



Invited review

A mechanistic hypothesis of the factors that enhance vulnerability to nicotine use in females



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ABSTRACT

Women are particularly more vulnerable to tobacco use than men. This review proposes a unifying hypothesis that females experience greater rewarding effects of nicotine and more intense stress produced by withdrawal than males. We also provide a neural framework whereby estrogen promotes greater rewarding effects of nicotine in females via enhanced dopamine release in the nucleus accumbens (NAcc). During withdrawal, we suggest that corticotropin-releasing factor (CRF) stress systems are sensitized and promote a greater suppression of dopamine release in the NAcc of females versus males. Taken together, females display enhanced nicotine reward via estrogen and amplified effects of withdrawal via stress systems. Although this framework focuses on sex differences in adult rats, it is also applied to adolescent females who display enhanced rewarding effects of nicotine, but reduced effects of withdrawal from this drug. Since females experience strong rewarding effects of nicotine, a clinical implication of our hypothesis is that specific strategies to prevent smoking initiation among females are critical. Also, anxiolytic medications may be more effective in females that experience intense stress during withdrawal. Furthermore, medications that target withdrawal should not be applied in a unilateral manner across age and sex, given that nicotine withdrawal is lower during adolescence. This review highlights key factors that promote nicotine use in females, and future studies on sex-dependent interactions of stress and reward systems are needed to test our mechanistic hypotheses. Future studies in this area will have important translational value toward reducing health disparities produced by nicotine use in females.

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1. Introduction

Tobacco use is the number one cause of preventable deaths in the United States (Center for Disease Control and Prevention, 2011). Epidemiological studies have provided important advances with regard to which populations are especially vulnerable to tobacco use. However, very little is known about the factors that lead to higher rates of tobacco use in these vulnerable populations.

The overarching goal of our laboratory is to understand the factors that contribute to tobacco use among vulnerable populations. Five years ago, we described a psychobiological hypothesis of adolescent nicotine use for the 35th anniversary of NIDA issue of this journal (O'Dell, 2009). Our hypothesis was that nicotine use in

adolescence is driven by strong rewarding effects of nicotine that are inadequately balanced by the negative effects of withdrawal from this drug. This hypothesis was derived largely from rodent studies showing that the rewarding effects of nicotine are higher, whereas the aversive effects of withdrawal are lower in adolescent versus adult rats. Subsequent studies in our laboratory revealed that age differences produced by nicotine withdrawal are mediated via dopaminergic mechanisms in the mesocorticolimbic pathway (Natividad et al., 2010, 2012). This review reflects an extension of our adolescent work to a new hypothesis that describes the interaction of biological systems, including dopamine, that are believed to contribute to nicotine use in females.

Our working hypothesis is that nicotine use in females is driven by stronger positive effects of nicotine and more intense stress produced by withdrawal from this drug as compared to males. This hypothesis was derived from pre-clinical studies showing that the rewarding effects of nicotine are enhanced in female versus male rodents (see Carroll et al., 2009; Perkins et al., 1999; Pogun and Yararbas, 2009). Also, the short-term aversive effects of nicotine

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are lower in female versus male rats (Torres et al., 2009). The overall result is that females may seek nicotine because of strong positive effects that are unopposed by short-term aversive effects. We recently observed that nicotine withdrawal produces more intense anxiety-like behavior and stronger biological responses within stress systems in females as compared to males. Thus, females may also seek nicotine because of intense negative affective states that emerge during withdrawal that promote relapse behavior compared to males.

This review also includes a mechanistic hypothesis that describes enhanced nicotine use among females in the context of hormone and stress regulation of mesocorticolimbic dopamine systems. Our hypothesis is that physiological substrates implicated in the rewarding effects of nicotine (dopamine) as well as those that are recruited during withdrawal from this drug (stress systems) promote nicotine use to a greater extent in females than males. Specifically, the enhanced drive to use nicotine in females is mediated, at least in part, by estrogen that facilitates dopamine release in terminal regions of the mesocorticolimbic pathway. During withdrawal, the drive to use nicotine is intensified by the emergence of stress that is stronger in females than males.

Lastly, this review considers the clinical implications of our hypothesis describing nicotine use in females. First, the finding that females experience strong rewarding effects of nicotine suggests that strategies to *prevent* smoking initiation in females are critical. Second, following chronic nicotine use, females display intense stress during nicotine withdrawal that likely promotes relapse behavior during abstinence. Thus, cessation medications that alleviate stress produced by nicotine withdrawal may be more effective in females versus males. Third, recent studies in our laboratory have shown that nicotine withdrawal is lower in adolescent versus adult females. Thus, medications that target withdrawal should not be applied in a unilateral manner across age and sex.

2. Clinical research

It is widely accepted that the motivational properties of tobacco are due, in large part, to the presence of nicotine (see Benowitz, 2010; Picciotto and Kenny, 2013). Nicotine use is motivated by the positive effects of this drug and avoiding negative affective states induced by withdrawal from long-term exposure to nicotine. We hypothesize that in females, strong positive effects of nicotine fuel this balance to a greater extent than males. In addition, we postulate that females experience more intense negative affective states during nicotine withdrawal than males. Thus, nicotine use in females is motivated by the avoidance of intense withdrawal states that promote relapse behavior during abstinence. Below clinical evidence is provided that supports our hypothesis regarding enhanced vulnerability to nicotine use in females.

2.1. Enhanced rewarding effects of nicotine in females

Clinical studies suggest that women are more sensitive to the rewarding effects of nicotine than men (see Greenfield et al., 2010; Mendelsohn, 2011; Perkins, 2009; Pogun and Yazarbas, 2009; Van Voorhees et al., 2012). Women consume more tobacco products and have a harder time quitting smoking than males (Perkins et al., 1999; Zilberman et al., 2003). Moreover, self-reports of positive mood effects following cigarette use are higher in women relative to men smokers (Perkins et al., 2006). In addition, women that use tobacco regularly display higher rates of responding for smoking-related cues than men (Perkins et al., 1999, 2001).

Epidemiological studies have shown that young females are especially vulnerable to nicotine use. Adolescent females are more likely to initiate smoking and are less likely to quit than adolescent

males (Anderson and Burns, 2000; James-Walke et al., 2007; Perkins, 2001). External factors also appear to contribute to nicotine use in adolescent females, including appetite suppression and a desire to project a more appealing self-image (Seguire and Chalmers, 2000). The recent rise in smoking initiation among female teenagers is believed to explain the slower decline in smoking prevalence rates in women relative to men, a phenomenon that has been referred to as the *telescoping effect* (Zilberman et al., 2003). In summary, these studies suggest that nicotine is more reinforcing in females relative to males regardless of age.

2.2. Enhanced aversive effects of nicotine withdrawal in females

Clinical studies have shown that women are also more sensitive to the aversive effects of nicotine withdrawal. For example, women exhibit lower rates of quitting and are less likely to benefit from tobacco cessation therapies than men (Cepeda-Benito et al., 2004; Cropsey et al., 2008; Hammond, 2009; Perkins, 2001; Perkins and Scott, 2008; Piper et al., 2010; Schnoll et al., 2007). During smoking abstinence, women report greater levels of anxiety, depression, and stress than men (Perkins and Scott, 2008; Schnoll et al., 2007; Xu et al., 2008). Women also report less relief from negative affective states with nicotine replacement therapy than men (Perkins, 2001). During abstinence from smoking, women also display higher levels of cortisol (a biological marker of stress in humans) as compared to men (Hogle and Curtin, 2006). Lastly, women report more often than men that the anxiety-reducing effects of cigarettes are the main reason for continued smoking and relapse (Perkins and Scott, 2008; Perkins et al., 2012, 2013; Piper et al., 2010). Adolescent females also report higher levels of stress and depression during nicotine abstinence as compared adolescent males (Colby et al., 2000; Nichter et al., 1997). Taken together, these studies suggest that intense stress experienced during nicotine withdrawal may be a significant factor contributing to relapse behavior in females.

On a related note, much work has illustrated that women use nicotine to cope with anxiety to a larger extent than men (Perkins, 2009; Perkins et al., 2012; Piper et al., 2010). In fact, nicotine has been shown to decrease anxiety elicited by a moderate stressor in women (File et al., 2001). Interestingly, the latter report demonstrated that nicotine administration increased anxiety following presentation of the moderate stressor in men. There is also evidence that pre-existing stress disorders lead to nicotine use in females. For example, there is a stronger co-morbid association between anxiety disorders and smoking rates in women than men (Mykletun et al., 2008). In addition, women with a prior history of an anxiety disorder are more likely to develop nicotine dependence later in life than men (Brook et al., 2012). These studies suggest that stress may be a more critical factor contributing to nicotine use and relapse in females as compared to males.

2.3. Other factors that contribute to nicotine use in females

There are a variety of external factors that may also contribute to nicotine use in females. For example, social factors such as having a friend who smokes contributes to smoking initiation in women (Holahan et al., 2012). Hunger suppression and weight control have also been shown to play an important role in smoking initiation among women. In fact, women consider nicotine use as a tool to control appetite and weight gain more than men (French et al., 1995; Meyers et al., 1997; Mendelsohn, 2011; Torchalla et al., 2012). This is consistent with the finding that adolescent females with a stronger desire to be thin are more likely to use nicotine later in life (Austin and Gortmaker, 2001). Lastly, one might argue that nicotine use is higher in females than males given that the

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