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Nicotine Addiction and Psychiatric Disorders

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Abstract

Even though smoking rates have long been on the decline, nicotine addiction still affects 20% of the US population today. Moreover, nicotine dependence shows high comorbidity with many mental illnesses including, but are not limited to, attention deficit hyperactivity disorder, anxiety disorders, and depression. The reason for the high rates of smoking in patients with mental illnesses may relate to attempts to self-medicate with nicotine. While nicotine may alleviate the symptoms of mental disorders, nicotine abstinence has been shown to worsen the symptoms of these disorders. In this chapter, we review the studies from animal and human research examining the bidirectional relationship between nicotine and attention deficit hyperactivity disorder, anxiety disorders, and depression as well as studies examining the roles of specific subunits of nicotinic acetylcholine receptors (nAChRs) in the interaction between nicotine and these mental illnesses. The results of these studies suggest that activation, desensitization, and upregulation of nAChRs modulate the effects of nicotine on mental illnesses.

1. INTRODUCTION

Since 1965, tobacco use has declined in the United States from 42% to 20% in 2004 (CDC, 2008; http://www.cdc.gov/tobacco/data_statistics/tables/trends/cig_smoking). However, use rates have remained relatively steady since 2004. While many reasons may contribute to absence of further decline in smoking, one possibility is that this population of smokers contains individuals that have increased vulnerability to nicotine addiction. Increasing evidence suggests individuals with mental illness and/or cognitive impairments may be at increased risk of smoking. In support, the rate of smoking in individuals that reported mental illness in the past month was 41% (Lasser et al., 2000). This is a doubling of what is reported by the CDC for the general population. In this chapter, we will examine the relationships between smoking/nicotine and psychiatric disorders of cognition and affect such as attention deficit hyperactivity disorder (ADHD), anxiety disorders, and depression. In addition, the nicotinic acetylcholinergic receptor (nAChR) subtypes associated with these relationships will be examined.

As discussed in other chapters of this book, nAChRs are pentameric, ionotropic receptors that gate Na+ and Ca++ and can be homomeric, consisting of all α subunits, or heteromeric, consisting of α and β subunits, in the central nervous system (Decker, Brioni, Bannon, & Arneric, 1995; Hogg, Raggenbass, & Bertrand, 2003; Jones, Sudweeks, & Yakel, 1999;

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McGehee, 1999). The predominant nAChRs in the central nervous system are the α7 and the α4β2 nAChRs (Marks & Collins, 1982; Whiteaker et al., 1999). α7 nAChRs are functionally different showing decreased affinity for agonists and increased sensitivity to desensitization as opposed to the α4β2 nAChRs (Alkondon & Albuquerque, 2004; Gotti et al., 2009; Marks, Burch, & Collins, 1983; Mihailescu & Drucker-Colin, 2000; Olale, Gerzanich, Kuryatov, Wang, & Lindstrom, 1997; Picciotto, Caldarone, King, & Zachariou, 2000; Schwartz & Kellar, 1983). Moreover, the addition of different types of β subunits or changes in stoichiometry of α4 and β2 subunits can change the functional properties of α4β2 nAChRs (Kuryatov, Luo, Cooper, & Lindstrom, 2005; Nelson, Kuryatov, Choi, Zhou, & Lindstrom, 2003; Salminen et al., 2007, 2004; Zwart & Vijverberg, 1998). Thus, understanding the contribution of different nAChR subtypes to the behavioral and neurochemical effects of nicotine in individuals with ADHD, anxiety disorders, and depression may provide insights into higher prevalence of tobacco smoking in people with these psychiatric conditions.

2. NICOTINE'S EFFECTS ON ADHD

ADHD may be one of the most common childhood disorders. The key symptoms of ADHD are inattention, hyperactivity, and impulsivity (Gehricke et al., 2007). It is estimated that ADHD affects approximately 6.5–8.4% of children (Barbaresi et al., 2002, 2004) and between 1.9% and 6% of adults (Kessler et al., 2006; Weiss & Murray, 2003). There are numerous risk factors and changes in brain function associated with ADHD. For instance, fMRI analysis suggests that ADHD may be associated with a decrease in connectivity between the dorsal anterior cingulate cortex and the posterior cingulate cortex and precuneus (Castellanos et al., 2008); brain regions associated with higher cognitive function including working memory (Hampson, Driesen, Skudlarski, Gore, & Constable, 2006). In addition to changes in brain regions involved in cognition, ADHD may also involve changes in neurotransmitter systems associated with cognition and attention such as acetylcholine (for review, see Beane & Marrocco, 2004). Furthermore, cognitive deficits associated with ADHD are similar to nicotine withdrawal-associated changes in cognition seen in smokers such as deficits in sustained attention, response inhibition, and working memory (Beane & Marrocco, 2004; Dovis, der Oord, Huizenga, Wiers, & Prins, 2014; Hughes, Keenan, & Yellin, 1989; Jacobsen et al., 2005; Mendrek et al., 2006; for review, see Ashare, Falcone, & Lerman, 2014).

The similarities between ADHD symptoms and nicotine withdrawal symptoms and the potential involvement of the cholinergic system in ADHD could suggest that individuals with ADHD may be an at-risk group for smoking; this is supported by data. Forty-two percent of males with ADHD were smokers and 38% of females with ADHD were smokers; this compares to 28.1% and 23.5% smokers for males and females without ADHD (Pomerleau, Downey, Stelson, & Pomerleau, 1995). Furthermore, the same study found that the quit ratio was substantially lower in individuals with ADHD compared to the rest of the non-mentally ill population, 29% versus 48.5%, respectively. These findings have been replicated by other scientists, for example, Lambert and Hartsough (1998) found lifetime tobacco dependence was 40% in individuals with ADHD compared to 19%. However, a

remaining important question is whether smoking is a result of ADHD or whether ADHD is a result of smoking.

2.1 Relationship Between Nicotine Exposure and ADHD in Humans

Evidence suggests a complex relationship exists between ADHD and smoking with ADHD contributing to smoking but smoking also contributing to the development of attention deficits. For example, ADHD predicted future smoking and the transition into associated nicotine addiction (Fuemmeler, Kollins, & McClernon, 2007) and adolescents with ADHD were more likely to experiment with cigarettes and become smokers (Tercyak, Lerman, & Audrain, 2002). Therefore, smoking may be an attempt to self-medicate for symptoms of ADHD. Acute nicotine administered via the patch improved attention in adults and young adults with ADHD (Levin et al., 1996; Potter & Newhouse, 2008). In addition, nicotine improved behavioral inhibition in highly impulsive people (Potter, Bucci, & Newhouse, 2012). However, individuals with ADHD may also be more susceptible to the negative effects of smoking. In a study of twins, a greater increase in attention deficits across years was seen for smokers versus never-smoking twin cohorts (Treur et al., in press). This study suggests that smoking can worsen attention problems. In addition, in a study that specifically examined individuals with ADHD, inattention symptoms during childhood, but not hyperactivity, was associated with greater nicotine withdrawal symptoms during adulthood (Ameringer & Leventhal, 2012). This relationship between ADHD and greater nicotine withdrawal symptoms is supported by other studies. Female, but not male, smokers with ADHD had greater withdrawal symptoms (McClernon et al., 2011), and in other studies, smokers with ADHD showed great withdrawal symptoms and willingness to work harder for cigarette puffs (Kollins et al., 2013; Pomerleau et al., 2003). Furthermore, another study found that both male and female smokers with ADHD had a greater level of nicotine dependence than smokers without ADHD (Wilens et al., 2008). The emergence of increased ADHD symptoms during periods of abstinence was associated with increased risk of relapse (Rukstalis, Jepson, Patterson, & Lerman, 2005), which demonstrates that the increased withdrawal symptoms impact successful quit attempts and thus health.

In order to improve treatment for both ADHD and nicotine dependence, an understanding of what factors underlie the increased risk of nicotine dependence in individuals with ADHD is necessary. While undoubtedly many factors contribute to this relationship, increasing evidence suggests that differences in attention processes and ADHD symptoms may be related to genetic variants in genes encoding nicotinic receptor subunits. Lee, Fuemmeler, McClernon, Ashley-Koch, and Kollins (2013) found a significant interaction between single nucleotide polymorphisms of CHRNB3 and ADHD where the AA variant and the ADHD symptom of inattention were associated with greater increase in the level of cigarette smoking across adolescence. The study also reported differences in cigarette smoking associated with variants of CHRNA6. Another study found that two alleles (rs578776 and rs3743078) in CHRNA3 were associated with an increased risk of smoking, but only among individuals with ADHD (Polina et al., 2014). Moreover, Viñals et al. (2012) showed that transgenic mice that overexpress α3/α5/β4 nAChRs exhibited less impulsive-like behavior than the wild-type controls. Also, Cohen et al. (2012) found that mutant mice with hypersensitive α6 nAChR subunits showed spontaneous hyperactivity in their home cages.

In addition, changes in other genes associated with cholinergic function may also contribute to ADHD as a study that examined polymorphisms in a gene encoding the high-affinity choline transporter (CHT; *SLC5A7*) found a two- to threefold increase in Val89 allele, which is associated with reduced choline transport function, in individuals with ADHD (English et al., 2009). These studies suggest that differences in nAChR function may contribute to increased vulnerability to nicotine addiction for individuals with ADHD and that genetics plays a role in this vulnerability.

The studies reviewed so far demonstrate a clear relationship between smoking and ADHD and suggest treating nicotine addiction in individuals with ADHD may be more challenging. Several studies, however, suggest that treating ADHD symptoms may reduce smoking. Methylphenidate is a stimulant commonly used to treat ADHD, and in adolescents, methylphenidate was also shown to reduce smoking (Hammerness et al., 2013; Schoenfelder, Faraone, & Kollins, 2014). In addition, another study found that osmotic controlled-release delivery of methylphenidate for 11 weeks to adult smokers with severe ADHD promoted abstinence to smoking in these individuals in part by improving ADHD symptoms (Nunes et al., 2013). In contrast, individuals with lower ADHD scores exhibited lower abstinence rates as opposed to the placebo-treated group. However, a study by Vansickel, Stoops, Glaser, Poole, and Rush (2011) reported that acutely administered methylphenidate increased smoking in adult ADHD subjects. It is possible that methylphenidate's effectiveness in reducing smoking in ADHD subjects may depend upon the duration of treatment and symptom severity. Further research is required to delineate behavioral and neural mechanisms that underlie the observed relation between stimulant medications and smoking in ADHD subjects.

2.2 Effects of Nicotine on Animal Models of ADHD

Studies in rats and mice have led to advances in understanding the neural substrates of attention, the effects of nicotine on attention and cognitive control, and the development of models of ADHD that allow further examining of the effects of nicotine on ADHD. Cholinergic deafferentation produced by infusion of the cholinotoxin 192-IgG saporin into the basal forebrain produced robust attentional impairments in rats (McGaughy, Kaiser, & Sarter, 1996). Moreover, studies employing microdialysis and electrochemical recordings to measure ACh release from animals performing attentional tasks show performance-associated increases in cortical cholinergic transmission (Arnold, Burk, Hodgson, Sarter, & Bruno, 2002; Howe et al., 2013; Parikh, Kozak, Martinez, & Sarter, 2007). Another study employing transgenic mice with a heterozygous deletion of the CHT gene reported attentional deficits in a signal detection task and reduced ability to sustain acetylcholine release (Parikh, Peters, Blakely, & Sarter, 2013). Together, these results provide support for the hypothesis that cholinergic function is required for normal attentional processes and that modulation of cholinergic signaling alters attention. As discussed earlier, polymorphism in the CHT gene was found in individuals exhibiting ADHD symptoms. Therefore, attentional impairments observed in ADHD subjects might occur as a consequence of disruption in cholinergic signaling.

Multiple studies have shown that nicotine alters behavioral processes that impact cognitive and attentional control in rodents. In rats performing a perceptual attentional set-shifting task, acute nicotine administration in rats enhanced extradimensional set-shifting that requires switching between the two perceptual dimensions of a compound stimulus (Allison & Shoaib, 2013). The same study also reported that intradimensional set-shifting that entails switching within the same dimension was also facilitated by acute nicotine. However in a recent study conducted in our laboratory, chronic nicotine treatment for 4 weeks did not alter strategy set-shifting in an operant-based cognitive flexibility task in mice (Ortega, Tracy, Gould, & Parikh, 2013). Rather, it impaired reversal learning and these cognitive deficits were associated with increased perseverative responding to the previously rewarded stimulus indicating deficits in response inhibition. Similarly, a study that examined inhibitory control found that in male C57BL/6J mice, acute nicotine enhanced inhibitory control and reduced impulsivity but tolerance developed to these effects with chronic nicotine treatment (Leach, Cordero, & Gould, 2013). Together, these studies suggest that initially nicotine may have positive effects on cognitive/attentional control and response inhibition but with prolonged used, the positive effects disappear and cognitive functions may worsen in ADHD.

The 5-choice serial reaction time task (5CSRTT), developed to assess visual attentional processes in rodents (Bari, Dalley, & Robbins, 2008), is sensitive to the effects of nicotine. This paradigm requires animals to detect brief flashes of light presented in a pseudorandom order in one out of multiple (five or nine) spatial locations over a large number of trials. Visual cues are detected by responding in the appropriate aperture within a certain amount of time. A correct choice is rewarded with a food pellet. If the animals fail to respond, respond in the wrong aperture or at an inappropriate time, a short period of darkness (time-out) is presented as punishment and no reward is delivered. A number of behavioral measures including correct responses, premature responses, perseverative responses, omissions, and response latencies are recorded to assess attentional control functions. Male hooded Lister rats administered nicotine prior to each 5CSRTT session initially had increased omissions but this effect dissipated between weeks 1 and 2 and thereafter increased correct responses and anticipatory response and decreased omissions were seen (Hahn & Stolerman, 2002). Half the rats received daily injections of nicotine but this did not alter the effects. Because the half-life of nicotine is 45 min in rats compared to 2 h in humans (Matta et al., 2007), it is difficult to determine whether this nicotine administration protocol reflects acute, subchronic, or chronic administration. However, given that nicotine initially enhanced attentional set-shifting and response inhibition but those cognitive effects disappeared with chronic administration in the aforementioned studies, the effects of nicotine on attentional measures observed on 5CSRTT task may reflect acute effects only.

In a similar study, nicotine administered prior to testing in the 5CSRTT improved accuracy while reducing omissions and reaction time in male hooded Lister rats (Hahn, Shoaib, & Stolerman, 2002). In addition, nicotine was able to reverse attentional deficits induced by the addition of auditory distractor cues. Another study, however, suggests that the effects of nicotine on 5CSRTT may be mediated by additional factors. Mirza and Bright (2001) found that nicotine administered prior to testing dose-dependently increased correct responses in male Sprague–Dawley rats but had no effect in male Lister hooded rats. Since similar doses of nicotine were used in the Mirza and Bright (2001) and Hahn et al. (2002) studies, which

use Lister hooded rats, unidentified environmental factors must have contributed to the difference in the effects of nicotine on the 5CSRTT in the Lister hooded rats.

Just as seen in human studies, nicotine withdrawal disrupts attention in rodent models. Lister Hooded rats withdrawn from chronic nicotine treatment had deficits in 5CSRTT that were related to increased omissions (Shoaib & Bizarro, 2005). Also, the α4β2 nAChR antagonist dihydro-β-erythroidine (DhβE) precipitated similar withdrawal deficits in rats treated with chronic nicotine but the α7 nAChR antagonist methyllycaconitine (MLA) produced no deficits. Similar to the Shoaib and Bizarro (2005) study, Semenova, Stolerman, and Markou (2007) found that nicotine withdrawal increased omissions and decreased correct response in Wistar rats. This study also found that acute nicotine increased correct responses and decreased omissions, while chronic nicotine increased premature response but also increased correct responses.

As found in the Shoaib and Bizarro (2005) study, multiple studies suggest that cholinergic signaling via α4β2 nAChRs is critically involved in the effects of nicotine on attention. For example, nicotine and the α4β2 nAChR agonist SIB 1765F increased correct responding and decreased response latency for the 5CSRTT in male Lister hooded rats but also increased premature responding. The α7 nAChR agonist AR-R 17779 was without effect, though only one dose was tested (Grottick & Higgins, 2000). In an operant sustained attention task, neither nicotine nor an α4β2 nAChR agonist, S38232, was effective but when a distractor cue was added, S38232 enhanced attention (Howe et al., 2010). Interestingly, if nicotine was paired with the α7 nAChR antagonist MLA, enhancement of attention under distracting conditions was seen; this suggests agonism of α4β2 nAChR has pro-attention effects but antagonism of α7 nAChRs improves attention. Similar effect was seen in C57BL/6N mice; nicotine and an α4β2 nAChR agonist, ABT-418, enhanced attention assessed in 5-choice continuous performance tests, whereas an α7 nAChR agonist, PNU 282987, was without effect (Young, Meves, & Geyer, 2013).

A series of experiments further demonstrated a role of α4β2 nAChRs in attention. Dizocilpine-induced deficits in a signal detection task in female Sprague–Dawley rats were ameliorated with an α4β2 nAChR agonist, AZD3480; donepezil, an acetylcholinesterase inhibitor; and sazetidine-A, which has high affinity for α4β2 nAChRs and after brief activation produces a long-lasting desensitization of the receptors (Rezvani, Cauley, Johnson, Gatto, & Levin, 2012; Rezvani et al., 2011; Rezvani, Cauley, Xiao, Kellar, & Levin, 2013). In addition, spontaneously hypertensive rats have been used as a model of ADHD and these rats have been shown to have lower levels of brain α4β2 nAChR binding but no changes in α7 nAChR binding (Wigestrand et al., 2011).

While overwhelming evidence suggests α4β2 nAChRs are involved in attention, other nAChR subunits may also be involved. In a study with α5 KO mice, the α5 KO decreased nicotinic currents in layer VI pyramidal neurons in prefrontal cortex and increased accuracy in the 5-CSRTT when task parameters were made more difficult (Bailey, De Biasi, Fletcher, & Lambe, 2010). This suggests that α4α5β2 nAChRs may also play a key role in attentional processes. Finally, while the pharmacology studies suggest α7 nAChRs are not critically involved in attention, gene knockout studies suggest complete absence of α7 nAChR may

alter attention. Young et al. (2004) found that α7 KO mice had increased omissions in the 5CSRTT. Similarly, Hoyle, Genn, Fernandes, and Stolerman (2006) reported that α7 KO mice have decreased correct responses but increased anticipatory responses. Thus, even though α7 agonists were without effect on attention (Grottick & Higgins, 2000; Young et al., 2013), the complete absence of α7 nAChRs could alter attention, possibly through changes during development or other compensatory changes that affect attention in adulthood. Clearly, this issue requires further examination.

2.3 Developmental Nicotine Exposure and Its Effects on ADHD

While genetic factors such as differences in nAChR expression and function could contribute to ADHD, environmental factors such as developmental exposure are also critical factors in ADHD. Individuals prenatally exposed to constituents of cigarette smoke have higher rates of ADHD but it is difficult to determine if this is directly related to nicotine or if other factors contribute to this relationship. For example, individuals with ADHD may smoke in an attempt to self-medicate (Gehricke et al., 2007), and thus, mothers that smoke during pregnancy may be smoking in an attempt to self-medicate ADHD or subclinical ADHD symptoms. Therefore, the offspring of these mothers could express ADHD because of an inherited risk factor. Studies of laboratory animals can address these issues.

In a study of prenatal cigarette smoke, male B6C3F1 mice, but not female mice, had increased hyperactivity, decreased striatal and cortical dopamine and serotonin, and reduced BDNF mRNA and protein (Yochum et al., 2014). These effects may be due to the nicotine in the cigarette smoke as Zhu et al. (2012) found that prenatal nicotine exposure increased hyperactivity and reduced cingulate cortical volume and dopamine turnover in male and female young adult C57BL/6J mice. Treatment with methylphenidate decreased hyperactivity in the mice, as in patients with ADHD, and increased dopamine turnover, suggesting that this model has strong external validity. Similarly, adult male and female Lister hooded rats prenatally exposed to nicotine had decreased correct responding, increased omission and increased anticipatory responses in the 5CSRTT, and increased expression of the D5 dopamine gene in the striatum (Schneider et al., 2011).

Prenatal nicotine exposure may also alter nAChR function. Adult mice prenatally exposed to nicotine had increased dendritic branching of medial prefrontal layer VI pyramidal neurons but also decreased nAChR signaling indicated by reduced nAChR responses to 1 mM acetylcholine (Bailey, Tian, Kang, O'Reilly, & Lambe, 2014). These effects were mediated by α5 nAChR subunits as they were reversed in α5 KO mice. In another study, prenatal nicotine exposure increased α4β2 nAChRs in the frontal cortex, hippocampus, caudate, and brainstem and increased both α4β2 and α7 nAChRs in the occipital cortex of rhesus monkeys (Slotkin et al., 2005). Changes in cholinergic signaling in frontal cortex and hippocampus could impact ADHD symptoms such as inattention and impulsivity.

The effects of prenatal nicotine on development of ADHD are greatly concerning but the effects of prenatal exposure may have an even greater effect on mental health and health care than original expected. Prenatal nicotine exposure may produce epigenetic changes that result in trans-generational inheritance of ADHD symptoms (Zhu, Lee, Spencer, Biederman, & Bhide, 2014). C57BL/6J female mice received nicotine in the drinking water starting 3

weeks prior to mating and continued throughout pregnancy. Locomotor activity was significantly increased in F2 and F3 generation male and female mice, even though the mice were not exposed to nicotine; however, inheritance occurred only through the maternal line. These results suggest that prenatal exposure to nicotine produces a transgenerational inheritance of the ADHD symptom of hyperactivity along the maternal line. Further work is needed but these findings could have potentially dramatic impact of public policy and health-care practices related to nicotine exposure.

The developmental effects of nicotine exposure may not be limited to prenatal exposure as adolescent nicotine exposure, but not adult nicotine exposure, produced long-lasting deficits in visuospatial divided and sustained attention, affecting accuracy and premature responses in rats (Counotte et al., 2011). In addition, mGluR2 protein levels and function on presynaptic prefrontal cortical terminals of glutamate synapses were reduced. However, they found local infusion of a group II mGluR agonist into the medial prefrontal cortex reversed deficits in attention. Collectively, these studies suggest that prenatal and adolescent nicotine exposure contribute to the development of ADHD, and thus, limiting nicotine exposure during development is of critical importance.

Likewise, considerable evidence from human studies indicates that developmental exposure to nicotine and/or smoking may increase the odds of developing ADHD. In a study examining males 6–17 years old, the odds ratio for ADHD when mothers smoked during pregnancy was 2.7 (Milberger, Biederman, Faraone, Chen, & Jones, 1996). The study also found that the odds ratio for ADHD when the mother had ADHD was 2.2 and was 1.8 when the father had ADHD, suggesting maternal ADHD and smoking have similar genetic contributions to offspring ADHD. In a follow-up study that contained both males and females (though heavily skewed toward male) with an average age of 13, the odds ratios for ADHD were even higher: 4.4 for ADHD when mothers smoked during pregnancy and 5.4 for when mothers had ADHD, but were lower for when the father had ADHD: 1.2 (Milberger, Biederman, Faraone, & Jones, 1998). Similarly, in a study conducted in male and female teenagers with an average age of 14 years, teachers, mothers, and fathers reported significantly higher scores for ADHD symptoms in offspring whose mothers smoked during pregnancy (Indredavik, Brubakk, Romundstad, & Vik, 2007). Finally, in a study of children aged 6–12 and diagnosed with ADHD, children exposed prenatally to maternal cigarette smoke had more severe ADHD symptoms and neurocognitive deficits as compared to unexposed children (Thakur et al., 2013). These studies strongly suggest that developmental exposure to constituents of cigarette smoke can exacerbate ADHD symptoms and may even contribute to the development of ADHD. Important unresolved issues include the underlying neurobiological substrates and whether nicotine is sufficient to increase susceptibility to ADHD. The latter issue is of increasing importance as pregnant women may be prescribed nicotine replacement therapy and the emergence of e-cigarettes as a nicotine free-base delivery system. Laboratory animal models provide a means to address these issues.

In summary, the relationship between nicotine and ADHD is complex. Individuals with ADHD may smoke in an attempt to self-medicate, but over time positive effects may dissipate and worsening of symptoms may develop. In addition, smoking and nicotine

exposure may facilitate the development of ADHD; nowhere may this be more critical than in developmental exposure to nicotine. Both prenatal and adolescent nicotine exposure were associated with increased expression of ADHD symptoms. Furthermore, prenatal nicotine exposure may produce epigenetic changes that increase ADHD symptoms in future generations that are not exposed to nicotine. The relationship between ADHD and nicotine/smoking may involve multiple mechanisms including signaling via α4β2 nAChRs and other nAChR subtypes. Further work is needed to fully understand the relationship between ADHD and nicotine and the underlying substrates in order to improve health care.

3. INVOLVEMENT OF nAChRs IN ANXIETY AND ANXIETY DISORDERS

Anxiety disorders including but not limited to panic disorders, phobias, generalized anxiety disorder, and posttraumatic stress disorder (PTSD) are a cluster of disorders that affects approximately 40 million Americans (18.1%; Kessler, 1997; Kessler, Chiu, Demler, & Walters, 2005) and costs more than $42 billion a year, almost one-third of the United States $148 billion total mental health costs (Greenberg et al., 1999). Disorders under the anxiety disorder category usually develop after a highly stressful traumatic event (Mineka & Zinbarg, 2006) and they are among the most frequently diagnosed psychological disorders (Breslau, Novak, & Kessler, 2004). In the following sections, we will review the literature on the relationship between anxiety disorders and nicotine dependence in humans. In addition, we will examine the effects of acute, chronic, and withdrawal from chronic nicotine and the involvement of specific nAChR subtypes on the animal models of fear and anxiety.

3.1 Relationship Between Nicotine Exposure and Anxiety Disorders in Humans

Numerous studies have identified a bidirectional link between nicotine dependence and anxiety disorders (Breslau, Davis, & Schultz, 2003; Breslau et al., 2004; Feldner, Babson, & Zvolensky, 2007; Fu et al., 2007; Koenen et al., 2005). Specifically, smoking rates have been shown to be significantly higher in the population with anxiety disorders than it is in the nonclinical population, 45.3% and 22.5%, respectively (Lasser et al., 2000; Ziedonis et al., 2008). On the other hand, anxiety disorders have also been shown to be significantly more prevalent in the people diagnosed with nicotine dependence (22%) than in the nondependent population (11.1%; Grant, Hasin, Chou, Stinson, & Dawson, 2004; Grant, Stinson, et al., 2004). Consistent with the high rates of nicotine dependence in patients with anxiety disorders, prior smoking has been found to be associated with increased susceptibility to develop PTSD in the event of a trauma (Koenen et al., 2005), an increased risk of panic attacks and development of panic disorders (Goodwin, Lewinsohn, & Seeley, 2005). In addition, following trauma, smoking initiation and daily smoking rates also increased (Breslau et al., 2003, 2004). PTSD patients also showed lower rates of quitting (Hapke et al., 2005; Lasser et al., 2000), suffered from worse nicotine withdrawal symptoms (Dedert et al., 2011), and as a result showed shorter times to first smoking lapse (Beckham, Calhoun, Dennis, Wilson, & Dedert, 2012) than non-PTSD population. Similarly, patients with social phobia have also demonstrated increased rates of smoking initiation (Sonntag, Wittchen, Höfler, Kessler, & Stein, 2000). Furthermore, several studies have shown that the presence of PTSD symptoms, such as hyperarousal and emotional numbing, is a predictor for nicotine dependence and these symptoms are reduced by nicotine intake (Beckham et al., 2005;

Feldner et al., 2007; Greenberg et al., 2012; Thorndike, Wernicke, Pearlman, & Haaga, 2006). Therefore, it is possible that while nicotine dependence increases one's vulnerability to anxiety disorders, smoking may serve as a mean to alleviate symptoms associated with anxiety disorders, which, in turn, increases nicotine dependence among patients with anxiety disorders.

Investigating the direct relationship between nAChRs and PTSD by using the radiotracer [^{123}I]5-IA-85380 ([^{123}I]5-IA) and single-photon emission computed tomography, Czermak et al. (2008) found that PTSD patients who never smoked showed significantly higher β2 nAChR density in the mesiotemporal cortex including the amygdala and hippocampus compared to healthy individuals who never smoked. Furthermore, the same study found a significant correlation between β2 nAChR binding in the thalamus and the reexperiencing symptom among the PTSD patients. Both thalamus and mesiotemporal cortex dysfunction have been functionally linked to the pathogenesis of PTSD (Lanius et al., 2001; Shin, Rauch, & Pitman, 2006). These results suggest that β2-containing nAChRs may play an important role in the epidemiology of PTSD. As discussed earlier, nicotine binds and modulates a variety of nAChR subunits. Therefore, it is possible that the modulation of β2-containing nAChRs by nicotine intake may also directly modulate PTSD symptomatology.

3.2 Effects of Nicotine on Animal Models of Anxiety Disorders

Fear conditioning, a behavioral paradigm in which the subject learns an association between a neutral stimulus and an aversive unconditioned stimulus akin to the associations formed during trauma, has been widely utilized as a transitional animal model to study the traumatic experience common for all anxiety disorders (Briscione, Jovanovic, & Norrholm, 2014). Previous studies have identified two types of fear memories: (1) hippocampus dependent (contextual and trace fear conditioning) and (2) hippocampus independent (cued fear conditioning; Clark & Squire, 1998; Logue, Paylor, & Wehner, 1997; McEchron, Bouwmeester, Tseng, Weiss, & Disterhoft, 1998; Phillips & LeDoux, 1992; Solomon, Vander Schaaf, Thompson, & Weisz, 1986). The effects of nicotine and other nAChR agonists/antagonists on fear conditioning have been extensively studied (see Gould & Leach, 2014 for a review). For example, there is ample evidence suggesting that acute nicotine enhances hippocampus-dependent contextual (Davis, Porter, & Gould, 2006; Gould, 2003; Gould, Feiro, & Moore, 2004; Gould & Higgins, 2003; Gould & Wehner, 1999; Wehner et al., 2004) and trace (Davis & Gould, 2007; Gould et al., 2004) fear conditioning, whereas it has no effect on hippocampus-independent cued fear conditioning (e.g., Gould & Higgins, 2003; Gould & Wehner, 1999). Furthermore, there is evidence suggesting that systemic administration of a high-affinity nAChR antagonist, DhβE, reverses the effects of nicotine, while a low-affinity α7 nAChR antagonist, MLA, has no effect (Davis, Kenney, & Gould, 2007). Similarly, several studies using knockout (KO) mice have shown that animals lacking β2 nAChRs did not show enhancement of contextual (Davis & Gould, 2007) or trace fear conditioning (Davis & Gould, 2007; Lotfipour et al., 2013) by nicotine. These results suggest that nicotine enhances hippocampal-dependent fear memories through activation of β2-containing nAChRs.

While the enhancing effects of acute nicotine are well documented, several studies have shown that while chronic nicotine has no effect on fear conditioning, withdrawal from chronic nicotine impairs contextual and trace fear conditioning (André, Gulick, Portugal, & Gould, 2008; Davis, James, Siegel, & Gould, 2005; Portugal & Gould, 2009; Portugal, Wilkinson, Kenney, Sullivan, & Gould, 2012; Raybuck & Gould, 2009). There is also evidence suggesting that during chronic nicotine administration, hippocampal nAChRs desensitize and upregulate and the resulting hypersensitive cholinergic system may be responsible for the effects of nicotine withdrawal on hippocampus-dependent learning (Dani & Heinemann, 1996; Gould et al., 2012; Marks, Grady, & Collins, 1993; Wilkinson & Gould, 2013). In support, Gould et al. (2012) found that chronic nicotine increased nAChR binding in the hippocampus and the duration of nAChR upregulation paralleled the duration of withdrawal deficits in hippocampus-dependent learning. Also supporting the role of hypersensitive nAChRs in the withdrawal effects, Wilkinson and Gould (2013) found that reintroducing acute nicotine into the system during nicotine withdrawal lead to an even greater enhancement of the contextual fear conditioning compared to the effects of acute nicotine in previously nicotine naïve mice. However, while upregulation seems to be necessary for the behavioral effects of nicotine withdrawal, there is evidence showing that nicotine withdrawal and tolerance are dissociable processes as tolerance was shown to occur before withdrawal and in the absence of nAChR upregulation (Gould, Wilkinson, Yildirim, Blendy, & Adoff, 2014). Therefore, this suggests that the rapidly developing nAChR desensitization may be responsible for the tolerance effects, whereas upregulation of nAChRs, which requires a longer period of time to develop, is necessary for the withdrawal effects.

Similar to the KO studies suggesting a central role of the β2 nAChRs in the acute effects of nicotine on hippocampal fear learning, Portugal, Kenney, and Gould (2008) found that β2 nAChR KO animals also did not show withdrawal deficits in contextual fear learning. In addition, infusions of the high-affinity nAChR antagonist DhβE into the dorsal hippocampus precipitated withdrawal deficits in both contextual (Davis & Gould, 2009) and trace fear learning (Raybuck & Gould, 2009). Overall, in line with the human studies linking hippocampal β2 nAChRs with PTSD (Czermak et al., 2008), results from the studies using acute, chronic, and withdrawal from chronic nicotine suggest that the effects of nicotine on hippocampus-dependent fear memories require the activation and upregulation of the high-affinity β2-containing nAChRs.

In addition to the effects of nicotine on acquisition of fear conditioning, several studies have also investigated the effects of nicotine on fear extinction, a form of inhibitory learning that occurs when the conditioned stimulus is repeatedly presented in the absence of the aversive unconditioned stimulus. Fear extinction has been widely utilized as a translational animal model for the exposure therapies used for anxiety disorders (Briscione et al., 2014; Myers & Davis, 2006; Quirk & Mueller, 2007). In humans, several studies have demonstrated that PTSD patients show impaired fear extinction (Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007; Michael, Blechert, Vriends, Margraf, & Wilhelm, 2007; Milad et al., 2009) as well as difficulty learning safety discrimination, another form of inhibitory learning where the subjects are trained to differentiate between a safe versus dangerous cue or context (Jovanovic, Kazama, Bachevalier, & Davis, 2012; Jovanovic et al., 2010, 2009; Lissek et al.,

2005; for a review, see Christianson et al., 2012). Therefore, according to some accounts, PTSD may be attributed to impaired safety learning (Davis, Falls, & Gewirtz, 2000; Lissek et al., 2005). The effects of nicotine exposure on safety learning and extinction have been investigated using the animal models of fear extinction and contextual safety discrimination (Elias, Gulick, Wilkinson, & Gould, 2010; Kutlu & Gould, 2014; Kutlu, Oliver, & Gould, 2014; Tian et al., 2008). For example, Elias et al. (2010) found that acute nicotine enhanced extinction and impaired renewal of cued fear memories when administered during the extinction phase, whereas nicotine administration during both training and extinction phases impaired extinction and enhanced renewal of cued fear. This suggests that acute nicotine may enhance recovery and extinction of cued fear conditioning by potentially strengthening encoding and facilitating new inhibitory learning during acquisition and extinction, respectively. On the other hand, Kutlu and Gould (2014) showed that acute nicotine impaired contextual fear extinction, which, unlike cued extinction, requires direct involvement of the hippocampus (Tronson et al., 2009). Also recently, Kutlu et al. (2014) examined the role of nicotine on contextual safety discrimination and found that acute nicotine impaired this form of safety learning. As mentioned above, safety learning is already compromised in the patients with PTSD, and therefore, these results suggest that nicotine may make treatment of PTSD even harder by further impairing this type of learning. Finally, Tian and colleagues (2008) tested the effects of prior chronic nicotine exposure on subsequent extinction and showed that prior nicotine impaired cued extinction while having no effect of contextual fear. In summary, these studies suggest that nicotine may cause further disruption of the already impaired safety learning in PTSD patients.

Overall, numerous studies that have investigated the relationship between nicotine and fear learning suggest that acute nicotine enhances acquisition and impairs extinction of hippocampus-dependent fear memories. In addition, multiple studies have also shown that withdrawal from chronic nicotine results in impaired hippocampus-dependent fear learning. Interestingly, as described above, acute nicotine administration during nicotine withdrawal results in even greater enhancement of fear learning than acute administration alone. This suggests that during withdrawal from chronic nicotine administration, the cholinergic system becomes hypersensitive to the enhancing effects of acute nicotine. Therefore, these results indicate that abstinence from nicotine may worsen the conditions of the PTSD patients. This is because while PTSD symptoms are reduced during nicotine intake (Beckham et al., 2005; Feldner et al., 2007; Greenberg et al., 2012; Thorndike et al., 2006), they resurface during abstinence (Dedert et al., 2011). Therefore, most PTSD patients reinitiate smoking to alleviate their symptoms (Beckham et al., 2012). However, while reinitiating smoking may help patients reduce their symptoms, Wilkinson and Gould's (2013) results showing increased sensitivity to the effects of reintroduction of nicotine during nicotine withdrawal suggest that it may also enhance fear memories associated with new trauma and could prolong the course of the disorder.

Animal models of anxiety have been widely utilized for the neurobiological and pharmacological investigation of the anxiety disorders (Rodgers, 1997). These behavioral paradigms take advantage of the innate explanatory behaviors of rodents and natural fears; these tasks include the open field (OF; decreased time spent in the central part of the OF arena), elevated plus maze (EPM; decreased time spent in open arms), and marble burying

test (increased duration of burying an object, e.g., glass marbles) as well as the social anxiety test (decreased time spent by pairs of male rats in social interaction; Lister, 1990). The effects of nicotine and nicotinic agents on anxiety-related paradigms are somewhat contradicting (Table 1). For example, Irvine et al. (2001) found that subcutaneous injections of acute nicotine (0.1 mg/kg) increased anxiety-like behavior in the EPM 30 min after injection. Similarly, Ouagazzal et al. (1999) showed that higher doses of acute nicotine (0.5 and 1 mg/kg) administered intraperitoneally (i.p.) also produced increased anxiety in the EPM. However, Irvine et al. (2001) also found that injections 5 min before the EPM test had an anxiolytic effect after 7 days of repeated administration. Finally, rats tested 24 h after the last nicotine injection showed increased anxiety during withdrawal and this effect was reversed by dorsal hippocampal infusions of nicotine (Irvine et al., 2001). The anxiogenic effects of nicotine withdrawal have also been shown to be reversed by acute nicotine challenge (Ericson et al., 2000). In contrast to the results of the Irvine et al. (2001) study on anxiety in the EPM, Irvine et al. (1999) previously found an opposite pattern for the effects of nicotine injection timing on anxiety-like behavior in a social interaction test. Specifically, Irvine et al. (1999) found that nicotine injections 5 min before the behavioral test decreased social interaction, an anxiogenic effect, while injections 30 min before the task increased social interaction, an anxiolytic effect. This shows that acute nicotine may have differential effects on different anxiety paradigms. Also in contrast to the studies reporting the anxiogenic effects of acute nicotine, O'Neill and Brioni (1994) found that i. p. injections of nicotine decreased anxiety as measured in the EPM paradigm. Moreover, Ericson et al. (2000) found that subcutaneous acute nicotine administration (0.35 mg/kg) significantly increased open arm duration in rats. Finally, File, Kenny, and Ouagazzal (1998) found that lower doses of acute nicotine (0.01 and 0.1 mg/kg) also had anxiolytic effects, while higher doses (0.5 and 1.0 mg/kg) had anxiogenic effects in a social interaction test. The contradicting effects of nicotine reported by different studies may also be explained by the different species and strains used in these experiments. For example, both Irvine et al. (1999, 2001) and Ouagazzal et al. (1999) studies, which found that nicotine has an anxiogenic effect, used male hooded Lister rats, whereas other studies showing anxiolytic effects of nicotine (Ericson et al., 2000; O'Neill & Brioni, 1994) used male Wistar rats or CD1 mice.

Several nAChR subtypes have been identified to play modulatory roles in the anxiety-like behavior. As in the effects of nicotine on fear conditioning, there is evidence that β2-containing nAChRs mediate nicotine's effects on anxiety. For example, an α4β2 nAChR agonist, ABT-418, was found to increase open arm time in the EPM and both ABT-418 and an α4β2 nAChR partial agonist, ABT-089, reversed the anxiogenic effects of nicotine withdrawal (Brioni et al., 1994; Decker et al., 1994; Yohn, Turner, & Blendy, 2014). Brioni et al. (1994) also showed that the anxiolytic effects of ABT-418 were reversed by the nAChR antagonist mecamylamine, which suggests that sustained nAChR activity is required for the anxiolytic effect of ABT-418. Similarly, McGranahan, Patzlaff, Grady, Heinemann, and Booker (2011) found that selective elimination of α4β2 nAChRs located on dopaminergic neurons reversed the anxiolytic effects of nicotine. There is also evidence that while genetically modified mice that lack β2 subtype of nAChRs showed normal levels of anxiety in the EPM (Picciotto et al., 1998), α4 KO mice showed increased anxiety in the same paradigm (Labarca et al., 2001; Ross et al., 2000). Also, Paylor et al. (1998) showed

that α7 nAChR-lacking KO mice show decreased levels of anxiety in the EPM paradigm, while an α7-selective agonist, PNU-282987, was shown to increase anxiety in the OF paradigm (Pandya & Yakel, 2013). Similarly, desensitization of α7 nAChRs by using an α7 partial agonist, ABT-107, was found to reverse the anxiogenic effects of nicotine withdrawal (Yohn et al., 2014). Overall, these results suggest that in animals, nicotine has differential effects on anxiety in different strains/species and anxiety-related animal models. Results from the studies using genetically modified mice and pharmacological nAChR agonist/antagonists also showed that while elimination of β2-containing nAChRs can prevent the anxiolytic effects of nicotine, activation of these receptors can reverse the anxiogenic effects of nicotine withdrawal. Conversely, while activation of α7 nAChRs has an anxiogenic effect, inactivation of these receptors via using a partial antagonist α7 reverses the anxiogenic effects of nicotine withdrawal. Additionally, there is also evidence showing that other nAChR subtypes may play a role in modulating anxiety as well. For example, Gangitano, Salas, Teng, Perez, and De Biasi (2009) demonstrated that α5 KO animals showed altered hypothalamus–pituitary–adrenal axis function as they were shown to have lower basal corticosterone levels. In addition, while α5 KO animals showed no behavioral changes in the OF and light–dark box paradigms, female KO mice, but not male mice, showed reduced anxiety-like behavior in the EPM. Another nAChR subtype that might be important for anxiety modulation is β4 nAChR. Salas, Pieri, Fung, Dani, and De Biasi (2003) showed that β4 KO mice showed reduced anxiety in the EPM compared to WT littermates as well as reduced heart rate in this paradigm. However, β4 KO animals showed higher heart rate in another anxiety paradigm, social isolation. These studies suggest that in addition to the involvement of the major nAChR subtypes such as β2 and α7, anxiety phenotypes are controlled by a variety of different nAChRs.

In summary, the studies cited above reveal a strong bidirectional relationship between nicotine, anxiety, and fear learning. While human studies suggest that smoking may alleviate the symptoms associated with anxiety disorders (Beckham et al., 2005; Feldner et al., 2007; Greenberg et al., 2012; Thorndike et al., 2006), nicotine abstinence worsens those symptoms (Dedert et al., 2011) and results in higher rates of reinitiation of smoking (Beckham et al., 2012; Hapke et al., 2005; Lasser et al., 2000). In line with these results, the animal studies using fear conditioning suggest that initial acute nicotine results in enhancement of hippocampus-dependent fear learning and impairment of fear extinction, whereas acute nicotine during nicotine withdrawal further enhances hippocampus-dependent fear memories, which may prolong the course of the disorder. Evidence from the animal studies also suggests that the effects of nicotine on hippocampus-dependent fear memories require the activation and upregulation of the high-affinity β2-containing nAChRs (Davis & Gould, 2006, 2007, 2009; Davis et al., 2007; Kenney, Raybuck, & Gould, 2012; Portugal et al., 2008; Raybuck & Gould, 2009). However, the results from the studies using animal models of anxiety are less conclusive as the effects of nicotine on anxiety-related behavior in animals vary based on the strains/species and the task used in the study. This suggests that anxiety measured in different animal models may actually have different underlying neurobiological and genetic mechanisms. Nevertheless, results from these studies converge on the importance of α7/α4-containing nAChRs in the effects of nicotine on anxiety. Further investigation of the relationship between nicotine, specific nAChR subtypes, and anxiety as

measured in animal models is still required to understand the underlying mechanisms of nicotine's effects on anxiety.

4. EFFECTS OF NICOTINE DEPENDENCE, WITHDRAWAL, AND nAChR REGULATION ON DEPRESSION

Depression is a common mental disorder that manifests itself with symptoms such as depressed mood, lowered interest in pleasure, fatigue, and psychomotor agitation or retardation (American Psychiatric Association, 2013). It has a lifetime prevalence of 10–25% in women and 6–10% in men (Moore & Bona, 2001), and affects approximately 20 million adults in the United States (CDC, 2010). Depression is especially common among the individuals with chronic health problems such as obesity, alcoholism, and smoking (Strine et al., 2008). In this section, we will review results suggesting a bidirectional relationship between depression and nicotine.

4.1 The Relationship Between Nicotine Dependence and Depression in Humans

An in-depth review of the relationship between depression and nicotine dependence in humans is provided in another chapter of this book. Similar to the link between anxiety disorders and smoking, depression and nicotine dependence have also a reciprocal relationship (Ischaki & Gratziou, 2009; John, Meyer, Rumpf, & Hapke, 2004). Previous studies have shown that depression symptoms are important determinants of smoking initiation, maintenance, and cessation, whereas nicotine dependence is associated with vulnerability for depression (Breslau, Kilbey, & Andreski, 1991; Fergusson, Goodwin, & Horwood, 2003; Glassman et al., 1990; Hall, Muñoz, Reus, & Sees, 1993; Morrell & Cohen, 2006; Paperwalla, Levin, Weiner, & Saravay, 2004). For example, nicotine dependence, as defined in Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition, predicted a threefold risk of developing major depression (Breslau & Johnson, 2000), and this relationship was maintained across different age groups such as adolescents (Killen et al., 2004), adults (Fergusson et al., 2003), and adults over age 60 (Glassman, Covey, Stetner, & Rivelli, 2001). There is also evidence suggesting that smoking during adolescence results in a fourfold increase in the likelihood of developing depressive symptoms later in life (Brook, Schuster, & Zhang, 2004; Choi, Patten, Gillin, Kaplan, & Pierce, 1997; Goodman & Capitman, 2000; Wu & Anthony, 1999). Another study found that the risk of developing depression was four times higher in heavy smokers than nonsmokers and increased time of smoking dependency was correlated with increased risk of depression (Klungsøyr, Nygård, Sørensen, & Sandanger, 2006), which suggests that the vulnerability for depression increases with higher rates of smoking.

Just as smokers show higher rates of depression, patients with major depression have been shown to have higher levels of smoking than the nonclinical population (Covey, Glassman, & Stetner, 1997, 1998; Fergusson et al., 2003). According to the self-medication hypothesis of nicotine dependence (Carmody, 1992; Markou, Kosten, & Koob, 1998; Pomerleau & Pomerleau, 1985), this might be because nicotine reduces negative affect and works as an antidepressant. In support, patients with major depression increased smoking when they experienced depressive symptoms (Schleicher, Harris, Catley, & Nazir, 2009). In line with

the self-medication hypothesis, there are also several studies showing that a majority of smokers enrolled in smoking cessation programs have a history of depressive episodes (Dalack, Glassman, Rivelli, Covey, & Stetner, 1995; Glassman et al., 1988; Lerman et al., 1996), and those with a history of depression failed to quit smoking twice as often as smokers without a prior depressive episode (Glassman et al., 1990). Similarly, it has also been indicated that smoking cessation increases the severity of depression symptoms (Covey et al., 1997; Swan, Ward, & Jack, 1996; West, Hajek, & Belcher, 1989). Furthermore, smokers with a history of depression have been shown to be more likely to experience another depressive episode 6 months after smoking cessation (Glassman et al., 2001). Consequently, these results suggest that the increased severity of depression and withdrawal symptoms upon smoking cessation might contribute to the lower levels of successful smoking cessation in people with depression.

4.2 Effects of Nicotine on Animal Models of Depression

Depression is a multifaceted mental disease with a distinct symptomatology, some of which can be captured in several different animal models (Matthews, Christmas, Swan, & Sorrell, 2005). Animal models of depression can be categorized as acute depression models (e.g., the forced swim test and tail-suspension test) and chronic depression models (e.g., learned helplessness and prolonged subordination stress; Stone & Lin, 2011). Consistent with the reports from human studies suggesting that nicotine decreases depressive symptoms, numerous studies have linked nicotine and nAChR agents with the modulation of depression-like behaviors in animals (see Mineur & Picciotto, 2010 for a review). In line with the above-described self-medication hypothesis of nicotine in depression, previous studies have shown that nicotine had an antidepressant effect in the forced swim test (Andreasen & Redrobe, 2009; Suemaru et al., 2006; Tizabi, Getachew, Rezvani, Hauser, & Overstreet, 2009, Tizabi et al., 1999; Vázquez-Palacios, Bonilla-Jaime, & Velázquez-Moctezuma, 2005), the chronic mild stress sucrose test (Andreasen, Henningsen, Bate, Christiansen, & Wiborg, 2011), and learned helplessness (Semba, Mataki, Yamada, Nankai, & Toru, 1998). Multiple studies have suggested that β2-containing nAChRs may play an important role in modulation of depression-like behavior. For example, KO mice that lack the β2 subunit of nAChRs show decreased amount of baseline immobility in both the FST and tail-suspension test, indication of reduced depression-like phenotype, compared to wild-type animals (Caldarone et al., 2004). Furthermore, it has also been shown that mecamylamine, a nonselective nAChR antagonist, has similar antidepressant-like effects in the FST and tail-suspension test in wild-type but not in β2 KO animals (Andreasen, Nielsen, & Redrobe, 2009; Caldarone et al., 2004; Rabenstein, Caldarone, & Picciotto, 2006). Also consistent with the modulatory role of β2-containing high-affinity nAChRs in the depression-like behavior, an α4β2 selective high-affinity nAChR antagonist, DHβE, has been found to decrease immobility in the FST and tail-suspension test (Andreasen, Olsen, Wiborg, & Redrobe, 2009; Rabenstein et al., 2006). Apart from the β2-containing nAChRs, there is also evidence showing that α7 subtype of nAChRs may also play a modulatory role in the depression-like behavior in animals. For example, Andreasen, Olsen, et al. (2009) found that MLA (α7-nAChR selective antagonist) also reduced immobility in the FST, while another study found that mecamylamine had antidepressant effects in the FST for wild-type but not on α7-nAChR KO mice. In addition to the β2 and α7 nAChRs, α5 may also be

involved in the modulation of depressive-like behavior. For example, using a tail-suspension test and α5 nAChR-null mice, Gangitano et al. (2009) found that female but not male α5 KO mice showed reduced depressive-like behavioral phenotype. These studies suggest that inactivation of β2-containing nAChRs along with α7 nAChR activation results in reduction of depression-like behavior in the animal models of depression. Nevertheless, other nAChR subtypes, such as α5, may also be involved in the depression-related behavioral phenotype.

Interestingly, like nAChR antagonists mecamylamine, DhβE, and MLA, varenicline, a partial agonist of the α4β2 nAChRs and a full α7 agonist developed to aid smoking cessation in humans (Mihalak, Carroll, & Luetje, 2006), has also been found to have antidepressant effects in the FST (Rollema et al., 2009). Being a partial agonist of the α4β2 nAChRs, varenicline increases nAChR activity and maintains it at a submaximal level, and therefore, it prevents binding of the endogenous acetylcholine and effectively desensitizes nAChRs (Mineur & Picciotto, 2010; Papke & Heinemann, 1994). Similarly, other nicotinic partial agonists such as sazetidine-A and ispronicline (TC-1734 or AZD3480) also have antidepressant effects (Gatto et al., 2004; Xiao et al., 2006). However, Turner, Castellano, and Blendy (2010) reported that sazetidine-A, but not varenicline, decreased immobility in the FST and tail-suspension test measures of depression. The discrepancy between Rollema et al. (2009) and Turner et al. (2010) results is likely to be due to the different mouse strains used by these two studies, C57BL/6J mice and 129SvJ-C57BL/6J F1 hybrid mice, respectively. In support, previous research showed that the parental lines of the 129SvJ-C57BL/6J F1 hybrid mice show differences in motor function, anxiety-related behavior, and sensorimotor responsivity, which may contribute to the differential effects of partial nAChR agonists on depression-like behavior (Tarantino, Gould, Druhan, & Bucan, 2000). Overall, the results from the studies using partial nAChR agonist and direct nAChR antagonists converge on the importance of the nAChR desensitization in the antidepressant effects of nicotine.

In summary, studies indicate that depression is strongly affected by nicotine exposure. The human studies cited suggest that initially smoking may alleviate symptoms of depression and works as a mean to self-medicate, whereas smoking cessation results in the exacerbation of the depressive symptoms. In line with the human studies, the studies utilizing animal models of depression also showed that nicotine reduced depressive-like behavior in animals in several different models of depression (e.g., FST, chronic mild stress sucrose test, and learned helplessness). Evidence from the pharmacological inactivation studies and studies using global KO animals suggest that nicotine's antidepressant effect seems to be modulated by the β2-containing and α7 nAChRs. Interestingly, partial agonists of the α4β2 nAChRs such as sazetidine-A, and varenicline, which was developed for smoking cessation, seem to also help with the alleviation of the depressive-like behavior. Future studies that clarify the role of nAChR subtypes in depression will help develop better nAChR-based pharmacological agents for depression treatment.

5. CONCLUSION

The significantly higher rates of smoking are seen in the population with mental disorders such as ADHD, anxiety disorders, and depression, in comparison to the nonpatient

population, suggesting a strong relationship between nicotine and symptomatology of these disorders. The studies reviewed in this chapter show that often acute nicotine produces effects that result in the short-term reduction of the symptoms associated with the mental illness. Consequently, patients with these disorders usually transition into chronic use of nicotine for the self-medication purposes. Nevertheless, there is also strong evidence suggesting that patients with mental disorders usually have difficulty quitting smoking. This is because the symptoms of the disorders usually worsen during the period of withdrawal, which results in shorter period of abstinence and eventually reinitiation of smoking. Several subunits of nAChRs, such as α4, β2, and α7, have been shown to directly modulate the severity of the symptoms of mental disorders and the effects of nicotine on these symptoms. Therefore, future studies examining the roles of specific nAChR subunits in mental illness may help to develop better treatments for mental disorders.

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Table 1

Effects of Acute Nicotine on Anxiety

Study	Strain/Species	Task	Nicotine Dose	Injection Time	Effect
Irvine, Cheeta, and File (2001)	Hooded Lister rats	EPM	0.1 mg/kg s.c.	30 min	Increased anxiety
				5 min	Decreased anxiety
Ouagazzal, Kenny, and File (1999)	Hooded Lister rats	EPM	0.5 and 1 mg/kg i.p.	5 min	Increased anxiety
O'Neill and Brioni (1994)	Wistar rats	EPM	0.3 mg/kg i.p.	30 min	Decreased anxiety
Ericson, Olausson, Engel, and Söderpalm (2000)	CD1 mice	EPM	0.35 mg/kg s.c.	Immediate	Decreased anxiety
Irvine, Cheeta, and File (1999)	Hooded Lister rats	Social interaction	0.1 mg/kg s.c.	30 min	Decreased anxiety
				5 min	Increased anxiety