling (Liu et al. 2000; Bibevski et al. 2000). As proposed, blockade of GRK 5 in mice attenuated physical nicotine withdrawal signs, measured as somatic signs and hyperalgesia response, and affective signs measured as anxiety-related response, implicating GRK 5 in both physical and affective nicotine withdrawal responses (Singh et al. 2013).

Taken together, these studies reveal a significant role and an interesting link between CRF, associated signaling molecules, and the physical and affective aspects of the nicotine withdrawal syndrome.

3.4.3. Orexin/hypocretin—Orexins, also known as hypocretins, are lateral hypothalamic neuropeptides that regulate feeding behavior, sleep, and wakefulness (Sakurai et al. 1998; Sakurai 2007). Recent evidence supports a role for hypocretin signaling in drug reward, addiction, and relapse (Aston-Jones et al. 2010; Plaza-Zabala et al. 2012b). While hypocretin signaling has been shown to regulate aspects of nicotine addiction, including nicotine reward and self-administration (Hollander et al. 2008; LeSage et al. 2010), acute nicotine anxiogenic-like response (Plaza-Zabala et al. 2010), and relapse to nicotine-seeking behavior (Plaza-Zabala et al. 2010; Plaza-Zabala et al. 2013), a recent study by Plaza-Zabala and colleagues (2012a) is among the first to examine the role of hypocretin signaling in somatic nicotine withdrawal. In preprohypocretin −/− mice, which do not produce hypocretin-1 or hypocretin-2 peptides, somatic nicotine withdrawal signs were significantly reduced following mecamylamine administration in nicotine-dependent mice. Similar results were observed in mice after treatment with a hypocretin-1 antagonist, but not a hypocretin-2 antagonist, indicating that the attenuation of withdrawal signs is specifically through a hypocretin-1 mechanism (Plaza-Zabala et al. 2012a). Additionally, mecamylamine led to the activation of neurons in the paraventricular nucleus of the hypothalamus (PVN), an effect that was absent in preprohypocretin −/− mice and blocked by hypocretin-1 antagonism, while intra-PVN injections of the hypocretin-1 antagonist decreased expression of somatic, mecamylamine-precipitated nicotine withdrawal signs in mice. Finally, increased hypocretin neuron activation in the perifornical area and dorsomedial hypothalamus (PFA/DMH), a brain region with a high proportion of hypocretin cells projecting to the PVN, was observed following precipitated nicotine withdrawal, and was blocked by hypocretin-1 receptor inhibition (Plaza-Zabala et al. 2012a). Overall, this study implicates a mechanism involving hypocretin and hypocretin-1 receptor activity in the PVN and PFA/DMH in the manifestation of somatic nicotine withdrawal signs. The role of this system in affective nicotine withdrawal behaviors has not been explored to date.

3.4.4. Neurokinins—Neurokinins (NK) are a group of peptides that includes substance P (SP), NKA, and NKB. Their effects are mediated by the GPCRs NK1, NK2, and NK3, respectively, and they act in the nervous system as neurotransmitters and neuromodulators (Pennefather et al. 2004). The peptides have been long known to participate in pain transduction, inflammation, smooth muscle contraction, vasodilation, gland secretion, and activation of the immune system (Kramer et al. 1998; Quartara and Maggi 1998; Severini et al. 2002), but more recently, they have been shown to influence affective and behavioral responses to stress and stress-related pathologies, including anxiety and depression (Ebner and Singewald 2006).

Substance P, NKB, and their respective receptors are expressed in the MHb, a brain area with major influence on the mechanisms underlying the somatic manifestations of nicotine abstinence (Lein et al. 2007; Salas et al. 2009). Using patch clamp electrophysiology in mouse brain slices, it was shown that nicotine increases intrinsic excitability in MHb neurons and that this phenomenon requires α5-containing nAChRs and depends on intact neurokinin signaling (Dao et al. 2014). In addition, microinjection of NK receptor antagonists into the MHb - but not the LHb-was sufficient to precipitate withdrawal behavior in chronic nicotine-treated mice. Therefore, this work implicates neurokinin

peptides as one of the neuromodulatory signal systems through which nicotine acts to influence intrinsic excitability and produce neuroadaptations that lead to the emergence of nicotine withdrawal behavior.

3.4.5. Brain-derived neurotrophic factor (BDNF)—BDNF signaling in the adult brain is involved in regulation of neuronal survival and behavior-related plasticity, and its synthesis and release are initiated by activation of glutamate receptors (Lipsky and Marini 2007). Earlier studies show that BNDF expression is increased in the rat hippocampus in response to chronic nicotine (Kenny et al. 2000), and the gene has been implicated in tobacco smoking behaviors in human genetic association studies (Beuten et al. 2005; Lang et al. 2007; Li et al. 2008). In a recent study by (Kivinummi et al. 2011), alterations in BDNF levels were analyzed in the mouse NAc, VTA, and substantia nigra (SN) following chronic oral nicotine treatment and withdrawal. While chronic nicotine did not alter BDNF levels in any brain region, BDNF levels were significantly increased in all brain regions examined for up to 29 days following nicotine withdrawal (Kivinummi et al. 2011). These studies support a biochemical role for brain BDNF signaling after nicotine withdrawal, and indicate that nicotine's effects on BNDF signaling may differ depending on the brain region. To date, the role of BDNF in nicotine withdrawal behaviors has not been examined, thus the behavioral relevance of these nicotine-induced alterations in neuronal BDNF level is unknown.

3.5. Opioid system

A growing number of studies suggest a role for the endogenous opioid system in mediating nicotine withdrawal in both humans and animals. The opioid receptor system consists of its endogenous peptides derived from three precursors; proopiomelanocortin (POMC), proenkephalin (PENK) and prodynorphin (PDYN) (Xue and Domino 2008). These precursors generate several peptides including β-endorphin, met- and leu-enkephalins, and dynorphins, which have varied affinities for the Gi/Go coupled opioid receptors. β–endorphin is the main peptide for mu-opioid receptors (MORs), enkephalins are the main peptide for delta-opioid receptors (DORs), and dynorphins are the main substrate for KORs (Roth-Deri et al. 2008). Early studies in humans and rodents suggest an alteration in the endogenous opiate system after smoking and nicotine withdrawal. Naloxone, a non-selective opioid antagonist, precipitated somatic and affective signs of withdrawal in a small group of smokers in a laboratory setting (Sutherland et al., 1995; Krishnan-Sarin et al., 1999), as well as in nicotine tolerant mice (Biala et al. 2005) and rats (Malin et al. 1993). In contrast, morphine was able to attenuate spontaneous and mecamylamine-induced nicotine withdrawal in rats (Malin et al. 1993; Ise et al. 2000). More recently, several studies using mice null for the various opiates receptors and their endogenous opiates investigated the role of individual opiate receptors in nicotine withdrawal. Nicotine physical dependence was reduced in both MOR and PENK (−/−) mice (Berrendero et al. 2002), suggesting an active involvement of MOR-dependent signaling in nicotine withdrawal. In contrast, the severity of nicotine physical withdrawal was not altered in β-endorphin and DOR (−/−) mice compared to the wild-type (+/+) counterparts (Galeote et al. 2009; Trigo et al. 2009; Berrendero et al. 2012). Interestingly, activation of DORs by the selective agonist TAN-67, was able to block nicotine withdrawal-induced CPA (Ise et al. 2000). Finally, several recent studies implicate

a role for KORs in nicotine withdrawal. For example, dynorphin and PDYN peptide levels were shown to increase during nicotine withdrawal in various brain regions and at different time points (Mathieu et al. 1996; Mathieu-Kia and Besson 1998). Furthermore, recent reports show that JDTIC and norBNI, selective KOR antagonists, decreased the expression of both physical (somatic signs and hyperalgesia) and affective (anxiety-related behavior and CPA) nicotine withdrawal signs (Jackson et al. 2010).

3.6. Endocannabinoid system

Recent studies indicate that cannabinoids have a role in alleviating the somatic and affective signs of nicotine withdrawal. The endocannabinoid system (EC) consists of the endogenous cannabinoids N-arachidonoylethanolamine (anandamide; AEA)(Devane et al. 1992) and 2-arachidonylglycerol (2-AG) (Mechoulam et al. 1995; Sugiura et al. 1995), which are synthesized “on demand” and act as retrograde messengers which are tightly regulated by their degradative enzymes, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively (Cravatt et al. 1996; Dinh et al. 2002). Both AEA and 2-AG primarily bind to Gprotein-coupled cannabinoid receptors (CB1 and CB2) (Matsuda et al. 1990; Munro et al. 1993). CB1 receptors are located in both the central and peripheral nervous systems whereas CB2 receptors are found in immune cells and microglia and brainstem neurons (Cabral and Marciano-Cabral 2005; Van Sickle et al. 2005). Recently, delta-9-tetrahydrocannabinol (THC), the primary active constituent of marijuana, was reported to decrease somatic signs and block CPA after withdrawal from chronic nicotine (Balerio et al. 2004). However, severity of physical nicotine withdrawal signs was not altered in CB1 −/− mice compared to wild-type animals or after pretreatment with rimonabant, a CB1 antagonist, in mice (Castane et al. 2002; Balerio et al. 2004; Merritt et al. 2008a). In addition, it was recently reported that genetic deletion of CB2 receptors does not alter the expression of anxiogenic-like withdrawal responses in the elevated plus maze, as CB2 −/− mice exhibited a similar magnitude of total somatic withdrawal signs to their control counterparts (Ignatowska-Jankowska et al. 2013). However,Navarrete et al. (2013) recently demonstrated a significant decrease in nicotine somatic withdrawal signs in CB2 −/− mice generated on CD-1 outbred genetic background. This discrepancy found in Navarrete et al. (2013) is likely due to differences in genetic background since previous results were obtained in CB2 −/− mice with a C57BL/6 genetic background (Ignatowska-Jankowska et al. 2013). Indeed, CB2 −/− generated on the same background did not display a different nicotine withdrawal phenotype compared to wild-type mice (Rafael Maldonado, personal communication). Such findings further emphasize the significant influence of genetics on nicotine withdrawal behaviors.

Recently, pharmacological and genetic approaches have been developed to prolong the availability of AEA and 2-AG by inhibiting their metabolic enzymes FAAH and MAGL, respectively. These inhibitors might have therapeutic utility without the undesirable side effects of direct CB1 agonists, such as THC (Cravatt et al. 1996; Solinas et al. 2007; Ahn et al. 2008; Long et al. 2009a; Long et al. 2009b). Two recent studies in rodents described the impact of FAAH inhibition on nicotine withdrawal. The first explored effects of URB597, a relatively selective FAAH inhibitor, on nicotine withdrawal in mice. While a high dose of URB597 (10mg/kg) significantly enhanced spontaneous nicotine somatic withdrawal signs,

it failed to alter nicotine-induced CPA in nicotine-dependent mice (Merritt et al. 2008a). Furthermore, FAAH −/− mice exhibited significantly worse somatic nicotine withdrawal signs and nicotine withdrawal-induced CPA compared to FAAH +/+ mice (Merritt et al. 2008b). In the second, more recent study, the effect of URB597 on nicotine withdrawal was reported in rats implanted with transdermal nicotine patches. Rats rendered dependent on nicotine showed spontaneous nicotine somatic and anxiety-like induced withdrawal signs as measured at 16 and 36 hours, respectively (Cippitelli et al. 2011). URB597 at 0.1 and 0.3 mg/kg reduced withdrawal-induced anxiety as assessed by the elevated plus maze test and the shock-probe defensive burying paradigm, but did not prevent the occurrence of somatic signs. The discrepancy between these two studies could suggest possible species differences in the regulation of nicotine withdrawal mechanisms by FAAH inhibition between rats and mice (Muldoon et al. 2013). Furthermore, it is possible that increased AEA levels resulting from FAAH inhibition by URB597 modulated nicotine withdrawal-induced behaviors by acting on non-CB targets, such as TRPV1 and nAChRs. Indeed, AEA can directly inhibit the function of expressed (Oz et al. 2003; Spivak et al. 2007) and native (Butt et al. 2008) nAChRs in a CB1 receptor independent manner.

4. Recent advances in mechanisms of nicotine withdrawal: Human genetic and clinical studies

The 15q25 nAChR gene cluster contains the CHRNA5-CHRNA3-CHRNB4 genes, which encode for the α5, α3, and β4 nAChR subunits, respectively. While several studies identify associations with the gene cluster in multiple aspects of nicotine addiction (Thorgeirsson et al. 2008; Bierut et al. 2008; Baker et al. 2009; Chen et al. 2009; Caporaso et al. 2009) and smoking related disease (Thorgeirsson et al. 2008; Amos et al. 2008; Hung et al. 2008; Wang et al. 2009; Falvella et al. 2009), fewer studies have examined the influence of this gene cluster in smoking cessation, with contradictory findings. Sarginson et al. (2011) identified variants in the gene cluster associated with higher craving after quitting, increased withdrawal symptoms, and sustained abstinence from smoking after treatment. More recent studies support these findings, identifying variants and haplotypes in the 15q25 gene cluster associated with response to pharmacological smoking cessation therapies (Chen et al. 2012; King et al. 2012), as well as a weak association with short-term smoking cessation independent of treatment (Munafo et al. 2011). Conversely, studies also found no variants in the 15q25 gene cluster associated with smoking cessation or abstinence (De Ruyck et al. 2010; Bousman et al. 2012). Differences in these findings may be attributed to differences in how smoking cessation is defined between studies, sample size, differences in study population characteristics, and evaluation of different variants and regions of the 15q25 gene cluster. While studies support a role for 15q25 in smoking cessation, further studies are necessary to identify genetic mechanisms for tailored pharmacotherapies.

Studies have also examined variants in signaling and neurotransmitter genes that may influence smoking cessation. Reports indicate variation in the OPRM1 gene as a significant predictor of smoking abstinence and cessation in subjects receiving nicotine replacement therapy (Lerman et al. 2004; Ray et al. 2007; Munafo et al. 2007), though results conflicted regarding the specific alleles attributing to the effect (Lerman et al. 2004; Munafo et al.

2007). A more recent study, however, failed to replicate associations with OPRM1 and smoking cessation (Munafo et al. 2013), suggesting only a modest role for OPRM1. Variants in the DRD1 gene, coding for the dopamine receptor subtype 1, were associated with increased smoking abstinence in slow, but not rapid nicotine metabolizers (Lee et al. 2012), while variants in the DRD2 gene were not associated with smoking cessation (Breitling et al. 2011; Lee et al. 2012). Findings likely reflect differences in dopamine receptor subtype activity in response to nicotine. Recent findings also identified variants in the BDNF gene associated with smoking cessation (Breetvelt et al. 2012). Interestingly, changes in plasma BDNF levels were identified in abstinent smokers compared to nonsmokers, regardless of smoking cessation pharmacotherapy (Bhang et al. 2010). Though unclear, it is of future interest to determine whether these changes in BDNF plasma level after smoking cessation are correlated with BDNF variants. Animal studies of galanin have also prompted further study using human genetic association analyses. Variants in the galanin receptor gene are associated with severity of tobacco craving in smokers seeking smoking cessation treatment (Lori et al. 2011) and with reduced odds of quitting success and a faster rate of relapse in subjects taking bupropion, but not placebo or nicotine replacement therapy (Gold et al. 2012). With GALR1, as observed in other studies, associations with smoking cessation may differ by pharmacotherapy.

5. Conclusions

The neurophysiological mechanisms underlying nicotine dependence are complex, involving genetic predispositions and, among others, influences from age, gender, and the environment. Due to the broad expression of nAChRs in the brain, nicotine affects a large number of signaling pathways and circuits. Prolonged nicotine use produces a wide range of neuroplastic adaptations that render quitting very difficult. Through work with genetically modified mice and pharmacological agents, we have learned that particular nAChR subtypes appear to mediate specific symptoms of nicotine withdrawal, and that those symptoms reflect the engagement of a variety of neurotransmitter and receptor systems. Those systems represent potentially druggable targets that can be used together with established therapies for more effective pharmacological interventions. Obviously, effective treatments will need to address the mechanisms involved in dependence and relapse, but studies of approaches to treat physical, emotional, and cognitive withdrawal symptoms will be critical to the development of comprehensive therapies. As this research begins to yield new pharmacological options for smokers attempting to quit, clinicians will be able to offer treatments that have fewer side effects and are better tailored to the unique characteristics of patients.

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References

Ahn K, McKinney MK, Cravatt BF. Enzymatic pathways that regulate endocannabinoid signaling in the nervous system. Chem Rev. 2008; 108:1687–1707. [PubMed: 18429637]

Allen SS, Bade T, Hatsukami D, Center B. Craving, withdrawal, and smoking urges on days immediately prior to smoking relapse. Nicotine Tob Res. 2008; 10:35–45. [PubMed: 18188743]

Amos CI, Wu X, Broderick P, Gorlov IP, Gu J, Eisen T, et al. Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. Nat Genet. 2008; 40:616–622. [PubMed: 18385676]

Aston-Jones G, Smith RJ, Sartor GC, Moorman DE, Massi L, Tahsili-Fahadan P, et al. Lateral hypothalamic orexin/hypocretin neurons: A role in reward-seeking and addiction. Brain Res. 2010; 1314:74–90. [PubMed: 19815001]

Baker TB, Weiss RB, Bolt D, von NA, Fiore MC, Dunn DM, et al. Human neuronal acetylcholine receptor A5-A3-B4 haplotypes are associated with multiple nicotine dependence phenotypes. Nicotine Tob Res. 2009; 11:785–796. [PubMed: 19436041]

Baldwin PR, Alanis R, Salas R. The Role of the Habenula in Nicotine Addiction. J Addict Res Ther. 2011; S1

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; 20:2737–2748. [PubMed: 15548217]

Balfour DJ. The neurobiology of tobacco dependence: a preclinical perspective on the role of the dopamine projections to the nucleus accumbens [corrected]. Nicotine Tob Res. 2004; 6:899–912. [PubMed: 15801566]

Balfour DJ, Fagerstrom KO. Pharmacology of nicotine and its therapeutic use in smoking cessation and neurodegenerative disorders. Pharmacol Ther. 1996; 72:51–81. [PubMed: 8981571]

Bauzo RM, Bruijnzeel AW. Animal models of nicotine withdrawal: intracranial self- stimulation and somatic signs of withdrawal. Methods Mol Biol. 2012; 829:257–268. [PubMed: 22231819]

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

Berrendero F, Kieffer BL, Maldonado R. Attenuation of nicotine-induced antinociception, rewarding effects, and dependence in mu-opioid receptor knock-out mice. J Neurosci. 2002; 22:10935–10940. [PubMed: 12486188]

Berrendero F, Plaza-Zabala A, Galeote L, Flores A, Bura SA, Kieffer BL, et al. Influence of delta-opioid receptors in the behavioral effects of nicotine. Neuropsychopharmacology. 2012; 37:2332–2344. [PubMed: 22669166]

Beuten J, Ma JZ, Payne TJ, Dupont RT, Crews KM, Somes G, et al. Single- and multilocus allelic variants within the GABA(B) receptor subunit 2 (GABAB2) gene are significantly associated with nicotine dependence. Am J Hum Genet. 2005; 76:859–864. [PubMed: 15759211]

Bhang SY, Choi SW, Ahn JH. Changes in plasma brain-derived neurotrophic factor levels in smokers after smoking cessation. Neurosci Lett. 2010; 468:7–11. [PubMed: 19850105]

Biala G, Budzynska B, Kruk M. Naloxone precipitates nicotine abstinence syndrome and attenuates nicotine-induced antinociception in mice. Pharmacol Rep. 2005; 57:755–760. [PubMed: 16382193]

Bibevski S, Zhou Y, McIntosh JM, Zigmond RE, Dunlap ME. Functional nicotinic acetylcholine receptors that mediate ganglionic transmission in cardiac parasympathetic neurons. J Neurosci. 2000; 20:5076–5082. [PubMed: 10864965]

Bierut LJ, Stitzel JA, Wang JC, Hinrichs AL, Grucza RA, Xuei X, et al. Variants in nicotinic receptors and risk for nicotine dependence. Am J Psychiatry. 2008; 165:1163–1171. [PubMed: 18519524]

Bousman CA, Rivard C, Haese JD, Ambrosone C, Hyland A. Alpha-5 and -3 nicotinic receptor gene variants predict nicotine dependence but not cessation: findings from the COMMIT cohort. Am J Med Genet B Neuropsychiatr Genet. 2012; 159B:227–235. [PubMed: 22223462]

Breetvelt EJ, Numans ME, Aukes MF, Hoeben W, Strengman E, Luykx JJ, et al. The association of the alpha-5 subunit of the nicotinic acetylcholine receptor gene and the brain-derived neurotrophic factor gene with different aspects of smoking behavior. Psychiatr Genet. 2012; 22:96–98. [PubMed: 22008662]

Breitling LP, Muller H, Illig T, Rujescu D, Winterer G, Dahmen N, et al. Dopamine- related genes and spontaneous smoking cessation in ever-heavy smokers. Pharmacogenomics. 2011; 12:1099–1106. [PubMed: 21806388]

Brody AL, Mandelkern MA, London ED, Olmstead RE, Farahi J, Scheibal D, et al. Cigarette smoking saturates brain alpha 4 beta 2 nicotinic acetylcholine receptors. Arch Gen Psychiatry. 2006; 63:907–915. [PubMed: 16894067]

Bruijnzeel AW, Ford J, Rogers JA, Scheick S, Ji Y, Bishnoi M, et al. Blockade of CRF1 receptors in the central nucleus of the amygdala attenuates the dysphoria associated with nicotine withdrawal in rats. Pharmacol Biochem Behav. 2012; 101:62–68. [PubMed: 22182462]

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. Biol Psychiatry. 2009; 66:110–117. [PubMed: 19217073]

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]

Budzynska B, Polak P, Biala G. Effects of calcium channel antagonists on the motivational effects of nicotine and morphine in conditioned place aversion paradigm. Behav Brain Res. 2012; 228:144–150. [PubMed: 22178315]

Butt C, Alptekin A, Shippenberg T, Oz M. Endogenous cannabinoid anandamide inhibits nicotinic acetylcholine receptor function in mouse thalamic synaptosomes. J Neurochem. 2008; 105:1235–1243. [PubMed: 18194436]

Cabral GA, Marciano-Cabral F. Cannabinoid receptors in microglia of the central nervous system: immune functional relevance. J Leukoc Biol. 2005; 78:1192–1197. [PubMed: 16204639]

Caporaso N, Gu F, Chatterjee N, Sheng-Chih J, Yu K, Yeager M, et al. Genome-wide and candidate gene association study of cigarette smoking behaviors. PLoS One. 2009; 4:e4653. [PubMed: 19247474]

Castane A, Valjent E, Ledent C, Parmentier M, Maldonado R, Valverde O. Lack of CB1 cannabinoid receptors modifies nicotine behavioural responses, but not nicotine abstinence. Neuropharmacology. 2002; 43:857–867. [PubMed: 12384171]

Changeux JP, Bertrand D, Corringer PJ, Dehaene S, Edelstein S, Lena C, et al. Brain nicotinic receptors: structure and regulation, role in learning and reinforcement. Brain Res Brain Res Rev. 1998; 26:198–216. [PubMed: 9651527]

Chen LS, Baker TB, Piper ME, Breslau N, Cannon DS, Doheny KF, et al. Interplay of genetic risk factors (CHRNA5-CHRNA3-CHRNB4) and cessation treatments in smoking cessation success. Am J Psychiatry. 2012; 169:735–742. [PubMed: 22648373]

Chen X, Chen J, Williamson VS, An SS, Hettema JM, Aggen SH, et al. Variants in nicotinic acetylcholine receptors alpha5 and alpha3 increase risks to nicotine dependence. Am J Med Genet B Neuropsychiatr Genet. 2009; 150B:926–933. [PubMed: 19132693]

Cippitelli A, Astarita G, Duranti A, Caprioli G, Ubaldi M, Stopponi S, et al. Endocannabinoid regulation of acute and protracted nicotine withdrawal: effect of FAAH inhibition. PLoS One. 2011; 6:e28142. [PubMed: 22140525]

Cohen A1, Treweek J, Edwards S, Leão 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. 2013 Jul 22. 2013.

Cooper BR, Wang CM, Cox RF, Norton R, Shea V, Ferris RM. Evidence that the acute behavioral and electrophysiological effects of bupropion (Wellbutrin) are mediated by a noradrenergic mechanism. Neuropsychopharmacology. 1994; 11:133–141. [PubMed: 7840865]

Cooper TB, Suckow RF, Glassman A. Determination of bupropion and its major basic metabolites in plasma by liquid chromatography with dual-wavelength ultraviolet detection. J Pharm Sci. 1984; 73:1104–1107. [PubMed: 6436464]

Cravatt BF, Giang DK, Mayfield SP, Boger DL, Lerner RA, Gilula NB. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. Nature. 1996; 384:83–87. [PubMed: 8900284]

Cryan JF, Gasparini F, van HG, Markou A. Non-nicotinic neuropharmacological strategies for nicotine dependence: beyond bupropion. Drug Discov Today. 2003; 8:1025–1034. [PubMed: 14690633]

Cummings KM, Mahoney M. Current and emerging treatment approaches for tobacco dependence. Curr Oncol Rep. 2006; 8:475–483. [PubMed: 17040625]

Damaj MI, Carroll FI, Eaton JB, Navarro HA, Blough BE, Mirza S, et al. Enantioselective effects of hydroxy metabolites of bupropion on behavior and on function of monoamine transporters and nicotinic receptors. Mol Pharmacol. 2004; 66:675–682. [PubMed: 15322260]

Damaj MI, Grabus SD, Navarro HA, Vann RE, Warner JA, King LS, et al. Effects of hydroxymetabolites of bupropion on nicotine dependence behavior in mice. J Pharmacol Exp Ther. 2010; 334:1087–1095. [PubMed: 20576796]

Damaj MI, Kao W, Martin BR. Characterization of spontaneous and precipitated nicotine withdrawal in the mouse. J Pharmacol Exp Ther. 2003; 307:526–534. [PubMed: 12970387]

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

Dao DQ, Perez EE, Teng Y, Dani JA, De BM. Nicotine enhances excitability of medial habenular neurons via facilitation of neurokinin signaling. J Neurosci. 2014; 34:4273–4284. [PubMed: 24647947]

Dautzenberg FM, Braun S, Hauger RL. GRK3 mediates desensitization of CRF1 receptors: a potential mechanism regulating stress adaptation. Am J Physiol Regul Integr Comp Physiol. 2001; 280:R935–R946. [PubMed: 11247813]

Davis JA, James JR, Siegel SJ, Gould TJ. Withdrawal from chronic nicotine administration impairs contextual fear conditioning in C57BL/6 mice. J Neurosci. 2005; 25:8708–8713. [PubMed: 16177040]

De Biasi M, Dani JA. Reward, addiction, withdrawal to nicotine. Annu Rev Neurosci. 2011; 34:105–130. [PubMed: 21438686]

De Biasi M, Salas R. Influence of neuronal nicotinic receptors over nicotine addiction and withdrawal. Exp Biol Med (Maywood). 2008; 233:917–929. [PubMed: 18480414]

De Ruyck K, Nackaerts K, Beels L, Werbrouck J, De VA, Meysman M, et al. Genetic variation in three candidate genes and nicotine dependence, withdrawal and smoking cessation in hospitalized patients. Pharmacogenomics. 2010; 11:1053–1063. [PubMed: 20712524]

Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science. 1992; 258:1946–1949. [PubMed: 1470919]

Dinh TP, Carpenter D, Leslie FM, Freund TF, Katona I, Sensi SL, et al. Brain monoglyceride lipase participating in endocannabinoid inactivation. Proc Natl Acad Sci U S A. 2002; 99:10819–10824. [PubMed: 12136125]

Domino EF, Tsukada H. Nicotine sensitization of monkey striatal dopamine release. Eur J Pharmacol. 2009; 607:91–95. [PubMed: 19232339]

Ebner K, Singewald N. The role of substance P in stress and anxiety responses. Amino Acids. 2006; 31:251–272. [PubMed: 16820980]

Engelmann JM, Radke AK, Gewirtz JC. Potentiated startle as a measure of the negative affective consequences of repeated exposure to nicotine in rats. Psychopharmacology (Berl). 2009; 207:13–25. [PubMed: 19669732]

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]

Erdtmann-Vourliotis M, Mayer P, Ammon S, Riechert U, Hollt V. Distribution of G- protein-coupled receptor kinase (GRK) isoforms 2, 3, 5 and 6 mRNA in the rat brain. Brain Res Mol Brain Res. 2001; 95:129–137. [PubMed: 11687284]

Ericson E, Ahlenius S. Suggestive evidence for inhibitory effects of galanin on mesolimbic dopaminergic neurotransmission. Brain Res. 1999; 822:200–209. [PubMed: 10082897]

Falvella FS, Galvan A, Frullanti E, Spinola M, Calabro E, Carbone A, et al. Transcription deregulation at the 15q25 locus in association with lung adenocarcinoma risk. Clin Cancer Res. 2009; 15:1837–1842. [PubMed: 19223495]

Fowler JS, Logan J, Wang GJ, Volkow ND. Monoamine oxidase and cigarette smoking. Neurotoxicology. 2003; 24:75–82. [PubMed: 12564384]

Fryer JD, Lukas RJ. Noncompetitive functional inhibition at diverse, human nicotinic acetylcholine receptor subtypes by bupropion, phencyclidine, and ibogaine. J Pharmacol Exp Ther. 1999; 288:88–92. [PubMed: 9862757]

Galeote L, Berrendero F, Bura SA, Zimmer A, Maldonado R. Prodynorphin gene disruption increases the sensitivity to nicotine self-administration in mice. Int J Neuropsychopharmacol. 2009; 12:615–625. [PubMed: 18937881]

George O, Ghozland S, Azar MR, Cottone P, Zorrilla EP, Parsons LH, et al. CRF-CRF1 system activation mediates withdrawal-induced increases in nicotine self-administration in nicotine-dependent rats. Proc Natl Acad Sci U S A. 2007; 104:17198–17203. [PubMed: 17921249]

George O, Grieder TE, Cole M, Koob GF. Exposure to chronic intermittent nicotine vapor induces nicotine dependence. Pharmacol Biochem Behav. 2010; 96:104–107. [PubMed: 20420848]

Gilpin NW, Whitaker AM, Baynes B, Abdel AY, Weil MT, George O. Nicotine vapor inhalation escalates nicotine self-administration. Addict Biol. 2012

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; 37:1683–1688. [PubMed: 22373943]

Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA. 2006; 296:47–55. [PubMed: 16820546]

Gorlich A, Antolin-Fontes B, Ables JL, Frahm S, Slimak MA, Dougherty JD, et al. Reexposure to nicotine during withdrawal increases the pacemaking activity of cholinergic habenular neurons. Proc Natl Acad Sci U S A. 2013; 110:17077–17082. [PubMed: 24082085]

Gould TJ, Portugal GS, Andre JM, Tadman MP, Marks MJ, Kenney JW, et al. The duration of nicotine withdrawal-associated deficits in contextual fear conditioning parallels changes in hippocampal high affinity nicotinic acetylcholine receptor upregulation. Neuropharmacology. 2012; 62:2118–2125. [PubMed: 22285742]

Grabus SD, Martin BR, Batman AM, Tyndale RF, Sellers E, Damaj MI. Nicotine physical dependence and tolerance in the mouse following chronic oral administration. Psychopharmacology (Berl). 2005a; 178:183–192. [PubMed: 15365686]

Grabus SD, Martin BR, Imad DM. Nicotine physical dependence in the mouse: involvement of the alpha7 nicotinic receptor subtype. Eur J Pharmacol. 2005b; 515:90–93. [PubMed: 15896732]

Hamilton KR, Berger SS, Perry ME, Grunberg NE. Behavioral effects of nicotine withdrawal in adult male and female rats. Pharmacol Biochem Behav. 2009; 92:51–59. [PubMed: 19000707]

Hamilton KR, Perry ME, Berger SS, Grunberg NE. Behavioral effects of nicotine withdrawal differ by genetic strain in male and female adolescent rats. Nicotine Tob Res. 2010; 12:1236–1245. [PubMed: 21071625]

Harris GC, Aston-Jones G. Critical role for ventral tegmental glutamate in preference for a cocaine-conditioned environment. Neuropsychopharmacology. 2003; 28:73–76. [PubMed: 12496942]

Harrison AA, Gasparini F, Markou A. Nicotine potentiation of brain stimulation reward reversed by DH beta E and SCH 23390, but not by eticlopride, LY 314582 or MPEP in rats. Psychopharmacology (Berl). 2002; 160:56–66. [PubMed: 11862374]

Hauger RL, Risbrough V, Oakley RH, Olivares-Reyes JA, Dautzenberg FM. Role of CRF receptor signaling in stress vulnerability, anxiety, and depression. Ann N Y Acad Sci. 2009; 1179:120–143. [PubMed: 19906236]

Hildebrand BE, Nomikos GG, Bondjers C, Nisell M, Svensson TH. Behavioral manifestations of the nicotine abstinence syndrome in the rat: peripheral versus central mechanisms. Psychopharmacology (Berl). 1997; 129:348–356. [PubMed: 9085404]

Hildebrand BE, Panagis G, Svensson TH, Nomikos GG. Behavioral and biochemical manifestations of mecamylamine-precipitated nicotine withdrawal in the rat: role of nicotinic receptors in the ventral tegmental area. Neuropsychopharmacology. 1999; 21:560–574. [PubMed: 10481840]

Hilleman DE, Mohiuddin SM, Del Core MG, Sketch MH Sr. Effect of buspirone on withdrawal symptoms associated with smoking cessation. Arch Intern Med. 1992; 152:350–352. [PubMed: 1739365]

Hilleman DE, Mohiuddin SM, Delcore MG. Comparison of fixed-dose transdermal nicotine, tapered-dose transdermal nicotine, and buspirone in smoking cessation. J Clin Pharmacol. 1994; 34:222–224. [PubMed: 8021329]

Hollander JA, Lu Q, Cameron MD, Kamenecka TM, Kenny PJ. Insular hypocretin transmission regulates nicotine reward. Proc Natl Acad Sci U S A. 2008; 105:19480–19485. [PubMed: 19033203]

Holmes A, Heilig M, Rupniak NM, Steckler T, Griebel G. Neuropeptide systems as novel therapeutic targets for depression and anxiety disorders. Trends Pharmacol Sci. 2003; 24:580–588. [PubMed: 14607081]

Hook SS, Means AR. Ca(2+)/CaM-dependent kinases: from activation to function. Annu Rev Pharmacol Toxicol. 2001; 41:471–505. [PubMed: 11264466]

Hughes JR. Effects of abstinence from tobacco: valid symptoms and time course. Nicotine Tob Res. 2007; 9:315–327. [PubMed: 17365764]

Hung RJ, McKay JD, Gaborieau V, Boffetta P, Hashibe M, Zaridze D, et al. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. Nature. 2008; 452:633–637. [PubMed: 18385738]

Ignatowska-Jankowska BM, Muldoon PP, Lichtman AH, Damaj MI. The cannabinoid CB receptor is necessary for nicotine-conditioned place preference, but not other behavioral effects of nicotine in mice. Psychopharmacology (Berl). 2013

Irvine EE1, Bagnalasta M, Marcon C, Motta C, Tessari M, File SE, Chiamulera C. Nicotine self-administration and withdrawal: modulation of anxiety in the social interaction test in rats. Psychopharmacology (Berl). 2001; 153:315–320. [PubMed: 11271403]

Ise Y, Narita M, Nagase H, Suzuki T. Modulation of opioidergic system on mecamylamine-precipitated nicotine-withdrawal aversion in rats. Psychopharmacology (Berl). 2000; 151:49–54. [PubMed: 10958116]

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; 210:285–294. [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; 36:2339–2348. [PubMed: 21796100]

Jackson KJ, Damaj MI. L-type calcium channels and calcium/calmodulin-dependent kinase II differentially mediate behaviors associated with nicotine withdrawal in mice. J Pharmacol Exp Ther. 2009; 330:152–161. [PubMed: 19336664]

Jackson KJ, Damaj MI. Beta2-containing nicotinic acetylcholine receptors mediate calcium/calmodulin-dependent protein kinase-II and synapsin I protein levels in the nucleus accumbens after nicotine withdrawal in mice. Eur J Pharmacol. 2013; 701:1–6. [PubMed: 23313759]

Jackson KJ, Kota DH, Martin BR, Damaj MI. The role of various nicotinic receptor subunits and factors influencing nicotine conditioned place aversion. Neuropharmacology. 2009a; 56:970–974. [PubMed: 19371584]

Jackson KJ, Martin BR, Changeux JP, Damaj MI. Differential role of nicotinic acetylcholine receptor subunits in physical and affective nicotine withdrawal signs. J Pharmacol Exp Ther. 2008; 325:302–312. [PubMed: 18184829]

Jackson KJ, McIntosh JM, Brunzell DH, Sanjakdar SS, Damaj MI. The role of alpha6- containing nicotinic acetylcholine receptors in nicotine reward and withdrawal. J Pharmacol Exp Ther. 2009b; 331:547–554. [PubMed: 19644040]

Jackson KJ, Sanjakdar SS, Chen X, Damaj MI. Nicotine reward and affective nicotine withdrawal signs are attenuated in calcium/calmodulin-dependent protein kinase IV knockout mice. PLoS One. 2012; 7:e51154. [PubMed: 23226481]

Jackson KJ, Sanjakdar SS, Muldoon PP, McIntosh JM, Damaj MI. The alpha3beta4* nicotinic acetylcholine receptor subtype mediates nicotine reward and physical nicotine withdrawal signs independently of the alpha5 subunit in the mouse. Neuropharmacology. 2013; 70:228–235. [PubMed: 23416040]

Jackson KJ, Walters CL, Miles MF, Martin BR, Damaj MI. Characterization of pharmacological and behavioral differences to nicotine in C57Bl/6 and DBA/2 mice. Neuropharmacology. 2009c; 57:347–355. [PubMed: 19619563]

Johnson PM, Hollander JA, Kenny PJ. Decreased brain reward function during nicotine withdrawal in C57BL6 mice: evidence from intracranial self-stimulation (ICSS) studies. Pharmacol Biochem Behav. 2008; 90:409–415. [PubMed: 18466962]

Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA. 2006; 296:56–63. [PubMed: 16820547]

Kenney JW, Gould TJ. Modulation of hippocampus-dependent learning and synaptic plasticity by nicotine. Mol Neurobiol. 2008; 38:101–121. [PubMed: 18690555]

Kenny PJ, File SE, Rattray M. Acute nicotine decreases, and chronic nicotine increases the expression of brain-derived neurotrophic factor mRNA in rat hippocampus. Brain Res Mol Brain Res. 2000; 85:234–238. [PubMed: 11146126]

King DP, Paciga S, Pickering E, Benowitz NL, Bierut LJ, Conti DV, et al. Smoking cessation pharmacogenetics: analysis of varenicline and bupropion in placebo-controlled clinical trials. Neuropsychopharmacology. 2012; 37:641–650. [PubMed: 22048466]

Kivinummi T, Kaste K, Rantamaki T, Castren E, Ahtee L. Alterations in BDNF and phospho-CREB levels following chronic oral nicotine treatment and its withdrawal in dopaminergic brain areas of mice. Neurosci Lett. 2011; 491:108–112. [PubMed: 21232579]

Koob GF, Heinrichs SC, Pich EM, Menzaghi F, Baldwin H, Miczek K, et al. The role of corticotropin-releasing factor in behavioural responses to stress. Ciba Found Symp. 1993; 172:277–289. [PubMed: 8491090]

Koob GF, Le Moal M. Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. Nat Neurosci. 2005; 8:1442–1444. [PubMed: 16251985]

Koob GF, Le Moal M. Review. Neurobiological mechanisms for opponent motivational processes in addiction. Philos Trans R Soc Lond B Biol Sci. 2008; 363:3113–3123. [PubMed: 18653439]

Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010; 35:217–238. [PubMed: 19710631]

Kota D, Martin BR, Damaj MI. Age-dependent differences in nicotine reward and withdrawal in female mice. Psychopharmacology (Berl). 2008; 198:201–210. [PubMed: 18338157]

Kota D, Martin BR, Robinson SE, Damaj MI. Nicotine dependence and reward differ between adolescent and adult male mice. J Pharmacol Exp Ther. 2007; 322:399–407. [PubMed: 17446302]

Kramer MS, Cutler N, Feighner J, Shrivastava R, Carman J, Sramek JJ, et al. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. Science. 1998; 281:1640–1645. [PubMed: 9733503]

Krystal JH, Webb E, Grillon C, Cooney N, Casal L, Morgan CA III, et al. Evidence of acoustic startle hyperreflexia in recently detoxified early onset male alcoholics: modulation by yohimbine and m-chlorophenylpiperazine (mCPP). Psychopharmacology (Berl). 1997; 131:207–215. [PubMed: 9203230]

Lang UE, Sander T, Lohoff FW, Hellweg R, Bajbouj M, Winterer G, et al. Association of the met66 allele of brain-derived neurotrophic factor (BDNF) with smoking. Psychopharmacology (Berl). 2007; 190:433–439. [PubMed: 17186223]

Le Foll B, Goldberg SR. Effects of nicotine in experimental animals and humans: an update on addictive properties. Handb Exp Pharmacol. 2009:335–367. [PubMed: 19184655]

Lee W, Ray R, Bergen AW, Swan GE, Thomas P, Tyndale RF, et al. DRD1 associations with smoking abstinence across slow and normal nicotine metabolizers. Pharmacogenet Genomics. 2012; 22:551–554. [PubMed: 22495174]

Leibowitz SF. Regulation and effects of hypothalamic galanin: relation to dietary fat, alcohol ingestion, circulating lipids and energy homeostasis. Neuropeptides. 2005; 39:327–332. [PubMed: 15944030]

Lein ES, Hawrylycz MJ, Ao N, Ayres M, Bensinger A, Bernard A, et al. Genome-wide atlas of gene expression in the adult mouse brain. Nature. 2007; 445:168–176. [PubMed: 17151600]

Lerman C, LeSage MG, Perkins KA, O'Malley SS, Siegel SJ, Benowitz NL, et al. Translational research in medication development for nicotine dependence. Nat Rev Drug Discov. 2007; 6:746–762. [PubMed: 17690709]

Lerman C, Wileyto EP, Patterson F, Rukstalis M, Audrain-McGovern J, Restine S, et al. The functional mu opioid receptor (OPRM1) Asn40Asp variant predicts short-term response to nicotine replacement therapy in a clinical trial. Pharmacogenomics J. 2004; 4:184–192. [PubMed: 15007373]

LeSage MG, Perry JL, Kotz CM, Shelley D, Corrigall WA. Nicotine self-administration in the rat: effects of hypocretin antagonists and changes in hypocretin mRNA. Psychopharmacology (Berl). 2010; 209:203–212. [PubMed: 20177882]

Li MD, Lou XY, Chen G, Ma JZ, Elston RC. Gene-gene interactions among CHRNA4, CHRNB2, BDNF, and NTRK2 in nicotine dependence. Biol Psychiatry. 2008; 64:951–957. [PubMed: 18534558]

Lipsky RH, Marini AM. Brain-derived neurotrophic factor in neuronal survival and behavior-related plasticity. Ann N Y Acad Sci. 2007; 1122:130–143. [PubMed: 18077569]

Liu DM, Cuevas J, Adams DJ. VIP and PACAP potentiation of nicotinic ACh-evoked currents in rat parasympathetic neurons is mediated by G-protein activation. Eur J Neurosci. 2000; 12:2243–2251. [PubMed: 10947803]

Liu JJ, Mohila CA, Gong Y, Govindarajan N, Onn SP. Chronic nicotine exposure during adolescence differentially influences calcium-binding proteins in rat anterior cingulate cortex. Eur J Neurosci. 2005; 22:2462–2474. [PubMed: 16307589]

Long JZ, Li W, Booker L, Burston JJ, Kinsey SG, Schlosburg JE, et al. Selective blockade of 2-arachidonoylglycerol hydrolysis produces cannabinoid behavioral effects. Nat Chem Biol. 2009a; 5:37–44. [PubMed: 19029917]

Long JZ, Nomura DK, Cravatt BF. Characterization of monoacylglycerol lipase inhibition reveals differences in central and peripheral endocannabinoid metabolism. Chem Biol. 2009b; 16:744–753. [PubMed: 19635411]

Lori A, Tang Y, O'Malley S, Picciotto MR, Wu R, Conneely KN, et al. The galanin receptor 1 gene associates with tobacco craving in smokers seeking cessation treatment. Neuropsychopharmacology. 2011; 36:1412–1420. [PubMed: 21430647]

Lotfipour S, Byun JS, Leach P, Fowler CD, Murphy NP, Kenny PJ, et al. Targeted deletion of the mouse alpha2 nicotinic acetylcholine receptor subunit gene (Chrna2) potentiates nicotine-modulated behaviors. J Neurosci. 2013; 33:7728–7741. [PubMed: 23637165]

Malin DH, Lake JR, Carter VA, Cunningham JS, Wilson OB. Naloxone precipitates nicotine abstinence syndrome in the rat. Psychopharmacology (Berl). 1993; 112:339–342. [PubMed: 7871039]

Malin DH, Lake JR, Newlin-Maultsby P, Roberts LK, Lanier JG, Carter VA, et al. Rodent model of nicotine abstinence syndrome. Pharmacol Biochem Behav. 1992; 43:779–784. [PubMed: 1448472]

Malin DH, Lake JR, Smith TD, Khambati HN, Meyers-Paal RL, Montellano AL, et al. Bupropion attenuates nicotine abstinence syndrome in the rat. Psychopharmacology (Berl). 2006; 184:494–503. [PubMed: 16163521]

Mannucci C, Navarra M, Pieratti A, Russo GA, Caputi AP, Calapai G. Interactions between endocannabinoid and serotonergic systems in mood disorders caused by nicotine withdrawal. Nicotine Tob Res. 2011; 13:239–247. [PubMed: 21324836]

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]

Markou A, Kosten TR, Koob GF. Neurobiological similarities in depression and drug dependence: a self-medication hypothesis. Neuropsychopharmacology. 1998; 18:135–174. [PubMed: 9471114]

Markou A, Paterson NE. The nicotinic antagonist methyllycaconitine has differential effects on nicotine self-administration and nicotine withdrawal in the rat. Nicotine Tob Res. 2001; 3:361–373. [PubMed: 11694204]

Mathieu AM, Caboche J, Besson MJ. Distribution of preproenkephalin, preprotachykinin A, and preprodynorphin mRNAs in the rat nucleus accumbens: effect of repeated administration of nicotine. Synapse. 1996; 23:94–106. [PubMed: 8723714]

Mathieu-Kia AM, Besson MJ. Repeated administration of cocaine, nicotine and ethanol: effects on preprodynorphin, preprotachykinin A and preproenkephalin mRNA expression in the dorsal and the ventral striatum of the rat. Brain Res Mol Brain Res. 1998; 54:141–151. [PubMed: 9526067]

Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature. 1990; 346:561–564. [PubMed: 2165569]

Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol. 1995; 50:83–90. [PubMed: 7605349]

Mennicken F, Hoffert C, Pelletier M, Ahmad S, O'Donnell D. Restricted distribution of galanin receptor 3 (GalR3) mRNA in the adult rat central nervous system. J Chem Neuroanat. 2002; 24:257–268. [PubMed: 12406501]

Merritt LL, Martin BR, Walters C, Lichtman AH, Damaj MI. The endogenous cannabinoid system modulates nicotine reward and dependence. J Pharmacol Exp Ther. 2008a; 326:483–492. [PubMed: 18451315]

Merritt LL, Martin BR, Walters C, Lichtman AH, Damaj MI. The endogenous cannabinoid system modulates nicotine reward and dependence. J Pharmacol Exp Ther. 2008b; 326:483–492. [PubMed: 18451315]

Miura M, Ishii K, Aosaki T, Sumikawa K. Chronic nicotine treatment increases GABAergic input to striatal neurons. Neuroreport. 2006; 17:537–540. [PubMed: 16543821]

Muldoon PP, Lichtman AH, Parsons LH, Damaj MI. The role of fatty acid amide hydrolase inhibition in nicotine reward and dependence. Life Sci. 2013; 92:458–462. [PubMed: 22705310]

Munafo MR, Elliot KM, Murphy MF, Walton RT, Johnstone EC. Association of the mu-opioid receptor gene with smoking cessation. Pharmacogenomics J. 2007; 7:353–361. [PubMed: 17224915]

Munafo MR, Johnstone EC, Aveyard P, Marteau T. Lack of association of OPRM1 genotype and smoking cessation. Nicotine Tob Res. 2013; 15:739–744. [PubMed: 22990223]

Munafo MR, Johnstone EC, Walther D, Uhl GR, Murphy MF, Aveyard P. CHRNA3 rs1051730 genotype and short-term smoking cessation. Nicotine Tob Res. 2011; 13:982–988. [PubMed: 21690317]

Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature. 1993; 365:61–65. [PubMed: 7689702]

Natividad LA, Buczynski MW, Parsons LH, Torres OV, O'Dell LE. Adolescent rats are resistant to adaptations in excitatory and inhibitory mechanisms that modulate mesolimbic dopamine during nicotine withdrawal. J Neurochem. 2012; 123:578–588. [PubMed: 22905672]

Natividad LA, Tejeda HA, Torres OV, O'Dell LE. Nicotine withdrawal produces a decrease in extracellular levels of dopamine in the nucleus accumbens that is lower in adolescent versus adult male rats. Synapse. 2010; 64:136–145. [PubMed: 19771590]

Navarrete F, Rodriguez-Arias M, Martin-Garcia E, Navarro D, Garcia-Gutierrez MS, Aguilar MA, et al. Role of CB2 Cannabinoid Receptors in the Rewarding, Reinforcing, and Physical Effects of Nicotine. Neuropsychopharmacology. 2013

Nomikos GG, Hildebrand BE, Panagis G, Svensson TH. Nicotine withdrawal in the rat: role of alpha7 nicotinic receptors in the ventral tegmental area. Neuroreport. 1999; 10:697–702. [PubMed: 10208533]

O'Dell LE1, Chen SA, Smith RT, Specio SE, Balster RL, Paterson NE, Markou A, Zorrilla EP, Koob GF. Extended access to nicotine self-administration leads to dependence: Circadian measures, withdrawal measures, and extinction behavior in rats. J Pharmacol Exp Ther. 2007; 320:180–193. [PubMed: 17050784]

O'Dell LE, Bruijnzeel AW, Smith RT, Parsons LH, Merves ML, Goldberger BA, et al. Diminished nicotine withdrawal in adolescent rats: implications for vulnerability to addiction. Psychopharmacology (Berl). 2006; 186:612–619. [PubMed: 16598454]

O'Dell LE, Torres OV, Natividad LA, Tejeda HA. Adolescent nicotine exposure produces less affective measures of withdrawal relative to adult nicotine exposure in male rats. Neurotoxicol Teratol. 2007; 29:17–22. [PubMed: 17184972]

Ohmura Y, Jutkiewicz EM, Domino EF. L-DOPA attenuates nicotine withdrawal- induced behaviors in rats. Pharmacol Biochem Behav. 2011a; 98:552–558. [PubMed: 21354201]

Ohmura Y, Jutkiewicz EM, Yoshioka M, Domino EF. 5-Hydroxytryptophan attenuates somatic signs of nicotine withdrawal. J Pharmacol Sci. 2011b; 117:121–124. [PubMed: 22001627]

Okere CO, Waterhouse BD. Nicotine withdrawal upregulates nitrergic and galaninergic activity in the rat dorsal raphe nucleus and locus coeruleus. Neurosci Lett. 2013; 536:29–34. [PubMed: 23305719]

Oz M, Ravindran A, Diaz-Ruiz O, Zhang L, Morales M. The endogenous cannabinoid anandamide inhibits alpha7 nicotinic acetylcholine receptor-mediated responses in Xenopus oocytes. J Pharmacol Exp Ther. 2003; 306:1003–1010. [PubMed: 12766252]

Pennefather JN, Lecci A, Candenas ML, Patak E, Pinto FM, Maggi CA. Tachykinins and tachykinin receptors: a growing family. Life Sci. 2004; 74:1445–1463. [PubMed: 14729395]

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. Biol Psychiatry. 2012a; 71:214–223. [PubMed: 21831361]

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; 38:1724–1736. [PubMed: 23518606]

Plaza-Zabala A, Maldonado R, Berrendero F. The hypocretin/orexin system: implications for drug reward and relapse. Mol Neurobiol. 2012b; 45:424–439. [PubMed: 22430644]

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. J Neurosci. 2010; 30:2300–2310. [PubMed: 20147556]

Portugal GS, Gould TJ. Genetic variability in nicotinic acetylcholine receptors and nicotine addiction: converging evidence from human and animal research. Behav Brain Res. 2008; 193:1–16. [PubMed: 18571741]

Portugal GS, Wilkinson DS, Kenney JW, Sullivan C, Gould TJ. Strain-dependent effects of acute, chronic, and withdrawal from chronic nicotine on fear conditioning. Behav Genet. 2012a; 42:133–150. [PubMed: 21822688]

Portugal GS, Wilkinson DS, Turner JR, Blendy JA, Gould TJ. Developmental effects of acute, chronic, and withdrawal from chronic nicotine on fear conditioning. Neurobiol Learn Mem. 2012b; 97:482–494. [PubMed: 22521799]

Quartara L, Maggi CA. The tachykinin NK1 receptor. Part II: Distribution and pathophysiological roles. Neuropeptides. 1998; 32:1–49. [PubMed: 9571643]

Rahman S, Zhang J, Engleman EA, Corrigall WA. Neuroadaptive changes in the mesoaccumbens dopamine system after chronic nicotine self-administration: a microdialysis study. Neuroscience. 2004; 129:415–424. [PubMed: 15501598]

Ray R, Jepson C, Wileyto EP, Dahl JP, Patterson F, Rukstalis M, et al. Genetic variation in mu-opioid-receptor-interacting proteins and smoking cessation in a nicotine replacement therapy trial. Nicotine Tob Res. 2007; 9:1237–1241. [PubMed: 17978999]

Rehni AK, Singh TG, Arora S. SU-6656, a selective Src kinase inhibitor, attenuates mecamylamine-precipitated nicotine withdrawal syndrome in mice. Nicotine Tob Res. 2012; 14:407–414. [PubMed: 22102627]

Roth-Deri I, Green-Sadan T, Yadid G. Beta-endorphin and drug-induced reward and reinforcement. Prog Neurobiol. 2008; 86:1–21. [PubMed: 18602444]

Rustay NR, Wrenn CC, Kinney JW, Holmes A, Bailey KR, Sullivan TL, et al. Galanin impairs performance on learning and memory tasks: findings from galanin transgenic and GAL-R1 knockout mice. Neuropeptides. 2005; 39:239–243. [PubMed: 15944016]

Sakurai T. The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. Nat Rev Neurosci. 2007; 8:171–181. [PubMed: 17299454]

Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, et al. 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]

Saladin ME, Drobes DJ, Coffey SF, Libet JM. The human startle reflex and alcohol cue reactivity: effects of early versus late abstinence. Psychol Addict Behav. 2002; 16:98–105. [PubMed: 12079261]

Salas R, Pieri F, De BM. Decreased signs of nicotine withdrawal in mice null for the beta4 nicotinic acetylcholine receptor subunit. J Neurosci. 2004; 24:10035–10039. [PubMed: 15537871]

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

Sarginson JE, Killen JD, Lazzeroni LC, Fortmann SP, Ryan HS, Schatzberg AF, et al. Markers in the 15q24 nicotinic receptor subunit gene cluster (CHRNA5-A3-B4) predict severity of nicotine addiction and response to smoking cessation therapy. Am J Med Genet B Neuropsychiatr Genet. 2011; 156B:275–284. [PubMed: 21268243]

Severini C, Improta G, Falconieri-Erspamer G, Salvadori S, Erspamer V. The tachykinin peptide family. Pharmacol Rev. 2002; 54:285–322. [PubMed: 12037144]

Shih PY, Engle SE, Oh G, Deshpande P, Puskar NL, Lester HA, et al. Differential expression and function of nicotinic acetylcholine receptors in subdivisions of medial habenula. J Neurosci. 2014; 34:9789–9802. [PubMed: 25031416]

Shram MJ, Siu EC, Li Z, Tyndale RF, Le AD. Interactions between age and the aversive effects of nicotine withdrawal under mecamylamine-precipitated and spontaneous conditions in male Wistar rats. Psychopharmacology (Berl). 2008; 198:181–190. [PubMed: 18385986]

Singh TG, Rehni AK, Arora S. Ro 32-0432 attenuates mecamylamine-precipitated nicotine withdrawal syndrome in mice. Naunyn Schmiedebergs Arch Pharmacol. 2013; 386:197–204. [PubMed: 23274455]

Skwara AJ, Karwoski TE, Czambel RK, Rubin RT, Rhodes ME. Influence of environmental enrichment on hypothalamic-pituitary-adrenal (HPA) responses to single-dose nicotine, continuous nicotine by osmotic mini-pumps, and nicotine withdrawal by mecamylamine in male and female rats. Behav Brain Res. 2012; 234:1–10. [PubMed: 22705101]

Slemmer JE, Martin BR, Damaj MI. Bupropion is a nicotinic antagonist. J Pharmacol Exp Ther. 2000; 295:321–327. [PubMed: 10991997]

Small E, Shah HP, Davenport JJ, Geier JE, Yavarovich KR, Yamada H, et al. Tobacco smoke exposure induces nicotine dependence in rats. Psychopharmacology (Berl). 2010; 208:143–158. [PubMed: 19936715]

Solinas M, Tanda G, Justinova Z, Wertheim CE, Yasar S, Piomelli D, et al. The endogenous cannabinoid anandamide produces delta-9-tetrahydrocannabinol-like discriminative and neurochemical effects that are enhanced by inhibition of fatty acid amide hydrolase but not by inhibition of anandamide transport. J Pharmacol Exp Ther. 2007; 321:370–380. [PubMed: 17210800]

Spivak CE, Lupica CR, Oz M. The endocannabinoid anandamide inhibits the function of alpha4beta2 nicotinic acetylcholine receptors. Mol Pharmacol. 2007; 72:1024–1032. [PubMed: 17628012]

Stine SM, Grillon CG, Morgan CA III, Kosten TR, Charney DS, Krystal JH. Methadone patients exhibit increased startle and cortisol response after intravenous yohimbine. Psychopharmacology (Berl). 2001; 154:274–281. [PubMed: 11351934]

Stoker AK, Olivier B, Markou A. Involvement of metabotropic glutamate receptor 5 in brain reward deficits associated with cocaine and nicotine withdrawal and somatic signs of nicotine withdrawal. Psychopharmacology (Berl). 2012a; 221:317–327. [PubMed: 22147259]

Stoker AK, Olivier B, Markou A. Role of alpha7- and beta4-containing nicotinic acetylcholine receptors in the affective and somatic aspects of nicotine withdrawal: studies in knockout mice. Behav Genet. 2012b; 42:423–436. [PubMed: 22009521]

Stoker AK, Semenova S, Markou A. Affective and somatic aspects of spontaneous and precipitated nicotine withdrawal in C57BL/6J and BALB/cByJ mice. Neuropharmacology. 2008; 54:1223–1232. [PubMed: 18452957]

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

Sugiura T, Kondo S, Sukagawa A, Nakane S, Shinoda A, Itoh K, et al. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. Biochem Biophys Res Commun. 1995; 215:89–97. [PubMed: 7575630]

Suzuki T, Ise Y, Mori T, Misawa M. Attenuation of mecamylamine-precipitated nicotine- withdrawal aversion by the 5-HT3 receptor antagonist ondansetron. Life Sci. 1997; 61:L249–L254.

Suzuki T, Ise Y, Tsuda M, Maeda J, Misawa M. Mecamylamine-precipitated nicotine- withdrawal aversion in rats. Eur J Pharmacol. 1996; 314:281–284. [PubMed: 8957247]

Swan GE, Ward MM, Jack LM. Abstinence effects as predictors of 28-day relapse in smokers. Addict Behav. 1996; 21:481–490. [PubMed: 8830906]

Takahashi H, Takada Y, Nagai N, Urano T, Takada A. Effects of nicotine and footshock stress on dopamine release in the striatum and nucleus accumbens. Brain Res Bull. 1998; 45:157–162. [PubMed: 9443833]

Talhout R, Opperhuizen A, van Amsterdam JG. Role of acetaldehyde in tobacco smoke addiction. Eur Neuropsychopharmacol. 2007; 17:627–636. [PubMed: 17382522]

Tejeda HA, Natividad LA, Orfila JE, Torres OV, O'Dell LE. Dysregulation of kappa- opioid receptor systems by chronic nicotine modulate the nicotine withdrawal syndrome in an age-dependent manner. Psychopharmacology (Berl). 2012; 224:289–301. [PubMed: 22659976]

Teli T, Markovic D, Levine MA, Hillhouse EW, Grammatopoulos DK. Regulation of corticotropin-releasing hormone receptor type 1alpha signaling: structural determinants for G protein-coupled receptor kinase-mediated phosphorylation and agonist-mediated desensitization. Mol Endocrinol. 2005; 19:474–490. [PubMed: 15498832]

Thorgeirsson TE, Geller F, Sulem P, Rafnar T, Wiste A, Magnusson KP, et al. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. Nature. 2008; 452:638–642. [PubMed: 18385739]

Trigo JM, Zimmer A, Maldonado R. Nicotine anxiogenic and rewarding effects are decreased in mice lacking beta-endorphin. Neuropharmacology. 2009; 56:1147–1153. [PubMed: 19376143]

Tsuda K, Tsuda S, Nishio I, Masuyama Y, Goldstein M. Effects of galanin on dopamine release in the central nervous system of normotensive and spontaneously hypertensive rats. Am J Hypertens. 1998; 11:1475–1479. [PubMed: 9880130]

Van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, et al. Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science. 2005; 310:329–332. [PubMed: 16224028]

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; 63:863–872. [PubMed: 22727822]

Varani AP, Moutinho LM, Calvo M, Balerio GN. Ability of baclofen to prevent somatic manifestations and neurochemical changes during nicotine withdrawal. Drug Alcohol Depend. 2011; 119:e5–e12. [PubMed: 21733642]

Vlachou S, Paterson NE, Guery S, Kaupmann K, Froestl W, Banerjee D, et al. Both GABA(B) receptor activation and blockade exacerbated anhedonic aspects of nicotine withdrawal in rats. Eur J Pharmacol. 2011; 655:52–58. [PubMed: 21262222]

Wang JC, Cruchaga C, Saccone NL, Bertelsen S, Liu P, Budde JP, et al. Risk for nicotine dependence and lung cancer is conferred by mRNA expression levels and amino acid change in CHRNA5. Hum Mol Genet. 2009; 18:3125–3135. [PubMed: 19443489]

Ward MM, Swan GE, Jack LM. Self-reported abstinence effects in the first month after smoking cessation. Addict Behav. 2001; 26:311–327. [PubMed: 11436924]

Watkins SS, Koob GF, Markou A. Neural mechanisms underlying nicotine addiction: acute positive reinforcement and withdrawal. Nicotine Tob Res. 2000; 2:19–37. [PubMed: 11072438]

West R, Hajek P, McNeill A. Effect of buspirone on cigarette withdrawal symptoms and short-term abstinence rates in a smokers clinic. Psychopharmacology (Berl). 1991; 104:91–96. [PubMed: 1882007]

Wilkinson DS, Gould TJ. The effects of galantamine on nicotine withdrawal-induced deficits in contextual fear conditioning in C57BL/6 mice. Behav Brain Res. 2011; 223:53–57. [PubMed: 21514327]

Wilkinson DS, Turner JR, Blendy JA, Gould TJ. Genetic background influences the effects of withdrawal from chronic nicotine on learning and high-affinity nicotinic acetylcholine receptor binding in the dorsal and ventral hippocampus. Psychopharmacology (Berl). 2013; 225:201–208. [PubMed: 22836371]

Wilkinson JL, Bevins RA. Intravenous nicotine conditions a place preference in rats using an unbiased design. Pharmacol Biochem Behav. 2008; 88:256–264. [PubMed: 17888504]

Wilmouth CE, Spear LP. Withdrawal from chronic nicotine in adolescent and adult rats. Pharmacol Biochem Behav. 2006; 85:648–657. [PubMed: 17173961]

Wonnacott S. Presynaptic nicotinic ACh receptors. Trends Neurosci. 1997; 20:92–98. [PubMed: 9023878]

Xue Y, Domino EF. Tobacco/nicotine and endogenous brain opioids. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32:1131–1138. [PubMed: 18215788]

Yuan Z, McCauley R, Chen-Scarabelli C, Abounit K, Stephanou A, Barry SP, et al. Activation of Src protein tyrosine kinase plays an essential role in urocortin-mediated cardioprotection. Mol Cell Endocrinol. 2010; 325:1–7. [PubMed: 20416357]

Zaniewska M, McCreary AC, Wydra K, Filip M. Effects of serotonin (5-HT)2 receptor ligands on depression-like behavior during nicotine withdrawal. Neuropharmacology. 2010; 58:1140–1146. [PubMed: 20153341]

Zhang L, Dong Y, Doyon WM, Dani JA. Withdrawal from chronic nicotine exposure alters dopamine signaling dynamics in the nucleus accumbens. Biol Psychiatry. 2012; 71:184–191. [PubMed: 21872847]

Zhao-Shea R, Liu L, Pang X, Gardner PD, Tapper AR. Activation of GABAergic neurons in the interpeduncular nucleus triggers physical nicotine withdrawal symptoms. Curr Biol. 2013; 23:2327–2335. [PubMed: 24239118]

Zhou X, Nonnemaker J, Sherrill B, Gilsenan AW, Coste F, West R. Attempts to quit smoking and relapse: factors associated with success or failure from the ATTEMPT cohort study. Addict Behav. 2009; 34:365–373. [PubMed: 19097706]

Zhu AZ, Cox LS, Nollen N, Faseru B, Okuyemi KS, Ahluwalia JS, et al. CYP2B6 and bupropion's smoking-cessation pharmacology: the role of hydroxybupropion. Clin Pharmacol Ther. 2012; 92:771–777. [PubMed: 23149928]