Published in final edited form as:
Addict Biol. 2010 July ; 15(3): 250–265. doi:10.1111/j.1369-1600.2010.00213.x.

Cognitive Effects of Nicotine: Genetic Moderators

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Abstract

Cigarette smoking is the main preventable cause of death in developed countries and the development of more effective treatments is necessary. Cumulating evidence suggests that cognitive enhancement may contribute to the addictive actions of nicotine. Several studies have demonstrated that nicotine enhances cognitive performance in both smokers and non-smokers. Genetic studies support the role of both dopamine (DA) and nicotinic acetylcholine receptors (nAChRs) associated with nicotine-induced cognitive-enhancement. Based on knock-out mice studies, β2 nAChRs are thought to be essential in mediating the cognitive effects of nicotine. α7 nAChRs are associated with attentional and sensory filtering response, especially in schizophrenic individuals. Genetic variation in D2 type DA receptors and the catechol-O-methyltransferase (COMT) enzyme appears to moderate cognitive deficits induced by smoking abstinence. Serotonin transporter (5-HTT) gene variation also moderates nicotine- induced improvement in spatial working memory. Less is known about the contribution of genetic variation in dopamine transporter (DAT) and D4 type DA receptor genetic variation on the cognitive effects of nicotine. Future research will provide a clearer understanding of the mechanism underlying the cognitive-enhancing actions of nicotine.

Keywords

Cognition; genetics; nicotine; smoking; dopamine; acetylcholine

1. INTRODUCTION

Cigarette smoking is the single most important source of preventable morbidity and premature mortality, and an estimated 19.8% of adults in the United States are classified as current smokers (Thorne et al., 2009). Smoking increases the risk for heart disease, respiratory disease, cancer, and stroke (2005) and results in an estimated 443,000 premature deaths annually in the United States (Adhikari et al., 2009). Smoking cessation decreases the risk of several smoking-related health consequences (Ezzati et al., 2005; Godtfredsen et al., 2002; Samet, 1992). However, even when smokers utilize evidence-based cessation treatments, the one year quit rates yield a 15%-25% success rate (Fiore et al., 2002). Thus, there is a great need to develop more effective treatments for nicotine addiction. The development of new treatments requires a better understanding of the individual factors contributing to maintenance of nicotine addiction.

Several lines of evidence suggest that dependence on nicotine may be partly due to its cognitive-enhancing actions (Giessing et al., 2006; Kumari et al., 2003; Lawrence et al., 2002; Mumenthaler et al., 2003; Rusted et al., 2000). First, smokers report beneficial effects

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of smoking on concentration and memory (Piper et al., 2004; Russell et al., 1974; Wesnes and Warburton, 1983), and nicotine abstinence in smokers is associated with decreased cognitive function including difficulty concentrating, impairment of sustained attention and poorer working memory efficiency (Harrison et al., 2009; Hatsukami et al., 1984; Hughes and Hatsukami, 1986; Jacobsen et al., 2005; McClernon et al., 2008; Xu et al., 2005). Second, nicotine enhances several domains of cognition including attention, working memory, and complex task performance in satiated smokers and non-smokers (Baschnagel and Hawk, 2008; Ernst et al., 2001; Foulds et al., 1996; Heishman, 1998; Lawrence et al., 2002; Meinke et al., 2006; Mumenthaler et al., 1998; Trimmel and Wittberger, 2004). Third, nicotine cognitive enhancement has been suggested to contribute to the high prevalence of smoking in individuals with schizophrenia and attention deficit hyperactivity disorder (ADHD), psychiatric disorders known to impair cognitive performance (Evans and Drobes, 2009; Gehricke et al., 2007; Gray and Upadhyaya, 2009; Ochoa and Lasalde-Dominicci, 2007; Sacco et al., 2005). However, some studies have failed to detect nicotine-induced cognitive enhancement in non-smokers (Heishman et al., 1993; Hindmarch et al., 1990; Wesnes and Revell, 1984). Taken together, most studies support that nicotine causes cognitive-enhancement in smokers and in non-smokers.

Genetic factors have been shown to contribute to initiation, severity and cessation of smoking (Koopmans et al., 1999; Li et al., 2003; Xian et al., 2003). An estimated 50% of variance in nicotine dependence is explained by genetic factors (Hoekstra et al., 2007; Li, 2003; Sullivan and Kendler, 1999; Wilson, 1978). Differences in gene sequences also contribute to individual variation in several domains of cognitive function such as cognitive flexibility, attention, speed of processing, set-shifting, working memory and cognitive impulsiveness (Bellgrove and Mattingley, 2008; Egan et al., 2001; Goldberg et al., 2003; Kebir et al., 2009). Gene polymorphisms and mutations throughout the genome may moderate the cognitive effects of nicotine. Ultimately, genetic studies have the potential to better characterize the neurobiological mechanisms of individual differences involved in the initiation and maintenance of smoking.

This review article summarizes relevant research on the genetics of cognitive-enhancement from nicotine. The first two sections of this review will focus on nicotine acetylcholine (nACh) and dopamine (DA) receptor genes because most genetic studies have focused on these systems. Next, we will address other gene systems thought to be relevant in clarifying the cognitive effects of nicotine. Finally, we will address possible future directions for this area of research.

2. NICOTINIC ACETYLCHOLINE RECEPTORS (nAChR)

Nicotine, the main addictive chemical in tobacco smoke, is essential in continued and compulsive tobacco use (Benowitz, 2009). Following a cigarette puff, nicotine enters cerebral circulation within 10 to 60 s and binds to the nACh receptors (nAChRs) (Henningfield and Keenan, 1993). The nAChRs are pentameric combinations of 12 subunits (α2-α10 and β2-β4), encoded by the *CHRNA2-10* and *CHRNB2-4* genes, respectively. The two most commonly expressed nAChRs in the brain are α4β2nAChRs or α7nAChRs (Dani, 2007). nAChRs can either be heteromeric channels formed by a combination of α and β subunits (e.g. α4β2, α3β4) or homomeric as formed by some α subunits (e.g., α6 or α7). Activation of nAChRs increases extracellular DA levels in the nucleus accumbens, which is thought to be critical in mediating the rewarding effects of nicotine (Balfour, 2009; Corrigall et al., 1992; Rahman et al., 2008). The neurobiological mechanisms of cognitive-enhancement by nicotine are not well-characterized, although both prefrontal cortex and hippocampal brain regions have been implicated (Leiser et al., 2009; Sarter et al., 2009). In the prefrontal cortex, the release of glutamate, ACh, and DA are likely essential steps in

mediating the cognitive-enhancing effects of nicotine (Parikh et al., 2008; Sarter et al., 2009). The specific roles of nAChR subtypes in these processes have not been fully elucidated, although both α7 and α4β2 nAChR are involved. A working model for mechanisms underlying the cognitive effects of nicotine is shown in Figure 1.

In several studies, nAChR genes have been associated with a number of smoking phenotypes including the Fagerström Test for Nicotine Dependence (FTND), the Revised Tolerance Questionnaire (RTQ) and the heaviness of smoking index (Feng et al., 2004; Li et al., 2005; Saccone et al., 2009). To a lesser extent, nAChR genes have been investigated as related to cognitive performance (Fernandes et al., 2006; Steinlein, 1999). As will be summarized below, most of these studies have focused on α7nAChRs and α4β2nAChRs (Kenney and Gould, 2008).

2.1 Nicotinic Receptors

α7nAChR—α7nAChRs are abundant in several brain regions associated with learning and memory including the hippocampus and prefrontal cortex (Gotti et al., 2007). These receptors, similar to NMDA receptors, are highly permeable to calcium, which allows them to enhance neurotransmitter release (e.g., glutamate) and modulate synaptic plasticity (Gray et al., 1996; Quik et al., 1997; Seguela et al., 1993). Compared to the α4β2nAChRs, α7nAChRs have low affinity for nicotine and do not desensitize at low nicotine concentrations (Quick and Lester, 2002; Wooltorton et al., 2003). This delayed desensitization of α7nAChRs has been suggested to maintain DA activity after the α4β2nAChRs are desensitized (Giniatullin et al., 2005). α7nAChRs located in the hippocampus and the prefrontal cortex have been studied in relation to cognitive processes including attention and performance in working and associative memory tasks (Leiser et al., 2009).

α7nAChR knock out (KO) mice do not show changes in nicotine self-administration or sensitivity to nicotine discrimination and α7nAChRs are not believed to play a role in the reinforcing effect of nicotine (Hoyle et al., 2006; Smith et al., 2007). In contrast, α7nAChR KO mice show reduced performance in attention and working memory tasks (Fernandes et al., 2006; Hoyle et al., 2006). In a study by Young et al., (2004), α7nAChR KO mice showed greater errors of commission in a sustained attention task compared to wild-type mice. α7nAChR KO mice may have additional compensatory changes in development; therefore, nAChR subtype distribution and density may significantly differ between wild-type and α7nAChR KO mice (Young et al., 2004a). A particular problem when studying adult gene knockouts is that the mutated gene is non-functional throughout its entire development, making the precise interpretation of unexpected phenotypes difficult. In order to disentangle developmental compensatory gene changes from the true effect of gene deletion, Curzon et al. (2006) utilized antisense oligonucleotide (aON) targeted at reducing 3′-and 5′-UTRs to reduce α7nAChR message levels. Rats treated with aON performed significantly worse on a task measuring spatial performance and exhibited reduced α7nAChR densities in the hippocampus and frontal cortex (Curzon et al., 2006). In a mouse strain known to exhibit deficits in α7nAChR expression, sensory gating impairments were significantly improved with the administration of a non-selective partial nicotine agonist (Simosky et al., 2001; Stevens et al., 1996; Stevens et al., 1998) or α7nAChR selective agonists (Felix and Levin, 1997; Kem, 2000; Levin and Simon, 1998; Mullen et al., 2000; Woodruff-Pak et al., 1994). Taken together, disruption or deletion of the gene encoding α7nAChR, *Chrna7*, may impact several domains of cognition, which may be rescued with nicotine or other agonist molecules that target α7nAChRs.

In humans, α7nAChRs may mediate the relationship between smoking and sensory gating sensitivity in individuals with schizophrenia (Adler et al., 1993; Nomikos et al., 2000;

Taiminen et al., 1998). Schizophrenia is a unique population to study nicotine's cognitive effects since 75%–85% of these individuals are observed to have cognitive deficits including attention, memory and executive functioning (Medalia et al., 2008; Reichenberg et al., 2006) and a similar percentage smoke cigarettes (Leonard et al., 2001; Poirier et al., 2002). Reduced α7nAChR density has been observed in hippocampal regions of schizophrenic patients (Breese et al., 2000; Freedman et al., 1995; Guan et al., 1999; Martin-Ruiz et al., 2003). The α7nAChRs have been linked to sensory gating dysfunction in schizophrenics (Potter et al., 2006). Sensory gating refers to a reduced response to a middle latency (50 msec) component of the auditory event-related potential (ERP), a mechanism thought to filter out irrelevant stimuli from meaningful ones, and may underlie sensory overload and cognitive fragmentation observed in those with schizophrenia (Croft et al., 2001). Genome wide linkage analysis of P50 gating deficits have been mapped to chromosome 15q13-14, the locus where *CHRNA7* is encoded (Freedman et al., 1997), a finding which has been replicated in several other studies (Fiedler et al., 2006; Neubauer et al., 1998; Raux et al., 2002). Nicotine, a non-selective nAChR agonist, and GTS-21 (DMXB-A), a partial α7nAChR agonist, have been shown to reverse auditory gating deficits in a number of animal models and in patients (Martin and Freedman, 2007). Given that nicotine appears to regulate, in part, inhibitory gating deficits (Adler et al., 1993), *CHRNA7* is an attractive candidate for investigating the relationship between nicotine and cognitive enhancement.

α4β2nAChR—α4β2 nAChRs have a high affinity for nicotine and desensitize at low concentrations of nicotine, within the range of those found in the blood of smokers (Gotti et al., 1997). Stimulation of α4β2nAChRs that are found in DA cell bodies and presynaptic terminals, increases DA release both in the nucleus accumbens and prefrontal cortex (Chen et al., 2003b), which may contribute to the rewarding and cognitive-enhancing effects of nicotine, respectively.

The β2nAChR subunit, found in over 90 percent of nAChR pentamers, is highly expressed in the basal ganglia, thalamus and hippocampus (Perry et al., 1992; Perry et al., 1995; Spurden et al., 1997). Mice lacking the β2nAChR subunit demonstrate deficits in executive function including hyperactivity and impairment in behavioral flexibility (Granon and Changeux, 2006; Granon et al., 2003). Picciotto et al. (1995) reported that in β2nAChR KO mice, nicotine did not boost associative memory performance, an expected response in wild-type mice (Decker et al., 1994; Oliverio, 1966). However, in the absence of nicotine, β2nAChR KO mice demonstrated improved associative memory compared to wild-type mice (Picciotto et al., 1995). In a more recent study, β2nAChR KO mice displayed deficits in exploratory behavior, which was partially rescued with the introduction of nicotine (Besson et al., 2008). To confirm the influence of the β2 subunit on the cognitive effects of nicotine, Maskos et al. (2005) used a lentiviral vector to re-express the β2nAChR subunit in the ventral tegmental area of β2nACh KO mice (Maskos et al., 2005). Re-expression of the β2nAChR subunit restored nicotine-induced DA release, nicotine self-administration and normalization of excessively slow exploratory behavior observed in β2nAChR KO mice (Maskos et al., 2005). A recent study investigated β2nACh KO and α7nAChR KO mice. Both types of KO mice exhibited spatial deficit impairments compared to wild-type mice (Levin et al., 2009). Only male mice were impaired by the β2nAChR KO whereas α7nAChR KO caused spatial impairments in both male and female mice. All mice were then allowed free access to nicotine. Results of this study indicate that β2nAChR KO exhibited short-term decreased nicotine consumption while α7nAChR KO developed long-term decreased nicotine consumption (Levin et al., 2009). Human studies investigating the effect of *CHRNB2* variation on cognitive responses to nicotine are lacking.

The role of the α4nAChR subunit in cognitive processes remains to be elucidated. Mutations in *CHRNA4* have been associated with seizure and EEG changes (Chen et al., 2009; Zhu et

al., 2008a). A synonymous *CHRNA4* SNP within exon 5 of the gene contains a thymine-to-cytosine (T1629C) polymorphism and has been associated with changes in N1 component ERPs, processing speed and attentional function (Espeseth et al., 2007; Reinvang et al., 2009). To our knowledge, this SNP or other genetic variations in *CHRNA4* have not been examined as moderators of cognitive actions of nicotine.

Other nAChR genetic associations—Nicotine stimulates all known nAChR subtypes with varying affinities; therefore, polymorphisms in other nAChR genes have the potential to mediate the influence of nicotine on cognitive performance. Recently, studies have determined that several polymorphisms in genes that encode nAChR subunits (*CHRNA2–CHRNA10* and *CHRNB2–CHRNB4*) relate to FTND score, smoking quantity, subjective response as well as other smoking related behaviors (Hutchison et al., 2007; Portugal and Gould, 2008; Saccone et al., 2007; Thorgeirsson et al., 2008). Although several of these studies have yielded intriguing results especially in the *CHRNB3–CHRNA6* and *CHRNA5–CHRNA3–CHRNB4* gene clusters, these studies did not include cognitive outcomes. One study investigated the association between cognitive performance and nAChR gene variation in female smokers and non-smokers (Rigbi et al., 2008). Results from this research indicated that nAChR SNPs and haplotypes were associated with various domains of cognition in the smoking group and non-smoking groups. Cognitive tests for response inhibition, selective attention and sustained attention were conducted. SNPS and haplotypes located in multiple nAChR subunit sequences (*CHRNA7*, *CHRNA4* and *CHRNB2)* were associated with cognitive performance in female smokers and non-smokers. These findings in addition to the nAChR genetic research described above warrant further investigation of nAChR subunit polymorphisms as moderators of cognitive-enhancing effects of nicotine.

3. DOPAMINERGIC SYSTEM

Nicotine-induced release of DA in the nucleus accumbens is believed to be essential in mediating nicotine reward (Corrigall et al., 1994; Di Chiara et al., 2004; Nisell et al., 1994). Studies have shown that DA system gene variation moderates smoking phenotypes including nicotine sensitivity (Perkins et al., 2008), smoking progression (Audrain-McGovern et al., 2004), early smoking onset (Ling et al., 2004), mood sensitivity (Cinciripini et al., 2004) as well as craving and stress induced cigarette craving (Erblich et al., 2004; Franklin et al., 2009; Preuss et al., 2007). DA genes are implicated in multiple cognitive functions including working memory, attention, and response inhibition (Colzato et al., 2009; Nieoullon, 2002; Tanila et al., 1998). DA dysfunction has also been implicated in psychiatric disorders associated with poor attention and working memory function such as attention deficit hyperactivity disorder (ADHD) and schizophrenia (Cheon et al., 2003; Seeman and Kapur, 2000). As will be summarized below, studies are beginning to elucidate the role of DA in nicotine-induced cognitive enhancement.

3.1 Dopamine Transporter

The DA transporter (DAT) regulates extracellular DA and controls the intensity and time-course of DA neurotransmission by re-uptake of extracellular DA into neurons. DAT is the principal target of stimulants (e.g., cocaine, methylphenidate, and d-amphetamine) in the brain (Coyle and Snyder, 1969; Giros et al., 1996; Seeman and Madras, 1998; Volkow et al., 1998). Some evidence suggests that genetic variation of *DAT1* is associated with diverse disorders including ADHD, smoking behavior and stimulant psychosis (Chen et al., 2003a; Curran et al., 2001; Jorm et al., 2000; Ujike et al., 2003). DAT also appears to be related to cognitive function. For example, DAT-1 KO mice demonstrate elevated extracellular DA (Budygin et al., 2002; Giros et al., 1996; Laakso et al., 2002; Sora et al., 1998; Spielewoy et al., 2000) and cognitive deficits including an inability to adapt their behavior to

environmental changes as well as deficits in spatial learning and memory (Morice et al., 2004). Cognitive deficits observed in DAT-1 KO mice such as cued and spatial learning, measured by the elevated plus maze, were significantly improved with both chronic and acute nicotine administration (Weiss et al., 2007). This improvement occurs potentially through nicotine–induced up-regulation of DAT mRNA in the substantia nigra and ventral tegmental area (Li et al., 2004).

The human *DAT1* gene, encoded by 15 exons on chromosome 5p15.3, contains a common 40 base pair (bp) variable number tandem repeat (VNTR) polymorphism in the 3′ untranslated part of the gene (Giros et al., 1996; Vandenbergh et al., 1992) yielding between 3 and 12 repeats with the most frequently observed alleles containing 9 and 10 repeats. The 10-repeat allele has been associated with an abnormally active DAT, eliciting increased re-uptake of DA and DA degradation leading to reduced DA transmission (Mill et al., 2002). Two studies found a unique gene-environment interaction of the DAT genotype and maternal smoking behavior on ADHD symptoms. The first study reported that children homozygous for the 10 repeat allele who were prenatally exposed to maternal smoke were more likely to exhibit hyperactive-impulsive symptoms (Kahn et al., 2003). The second study observed similar findings, but the effect was only detected in males (Becker et al., 2008). Both articles hypothesized that carrying the 10 repeat allele may increase transcription and expression of DAT leading towards low synaptic levels of DA (Michelhaugh et al., 2001; Miller and Madras, 2002). The role of *DAT1* genetic variation on cognitive responses to nicotine remains to be elucidated.

3.2 Dopamine Receptors

DA acts through five receptor subtypes (D1-D5) (Sealfon and Olanow, 2000; Sokoloff and Schwartz, 1995; Zhu et al., 2008b). The DA receptors are also classified under two receptor families: D1 –like (D1 and D5 receptors) and D2–like (D2, D3 and D4 receptors). The D2 receptor family also functions as an autoreceptor that reduces DA release (Missale et al., 1998). Among the DA receptors, D2 and D4 are the primary receptors examined in relation to cognitive effects of nicotine.

D2 Receptor—Several studies have shown that genetic variation of the human D2 receptor gene, *DRD2*, moderates the influence of nicotine deprivation on cognitive performance in smokers. Short-term abstinence (10 days) from nicotine results in the slowing of EEG frequency in smokers, coinciding with reduced cognitive performance and alertness (Knott, 1990; Pickworth et al., 1989). Gilbert et al. (2004) tested if a common polymorphism located in exon 8 of the ankyrin repeat and kinase domain containing (*ANKK1)* gene, previously known as ‘DRD2 TaqI ‘A’’, moderated EEG activation in recently abstinent female smokers (Gilbert et al., 2004). *ANKK1* is located 10 kb 3′ downstream from *DRD2*. Individuals who are carriers of the *ANKK1* A1 allele may have decreased D2 receptor density compared with individuals who were homozygous for the A2 allele (Young et al., 2004b). Gilbert at al. (2004) reported that females who carried at least one A1 allele experienced a greater decrease in EEG activation following nicotine abstinence across all scalp sites.

Similar results to Gilbert et al. (2004) have been observed using event-related potentials (ERPs), a specific type of electroencephalogram (EEG) time-locked to stimuli presented within the context of a cognitive task. The P3 is a type of ERP characterized by positive deflection occurring about 300–500 ms after the stimulus during target detection in an oddball task (Jones et al., 2006) and reflects response inhibition, conflict detection, and working memory (Roche et al., 2005). Abstinent smokers who carried at least one A1 allele had reduced NoGo P3 amplitudes relative to smokers who have two copies of the A2 allele

at the *ANKK1* site (Evans et al., 2009). In contrast, non-abstinent smokers with at least one A1 allele had greater NoGo posterior P3 amplitude relative to smokers who carried two A2 alleles. The researchers speculate that either dopamine deficiency (A1 individuals when smoking deprived) or excess (A2 when satiated) may be associated with reduced cognitive-attentional function.

A synonymous SNP located within the *DRD2* gene C957T, has been demonstrated to moderate striatal D2 binding in vivo and mRNA stability in vitro (Duan et al., 2003; Hirvonen et al., 2004). Jacobsen et al. (2006) reported that following nicotine patch administration, smokers who carried the 957T allele experienced worsened working memory during a high verbal working memory load. Each 957T allele increases D2 binding availability (Hirvonen et al., 2004). Reduced working memory functions may be due to excess baseline DA levels in carriers of the 957T allele. Alternatively, working memory performance in individuals who were homozygous for the 957C allele did not appreciably change between placebo and nicotine conditions. The authors further suggested that individuals who carry two copies of the 957C allele may not be able to further increase DA activity during performance of tasks with a high working memory load (Jacobsen et al., 2006). These examples illustrate that these *DRD2* gene variants influence cognitive domains of attention and working memory, possibly through the regulation of DA tone.

D4 Receptor—The structure and pharmacology of the D4 receptor is similar to the D2 receptor (Van Tol et al., 1991). The gene encoding the D4 receptor (*DRD4*) contains a 48 bp VNTR polymorphism located in exon 3. The DRD4 7 repeat (long) allele is reported to be associated with reduced DA activity in comparison with the 2 or 4 repeat variants (short) (Asghari et al., 1995). The long variant is also associated with an increased risk for smoking, reduced likelihood of quitting smoking and greater responses to smoking cues (David et al., 2008; Hutchison et al., 2002). Recently, a research report found that smoking status moderated the effect between *DRD4* genotype and attentional bias for smoking related cues (Munafo and Johnstone, 2008). In this study, smokers were required to smoke normally one hour prior to testing, and ex-smokers who were abstinent for approximately 10 years were also enrolled in the study. All participants were administered a modified Stroop task. Ex-smokers who carried at least one allele with 7 (long) or more repeats had significantly increased color naming interference (Stroop effect) for smoking related words compared with ex-smokers who carried 6 or less repeats on both alleles. Conversely, the *DRD4* genotype was unrelated to Stroop performance in current smokers (Munafo and Johnstone, 2008). The study, however, did not assess current smokers during abstinence. These findings suggest that the long allele of *DRD4* VNTR predicts greater attentional bias for smoking cues in abstinent smokers possibly through reduced DA activity (Asghari et al., 1995).

3.3 Catechol-O-methyltransferase (COMT)

Catechol-O-methyltransferase (COMT), a major enzyme that inactivates DA, controls DAergic transmission along with DAT and DA receptors (Mannisto et al., 1992). Several studies have independently associated *COMT* gene variation both with smoking related phenotypes including smoking severity, age of smoking initiation, smoking cessation and heavy smoking (Bitner et al., 2000; Guo et al., 2007; Munafo et al., 2008; Tochigi et al., 2007) as well as cognitive functions including working memory, long term memory, attention and executive function (Egan et al., 2001; Enoch et al., 2009; Sheldrick et al., 2008). COMT is associated with DA regulation, cognitive processes and smoking related behaviors; therefore, the gene encoding this enzyme is an important target to explore the cognitive effects of nicotine.

COMT contains a well-studied single nucleotide polymorphism (C**G**TG vs C**A**TG) that results in the presence of methionine (Met) or valine (Val) at codon 108 (in s-COMT) or codon 158 (in m-COMT) (Sengupta et al., 2008). The COMT enzyme containing Met is unstable at 37°C and has one fourth of the activity of the enzyme containing Val (Lotta et al., 1995). Lower DA levels in the prefrontal cortex occur as a consequence of the Val allele having increased enzymatic efficiency compared with the Met allele (Guo et al., 2007). Although this COMT Val/Met polymorphism is functionally relevant and well-characterized, this SNP has not been extensively investigated for its contribution to nicotine-induced cognitive-enhancement.

Loughead et al. (2008) studied *COMT*, brain function and cognitive deficits during abstinence from smoking, as compared with a normal smoking state, using a within-subject design. Smokers were exposed to two conditions: normal smoking and overnight (14 h) abstinence. In each condition, working memory performance of smokers was tested using the visual N-back task. During smoking abstinence, smokers who carried two copies of the Val allele exhibited decreased fMRI BOLD signal in both the bilateral dorsal lateral prefrontal cortex and dorsal cingulate/medial PFC and slower reaction time in the N-back task compared to the normal smoking condition (Loughead et al., 2008). These differences were not observed in smokers who carried at least one copy of the Met allele. The authors suggested that cognitive performance and brain activation in individuals who carry two copies of the Val allele may be due to larger changes in DA tone between smoking satiation and abstinence (Loughead et al., 2008). Specifically, the presence of two Val alleles may elicit increased DA deactivation when tonic DA is available, but DA deactivation is less efficient when larger amounts of DA are released.

The studies summarized here point to an essential role of the DAergic pathway in mediating the cognitive effects of smoking. Genetic variation in DA genes such as *DAT1*, *DRD2* and *DRD4*, and *COMT* appear to fine-tune DA transmission and influence the effects of nicotine on cognitive function. Importantly, genetic variation appears to have differential effects depending on the nicotine exposure (abstinent vs. non-abstinent) of smokers.

4. OTHER GENE VARIANTS

In addition to the nicotinic and DA genes, other genes have been studied and may potentially influence the cognitive effects of nicotine. A recent study examined the interaction between the serotonin transporter linked polymorphism (5-HTTLPR) genotype (L or S form) and the effects of the nicotine patch on spatial working memory in smokers (Carlson et al., 2009). Humans that are homozygous for the L allele are thought to have greater 5-HT reuptake and possibly lower levels of synaptic 5-HT levels, compared to the S allele carriers (Heils et al., 1997; Lesch et al., 1996). The study reported that nicotine enhanced spatial working memory in 5-HTT S allele carriers, compared to patients with two L alleles. Furthermore, in smokers with greater depressive symptoms, these gene-by-nicotine interactions were stronger. These results suggest that 5-HT may also play an important role in medicating the cognitive-enhancing effects of nicotine (Carlson et al., 2009).

The GABA inhibitory interneurons in the hippocampus and the prefrontal cortex have been proposed to have an essential role in modulating the pharmacological effects of nicotine. Li et al. (2002) determined that chronic nicotine and smoking exposure decreased mRNA levels of $GABA_B$ receptors in the rat hippocampus (Li et al., 2002). Although this study did not investigate cognitive performance, the authors speculate that nicotine-induced moderation of $GABA_B$ mRNA expression, in the hippocampus, may provide a partial mechanism of nicotine and smoking on learning and memory (Li et al., 2002).

Jacobsen et al. (2009) investigated adolescents exposed to prenatal and adolescent smoke using verbal and visuospatial memory tasks while undergoing a fMRI. The two genes studied, CLSTN2 (encoding synaptic protein calsyntenin 2) and KIBRA (a novel WW domain-containing protein that modulates cell processes), were investigated because of previous studies demonstrating their sequence variation regulates verbal memory, hippocampus function in memory retrieval and delayed recall (Almeida et al., 2008; Papassotiropoulos et al., 2006; Schaper et al., 2008). The *KIBRA* SNP studied did not appear to exert a significant effect on verbal or visuospatial memory on adolescents exposed to prenatal of adolescent tobacco smoke. Jacobsen et al. (2009) replicated the finding that gene variation in *CLSTN2* influences verbal memory, and additionally found that the beneficial cognitive effects of carrying at least one C allele were reversed in adolescents who were exposed to tobacco smoke. Furthermore, adolescents exposed to tobacco smoke experienced delayed recognition compared with other individuals in the study.

5. FUTURE DIRECTIONS

The main findings of our review are summarized in Table 1. Genetic studies support the role of nAChR, DA, and 5-HT-related genes in nicotine effects on cognitive processes. These include α7 nAChR, β 2 nAChR, DAT, ANKK1, DRD2, COMT, and 5-HTT genes. Several key issues should be considered in designing future studies examining genetic associations with the cognitive effects of nicotine in humans.

1) Baseline nicotine exposure

Assessment of the cognitive effects of nicotine is complicated by the smoking status of the subjects and their last use of nicotine. Chronic nicotine exposure, as with smoking, is associated with adaptive changes that lead to development of nicotine tolerance and dependence (Benowitz, 2008; Brunzell et al., 2003; Trauth et al., 2001). As mentioned before, following abstinence from smoking, dependent smokers experience withdrawal symptoms including cognitive dulling. However, it has been difficult to dissect whether the cognitive effects of nicotine in smokers reflect nicotine's direct effects or simply the alleviation of nicotine withdrawal (Heishman, 1998). For studies examining cognitive effects of nicotine, it is important to carefully control for smoking status and nicotine intake before testing. A recent study demonstrated significant differences in cognitive-enhancing effects of nicotine depending on whether nicotine administration was done under smoking abstinence or satiety conditions (Myers et al., 2008).

2) Nicotine delivery

Cigarette smoke contains numerous other compounds in addition to nicotine; therefore, delivery via smoking is not optimal for behavioral genetic studies of nicotine. There are several pure nicotine products including the nicotine patch, gum, lozenge, inhaler, or spray. These products deliver nicotine at different rates: the nicotine patch provides a slow delivery, whereas the spray or inhaler provides faster delivery of nicotine (Le Houezec, 2003). Accurate nicotine dose delivery is also another consideration. The amount of nicotine absorbed can vary when the nicotine gum, spray and inhaler are used (Teter et al., 2002). The nicotine lozenge can provide accurate dose delivery because the lozenge fully dissolves in the mouth (Choi et al., 2003; Kotlyar et al., 2007; Sofuoglu et al., 2006). Another alternative is to use intravenous nicotine administration that provides accurate and rapid nicotine delivery, comparable to smoking, and use saline as the placebo (Sofuoglu et al., 2009; Sofuoglu et al., 2008). A critical issue in nicotine administration studies involves using a matching placebo and multiple doses of nicotine. As commented by Heishman, the dose-dependent effects of nicotine are essential for psychopharmacological studies

(Heishman, 1999). Careful consideration of these issues is important for studies examining the cognitive effects of nicotine.

3) Pharmacological selectivity

As reviewed above, nAChR subtypes have different roles in cognitive processes, but it has been difficult to separate their roles in humans due to the lack of selective medications for nAChR subtypes (Gotti et al., 2006). Nicotine is a non-selective agonist at both α4β2 and α7 nAChRs. Recently, varenicline, a partial agonist at the $\alpha_4\beta_2$ nAChR, has been marketed for smoking cessation. Several other non-selective partial nAChR agonists are also undergoing human studies for smoking cessation and treatment of dementia (Dunbar et al., 2007). Unfortunately, selective α7 nicotinic medications are not yet available for human use (Olincy et al., 2006). With the increased availability of subtype selective nicotinic medications, the role of nAChR subtypes can be better characterized. These medications may help to identify the relative roles of nicotinic receptor subtypes in mediating the cognitive-enhancing actions of nicotine.

4) Selection of cognitive tasks

The studies reviewed here have used several different cognitive tasks to examine the cognitive effects of nicotine such as measures of attention, working memory, response inhibition and attentional bias (Dawkins et al., 2007; Levin et al., 2006; Waters and Feyerabend, 2000). It will be important to compare these studies systematically to determine which cognitive function is most sensitive to nicotine in non-deprived smokers and non-smokers (Heishman, 1998). Availability of validated cognitive tests with good psychometric properties that are sensitive to nicotine will facilitate the identification of genetic factors in the cognitive effects of nicotine.

Acknowledgments

This research was supported by the Veterans Administration Mental Illness Research, Education and Clinical Center and National Institute on Drug Abuse grants K02 DA021304 (MS) and K12 DA00167 (AH). We gratefully acknowledge Jonathan Covault, M.D., Ph.D. and Marc Rosen, M.D. for their comments and suggestions on this manuscript.

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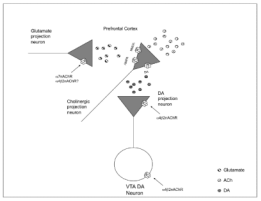

Figure 1.

A cartoon illustrating the hypothesized effects of nicotine on the regulation of dopamine (DA), glutamate and acetylcholine (ACh) release in the prefrontal cortex (PFC), a region thought to be essential in mediating cognitive enhancement from nicotine. Nicotine enhances the release of glutamate and DA, which leads to increased Ach release and the potential activation of presynaptic glutamate and DA receptors on cholinergic terminals. The type and exact location of these receptors remains to be elucidated. See (Briand et al., 2007; Parikh et al., 2008; Sarter et al., 2009) for details.

Table 1

Summary of studies on DA, nACh and 5-HTT genetics related to nicotine and cognition Genetic studies related to cognitive effects of nicotine

Gene (polymorphism)	Cognitive measures	Sample	Finding
DAT (VNTR)	Morris watermaze (mouse)	Variable depending on dose	KO + low dose nicotine → ↑locomotor effects KO + high dose nicotine →↓locomotor effects Weiss et al., 2007
DAT (VNTR)	Kiddie-Sads-Present and Lifetime Version	305 adolescents	10 repeat + prenatal nicotine → ↑ hyperactivity (males only) Becker at al., 2008
ANKK1 (rs1800497)	EEG activation	67 female smokers	Taq A1 + depression or nicotine → ↑ EEG deactivation Gilbert et al., 2004
ANKK1 (rs1800497)	ERP during go-nogo task	62 heavy smokers 26 nonsmokers	Taq A1 + acute nicotine →↑nogo P3 Taq A1 + deprived nicotine →↓nogo P3 Evans et al., 2009
DRD2 (rs6277)	Auditory *n*-back task	22 regular smokers 14 nonsmokers	T-carriers + nicotine patch →↓ attention/ working memory Jacobsen et al., 2006
DRD4 (VNTR)	Stroop task	31 current smokers 17 ex-smokers	Past nicotine use + 7≥ repeats → ↓ selective attention and processing speed Munafo and Johnstone 2008
COMT rs4680	Visual N-back working memory task	36 healthy smokers	Val homozygous+ nicotine →↓ attention/ working memory Loughead et al., 2008
α7	5-choice serial reaction-time test of sustained attention (mouse)	Variable	WT + nicotine →↑sustained attention KO →↓ sustained attention Young et al., 2004
α7	Morris watermaze (rat)	6 aON* 7 saline 9 aON-controls	aON treated →↓ spatial learning ability Curzon et al., 2006
α7 and β2	Radial-arm maze (mouse)	16 WT 6 β2 KO 10α7 KO	β2 KO or α7 KO →↓ spatial learning ability β2 KO →↓ nicotine consumption relative to wildtype mice (short term) α7 KO →↓ nicotine consumption relative to wildtype mice (long term)
β2	Morris watermaze and passive avoidance test (mouse)	8 KO 8 WT	KO mice + nicotine → no associative memory enhancement Picciotto et al., 1995
β2	M-diameter circular open-field exploratory behavior (mouse)	15 KO 20 WT	KO + chronic nicotine →↑ exploratory behavior and spontaneous rearing to the level of WT Besson et al., 2008
β2	Y maze (mouse)	7 WT 10 KO 9 KO + VEC#	KO →↓ sensory processing KO + VEC →↑ normalizes sensory processing to WT level Maskos et al., 2005
SLC6A4 (5-HTTLPR)	Spatial working memory task	64 smoking deprived habitual smokers	S allele + nicotine replacement → ↑ Spatial working memory Carolson et al., 2009

*aON= antisense oligonucleotide (aON) targeted toward the 3′- and 5′-UTR coding regions of the rat α7nAChR

#eGFP bi-cistronic vector