Mesolimbic Dopamine and Habenulo-Interpeduncular Pathways in Nicotine Withdrawal

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The majority of people who attempt to quit smoking without some assistance relapse within the first couple of weeks, indicating the increased vulnerability during the early withdrawal period. The habenula, which projects via the fasciculus retroflexus to the interpeduncular nucleus, plays an important role in the withdrawal syndrome. Particularly the $\alpha 2$, $\alpha 5$, and $\beta 4$ subunits of the nicotinic acetylcholine receptor have critical roles in mediating the somatic manifestations of withdrawal. Furthermore, withdrawal from nicotine induces a hypodopaminergic state, but there is a relative increase in the sensitivity to phasic dopamine release that is caused by nicotine. Therefore, acute nicotine re-exposure causes a phasic DA response that more potently reinforces relapse to smoking during the withdrawal period.

Long-term use of an addictive drug produces physiological and neurological adaptations that are often accompanied by physical and/or psychological dependence. On discontinuation of the drug, a set of withdrawal symptoms occur for a period of time. Depending on the half-life of the drug in the body, withdrawal may begin within hours of discontinuing use and last for days, weeks, or longer depending on the drug and overall circumstances. The severity of the symptoms depends on the particular individual, the drug in question (e.g., cocaine, benzodiazepines, or nicotine), the route of administration (e.g., intravenous, oral, or inhaled), the doses used, and the abruptness of quitting. Whereas most cigarette smokers quit their nicotine addiction without medical assistance, the physical

dependence that may develop to other addictive drugs, such as benzodiazepine and alcohol, can produce life threatening withdrawal symptoms when these drugs are abruptly stopped. In this chapter, we will focus on withdrawal from nicotine, which is the main addictive component found in tobacco (Marti et al. 2011).

In developed countries, tobacco use is estimated to be the largest single cause of premature death, and about one-half of those who smoke from adolescence throughout life will die from smoking-related complications (WHO 1997; Doll et al. 2004). About one-third of the world's adult population smokes tobacco, and in less developed countries, tobacco use is on the rise (Peto et al. 1996; Mathers and Loncar 2006; Benowitz 2008). Thus, it is one of the few causes

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of mortality that is increasing worldwide (Mathers and Loncar 2006). Tobacco is projected to be responsible for 10% of all deaths globally by 2015 (Mathers and Loncar 2006; Benowitz 2008).

In the U.S., about 45 million people smoke, 70% express a desire to quit, and nearly 50% try to quit each year (Kenford and Fiore 2004; Benowitz 2010). After one year's time, however, only about 3% to 7% of those who attempt to quit on their own are still tobacco free (Kenford and Fiore 2004; MMWR 2005). There are many behavioral and environmental issues that contribute to the low success rate (Dani and Harris 2005; Dani et al. 2009; Benowitz 2010; De Biasi and Dani 2011). An important motivation to relapse is the withdrawal syndrome that arises from chronic nicotine use. Consequently, the majority of people who attempt unaided to quit smoking relapse within the first 2 wk (Ward et al. 1997; Shiffman 2006), indicating that the early withdrawal period is a critical time for relapse and, potentially, for intervention.

THE DOPAMINE SYSTEMS

The mesocorticolimbic dopamine (DA) system has received the most attention for its role in reinforcing rewarding behaviors, including those behaviors that contribute to addictions (Wise 2009; Ikemoto 2010; Schultz 2010; De Biasi and Dani 2011). The midbrain DA neurons from the ventral tegmental area (VTA) project extensively to cortical sites, and the innervation to the prefrontal cortex has received much attention for its role in addiction (Hyman et al. 2006; Koob and Volkow 2010). The most dense DA innervation of the brain, however, is into the striatum. The DA neurons in the substantia nigra compacta (SNc) and the VTA generally project topologically to the striatum, which may be divided into the dorsal and ventral portions (Björklund 1984; Wilson 1998; Parent et al. 2000; Zhou et al. 2002). The dorsal striatum (neostriatum) comprises the caudate nucleus and the putamen, and the ventral striatum includes the ventral conjunction of the caudate and putamen, portions of the olfactory tubercle, and the nucleus accumbens (NAc).

The phylogenetically older ventral striatum along with the amygdala and hippocampus contribute to the mesolimbic DA system, and the projection from the VTA to the NAc has a major role particularly during the initiation of addiction.

Besides having a role in behavior to achieve natural hedonic/pleasurable responses to reinforcers and drugs, the VTA is now recognized to also participate in the responses to punishment, aversion, or lack of expected reward (Schultz 1998b; Ungless et al. 2004; Schultz 2007a; Birschoux et al. 2009; Jhou et al. 2009a; De Biasi and Dani 2011). Such a dual role in reward processing is defined by inputs received from multiple structures in the cortex, basal forebrain, and brainstem (Nauta et al. 1978; Phillipson 1979; Wallace et al. 1989, 1992; Geisler et al. 2007, 2008; Omelchenko and Sesack 2010; Balcita-Pedicino et al. 2011). Those inputs translate into activation of DA neurons whenever a behaviorally salient stimulus, such as one predicting reward, is encountered (Schultz 1998a). Inhibition occurs in cases in which the expected reward is omitted, or an aversive stimulus is delivered (Ungless et al. 2004; Schultz 2007a,b). Major GABA inhibitory inputs to the VTA are provided by feedback projections from the NAc and the ventral pallidum (Usuda et al. 1998; Zahm 2000; Geisler and Zahm 2005). Additional inhibitory afferents arise from the hypothalamus, diagonal band, bed nucleus, lateral septum, periaqueductal gray, pedunculopontine/laterodorsal tegmentum, as well as parabrachial and raphe nuclei (Geisler and Zahm 2005). Another major ascending source of GABAergic inhibition that has been characterized only in recent years is the mesopontine rostromedial tegmental nucleus (RMTg) (Jhou et al. 2009a; Kaufling et al. 2009; Hong et al. 2011; Lecca et al. 2011). Located at the "tail" of the VTA, the RMTg (Perrotti et al. 2005; Olson and Nestler 2007; Geisler et al. 2008; Jhou et al. 2009b; Kaufling et al. 2009; Sesack and Grace 2010) participates in the processing of both aversive and appetitive stimuli (Jhou et al. 2009a). Opposite to the VTA, RMTg neurons are activated by noxious stimuli and inhibited by rewarding stimuli (Jhou et al. 2009a; Hong et al. 2011) so

that in the presence of aversive stimuli, RMTg activation leads to inhibition of DA cell activity (Grace and Bunney 1979; Ungless et al. 2004; Jhou et al. 2009a).

The RMTg receives afferents from many forebrain and brainstem structures (Jhou et al. 2009b), but the excitatory glutamatergic projections received from the lateral nucleus of the habenula (LHb) are of particular relevance. The LHb, together with the medial habenula (MHb) forms the habenula complex, an epithalamic structure located by the third ventricle. Although adjacent, LHb and MHb have very different anatomical connections and transcriptional profiles (Klemm 2004). The habenula participates in the processing of fear, anxiety, depression, and stress and, in general, seems to be activated by negative emotional states (Ullsperger and von Cramon 2003; Geisler and Trimble 2008; Matsumoto and Hikosaka 2009; Ikemoto 2010; De Biasi and Dani 2011; Winter et al. 2011). Projections from the habenula are bundled in the fasciculus retroflexus, which is divided into a core region and an outer region. The core of the fasciculus retroflexus originates in the MHb and ends at the interpeduncular nucleus (IPN) whereas the outer region originates in the LHb and ends at the RMTg. Through its connections with the RMTg, the LHb exerts potent influence on DAergic activity and reward prediction (Herkenham and Nauta 1979; Araki et al. 1988; Ji and Shepard 2007; Matsumoto and Hikosaka 2007; Hikosaka et al. 2008; Jhou et al. 2009b; Kaufling et al. 2009). The activities of the LHb and the VTA/SNc are anti-correlated so that, opposite to the VTA, LHb activity increases when an expected reward is not delivered (signaling a negative prediction error), and decreases when a reward is delivered unexpectedly (signaling a positive prediction error) (Matsumoto and Hikosaka 2007). The MHb sends projections to the LHb (Kim et al. 2005), but it is currently unknown whether the MHb contributes directly to the regulation of monoamine transmission. Because most projections from the MHb reach the IPN (Klemm 2004), which in turn sends projections to the VTA (Groenewegen et al. 1986; Montone et al. 1988; Klemm 2004), the MHb most likely influences

DAergic activity through its connections with the IPN. Data from the literature support an involvement of the MHb/IPN axis with brain reward areas. For example, electrical stimulation of the MHb and the fasciculus retroflexus, the primary efferent pathway of the MHb, produces rewarding effects (Sutherland and Nakajima 1981).

Nicotine Modulation of Dopamine Signaling

Acute nicotine exposure both activates and desensitizes nicotinic acetylcholine receptors (nAChRs) in a subtype-dependent manner throughout the brain (Dani et al. 2000; Mansvelder and McGehee 2002; Wooltorton et al. 2003; Pidoplichko et al. 2004). At the midbrain DA centers, nicotine acts mainly through nicotinic receptors containing the $\alpha 4$ and $\beta 2$ subunits, often in combination with the $\alpha 6$ subunit (Picciotto et al. 1998; Tapper et al. 2004; Mamelì-Engvall et al. 2006; Pons et al. 2008; Brunzell et al. 2010; Drenan et al. 2010), and induces increased firing of DA neurons that can last for significant periods of time because long-term synaptic potential is induced at some excitatory glutamate synapses arriving particularly from the cortex (Mansvelder and McGehee 2000; Mansvelder et al. 2002) and from the peduncular pontine and lateral dorsal tegmentum (Pidoplichko et al. 2004). On the arrival of nicotine in the midbrain, a majority of midbrain DA neurons increase their firing rates and the firing patterns change (Grenhoff et al. 1986; Mamelì-Engvall et al. 2006; Zhang et al. 2009b; Zhao-Shea et al. 2011). Nicotine induces an increased firing rate that in general expresses more phasic bursts, and the bursts of firing become longer, containing more individual spikes. This increase in phasic burst firing has profound and varying consequences on DA release in target areas.

Studies using fast-scan cyclic voltammetry in rodents have shown that DA release varies within regions, subregions, and local environments of the brain, suggesting that controls intrinsic and extrinsic to the DA fibers and terminals regulate release (Zachek et al. 2010). This property has been most extensively studied within the dorsal and ventral striatum. DA

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axon terminals in the dorsolateral striatum and NAc shell of the ventral striatum release DA differently, and the DA release evoked by various afferent action potential patterns is modulated differently (Cragg et al. 2002; Zhang et al. 2009a,b). For example, as indicated by the inset vertical lines of Figure 1A,B, two stimulus trains were applied to evoke DA release in brain slices from either the dorsal lateral striatum (d. striatum) or the NAc shell (Zhang et al. 2009b). The two stimulus trains are modeled after in vivo measurements of firing under control conditions (a brief burst and simple spikes, e.g., Fig. 1Aa1) and of firing after administration of nic-

otine (longer and more frequent bursts, e.g., Fig. 1Aa2). These stimulus trains were applied to brain slices bathed in control solutions or in a solution containing a biologically reasonable concentration of nicotine ($0.1 \mu\text{M}$). In the dorsal striatum (Fig. 1A), the two stimulus trains evoke comparable amounts of DA release, indicated by the area under the curves of the two traces (Fig. 1C). In the NAc shell (Fig. 1B), the stimulation with more and longer phasic bursts induced a greater facilitation of DA release than the other stimulus train (Fig. 1D).

These results indicate that the probability of DA release is greater in the dorsal striatum.

Figure 1. Measurements of DA release by fast-scan cyclic voltammetry from brain slices. The burst firing by DA neurons was measured in vivo and then was used to construct stimulus trains to evoke DA release in the presence and absence of nicotine ($0.1 \mu\text{M}$). The stimulus trains were applied to brain slices containing either (A) the dorsolateral striatum (d. striatum) or (B) the nucleus accumbens shell (NAc shell). The DA traces shown in bold are those expected biologically in the absence (a1, b1) or in the presence (a4, b4) of nicotine. Patterned stimulus trains based on the in vivo DA-unit recordings are shown below the evoked DA release in the absence (control) or presence of nicotine bathing the slices. Scale bar, $0.1 \mu\text{M}$, 1 sec. The relative DA signal (area-under-curve) is normalized to a1 (horizontal line) in C, the dorsal striatum and to b1 (horizontal line) in D, the NAc shell. The relative (i.e., area under the curve) DA signal was unchanged by nicotine in the dorsal striatum (a4 relative to a1) but was increased in the NAc shell (b4 relative to b1) with $p < 0.01$. (Modified and adapted from Zhang et al. 2009b.)

Thus, there is less potential for facilitation of release by a long burst. Conversely, the NAc shell has a lower basal probability of release than the dorsolateral striatum (Cragg 2003; Rice and Cragg 2004; Zhang and Sulzer 2004; Zhang et al. 2009a,b). Therefore, phasic burst activity into the NAc shell causes more facilitation of DA release.

Acutely administered nicotine, while acting in the midbrain to increase DA neuron firing, acts in the striatal target areas to decrease DA release evoked by single tonic action potentials arriving at the presynaptic terminals. The amount of DA release evoked by identical low frequency, tonic afferent activity is lower in both the dorsal striatum and NAc after nicotine administration as indicated by Figures 1Ca3 and 1Db3 (Zhou et al. 2001; Rice and Cragg 2004; Zhang et al. 2004). In the dorsal striatum, a short burst or a single pulse along the DA fibers produces less DA release in the presence of nicotine (Fig. 1Aa3) than it does in the absence of nicotine (Fig. 1Aa1). If we consider that nicotine increases the burst firing from midbrain DA neurons, then in the nicotine case, we should compare DA release with a stimulus train containing more and longer bursts (Fig. 1Aa4). When you compare the area under the curve, which is the overall DA signal, in the control case (Fig. 1Aa1) to the area under the curve in the nicotine administration case (Fig. 1Aa4) they are the same in the dorsolateral striatum (Fig. 1Ca4). Likewise in the dorsolateral striatum, the overall DA signal, as measured by microdialysis, is not dramatically increased during the first administration of nicotine to a rat (Zhang et al. 2009b). If the same comparison is made in the NAc shell, the DA signal in the control (Fig. 1Bb1) is considerably smaller than the DA signal in the presence of nicotine (Fig. 1Bb4). As measured by microdialysis, the first injection of nicotine causes a significant increase in the DA concentration in the NAc shell (Zhang et al. 2009b), and this result is consistent with the nicotine-induced increase in DA release (Fig. 1Db4).

Because nicotine decreases tonic DA release much more effectively than release evoked by phasic bursts, nicotine stretches the range of mesostriatal/mesolimbic DA signaling. The low fre-

quency tonic signals are diminished whereas phasic-burst signals (like those induced in the midbrain by nicotine) are favored even more than usual when nicotine is present at the target area (Rice and Cragg 2004; Dani and Harris 2005; Kumari and Postma 2005; Benowitz 2008; Zhang et al. 2009a,b). Thus, the relationship between DA neuron firing patterns and DA release varies depending on the local area of interest (Garris and Wightman 1994; Wu et al. 2002; Cragg 2003; Montague et al. 2004; Zhang and Sulzer 2004). This variability arises because DA neurons in the midbrain do not have identical properties, and they project, generally, in a topological manner to distant targets. Even when the DA neurons have similar firing trains, different frequency-dependent DA release occurs depending on the region where they project (Cragg 2003; Exley et al. 2008; Zhang et al. 2009a,b). Phasic burst firing by DA neurons and the consequent downstream phasic DA signals produced in the targets are vital for processing reward-related information associated with the drug-use behavior. This process is an important step for the initial phase of nicotine addiction. Like other addictive drugs, nicotine initially increases the basal DA concentration in the NAc shell as measured by microdialysis (Pontieri et al. 1996; Di Chiara 1999; Zhang et al. 2009b). As measured by microdialysis, the elevated dopamine in the NAc shell is considered an identifying functional characteristic of addictive drugs.

Adaptations in Dopamine Signaling on Nicotine Withdrawal

As well as mediating aspects of reward and behavioral reinforcement, alterations in DA signaling also mediate aspects of nicotine withdrawal (Corrigall et al. 1994; Dani and Heineemann 1996; De Biasi and Dani 2011; Zhang et al. 2012). Withdrawal from various addictive drugs results in a decrease in basal DA that is thought to motivate drug seeking and taking (Weiss et al. 1996; Shen 2003). Likewise, withdrawal from chronic nicotine use also induces a hypodopaminergic state (Epping-Jordan et al. 1998; Zhang et al. 2012). This deficiency in basal DA alters brain reward function and may mo-

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tivate drug seeking to reverse the nicotine-induced DA deficiency (Epping-Jordan et al. 1998). Consistent with these kinds of data, the majority of people who attempt to quit smoking unaided by medical supports relapse within the first 2 wk (Ward et al. 1997; Shiffman 2006), suggesting that the early period following nicotine withdrawal is a critical time.

When nicotine was self-administered by mice in their home cage drinking water for 4 or 12 wk followed by 1 d of withdrawal, the mean basal DA concentration measured by microdialysis in the NAc was significantly and comparably lower after both treatments compared with control (Fig. 2A). Acute administra-

tion of nicotine (1 mg/kg, i.p., nicotine upward arrow, Fig. 2A) increased the absolute DA concentrations to similar levels for both control mice and for those in withdrawal. Because the nicotine-treated mice had lower baseline DA concentrations than the control mice, the baselines were normalized to compare the relative amplitudes of the nicotine-induced DA concentration changes (Fig. 2B). Both the 4-wk and 12-wk withdrawal groups showed a significantly higher relative nicotine-induced DA response compared with the control mice (Fig. 2C).

To understand the changes in DA signaling caused by withdrawal, fast-scan cyclic voltammetry measurements were made in brain slices

Figure 2. Measurements of DA concentrations by in vivo microdialysis in freely moving mice. Nicotine was self-administered via the drinking water for 4 or 12 wk followed by 1 d of withdrawal. (A) Dialysate DA concentrations at baseline and after an i.p. injection of saline and nicotine (1 mg/kg) following 1 d of withdrawal from 4 or 12 wk (wk) of chronic nicotine. Nicotine withdrawal decreased basal DA levels compared with the control. (B) Normalization of the dialysate DA signals revealed that the response to acute nicotine was enhanced in both withdrawal groups compared with the control. (C) The peak nicotine-induced DA responses are re-plotted as bar graphs showing that the nicotine evoked peak was higher in both withdrawal groups than in the control. * $p < 0.05$ by t -test. (Modified and adapted from Zhang et al. 2012.)

cut from the NAc 1 d into withdrawal. It was found that during nicotine withdrawal both tonic and phasic DA release was decreased. The basal DA concentration and tonic DA signals, however, were disproportionately lower than the phasic DA signals. Therefore, the phasic/tonic DA signaling ratio was increased during the withdrawal period. Consistent with the microdialysis results, the DA signal produced by acute nicotine re-exposure during withdrawal produces a DA response that may strongly reinforce relapse to drug use (i.e., smoking). After chronic nicotine, the stronger inhibition of tonic DA release enhances the contrast between tonic and phasic DA signaling. It also switches the pattern of DA release so that it is more highly dependent on the number of spikes within a burst. That change increases the dependence of NAc DA release on bursts. Therefore, during the withdrawal period, phasic DA neuron activity of the kind induced by nicotine (Zhang et al. 2009b; Exley et al. 2011) re-exposure induces DA signals that may make abstinent smokers more vulnerable to the reinforcing influence of nicotine (De Biasi and Dani 2011; Zhang et al. 2012).

ROLE OF HABENULA AND IPN IN NICOTINE WITHDRAWAL

Withdrawal manifests as a collection of affective and somatic symptoms that emerge a few hours after nicotine abstinence. The seven major symptoms of nicotine withdrawal appearing in the DSM-IV-TR (American Psychiatric Association 2000; Hughes 2007) include irritability/anger/frustration, anxiety, depression/negative affect, concentration problems, impatience, insomnia, and restlessness. Nicotine withdrawal symptoms typically peak within the first week of abstinence and taper off in the following 3–4 wk (Hughes et al. 1991; Hughes 2007). However, the duration of the nicotine withdrawal syndrome has been reported to be as short as 10 d (Shiffman 2006), or last more than a month (Gilbert et al. 1999; Gilbert et al. 2002). The severity of nicotine withdrawal symptoms varies among individuals, but a severe abstinence syndrome predicts increased risk of re-

lapse (West et al. 1989; Piasecki et al. 2003a,b,c; al'Absi et al. 2004). Powerful cravings also accompany withdrawal, which may be precipitated by cues such as the sight of a cigarette or a situation/place associated with the act of smoking (Shiffman et al. 2002). The onset of negative affective symptoms, such as dysphoria, anxiety, and irritability and, to a lesser extent, the somatic manifestations of withdrawal, provide negative reinforcement that perpetuates addiction (Koob and Le Moal 2001, 2005; Allen et al. 2008; Koob and Volkow 2010; Piper et al. 2011). Continued cigarette 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.

Given the involvement of the LHb in the processing of negative emotional states, it is tempting to speculate that the nucleus might also be involved in the mechanisms of nicotine withdrawal, especially for symptoms like anxiety, depression, and negative affect. Research in both humans and animal models will be required to test this hypothesis. The putative involvement of the LHb in the nicotine abstinence syndrome contrasts with compelling data on the influence of the MHb on the somatic manifestations of withdrawal (Salas et al. 2004, 2007, 2009). Mice display both somatic (e.g., shaking, paw tremors, or scratching) and affective signs of nicotine withdrawal (e.g., increased anxiety-like behavior in the elevated plus maze or increased threshold for intracranial self-stimulation) (De Biasi and Salas 2008). A survey of various nAChR mutant mice in which withdrawal was precipitated by the injection of the nAChR antagonist, mecamylamine (MEC), has revealed the prominent influence of three nAChR subunits (Fig. 3) (Salas et al. 2004, 2007, 2009). Absence of $\alpha 2$ or $\alpha 5$ or $\beta 4$ abolishes the somatic signs of withdrawal (Salas et al. 2004, 2007, 2009), lack of $\alpha 7$ attenuates withdrawal symptoms (Salas et al. 2007), but physical signs of dependency are still observed in the absence of $\beta 2$ (Salas et al. 2004; Besson et al. 2006). Both $\alpha 5$ and $\beta 4$ null mice also manifest reduced anxiety-related behaviors (Salas et al. 2003; Gangitano et al. 2009), in contrast with $\beta 2$ null mice, which show normal anxiety-like

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Figure 3. Lack of $\beta 4$, $\alpha 5$, or $\alpha 2$ nAChR subunits protect against nicotine withdrawal-induced somatic signs. nAChR null mice and their wild type littermates were treated chronically with nicotine (24 mg/kg/d free base) or saline using a mini-osmotic pump for 2 wk. On day 14, mice received a 3 mg/kg injection of the nonselective nicotinic antagonist, mecamylamine. Somatic signs, which include scratching, shaking, chewing, grooming, ptosis, head nodding, and jumping, were measured for 20 min. Mecamylamine injection produced an increase in somatic signs in wild-type, $\beta 2$ null, and $\alpha 7$ null mice treated with nicotine. Similar increases were not observed in the $\beta 4$, $\alpha 5$, or $\alpha 2$ null mice suggesting that nAChRs that contain these subunits play a role in the modulation of nicotine withdrawal signs. * $p < 0.05$. (Modified and adapted from Salas et al. 2004, 2007, 2009.)

responses (Maskos et al. 2005). Considering the role of anxiety and stress in nicotine withdrawal and relapse, the latter result points to another potential influence of $\alpha 5$ - and $\beta 4$ -containing nAChRs (De Biasi and Salas 2008).

In the mouse, the $\alpha 5$, $\alpha 2$, and $\beta 4$ nAChR subunits are expressed at high levels in MHB and/or IPN (Grady et al. 2009; De Biasi and Dani 2011), whereas no mRNA encoding for those nAChR subunits can be detected in the LHb. The definitive role of the MHB/IPN axis in the somatic manifestations of nicotine abstinence was established when MEC was microinjected into the MHB and IPN of mice chronically treated with nicotine. MEC microinjection in those two brain areas—but not VTA, hippocampus, or cortex, was sufficient to precipitate nicotine withdrawal symptoms (Salas et al. 2009). An interesting question is whether the MHB and IPN influence only the mechanisms of nicotine withdrawal or whether they have a more global influence on other drugs of abuse.

A recent report suggests that $\alpha 5$ -containing nAChRs in the MHB/IPN axis are also key to the control of the amounts of nicotine self-administered. Nicotine follows an inverted U-shaped dose-response curve (Picciotto 2003; De Biasi and Dani 2011), and smokers titrate their nicotine intake to experience the rewarding while avoiding the aversive effects produced by high nicotine doses (Benowitz and Jacob 2001; Hutchison and Riley 2008; Dani et al. 2009). In the absence of $\alpha 5$, mice continue to self-administer nicotine at doses that normally elicit aversion in wild-type animals (Fowler et al. 2011). However, re-expression of the nAChR subunit in the MHB or the IPN is sufficient to bring nicotine self-administration back to wild-type levels (Fowler et al. 2011). These data suggest a role for both LHb and MHB in the processing of aversive stimuli, including those associated with high nicotine doses.

The $\alpha 5$ and $\beta 4$ subunit genes belong to a cluster that also encodes the $\alpha 3$ nAChR subunit.

This gene cluster, located in mouse chromosome 9 (syntenic to human chromosome 15q25), has acquired notoriety after a number of genome-wide association studies (GWAS) linked single nucleotide polymorphisms (SNP) within *CHRNA5-CHRNA3-CHRNA4* to tobacco use, lung cancer, peripheral disease, and alcohol abuse (Amos et al. 2008; Berrettini et al. 2008; Bierut et al. 2008; Thorgeirsson et al. 2008; Wang et al. 2009; Chen et al. 2011). The nonsynonymous SNP rs16969968 in *CHRNA5* correlates with nicotine dependency risk, heavy smoking, and the pleasurable sensation produced by a cigarette (Saccone et al. 2007; Berrettini et al. 2008; Bierut et al. 2008; Thorgeirsson et al. 2008). This SNP leads to an amino acid substitution in the second intracellular loop of the $\alpha 5$ subunit, which results in lower Ca^{2+} permeability and increased desensitization in nAChRs with certain subunit compositions (Kuryatov et al. 2011). Because the $\alpha 5$ nAChR subunit influences the aversive effects of nicotine and drives its consumption, it is tempting to speculate that people with SNP rs16969968 smoke more and become addicted at a younger age because of hypofunctional $\alpha 5$ -containing nAChRs. The presence of fewer aversive effects (especially at higher nicotine doses) during the initial exposure to nicotine would promote the hedonic drive and facilitate the transition from use to abuse and dependency. New mouse models examining the role of nAChR gene variants will help investigators explore the role of gene polymorphisms in nicotine addiction and will provide insight into cessation therapies tailored for specific subpopulations of smokers.

CONCLUSIONS

Animal studies and human genetic data point to the MHb/IPN axis and the nAChRs expressed therein as critical mediators of the mechanisms of nicotine withdrawal. As a whole, the habenula complex emerges as part of a circuitry that may control the negative emotional states driven by abstinence or aversive drug concentrations. In the next phase of research, new animal models and more selective nAChR antagonists will be used to understand the underlying

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mechanisms of tobacco addiction and withdrawal, providing targets for drugs aimed at aiding smoking cessation.

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Mesolimbic Dopamine and Habenulo-Interpeduncular Pathways in Nicotine Withdrawal

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