Sex Differences and the Role of Ovarian Hormones in Modulating the Behavioral Effects of Nicotine in Rodent Models

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Overview

Sex differences are pronounced in tobacco use, with females displaying higher rates of smoking and greater susceptibility to the negative health consequences associated with long-term tobacco use (Lombardi et al., 2011; Park et al., 2016). Women are also less likely to quit smoking, and cessation medications appear to be less effective in women than men (McKee et al., 2016; Smith et al., 2016). Unfortunately, our understanding of the factors that promote tobacco use in females is lacking. Thus, more research is needed to provide information that will help reduce health disparities between women and men. Additional work in this area will also help researchers respond to the recent mandate from national funding agencies to address sex differences in various public health problems, such as substance abuse. This chapter summarizes existing preclinical work in rodents examining sex differences and the role of ovarian hormones in modulating the behavioral effects of nicotine, the major addictive compound in tobacco products. We also consider the unique challenges of studying nicotine use in female rats and present new data examining the effects of nicotine on the estrous cycle.

Behavioral Effects of Nicotine in Rodent Models

The most frequently used rodent models for assessing the rewarding effects of nicotine involve operant responding for intravenous self-administration (IVSA) or an increase in time spent in an environment paired previously with nicotine in conditioned place preference (CPP) procedures. IVSA involves operant learning, in which the reinforcing properties of a drug are assessed based on its ability to increase a behavioral response. CPP involves classical conditioning, in which the drug serves as the unconditioned stimulus and the environmental context serves as the conditioned stimulus. During conditioning, the animals are administered nicotine and are then confined to a compartment with distinct environmental cues. On intervening days, the rats are given vehicle and confined to the alternate compartment. After conditioning, rats are allowed to explore both compartments in a drug free state. CPP is operationally defined as an increase in time spent in the drug-paired side versus the neutral location.

During abstinence from chronic nicotine exposure, a withdrawal syndrome emerges in rodents that includes physical signs and negative affective states. A common method for inducing nicotine dependence in rodents involves surgical implantation of osmotic pumps that deliver nicotine for at least 5–7 days. Nicotine withdrawal has been studied following the removal of the nicotine pump (spontaneous withdrawal) or administration of a nicotinic receptor antagonist (precipitated withdrawal). A common behavioral model to study negative affective states produced by withdrawal involves avoidance of a chamber paired previously with nicotine withdrawal in conditioned place aversion (CPA) procedures. An array of measures can be used to assess anxiety-like behavior produced by withdrawal. These include an increase in time spent in the closed arms of an elevated plus maze or the dark side of the light/dark transfer apparatus.

The sections below describe sex differences and the role of ovarian hormones in modulating nicotine reward and withdrawal. The chapter is organized following a prescribed approach that first assesses whether sex differences exist (Becker et al., 2005). If differences exist between female and male rats, then the role of ovarian hormones can be assessed in ovariectomized (OVX) female rodents. If ovarian hormones appear to modulate a particular effect, then subsequent studies might examine the effects of hormone replacement in OVX rats and/or examine whether behavioral effects fluctuate across the estrous cycle.

Sex differences

Differences between female and male rodents result from a complex interplay of biological and developmental factors. The results from studies of sex differences in nicotine IVSA are mixed, with some reports showing greater nicotine intake in females and other reports showing greater intake in males. To more clearly understand the nature of sex differences in nicotine IVSA, we recently conducted a meta-analysis that combined effect-size values from studies that compared nicotine IVSA in female and male rats under various experimental conditions (Flores et al., 2017). Overall, the analysis revealed that female rats display greater nicotine IVSA than males. A subsequent moderator-variable analysis also revealed that female rats also display greater nicotine intake in procedures involving extended access to IVSA, a cue light that signals nicotine delivery, and higher reinforcement requirements for nicotine administration. This finding suggests that certain experimental parameters can influence the magnitude of sex differences in nicotine IVSA. Consistent with findings from IVSA studies, females also display more robust CPP produced by nicotine compared with male rats (Torres et al., 2009) and mice (Kota et al., 2007, 2008).

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With regard to nicotine withdrawal, females display greater CPA produced by nicotine withdrawal compared with male rats (Torres et al., 2009) and mice (Kota et al., 2007, 2008). Subsequent work has revealed that female rats display larger increases in anxiety-like behavior, corticosterone levels, and changes in the expression of stress-associated genes in the brain as compared with males (Torres et al., 2013). Consistent with work from other laboratories, female rats display greater increases in plasma corticosterone levels during nicotine withdrawal than males (Gentile et al., 2011; Skwara et al., 2012). Together, these studies suggest that both the rewarding effects of nicotine and the aversive effects of withdrawal are greater in female versus male rodents. These findings provided the foundation for our hypothesis that greater sensitivity to nicotine reward and withdrawal contributes to enhanced vulnerability to nicotine use in females (O'Dell and Torres, 2014).

Studies comparing sex differences in nicotine reward and withdrawal involve unique challenges. In procedures involving extended access to nicotine IVSA, we have noted that catheter patency is generally longer in male versus female rats. This may be related to greater tissue growth that envelops the catheter entry port into the jugular vein, which likely produces greater insulation of the catheter in males. Also, female rats are smaller, with thinner skin, and these characteristics appear to contribute to more abrasions and greater shifting of the catheter port on the ventral surface of female rats. The latter effects may also be related to the fact that nicotine produces a greater suppression of body weight in female versus male rats (Grunberg et al., 1985). We have also noticed that a greater percentage of female rats self-administer high doses of nicotine, sometimes to the point of death. Female rats may be less sensitive to the aversive effects of nicotine, a hypothesis that is consistent with the finding that high doses of nicotine produce less CPA in female versus male rats (Torres et al., 2009). A final point to consider is that nicotine administration increases locomotor behavior to a larger extent in female than male rats, an effect that has been observed across different strains (Faraday et al., 2003). Thus, strong stimulant effects have the potential to alter behavioral assessments of sex differences in nicotine IVSA in rats.

Ovarian hormones

The role of ovarian hormones in modulating the behavioral effects of nicotine has been assessed following ovariectomy procedures that remove the major source of ovarian hormones. Previous studies have revealed that OVX rats display a reduction in nicotine IVSA (Flores et al., 2016) and CPP (Torres et al., 2009) as compared with intact females. Also, estradiol replacement in OVX rats returned nicotine IVSA to intact-female levels (Flores et al., 2016). Estradiol appears to have intrinsic rewarding properties, as this hormone produced CPP in OVX rats (Frye and Rhodes, 2006), and conversely, administration of an estrogen receptor antagonist inhibited the formation of CPP produced by estradiol in OVX rats (Walf et al., 2007).

With regard to withdrawal, previous work has shown that OVX female rats display less anxiety-like behavior produced by nicotine withdrawal as compared with intact females (Torres et al., 2015). This report also showed that the expression of stress-associated genes was reduced in the brains of OVX versus intact females. OVX female rats also displayed a reduction in dopamine and estradiol receptor gene expression, suggesting that estradiol regulates gene expression in female rats. To our knowledge, the role of progesterone in modulating nicotine reward and withdrawal has not been examined in OVX rodents.

There are several issues to consider when employing ovariectomy procedures. First, ovariectomy can be done either early in development to study the organizational effects of hormones or following puberty to examine the activational effects in a developed rodent. This presents a challenge because there is no clear agreement about how early to perform the ovariectomy to study the organizational effects of ovarian hormones. The onset of puberty has also been shown to be species dependent (Gillies and McArthur, 2010; Sengupta, 2011). Another challenge in ovariectomy studies is that hormone replacement procedures vary with regard to doses and the frequency of the injection procedure. Some studies administer estradiol in a 2 day on, 2 day off procedure that mimics the two peak increases in estradiol that occur across the estrous cycle. Progesterone is typically administered via injections or silastic implants that attempt to mimic reduced peak changes and the steady rise in this hormone across the estrous cycle.

Estrous cycle

The estrous cycle in rodents is categorized into the luteal and follicular phases. The luteal phase is characterized by a gradual rise in progesterone and decreasing levels of estradiol. During the follicular phase, estradiol levels peak, and progesterone levels slowly increase, leading to ovulation. The luteal phase can be subdivided into metestrus and diestrus, and the follicular phase comprises proestrus and

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estrus. The fluctuations in ovarian hormones change the cellular cytology of the vaginal wall in a manner that allows researchers to identify particular phases of the estrous cycle in female rodents using vaginal lavage procedures.

With regard to the rewarding effects of nicotine, an early report revealed that female rats displayed high levels of nicotine IVSA that did not fluctuate across the estrous cycle (Donny et al., 2000). Consistent with this, a subsequent report revealed that the magnitude of CPP produced by nicotine was similar in rats that were tested during different phases of the estrous cycle (Torres et al., 2009). Both studies used lavage procedures. However, another report revealed that adolescent female rats displayed high levels of nicotine intake that were negatively associated with progesterone levels but positively associated with the ratio of estradiol to progesterone (Lynch, 2009). This latter finding suggests that plasma levels of estradiol and progesterone may influence nicotine reward in a manner that may not be evident in studies utilizing vaginal lavage procedures. To our knowledge, no studies have compared nicotine withdrawal in female rats during different phases of the estrous cycle.

When using vaginal lavage procedures, several factors should be considered. First, a previous report found that repeated lavage can induce a pseudo-pregnancy involving constant diestrus (Goldman et al., 2007). Thus, repeated lavage may alter the vaginal cytology in a manner that makes it difficult to assess whether behavioral effects fluctuate across the estrous cycle. Second, the classification of estrous cycles based on cellular cytology is subjective, and there is overlap in the cell cytology across stages. Third, nicotine exposure possibly alters the estrous cycle in female rats. To address the third issue, the following section examines whether nicotine alters the estrous cycle in freely cycling female rats.

Does nicotine exposure alter the estrous cycle?

We conducted repeated vaginal lavage procedures in 54 intact-female adult Wistar rats. The cytology was classified into one of four phases of the estrous cycle. Briefly, a sterile plastic pipette was filled with 0.9% saline to collect epithelial cells, which were then transferred to a glass microscope slide. The cells were then fixed with methylene blue stain and viewed under a microscope to examine their shape. Each phase was classified using the following criteria: proestrus (presence of round nucleated epithelial cells), estrus (presence of cornified, nonnucleated epithelial cells), metestrus (limited presence of epithelium cell and leukocytes), and diestrus (presence of leukocytes) (Cora et al., 2015). The lavage procedures were conducted for 8 days before and after implantation of an osmotic pump that delivered nicotine (3.2 mg/kg/day; expressed as base). The rats were pair-housed in a colony room that was kept on a 12 hour reverse light/dark cycle with lights off at 8:00 A.M. The lavage procedures were conducted every 24 hours at approximately 9:00 A.M.

First, we assessed the effects of nicotine on the estrous cycle by computing the frequency at which each stage was sampled before and then during nicotine exposure. The resulting pie chart (Fig. 1) displays the percentage of times the rats were sampled during each phase of the estrous cycle. During the luteal phase, the rats were sampled less frequently in metestrus pre-nicotine (31%) than during nicotine exposure (37%). Also, the rats were sampled less frequently in the diestrus phase pre-nicotine (25%) than during nicotine exposure (27%). The increase in sampling frequency within the luteal phase during nicotine exposure resulted in a concomitant reduction in the follicular phase. Specifically, the rats were sampled more frequently in estrus pre-nicotine (32%) than during nicotine exposure (25%). Also, there was a small decrease in sampling frequency in diestrus pre-nicotine (12%) compared with during nicotine exposure (11%). These results suggest that nicotine exposure produced a lengthening of the luteal phase and a concomitant decrease in the follicular phase.

To better understand how nicotine altered the estrous cycle, we conducted an analysis that quantified the transitions between each individual phase of the estrous cycle. The results of this analysis are depicted in the heat map shown in Figure 2. Our assessment of the heat map revealed that nicotine exposure produced an increase in transitions in the luteal phase and a decrease in transitions in the follicular phase. To assess whether the latter observations reached statistical significance, we compared the average number of transitions pre-nicotine versus during nicotine exposure ($p \leq 0.05$). We observed a significant increase in transitions from metestrus ~ metestrus and from metestrus ~ diestrus. We also noted a decrease in transitions from estrus ~ estrus. Altogether, our results imply that nicotine extended the luteal phase, as evidenced by an increase in the number of transitions in this phase. We also observed a concomitant shortening of the follicular phase that appears to be caused by a decrease in transitions during nicotine exposure. In general, we observed a greater number of changes in transitions in the luteal phase (significant changes in two green cells) as compared

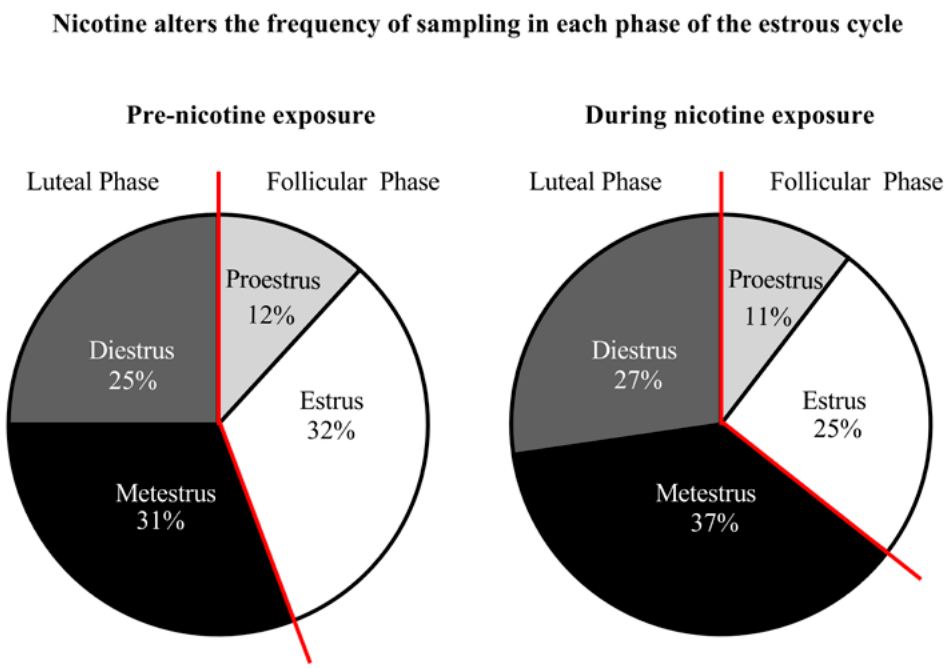

Figure 1. Pie charts denoting the frequency of sampling in each phase of the estrous cycle. During the luteal phase, the rats were sampled less frequently in metestrus pre-nicotine than during nicotine exposure. The rats were sampled less frequently in the diestrus phase pre-nicotine than during nicotine exposure. The increase in sampling frequency within the luteal phase during nicotine exposure resulted in a reduction in the follicular phase. These results suggest that nicotine exposure lengthened the luteal phase and concomitantly decreased the follicular phase.

with the follicular phase (significant change in one red cell). This might have been expected given that the rats were sampled once every 24 hours, and one might expect a higher incidence of transitions in the longer luteal phase (metestrus ~21 hours; diestrus ~57 hours) relative to the shorter follicular phase (proestrus ~12 hours; estrus ~12 hours). These time estimates are based on a publication using lavage procedures in female Wistar rats (Paccola et al., 2013).

In conclusion, it appears that nicotine exposure might have expanded the luteal phase and shortened the follicular phase of the estrous cycle. One possible explanation is that the antiestrogenic effects of nicotine blunt peak increases in ovarian hormones. If so, this would result in a cytology phenotype that reflects a shortened follicular phase and a longer luteal phase during which hormone levels are relatively lower. Consistent with these findings, clinical reports have shown that heavy smokers display a shorter follicular phase as compared with nonsmokers (Windham et al., 1999). Our hypothesis that nicotine lowers hormone levels is also consistent with the finding that women who smoke display increased breakdown of estradiol (Michnovicz et al., 1986) and excrete less estradiol during the luteal phase, suggesting a decrease in estrogen production (MacMahon et al., 1982). Moreover, epidemiological reports suggest that women who smoke are relatively estrogen deficient and reach menopause at an earlier age compared with female nonsmokers (Midgette and Baron, 1990). The limited literature on the effects of nicotine on the estrous cycle have yielded mixed results, with one study showing that nicotine does not alter the sampling frequency across the estrous cycle (Halder et al., 2015) and another study showing that nicotine increases sampling frequency in estrus (Wenning et al., 2017). Future studies are needed to more clearly resolve the influence of nicotine on the estrous cycle.

Neural circuitry

Preclinical studies have shown that the neural circuitry that governs the behavioral effects of nicotine is mediated largely by dopamine in the mesocorticolimbic pathway, which originates in the ventral tegmental area (VTA) and terminates in several forebrain structures, including the nucleus accumbens (NAc) (Dani et al., 2011; Pistillo et al., 2015). Following nicotine administration, dopamine levels in the NAc are increased, and during nicotine withdrawal, dopamine levels in this region are decreased. NAc dopamine release from VTA projections is regulated by a balance

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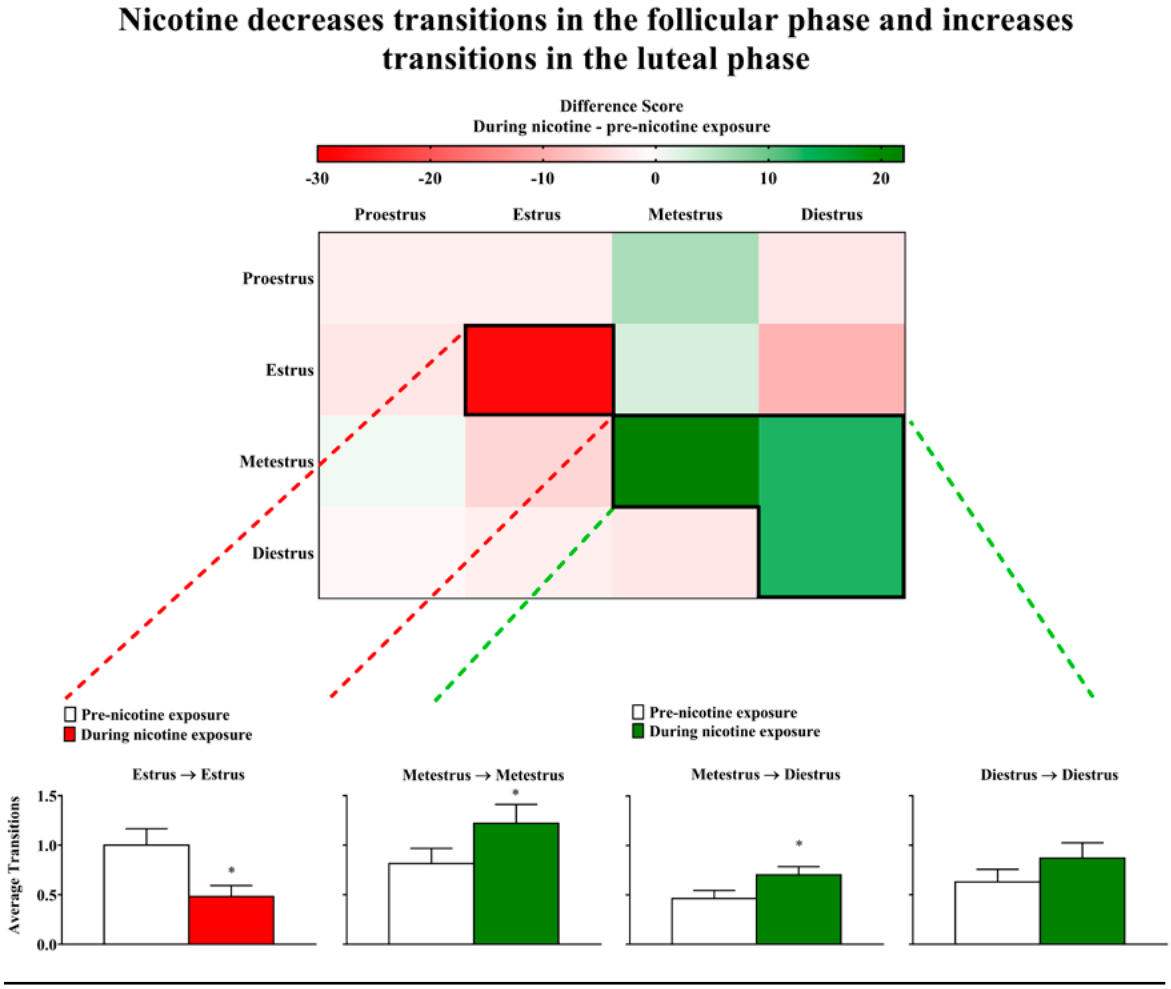

Figure 2. Heat map showing the frequency of transitions from each phase of the estrous cycle (vertical axis) to the other phases of the cycle (horizontal axis). To illustrate changes in the number of transitions produced by nicotine exposure, a difference score was calculated by subtracting the frequency of transitions during nicotine exposure from pre-nicotine values. The green shade reflects an increase, and the red shade denotes a decrease in the frequency of transitions produced by nicotine exposure. White boxes denote a lack of change in transitions following nicotine exposure. A greater number of changes in transitions were observed in the luteal phase (significant changes in 2 green cells) than in the follicular phase (significant change in 1 red cell).

between excitatory and inhibitory inputs on VTA dopamine neurons. To our knowledge, nicotine-induced dopamine release in the NAc has not been directly compared in female and male rodents. Work in our laboratory has shown that, during nicotine withdrawal, the decrease in dopamine release in the NAc is larger in female than in male rats (Carcoba et al., 2017). This large decrease in dopamine appears to be caused by greater GABAergic inhibition of dopamine release in the NAc of female versus male rats. The notion that the NAc modulates sex differences produced by nicotine withdrawal is consistent with the finding that nicotine withdrawal produces a larger upregulation of stress-associated genes in the NAc of female versus male rats, an effect that was not observed in the amygdala or hypothalamus (Torres et al., 2013). A subsequent report found that the upregulation of stress-associated genes in the NAc is blunted in female rats lacking ovarian hormones (Torres et al., 2015). These studies suggest that the NAc plays a key role in modulating sex differences in nicotine withdrawal.

In addition, a growing body of literature suggests that the aversive effects of nicotine withdrawal are also modulated via the habenula-interpeduncular nucleus (Hb-IPN) pathway (Dani and De Biasi 2013; Fowler and Kenny, 2014; Molas et al., 2017). In our assessment of this literature, studies that have examined the role of the Hb-IPN pathway in the behavioral effects of nicotine have used male rodents. Thus, future studies are needed to better understand how different brain pathways (e.g., mesocorticolimbic and Hb-IPN) modulate sex differences in the behavioral effects of nicotine.

Stimulant drugs other than nicotine

Previous studies using drugs of abuse other than nicotine have found that female rats display greater cocaine-induced IVSA (Lynch and Caroll, 1999; Swalve et al., 2016) and CPP (Zakharova et al., 2009). Similarly, female rats display greater methamphetamine IVSA (Reichel et al., 2012) and CPP (Chen et al., 2003) than males. With regard to the contribution of ovarian hormones, previous studies have found that OVX females display a reduction in the rewarding effects of cocaine that returns to control levels following estradiol replacement (Lynch et al., 2001; Russo et al., 2003, 2008; Larson et al., 2007). Moreover, female rats also display higher levels of cocaine-induced reinstatement than do males (Kerstetter et al., 2008). Interestingly, the latter effect was more pronounced in female rats that were tested during estrus.

Conclusions and Remaining Questions

A novel finding presented here is that nicotine exposure lengthened the luteal phase and shortened the follicular phase of the estrous cycle. This conclusion is based on an increase in sampling frequency during metestrus and diestrus, and a decrease in sampling during estrus. Consistent with this pattern, previous studies in female rats have shown that repeated exposure to methamphetamine (Siato et al., 1995) or cocaine (King et al., 1990) increases sampling frequency in diestrus. Our pattern of changes is also consistent with studies showing that chronic alcohol exposure increases sampling frequency in metestrus and diestrus and decreases sampling in estrus (Sanchis et al., 1985). Together, these studies suggest that females display strong rewarding effects across a number of drugs of abuse and that proper estrous cyclicity is altered by chronic drug exposure.

In the present assessment of the literature, many questions remain to be addressed in order to better understand sex differences and the role of ovarian hormones in the behavioral effects of nicotine. Below we offer a few remaining questions that might be addressed in future studies using preclinical models:

- Do compounds other than nicotine in tobacco products promote the behavioral effects of nicotine in females?
- Are there sex differences in nicotine metabolism that promote the behavioral effects of nicotine?
- Are there sex differences in nicotine withdrawal? If so, are these effects ovarian-hormone dependent?

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