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Invited review

Dual role of nicotine in addiction and cognition: A review of neuroimaging studies in humans

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ABSTRACT

Substantial evidence demonstrates both nicotine's addiction liability and its cognition-enhancing effects. However, the neurobiological mechanisms underlying nicotine's impact on brain function and behavior remain incompletely understood. Elucidation of these mechanisms is of high clinical importance and may lead to improved therapeutics for smoking cessation as well as for a number of cognitive disorders such as schizophrenia. Neuroimaging techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI), which make it possible to study the actions of nicotine in the human brain *in vivo*, play an increasingly important role in identifying these dual mechanisms of action. In this review, we summarize the current state of knowledge and discuss outstanding questions and future directions in human neuroimaging research on nicotine and tobacco. This research spans from receptor-level PET and SPECT studies demonstrating nicotine occupancy at nicotinic acetylcholine receptors (nAChRs) and upregulation of nAChRs induced by chronic smoking; through nicotine's interactions with the mesocorticolimbic dopamine system believed to mediate nicotine's reinforcing effects leading to dependence; to functional activity and connectivity fMRI studies documenting nicotine's complex behavioral and cognitive effects manifest by its actions on large-scale brain networks engaged both during task performance and at rest.

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1. Introduction

Nicotine's addiction liability is demonstrated by the high prevalence of cigarette smoking and low quit success rates, despite well-documented health risks (Bartal, 2001; Mokdad et al., 2004) and societal costs (Leistikow, 2000; Leistikow et al., 2000; Leistikow and Miller, 1998) of smoking. Approximately 20% of Americans still smoke (Brown, 2009; CDC, 2009), and although most smokers endorse a desire to quit (Fiore et al., 2000), very few (<5%) will actually do so in a given year without treatment, and only about 20–25% will achieve abstinence with 6 months or more of effective treatment (Cahill et al., 2011; Holmes et al., 2004; Hughes et al., 1999; Hurt et al., 1997; Jorenby et al., 1999; Killen et al., 1999, 2000). Therefore, there continues to be a vital need to improve outcomes for cigarette smokers seeking treatment (Ray et al., 2009).

Nicotine, an alkaloid found in tobacco leaves, has been used by humans for its psychoactive properties for thousands of years. But it is only in the last several decades that the cellular and physiological mechanisms underlying nicotine's complex effects on brain function and behavior, including nicotine's abuse and dependence liability and its effects on cognitive function, have begun to be revealed. Most of this fundamental knowledge has been obtained from preclinical models and *in vitro* tissue preparations. More recently, neuroimaging techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) have made it possible to study the actions of nicotine and cigarette smoking on brain circuits and processes underlying addiction and cognition in the human brain *in vivo*.

In this review, we summarize the current state of knowledge and list some outstanding questions and possible future directions in human neuroimaging research on nicotine and tobacco. This

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research has both clinical and basic-science importance. A better understanding of the effects of nicotine and tobacco smoking on the human brain is a critical step toward the development of more effective smoking cessation treatments, for which there is a pressing need (CDC, 2009). At the same time, experimenter administered nicotine can be used as a research tool to interrogate a range of brain processes in both healthy and patient populations, as well as to develop novel therapeutic drugs for such cognitive disorders as schizophrenia, Alzheimer's disease (AD), and attention-deficit hyperactivity disorder (ADHD).

2. Brain imaging of nicotinic acetylcholine receptors

Most psychoactive agents exert their effects by mimicking an endogenous neurotransmitter and binding to its neuronal receptors. In this case, nicotine serves as a ligand at nicotinic acetylcholine receptors (nAChRs). nAChRs are ligand-gated ion channels consisting of unique combinations from a family of at least seventeen ($\alpha1-\alpha10$, $\beta1-\beta4$, γ, δ, ε) similar, but distinct, subunits (Wu and Lukas, 2011). While many nAChR subtypes have been identified, the heteromeric $\alpha4\beta2^*$ receptor is one of the most common in the mammalian brain (Wu et al., 2006), and will be the focus of this section because the majority of brain imaging studies of smokers have focused on this receptor. Receptors containing the $\alpha4$ subunit are reported to be central to the mediation of nicotine-induced reward, tolerance, and sensitization (Perry et al., 2002), while those containing the $\beta2$ subunit have been shown to be functionally significant in nicotine self-administration (Epping-Jordan et al., 1999; Picciotto et al., 1998; Walters et al., 2006). Nicotinic acetylcholine receptors are located throughout the brain, with the highest density seen in the thalamus, followed by the basal ganglia, and frontal, cingulate, occipital, and insular cortices (Clarke et al., 1984; Ding et al., 1996; Mamede et al., 2004).

For examining the acute and chronic effects of cigarette smoking, PET and SPECT scanning have been performed in human smokers, with the most commonly used radiotracers being 2-[^{18}F]fluoro-3-(2(*S*)azetidinylmethoxy) pyridine (abbreviated as 2-FA) for PET scanning (Koren et al., 1998) and 123-labeled 5-iodo-A-85380 (abbreviated as 5-IA) for SPECT scanning (Horti et al., 1999). These radiotracers bind with high affinity and relative specificity to $\alpha4\beta2^*$ nAChRs (Koren et al., 1998), and the safety and reliability of these radiotracers have been verified (Bottlaender et al., 2003; Chefer et al., 2003; Fujita et al., 2002; Kimes et al., 2008; Valette et al., 1999).

In examining the acute effects of smoking/nicotine administration, 2-FA PET and 5-IA SPECT studies have demonstrated the effect of cigarette smoking on $\alpha4\beta2^*$ nAChR occupancy. In one PET study, smoking varying amounts of a regular cigarette (none, 1 puff, 3 puffs, 1 full cigarette, or to satiety [2 ½–3 cigarettes]) resulted in 0, 33, 75, 88, and 95% receptor occupancy, respectively (Brody et al., 2006a) (Fig. 1A). This study also demonstrated that smoking only 13% (1–2 puffs) of a cigarette and having a venous plasma nicotine concentration of 0.87 ng/mL (roughly 1/25th of the level achieved in typical daily smokers) resulted in 50% occupancy of $\alpha4\beta2^*$ nAChRs for 3.1 h after smoking. Therefore, cigarette smoking in amounts used by typical daily smokers leads to nearly complete occupancy of $\alpha4\beta2^*$ nAChRs, such that tobacco-dependent smokers maintain $\alpha4\beta2^*$ nAChR saturation throughout the day. In a similar study using 5-IA SPECT (Esterlis et al., 2010), smoking to satiety (mean − 2.4 cigarettes) also resulted in a prolonged period of occupancy of the majority of $\beta2^*$-containing nAChRs (mean − 67% [range, 55–80%]). The actual percent occupancy from smoking to satiety for the second study was lower than the first, and these slightly discrepant results may have been due to differences in abstinence period before scanning, number of cigarettes smoked during scanning, imaging methodology/timing issues, brain regions studied, and/or statistical calculation methods for determining percent occupancy.

In addition to studies examining regular cigarette smoking, other acute cigarette smoke exposures (namely denicotinized and low nicotine cigarettes, and secondhand smoke) have recently been examined for their effects on $\alpha4\beta2^*$ nAChR occupancy. In one study (Brody et al., 2009a) (Fig. 1B), denicotinized cigarettes containing only trace amounts of nicotine (0.05 mg) and low nicotine cigarettes (0.6 mg nicotine) were smoked during 2-FA PET scanning to determine if components of smoking other than nicotine (e.g., other constituents of tobacco smoke or the touch, feel, smell, and taste of a cigarette) result in $\alpha4\beta2^*$ nAChR occupancy. This study demonstrated that smoking a denicotinized and a low-nicotine cigarette resulted in 26% and 79% $\alpha4\beta2^*$ nAChR occupancies, respectively. Given the consistency of findings between this study and the one cited above with standard cigarettes (Brody et al., 2006a), the denicotinized/low nicotine cigarette study demonstrates that nicotine inhalation during smoking appears to be solely responsible for $\alpha4\beta2^*$ nAChR occupancy, with other factors (if present at all) having either short-lived or very minor effects. And in a second study, secondhand smoke exposure (Brody et al., 2011) was also found to occupy a substantial percentage of $\alpha4\beta2^*$ nAChRs (Fig. 1C). In this study, smokers and nonsmokers underwent two PET scanning sessions, during which they sat in the passenger's seat of a car for 1 h and either were or were not exposed to secondhand smoke from a smoker seated in the driver's seat. In this study, the secondhand smoke exposure resulted in 19% occupancy of $\alpha4\beta2^*$ nAChRs, with no significant differences between smokers and nonsmokers, again demonstrating substantial receptor occupancy from cigarette smoke exposure.

Medications for treating tobacco dependence have also been examined for their acute effects on $\alpha4\beta2^*$ nAChR occupancy. In one SPECT scanning study (Esterlis et al., 2011), use of a nicotine inhaler produced an average 55.9% occupancy of $\beta2^*$-nAChRs 2–5 h post-challenge, which was less than the occupancy produced by smoking a standard cigarette (67.6%). Use of the nicotine inhaler was associated with diminished cigarette withdrawal, but not craving, possibly indicating that higher nAChR occupancy than is achieved with the nicotine inhaler is needed to reduce craving (or perhaps other conditional stimuli such as the taste and feel of the smoke in the throat, etc, may be required to diminish craving). In a similar study comparing varenicline (Chantix®) to placebo administration during PET scanning sessions (Lotfipour et al., 2012), low dose varenicline administration (0.5 mg) was associated with complete saturation of available $\alpha4\beta2^*$ nAChRs. Smoking to satiety, but not low-dose varenicline, significantly reduced withdrawal symptoms, indicating that factors other than varenicline binding to $\alpha4\beta2^*$ nAChRs lead to reduced withdrawal.

As for chronic effects of smoking/nicotine administration, several lines of research demonstrate that smoking leads to up-regulation of nAChRs in the human brain, including the common $\alpha4\beta2^*$ nAChR (Gentry and Lukas, 2002). Human postmortem tissue studies show that chronic smokers have increased numbers of $\alpha4\beta2^*$ nAChRs compared to non-smokers (Benwell et al., 1988; Breese et al., 1997), and that former smokers (>1 year abstinent) have nAChR densities similar to non-smokers (Breese et al., 1997). Many laboratory animal studies also demonstrate up-regulation of nAChRs in response to chronic nicotine administration (Marks et al., 2011; Pauly et al., 1989, 1996; Shoaib et al., 1997; Yates et al., 1995; Zhang et al., 2002). Taken together, these studies indicate that nAChRs up-regulate with smoking or nicotine administration, but that this up-regulation is reversible with an extended period of abstinence from smoking.

PET and SPECT brain imaging studies of human smokers, using 2-FA and 5-IA, have demonstrated up-regulation of available $\alpha4\beta2^*$

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