THE NEUROBIOLOGY OF NICOTINE ADDICTION: CLINICAL AND PUBLIC POLICY IMPLICATIONS

PAUL D. GARDNER, ANDREW R. TAPPER, JEAN A. KING, JOSEPH R. DIFRANZA, DOUGLAS M. ZIEONDIS

Clinicians, social scientists, researchers, and policy makers appreciate the need to understand the neurobiology of nicotine addiction and how this information can lead to new treatments and provide support for public policy debates on parity and preventing adolescent tobacco use. In a “bench-to-bedside” manner, this review covers both clinical and basic science perspectives. Both the reward and sensitization-homeostasis theories of nicotine addiction are supported by new understanding of clinical issues of rapid tolerance, withdrawal, sensitization, and craving when examined by functional brain imaging, genetics, and basic science studies of nicotinic acetylcholine receptors. This review provides information to help shape public policy, fight stigma, and improve clinical treatment and research. The fight for parity in health care requires education about the neurobiological basis of addiction versus the stigmatized bad habit or simple socialization. Parity must support reimbursement for nicotine replacement medications or other FDA-approved medications and psychosocial treatments.

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INTRODUCTION

Aggressive educational and legislative efforts as well as improved tobacco dependence treatments resulting from basic and clinical research findings have helped reduce the prevalence of tobacco dependence in the United States; however, there is a need to continue to improve the treatment outcomes and better match individual patients to specific treatments. In addition to education about the health consequences of tobacco use, an important component of ongoing public education must be on the addictive potential of nicotine and tobacco use. A neurobiological understanding of nicotine addiction helps reduce stigma put on those who have difficulty quitting and provides increased understanding of the problem and possible solutions for individuals not responding to current treatments (Brewster et al., 2002). Implementation of health care parity requires having an underlying biological basis for the disorders that are to be reimbursed in health care plans. A clear neurobiological explanation of tobacco addiction helps these efforts. This paper will initially review some of the key clinical phenomena explaining nicotine addiction (early tolerance, nicotine withdrawal, and craving) and place these important issues in the context of the reward and sensitization-homeostasis theories of nicotine addiction and current information from imaging, genetic, and basic laboratory studies, including nicotine receptor subtypes. This information provides a foundation for the concluding section on potential therapeutic targets. A better understanding of the rapid clinical progression to tobacco dependence can inform neurobiological research questions which may lead to new advances in treatment.

ADDITION DUE TO EARLY TOLERANCE AND NICOTINE WITHDRAWAL

Until a few years ago, it was widely assumed that nicotine dependence did not begin until a person had smoked for several years (American Psychiatric Association, 2000). It was thought that nicotine withdrawal symptoms were experienced only by people who smoked more than five cigarettes every day, and that people who experienced nicotine withdrawal had to maintain the presence of nicotine in the blood throughout the day to suppress withdrawal symptoms. Thus, nicotine dependence was envisioned as developing very slowly in the face of long exposures to constant heavy doses of nicotine. Basic science researchers attempted to replicate prolonged heavy exposures in animal models of nicotine addiction. This assumption is proving to be inaccurate.

The past few years have brought the revelation that nicotine withdrawal symptoms are quite commonly experienced by novice smokers who smoke only a few cigarettes per week (DiFranza et al., 2007a; Gervais et al., 2006; Kandel et al., 2007). These smokers do not have to smoke at least five cigarettes daily, because their withdrawal symptoms can be suppressed for many days at a time by smoking a single cigarette. The duration of relief from withdrawal that is provided by smoking a single cigarette shrinks with repeated exposure to nicotine. A youth who was able to keep withdrawal symptoms at bay for many years (Wellman et al., 2006). The fact that relapsed smokers retain a short latency to withdrawal is an indication that the brain does not revert to its nicotine-unresponsive state. The challenge for neurobiologists is to determine not only what causes withdrawal, but why the latency to withdrawal shortens with repeated exposure to nicotine. The least vulnerable youth can smoke more than 100 cigarettes before experiencing symptoms (Scragg et al., 2008). What could change in the brain with such rapidity? The least vulnerable youth can smoke more than 100 cigarettes before experiencing symptoms (Scragg et al., 2008). What could change in the brain with such rapidity? The least vulnerable youth can smoke more than 100 cigarettes before experiencing symptoms. The most vulnerable youth can experience symptoms after smoking just 20 cigarettes. They are not at risk of addiction. Nicotine metabolism is a key factor affecting the duration of nicotine addiction, although nicotine and its metabolites are not the primary cause of nicotine dependence. These mild smokers have tremendous public policy and public education impact. They also highlight the need to focus on intervention strategies for vulnerable youth.

Are these findings about nicotine addiction consistent with the idea that the reaction to the first inhalation from a cigarette is the best predictor of which youth will become addicted to nicotine? The answer to this question is “yes.” The risk of addiction to nicotine is not just due to the amount of nicotine used; it is due to the metabolism of nicotine and the development of nicotine dependence. The metabolism of nicotine and the development of nicotine dependence are very complex processes, and many factors can influence them. These factors include genetics, environment, and individual differences in responses to nicotine. Understanding these factors is crucial for developing effective strategies to prevent nicotine addiction and its consequences.
The duration of relief from withdrawal that is provided by smoking a single cigarette shrinks with repeated exposure to nicotine. A youth who was able to keep withdrawal in check by smoking one cigarette every few days finds that, over time, he or she must smoke at more and more frequent intervals to keep withdrawal in check. Eventually, most smokers who have ready access to tobacco will find that they are smoking 10 to 20 cigarettes per day just to keep withdrawal under control. The interval between finishing a cigarette and the onset of withdrawal is termed the latency to withdrawal (DiFranza & Ursprung, 2008). It can vary from many days in length in novice smokers, to just a few minutes in smokers with advanced dependence. The shortening of the latency to withdrawal represents dependence-related tolerance. The challenge for neurobiologists is to determine not only what causes withdrawal, but why the latency to withdrawal shortens with repeated exposure to nicotine. The fact that the impact of one cigarette can last long after nicotine has been cleared from the blood suggests that perhaps other factors are responsible for propagating or sustaining nicotine’s effects after it is gone. Nicotine stimulates the release of dopamine, but many other brain neurotransmitters, including g-aminobutyric acid (GABA), glutamate, neurepinephrine, serotonin, cannabanoid and beta-endorphin are also involved (Benowitz, 2008).

Another challenge for researchers is to determine how the processes that produce nicotine addiction can develop as quickly as they do. The most vulnerable youth experience symptoms of nicotine addiction after smoking only one or two cigarettes (Scragg et al., 2008). What could change in the brain with such rapidity? The least vulnerable youth can smoke more than 100 cigarettes before experiencing symptoms of nicotine addiction, and about 95 percent of individuals smoking 100 cigarettes in their lifetime will become addicted to tobacco (Scragg et al., 2008). These facts have tremendous public policy and public education impact. They also highlight the need to focus clinical and neurobiological research on these phenomena.

Are these differences in individual vulnerability genetically determined? The reaction to the first inhalation from a cigarette is the best predictor of which youth will become addicted. Those who experience a sense of relaxation are at triple the risk of addiction (DiFranza et al., 2007b). Do individuals differ in their responses to nicotine and their vulnerability to addiction because they have a different compliment of nicotinic receptors? Other neurobiological changes with mental illness or other addictions are associated with increased rates of nicotine addiction and more difficulty quitting (Ziedonis & Williams, 2003).

Novice smokers can keep withdrawal in check by smoking only a few cigarettes per week, but long-term smokers cannot do this, even after having quit smoking for many years (Wellman et al., 2006). The fact that relapsed smokers retain a short latency to withdrawal is an indication that the brain does not revert to its nicotine-
Naïve state after smoking cessation. This has been confirmed in animal experiments (Slotkin et al., 2007).

**The Sensitization-Homeostasis Theory of Nicotine Addiction**

Based on the new discoveries about the clinical nature of nicotine addiction, members of our team have postulated the sensitization-homeostasis theory to explain how nicotine might act on the brain to cause addiction (DiFranza & Wellman, 2005). In a departure from traditional theories that postulate that drugs cause addiction by stimulating pleasure centers in the brain, the sensitization-homeostasis theory postulates that nicotine causes addiction by inhibiting brain circuits that are responsible for generating craving for rewarding experiences (DiFranza & Wellman, 2005). This is consistent with the observation that many individuals do not find nicotine to be pleasurable until after they are addicted. Throughout this paper we will expand the description of the sensitization-homeostasis theory as it relates to the particular neurobiological research being described. Also, although we have focused on this theory in the article, we acknowledge that the reward theory and other models continue to be important to understand the complex and multidimensional components of addiction. The sensitization-homeostasis theory provides a framework for clinicians and policy makers to better organize the findings being presented. Other important models include the reward model, social-ecological model, genetic theories, biological and conditioning exposure theories, and adaptation theories. We will not review these other approaches, although we recognize that they have been helpful in developing current tobacco control and psychosocial clinical interventions (Ziedonis, 2004).

**Dopamine, the Reward Theory, and the Neuroanatomy of Dependence and Withdrawal**

The idea that addiction may be initiated by the first dose of nicotine strongly supports a neurobiological basis of this addiction versus being based on habit or socialization. Consistent with this idea, laboratory studies have shown that reward, sensitization, withdrawal, tolerance, conditioned cues/memory, motivation, executive functioning, and impulse control are all components of addiction with a neurobiological basis (DiFranza & Wellman, 2005).

The main action of nicotine’s addictive effects is thought to be mediated through the mesocorticolimbic dopamine pathways. Dopamine neurons within these circuits originate in the ventral tegmental area (VTA) and project to the nucleus accumbens (NAc) and the prefrontal cortex (PFC, mesocortical). The amount of nicotine typically inhaled by smoking and found in smokers’ blood is able to acutely increase the firing of dopaminergic neurons in the VTA, which causes increased dopamine release in the nucleus accumbens (Pidoplichko, DeBiasi, Williams, & Dani, 1997). Originally thought to directly mediate the rewarding effects of abused drugs, more...
The main action of nicotine's addictive effects is thought to be mediated through nicotine receptors (nAChRs) expressed both at the cell body, where they contribute to dopamine neurons, as well as GABA interneurons, within the VTA are rich in nicotinic receptors. Antagonist naloxone that precipitated withdrawal in nicotine dependent rats and in animals but not in human smokers (Rose et al., 2001). Interestingly it was the opioid antagonist naloxone that precipitated withdrawal in nicotine dependent, but not nicotine naive, rats (Hildebrand, Panagis, Svensson, & Nomikos, 1999). Caution must be used in the interpretation of these animal models of withdrawal symptoms; these physical withdrawal symptoms can occur without changes in brain striatal dopamine levels (Carboni, Bortone, Giua, & DiChiara, 2000). The affective withdrawal behaviors and symptoms appear to be directly correlated with decreases in brain dopamine levels (Kenny & Markou, 2001). Local injection of the non-specific nicotine receptor antagonist, mecamylamine, into the VTA decreases dopamine release in the nucleus accumbens and precipitates both somatic and affective withdrawal symptoms in nicotine dependent, but not nicotine naive, rats (Hildebrand, Panagis, Svensson, & Nomikos, 1999). Caution must be used in the interpretation of these animal models of withdrawal. For example, the blocker mecamylamine induces withdrawal in animals but not in human smokers (Rose et al., 2001). Interestingly it was the opioid antagonist naloxone that precipitated withdrawal in nicotine dependent rats and in human smokers (Malin, Lake, Carter, Cunnigham, & Wilson, 1993).

Nicotinic Receptors

Of particular importance to nicotine addiction and withdrawal is the fact that dopamine neurons, as well as GABA interneurons, within the VTA are rich in nicotine receptors (nAChRs) expressed both at the cell body, where they contribute to recent evidence suggests that dopamine release may be a predictor of reward (Schultz, 2004). Regardless of dopamine’s exact role, nicotine-induced release of dopamine is critical for the onset and maintenance of dependence (Corrigall & Coen, 1991; Picciotto et al., 1998). Pharmacological blockade of dopamine receptors or destruction of dopamine neurons or the nucleus accumbens reduces self administration in rats (Corrigall & Coen, 1991; Corrigall, & Coen, 1992). These findings support the dopamine reward theory; however, the recognized importance of other neurotransmitters, such as GABA and glutamate, cannot be easily explained with only this theory. GABA (a major inhibitory neurotransmitter) inhibits dopamine release, and glutamate (a major excitatory neurotransmitter) provides excitatory input into the VTA coming from multiple regions of the brain (George, 2007). In humans, nicotine withdrawal causes craving, irritability, insomnia, restlessness, and impatience (Hughes, 2007; Kenny & Markou, 2001). Some of these symptoms are mood-subjective feelings oriented (affective) and some are physical (somatic). Given the varied nature of these symptoms, the sensitization-homeostasis theory proposes that withdrawal symptoms result from homeostatic imbalance in multiple independent brain systems, so there may be several mechanisms underlying withdrawal (DiFranza & Wellman, 2005). Central affective withdrawal symptoms have been associated with a decrease in dopamine release in the nucleus accumbens and striatum (Fung, Schmid, Anderson, & Lau, 1996; Hildebrand, Nomikos, Hertel, Schilström, & Svensson, 1998). Somatic withdrawal has both central and peripheral nervous system components to explain the symptoms; these physical withdrawal symptoms can occur without changes in brain striatal dopamine levels (Carboni, Bortone, Giua, & DiChiara, 2000). The affective withdrawal behaviors and symptoms appear to be directly correlated with decreases in brain dopamine levels (Kenny & Markou, 2001). Local injection of the non-specific nicotine receptor antagonist, mecamylamine, into the VTA decreases dopamine release in the nucleus accumbens and precipitates both somatic and affective withdrawal symptoms in nicotine dependent, but not nicotine naive, rats (Hildebrand, Panagis, Svensson, & Nomikos, 1999). Caution must be used in the interpretation of these animal models of withdrawal. For example, the blocker mecamylamine induces withdrawal in animals but not in human smokers (Rose et al., 2001). Interestingly it was the opioid antagonist naloxone that precipitated withdrawal in nicotine dependent rats and in human smokers (Malin, Lake, Carter, Cunnigham, & Wilson, 1993).
neuronal excitability, and in presynaptic terminals, where they modulate the release of either excitatory neurotransmitters such as glutamate or inhibitory factors such as GABA. Thus, nicotine activates or inhibits dopaminergic VTA neurons through multiple mechanisms. VTA neurons express multiple nicotinic receptor (nAChR) subunits (including α4, α5, α6, α7, β2 and β3 to be discussed later in the article), and these different combinations of subunits imply that different receptors have different properties (Dani, 2001).

A major goal of nicotine addiction research is to identify specific nicotine receptor (nAChR) subtypes critical for nicotine dependence and withdrawal (Laviolle & van der Kooy, 2004). Once identified, these receptors should provide therapeutic targets for smoking cessation. Because nicotinic receptors serve as modulators of virtually every neurotransmitter system in the brain (Benowitz, 2008), the transition to a nicotine-dependent state likely involves many brain regions outside of the traditional dopaminergic “reward pathway.” Thus, another major goal is to understand how other brain regions and neurotransmitters are involved in nicotine dependence and withdrawal. Brain imaging is an invaluable tool in this effort.

**Sensitization**

The potential role of sensitization in human addiction has been the focus of basic science research for over seven decades (Post, 1980). Sensitization refers to a process whereby subsequent doses of a drug have a greater impact than the initial dose. Like other addictive drugs, nicotine induces sensitization in animals which is seen as increased stimulation of locomotion. Following its induction, sensitization persists as a latent state: activity is normal when nicotine is absent, but when nicotine is re-administered, sensitization is expressed as augmented locomotion (DiFranza & Wellman, 2007). The sensitization-homeostasis theory proposes that sensitization to nicotine causes an exaggerated response to subsequent doses of nicotine. Since the postulated effect of nicotine is to inhibit activity in a craving generation system, sensitization of the response to nicotine would cause a “super physiologic” inhibition of activity in this system. The sensitization-homeostasis theory contends that the process that results in nicotine addiction can be set in motion by the first cigarette (DiFranza & Wellman, 2005). This is consistent with data suggesting that the neurological adaptations underlying sensitization begin with the first dose. Sensitization can be observed when the second dose of nicotine is administered in rats (Bevins & Besheer, 2001; Hahn, Stolerman, & Shoaib, 2000).

Unpublished data show that rats express sensitization in the form of increased locomotion only when nicotine is given after a period of abstinence (King, Shields, DiFranza, & Rane, 2009). When doses are too closely spaced, a sensitized response cannot be evoked. For this reason, the sensitization-homeostasis theory postulates that novel sensitization in human addiction has been the focus of basic science research for over seven decades (Post, 1980). Sensitization refers to a process whereby subsequent doses of a drug have a greater impact than the initial dose. Like other addictive drugs, nicotine induces sensitization in animals which is seen as increased stimulation of locomotion. Following its induction, sensitization persists as a latent state: activity is normal when nicotine is absent, but when nicotine is re-administered, sensitization is expressed as augmented locomotion (DiFranza & Wellman, 2007). The sensitization-homeostasis theory proposes that sensitization to nicotine causes an exaggerated response to subsequent doses of nicotine. Since the postulated effect of nicotine is to inhibit activity in a craving generation system, sensitization of the response to nicotine would cause a “super physiologic” inhibition of activity in this system. The sensitization-homeostasis theory contends that the process that results in nicotine addiction can be set in motion by the first cigarette (DiFranza & Wellman, 2005). This is consistent with data suggesting that the neurological adaptations underlying sensitization begin with the first dose. Sensitization can be observed when the second dose of nicotine is administered in rats (Bevins & Besheer, 2001; Hahn, Stolerman, & Shoaib, 2000).

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Like addiction in general, sensitization cannot be attributed to a single neurological alteration, but rather entails changes in multiple systems (Pierce & Kalivas, 1997). Researchers (Kalivas, Sorg, & Hooks, 1993) have proposed that sensitization involves alterations in the neural circuitry that is subservient to how the brain translates motivationally relevant stimuli into adaptive motor responses. Sensitization has been induced and expressed by direct injection of nicotine into the VTA brain region (Kita, Okamoto, & Nakashima, 1992; Panagis, Nisell, Nomikos, Chergui, & Svensson, 1996); however, this effect is complex and is linked with different neurotransmitter systems (Benowitz, 2008). Researchers have recently demonstrated that the nicotine from a single cigarette is sufficient to occupy 88% of the nicotinic receptors (nAChRs) in the brain (Brody et al., 2006). Widely spaced doses of nicotine are sufficient to invoke sensitization in rats, and to trigger the development of nicotine withdrawal symptoms in novice adolescent human smokers (DiFranza et al., 2007a; Gervais et al., 2006; Kandel et al., 2007; DiFranza & Wellman, 2005). These are very important findings in the public policy and education on adolescent smoking risks. The challenge for neurobiologists is to determine if there is a common mechanism behind these phenomena.

Functional magnetic imaging (fMRI) has been utilized to determine which brain regions are involved with sensitization. In our own laboratory, we have utilized fMRI to show that when nicotine is administered to sensitized animals as compared to controls, brain activation is more prolonged in many key regions for nicotine addiction (i.e., the hippocampus, nucleus accumbens, prefrontal cortex, ventral pallidum, and ventral tegmentum), and there is more intense maximal activation in the hippocampus, prefrontal cortex, and ventral tegmentum area (Li, DiFranza, Wellman, Kulkarni, & King, 2008). In addition, sensitization was associated with a relative decrease in activation in the anterior cingulate gyrus (Li et al., 2008). Furthermore, despite the rich endowment of nicotinic receptors in the visual cortex, there were no changes in activation with sensitization, thus establishing the selectivity of the process (Li et al., 2008). The relative inhibition in activity seen in the anterior cingulate gyrus in sensitized animals is of interest because the sensitization-homeostasis theory holds that nicotine works through inhibition of key circuits.
The clinical and public policy take-home message from these imaging studies is that within four days of the initial dose of nicotine, the brain already demonstrates striking changes in how it responds to nicotine. This corresponds well with reports from youth that some of them are already feeling symptoms of addiction within days of their first cigarette.

**Human Imaging Studies and Craving**

Traditional addiction theories have commonly discussed a reward pathway, but not a craving generation system. With the ability to image brain activity in humans there has been a burst of interest in identifying brain structures tied to craving. Cue-induced craving for nicotine is associated with increased fMRI activity in the anterior cingulate gyrus, the orbitofrontal cortex, the temporal lobe, nucleus accumbens, the amygdala, and the ventral striatum (McBride, Barrett, Kelly, Aw, & Dagher, 2006; McClernon et al., 2007; Smolka et al., 2006). In a perfusion fMRI study, researchers (Franklin et al., 2007) demonstrated that craving intensity correlated positively with increases in neural activation in the dorsolateral prefrontal cortex and posterior cingulated cortex. Many similar experiments demonstrate brain activation with similar patterns in addicts in response to cues for many addictive substances and underlying mechanisms that may modulate activation of this drug craving network (Volkow et al., 2008). Together these studies provide strong support for the idea that there are circuits of neurons that are responsible for the generation of craving for addictive substances as proposed by the sensitization-homeostasis theory.

The sensitization-homeostasis theory postulates that nicotine’s addictive potential comes from its ability to suppress activity in a postulated “craving generation system.” With sensitization, nicotine would elicit super-physiological levels of inhibition in this circuit. Homeostatic adaptations would develop in the presence of nicotine to restore the activity of the craving generation system to normal. If these neuroadaptations could develop literally overnight, craving for another cigarette could develop very soon thereafter. Indeed, many smokers report that their first cigarette tasted terrible and provided no pleasure, and yet, within a day or two they had a strong craving for another.

Further support for this theory comes from a recent report that nicotine perfusion decreased craving and regional cerebral blood flow in a distributed network of brain regions including the cingulate cortex and amygdala (Zubieta et al., 2005). Much more work will be needed to establish that nicotine’s primary addiction-related mode of action is through the inhibition of activity in the craving generation system, but the accumulated evidence encourages additional exploration.

**Which nAChR Subtypes are Involved in Nicotine Dependence?**

Identifying the role of specific nicotinic receptor (nAChR) subtypes is important to efforts to design new drug therapies. Nicotine exerts its physiological effects through activation of brain receptors that are receptive to the natural neurotransmitter, acetylcholine. Nicotinic receptors (nAChRs) straddle the nerve cell membrane and allow positively charged ions to pass through a central channel when they are activated. These receptors are comprised of five subunits, and the subunit composition of each channel determines its electrophysiological properties and agonist binding affinities.

There are 12 varieties of nicotinic receptor (nAChR) subunits thus far identified (α2 to α10 and β1 to β4). In some cases, there are multiple α subunits (e.g., αδβ2) or multiple β subunits (e.g., αδβδ) (e.g., αδβδ). In some cases, they can form homeric receptors (composed of 5 identical subunits) that are blocked by the chemical α-bungarotoxin. In contrast, the α7, α8, and α9 subunits are able to form homeric receptors (composed of 5 identical subunits) that are blocked by the chemical α-bungarotoxin. While the complete repertoire of native nAChR subtypes has not been fully elucidated, it is pharmacologically and functionally distinct nicotinic receptor subtypes. There appears to be a great number of possible varieties of nicotinic receptors with each having different properties. The α2 to α6 subunits can assemble with either the β2, β3, or β4 subunits to form heteromeric nicotinic receptors (e.g., α4β2 or α3β4).

**Sensitization and Brain Epigenetic Changes on a Molecular Level**

Consistent with the proposal that early exposures to nicotine trigger brain changes resulting in long-term sensitization (Nestler, 2001), there has been a burst of interest in identifying brain structures tied to craving. Cue-induced craving for nicotine is associated with increased fMRI activity in the anterior cingulate gyrus, the orbitofrontal cortex, the temporal lobe, nucleus accumbens, the amygdala, and the ventral striatum (McBride, Barrett, Kelly, Aw, & Dagher, 2006; McClernon et al., 2007; Smolka et al., 2006). In a perfusion fMRI study, researchers (Franklin et al., 2007) demonstrated that craving intensity correlated positively with increases in neural activation in the dorsolateral prefrontal cortex and posterior cingulated cortex. Many similar experiments demonstrate brain activation with similar patterns in addicts in response to cues for many addictive substances and underlying mechanisms that may modulate activation of this drug craving network (Volkow et al., 2008). Together these studies provide strong support for the idea that there are circuits of neurons that are responsible for the generation of craving for addictive substances as proposed by the sensitization-homeostasis theory.

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Consistent with the proposal that early exposures to nicotine trigger brain changes in the nucleus accumbens and prefrontal cortex, nicotine sensitization is associated with an increase of a non-specific indicator of neuronal metabolic activation called c-fos-like (Panagis et al., 1996; Shim et al., 2001), as well as marked alterations in the early response genes (Schochet, Kelley, & Landry, 2005). In early addiction, the drug can cause tolerance and reduce the individual's reward circuit by switching on a molecule (CREB - cyclic AMP response element-binding protein) which causes a cascade of events, including binding to specific genes and causing them to produce new proteins that these genes encode. Whether the drug causes tolerance or sensitization rapidly is due to the balance of the CREB versus fos-like molecule activity in the nucleus accumbens (Nestler, 2001). Usually there is an initial increase in CREB leading to tolerance and then a fall in levels. In contrast, fos-like substances will stay increased for an extended period of time after the substance use occurs, resulting in long-term sensitization (Nestler, 2001).

Neurobiology of Nicotine Addiction

Sensitization and Brain Epigenetic Changes on a Molecular Level

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Which nAChR Subtypes are Involved in Nicotine Dependence?

There are 12 varieties of nicotinic receptor (nAChR) subunits thus far identified (α2 to α10 and β2 to β4) (Elgoyhen et al., 2001; Gotti et al., 2007; Lustig Peng, Hiel, Yamamoto, & Fuchs, 2001; Wonnacott, 1997). Each of these is part of the five units needed to assemble a receptor. Although all combinations have not been identified, there appears to be a great number of possible varieties of nicotinic receptors with each having different properties. The α2 to α6 subunits can assemble with either the β2, β3, or β4 subunits to form heteromeric nicotinic receptors (e.g., α4β2 or α3β4). In some cases, there are multiple a subunits (e.g., α4α5β2) or multiple β subunits (e.g., α6β2β3) (Gotti et al., 2007). In contrast, the α7, α8, and α9 subunits are able to form homomeric receptors (composed of 5 identical subunits) that are blocked by the chemical a-bungarotoxin.

The critical point is that the various mixtures of receptor subunits generate pharmacologically and functionally distinct nicotinic receptor subtypes. While the complete repertoire of native nAChR subtypes has not been fully elucidated, it is
clear that a staggering diversity of receptor subtypes may exist, with each subtype playing a specific physiological role. Nicotine receptors are involved in several fundamental physiological processes such as learning, memory and attention (Dani & Bertrand, 2007). The diversity of assembled nAChR types might provide neurons with an ability to engage in homeostatic regulation by switching the type of receptor that is displayed or the relative proportions of mixtures of receptor types.

Nicotine stimulates an increase in the number of nAChRs in the brain (Volk et al., 2007). When it was discovered that some youth experienced symptoms of nicotine addiction soon after smoking their first cigarette, there was an interest in determining how rapidly the brain could undertake a remodeling of nAChRs. Animal studies revealed that one dose of nicotine and one day was all that were required to demonstrate an increase in the number of nicotine receptors (Abreu-Villaca et al., 2003). This rapid increase in number of receptors (upregulation) shows the brain’s ability and effort to change for homeostasis—even in response to one dose.

Much of what we know about the individual nicotinic receptor (nAChR) subtypes involved in nicotine dependence stems from mouse genetic studies where a given gene encoding a specific nAChR subunit is either interrupted in the animal such that the protein product is not expressed (i.e., “knock out”, KO, mouse) or modified such that the subunit being studied forms hypersensitive nAChRs (i.e., “knock in” mice), allowing for selective activation by exquisitely small doses of nicotine that do not activate non-mutant, wild-type receptors (Champtiaux & Changeux, 2004). This strategy allows one to answer the question, “Is a nAChR subtype containing subunit X necessary and/or sufficient for nicotine dependence?”

Neuronal nAChRs containing the β2 subunit represent the most abundant high affinity nAChR in the central nervous system (CNS) (Picciotto et al., 1995). Mice that do not express these receptors (β2 KO mice) fail to maintain self-administration of nicotine and exhibit impaired tolerance to the drug (McCallum, Collins, Paylor, & Marks, 2006; Picciotto et al., 1998). In addition, an injection of nicotine fails to increase the concentration of dopamine in the nucleus accumbens in these animals (Picciotto et al., 1998). Furthermore, re-expression of β2 nAChRs in the VTA via viral-mediated gene delivery restores nicotine self-administration, drug-induced dopaminergic neuron activation, and DA elevation in nucleus accumbens (Maskos et al., 2005).

Neuronal nicotinic receptors containing the α4* nicotinic receptor subunit have also been strongly implicated in nicotine dependence (the * indicates that other unidentified, nicotinic subunits co-assemble with α4 subunits to form functional receptors). Knock in mice genetically engineered to express α4* nAChR with a single point mutation that render these receptors hypersensitive to agonists are fifty-fold more sensitive to nicotine tolerance, sensitization, and reward, indicating that selective activation of α4* nAChRs are sufficient for these behaviors (Tapper et al., 2006). Not surprisingly, the majority of β2* nAChRs are assembled from combinations of different subunit types, a vast array of receptor subtypes exist in the reward circuitry, several versions contain α4 and β2 subunits (Grady et al., 2007; Salminen et al., 2004). Future studies will likely address the role of non-α4β2 subunits in nicotine addiction.

Withdrawing from nicotine results in increased anxiety, hypo-locomotion, and conditioned place aversion when they receive nicotinic receptor antagonist chemicals/medications (Damaj et al., 2003; Jackson, Martin, Changeux, & Damaj, 2008; Suzuki, Ise, Tsuda, Kao, & Martin, 2003; Kenny & Markou, 2001; Malin et al., 1994). Mouse affective symptoms include increased licking, grooming, shaking, and scratching (Damaj, 2004). Supportive evidence for the existence of α7 nAChR γ2* nAChR knockout mice do not demonstrate an increase in anxiety, hypo-locomotion, and conditioned place aversion when challenged with the drug (McCallum, Collins, Paylor, & Marks, 2006; Picciotto et al., 1998). Thus, nicotine withdrawal is linked to the activation of α7 nAChR, which are characterized by increased licking, grooming, shaking, and scratching (Damaj, 2004). As animal studies revealed that one dose of nicotine and one day was all that were required to demonstrate an increase in the number of nicotine receptors (Abreu-Villaca et al., 2003). This rapid increase in number of receptors (upregulation) shows the brain’s ability and effort to change for homeostasis—even in response to one dose.

How Do Specific Nicotinic Receptor Subtypes Mediate Different Symptoms of Withdrawal?

In an effort to both better understand the neurobiology of nicotine withdrawal and as well as determining the pharmacological targets for smoking cessation. The relevance of these withdrawal symptoms include increased anxiety, hypo-locomotion, and conditioned place aversion when they receive nicotinic receptor antagonist chemicals/medications (Damaj et al., 2003; Jackson, Martin, Changeux, & Damaj, 2008; Suzuki, Ise, Tsuda, Kao, & Martin, 2003; Kenny & Markou, 2001; Malin et al., 1994). Mouse affective symptoms include increased licking, grooming, shaking, and scratching (Damaj, 2004). Supportive evidence for the existence of α7 nAChR γ2* nAChR knockout mice do not demonstrate an increase in anxiety, hypo-locomotion, and conditioned place aversion when challenged with the drug (McCallum, Collins, Paylor, & Marks, 2006; Picciotto et al., 1998). Thus, nicotine withdrawal is linked to the activation of α7 nAChR, which are characterized by increased licking, grooming, shaking, and scratching (Damaj, 2004). As animal studies revealed that one dose of nicotine and one day was all that were required to demonstrate an increase in the number of nicotine receptors (Abreu-Villaca et al., 2003). This rapid increase in number of receptors (upregulation) shows the brain’s ability and effort to change for homeostasis—even in response to one dose.
Neurobiology of Nicotine Addiction

How Do Specific Nicotinic Receptor Subtypes Mediate Different Symptoms of Withdrawal?

In an effort to both better understand the neurobiology of nicotine withdrawal as well as develop new medication treatments to better manage withdrawal, animal studies have focused on specific nicotine receptor subtypes and compared them in regards to the physical (somatic) symptoms of withdrawal versus the affective (mood and anxiety) symptoms. In the mouse model, somatic withdrawal symptoms in mice are characterized by increased licking, grooming, shaking, and scratching (Damaj, Kao, & Martin, 2003; Kenny & Markou, 2001; Malin et al., 1994). Mouse affective symptoms include increased anxiety, hypo-locomotion, and conditioned place aversion when they receive nicotinic receptor antagonist chemicals/medications (Damaj et al., 2003; Jackson, Martin, Changeux, & Damaj, 2008; Suzuki, Ise, Tsuda, Maeda, & Misawa, 1996). In animals, but not people, withdrawal symptoms can be precipitated by administration of nicotinic receptor antagonist chemicals during a time of chronic nicotine exposure. To date, knockout mouse lines that do not express α7, β2 or β4 nAChR subunits have been utilized to analyze the role of these subunits in withdrawal. Our own summary review of the literature suggests a role for α7 and β4* nAChRs in somatic withdrawal symptoms, whereas high affinity β2* nAChR expression may be necessary for affective symptoms (Jackson et al., 2008; Salas, Main, Gangitano, & De Biasi, 2007). The results from these studies reinforce the idea that different withdrawal symptoms may be linked to activation of different nAChR subtypes. Identification of these subtypes may provide unique pharmacological targets for smoking cessation. The relevance of these withdrawal studies to humans is unclear as smokers do not display similar withdrawal symptoms (except anxiety) and nicotinic blockers do not trigger withdrawal in humans.
Neuronal Nicotine Receptors in Alcohol Dependence and Psychiatric Disorders

Many current smokers in the United States have a mental illness or another addiction (Ziedonis, 2004; Ziedonis & Williams, 2003), and this group appears to have particular difficulty with nicotine withdrawal. There is a need for treatment to be available for these individuals with multiple disorders. Also, all these disorders have their primary biological basis in the central nervous system and new discoveries in one area may help others. Clinicians and public policy makers need to target these populations, including encouraging research to examine possible common ground.

For example, most drugs of abuse increase dopamine release; however, alcohol (ethanol) is a non-specific drug that must interact with a myriad of receptors and ion channels to get the effect on dopamine release (Harris, 1999). Ethanol only modestly increases dopamine activity via direct action on the dopamine neuron, and its activation of nicotine receptors appears paramount for alcohol dependence (Lupica & Brodie, 2006). Interestingly, a nicotine receptor blocker, mecamylamine, can block the reinforcing aspects of alcohol in rats (Larsson et al., 2002), and humans given this type of medication report reduced pleasurable effects of alcoholic beverages (Chi & de Wit, 2003). Specific nicotine receptor subtype(s) may underlie ethanol reinforcement and addiction, and understanding other psychiatric disorders may be helped by better understanding nicotinic receptors (George, 2007).

Neuronal Nicotinic Acetylcholine Receptors: The Genes

Important to understanding the functions of the nicotinic receptors is the need to discover how and where the nAChR genes and proteins are expressed. These receptors are found throughout the body in such diverse sites as the intestinal epithelium, adipose tissue, skin, the thymus, and the oral epithelium where they are thought to be involved in inflammation, cell adhesion, and wound healing (Gahring & Rogers, 2006). The expression of nicotinic receptors in the respiratory system is thought to contribute directly to the etiology of lung cancer (Dasgupta & Chellappan, 2006; Minna, 2003). Thus, understanding the mechanisms underlying the complex expression patterns of the nAChR genes is likely to have a large impact on our understanding of a number of pathological conditions in which nicotinic signaling is disrupted.

A family of closely related genes encodes the subunits that assemble to form functional nicotinic receptors. Clinically, this raises the possibility that each subtype may represent a distinct drug target in treating nicotine dependence. Each of the receptor subunit genes exhibits distinct and common patterns of expression suggesting that they are both commonly and independently regulated (Drago, McColl, Horne, Finkelstein, & Ross, 2003; Wada et al., 1989; Zoli, Le Novere, Hill, & Changeux, 1995) and both transcriptional (RNA level) and post-transcriptional (post-RNA synthesis) processes are involved (Fornasari, Battaglioli, Terzano, &...
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The presence of these or another nicotine receptor subtype appears to be an important treatment to consider. These disorders are thought to be involved in the development of nicotine addiction. Varenicline is a partial agonist of the α4β2 subtype, which may be helpful in treating nicotine addiction.

Potential Therapeutic Targets for Nicotine Addiction

Nicotine Receptor

Progress has been made over the past two decades in understanding the physiological basis of nicotine addiction, and this has resulted in the development of several Food and Drug Administration (FDA) approved medications. These include nicotine replacement therapy (e.g., patch, gum, spray, inhaler, and lozenge), varenicline (Chantix®), and the monoamine uptake inhibitor, bupropion (Zyban®). The research that led to the development of these medications has focused on the suppression of craving and withdrawal and particularly the nicotine receptor agonists, partial agonists. Other medications are in investigation, such as dianicline (SSR591813, Sanofi-Aventis) which recently completed Phase III clinical trials and is an α4b2 complete agonist.

In spite of these advances, there continues to be a need to develop better pharmacological treatments and to integrate these with psychosocial treatments. Patient matching may be an important strategy. Even with finding improved new medications, the success rate of smoking cessation continues to be about 20% to 25% at one year (Gonzales et al., 2006), and with longer clinical experience there has been an increased awareness of potential adverse side effects (e.g., Nides, 2008; Popkin, 2008). For example, varenicline, a partial agonist of α4b2 nAChRs, has demonstrated the best effectiveness of the FDA approved options, but has also had concerns about rare but serious side effects including vision problems, heart trouble, depression, suicide, and changes in mood and behavior (Moore, Cohen, & Furberg, 2008). These concerns prompted the FDA to issue two alerts regarding its use in 2008 and the Federal Aviation Administration banned varenicline use by pilots and air traffic controllers (Moore et al., 2008; Federal Aviation Authority, 2008; Food and Drug Administration, 2007, 2008). These concerns resulted in a drop in varenicline prescriptions of 50% in the first 5 months of 2008 (Hensley, 2008). For the clinician, the rare serious side effects of varenicline are weighed against the efficacy of the medication and the 50% mortality associated with continued smoking (Doll et al., 2004). These issues highlight the need to develop new medications.

Drugs targeting the α4β2 and α7 subtypes remain attractive targets for potential therapies and considerable effort is being expended to identify other, hopefully more potent and safe, drugs for smoking cessation (Arneric, Holladay, & Williams, 2007). A recent wave of research has raised the idea that the α3α5β4 subtype may also be a good target. The genes encoding the α3, α5, and β4 subunits are tightly clustered...
in the genome suggesting that their expression may be co-regulated (Boulter et al., 1990). This is important in light of recent genome-wide association studies (GWAS) suggesting a critical role for the α3α5β4 subtype in nicotine dependence. Two groups have shown that variability (i.e., single nucleotide polymorphisms) within the α3/α5/β4 gene cluster is a critical determinant of tobacco use, age of onset of use, and even lung cancer (Berrettini et al., 2008; Schlaepfer et al., 2008), and the referenced articles will provide details of interest to genetics and pharmacology experts. The α6 and β3 subunits may prove to be effective drug targets for nicotine intervention given their role in dopamine release (Exley et al., 2007). Given the complexity of nicotine dependence, it is not surprising that a number of functionally distinct nicotine receptor subtypes appear important for drug discovery (George, 2007).

**Other Medication Development Strategies**

Nicotine addiction is a complex disorder, and as such requires that we look beyond a limited number of nicotinic receptor subtypes as drug targets. Other receptors and chemical messengers modulated by nicotine are also important, including the mu opioid receptor (Xue & Domino, 2008) and the chemical GABA. On another front, a novel approach to tackle nicotine dependence has been the development of anti-nicotine vaccines (Cerny & Cerny, 2008). The vaccines are composed of nicotine molecules coupled to a carrier protein and an adjuvant. These complexes are used to stimulate antibody production. An attractive aspect of vaccination is that the target is the drug rather than a critical component of the brain. Thus far, results in early clinical studies are encouraging, suggesting lower rates of smoking or increased cessation in vaccinated subjects (Maurer et al., 2005; Wagena, de Vos, Horwith, & van Schayck, 2008). Treatment matching based on genetic profiles may be a strategy in the future. Clusters of gene variants have been identified that are present more frequently in successful quitters, and the gene variants differed in subjects who were successful with bupropion treatment versus those who were successful with nicotine replacement therapy (Uhl et al., 2008). The identified genes encode proteins spanning a wide variety of biological functions such as cell adhesion, transcription, receptors, and enzymes. These results make sense if neuroplasticity is crucial to cessation—supporting the sensitization-homeostasis theory. The results provide molecular genetic evidence for the hypothesis that a person’s ability to quit smoking has polygenic genetic components and suggest potential biological pathways for further research.

**Conclusion**

Tobacco addiction continues to be the most preventable cause of increased morbidity and mortality. Clinicians, researchers, and policy makers must work together to reduce the level to quit smoking and help address treatment, the neurobiology, and the development of the underpinnings of tobacco use, age of onset of use, and even lung cancer (Berrettini et al., 2008; Schlaepfer et al., 2008), and the referenced articles will provide details of interest to genetics and pharmacology experts. The α6 and β3 subunits may prove to be effective drug targets for nicotine intervention given their role in dopamine release (Exley et al., 2007). Given the complexity of nicotine dependence, it is not surprising that a number of functionally distinct nicotine receptor subtypes appear important for drug discovery (George, 2007).

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The neurobiology of nicotine addiction continues to be the most preventable cause of increased morbidity and mortality. Clinicians, researchers, and policy makers must work together to reduce tobacco use and help individuals on a clinical and population level to quit smoking. This review reinforces the strong genetic and neurobiological underpinnings of this addiction. These hard facts must be known in public policy and education as they inform the parity discussion, stigma, the role of medications in treatment, the need for psychosocial treatments to help address cue-induced cravings, and the development of new medications. The article included a discussion of the reward and sensitization-homeostasis theories of nicotine addiction as models to organize animal and human laboratory findings. There is a need for more research to better understand the different subtypes of nicotinic acetylcholine receptors and important clinical phenomena such as rapid tolerance, withdrawal, sensitization, and craving. A better understanding of the biological basis of nicotine dependence may lead to parity in insurance coverage for medications and psychosocial treatments. In addition, information about the neurobiology of tobacco addiction can help inform public policy, fight stigma, and improve clinical treatment and research.

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