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Mechanistic insights into nicotine withdrawal

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Abstract

Smoking is responsible for over 400,000 premature deaths in the United States every year, making it the leading cause of preventable death. In addition, smoking-related illness leads to billions of dollars in healthcare expenditures and lost productivity annually. The public is increasingly aware that successfully abstaining from smoking at any age can add years to one's life and reduce many of the harmful effects of smoking. Although the majority of smokers desire to quit, only a small fraction of attempts to quit are actually successful. The symptoms associated with nicotine withdrawal are a primary deterrent to cessation and they need to be quelled to avoid early relapse. This review will focus on the neuroadaptations caused by chronic nicotine exposure and discuss how those changes lead to a withdrawal syndrome upon smoking cessation. Besides examining how nicotine usurps the endogenous reward system, we will discuss how the habenula is part of a circuit that plays a critical role in the aversive effects of high nicotine doses and nicotine withdrawal. We will also provide an updated summary of the role of various nicotinic receptor subtypes in the mechanisms of withdrawal. This growing knowledge provides mechanistic insights into current and future smoking cessation therapies.

Keywords

Reward; negative motivation; dopamine; withdrawal; VTA; nucleus accumbens; habenula; addiction; drug abuse; nicotinic receptors; nicotinic knockout mice

1 Introduction

In the United States, about 21% of adults currently smoke cigarettes [1]. Cigarette smoking is the leading cause of preventable death, responsible for 443,000 premature deaths every year. The economic impact is staggering, with a cost to the health care system of about $96 billion and $97 billion in lost productivity [2]. Smoking decreases one's life expectancy mostly due to tobacco-related vascular, neoplastic, and respiratory disease [3]. Specifically, lung cancer is highly attributable to smoking and is the leading cause of cancer death among men and women [4]. To never smoke is obviously the best strategy to avoid the deleterious consequences of smoking, but for those who have become addicted, quitting brings

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significant benefits. A smoker who quits at 35 years of age will live about 8 years longer than a continuing smoker [5], and will have a similar life expectancy as a never smoker [3]. Even quitting in old age can add years to one's life [5]. However, in a given year, only 3% of smokers are actually successful in their cessation attempts, even though 70% of smokers express desire to quit [6].

Nicotine, the major addictive component of tobacco, binds to nicotinic acetylcholine receptors (nAChR). nAChRs are ligand gated ion channels activated by the endogenous neurotransmitter acetylcholine (ACh). Neuronal type nAChRs are composed of differing combinations of α and β subunits, with nine genes encoding α subunits (α2–10) and three encoding β subunits (β2–4)[7–9]. α7 homomers and α4β2 heteromers represent the two major nAChR subtypes found throughout the brain but other nAChR subunit combinations are expressed in selected brain areas [9–13].

Genetic, developmental, and environmental factors determine whether someone will become addicted to the nicotine contained in tobacco [6, 14, 15] and will start to smoke compulsively, despite well known health consequences [16, 17]. The addiction process involves the activation of various brain circuits, including the dopaminergic (DAergic) reward system and the circuits that underlie motivation, decision making, and habit formation [18]. Many neurotransmitters and neuropeptides are involved in the process, as nAChRs are strategically positioned to modulate the release of virtually every major neurotransmitter [8, 19, 20]. The neuroadaptations arising from chronic nicotine exposure cause widespread alterations in brain neurotransmission that promote and sustain the use of tobacco [21–24]. Smoking cessation disrupts the equilibrium maintained in the presence of nicotine and leads to the manifestations of withdrawal. The symptoms associated with the nicotine abstinence syndrome contribute to the maintenance of the smoking habit and are a potent deterrent for those who are trying to quit [25–27]. The following sections summarize our current understanding of the mechanisms underlying the behavioral manifestations of nicotine withdrawal and discuss existing and potential strategies for smoking cessation.

2 The Dopaminergic system, goal-directed behavior, and nicotine's effects

2.1 Role of the Dopaminergic system

The ventral tegmental area (VTA) and substantia nigra provide the major source of dopamine (DA) in the brain. The role of the DAergic system (in particular the mesocorticolimbic pathway) in drug addiction derives from DA's ability to modulate many of the limbic and cortical sites involved in goal-directed behavior (Fig. 1) [18, 28–31]. Presentation of natural reinforcers, such as food and sex, causes DA neurons to switch from low-frequency tonic activity at rest to phasic bursting. The DA released encodes reward prediction errors and incentive salience and provides a learning signal for the optimization of goal-directed behavior [31, 32]. Addictive drugs, including nicotine, hijack the mechanisms of experience-dependent adaptive behavior and lead to abnormally high DA levels [33]. Repeated exposure to the drug results in synaptic adaptations that produce behavioral changes. Although changes in DA levels are the main feature of addictive drugs, it should be kept in mind that other neurotransmitters and neuropeptides participate in nicotine reward, including glutamate, cannabinoids, and opioids [34–37].

2.2 Cholinergic influences over midbrain DA neurons and ventral striatum

The cholinergic system exerts a profound effect on DAergic activity as ACh released in the VTA promotes the switch between tonic and phasic activity in DAergic neurons that signals reward and salience [38, 39]. Cholinergic inputs to the midbrain DA center originate from the pedunculopontine tegmentum (PPT) and the laterodorsal tegmentum (LDT) in which cholinergic neurons are interspersed with GABAergic and glutamatergic neurons [40–42].

The PPT/LDT are also the source of the excitatory glutamatergic inputs to the DA neurons projecting to the nucleus accumbens (NAcc) [40]. Various nAChR subtypes are expressed on midbrain DA, GABA, and glutamatergic neurons, and nAChRs are also expressed on afferent projections including those from cortex, PPT/LDT, and the NAcc [43–45]. nAChRs are also present on DAergic axon terminals [13, 46] and GABA interneurons in the NAcc [47]. In the NAcc, cholinergic innervation arises from striatal interneurons [48–50]. Each of these neuronal subpopulations expresses nAChRs of differing subunit compositions and with differing cellular localizations [8, 9, 51]. By binding to those nAChRs, nicotine can alter DAergic activity by directly activating DA neurons in the VTA and by modulating the release probability of both inhibitory and excitatory neurotransmitters from presynaptic terminals in VTA and NAcc. These actions result in enhanced neuronal firing beyond that normally driven by environmental cues and contribute to the addiction process [52]. Pharmacological experiments, the analysis of nAChR null mice, and lentivirus-based re-expression studies are providing constant refinement to our understanding of the effects of nicotine on the circuits underlying goal-directed behavior (Table 1).

2.3 The habenula as a source of anti-reward

Although it was originally postulated that the DA released from the VTA only mediates the hedonic or pleasurable effects of natural reinforcers, it is now clear that changes in DAergic activity can also signal punishment, aversion, or lack of expected reward [53–58]. Reward omission induces phasic inhibition of VTA neurons [56, 57] and aversive stimuli excite ventral [58] and inhibit dorsal [55] VTA neurons. Moreover, aversive stimuli increase the firing of NAcc neurons [59]. The fact that inhibition of VTA neurons can signal the motivational value of unexpected and aversive stimuli suggests the existence of neuronal circuits that interact, and partially overlap, to maximize reward and minimize aversive effects. Nicotine follows an inverted U-shaped dose-response curve [18, 60], and smokers titrate their nicotine intake to experience the rewarding while avoiding the aversive effects produced by high nicotine doses [61–64]. Our understanding of the circuits and molecular mechanisms governing the processing of aversive stimuli, including the effects of high nicotine doses, is still limited. However, the habenular complex, which receives inputs from the VTA, is emerging as an important component in the process.

The habenula is an epithalamic nucleus involved in the mechanisms of fear, anxiety, depression, and stress [18, 30, 65, 66]. It is divided into the medial nucleus (MHb) and the two divisions of the lateral nucleus (LHb). The LHb receives inputs mainly from the basal ganglia and sends outputs to DAergic neurons and serotonergic neurons, while the MHb receives inputs mainly from the limbic system and sends outputs to the interpeduncular nucleus (IPN) [67]. Studies conducted in recent years have identified the LHb as a source of anti-reward signals that plays an important role in determining the reward-related activity of DA neurons [18, 30, 68–70]. The firing patterns of glutamatergic LHb neurons mirror those of DA cells: spike activity increases in LHb neurons in the absence of predicted reward and decreases upon delivery of reward [69, 70]. Furthermore, electrical stimulation of the LHb inhibits the vast majority of DA neurons [69, 71, 72]. Such inhibition is not direct, but rather occurs through the stimulation of neurons in the rostromedial tegmental nucleus (RMTg) [73]. The RMTg sends GABAergic inhibitory projections to the VTA and substantia nigra [54, 74, 75] and provides tonic inhibition of DA cells [30]. Similarly to the LHb, RMTg neurons are phasically activated by aversive stimuli and inhibited by natural rewards like food or reward predictive stimuli [54].

Although it is currently unknown whether the MHb contributes directly to the regulation of monoamine transmission, the literature suggests an involvement of the MHb/IPN axis with brain reward areas. Electrical stimulation of the MHb and the fasciculus retroflexus, the primary efferent pathway of the MHb, produces rewarding effects [76], and most stimulant

drugs of abuse cause axonal degeneration in the lateral habenula and the fasciculus retroflexus. In particular, nicotine causes degeneration of neurons in the portion of the fasciculus retroflexus that connects the MHb to the IPN [77, 78]. A recent report suggests that α5-containing nAChRs in the MHb are key to the control of the amounts of nicotine self-administered as α5−/− mice continue to self-administer nicotine at doses that normally elicit strong aversion in wild type animals [79, 80]. However, lentiviral-based re-expression of the α5 subunit in the MHb or the IPN is sufficient to bring nicotine self-administration back to wild type levels [80]. Additionally, blocking cholinergic transmission in either the MHb or IPN is sufficient to precipitate somatic signs of nicotine withdrawal [81]. Taken together, these data suggest a prominent role of the MHb/IPN axis in nicotine dependence because of its involvement in mediating nicotine's aversive effects and somatic symptoms of withdrawal.

2.4 Nicotine induced neuroadaptations

Nicotine dependence is accompanied by neuroadaptive changes that occur especially in the circuits underlying emotion and motivation [23, 82]. Neuronal nAChR upregulation is an important adaptive change and a major contributor to the addictive properties of nicotine [83–86]. Nicotine desensitizes nAChRs and renders them unresponsive and this phenomenon drives an increase in receptor levels as part of an attempt to maintain circuit-level homeostasis [87–89]. Upregulation of nAChRs is the product of several concurrent mechanisms, including changes in receptor assembly, trafficking, and degradation [18, 90]. Isomerization of surface nAChRs to high-affinity nicotinic sites has also been proposed to result from prolonged nicotine exposure [91, 92]. Relevant to the understanding of the neuroadaptations produced by nicotine is the fact that nAChR upregulation differs among receptor subtypes, varies among brain regions for the same subtype, and even depends on the contingency of nicotine administration [9, 90, 93]. Because of this phenomenon, the way in which cholinergic inputs modulate neurotransmitter release is completely altered.

Besides altering cholinergic function, repeated nicotine exposure produces heterologous adaptations. For example, nicotine increases AMPA/NMDA current ratios (a hallmark of long-term potentiation) at DA neurons [94–96] and other locations involved in drug-associated memory [97–99]. In the NAcc, nicotine leads to an increase in high affinity DA D2 receptors [100]. Such a phenomenon is analogous to that observed upon cocaine exposure, which leads to an increase in G-protein coupled DA D2 receptors and consequent DA supersensitivity in cocaine-treated animals [101]. A similar form of plasticity might occur during nicotine exposure. Nicotine self-administration also decreases expression of the cystine-glutamate exchanger, xCT, in the NAcc and VTA, and decreases the glial glutamate transporter, GLT-1, in the NAcc [102]. Synaptic function might also be altered by changes in the turnover of scaffolding proteins, a phenomenon reflecting nicotine's partial inhibition of proteasomal function [86, 103, 104].

Another system that is affected by nicotine exposure is the endogenous opioid system [105–107]. The endogenous opioid system influences both negative and positive motivational and affective states [108]. Opioid peptides affect DA function in the VTA and the striatum. In particular, dynorphins decrease and enkephalins increase DA release [109–115]. Conversely, DA controls the synthesis of striatal dynorphin and enkephalin by affecting their mRNA levels [106, 116]. Nicotine affects these system-level and cellular interactions by altering synthesis and release of opioid peptides in a time- and peptide-specific fashion [36]. The ensuing plasticity participates in the mechanisms that maintain nicotine consumption but also participate in the nicotine-withdrawal syndrome [7, 106]. What we discussed above are examples of the complex changes produced by nicotine. As nAChR activation affects the release of virtually every major neurotransmitter [106, 117, 118], chronic nicotine exposure is likely to cause global alterations in brain neurotransmission.

These complex, within-system and between-system adaptations create a new equilibrium that requires the presence of nicotine to be maintained.

3. Nicotine Withdrawal: Definition, Neurobiology, Animals models

3.1 Definition of Nicotine Withdrawal

Withdrawal is a collection of affective and somatic symptoms that emerge a few hours after nicotine abstinence and reflect the imbalance in brain neurochemistry created by the absence of nicotine. Seven nicotine withdrawal symptoms were validated in a recent comprehensive review on the topic [119] and appear in the DSM-IV-TR [120]. The symptoms are irritability/anger/frustration, anxiety, depression/negative affect, concentration problems, impatience, insomnia, and restlessness. Other symptoms (including altered neurohormonal profiles, perturbations of learned behaviors, weight gain, decreased heart rate, constipation, and mouth ulcers) are also likely valid symptoms but require further study [119, 121, 122]. Many of these symptoms are common to other drugs of abuse, but weight gain and decreased heart rate appear to be more specific to nicotine withdrawal [123]. Nicotine withdrawal symptoms are typically reported to reach a peak within the first week of abstinence and taper off for the next 3–4 weeks [119, 124]. However, some reports indicate that symptoms can subside within 10 days [125], while others indicate that withdrawal symptoms may persist past 31 days [126, 127].

Nicotine withdrawal symptoms are highly variable between patients and can be quite severe, with increased severity of withdrawal being predictive of increased rates of relapse [25, 27, 128–130]. Powerful cravings also accompany withdrawal, which may be precipitated by the sight of a cigarette, or a situation/place associated with the act of smoking [131]. The emergence of negative affective symptoms, such as dysphoria, anxiety and irritability and, to a lesser extent, the somatic manifestations of withdrawal, serve as negative reinforcers that sustain the vicious cycle of addiction [23, 121, 132–134]. Continued use or relapse is therefore driven not only by the pursuit of hedonically positive effects but also the avoidance of negative states associated with withdrawal.

3.2 Neural Basis of Withdrawal

Abrupt cessation of nicotine alters the neurochemistry of the addicted brain, thus triggering the affective and somatic signs of withdrawal. Acute withdrawal from all major drugs of abuse, including nicotine, decreases activity of the mesolimbic DAergic system, [135–139] and the consequent decrease in accumbal DA levels is likely the main trigger of the withdrawal syndrome. The hypodopaminergic state associated with withdrawal is produced by both a reduction in DA release and an increase in DA re-uptake [140]. Increased DA re-uptake is due to upregulation of the DA transporter (DAT) [137, 141]. Interestingly, the deficits in DA transmission observed in the NAcc during withdrawal are paralleled by an increase in DA output in the prefrontal cortex (PFC) [138]. Such increases in PFC DA release may be important in mediating some of the aversive aspects of nicotine withdrawal. Enhanced DA transmission in the PFC occurs during exposure to stressful and aversive stimuli [142–144], and contributes to anxiety-related behaviors [145, 146]. Anxiety and stress exert complex influences on all aspects of nicotine dependence, including the withdrawal syndrome. Due to its perceived calming effects, smoking is often used by smokers as a tool to attenuate stress and anxiety [147–149]. Anxiety is a symptom of withdrawal and it acts as a potent negative reinforcer that promotes smoking [120, 124, 150–152]. Besides being a product of nicotine withdrawal, stress and anxiety can exacerbate the symptoms of withdrawal, which leads to increased craving and relapse [151, 153–156].

The central nucleus of the amygdala (CeA), together with the bed nucleus of the stria terminalis and the posterior shell of the NAcc is part of the “extended amygdala” [157]. This

circuit and the HPA axis play crucial roles in the processing of the negative affective states associated with drug withdrawal [23, 24, 157]. Elevations in corticosterone and corticotropin-releasing factor (CRF) are observed during acute withdrawal from many drugs, including nicotine [21, 24]. CRF levels increase by >500% in the CeA after nicotine withdrawal is precipitated with the nAChR antagonist mecamylamine [158]. Injection of a CRF_1 receptor antagonist into the CeA blunts anxiety-like behavior during nicotine withdrawal [158]. These data collectively suggest that smoking cessation rates could be improved by quelling anxiety with drugs that address the dysregulation of the stress response system observed during withdrawal.

As already discussed in section 2.4, nicotine-induced neuroadaptations occur at many brain sites and affect several neurotransmitter systems. Therefore, nicotine withdrawal is expected to disrupt many of the neurotransmitter and neuropeptide systems that had adapted to the chronic presence of the drug [132]. The opioid system, dynorphin in particular, seems to be engaged in the mechanisms of nicotine withdrawal [106]. Other candidates are the serotoninergic and the noradrenergic systems which are known to mediate the manifestations of withdrawal from other drugs of abuse [159–162].

3.3 Animal Models of Withdrawal

Animal models of nicotine deprivation are invaluable tools for the understanding of the molecular underpinning of nicotine withdrawal symptoms and provide a way to test potential smoking cessation agents. Rodents chronically exposed to nicotine undergo a characteristic withdrawal syndrome which develops spontaneously, after removing the nicotine source, or can be precipitated by administration of a nAChR antagonist such as mecamylamine [7, 11, 81, 163–166]. Several behavioral tests are available to explore both the somatic and affective dimensions of withdrawal. The distinction between somatic and affective symptoms originated from the notion that the somatic signs reflect mainly peripheral, “bodily” mechanisms in contrast with the affective symptoms which are produced by centrally based mechanisms [167, 168]. This distinction is still maintained although there is evidence that, besides a peripheral nAChR component, somatic signs might have a central component that reflects a dysphoric state of heightened irritability [166, 169].

The following section briefly describes the tests most commonly used to assess nicotine withdrawal symptoms in rodents. In addition, based on pharmacologic studies and the analysis of nAChR mutant mice, it provides a summary of the most recent advances in the understanding of the nAChR subtypes and the brain areas involved in the nicotine withdrawal syndrome.

3.3.1 Somatic signs of withdrawal—The somatic manifestations of nicotine withdrawal in rodents can be detected as an increase in several stereotypic behaviors. Somatic signs of withdrawal include chewing, teeth-chattering, shakes, tremors, writhing, palpebral ptosis, gasps, and yawns [7, 163]. The analysis of nAChR mutant mice has helped to identify the brain region and the nAChR subtypes that are responsible for the somatic manifestations of nicotine withdrawal (Table 2). Somatic withdrawal can be precipitated by mecamylamine microinjection into the MHb or the IPN, but not into hippocampus, cortex, or VTA [81]. The MHb/IPN express nAChRs comprising the α2 (IPN), α5, and/or β4 nAChR subunits and absence of any one of those nAChR subunits abolishes the somatic manifestations of nicotine withdrawal [11, 81, 170]. α7-containing nAChRs might contribute to, but are not necessary for, the somatic manifestation of nicotine abstinence [171]. Interestingly, somatic signs of withdrawal are preserved in mice lacking the β2 or the α6 nAChR subunits [11, 172] even though, as seen in section 3.3.2, those subunits are critical for other aspects of withdrawal. These studies demonstrate that the MHb/IPN axis

and specific nAChRs expressed within that axis are critical for at least the somatic signs of the nicotine withdrawal syndrome. In combination with the data showing that a circuit comprising the MHb and IPN is involved in controlling the intake of normally aversive doses of nicotine [80], the results suggest that, similarly to the LHb, the MHb may process signals with aversive valence.

3.3.2 Affective/cognitive symptoms of withdrawal—Affective symptoms such as anhedonia (inability to find pleasure in previously enjoyable activities), anxiety, and irritability are some of the most commonly reported manifestations of nicotine withdrawal in humans [119]. Affective signs of withdrawal can also be examined in rodents using behavioral paradigms that test for anhedonia, conditioned place aversion, anxiety, and conditioned fear [7, 165–167, 173].

Reward/Anhedonia: Intracranial self stimulation is a well established experimental procedure used to measure reward [174, 175]. Rodents will repeatedly self stimulate in reward-related areas such as the posterior lateral hypothalamus and the VTA where changes in thresholds for self stimulation can be monitored [167, 174, 176]. The threshold for intracranial self stimulation decreases with increased function of the brain reward systems and increases when activity in the same centers is reduced. Drugs of abuse, including nicotine, lower reward thresholds [174, 177–179]. The effects of nicotine are long lasting and are blocked by nicotinic, but not muscarinic, antagonists [178–181]. Like many of the effects of nicotine, reward threshold also presents a U-shaped dose-response curve: at higher doses of nicotine the reward threshold increases above baseline. This effect is dependent upon the α5 nAChR subunit in the MHb, since a rat will maintain a decreased reward threshold at higher doses when α5 is knocked down with lentiviral vector-based shRNA [80].

Withdrawal from drugs of abuse leads to decreased function of the reward system and changes ICSS thresholds [175, 182]. Such a phenomenon is thought to represent a negative affective state associated with withdrawal. Rats undergoing spontaneous withdrawal from chronic nicotine treatment show a dramatic increase in reward thresholds [167]. Normally neutral stimuli, such as a light or a tone, will also increase ICSS thresholds if that stimulus is paired with withdrawal from nicotine [183]. This phenomenon indicates that environmental cues associated with abstinence from nicotine may reduce the function of brain reward centers.

Conditioned Place Aversion: Conditioned place aversion (CPA) is a paradigm designed to test an animal's drive to avoid contextual cues associated with a negative affect. Animals chronically treated with nicotine are confined in one of two chambers of the CPA apparatus while experiencing nicotine withdrawal symptoms triggered by the injection of a nAChR antagonist. On a different day, the same mice are injected with saline and exposed to the other chamber of the CPA apparatus. During training, associations are made between the negative affective state produced by withdrawal and the withdrawal-paired chamber so that exposure to the apparatus on testing day triggers avoidance of the compartment associated with the withdrawal effects. Both the α4β2 nAChR antagonist dihydro-β-erythroidine (DHβE) and mecamylamine produce CPA in nicotine-treated rats, although the doses needed to elicit the behavior may be higher than those required to increase ICSS thresholds [184–188]. These differences may signify the existence of different mechanisms for ICSS and CPA, but might also reflect strain-specific differences [186, 187]. Pharmacological studies in nAChR null mice indicate that β2-containing and α6-containing nAChRs are necessary for CPA, but neither the α5, nor the α7 subunits affect CPA behavior [170, 172, 189].

Anxiety-related behaviors: Nicotine withdrawal can elicit anxiety-like behaviors in mice [190–192]. The most common paradigm used to observe these behaviors is the elevated plus maze (EPM) [193]. When nicotine withdrawal is precipitated in mice or rats, the animals spend significantly less time in the open arms of the EPM than saline-treated mice, a phenomenon that signals increased anxiety [165, 194]. In the open field paradigm, mecamylamine-precipitated nicotine withdrawal is accompanied by a dramatic increase in thigmotaxis, i.e. an increase in the time spent in the periphery of the open field [195, 196]

Other animal models of anxiety are also altered by nicotine withdrawal. The light-dark box is a testing paradigm in which a mouse is placed in a novel environment that contains a brightly lit compartment and a dark compartment. The mouse will preferentially remain in the dark half of the box. The amount of time spent in the lit half and the time it takes for the mouse to cross into the lit half are measures of anxiety-like behaviors. Mice undergoing spontaneous withdrawal from nicotine will spend less time in the lit compartment relative to nicotine naïve mice [190, 192]. The influence of various nAChR subtypes on withdrawal-induced anxiety-like behaviors has not been examined exhaustively. So far, it has been established that the β2 and α6 nAChR subunits are necessary for increased anxiety during withdrawal [170, 172], whereas, α5 and α7 may not be required [170].

Fear Conditioning: Trace fear conditioning is a conditioning paradigm in which the conditioned stimulus (CS) is presented and then terminated with a time interval before the unconditioned stimulus (US) is applied [197]. Cued delay fear conditioning, in which the CS co-terminates with the US, is known to be hippocampus independent, whereas trace fear conditioning is dependent on the hippocampal circuitry [197]. Nicotine is known to enhance hippocampus-dependent contextual and cued trace fear conditioning, but not cued delay fear conditioning [198]. This enhancement by nicotine requires β2-containing but not α7-containing nAChRs [199]. Also, systemic administration of NMDA receptor antagonists inhibits acquisition of contextual fear conditioning [200]. This effect is ameliorated by co-administration of systemic nicotine acting at α4β2-containing nAChRs, as indicated by antagonism with DHβE [200].

As with many effects of acute or chronic drug use, the withdrawal syndrome often results in an opposite effect. Since nicotine enhances trace fear conditioning, one could expect withdrawal to cause a deficit in the same paradigm. Raybuck and Gould [201] demonstrated that spontaneous withdrawal from chronic nicotine leads to deficits in the acquisition of trace fear conditioning. Withdrawal precipitated by DHβE, but not methyllycaconitine (MLA), led to a similar deficit, implicating high-affinity receptors such as those containing the α4, and the β2/β4 nAChR subunits. Confirming this result, β2-null mice were not observed to have a deficit in trace fear conditioning upon spontaneous nicotine withdrawal [201].

Five-choice serial reaction time task: Tobacco deprivation impairs attention and cognitive abilities within 12 h of smoking cessation [202–204]. Models of attention might be useful to test this dimension of the nicotine withdrawal syndrome. The five-choice serial reaction time task (5-CSRTT) is a visual attention task [205] that can reliably detect cognitive aspects of nicotine withdrawal [206, 207]. Significant deficits in sustained attention were seen after spontaneous withdrawal from nicotine in male rats [206], as well as during withdrawal precipitated with DHβE [206]. The α7 nAChR antagonist MLA failed to precipitate attention deficits in nicotine-treated rats [206], suggesting that α4β2-containing, but not α7-containing nAChRs are important for 5-CSRTT.

4. Pharmacotherapy of nicotine addiction

4.1 Current therapies

To be successful, anti-smoking strategies need to reduce the motivation to smoke and the physiological and psychomotor symptoms experienced during a quit attempt. All current therapeutic strategies, albeit with different mechanisms, address the hypodopaminergic state produced by withdrawal in the VTA. Other mechanisms of action might also contribute to their ability to promote smoking cessation.

Nicotine replacement therapy—Nicotine replacement therapy (NRT) has been the primary pharmacologic aid for tobacco cessation. As nicotine is the principal addictive component of cigarettes and other tobacco products, supplementing the user with nicotine during abstinence will ease the transition from smoking to complete abstinence by relieving withdrawal and nicotine craving [6, 208]. Because nicotine undergoes first pass metabolism in the liver, the bioavailability of nicotine administered *per os* is reduced. To avoid this problem, nicotine replacement products are formulated for absorption through the oral mucosa (chewing gum, lozenges, sublingual tablets, inhaler) or the skin (transdermal patches). Regardless of the route of administration (gum, patch, nasal spray, or inhaler), NRT decreases withdrawal scores by a similar degree [209]. NRT roughly doubles quit rates compared to placebo, but a large percentage of subjects relapses to smoking within 6 to 12 months [210, 211]. For smokers who declare unwillingness or inability to attempt an abrupt quit, the 12-month sustained abstinence success rate is 5.3% with NRT versus approximately 2.6% with placebo. In smokers willing to attempt an abrupt quit with NRT, the success rate is around 16% with NRT versus 10% with placebo [212]. Newer, more targeted pharmacotherapies have led to significant improvements in aiding tobacco cessation rates [213].

Bupropion—Bupropion is an atypical antidepressant and smoking cessation aid that exerts its actions by targeting multiple neurotransmitter systems [214]. Inhibition of catecholamine reuptake is one of bupropion's mechanisms of action [215]. Microdialysis studies indicate that bupropion treatment increases extracellular concentrations of DA and norepinephrine (NE) in the hypothalamus, PFC, and NAcc [216]. The drug may also function by increasing NE levels in the dorsal raphe nucleus, thus leading to increased serotonin (5-HT) levels [217]. Besides reducing NE, DA, and 5-HT reuptake, the drug increases the activity of vesicular monoamine transporters [214]. Bupropion also functions as a non-competitive antagonist at many nAChR subtypes [218]. Bupropion inhibits the function of α3β2-, α4β2-, and α7-nAChRs heterologously expressed in Xenopus oocytes [219]. It also non-competitively inhibits carbamylcholine-induced $^{86}Rb^{+}$ efflux from human neuroblastoma cells expressing α3β4-containing nAChRs [218]. α3β4-containing nAChRs are believed to play a major role in nicotine-evoked NE release from the hippocampus [220, 221]. In addition, the α3 and β4 nAChR subunits are expressed at high levels in the MHb/IPN axis [222–224], which, as discussed in section 2.3, is emerging as a brain circuit involved in the processing of anti-reward stimuli and nicotine withdrawal [11, 80, 222].

Preclinical studies suggest that bupropion and nicotine might exert similar systems level effects. Both drugs are psychomotor stimulants [225, 226] and both increase catecholamine concentrations in midbrain limbic regions [214, 227]. In addition, both nicotine and bupropion serve as primary reinforcers in non-human subjects [228] and increase responding for reinforcing non-drug stimuli [229–231]. Therefore, the anti-smoking properties of bupropion may depend on its ability to substitute some of the psychomotor and/or reinforcement-related effects of nicotine [232]. Bupropion improves rates of abstinence to

14–18% of subjects [150, 233], which are further augmented to 29% when the drug is combined with NRT [210, 234, 235].

Varenicline—Varenicline is the third medication, besides NRT and bupropion, to be approved by the Food and Drug Administration for smoking cessation. It is a derivative of cytisine, a plant alkaloid with selective affinity and partial agonism for α4β2 nAChRs [236–238]. Varenicline has been touted as being effective through its partial agonism of α4β2 nAChRs. This effect is thought to decrease withdrawal and cravings [239]. Varenicline can block nicotine-induced decreases in brain stimulation thresholds, suggesting that it makes smoking less enjoyable [240]. Varenicline's effect is removed by pre-treatment with the non-selective nicotinic antagonist mecamylamine, or the α4-containing nAChR specific antagonist DHβE. On the other hand, the α7-specific antagonist, MLA, has no effect on reward thresholds [240]. Besides acting at α4β2-containing nAChRs, varenicline has significant effects at other nAChR subtypes. It acts as a partial agonist at α3β4-, α2-, and α6-containing nAChRs, and a full agonist at α7 nAChRs [238]. Varenicline's interactions with α3β4-, α2-, or α6-containing nAChRs might also contribute to its therapeutic effects given the role of those receptors in both the rewarding and/or aversive effects of nicotine [11, 13, 80, 81].

Two large, randomized, placebo-controlled studies released in 2006 related the efficacy of varenicline to that of bupropion in aided smoking cessation [233, 241]. Nearly one quarter (21–23%) of patients taking varenicline for a short period of time (12 weeks) maintained abstinence at 52 weeks of follow-up. This represents a significant improvement over sustained-release bupropion (14–16%) and placebo (8–10%). Further analyzing the mechanisms of this effect, negative affect and craving associated with abstinence were decreased in patients taking varenicline relative to placebo [233]. However, the drug had no significant effect on restlessness, insomnia, or increased appetite. Gonzales and colleagues [241] found a similar decrease in negative affect, but also found a significant decrease in restlessness in patients taking varenicline. Individuals who relapsed derived less enjoyment from smoking while taking varenicline [241]. A very recent review of the literature suggests that, overall, varenicline works better than bupropion as a smoking cessation aid, although it is not clear how superior it is to NRT in the long term. Two open label, randomized controlled trial were unable to confirm significant improvements with varenicline over NRT in continuous abstinence rates at 52 weeks following short term treatment [213, 242, 243]. However, it should be noted that the 52 week abstinence rate for NRT was found to be 20.4%, higher than most previously reported rates, while varenicline maintained the usual reported rate (26.1%) [242].

Although bupropion and varenicline were proven safe in clinical trials, safety concerns have arisen based on post-marketing reports that led to the addition of warnings in the prescribing information of the two drugs. Although a causal relationship has not been established, serious adverse events in patients treated with bupropion or varenicline include changes in behavior, depression, self-injurious thoughts, and suicidal behavior [234, 244]. Because long-term tobacco use causes morbidity in a high percentage of subjects and ends up killing half of all long-term smokers, the benefits of the two drugs outweigh the risks of serious adverse events in a small percentage of subjects. However, the occurrence of serious side effects and the relatively small, long-term rates of abstinence in smokers serve as an impetus for the development of new, safer therapeutic interventions [239, 245].

Nicotine vaccine—All the previously described pharmacotherapies require compliance to maintain efficacy. Nicotine vaccination offers a promising, more permanent approach to aid the willing addict in cessation attempts. Exposure to nicotine conjugated to immunogenic proteins (e.g. cholera toxin b, a virus-like particle, and Pseudomonas exotoxin A) leads to

production of IgGs, some of which will be targeted against nicotine [239, 246]. Anti-nicotine antibodies will bind to nicotine with high affinity and specificity, thus preventing or at least slowing nicotine's entry into the brain [247]. Decreasing the rate of absorption and the actions of an addictive drug on its targets reduce its rewarding effects and may aid in quitting [247, 248]. A recent preclinical study demonstrated the efficacy of this approach [249]. After immunization using Pseudomonas exoprotein A conjugated to nicotine, rats exposed to cigarette smoke demonstrated a significant increase in serum nicotine levels, indicating prevention of nicotine entry into the brain. With a 10 minute nose-only exposure, modeling one cigarette, brain levels of nicotine were reduced by 90% in the vaccinated animals. After a 2 hour whole body exposure to smoke, a 35% reduction in brain nicotine was detected [249]. These results confirm other studies using non-inhalation routes of administration [250–252]. Early phase 1/2 clinical trials in humans have demonstrated drug safety, effective immunogenicity, and promising increases in abstinence rates, especially among individuals with higher levels of anti-nicotine IgGs [253–256]. Whether a nicotine vaccine is going to be effective for real-world use remains an open question. The results of ongoing clinical trials are eagerly awaited.

5. Conclusions

Chronic exposure to nicotine produces neuroadaptations in a host of neurotransmitter and neuropeptide systems. Those neuroadaptations are responsible for the psychological and behavioral symptoms associated with nicotine abstinence and make nicotine addiction so hard to break. Driven by preclinical studies in various animal models as well as human studies, the improved understanding of the mechanisms involved in nicotine dependence has led to new treatments. Targeting of the α4β2 nAChR subtype with varenicline significantly improves abstinence rates, and recent studies provide additional nAChR targets that might help to design more effective pharmacological agents. A multipronged approach that could simultaneously address the dysfunction of the DAergic system, the deficits in executive control over the drug, and the connection between stress/anxiety and nicotine consumption would indeed offer the best relief from the symptoms of withdrawal. Finally, a nicotine vaccine, if effective, could provide a paradigm shift in the treatment of nicotine dependence. The concerted effort of basic scientists and clinicians will be needed to stop the global epidemic of tobacco-related disease and premature mortality.

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Abbreviations

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
BLA	basolateral amygdala
BNST	bed nucleus of the stria terminalis
CeA	central nucleus of the amygdala

5-CSRTT	five-choice serial reaction time task
CPA	conditioned place aversion
CRF	corticotropin-releasing factor
DA	dopamine
DHβE	dihydro-β-erythroidine
EPM	elevated plus maze
GABA	γ-aminobutyric acid
5-HT	5-hydroxytryptophan
ICSS	intracranial self-stimulation
LDT	laterodorsal tegmentum
MLA	methyllycaconitine
NMDA	N-methyl-D-aspartic acid
NAcc	nucleus accumbens
NE	norepinephrine
PFC	prefrontal cortex
PPT	pedunculopontine tegmentum
VTA	ventral tegmental area

References

1. CDC. Vital signs: current cigarette smoking among adults aged >or=18 years --- United States, 2009. MMWR Morb Mortal Wkly Rep. 2010; 59(35):1135–40. [PubMed: 20829747]
2. CDC. Smoking-attributable mortality, years of potential life lost, and productivity losses--United States, 2000–2004. MMWR Morb Mortal Wkly Rep. 2008; 57(45):1226–8. [PubMed: 19008791]
3. Doll R, et al. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ. 2004; 328(7455):1519. [PubMed: 15213107]
4. Jemal A, et al. Cancer statistics, 2010. CA Cancer J Clin. 2010; 60(5):277–300. [PubMed: 20610543]
5. Taylor DH Jr, et al. Benefits of smoking cessation for longevity. Am J Public Health. 2002; 92(6): 990–6. [PubMed: 12036794]
6. Benowitz NL. Nicotine addiction. N Engl J Med. 2010; 362(24):2295–303. [PubMed: 20554984]
7. De Biasi M, Salas R. Influence of neuronal nicotinic receptors over nicotine addiction and withdrawal. Exp Biol Med (Maywood). 2008; 233(8):917–29. [PubMed: 18480414]
8. Dani JA, Bertrand D. Nicotinic acetylcholine receptors and nicotinic cholinergic mechanisms of the central nervous system. Annu Rev Pharmacol Toxicol. 2007; 47:699–729. [PubMed: 17009926]
9. Gotti C, et al. Structural and functional diversity of native brain neuronal nicotinic receptors. Biochem Pharmacol. 2009; 78(7):703–11. [PubMed: 19481063]
10. Salas R, et al. The nicotinic acetylcholine receptor subunit alpha 5 mediates acute effects of nicotine in vivo. Molecular Pharmacology. 2003; 63:1059–1066. [PubMed: 12695534]
11. Salas R, Pieri F, De Biasi M. Decreased signs of nicotine withdrawal in mice null for the beta4 nicotinic acetylcholine receptor subunit. J Neurosci. 2004; 24(45):10035–9. [PubMed: 15537871]
12. Exley R, et al. Alpha6-containing nicotinic acetylcholine receptors dominate the nicotine control of dopamine neurotransmission in nucleus accumbens. Neuropsychopharmacology. 2008; 33(9): 2158–66. [PubMed: 18033235]

13. Exley R, et al. Distinct contributions of nicotinic acetylcholine receptor subunit {alpha}4 and subunit {alpha}6 to the reinforcing effects of nicotine. Proc Natl Acad Sci U S A. 2011
14. Bierut LJ. Genetic vulnerability and susceptibility to substance dependence. Neuron. 2011; 69(4): 618–27. [PubMed: 21338875]
15. Carpenter CM, Wayne GF, Connolly GN. The role of sensory perception in the development and targeting of tobacco products. Addiction. 2007; 102(1):136–47. [PubMed: 17207131]
16. Samet JM. The 1990 Report of the Surgeon General: The Health Benefits of Smoking Cessation. Am Rev Respir Dis. 1990; 142(5):993–4. [PubMed: 2240852]
17. CDC. Publications and Reports of the Surgeon General. 2010. Smoking-Attributable Disease: A Report of the Surgeon General.
18. De Biasi M, Dani JA. Reward, Addiction, Withdrawal to Nicotine. Annu Rev Neurosci. 2011
19. Albuquerque EX, et al. Mammalian nicotinic acetylcholine receptors: from structure to function. Physiol Rev. 2009; 89(1):73–120. [PubMed: 19126755]
20. Wonnacott S, et al. Nicotinic receptors modulate transmitter cross talk in the CNS: nicotinic modulation of transmitters. J Mol Neurosci. 2006; 30(1–2):137–40. [PubMed: 17192660]
21. Koob G, Kreek MJ. Stress, Dysregulation of Drug Reward Pathways, and the Transition to Drug Dependence. Am J Psychiatry. 2007; 164(8):1149–1159. [PubMed: 17671276]
22. Kenny PJ, Markou A. Neurobiology of the nicotine withdrawal syndrome. Pharmacol Biochem Behav. 2001; 70(4):531–49. [PubMed: 11796152]
23. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010; 35(1):217–38. [PubMed: 19710631]
24. Koob GF, Le Moal M. Addiction and the brain antireward system. Annu Rev Psychol. 2008; 59:29–53. [PubMed: 18154498]
25. West RJ, Hajek P, Belcher M. Severity of withdrawal symptoms as a predictor of outcome of an attempt to quit smoking. Psychol Med. 1989; 19(4):981–5. [PubMed: 2594893]
26. Piasecki TM, Fiore MC, Baker TB. Profiles in discouragement: two studies of variability in the time course of smoking withdrawal symptoms. J Abnorm Psychol. 1998; 107(2):238–51. [PubMed: 9604553]
27. al'Absi M, et al. Prospective examination of effects of smoking abstinence on cortisol and withdrawal symptoms as predictors of early smoking relapse. Drug Alcohol Depend. 2004; 73(3): 267–78. [PubMed: 15036549]
28. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science. 1997; 275(5306):1593–9. [PubMed: 9054347]
29. Wise RA. Roles for nigrostriatal--not just mesocorticolimbic--dopamine in reward and addiction. Trends Neurosci. 2009; 32(10):517–24. [PubMed: 19758714]
30. Ikemoto S. Brain reward circuitry beyond the mesolimbic dopamine system: A neurobiological theory. Neuroscience & Biobehavioral Reviews. 2010; 35(2):129–150. [PubMed: 20149820]
31. Schultz W. Dopamine signals for reward value and risk: basic and recent data. Behav Brain Funct. 2010; 6:24. [PubMed: 20416052]
32. Bromberg-Martin ES, Matsumoto M, Hikosaka O. Dopamine in motivational control: rewarding, aversive, and alerting. Neuron. 2010; 68(5):815–34. [PubMed: 21144997]
33. Blum K, et al. Reward Circuitry Dopaminergic Activation Regulates Food and Drug Craving Behavior. Curr Pharm Des. 2011
34. Liechti ME, Markou A. Role of the glutamatergic system in nicotine dependence : implications for the discovery and development of new pharmacological smoking cessation therapies. CNS Drugs. 2008; 22(9):705–24. [PubMed: 18698872]
35. Wooters TE, Bevins RA, Bardo MT. Neuropharmacology of the interoceptive stimulus properties of nicotine. Curr Drug Abuse Rev. 2009; 2(3):243–55. [PubMed: 20443771]
36. Berrendero F, et al. Neurobiological mechanisms involved in nicotine dependence and reward: participation of the endogenous opioid system. Neurosci Biobehav Rev. 2010; 35(2):220–31. [PubMed: 20170672]
37. Maldonado R, Berrendero F. Endogenous cannabinoid and opioid systems and their role in nicotine addiction. Curr Drug Targets. 2010; 11(4):440–9. [PubMed: 20017727]

38. Wanat MJ, et al. Phasic dopamine release in appetitive behaviors and drug addiction. Curr Drug Abuse Rev. 2009; 2(2):195–213. [PubMed: 19630749]
39. Grace AA, et al. Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. Trends Neurosci. 2007; 30(5):220–7. [PubMed: 17400299]
40. Omelchenko N, Sesack SR. Laterodorsal tegmental projections to identified cell populations in the rat ventral tegmental area. J Comp Neurol. 2005; 483(2):217–35. [PubMed: 15678476]
41. Maskos U. The cholinergic mesopontine tegmentum is a relatively neglected nicotinic master modulator of the dopaminergic system: relevance to drugs of abuse and pathology. Br J Pharmacol. 2008; 153(S1):S438–S445. [PubMed: 18223661]
42. Maskos U. Role of endogenous acetylcholine in the control of the dopaminergic system via nicotinic receptors. J Neurochem. 2010; 114(3):641–6. [PubMed: 20477938]
43. Kalivas PW. Neurotransmitter regulation of dopamine neurons in the ventral tegmental area. Brain Res Brain Res Rev. 1993; 18(1):75–113. [PubMed: 8096779]
44. Steffensen SC, et al. Electrophysiological characterization of GABAergic neurons in the ventral tegmental area. J Neurosci. 1998; 18(19):8003–15. [PubMed: 9742167]
45. Walaas I, Fonnum F. Biochemical evidence for gamma-aminobutyrate containing fibres from the nucleus accumbens to the substantia nigra and ventral tegmental area in the rat. Neuroscience. 1980; 5(1):63–72. [PubMed: 7366843]
46. Threlfell S, Cragg SJ. Dopamine signaling in dorsal versus ventral striatum: the dynamic role of cholinergic interneurons. Front Syst Neurosci. 2011; 5:11. [PubMed: 21427783]
47. de Rover M, et al. Cholinergic modulation of nucleus accumbens medium spiny neurons. Eur J Neurosci. 2002; 16(12):2279–90. [PubMed: 12492422]
48. Woolf NJ. Cholinergic systems in mammalian brain and spinal cord. Prog Neurobiol. 1991; 37(6): 475–524. [PubMed: 1763188]
49. Contant C, et al. Ultrastructural characterization of the acetylcholine innervation in adult rat neostriatum. Neuroscience. 1996; 71(4):937–47. [PubMed: 8684624]
50. Calabresi P, et al. Acetylcholine-mediated modulation of striatal function. Trends Neurosci. 2000; 23(3):120–6. [PubMed: 10675916]
51. Klink R, et al. Molecular and physiological diversity of nicotinic acetylcholine receptors in the midbrain dopaminergic nuclei. J Neurosci. 2001; 21(5):1452–63. [PubMed: 11222635]
52. Sulzer D. How addictive drugs disrupt presynaptic dopamine neurotransmission. Neuron. 2011; 69(4):628–49. [PubMed: 21338876]
53. Schultz W. Predictive reward signal of dopamine neurons. J Neurophysiol. 1998; 80(1):1–27. [PubMed: 9658025]
54. Jhou TC, et al. The rostromedial tegmental nucleus (RMTg), a GABAergic afferent to midbrain dopamine neurons, encodes aversive stimuli and inhibits motor responses. Neuron. 2009; 61(5): 786–800. [PubMed: 19285474]
55. Ungless MA, Magill PJ, Bolam JP. Uniform inhibition of dopamine neurons in the ventral tegmental area by aversive stimuli. Science. 2004; 303(5666):2040–2. [PubMed: 15044807]
56. Schultz W. Multiple dopamine functions at different time courses. Annu Rev Neurosci. 2007; 30:259–88. [PubMed: 17600522]
57. Schultz W. Behavioral dopamine signals. Trends in Neurosciences. 2007; 30(5):203–210. [PubMed: 17400301]
58. Brischoux F, et al. Phasic excitation of dopamine neurons in ventral VTA by noxious stimuli. Proc Natl Acad Sci U S A. 2009; 106(12):4894–9. [PubMed: 19261850]
59. Roitman MF, Wheeler RA, Carelli RM. Nucleus accumbens neurons are innately tuned for rewarding and aversive taste stimuli, encode their predictors, and are linked to motor output. Neuron. 2005; 45(4):587–97. [PubMed: 15721244]
60. Picciotto MR. Nicotine as a modulator of behavior: beyond the inverted U. Trends Pharmacol Sci. 2003; 24(9):493–9. [PubMed: 12967775]
61. Hutchison MA, Riley AL. Adolescent exposure to nicotine alters the aversive effects of cocaine in adult rats. Neurotoxicol Teratol. 2008; 30(5):404–11. [PubMed: 18558472]

62. Benowitz NL, Jacob P 3rd. Trans-3′-hydroxycotinine: disposition kinetics, effects and plasma levels during cigarette smoking. Br J Clin Pharmacol. 2001; 51(1):53–9. [PubMed: 11167665]
63. Kassel JD, et al. Smoking topography in response to denicotinized and high-yield nicotine cigarettes in adolescent smokers. J Adolesc Health. 2007; 40(1):54–60. [PubMed: 17185206]
64. Dani, JA.; Kosten, TR.; Benowitz, NL. The pharmacology of nicotine and tobacco. In: Ries, RK., et al., editors. Principles of Addiction Medicine. Wolters Kluwer/Lippincott, Williams & Wilkins; Philadelphia, PA: 2009. p. 179-91.
65. Winter C, et al. Pharmacological inhibition of the lateral habenula improves depressive-like behavior in an animal model of treatment resistant depression. Behav Brain Res. 2011; 216(1): 463–5. [PubMed: 20678526]
66. Geisler S, Trimble M. The lateral habenula: no longer neglected. CNS Spectr. 2008; 13(6):484–9. [PubMed: 18567972]
67. Hikosaka O. The habenula: from stress evasion to value-based decision-making. Nat Rev Neurosci. 2010; 11(7):503–13. [PubMed: 20559337]
68. Matsumoto M. Role of the lateral habenula and dopamine neurons in reward processing. Brain Nerve. 2009; 61(4):389–96. [PubMed: 19378808]
69. Matsumoto M, Hikosaka O. Lateral habenula as a source of negative reward signals in dopamine neurons. Nature. 2007; 447(7148):1111–5. [PubMed: 17522629]
70. Hikosaka O, et al. Habenula: crossroad between the basal ganglia and the limbic system. J Neurosci. 2008; 28(46):11825–9. [PubMed: 19005047]
71. Christoph GR, Leonzio RJ, Wilcox KS. Stimulation of the lateral habenula inhibits dopamine-containing neurons in the substantia nigra and ventral tegmental area of the rat. J Neurosci. 1986; 6(3):613–9. [PubMed: 3958786]
72. Ji H, Shepard PD. Lateral Habenula Stimulation Inhibits Rat Midbrain Dopamine Neurons through a GABAA Receptor-Mediated Mechanism. J Neurosci. 2007; 27(26):6923–30. [PubMed: 17596440]
73. Perrotti LI, et al. DeltaFosB accumulates in a GABAergic cell population in the posterior tail of the ventral tegmental area after psychostimulant treatment. Eur J Neurosci. 2005; 21(10):2817–24. [PubMed: 15926929]
74. Jhou TC, et al. The mesopontine rostromedial tegmental nucleus: A structure targeted by the lateral habenula that projects to the ventral tegmental area of Tsai and substantia nigra compacta. J Comp Neurol. 2009; 513(6):566–96. [PubMed: 19235216]
75. Balcita-Pedicino, J., et al. rostromedial mesopontine tegmentum as a relay between the lateral habenula and dopamine neurons in the ventral tegmental area: ultrastructural evidence in the rat. 2009 Annual Meeting Society for Neuroscience; 2009; Chicago, IL.
76. Sutherland RJ, Nakajima S. Self-stimulation of the habenular complex in the rat. J Comp Physiol Psychol. 1981; 95(5):781–91. [PubMed: 6975784]
77. Ellison G, et al. The neurotoxic effects of continuous cocaine and amphetamine in Habenula: implications for the substrates of psychosis. NIDA Res Monogr. 1996; 163:117–45. [PubMed: 8809856]
78. Ellison G. Neural degeneration following chronic stimulant abuse reveals a weak link in brain, fasciculus retroflexus, implying the loss of forebrain control circuitry. Eur Neuropsychopharmacol. 2002; 12(4):287–97. [PubMed: 12126867]
79. Fowler, C.; Kenny, P. Intravenous nicotine self-administration in wildtype and α5 nicotinic acetylcholine receptor subunit knockout mice. Society for Neuroscience Annual Meeting; 2009; Chicago, IL.
80. Fowler CD, et al. Habenular alpha5 nicotinic receptor subunit signalling controls nicotine intake. Nature. 2011; 471(7340):597–601. [PubMed: 21278726]
81. Salas R, et al. Nicotinic receptors in the habenulo-interpeduncular system are necessary for nicotine withdrawal in mice. J Neurosci. 2009; 29(10):3014–8. [PubMed: 19279237]
82. Solomon RL, Corbit JD. An opponent-process theory of motivation. I. Temporal dynamics of affect. Psychol Rev. 1974; 81(2):119–45. [PubMed: 4817611]
83. Wonnacott S. The paradox of nicotinic acetylcholine receptor upregulation by nicotine. Trends Pharmacol Sci. 1990; 11(6):216–9. [PubMed: 2200178]

84. Marks MJ, et al. Nicotine binding and nicotinic receptor subunit RNA after chronic nicotine treatment. J Neurosci. 1992; 12(7):2765–84. [PubMed: 1613557]

85. Buisson B, Bertrand D. Chronic exposure to nicotine upregulates the human (alpha)4((beta)2 nicotinic acetylcholine receptor function. J Neurosci. 2001; 21(6):1819–29. [PubMed: 11245666]

86. Rezvani K, et al. Nicotine regulates multiple synaptic proteins by inhibiting proteasomal activity. J Neurosci. 2007; 27(39):10508–19. [PubMed: 17898222]

87. Fenster CP, et al. Upregulation of surface alpha4beta2 nicotinic receptors is initiated by receptor desensitization after chronic exposure to nicotine. J Neurosci. 1999; 19(12):4804–14. [PubMed: 10366615]

88. Dani JA, Heinemann S. Molecular and cellular aspects of nicotine abuse. Neuron. 1996; 16(5): 905–8. [PubMed: 8630247]

89. Picciotto MR, et al. It is not “either/or”: activation and desensitization of nicotinic acetylcholine receptors both contribute to behaviors related to nicotine addiction and mood. Prog Neurobiol. 2008; 84(4):329–42. [PubMed: 18242816]

90. Lester HA, et al. Nicotine is a selective pharmacological chaperone of acetylcholine receptor number and stoichiometry. Implications for drug discovery. Aaps J. 2009; 11(1):167–77. [PubMed: 19280351]

91. Buisson B, Bertrand D. Nicotine addiction: the possible role of functional upregulation. Trends Pharmacol Sci. 2002; 23(3):130–6. [PubMed: 11879680]

92. Vallejo YF, et al. Chronic nicotine exposure upregulates nicotinic receptors by a novel mechanism. J Neurosci. 2005; 25(23):5563–72. [PubMed: 15944384]

93. Gentry CL, Lukas RJ. Regulation of nicotinic acetylcholine receptor numbers and function by chronic nicotine exposure. Curr Drug Targets CNS Neurol Disord. 2002; 1(4):359–85. [PubMed: 12769610]

94. Gao M, et al. Mechanisms involved in systemic nicotine-induced glutamatergic synaptic plasticity on dopamine neurons in the ventral tegmental area. J Neurosci. 2010; 30(41):13814–25. [PubMed: 20943922]

95. Placzek AN, Zhang TA, Dani JA. Nicotinic mechanisms influencing synaptic plasticity in the hippocampus. Acta Pharmacol Sin. 2009; 30(6):752–60. [PubMed: 19434057]

96. Saal D, et al. Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. Neuron. 2003; 37(4):577–82. [PubMed: 12597856]

97. Dani JA, De Biasi M. Cellular mechanisms of nicotine addiction. Pharmacol Biochem Behav. 2001; 70(4):439–46. [PubMed: 11796143]

98. Kauer JA, Malenka RC. Synaptic plasticity and addiction. Nat Rev Neurosci. 2007; 8(11):844–58. [PubMed: 17948030]

99. Tang J, Dani JA. Dopamine Enables In Vivo Synaptic Plasticity Associated with the Addictive Drug Nicotine. Neuron. 2009; 63(5):673–682. [PubMed: 19755109]

100. Novak G, Seeman P, Le Foll B. Exposure to nicotine produces an increase in dopamine D2(High) receptors: a possible mechanism for dopamine hypersensitivity. Int J Neurosci. 2010; 120(11): 691–7. [PubMed: 20942582]

101. Briand LA, et al. Cocaine self-administration produces a persistent increase in dopamine D2 High receptors. Eur Neuropsychopharmacol. 2008; 18(8):551–6. [PubMed: 18284941]

102. Knackstedt LA, et al. The role of cystine-glutamate exchange in nicotine dependence in rats and humans. Biol Psychiatry. 2009; 65(10):841–5. [PubMed: 19103434]

103. Hwang YY, Li MD. Proteins differentially expressed in response to nicotine in five rat brain regions: identification using a 2-DE/MS-based proteomics approach. Proteomics. 2006; 6(10): 3138–53. [PubMed: 16622831]

104. Rezvani K, et al. UBXD4, a UBX-containing protein, regulates the cell surface number and stability of alpha3-containing nicotinic acetylcholine receptors. J Neurosci. 2009; 29(21):6883–96. [PubMed: 19474315]

105. Berrendero F, et al. Nicotine-induced antinociception, rewarding effects, and physical dependence are decreased in mice lacking the preproenkephalin gene. J Neurosci. 2005; 25(5):1103–12. [PubMed: 15689546]

106. Hadjiconstantinou M, Neff NH. Nicotine and endogenous opioids: Neurochemical and pharmacological evidence. Neuropharmacology. 2011; 60(7–8):1209–20. [PubMed: 21108953]
107. Trigo JM, et al. The endogenous opioid system: a common substrate in drug addiction. Drug Alcohol Depend. 2010; 108(3):183–94. [PubMed: 19945803]
108. Steiner H, Gerfen CR. Role of dynorphin and enkephalin in the regulation of striatal output pathways and behavior. Exp Brain Res. 1998; 123(1–2):60–76. [PubMed: 9835393]
109. Devine DP, et al. Differential involvement of ventral tegmental mu, delta and kappa opioid receptors in modulation of basal mesolimbic dopamine release: in vivo microdialysis studies. J Pharmacol Exp Ther. 1993; 266(3):1236–46. [PubMed: 7690399]
110. Di Chiara G, Imperato A. Opposite effects of mu and kappa opiate agonists on dopamine release in the nucleus accumbens and in the dorsal caudate of freely moving rats. J Pharmacol Exp Ther. 1988; 244(3):1067–80. [PubMed: 2855239]
111. Longoni R, et al. (D-Ala2)deltorphin II: D1-dependent stereotypies and stimulation of dopamine release in the nucleus accumbens. J Neurosci. 1991; 11(6):1565–76. [PubMed: 1646295]
112. Pentney RJ, Gratton A. Effects of local delta and mu opioid receptor activation on basal and stimulated dopamine release in striatum and nucleus accumbens of rat: an in vivo electrochemical study. Neuroscience. 1991; 45(1):95–102. [PubMed: 1661389]
113. Spanagel R, Herz A, Shippenberg TS. The effects of opioid peptides on dopamine release in the nucleus accumbens: an in vivo microdialysis study. J Neurochem. 1990; 55(5):1734–40. [PubMed: 1976759]
114. Spanagel R, Herz A, Shippenberg TS. Identification of the opioid receptor types mediating beta-endorphin-induced alterations in dopamine release in the nucleus accumbens. Eur J Pharmacol. 1990; 190(1–2):177–84. [PubMed: 1981749]
115. Spanagel R, Herz A, Shippenberg TS. Opposing tonically active endogenous opioid systems modulate the mesolimbic dopaminergic pathway. Proc Natl Acad Sci U S A. 1992; 89(6):2046–50. [PubMed: 1347943]
116. Angulo JA, McEwen BS. Molecular aspects of neuropeptide regulation and function in the corpus striatum and nucleus accumbens. Brain Res Brain Res Rev. 1994; 19(1):1–28. [PubMed: 7909470]
117. Kenny PJ. Tobacco dependence, the insular cortex and the hypocretin connection. Pharmacol Biochem Behav. 2011; 97(4):700–7. [PubMed: 20816891]
118. Picciotto MR. Common aspects of the action of nicotine and other drugs of abuse. Drug Alcohol Depend. 1998; 51(1–2):165–72. [PubMed: 9716938]
119. Hughes JR. Effects of abstinence from tobacco: valid symptoms and time course. Nicotine Tob Res. 2007; 9(3):315–27. [PubMed: 17365764]
120. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4. Washington, D.C: 2000. text revision ed
121. Koob GF, Le Moal M. Plasticity of reward neurocircuitry and the ‘dark side’ of drug addiction. Nat Neurosci. 2005; 8(11):1442–4. [PubMed: 16251985]
122. Buchhalter, AR.; Fant, RV.; Henningfield, JE. Nicotine. In: Sibley, DR., et al., editors. Handbook of contemporary neuropharmacology. John Wiley & Sons, Inc; 2007. p. 535-566.
123. Hughes JR, Higgins ST, Bickel WK. Nicotine withdrawal versus other drug withdrawal syndromes: similarities and dissimilarities. Addiction. 1994; 89(11):1461–70. [PubMed: 7841857]
124. Hughes JR, et al. Symptoms of tobacco withdrawal. A replication and extension. Arch Gen Psychiatry. 1991; 48(1):52–9. [PubMed: 1984762]
125. Shiffman S, et al. Natural history of nicotine withdrawal. Addiction. 2006; 101(12):1822–32. [PubMed: 17156182]
126. Gilbert DG, et al. EEG, physiology, and task-related mood fail to resolve across 31 days of smoking abstinence: relations to depressive traits, nicotine exposure, and dependence. Exp Clin Psychopharmacol. 1999; 7(4):427–43. [PubMed: 10609977]
127. Gilbert DG, et al. Mood disturbance fails to resolve across 31 days of cigarette abstinence in women. J Consult Clin Psychol. 2002; 70(1):142–52. [PubMed: 11860040]

128. Piasecki TM, et al. Smoking withdrawal dynamics: II. Improved tests of withdrawal-relapse relations. J Abnorm Psychol. 2003; 112(1):14–27. [PubMed: 12653410]
129. Piasecki TM, et al. Smoking withdrawal dynamics: III. Correlates of withdrawal heterogeneity. Exp Clin Psychopharmacol. 2003; 11(4):276–85. [PubMed: 14599261]
130. Piasecki TM, et al. Smoking withdrawal dynamics: I. Abstinence distress in lapsers and abstainers. J Abnorm Psychol. 2003; 112(1):3–13. [PubMed: 12653409]
131. Shiffman S, et al. Immediate antecedents of cigarette smoking: an analysis from ecological momentary assessment. J Abnorm Psychol. 2002; 111(4):531–45. [PubMed: 12428767]
132. Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology. 2001; 24(2):97–129. [PubMed: 11120394]
133. Piper ME, et al. Anxiety diagnoses in smokers seeking cessation treatment: relations with tobacco dependence, withdrawal, outcome and response to treatment. Addiction. 2011; 106(2):418–27. [PubMed: 20973856]
134. Allen SS, et al. Craving, withdrawal, and smoking urges on days immediately prior to smoking relapse. Nicotine Tob Res. 2008; 10(1):35–45. [PubMed: 18188743]
135. Hildebrand BE, et al. Reduced dopamine output in the nucleus accumbens but not in the medial prefrontal cortex in rats displaying a mecamylamine-precipitated nicotine withdrawal syndrome. Brain Res. 1998; 779(1–2):214–25. [PubMed: 9473676]
136. Rada P, Jensen K, Hoebel BG. Effects of nicotine and mecamylamine-induced withdrawal on extracellular dopamine and acetylcholine in the rat nucleus accumbens. Psychopharmacology (Berl). 2001; 157(1):105–10. [PubMed: 11512050]
137. Rahman S, et al. Neuroadaptive changes in the mesoaccumbens dopamine system after chronic nicotine self-administration: a microdialysis study. Neuroscience. 2004; 129(2):415–24. [PubMed: 15501598]
138. Carboni E, et al. Dissociation of physical abstinence signs from changes in extracellular dopamine in the nucleus accumbens and in the prefrontal cortex of nicotine dependent rats. Drug Alcohol Depend. 2000; 58(1–2):93–102. [PubMed: 10669059]
139. Weiss F, et al. Basal extracellular dopamine levels in the nucleus accumbens are decreased during cocaine withdrawal after unlimited-access self-administration. Brain Res. 1992; 593(2):314–8. [PubMed: 1450939]
140. Duchemin AM, et al. Increased expression of VMAT2 in dopaminergic neurons during nicotine withdrawal. Neurosci Lett. 2009; 467(2):182–6. [PubMed: 19835933]
141. Hadjiconstantinou M, et al. Enhanced dopamine transporter function in striatum during nicotine withdrawal. Synapse. 2011; 65(2):91–8. [PubMed: 20506223]
142. Thierry AM, et al. Selective activation of mesocortical DA system by stress. Nature. 1976; 263(5574):242–4. [PubMed: 958479]
143. Inglis FM, Moghaddam B. Dopaminergic innervation of the amygdala is highly responsive to stress. J Neurochem. 1999; 72(3):1088–94. [PubMed: 10037480]
144. Kawasaki H, et al. Single-neuron responses to emotional visual stimuli recorded in human ventral prefrontal cortex. Nat Neurosci. 2001; 4(1):15–6. [PubMed: 11135639]
145. Bradberry CW, Lory JD, Roth RH. The anxiogenic beta-carboline FG 7142 selectively increases dopamine release in rat prefrontal cortex as measured by microdialysis. J Neurochem. 1991; 56(3):748–52. [PubMed: 1993892]
146. Broersen LM, et al. Prefrontal dopamine is directly involved in the anxiogenic interoceptive cue of pentylenetetrazol but not in the interoceptive cue of chlordiazepoxide in the rat. Psychopharmacology (Berl). 2000; 149(4):366–76. [PubMed: 10867964]
147. Parrott AC. Stress modulation over the day in cigarette smokers. Addiction. 1995; 90(2):233–44. [PubMed: 7703817]
148. Cohen S, Lichtenstein E. Perceived stress, quitting smoking, and smoking relapse. Health Psychol. 1990; 9(4):466–78. [PubMed: 2373070]
149. Pomerleau OF, Pomerleau CS. Neuroregulators and the reinforcement of smoking: towards a biobehavioral explanation. Neurosci Biobehav Rev. 1984; 8(4):503–13. [PubMed: 6151160]

150. Jorenby DE, et al. Characterization of tobacco withdrawal symptoms: transdermal nicotine reduces hunger and weight gain. Psychopharmacology (Berl). 1996; 128(2):130–8. [PubMed: 8956374]

151. Brown RA, et al. Anxiety sensitivity: relationship to negative affect smoking and smoking cessation in smokers with past major depressive disorder. Addict Behav. 2001; 26(6):887–99. [PubMed: 11768550]

152. Doherty K, et al. Urges to smoke during the first month of abstinence: relationship to relapse and predictors. Psychopharmacology (Berl). 1995; 119(2):171–8. [PubMed: 7659764]

153. Morissette SB, et al. Anxiety, anxiety disorders, tobacco use, and nicotine: a critical review of interrelationships. Psychol Bull. 2007; 133(2):245–72. [PubMed: 17338599]

154. Sinha R. How does stress increase risk of drug abuse and relapse? Psychopharmacology (Berl). 2001; 158(4):343–59. [PubMed: 11797055]

155. Perkins KA, Grobe JE. Increased desire to smoke during acute stress. Br J Addict. 1992; 87(7): 1037–40. [PubMed: 1643396]

156. Carey MP, et al. Stress and unaided smoking cessation: a prospective investigation. J Consult Clin Psychol. 1993; 61(5):831–8. [PubMed: 8245280]

157. Koob GF. The role of CRF and CRF-related peptides in the dark side of addiction. Brain Res. 2010; 1314:3–14. [PubMed: 19912996]

158. George O, 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(43):17198–203. [PubMed: 17921249]

159. Slotkin TA, Seidler FJ. A unique role for striatal serotonergic systems in the withdrawal from adolescent nicotine administration. Neurotoxicol Teratol. 2007; 29(1):10–6. [PubMed: 16919421]

160. Fletcher PJ, Le AD, Higgins GA. Serotonin receptors as potential targets for modulation of nicotine use and dependence. Prog Brain Res. 2008; 172:361–83. [PubMed: 18772042]

161. Bruijnzeel AW, et al. Effects of prazosin, clonidine, and propranolol on the elevations in brain reward thresholds and somatic signs associated with nicotine withdrawal in rats. Psychopharmacology (Berl). 2010; 212(4):485–99. [PubMed: 20697697]

162. Semenova S, Markou A. The alpha2 adrenergic receptor antagonist idazoxan, but not the serotonin-2A receptor antagonist M100907, partially attenuated reward deficits associated with nicotine, but not amphetamine, withdrawal in rats. Eur Neuropsychopharmacol. 2010; 20(10): 731–46. [PubMed: 20627663]

163. Malin DH, et al. Rodent model of nicotine abstinence syndrome. Pharmacol Biochem Behav. 1992; 43(3):779–84. [PubMed: 1448472]

164. Hildebrand BE, et al. Behavioral manifestations of the nicotine abstinence syndrome in the rat: peripheral versus central mechanisms. Psychopharmacology (Berl). 1997; 129(4):348–56. [PubMed: 9085404]

165. Damaj MI, Kao W, Martin BR. Characterization of spontaneous and precipitated nicotine withdrawal in the mouse. J Pharmacol Exp Ther. 2003; 307(2):526–34. [PubMed: 12970387]

166. Malin DH, Goyarzu P. Rodent models of nicotine withdrawal syndrome. Handb Exp Pharmacol. 2009; 192:401–34. [PubMed: 19184657]

167. Epping-Jordan MP, et al. Dramatic decreases in brain reward function during nicotine withdrawal. Nature. 1998; 393(6680):76–9. [PubMed: 9590692]

168. Watkins SS, et al. Reward and Somatic Changes during Precipitated Nicotine Withdrawal in Rats: Centrally and Peripherally Mediated Effects. J Pharmacol Exp Ther. 2000; 292(3):1053–1064. [PubMed: 10688623]

169. Salas R, et al. Nicotinic Receptors in the Habenulo-Interpeduncular System Are Necessary for Nicotine Withdrawal in Mice. 2009:3014–3018.

170. Jackson KJ, et al. Differential role of nicotinic acetylcholine receptor subunits in physical and affective nicotine withdrawal signs. J Pharmacol Exp Ther. 2008; 325(1):302–12. [PubMed: 18184829]

171. Salas R, et al. Decreased withdrawal symptoms but normal tolerance to nicotine in mice null for the [alpha]7 nicotinic acetylcholine receptor subunit. Neuropharmacology. 2007; 53(7):863–869. [PubMed: 17920082]

172. Jackson KJ, et al. The role of alpha6-containing nicotinic acetylcholine receptors in nicotine reward and withdrawal. J Pharmacol Exp Ther. 2009; 331(2):547–54. [PubMed: 19644040]

173. Davis JA, et al. Withdrawal from chronic nicotine administration impairs contextual fear conditioning in C57BL/6 mice. J Neurosci. 2005; 25(38):8708–13. [PubMed: 16177040]

174. Kornetsky C, et al. Intracranial self-stimulation thresholds: a model for the hedonic effects of drugs of abuse. Arch Gen Psychiatry. 1979; 36(3):289–92. [PubMed: 420547]

175. Markou A, Koob GF. Construct validity of a self-stimulation threshold paradigm: effects of reward and performance manipulations. Physiol Behav. 1992; 51(1):111–9. [PubMed: 1741436]

176. Hayes DJ, Clements R, Greenshaw AJ. Effects of systemic and intra-nucleus accumbens 5-HT2C receptor compounds on ventral tegmental area self-stimulation thresholds in rats. Psychopharmacology (Berl). 2009; 203(3):579–88. [PubMed: 19031071]

177. Kornetsky C, Esposito RU. Euphorigenic drugs: effects on the reward pathways of the brain. Fed Proc. 1979; 38(11):2473–6. [PubMed: 488370]

178. Ivanova S, Greenshaw AJ. Nicotine-induced decreases in VTA electrical self-stimulation thresholds: blockade by haloperidol and mecamylamine but not scopolamine or ondansetron. Psychopharmacology (Berl). 1997; 134(2):187–92. [PubMed: 9399383]

179. Markou A. Review. Neurobiology of nicotine dependence. Philos Trans R Soc Lond B Biol Sci. 2008; 363(1507):3159–68. [PubMed: 18640919]

180. Kenny PJ, et al. Conditioned withdrawal drives heroin consumption and decreases reward sensitivity. J Neurosci. 2006; 26(22):5894–900. [PubMed: 16738231]

181. Kenny PJ, Markou A. Nicotine self-administration acutely activates brain reward systems and induces a long-lasting increase in reward sensitivity. Neuropsychopharmacology. 2006; 31(6): 1203–11. [PubMed: 16192981]

182. Markou A, Koob GF. Postcocaine anhedonia. An animal model of cocaine withdrawal. Neuropsychopharmacology. 1991; 4(1):17–26. [PubMed: 2003866]

183. Kenny PJ, Markou A. Conditioned nicotine withdrawal profoundly decreases the activity of brain reward systems. J Neurosci. 2005; 25(26):6208–12. [PubMed: 15987950]

184. Watkins SS, et al. Reward and somatic changes during precipitated nicotine withdrawal in rats: centrally and peripherally mediated effects. J Pharmacol Exp Ther. 2000; 292(3):1053–64. [PubMed: 10688623]

185. Ise Y, et al. Modulation of opioidergic system on mecamylamine-precipitated nicotine-withdrawal aversion in rats. Psychopharmacology (Berl). 2000; 151(1):49–54. [PubMed: 10958116]

186. Suzuki T, et al. Mecamylamine-precipitated nicotine-withdrawal aversion in Lewis and Fischer 344 inbred rat strains. Eur J Pharmacol. 1999; 369(2):159–62. [PubMed: 10206173]

187. Suzuki T, et al. Attenuation of mecamylamine-precipitated nicotine-withdrawal aversion by the 5-HT3 receptor antagonist ondansetron. Life Sci. 1997; 61(16):PL249–54. [PubMed: 9353175]

188. Suzuki T, et al. Mecamylamine-precipitated nicotine-withdrawal aversion in rats. Eur J Pharmacol. 1996; 314(3):281–4. [PubMed: 8957247]

189. Jackson KJ, et al. The role of various nicotinic receptor subunits and factors influencing nicotine conditioned place aversion. Neuropharmacology. 2009; 56(6–7):970–4. [PubMed: 19371584]

190. Costall B, et al. The actions of nicotine and cocaine in a mouse model of anxiety. Pharmacol Biochem Behav. 1989; 33(1):197–203. [PubMed: 2780777]

191. Damaj IM, Kao W, Martin BR. Characterization of spontaneous and precipitated nicotine withdrawal in the mouse. J Pharmacol Exp Ther. 2003

192. Jonkman S, et al. Mild anxiogenic effects of nicotine withdrawal in mice. Eur J Pharmacol. 2005; 516(1):40–5. [PubMed: 15922326]

193. Pellow S, et al. Validation of open:closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. J Neurosci Methods. 1985; 14(3):149–67. [PubMed: 2864480]

194. Irvine EE, Cheeta S, File SE. Tolerance to nicotine's effects in the elevated plus-maze and increased anxiety during withdrawal. Pharmacol Biochem Behav. 2001; 68(2):319–25. [PubMed: 11267637]

195. Tzavara ET, et al. Nicotine withdrawal syndrome: behavioural distress and selective up-regulation of the cyclic AMP pathway in the amygdala. Eur J Neurosci. 2002; 16(1):149–53. [PubMed: 12153540]

196. Treit D, Fundytus M. Thigmotaxis as a test for anxiolytic activity in rats. Pharmacol Biochem Behav. 1988; 31(4):959–62. [PubMed: 3252289]

197. McEchron MD, et al. Hippocampectomy disrupts auditory trace fear conditioning and contextual fear conditioning in the rat. Hippocampus. 1998; 8(6):638–46. [PubMed: 9882021]

198. Gould TJ, Feiro O, Moore D. Nicotine enhances trace cued fear conditioning but not delay cued fear conditioning in C57BL/6 mice. Behav Brain Res. 2004; 155(1):167–73. [PubMed: 15325790]

199. Davis JA, Gould TJ. beta2 subunit-containing nicotinic receptors mediate the enhancing effect of nicotine on trace cued fear conditioning in C57BL/6 mice. Psychopharmacology (Berl). 2007; 190(3):343–52. [PubMed: 17136517]

200. Andre JM, Leach PT, Gould TJ. Nicotine ameliorates NMDA receptor antagonist-induced deficits in contextual fear conditioning through high-affinity nicotinic acetylcholine receptors in the hippocampus. Neuropharmacology. 2011; 60(4):617–25. [PubMed: 21167848]

201. Raybuck JD, Gould TJ. Nicotine withdrawal-induced deficits in trace fear conditioning in C57BL/6 mice--a role for high-affinity beta2 subunit-containing nicotinic acetylcholine receptors. Eur J Neurosci. 2009; 29(2):377–87. [PubMed: 19200240]

202. Gross TM, Jarvik ME, Rosenblatt MR. Nicotine abstinence produces content-specific Stroop interference. Psychopharmacology (Berl). 1993; 110(3):333–6. [PubMed: 7831427]

203. Bell SL, et al. Smoking after nicotine deprivation enhances cognitive performance and decreases tobacco craving in drug abusers. Nicotine Tob Res. 1999; 1(1):45–52. [PubMed: 11072387]

204. Lyvers M, Maltzman I, Miyata Y. Effects of Cigarette Smoking and Smoking Deprivation on Wisconsin Card Sorting Test Performance. Exp Clin Psychopharmacol. 1994; 2(3):283–289.

205. Grottick AJ, Higgins GA. Effect of subtype selective nicotinic compounds on attention as assessed by the five-choice serial reaction time task. Behav Brain Res. 2000; 117(1–2):197–208. [PubMed: 11099773]

206. Shoaib M, Bizarro L. Deficits in a sustained attention task following nicotine withdrawal in rats. Psychopharmacology (Berl). 2005; 178(2–3):211–22. [PubMed: 15338107]

207. Semenova S I, Stolerman P, Markou A. Chronic nicotine administration improves attention while nicotine withdrawal induces performance deficits in the 5-choice serial reaction time task in rats. Pharmacol Biochem Behav. 2007; 87(3):360–8. [PubMed: 17582477]

208. Benowitz NL. Nicotine replacement therapy. What has been accomplished--can we do better? Drugs. 1993; 45(2):157–70. [PubMed: 7681369]

209. Hajek P, et al. Randomized comparative trial of nicotine polacrilex, a transdermal patch, nasal spray, and an inhaler. Arch Intern Med. 1999; 159(17):2033–8. [PubMed: 10510989]

210. Jorenby DE, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med. 1999; 340(9):685–91. [PubMed: 10053177]

211. Helge TD, Denelsky GY. Pharmacologic aids to smoking cessation. Cleve Clin J Med. 2000; 67(11):818, 821–4. [PubMed: 11104332]

212. Wang D, et al. 'Cut down to quit' with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis. Health Technol Assess. 2008; 12(2):iii–iv. ix–xi, 1–135.

213. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2011; 2:CD006103. [PubMed: 21328282]

214. Dwoskin LP, et al. Review of the pharmacology and clinical profile of bupropion, an antidepressant and tobacco use cessation agent. CNS Drug Rev. 2006; 12(3–4):178–207. [PubMed: 17227286]

215. Stahl SM, et al. A Review of the Neuropharmacology of Bupropion, a Dual Norepinephrine and Dopamine Reuptake Inhibitor. Prim Care Companion J Clin Psychiatry. 2004; 6(4):159–166. [PubMed: 15361919]
216. Li SX, Perry KW, Wong DT. Influence of fluoxetine on the ability of bupropion to modulate extracellular dopamine and norepinephrine concentrations in three mesocorticolimbic areas of rats. Neuropharmacology. 2002; 42(2):181–90. [PubMed: 11804614]
217. El Mansari M, et al. Sustained administration of bupropion alters the neuronal activity of serotonin, norepinephrine but not dopamine neurons in the rat brain. Neuropharmacology. 2008; 55(7):1191–8. [PubMed: 18708076]
218. 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(1):88–92. [PubMed: 9862757]
219. Slemmer JE, Martin BR, Damaj MI. Bupropion is a nicotinic antagonist. J Pharmacol Exp Ther. 2000; 295(1):321–7. [PubMed: 10991997]
220. Makhay MM, O'Donnell JM. Effects of antidepressants in rats trained to discriminate the beta-2 adrenergic agonist clenbuterol. Pharmacol Biochem Behav. 1999; 63(2):319–24. [PubMed: 10371662]
221. Reuben M, Boye S, Clarke PB. Nicotinic receptors modulating somatodendritic and terminal dopamine release differ pharmacologically. Eur J Pharmacol. 2000; 393(1–3):39–49. [PubMed: 10770996]
222. Salas R, et al. Altered anxiety-related responses in mutant mice lacking the beta4 subunit of the nicotinic receptor. J Neurosci. 2003; 23(15):6255–63. [PubMed: 12867510]
223. Grady SR, et al. Rodent habenulo-interpeduncular pathway expresses a large variety of uncommon nAChR subtypes, but only the alpha3beta4* and alpha3beta3beta4* subtypes mediate acetylcholine release. J Neurosci. 2009; 29(7):2272–82. [PubMed: 19228980]
224. Salas R, et al. The alpha3 and beta4 nicotinic acetylcholine receptor subunits are necessary for nicotine-induced seizures and hypolocomotion in mice. Neuropharmacology. 2004; 47(3):401–7. [PubMed: 15275829]
225. Bevins RA, Palmatier MI. Nicotine-conditioned locomotor sensitization in rats: assessment of the US-preexposure effect. Behav Brain Res. 2003; 143(1):65–74. [PubMed: 12842297]
226. Wilkinson JL, Bevins RA. Bupropion hydrochloride produces conditioned hyperactivity in rats. Physiol Behav. 2007; 90(5):790–6. [PubMed: 17300819]
227. Balfour DJ, et al. The putative role of extra-synaptic mesolimbic dopamine in the neurobiology of nicotine dependence. Behav Brain Res. 2000; 113(1–2):73–83. [PubMed: 10942034]
228. Chaudhri N, et al. Operant responding for conditioned and unconditioned reinforcers in rats is differentially enhanced by the primary reinforcing and reinforcement-enhancing effects of nicotine. Psychopharmacology (Berl). 2006; 189(1):27–36. [PubMed: 17019569]
229. Chaudhri N, et al. Complex interactions between nicotine and nonpharmacological stimuli reveal multiple roles for nicotine in reinforcement. Psychopharmacology (Berl). 2006; 184(3–4):353–66. [PubMed: 16240165]
230. Palmatier MI, et al. Bupropion and nicotine enhance responding for nondrug reinforcers via dissociable pharmacological mechanisms in rats. Psychopharmacology (Berl). 2009; 207(3):381–90. [PubMed: 19760281]
231. Robbins TW. Relationship between reward-enhancing and stereotypical effects of psychomotor stimulant drugs. Nature. 1976; 264(5581):57–9. [PubMed: 12471]
232. Warner C, Shoaib M. How does bupropion work as a smoking cessation aid? Addict Biol. 2005; 10(3):219–31. [PubMed: 16109583]
233. Jorenby DE, 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(1):56–63. [PubMed: 16820547]
234. McNeil JJ, Piccenna L, Ioannides-Demos LL. Smoking cessation-recent advances. Cardiovasc Drugs Ther. 2010; 24(4):359–67. [PubMed: 20602163]
235. Smith SS, et al. Comparative effectiveness of 5 smoking cessation pharmacotherapies in primary care clinics. Arch Intern Med. 2009; 169(22):2148–55. [PubMed: 20008701]

236. Luetje CW, Patrick J. Both alpha- and beta-subunits contribute to the agonist sensitivity of neuronal nicotinic acetylcholine receptors. J Neurosci. 1991; 11(3):837–45. [PubMed: 1705971]
237. Papke RL, Heinemann SF. Partial agonist properties of cytisine on neuronal nicotinic receptors containing the beta 2 subunit. Mol Pharmacol. 1994; 45(1):142–9. [PubMed: 8302273]
238. Mihalak KB, Carroll FI, Luetje CW. Varenicline is a partial agonist at alpha4beta2 and a full agonist at alpha7 neuronal nicotinic receptors. Mol Pharmacol. 2006; 70(3):801–5. [PubMed: 16766716]
239. Polosa R, Benowitz NL. Treatment of nicotine addiction: present therapeutic options and pipeline developments. Trends Pharmacol Sci. 2011
240. Spiller K, et al. Varenicline attenuates nicotine-enhanced brain-stimulation reward by activation of alpha4beta2 nicotinic receptors in rats. Neuropharmacology. 2009; 57(1):60–6. [PubMed: 19393252]
241. Gonzales D, 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(1):47–55. [PubMed: 16820546]
242. Aubin HJ, et al. Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. Thorax. 2008; 63(8):717–24. [PubMed: 18263663]
243. Tsukahara H, Noda K, Saku K. A randomized controlled open comparative trial of varenicline vs nicotine patch in adult smokers: efficacy, safety and withdrawal symptoms (the VN-SEESAW study). Circ J. 2010; 74(4):771–8. [PubMed: 20154405]
244. Hays JT, Ebbert JO. Adverse effects and tolerability of medications for the treatment of tobacco use and dependence. Drugs. 2010; 70(18):2357–72. [PubMed: 21142259]
245. Aubin HJ, Karila L, Reynaud M. Pharmacotherapy for Smoking Cessation: Present and Future. Curr Pharm Des. 2011
246. Orson FM, et al. Substance abuse vaccines. Ann N Y Acad Sci. 2008; 1141:257–69. [PubMed: 18991962]
247. Kosten T, Owens SM. Immunotherapy for the treatment of drug abuse. Pharmacol Ther. 2005; 108(1):76–85. [PubMed: 16023218]
248. Swanson JM, Volkow ND. Pharmacokinetic and pharmacodynamic properties of stimulants: implications for the design of new treatments for ADHD. Behav Brain Res. 2002; 130(1–2):73–8. [PubMed: 11864720]
249. Pravetoni M, et al. Vaccination against nicotine alters the distribution of nicotine delivered via cigarette smoke inhalation to rats. Biochem Pharmacol. 2011; 81(9):1164–70. [PubMed: 21333633]
250. Hieda Y, et al. Vaccination against nicotine during continued nicotine administration in rats: immunogenicity of the vaccine and effects on nicotine distribution to brain. Int J Immunopharmacol. 2000; 22(10):809–19. [PubMed: 10963853]
251. Moreno AY, et al. A critical evaluation of a nicotine vaccine within a self-administration behavioral model. Mol Pharm. 2010; 7(2):431–41. [PubMed: 20104903]
252. Roiko SA, et al. Combined active and passive immunization enhances the efficacy of immunotherapy against nicotine in rats. J Pharmacol Exp Ther. 2008; 325(3):985–93. [PubMed: 18305013]
253. Cornuz J, et al. A vaccine against nicotine for smoking cessation: a randomized controlled trial. PLoS One. 2008; 3(6):e2547. [PubMed: 18575629]
254. Wagena EJ, et al. The immunogenicity and safety of a nicotine vaccine in smokers and nonsmokers: results of a randomized, placebo-controlled phase 1/2 trial. Nicotine Tob Res. 2008; 10(1):213–8. [PubMed: 18188762]
255. Hatsukami DK, et al. Safety and immunogenicity of a nicotine conjugate vaccine in current smokers. Clin Pharmacol Ther. 2005; 78(5):456–67. [PubMed: 16321612]
256. Maurer P, et al. A therapeutic vaccine for nicotine dependence: preclinical efficacy, and Phase I safety and immunogenicity. Eur J Immunol. 2005; 35(7):2031–40. [PubMed: 15971275]
257. Swanson LW. The projections of the ventral tegmental area and adjacent regions: a combined fluorescent retrograde tracer and immunofluorescence study in the rat. Brain Res Bull. 1982; 9(1–6):321–53. [PubMed: 6816390]

258. Georges F, Aston-Jones G. Potent regulation of midbrain dopamine neurons by the bed nucleus of the stria terminalis. J Neurosci. 2001; 21(16):RC160. [PubMed: 11473131]

259. Georges F, Aston-Jones G. Activation of ventral tegmental area cells by the bed nucleus of the stria terminalis: a novel excitatory amino acid input to midbrain dopamine neurons. J Neurosci. 2002; 22(12):5173–87. [PubMed: 12077212]

260. Geisler S, et al. Glutamatergic afferents of the ventral tegmental area in the rat. J Neurosci. 2007; 27(21):5730–43. [PubMed: 17522317]

261. Omelchenko N, Sesack SR. Glutamate synaptic inputs to ventral tegmental area neurons in the rat derive primarily from subcortical sources. Neuroscience. 2007; 146(3):1259–74. [PubMed: 17391856]

262. Johnson SW, North RA. Two types of neurone in the rat ventral tegmental area and their synaptic inputs. J Physiol. 1992; 450:455–68. [PubMed: 1331427]

263. Ikemoto S, Wise RA. Mapping of chemical trigger zones for reward. Neuropharmacology. 2004; 47(Suppl 1):190–201. [PubMed: 15464137]

264. Corrigall WA, Coen KM, Adamson KL. Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. Brain Res. 1994; 653(1–2):278–84. [PubMed: 7982062]

265. Pons S, et al. Crucial role of alpha4 and alpha6 nicotinic acetylcholine receptor subunits from ventral tegmental area in systemic nicotine self-administration. J Neurosci. 2008; 28(47):12318–27. [PubMed: 19020025]

266. Reperant C, et al. Effect of the alpha4beta2* nicotinic acetylcholine receptor partial agonist varenicline on dopamine release in beta2 knock-out mice with selective re-expression of the beta2 subunit in the ventral tegmental area. Neuropharmacology. 2010; 58(2):346–50. [PubMed: 19887076]

267. Drenan RM, et al. In vivo activation of midbrain dopamine neurons via sensitized, high-affinity alpha 6 nicotinic acetylcholine receptors. Neuron. 2008; 60(1):123–36. [PubMed: 18940593]

268. Gotti C, et al. Nicotinic acetylcholine receptors in the mesolimbic pathway: primary role of ventral tegmental area alpha6beta2* receptors in mediating systemic nicotine effects on dopamine release, locomotion, and reinforcement. J Neurosci. 2010; 30(15):5311–25. [PubMed: 20392953]

269. Livingstone PD, et al. alpha7 and non-alpha7 nicotinic acetylcholine receptors modulate dopamine release in vitro and in vivo in the rat prefrontal cortex. Eur J Neurosci. 2009; 29(3): 539–50. [PubMed: 19187266]

270. Wooltorton JR, et al. Differential desensitization and distribution of nicotinic acetylcholine receptor subtypes in midbrain dopamine areas. J Neurosci. 2003; 23(8):3176–85. [PubMed: 12716925]

271. Yang K, et al. Distinctive nicotinic acetylcholine receptor functional phenotypes of rat ventral tegmental area dopaminergic neurons. J Physiol. 2009; 587(Pt 2):345–61. [PubMed: 19047205]

272. Avale ME, et al. Prefrontal nicotinic receptors control novel social interaction between mice. FASEB J. 2011

273. Parikh V, et al. Prefrontal beta2 subunit-containing and alpha7 nicotinic acetylcholine receptors differentially control glutamatergic and cholinergic signaling. J Neurosci. 2010; 30(9):3518–30. [PubMed: 20203212]

274. Addy NA, Nakijama A, Levin ED. Nicotinic mechanisms of memory: effects of acute local DHbetaE and MLA infusions in the basolateral amygdala. Brain Res Cogn Brain Res. 2003; 16(1):51–7. [PubMed: 12589888]

275. Levin ED. Nicotinic receptor subtypes and cognitive function. J Neurobiol. 2002; 53(4):633–40. [PubMed: 12436426]

276. Barazangi N, Role LW. Nicotine-induced enhancement of glutamatergic and GABAergic synaptic transmission in the mouse amygdala. J Neurophysiol. 2001; 86(1):463–74. [PubMed: 11431525]

277. Jiang L, Role LW. Facilitation of cortico-amygdala synapses by nicotine: activity-dependent modulation of glutamatergic transmission. J Neurophysiol. 2008; 99(4):1988–99. [PubMed: 18272879]

278. Girod R, et al. Facilitation of glutamatergic neurotransmission by presynaptic nicotinic acetylcholine receptors. Neuropharmacology. 2000; 39(13):2715–25. [PubMed: 11044742]

279. Yang K, et al. Functional nicotinic acetylcholine receptors containing alpha6 subunits are on GABAergic neuronal boutons adherent to ventral tegmental area dopamine neurons. J Neurosci. 2011; 31(7):2537–48. [PubMed: 21325521]

280. Yang KC, Jin GZ, Wu J. Mysterious alpha6-containing nAChRs: function, pharmacology, and pathophysiology. Acta Pharmacol Sin. 2009; 30(6):740–51. [PubMed: 19498417]

281. Grilli M, et al. Nicotinic and muscarinic cholinergic receptors coexist on GABAergic nerve endings in the mouse striatum and interact in modulating GABA release. Neuropharmacology. 2009; 56(3):610–4. [PubMed: 19027759]

282. Zhu PJ, et al. Activation of nicotinic acetylcholine receptors increases the frequency of spontaneous GABAergic IPSCs in rat basolateral amygdala neurons. J Neurophysiol. 2005; 94(5):3081–91. [PubMed: 16033935]

283. Luo S, et al. alpha-conotoxin AuIB selectively blocks alpha3 beta4 nicotinic acetylcholine receptors and nicotine-evoked norepinephrine release. J Neurosci. 1998; 8(21):8571–9. [PubMed: 9786965]

284. Azam L, McIntosh JM. Characterization of nicotinic acetylcholine receptors that modulate nicotine-evoked [3H]norepinephrine release from mouse hippocampal synaptosomes. Mol Pharmacol. 2006; 70(3):967–76. [PubMed: 16735605]

285. Amtage F, et al. Characterization of nicotinic receptors inducing noradrenaline release and absence of nicotinic autoreceptors in human neocortex. Brain Res Bull. 2004; 62(5):413–23. [PubMed: 15168907]

286. Grabus SD, Martin BR, Imad Damaj M. Nicotine physical dependence in the mouse: involvement of the alpha7 nicotinic receptor subtype. Eur J Pharmacol. 2005; 515(1–3):90–3. [PubMed: 15896732]

287. 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(4): 361–73. [PubMed: 11694204]

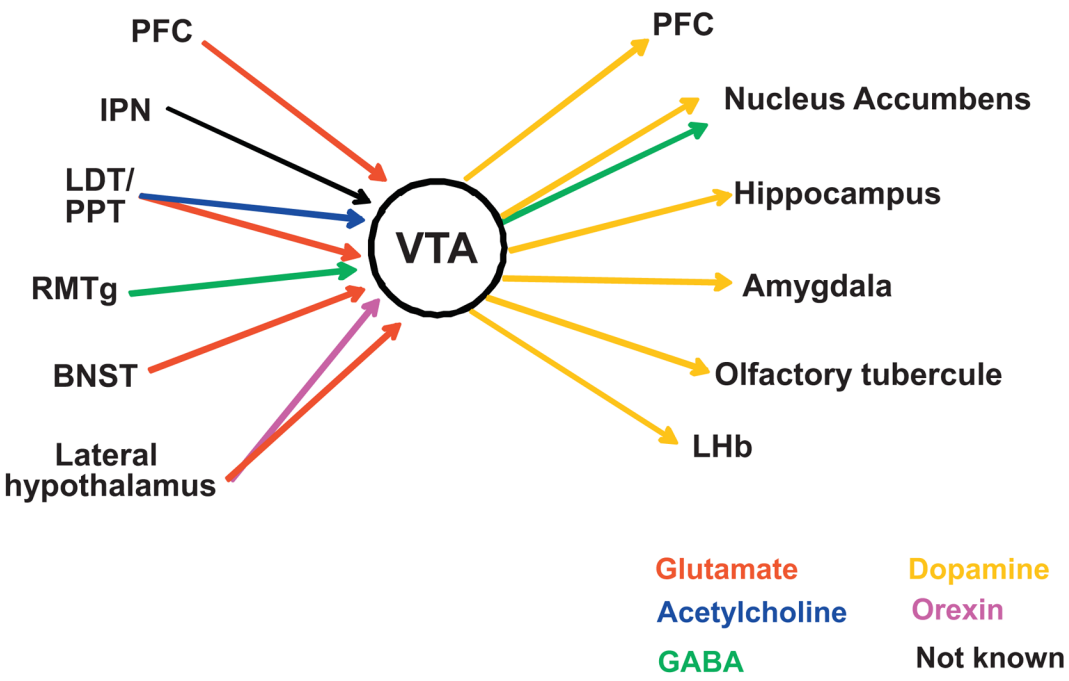

Fig. 1.

Major VTA afferent and efferent projections. VTA DA neurons send projections to NAcc, PFC, the hippocampus, the amygdala and the olfactory tubercule [256]. Through those projections, the DAergic system influences reward-related behavior by affecting reinforcement (NAcc), learning and declarative memory (hippocampus), emotional memory (amygdala), habit formation (ventral and dorsal striatum), and executive functions and working memory (PFC and orbitofrontal cortex). The activity of the VTA is in turn regulated by inputs from the PFC, the laterodorsal and pedunculopontine tegmental nuclei (LDT/PPT), the rostromedial tegmental nucleus (RMT), the lateral hypothalamus, the bed nucleus of the stria terminalis (BNST) and the interpeduncular nucleus (IPN) [257–260]. DA neurons also receive inhibitory inputs from intra-VTA GABAergic neurons, NAcc, and ventral pallidum [261,262]. Neurotrasmitters are color coded as indicated.

Table 1
nAChR influences on neurotransmitter release

Neurotransmitters released in response to nicotine, the brain areas where this release is known to occur, and nAChR subtypes known to facilitate this action.

Neurotransmitter Released	Brain Region	nAChRs involved	References
Dopamine	VTA NAcc PFC	α4β2*, α4*,α6*, α6β2* α4β2*; α7	[13, 264–266] [12, 13, 267, 268] [269]
Glutamate	VTA NAcc PFC Amygdala IPN	α7 β2* ? α4β2*; α7 α4β2*; α7 α7	[270, 271] [272] [269, 273] [272, 274–277] [278]
GABA	VTA NAcc Amygdala	α6β2* α4β2* α3β4*; α7	[279, 280] [47, 281] [276, 282]
Acetylcholine	MHb IPN	α3β4*, α3β3β4	[223]
Norepinephrine	Hippocampus Cortex	α3β4*, β4* (rat); α6β2β3* (mouse) α3β2*, α6*	[283, 284] [285]

VTA, ventral tegmental area; NAcc, nucleus accumbens; PFC, prefrontal cortex; IPN, interpeduncular nucleus; GABA, γ-aminobutyric acid; MHb, medial habenula. The asterisk denotes the potential presence of other nAChR subunits.

Table 2

Effect of nAChR Subunits on Rodent Models of Nicotine Withdrawal

Signs	Effect	No Effect
Somatic	α2 X [81] α5 ↓ or X [81, 170] α7 ↓ [165, 171] β4 X [11]	α6 [172] α7 [170, 286] β2 [11]
Affective Anxiety-related Behavior Attention Tasks (5-CSRTT) Intracranial Self Stimulation Conditioned Place Aversion Trace Fear Conditioning	α6 X dd [172] β2 X EPoa [170]	α5 [170] α7 [170]
	---	α7 [206]
	α5 ↓ [80]	α7 [287]
	α6 X dd [172] β2 X [170]	α5 [170] α7 [170]
	β2 X [201]	α7 [201]

X = Withdrawal phenotype abolished; ↓ = Withdrawal phenotype diminished; EPoa = effect seen in the elevated plus maze, open arm time only; dd = dose dependent