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Sex differences in the nicotinic acetylcholine and dopamine receptor systems underlying tobacco smoking addiction

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Abstract

Converging lines of evidence suggest that men generally smoke for nicotine-related reinforcement, whereas women smoke for non-nicotine factors. Women have more difficulty quitting smoking and are less responsive to nicotine replacement therapies than men, underscoring the importance of examining sex differences in the neurochemical mechanisms underlying nicotine-motivated behavior. We review the recent imaging literature on sex differences in the nicotinic acetylcholine receptor system and in the dopaminergic system in response to nicotine administration and tobacco smoking. We offer an explanation to unify imaging findings related to the dopamine system. We then propose a course of action for future medication development for tobacco smoking addiction.

Keywords

sex differences; tobacco smoking; tobacco smoking addiction; nicotinic; nAChR; dopamine; imaging

Introduction

Tobacco smoking is the leading cause of morbidity and mortality in the United States [1], with nearly 556,000 deaths attributable to smoking-related causes each year [2]. The prevalence of smoking continues to be greater in men (20.5%) than women (15.3%) [3]; however, women have worse treatment outcomes. Specifically, women have a more difficult time quitting smoking than men [4] and currently-approved treatments for smoking, including nicotine replacement therapies (NRT) and bupropion, are not as effective in women as in men [5]. This underscores the importance of examining sex differences in the neurobiological mechanisms underlying tobacco smoking-related behaviors to optimize gender-sensitive treatment strategies for nicotine dependence.

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In the following sections, we will review the recent receptor imaging literature on sex differences in the tobacco smoking field in 1) nicotinic acetylcholine receptor (nAChR) availability, and 2) dopamine (DA) receptor availability and neurotransmission. We conclude with a figure integrating findings of sex differences within the mesolimbic and mesocortical dopaminergic (DA-ergic) neural systems. We outline how these findings can inform gender-sensitive treatment development and guide future research focusing on sex differences in the neurobiological framework of tobacco smoking addiction.

The nAChR system

Background

Nicotine is the primary addictive chemical in cigarettes. In the brain, nicotine binds to and activates nAChRs. Some of the most abundant nAChRs in the brain are those containing the $\alpha 4$ and $\beta 2$ subunits, and the reinforcing effects of nicotine are mediated by nAChRs, specifically containing the $\beta 2$ subunit [6,7]. The $\beta 2$ subunit is critical for nicotine-induced DA release, behavioral responses to nicotine such as nicotine self-administration, conditioned reinforcement, conditioned place preference (CPP), and locomotor activation [7]. Seminal preclinical and postmortem human studies consistently demonstrate that nicotine robustly increases or “upregulates” the $\beta 2$ -subunit containing nAChRs ($\beta 2$ -nAChRs) throughout the brain (for review see Cosgrove et al. [8]). Imaging studies have translated these findings to humans, in vivo.

Imaging the upregulation of $\beta 2$ -nAChRs in smokers

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are important imaging techniques used to measure chemicals in the living brain, such as receptors, and fluctuations in neurotransmitter levels. Radiotracers, when injected into a living subject, allow us to measure these brain chemicals with a PET or SPECT camera. Several radiotracers have been designed to bind to $\beta 2$ -nAChRs and are used to measure $\beta 2$ -nAChR availability. This is particularly useful for identifying neurochemical mechanisms underlying tobacco smoking and relating the brain mechanisms to important clinical tobacco smoking outcomes. Since nicotine and radiotracers that label $\beta 2$ -nAChRs bind to the same site, it is critical that nicotine not be present in the brain when imaging $\beta 2$ -nAChR availability. In our studies, tobacco smokers are helped to quit smoking for up to 9 days before imaging studies are performed. Using these techniques, we confirmed the preclinical findings and demonstrated that human tobacco smokers imaged at 7–9 days of smoking abstinence have significantly higher $\beta 2$ -nAChR availability in the cortex and striatum compared to non-smokers [9,10]. This finding in humans set the stage to examine sex differences in $\beta 2$ -nAChR availability.

Sex differences in $\beta 2$ -nAChRs availability in smokers

As stated, the $\beta 2$ -nAChR is critical for the reinforcing effects of nicotine. Thus, sex differences in the availability of $\beta 2$ -nAChRs may underlie sex differences in tobacco smoking behaviors. Within the large literature that demonstrates nicotine administration leads to a robust upregulation of $\beta 2$ -nAChRs, there are two preclinical studies demonstrating that nicotine-exposed male rodents have significantly more $\beta 2$ -nAChRs than their nicotine-

naïve counterparts [11,12](but also see Donny et al. [13]). However, nicotine-exposed female rodents are not different when compared to nicotine-naïve females, suggesting that nicotine does not lead to an upregulation of $\beta 2$ -nAChRs in the female rodent brain. To date, only one study has investigated sex differences in the availability of $\beta 2$ -nAChRs in male and female tobacco smokers compared to non-smokers [14]. The preclinical findings were again translated to humans. Receptor imaging demonstrated that $\beta 2$ -nAChR availability is significantly higher in male smokers in the striatum, cortex, and cerebellum compared to male non-smokers, whereas female smokers do not have different $\beta 2$ -nAChR availability than non-smokers. These findings provide one possible neurochemical explanation for the sex difference in treatment response using NRT. Specifically, NRT is more effective in helping men quit smoking than women [31]. Because men exhibit an upregulation of $\beta 2$ -nAChRs in response to tobacco smoking compared to women, it is possible that NRT may help ‘wean’ men’s $\beta 2$ -nAChRs down to non-smoker levels over time.

The DA receptor system

Background

The mesolimbic DA system is comprised of pathways projecting from the ventral tegmental area (VTA) to the ventral striatum, and includes regions such as the nucleus accumbens (NAc), corpus striatum, and prefrontal cortex (PFC) [6], areas critical in drug reward. DA and DA-ergic pathways are largely implicated in the reinforcing effects of nicotine [15]. Acute nicotine administration activates $\beta 2$ -nAChRs on DA neurons leading to the release of DA within the mesolimbic DA system [16]. The magnitude of ventral striatal DA release correlates positively with the pleasurable response to nicotine in humans [15]. Conversely, selective lesions of DA projections to the NAc or administration of nAChR antagonists into the VTA blocks nicotine-motivated behavior [16].

Imaging DA D2/3 receptor availability and changes in synaptic DA levels

PET imaging is also used to measure DA D2/D3 receptor availability and DA release in tobacco smokers in vivo. Striatal DA release is typically measured in a two-component process using stimulants such as amphetamine or tobacco smoking as challenges and radiotracers that bind to DA D2/D3 receptors as probes. Drugs such as amphetamine or nicotine increase synaptic DA levels. The increase in synaptic DA increases competition with the radiotracer for binding to the DA D2/D3 receptor. Thus, an increase in DA results in a decrease in radiotracer binding, allowing for the indirect measurement of DA release in the brain (for review see Cosgrove et al. [8]). Using this method, several studies have imaged changes in synaptic DA release in smokers but only recently have studies systematically examined sex differences in DA D2/D3 receptor availability and synaptic DA release.

Sex differences in DA receptor availability in smokers

Important clinical investigations in human tobacco smokers have investigated mechanisms underlying sex differences in the regulatory effects of smoking on the mesolimbic DA system. Initial findings showed lower DA D2 receptor availability in the caudate and putamen of male nicotine-dependent smokers compared to non-smokers [17] but females were not included in the study. Dr. Edythe London’s group [18] confirmed this finding in

males, reporting that male smokers exhibited lower DA D2/D3 receptor availability in the dorsal striatum (e.g., caudate and putamen) compared to male non-smokers. Interestingly, female smokers exhibited *similar* DA D2/D3 receptor availability compared to female non-smokers [18]. This suggests chronic tobacco smoking does not downregulate striatal DA D2/D3 receptor availability in females and highlights the importance of including females in studies. Because striatal DA-ergic neurons originate in the midbrain, Dr. London's group then examined sex differences in midbrain DA D2/D3 receptor availability [19]. Female smokers had higher midbrain DA D2/D3 receptor availability compared to female non-smokers. There was no difference in midbrain DA D2/D3 receptor availability between male smokers and male non-smokers. Dr. London's group suggests that higher midbrain DA D2/D3 receptor availability in female smokers may mitigate against the downregulation of DA D2/D3 receptors previously found in the striatum of male smokers. These studies inform our understanding of DA D2/D3 receptor levels, but do not index the function of the DA system.

Novel PET techniques introduced by Morris and Cosgrove to examine dynamic changes in DA release during in vivo smoking revealed that male smokers increase DA levels consistently and rapidly in the ventral striatum while smoking a cigarette, whereas women do not show an increase in DA levels in the ventral striatum while smoking [20]. Exploratory analyses in the same study found that women respond faster to smoking than men in a discrete subregion of the dorsal putamen. Taking the London and Cosgrove findings together, male tobacco smokers generally display lower D2 availability and higher DA release in the striatum, whereas female tobacco smokers display higher D2 availability in the midbrain and lower DA release in the striatum.

Preclinical studies examining sex differences in the DA-ergic system in nicotine dependence are limited in quantity and focus on sex-related differences in the NAc only, making it difficult to pinpoint consistencies between animal and human findings. While female and male rats exhibit low NAc DA levels during nicotine withdrawal, this effect is significantly lower in female rats [21]. This finding suggests a larger deficit in the DA system during withdrawal, and makes sense considering previous claims that decrements in DA activity in the NAc may be related to negative affective states [22]. Indeed, in humans, studies suggest that women experience greater increases in negative affect following a quit attempt and greater urge to smoke to relieve tobacco withdrawal distress compared to men [23,24].

Bridging the gap between brain mechanism and treatment outcome

The preclinical and clinical literature of the nAChR system is in general agreement on sex differences (Table 1); males tend to exhibit an upregulation in $\beta 2$ -nAChR availability in response to nicotine whereas females do not. Sex differences in the DA-ergic system have yet to be proved but a picture is emerging (Figure 1). The mesolimbic DA circuitry originates in the VTA in midbrain, and projects to the striatum and the PFC. Female smokers have higher levels of D2 receptors in the midbrain than both female non-smokers and male smokers [19]. Because the DA neurons originating in the midbrain are inhibitory, it has been hypothesized [19] that higher midbrain DA D2R availability in female smokers may inhibit DA release in the ventral striatum [20], which in turn may mitigate against a downregulation

of D2 receptors in this region [18]. We think that these findings in the mesolimbic system may similarly extend to the mesocortical system and we have an ongoing study to examine this. Specifically, we hypothesize the female smokers will have lower drug-induced DA release in the PFC compared to female non-smokers and male smokers and that female smokers will not evidence the same degree of downregulation in DA D2Rs in the PFC compared to male smokers.

Limited smoking-induced DA release in the ventral striatum of female tobacco smokers may be related to findings that women are less sensitive to smoking reward and less responsive to NRT than men. Male smokers (compared to females) who reportedly smoke more for the reinforcing effects of nicotine than women also have a more 'activated' ventral striatum, which is the hub of DA release and mediates the reinforcing properties of nicotine. Repeated DA release in the striatum may then lead to the downregulation of striatal DA D2 receptors observed in males [17]. In summary, male smokers exhibit nicotine-induced upregulation of $\beta 2$ -nAChRs and smoking-induced DA release in the ventral striatum, whereas women do not. This, combined with the findings that men smoke for the reinforcing effects of nicotine, suggests why treatments targeting the nicotinic and reward systems are more effective in men than in women.

Future Considerations

Preclinical and clinical studies examining potential sex differences in molecular and neurobiological mechanisms underlying nicotine dependence and tobacco smoking remain limited. This is regrettable considering the growing body of literature demonstrating sex differences in nicotine-motivated behavior and treatment response. Preclinical work lends the opportunity to thoroughly investigate underlying genetic, molecular, neurochemical, and biobehavioral pathways to further elucidate our understanding of differential responses to nicotine between women and men, but preclinical studies often do not take sex into consideration. Human studies have made some progress in studying sex-specific differences in neurochemical pathways associated with smoking. New neuroimaging technology is promising and has helped identify sex differences related to $\beta 2$ -nAChR availability and dynamic changes in dopamine release in response to smoking [25,26]. However, the disparity in treatment outcomes remains, with men more likely to remain abstinent over time [5,27].

Converging lines of preclinical and clinical evidence suggest that gender-specific mechanisms underlying nicotine dependence and tobacco smoking addiction may extend beyond the nAChR and DA-ergic systems. The corticotropin-releasing factor (CRF), hypothalamic-pituitary-adrenal (HPA) axis, and noradrenergic systems are promising brain targets that may modulate sex differences in nicotine-motivated behavior. During nicotine withdrawal, female rodents demonstrate greater levels of anxiety-like behavior, higher plasma corticosterone, and larger increases in stress-associated gene expression in the NAc compared to their male counterparts [28–30]. Recent evidence also suggests that noradrenergic targets for nicotine dependence result in differential outcomes and attenuate stress reactivity in women and nicotine-related reinforcement in men [24]. Pharmacologic activation of the noradrenergic system increases stress-induced responding for nicotine to a

greater degree in female than in male rodents [32]. Guanfacine, an α_2 -adrenergic agonist that reduces noradrenergic activity, preferentially decreases smoking lapse, tobacco craving, and smoking self-administration following stress in women compared to men [33]. Thus, nicotine may act on the CRF, HPA, and noradrenergic systems in a sexually dimorphic manner during nicotine exposure and withdrawal. Future work is needed to elucidate the role of brain stress pathways on gender-specific mechanisms underlying nicotine dependence.

Prior work has shown that women are more likely than men to smoke to reduce negative affect and stress [34]. Women anticipate greater negative affect associated with quitting smoking and are more likely to relapse following a stressful event (for review see Verplaetse et al. [24]). Acute and chronic stress exposure impairs PFC function in humans [35], and reduced PFC function may be one mechanism by which stress induces smoking relapse [36], particularly in women. In brief, acute stress causes a cascade of effects in the brain that results in weakened PFC connectivity related to working memory and behavioral inhibition. Either too little or too high levels of norepinephrine and DA release within the PFC may impair cognitive function [35]. Thus, stress-induced impairment of the PFC and associated alterations in DA signaling may dysregulate the ability of smokers to respond appropriately to negative affect and stressful events, thereby increasing the likelihood of smoking to manage these symptoms.

Studies examining sex-specific differences in the nAChR and DA-ergic systems of adolescents in response to nicotine are lacking. In rodents, brief exposure to nicotine during adolescence robustly upregulates β_2 -nAChRs but sex differences were inconsistent across brain regions [37]. Others have demonstrated a more persistent upregulation of nAChRs in male rodents than in female rodents in response to adolescent nicotine exposure [38]. Future work should examine whether adolescent males and females display similar sex differences in β_2 -nAChR availability as adults in response to nicotine. This has important clinical implications since initiation of tobacco smoking typically occurs in adolescence.

Summary

Emerging evidence suggests that sex differences within the nAChR and DA-ergic neural systems may mediate nicotine addiction. Findings of sex-differences in β_2 -nAChR and D2R availability via imaging provide mechanistic support for the behavioral findings that men are more likely to smoke for the positive reinforcing effects of nicotine and that women are more likely to smoke for negative affect regulation and are less responsive to NRT than men. While the midbrain and ventral striatum are key brain regions involved in sex-related differences of DA D2R availability and DA release, we propose that these findings may extend to the PFC. The PFC is a critical component in the stress pathway and recent evidence suggesting that sex may mediate the effect of brain stress systems on nicotine-motivated behavior highlights a way forward. We propose that significant effort should be made to develop gender-sensitive treatments for smoking cessation. In particular, these efforts should target the brain's stress pathways. In sum, this review highlights the critical need for future translational studies to examine sex-differences in neural systems that mediate nicotine addiction and to translate findings to the human brain to better inform treatment strategies.

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Figure 1.

Study outcomes by brain region in female smokers (*left*) and male smokers (*right*). Outcomes are relative to 'normal' same sex control groups except where noted. The mesolimbic DA circuitry originates in the VTA in the midbrain, and projects to the striatum and the PFC. 1. Female smokers have higher levels of D2 receptors in the midbrain than both female non-smokers and male smokers [19]. 2. Because the DA neurons originating in the midbrain are inhibitory, higher midbrain D2R availability in female smokers may inhibit DA release in the VS [20]. This may mitigate a downregulation of D2 receptors in this region [18]. 3. We hypothesize that female smokers will have lower drug-induced DA release in the PFC compared to female non-smokers and male smokers, and that female smokers will not evidence the same degree of downregulation in DA D2Rs in the PFC compared to male smokers. 4. Male smokers have similar midbrain D2R levels compared to male non-smokers. 5. Male smokers have an 'activated' VS, which is the hub of DA release and mediates the reinforcing properties of nicotine [20]. Repeated DA release in the striatum may lead to the downregulation of striatal DA D2Rs [17]. 6. We hypothesize that these findings in the VS of male smokers will also similarly extend to the PFC. Abbreviations; dopamine (DA), ventral tegmental area (VTA), ventral striatum (VS), prefrontal cortex (PFC), dorsolateral prefrontal cortex (dIPFC), dopamine D2 receptor (D2R).

Table 1.

Summary of outcomes

Study	Population	Region	Dopamine		Preclinical		Nicotinic	
			Male	Female	Male	Female	Male	Female
Carcoba et al., 2017	Rat	Nucleus Accumbens	Nicotine withdrawal: ↓ DA in NAc	Nicotine withdrawal: larger ↓ DA in NAc in females vs. males				
Mochizuki et al., 1998	Mouse	Cerebellum, Striatum, Frontal Cortex, Thalamus, Superior Colliculi					Nicotine-induced ↑ (upregulation) of nAChR in males vs. females	
Koylu et al., 1997	Rat	Whole Brain Minus Cerebellum					Chronic nicotine ↑ (upregulation) nAChR densities in males	
Clinical								
Okita et al., 2016	Human	Midbrain		↑ midbrain D2 receptor availability in female smokers vs. non-smokers			No difference in midbrain D2 receptor availability in male smokers vs. non-smokers	
Cosgrove et al., 2014	Human	Ventral Striatum and Dorsal Putamen	Male smokers activate DA rapidly in the ventral striatum; women do not	Women respond faster in a discrete subregion of dorsal putamen				
Brown et al., 2012	Human	Caudate and Putamen	↓ DA D2/D3 receptor availability in male smokers vs. male non-smokers and female smokers	Female smokers did not differ from female non-smokers in DA D2/D3 receptor availability				
Cosgrove et al., 2012	Human	Striatum, Cortex and Cerebellum					↑ B2* nAChR availability in male smokers in striatum, cortex, cerebellum compared to male non-smokers	

Note. dopamine (DA), nucleus accumbens (NAc), nicotinic acetylcholine receptor (nAChR).