Overview of Nicotine Withdrawal and Negative Reinforcement (Preclinical)

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INTRODUCTION

Studies on the neurobiological substrates of tobacco addiction largely depend on the availability of suitable animal models. In this review, we first describe the features of tobacco smoking and nicotine abuse and dependence in humans and animal models. We then discuss the roles of positive and negative reinforcement in nicotine use and dependence. Lastly, we provide an overview of the possible neurobiological mechanisms of nicotine that underlie positive and negative reinforcement.

TOBACCO DEPENDENCE AND NICOTINE

Tobacco smoking is the leading avoidable cause of disease and premature death in the United States, and it is responsible for over 480,000 deaths annually (Agaku, King, & Dube, 2014) and USD$289 billion in direct healthcare costs and productivity losses each year. Smoking is implicated in ~70% of deaths from lung cancer, ~80% of deaths from chronic obstructive pulmonary disease, and ~50% of deaths from respiratory disease (Agaku et al., 2014). Much evidence indicates that individuals use tobacco primarily to experience the psychopharmacological properties of nicotine and that a large proportion of smokers eventually become dependent on
nicotine, significantly contributing to the motivation to smoke (Balfour, 1984; Stolerman, 1991). An estimated 13.7% of the US population age 18 and over smoked every day in the past month (Agaku et al., 2014). Electronic cigarette use has rapidly grown in the general population, further emphasizing the key role of nicotine in tobacco dependence (Palazzolo, 2013). According to the latest report from Bloomberg Industries, the combined sales of electronic cigarettes have doubled every year for the past 5 years, generating over USD$1 billion in revenue in the United States in 2014. The sale of electronic cigarettes is predicted to pass that of traditional cigarettes by 2047. Moreover, electronic cigarettes are marketed and viewed by the general public as safe because they do not produce compounds other than nicotine. However, considering the high level of nicotine in electronic cigarette vapor (¢500–750 mg/m$^3$; Goniewicz, Hajek, & McRobbie, 2014), such nicotine intake likely has profound effects on the brain that can facilitate the transition to tobacco dependence, particularly in adolescents. Indeed, preliminary reports demonstrated that high levels of nicotine vapor exposure alone can lead to increased dependence and motivation to take nicotine in rodent models (George, Grieder, Cole, & Koob, 2010; Gilpin et al., 2014). The pervasiveness of tobacco use and the rapid growth of electronic cigarettes associated with the extensive costs to smokers and society provide a compelling basis for elucidating the actions of nicotine within the central nervous system that lead to potential neuroadaptations in the motivational systems that mediate the development of dependence and withdrawal symptoms.

THEORETICAL FRAMEWORK

Nicotine addiction can be defined as a chronic, relapsing disorder that has been characterized by a compulsion to seek and take nicotine, loss of control over nicotine intake, and emergence of a negative emotional state (eg, dysphoria, anxiety, and/or irritability) that defines a motivational withdrawal syndrome when access to nicotine is prevented (Koob & Le Moal, 2008). Addiction has been conceptualized as a three-stage cycle—binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation—that worsens over time and involves allostatic changes in the brain reward and stress systems. Two primary sources of reinforcement, positive and negative reinforcement, have been hypothesized to play a role in this allostatic process (Fig. 1.1A). The term reinforce means “to strengthen” and refers to any stimulus (reinforcer) that increases the probability of a specific response that follows. Positive reinforcement is defined as the process by which the presentation of a stimulus increases the probability of a response. Negative reinforcement is defined as the process by which removal of an aversive stimulus (or aversive state of withdrawal
in the case of addiction) increases the probability of a response. In the case of nicotine use and dependence, nicotine is the positive reinforcer, and the negative affective state of nicotine withdrawal is the negative reinforcer (Fig. 1.1B).

Nicotine acts as a positive reinforcer in only a very narrow dose range in both humans and rodents. Moderate to high doses of nicotine can be aversive, particularly in nondependent subjects, producing conditioned place aversion and leading to decreases in nicotine self-administration (Fowler & Kenny, 2014). From an experimental psychology perspective, at a high dose, nicotine can be considered an aversive stimulus that produces punishing effects that lead to a decrease in the probability of nicotine self-administration (Goldberg & Spealman, 1983; Koffarnus & Winger, 2015). The roles of positive reinforcement, negative reinforcement, and punishment are key to understanding nicotine use and the development of nicotine addiction. This review mainly focuses on
positive and negative reinforcement, but emerging work on the punishing effects of nicotine has recently suggested that it may be an important factor in excessive nicotine intake in dependent subjects (Fowler, Lu, Johnson, Marks, & Kenny, 2011).

### POSITIVE REINFORCEMENT ASSOCIATED WITH NICOTINE USE

Although many components in cigarette smoke may contribute to smoking, much evidence indicates that individuals use tobacco primarily to experience the psychopharmacological properties of nicotine. A large proportion of smokers eventually become dependent on nicotine (Balfour, 1984; Stolerman, 1991). Nicotine acts as a positive reinforcer and will support intravenous self-administration in various species, including humans, nonhuman primates, and rodents (Fig. 1.2), even at doses and regimens that do not lead to a withdrawal syndrome (Corrigall & Coen, 1989; Donny, Caggiula, Knopf, & Brown, 1995; Goldberg & Henningfield, 1988; Goldberg & Spealman, 1982; Henningfield, Miyasato, & Jasinski, 1983).

**FIGURE 1.2** Pattern of nicotine self-administration in humans and rats. Vertical lines indicate a single nicotine self-administration. Notice the similarity in the pattern of nicotine self-administration in humans and rats. The unit dose for each subject is indicated on the right side of each record. Letters and numbers on the left axis are the initials (humans) or number of subjects (rats). Human data are reproduced from Henningfield, J. E., Miyasato, K., Jasinski, D. R. (1983). Cigarette smokers self-administer intravenous nicotine. Pharmacology, Biochemistry, and Behavior, 19, 887–890. Rat data are from George et al. (unpublished results).
Goldberg, Spealman, & Goldberg, 1981; Goldberg, Spealman, Risner, & Henningfield, 1983; Goodwin, Hiranita, & Paule, 2015; Watkins, Epping-Jordan, Koob, & Markou, 1999). For example, nicotine-containing cigarettes support higher breakpoints on a progressive-ratio schedule of reinforcement than denicotinized cigarettes in humans (Rusted, Mackee, Williams, & Willner, 1998; Shahan, Bickel, Badger, & Giordano, 2001; Shahan, Bickel, Madden, & Badger, 1999). The positive reinforcing effects of nicotine are generally attributed to its acute effects on mood and cognition. In humans, nicotine acutely produces positive rewarding effects, including mild euphoria (Pomerleau & Pomerleau, 1992), increased energy, and heightened arousal (Benowitz, 1996; Stolerman & Jarvis, 1995). Smoking cigarettes produces arousal, particularly with the first cigarette of the day, and relaxation when under stress (Benowitz, 1988). In animals, intravenous nicotine self-administration has been reliably demonstrated in numerous strains of rodents and different laboratories (Corrigall, 1999; Donny et al., 1995; Rose & Corrigall, 1997; Watkins et al., 1999). Systemic injections of the competitive nicotinic receptor antagonist dihydro-β-erythroidine and noncompetitive antagonist mecamylamine decrease intravenous nicotine self-administration in rats with limited access to nicotine (1 h/day; Corrigall & Coen, 1989; Watkins et al., 1999). Moreover, nicotine increases attentional processes (Kaye et al., 2014; Young et al., 2004; Young, Meves, & Geyer, 2013), lowers brain reward thresholds (Epping-Jordan, Watkins, Koob, & Markou, 1998), increases wakefulness (Salin-Pascual, Moro-Lopez, Gonzalez-Sanchez, & Blanco-Centurion, 1999), and increases learning and memory (Davis, Kenney, & Gould, 2007; Gould & Leach, 2014) in rodents and humans. The similar effects of nicotine on mood and cognition reported in humans and rodents provide a behavioral mechanism of action for the positive reinforcing effects of nicotine. However, preclinical studies have found that nicotine is a weak reinforcer. The reinforcing effectiveness of nicotine is approximately 10 times lower than that of cocaine in a progressive-ratio schedule of reinforcement (Risner & Goldberg, 1983). Although the acute positive reinforcing effects of nicotine are important in establishing self-administration behavior and may be sufficient to maintain nicotine self-administration in nondependent subjects, they do not appear to be sufficient to explain the intense craving for nicotine that is observed in dependent subjects and the escalation of nicotine intake during the transition from initial nicotine use to nicotine dependence and after relapse (Cohen, Koob, & George, 2012). Our hypothesis is that during the transition from nicotine use to nicotine dependence, there is a switch in the neurobiological mechanisms that underlie the motivation for nicotine self-administration that reflects a transition from positive to negative reinforcement mechanisms (Fig. 1.1).
NEGATIVE REINFORCEMENT ASSOCIATED WITH NICOTINE USE

A nicotine withdrawal or abstinence syndrome after chronic nicotine exposure has been characterized in both humans (Hughes, Gust, Skoog, Keenan, & Fenwick, 1991; Shiffman & Jarvik, 1976) and animals (Epping-Jordan et al., 1998; Hildebrand, Nomikos, Bondjers, Nisell, & Svensson, 1997; Malin et al., 1994, 1992; Malin, Lake, Carter, Cunningham, & Wilson, 1993; Watkins, Koob, & Markou, 2000) and has both somatic and affective components. In humans, acute nicotine withdrawal is characterized by affective symptoms, including depressed mood, dysphoria, irritability, anxiety, frustration, increased reactivity to environmental stimuli, and difficulty concentrating, as well as somatic symptoms, such as bradycardia, gastrointestinal discomfort, and increased appetite that leads to weight gain (American Psychiatric Association, 2000; Hughes et al., 1991). The enduring symptoms of nicotine withdrawal (protracted abstinence) include continued affective changes, such as depressed mood, irritability, sleep disturbances, and stress responsivity (Hughes et al., 1991), with abstinent smokers often reporting powerful cravings for tobacco (Hughes et al., 1984). Although the somatic symptoms of withdrawal from drugs of abuse are unpleasant and annoying, it has been hypothesized that avoidance of the affective components of drug withdrawal, including those associated with nicotine withdrawal (negative reinforcement), play a more important role in the maintenance of nicotine dependence than the somatic symptoms of withdrawal (Koob, Markou, Weiss, & Schulteis, 1993; Markou, Kosten, & Koob, 1998).

Abrupt abstinence from chronic nicotine administration also leads to a withdrawal syndrome in rodents (Malin et al., 1992) that has somatic and motivational components. Both spontaneous and antagonist-precipitated nicotine withdrawal produce various somatic signs (eg, eye blinks, body shakes, chewing, gasping, writhing, ptosis, and teeth chattering) and motivational effects (eg, elevated reward thresholds, anxiety-like responses, and conditioned place aversion; Epping-Jordan et al., 1998; Ghozland, Zorrilla, Parsons, & Koob, 2004; Stinus, Cador, Zorrilla, & Koob, 2005; Watkins, Stinus, Koob, & Markou, 2000). Several groups have established that rats will self-administer nicotine when given chronic extended access to the drug (Fu, Matta, Kane, & Sharp, 2003; LeSage, Keyler, Collins, & Pentel, 2003; O’Dell et al., 2007; Paterson & Markou, 2004; Valentine, Hokanson, Matta, & Sharp, 1997). Passive nicotine administration decreases nicotine self-administration in chronic self-administration paradigms (LeSage et al., 2003), and mecamylamine increases nicotine self-administration (O’Dell et al., 2007). Rats that are dependent on nicotine show anxiogenic-like effects during spontaneous withdrawal (Pandey, Roy, Xu, & Mittal, 2001; Slawecki, Thorsell, Khoury, Mathe, & Ehlers, 2005).
and mecamylamine-precipitated anxiety-like responses in the elevated plus maze (George et al., 2007). Rats that self-administer nicotine when given limited access to it (1h/day, 5days/week) show very limited, if any, signs of somatic or motivational withdrawal (Paterson & Markou, 2004) and do not exhibit the escalation of nicotine intake after abstinence (Cohen et al., 2012, 2015; George et al., 2007), suggesting that nicotine self-administration is mostly driven by positive reinforcement mechanisms in this model. However, rats that are given extended access to nicotine self-administration with days of deprivation between each session (23/day, every 24–48h) show the escalation of nicotine intake (Fig. 1.3C) and emergence of somatic and motivational signs of withdrawal, including anxiety-like behavior and hyperalgesia (Fig. 1.3D and E; Cohen et al., 2012, 2015) that predict the magnitude of nicotine intake after abstinence, suggesting that nicotine self-administration in this model is mainly driven by negative reinforcement.

One hypothesis to explain the increased self-administration of nicotine during 23h access, particularly after periods of deprivation, is that nicotine self-administration becomes more heavily motivated by negative reinforcement mechanisms that are driven by recruitment of brain systems that are involved in anxiety-like symptoms and dysphoria (Koob & Le Moal, 2005, 2006). Recent work has confirmed this hypothesis by demonstrating that 2 days of nicotine abstinence was sufficient to increase nicotine self-administration when access to nicotine resumed (Cohen et al., 2012). Moreover, this nicotine deprivation effect was observed even after 6 weeks of abstinence (Fig. 1.3B) and was only observed in dependent rats with extended access to nicotine and not limited access (George et al., 2007). The reinforcing effects of nicotine can also be measured by using a progressive-ratio schedule of reinforcement, in which the responses that are required to obtain a discrete dose of nicotine increase after each trial until the animal stops responding (breakpoint). Both increasing doses of nicotine and nicotine withdrawal increase breakpoints under a progressive-ratio schedule (Cohen et al., 2012, 2015), demonstrating that the reinforcing effects of nicotine are dose- and withdrawal-dependent. Moreover, repeated periods of 2–3 days of abstinence lead to the escalation of nicotine self-administration with increased responding under a progressive-ratio schedule (Cohen et al., 2012). Again, only dependent rats with extended access to nicotine self-administration were sensitive to the effect of abstinence and showed the escalation of intake. We also recently showed that abstinence-induced anxiety-like behavior and hyperalgesia predicted subsequent nicotine self-administration when access to nicotine resumed (Fig. 1.3D and E; Cohen et al., 2015), suggesting that the removal of an aversive state that is characterized by increased anxiety-like behavior and pain is a key driving force behind excessive nicotine intake in dependent subjects (Fig. 1.1).
1. OVERVIEW OF NICOTINE WITHDRAWAL AND NEGATIVE REINFORCEMENT

FIGURE 1.3 Evidence of negative reinforcement in rats given extended access to nicotine self-administration. (A) 72 h of nicotine deprivation (ND1-4) produces a robust increase in nicotine intake in rats with access to nicotine self-administration for 23 h/day. (B) Abstinence-induced increase in nicotine intake is observed after acute (24 h) and protracted (6 weeks) abstinence. (C) Repeated periods of abstinence (48 h) between each session produce a robust and sustained escalation of nicotine intake only in rats with long access (LgA) but not short access (ShA). (D) Abstinence-induced anxiety-like behavior (low percentage time on open arms) predicts high nicotine intake when access to nicotine resumes. (E) Abstinence-induced hyperalgesia (low withdrawal threshold) predicts high nicotine intake when access to nicotine resumes. Reproduced from (A and B) George, O., Ghozland, S., Azar, M. R., Cottone, P., Zorrilla, E. P., Parsons L. H., et al. (2007). CRF-CRF1 system activation mediates withdrawal-induced increases in nicotine self-administration in nicotine-dependent rats. Proceedings of the National Academy of Sciences of the USA, 104, 17198–17203; (C) Cohen, A., Koob, G. F., George, O. (2012). Robust escalation of nicotine intake with extended access to nicotine self-administration and intermittent periods of abstinence. Neuropsychopharmacology, 37, 2153–2160; (D and E) Cohen, A., Treweek, J., Edwards, S., Leão, K. M., Schulteis, G., Koob, G. F., et al. (2015). Extended access to nicotine leads to a CRF1 receptor dependent increase in anxiety-like behavior and hyperalgesia in rats. Addiction Biology, 20, 56–68.
There is significant face validity of the deprivation model to the human condition. The nicotine deprivation effect in rats is similar to the human condition, in which one observes an increase in smoking after abstinence (i.e., an increase in the number and duration of puffs) followed by a titration period of nicotine intake (Benowitz & Jacob, 1984; Isaac & Rand, 1972; Madden & Bickel, 1999; Nil, Woodson, & Battig, 1987; Rusted et al., 1998). A critical point is that rats with 23 h access (without an abstinence period) show, as in humans, stable nicotine intake for months, and the nicotine deprivation effect is a short-lasting phenomenon that allows one to unveil and investigate the neural basis of the motivation to take nicotine under a negative reinforcement framework. Additionally, the similarity in blood nicotine levels in dependent humans and rats in a chronic access/deprivation model supports the relevance of this model to human addiction. Blood nicotine levels range between 10 and 25 ng/ml over the course of 24 h in humans who smoke at least one pack of cigarettes per day and reach 15 ng/ml after one cigarette (Benowitz & Jacob, 1984; Benowitz, Porchet, Sheiner, & Jacob, 1988). In previous studies, we measured blood nicotine levels in rats (O’Dell et al., 2006) and found that 1.0 mg/kg/day of nicotine via a minipump produced blood levels of 22 ng/ml. The rats in our self-administration studies self-administer 0.8–1.2 mg/kg/day using a unit dose of 0.03 mg/kg (Cohen et al., 2012; George et al., 2007; O’Dell et al., 2007). In actual measurements after an infusion of nicotine at the dose used for self-administration, nicotine levels ranged from 10 to 30 ng/ml (see Guillem et al., 2005, from our laboratory, and LeSage et al., 2002). These results suggest that under certain conditions, intravenous nicotine self-administration in rodents reaches levels well beyond those that are required to produce dependence as defined by the manifestation of a withdrawal syndrome during abstinence.

Altogether, these results suggest that extended access to nicotine itself can lead to the escalation of intake and dependence (as measured by withdrawal when nicotine is removed or nicotinic receptors are blocked). Dependence appears to be manifested by a negative emotional state, and negative reinforcement processes drive escalation. Thus, the transition from nicotine use to nicotine dependence is hypothesized to involve neuroadaptations within brain reward and stress circuitries and neuroadaptations (Koob & Le Moal, 2005) that contribute to negative emotional states that drive negative reinforcement (Koob & Bloom, 1988).
effects of indirect sympathomimetics, such as cocaine and amphetamine (Koob, Sanna, & Bloom, 1998). Nicotine is an agonist at nicotinic acetylcholine receptors (Lindstrom, 1997), and nicotinic acetylcholine receptors have been shown to be localized on cell bodies and dendrites of dopamine neurons in the ventral tegmental area and terminal fields of the mesocorticolimbic dopamine system, such as the nucleus accumbens (Clarke & Pert, 1985; Swanson, Simmons, Whiting, & Lindstrom, 1987). Systemic nicotine administration also increases extracellular dopamine levels in the shell of the nucleus accumbens, an effect that is observed with other major drugs of abuse (Nisell, Marcus, Nomikos, & Svensson, 1997; Pontieri, Passarelli, Calo, & Caronti, 1998; Pontieri, Tanda, Orzi, & Di Chiara, 1996). Neurochemical in vivo microdialysis studies have shown that nicotine can release dopamine via actions at both sites, with more evidence for the actions of nicotine at the level of the ventral tegmental area (Corrigall & Coen, 1991; Corrigall, Coen, & Adamson, 1994; Corrigall, Franklin, Coen, & Clarke, 1992; Enrico et al., 2013; Nisell, Nomikos, & Svensson, 1994; Panin, Lintas, & Diana, 2014). The recruitment of dopamine and γ-aminobutyric acid (GABA) neurons in the ventral tegmental area through the activation of α4β2*, α6β2*, and α5* but not α7* subunit-containing receptors appears to be critical for the positive reinforcing effects of nicotine (Maskos et al., 2005; Morel et al., 2014; Orejarena et al., 2012; Pons et al., 2008; Tolu et al., 2013). Other neuropharmacological systems that are implicated in the positive reinforcing effects of nicotine include cholinergic (Azam, Winzer-Serhan, Chen, & Leslie, 2002; Oakman, Faris, Kerr, Cozzari, & Hartman, 1995; Tago, McGeer, McGeer, Akiyama, & Hersh, 1989), serotonergic (Carboni, Acquas, Leone, & Di Chiara, 1989), glutamatergic (McGehee, Heath, Gelber, Devay, & Role, 1995; Schilstrom, Nomikos, Nisell, Hertel, & Svensson, 1998), GABAergic (Corrigall, Coen, Adamson, Chow, & Zhang, 2000; Corrigall, Coen, Zhang, & Adamson, 2001; Dewey et al., 1999), and opioidergic (Houdi, Pierzchala, Marson, Palkovits, & Van Loon, 1991; Pomerleau & Pomerleau, 1984) systems.

NEUROBIOLOGICAL MECHANISMS OF NEGATIVE REINFORCEMENT

The neurobiological substrates for the dependence-inducing effects of nicotine are beginning to be elucidated. Neurotransmitter systems that are implicated in nicotine withdrawal include decreases in dopamine and opioid peptide system activity, increases in corticotropin-releasing factor (CRF), dynorphin, and norepinephrine activity, and changes in serotonin activity (Cohen & George, 2013; Tejeda, Natividad, Orfila, Torres, & O’Dell, 2012; Watkins, Koob, et al., 2000). Decreases in the extracellular levels of dopamine in the nucleus accumbens and central nucleus of the
Amygdala, but not the prefrontal cortex, have been observed during nicotine withdrawal (Hildebrand, Nomikos, Hertel, Schilstrom, & Svensson, 1998; Panagis, Hildebrand, Svensson, & Nomikos, 2000), with decreased tonic activity of ventral tegmental area dopamine neurons (Grieder et al., 2012). Decreases in serotonin synthesis have also been observed during chronic nicotine exposure (Benwell & Balfour, 1979). Increases in CRF have been observed in the central nucleus of the amygdala during withdrawal (George et al., 2007). The somatic and affective/aversive signs of nicotine withdrawal have also been precipitated by the opioid receptor antagonist naloxone and nicotinic receptor antagonist mecamylamine, and opioid and nicotinic receptor agonists can reverse the somatic signs of nicotine withdrawal (Hildebrand et al., 1997; Malin et al., 1993). Moreover, nicotinic receptor blockade in the ventral tegmental area and interpeduncular nucleus produces somatic and motivational withdrawal (anxiety-like behavior) in nicotine-dependent rats (Hildebrand, Panagis, Svensson, & Nomikos, 1999; Zhao-Shea et al., 2015), possibly through the blockade of α7 nicotinic receptors (Nomikos, Hildebrand, Panagis, & Svensson, 1999).

Acute nicotine administration has also been shown to activate hormonal and neurotransmitter stress responses (Faraday, Blakeman, & Grunberg, 2005; Matta, Beyer, McAllen, & Sharp, 1987; Okada, Shimizu, & Yokotani, 2003; Sharp & Matta, 1993), and such activation is dose dependent (Mendelson, Sholar, Goletiani, Siegel, & Mello, 2005). Nicotine not only acutely activates the hypothalamic-pituitary-adrenal (HPA) axis (Matta et al., 1987) but also activates CRF neurons extrahypothalamically (Matta, Valentine, & Sharp, 1997). Withdrawal from chronic nicotine elevates CRF in the basal forebrain (Slawecki et al., 2005), and a CRF receptor antagonist that was injected intracerebroventricularly blocked the anxiogenic-like effects of withdrawal from bolus injections of nicotine (Tucci, Cheeta, Seth, & File, 2003). The hypothesis that CRF is activated during nicotine withdrawal (Bruijnzeel & Gold, 2005) is based on the observation that acute withdrawal from nicotine can increase circulating corticosterone, and extracellular CRF has been shown to be increased in the central nucleus of the amygdala during withdrawal from chronic nicotine (George et al., 2007) as well as during withdrawal from chronic administration of other major drugs of abuse (Koob et al., 1998). The anxiogenic-like effects of precipitated nicotine withdrawal were blocked by a CRF1 receptor antagonist, and local infusion of CRF in the central nucleus of the amygdala produced anxiety-like behavior (George et al., 2007). Nicotine also enhanced norepinephrine release in the paraventricular nucleus of the hypothalamus (Sharp & Matta, 1993). However, activation of the HPA axis showed a subsensitive response during withdrawal from chronic nicotine administration (Matta, Fu, Valentine, & Sharp, 1998; Mendelson et al., 2005; Semba, Wakuta, Maeda, & Suhara, 2004). Chronic self-administration increases norepinephrine release in the paraventricular
nucleus of the hypothalamus (Fu, Matta, Brower, & Sharp, 2001) and amygdala (Fu et al., 2003). The blockade of noradrenergic α1 receptors can decrease nicotine self-administration and nicotine reinstatement (Forget et al., 2010). Given that norepinephrine, CRF, and glucocorticoids interact in the basal forebrain in a feedforward system, in which each system enhances the release of the other neurotransmitters (Koob, 1999; Vendruscolo et al., 2012), these results would be consistent with the hypothesis that chronic nicotine activates extrahypothalamic CRF systems during the development of dependence. From a developmental perspective, increased CRF-like immunoreactivity was observed in adult rats that were exposed to nicotine during adolescence and has been linked to an anxiety-like phenotype (Slawecki et al., 2005).

Animal models that incorporate aspects of negative reinforcement in nicotine dependence have unveiled the existence of a novel CRF–CRF₁ system in the ventral tegmental area–interpeduncular nucleus pathway. Indeed, chronic nicotine exposure and withdrawal from nicotine recruit a population of dopamine–CRF neurons in the ventral tegmental area, and the activation of such dopamine–CRF neurons produces anxiety-like behavior and the escalation of nicotine intake (Grieder et al., 2014; Zhao-Shea et al., 2015). Moreover, the recruitment of CRF neurons in the ventral tegmental area during withdrawal is paralleled by a decrease in the tonic activity of ventral tegmental area dopamine neurons (Grieder et al., 2012), suggesting that the decrease in dopaminergic tone that is observed in human smokers may be caused by the recruitment of CRF neurons. Altogether, these reports suggest that downregulation of the dopamine system in the ventral tegmental area, nucleus accumbens, and central nucleus of the amygdala, together with the upregulation of CRF and norepinephrine systems in the central nucleus of the amygdala and ventral tegmental area, may underlie excessive nicotine intake, driven by negative reinforcement in dependent subjects.

TRANSLATIONAL ASPECTS OF THE NEUROBIOLOGY OF NEGATIVE REINFORCEMENT

Three medications are currently on the market for the treatment of tobacco addiction: nicotine replacement therapy (gum, lozenge, and patch), bupropion (Zyban), and varenicline (Chantix). These medications have actions that can be considered relevant to treating the withdrawal/negative affect stage of the addiction cycle and thus the negative reinforcement processes associated with nicotine withdrawal. There are a number of neurotransmitter systems that are implicated in the negative reinforcing effects of nicotine withdrawal, may contribute to the development of dependence, and can be targeted to develop new medications for smoking cessation.
The vulnerability to nicotine addiction may be related to initial sensitivity to the reinforcing effects of nicotine, but recent conceptualizations regarding the development of addiction have introduced the hypothesis that vulnerability may engage other aspects of the addiction process (Koob & Le Moal, 1997, 2001, 2005, 2006; Robinson & Berridge, 1993). Under this framework, incentive salience via a sensitization-like process (Robinson & Berridge, 1993) may be initially engaged, but compulsive nicotine seeking and taking likely involve negative reinforcement that is driven by the loss of reward system activity and recruitment of brain stress system activity (Koob & Le Moal, 2005). The combination of excellent and validated animal models that incorporate the negative reinforcement processes that are associated with nicotine withdrawal and a better understanding of the neurocircuitry and neuropharmacological mechanisms that underlie nicotine motivational withdrawal has provided viable targets for future drug development. Human laboratory models of the withdrawal/negative affect stage permit the proof-of-concept testing of potential therapeutics and the clinical validation of relevant pharmacological targets. The results of such studies can loop back to validate the animal models. Such a domain approach rather than syndrome approach to drug development has the potential to reveal pharmacogenetic approaches to drug development and utility, and thus should fit well with new concepts related to precision medicine.

References


1. OVERVIEW OF NICOTINE WITHDRAWAL AND NEGATIVE REINFORCEMENT


