Winter January 1, 2015

Stress is a principal factor that promotes tobacco use in females

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Progress in Neuro-Psychopharmacology & Biological Psychiatry xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Stress is a principal factor that promotes tobacco use in females

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ARTICLE INFO

Available online xxxx

Keywords:
dependence
nicotine
sex differences
withdrawal
women

ABSTRACT

Tobacco use is a major economic and health problem. It is particularly concerning that women consume more tobacco products, have a more difficult time quitting smoking, and are less likely to benefit from smoking cessation therapy than men. As a result, women are at higher risk of developing tobacco-related diseases. Clinical evidence suggests that women are more susceptible to anxiety disorders, and are more likely to smoke in order to cope with stress than men. During smoking abstinence, women experience more intense anxiety than men and report that the anxiety-reducing effects of smoking are the main reason for their continued tobacco use and relapse. Consistent with this, pre-clinical studies using rodent models suggest that females display more intense stress during nicotine withdrawal than males. This review posits that in women, stress is a principal factor that promotes the initiation of tobacco use and relapse behavior during abstinence. Studies are reviewed at both the clinical and pre-clinical levels to provide support for our hypothesis that stress plays a central role in promoting tobacco use vulnerability in females. The clinical implications of this work are also considered with regard to treatment approaches and the need for more research to help reduce health disparities produced by tobacco use in women.

Contents

1. The problem of tobacco use

Tobacco use is the number one cause of preventable deaths in the US, as it claims the lives of over 400,000 individuals each year (Center for Disease Control [CDC], 2008, 2011). Long-term tobacco use leads to deleterious health consequences such as lung cancer, emphysema, and a variety of cardiovascular diseases (D'Alessandro et al., 2012; Hecht, 2012; Milara and Cortijo, 2012). In addition, the consumption of tobacco

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http://dx.doi.org/10.1016/j.pnpbp.2015.04.005
0278-5846/

products is reported to have a health-care cost of over 97 billion dollars per year (CDC, 2010). Given the magnitude of the problem, more research is needed to understand the underlying factors that promote tobacco use. (See Fig. 1.)

Several clinical reports have suggested that women are more susceptible to tobacco use than men (Pauly, 2008; Perkins and Scott, 2008; Perkins et al., 2012a, 2012b; Schnoll et al., 2007). For example, although the global incidence of smoking has declined, women consume more cigarettes relative to men (Hammond, 2009, Ng et al., 2014). Women also exhibit lower quit rates of smoking and are less likely to benefit from nicotine replacement therapy (NRT) than men (Cepeda-Benito et al., 2004; Perkins, 2001; Perkins and Scott, 2008; Piper et al., 2010). As a result, women who smoke are at a higher risk of developing tobacco-related diseases, including various types of cancer and chronic obstructive pulmonary disease (Dance, 2012; Kiyohara and Ohno, 2010; Langhammer et al., 2000, 2003). Despite this evidence, in 2010, the USDHHS reported that mortality rates associated with smoking-related diseases are similar across women and men in the US. There is also evidence suggesting that mortality rates are similar in women and men who smoke (Rostron et al., 2014; Thun et al., 2013). Although the problems associated with smoking in women are well recognized, there remains a critical knowledge gap regarding the factors that contribute to enhanced vulnerability to tobacco use in females.

Recent work in our laboratory has utilized rodent models to study the underlying factors that promote tobacco use in females. Based on this work, we presented a review suggesting that both the rewarding effects of nicotine and the aversive effects of withdrawal from this drug are enhanced in female versus male rodents (see O'Dell and Torres, 2014). In the latter review paper, we also presented a mechanistic hypothesis suggesting that both the rewarding effects of nicotine and the aversive effects of withdrawal are modulated via a complex interaction between CRF, dopamine, and inhibitory gamma-aminobutyric acid (GABA) systems. Specifically, we posited that during withdrawal, CRF promotes a decrease in dopamine via an increase in GABAergic inhibition in the nucleus accumbens (NAcc). Indeed, a recent report illustrated that, within the VTA, CRF systems modulate dopamine via GABA transmission during nicotine withdrawal (Grieder et al., 2014). In support of our hypothesis, we recently demonstrated that the stress-associated genes corticotropin releasing factor (CRF) and urocortin (UCN) are elevated in the NAcc of female rats experiencing nicotine withdrawal (Torres et al., 2015). This work has led us to an overarching hypothesis, presented here, that *stress is a central factor that promotes tobacco use in females.* There is also recent emerging clinical evidence suggesting that stress and negative affect mood states play an important role in modulating tobacco use in women (Panagiotakopoulosa and Neigh, 2014; Perkins et al., 2012a, 2012b; Weinberger and McKee, 2012). Thus, the present review focuses primarily on the importance of stress in promoting tobacco use in females.

Although the terms anxiety and stress are often used interchangeably, they can have different connotations. For the purposes of this review, the term anxiety is reserved to describe a negative psychological mood state in humans that is induced by an ongoing or anticipated aversive event. The term stress is used to describe a negative psychological state that is accompanied by a biological response elicited by changing environmental demands.

2. The neuroendocrine stress response

The stress response is largely modulated within the hypothalamic-pituitary-adrenal (HPA) axis (Sawchenko et al., 1993; Vale et al., 1981). CRF is secreted from the hypothalamus when high levels of stress are experienced. CRF is a 41-amino acid polypeptide that is primarily synthesized in the paraventricular nucleus (PVN) of the hypothalamus (Dunn and Berridge, 1990; Olschowka et al., 1982). The release of CRF stimulates adrenocorticotropic hormone (ACTH) release from the anterior pituitary gland (Semba et al., 2004). ACTH release stimulates the secretion of cortisol, a stress marker in humans, and other glucocorticoids from the adrenal cortex located above the kidneys (Semba et al., 2004). The release of cortisol by the adrenal cortex circulates in the bloodstream and serves as a major negative feedback signal for the HPA axis (Keller-Wood and Dallman, 1984). Although CRF in the hypothalamus plays a primary role in mediating the stress response, CRF is widely distributed throughout the brain (De Souza and Grigoriadis, 2002). For example, CRF is present in the neocortex, periaqueductal gray, olfactory bulb, hippocampus, pons, raphe nucleus, bed nucleus of the stria terminalis, and the shell of the NAcc (Hsu and Price, 2009; Palkovits et al., 1992; Sarnyai et al., 2001). In addition, CRF producing neurons and CRF receptors have been found in the substantia nigra, ventral tegmental area, medulla oblongata, central nucleus of the amygdala, and locus coeruleus (Caberlotto et al., 2004; Ungless et al., 2003, 2010).

3. Sex differences in baseline stress and anxiety levels

There is pre-clinical evidence showing that there are sex differences in HPA activation. For example, female rats display a more extended HPA activation following administration of a footshock stress than males (Heinsbroek et al., 1991). In addition, female rats display higher CRF neuronal activation in the PVN after restraint stress as compared to males (Babb et al., 2013). Previous reports have also proposed that there are sex differences within the molecular architecture of the CRF system. Specifically, the CRF receptor 1 subtype is internalized via beta-arrestin2 into the cell cytoplasm, which prevents CRF from binding to this receptor (Holmes et al., 2006). Bangasser et al. (2010) demonstrated that female rats display lower levels of beta-arrestin2 than males. Based on these findings, these authors have suggested that females are more responsive to CRF stimulation due to reduced internalization of the CRF-1 receptor than males (Bangasser and Valentino, 2012). Consistent with the notion that females display an enhanced stress response, Viau et al. (2005) showed that baseline levels of CRF mRNA are higher in the hypothalamus of female versus male rats. In addition, female rats display higher baseline plasma corticosterone levels than males (Babb et al., 2013). Taken together, these data suggest that females display a greater pre-disposition to elevated stress responses than males.

Consistent with pre-clinical studies, clinical studies have shown that women display a stronger pre-disposition to stress responses. For example, women report higher rates of depression and generalized anxiety disorders than men (Hankin and Abramson, 2001; McLaughlin et al., 2011; Pigott, 2003; Somers et al., 2006). Women are also at greater risk of developing long-term anxiety disorders following a traumatic event as compared to men (Kobayashi and Mellman, 2012; Seedat and Stein, 2000). It is also reported that women take more days off from work due to anxiety-related causes (CDC, 2004), and they are three times more likely to suffer from social anxiety than men (Bourke et al., 2012, Xu et al., 2008; Xu et al., 2012). Additionally, high levels of anxiety in adolescent females are correlated with a higher risk of developing depression and stress disorders later during adulthood, a relationship that has not been observed in adolescent males (Merikangas and Pine, 2002; Piccinelli and Wilkinson, 2000). It is important to note that there are some indices of anxiety that are more prevalent in men as compared to women. For example, chronic stress produces greater immune- and metabolic-associated health complications in men as compared to women (Kudielka and Kirschbaum, 2005; Penninx et al., 2003; Vogelzangs et al., 2012). Taken together, there is strong pre-clinical and clinical evidence to suggest that females have a greater pre-disposition to stress and anxiety than males.

4. Anxiety and tobacco use

Much work has shown that there is a strong link between anxiety and tobacco use. First, smoking is a common tool that is used to cope

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with anxiety (Park and Breland, 2007; Parrott and Murphy, 2012; Perkins et al., 2010; Slopen et al., 2012). Self-report studies have indicated that the main reason that people use tobacco is to reduce anxiety and induce a state of relaxation (Aronson et al., 2008; Fidler and West, 2009; McEwen et al., 2008). Furthermore, regular smokers report they do not quit because cigarettes help them cope with anxiety (Dupont et al., 2012; Perkins et al., 2012a, 2012b). A nation-wide survey also indicates that people primarily use cigarettes to manage their anxiety levels (American Psychological Association, 2012). College students also report smoking cigarettes to alleviate anxiety, but not to induce positive mood states such as happiness or satisfaction (Brown et al., 2011).

Second, research has shown that nicotine is the major habit forming compound in tobacco products (USDHHS, 2010). Long-term tobacco use produces dependence that is driven in large part by avoiding anxiety elicited by the removal of nicotine during abstinence (Aronson et al., 2008; Hughes and Callas, 2010; Perkins et al., 2010). The psychological effects elicited during smoking abstinence in humans include, but are not limited to, anxiety, depression, irritability, restlessness, and agitation (Parrott, 2004; Parrott and Zeichner, 2001; Pauly, 2008). The physical signs of dependence include nausea, headache, sleep disturbances, and hunger (Perkins et al., 2009, 2012a, 2012b). Studies designed to assess the motivation for relapse to smoking have identified the avoidance of anxiety as the primary reason for relapse behavior (Battista et al., 2008; Fidler and West, 2009; Lawrence et al., 2010). During smoking abstinence, a physiological stress response is also elicited, including an increase in blood cortisol levels (Hogle and Curtin, 2006; Steptoe and Ussher, 2006). Studies by Mendelson et al. (2005, 2008) have also shown that plasma cortisol levels increase 24 hours after smoking abstinence. The latter studies were conducted in a laboratory setting after smoking two or three cigarettes containing high levels of nicotine. These studies suggest that withdrawal from chronic tobacco use leads to an increase in anxiety and a biological stress response that may promote relapse to smoking.

5. Proposed model of stress and tobacco use in females

The diagram below depicts our proposed model of the contribution of stress to enhanced vulnerability to tobacco use in females. We postulate that anxiety plays a larger role in the initiation of tobacco use in females, and that a strong stress response during abstinence leads to relapse to a greater extent in females as compared to males. The color-coding reflects a larger relapse effect in women (pink) versus men (blue). First, our model posits that women may be more susceptible to initiate smoking behavior, because smoking is largely used to cope with anxiety in females. This may involve a pre-existing propensity to anxiety disorders or heredity factors, as reviewed below. Second, our model posits that stress produced by nicotine withdrawal is greater in females as compared to males. Because females experience a larger stress response during withdrawal, it is posited that they are more susceptible to relapse than males.

Below we present clinical and pre-clinical evidence to support our hypothesis that stress is a principal factor that promotes greater vulnerability to tobacco use in females. We consider the importance of stress in both the initiation and abstinence phases of tobacco use.

6. The role of stress in tobacco use initiation in females

There is evidence to suggest that a pre-existing anxiety disorder may promote tobacco use. For example, a survey conducted by Lasser et al. (2000) suggests that 55 percent of people meeting the criteria for an anxiety disorder are also regular smokers. Furthermore, people who are nicotine-dependent and are also diagnosed with an anxiety disorder consume more than 30 percent of all cigarettes in the US (Grant et al., 2004). These findings are consistent with other reports showing that the rate of anxiety disorders is higher in individuals who smoke as compared to non-smokers (Lawrance et al., 2005; McClave et al., 2009). With regard to women, clinical studies have suggested that females use nicotine to cope with anxiety to a larger extent than men (Perkins, 2009; Perkins et al., 2012a, 2012b; Piper et al., 2010). In fact, nicotine has been shown to decrease anxiety elicited by a moderate stressor in women; however, nicotine increased anxiety and negative mood states in men (File et al., 2001). Furthermore, compared to males, female college students report more often that they initiate tobacco use to relieve negative mood states (Morrell et al., 2010). These findings corroborate with previous work showing that women report more often than men that the anxiety-reducing effects of cigarettes are the main reason for smoking (Nichter et al., 1997; Perkins et al., 1999).

There is also strong evidence that pre-existing anxiety disorders lead to tobacco use more often in women than men. For example, a large population survey showed that there is a stronger co-morbid association between anxiety disorders and smoking rates in women as compared to men (Mykletun et al., 2008). In addition, Stewart et al. (1997) showed that women with hypersensitivity to stressful stimuli are more likely to engage in cigarette use to cope with anxiety as compared to males. In a more recent study, Brook et al. (2012) showed that women with prior history of an anxiety disorder are more likely to develop tobacco dependence later in life relative to men. Women with posttraumatic stress disorder (PTSD) are also more likely to use cigarettes and report

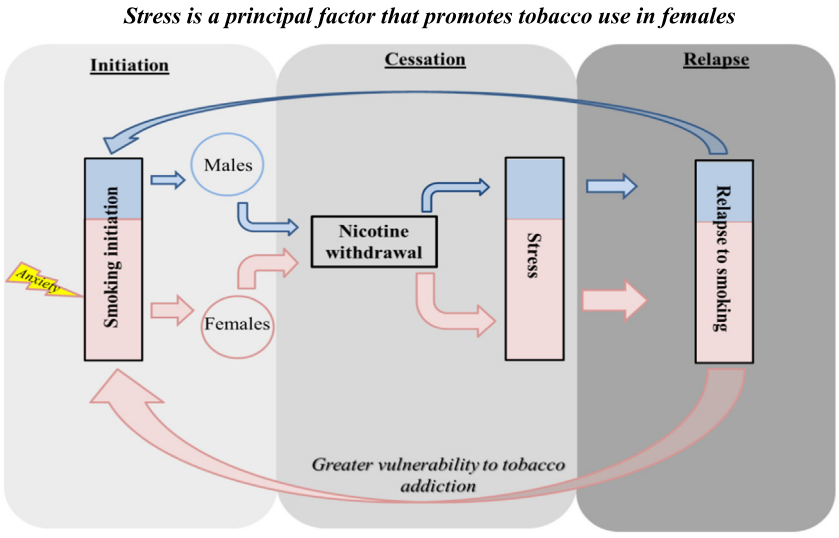

Fig. 1. Stress is a principal factor that promotes tobacco use in females.

Please cite this article as: Torres OV, O'Dell LE, Stress is a principal factor that promotes tobacco use in females, Prog Neuro-Psychopharmacol Biol Psychiatry (2015), http://dx.doi.org/10.1016/j.pnpbp.2015.04.005

relapse to smoking more often than men with PTSD (Weinberger et al., 2009). Interestingly, John et al. (2004) also found that women have a greater likelihood of developing an anxiety disorder after a year of smoking than men. Taken together, these studies suggest that there is a strong relationship between anxiety and smoking, especially among women who are most susceptible to tobacco abuse.

Pre-clinical studies have examined the effects of stress on the rewarding effects of nicotine in female and male rodents. For example, female mice display more anxiety-like behavior compared to their male counterparts following chronic oral nicotine intake (Caldarone et al., 2008). Female rats also display a larger increase in nicotine intake following a pharmacological stressor as compared to males (Li et al., 2014). The authors of the latter report suggested that females are more sensitive to the effects of stress on nicotine intake as compared to males. Consistent with this, a recent report showed that chronic administration of nicotine in combination with immobilization stress produced a larger suppression of feeding behavior and body weight in females as compared to males (Faraday et al., 2005). However, we acknowledge a report showing that female and male rats display similar levels of nicotine intake and stress-induced reinstatement of nicotine-seeking behavior (Feltenstein et al., 2011). Future studies are needed to examine whether females are more sensitive to the effects of stress on the rewarding effects of nicotine.

Pre-clinical studies have compared the biological stress response produced by nicotine exposure in male and female rodents. Studies comparing the biological response to stress have revealed that plasma corticosterone levels are increased to a greater extent in female versus male rats following repeated nicotine injections (Gentile et al., 2011; Moidel et al., 2006; Rhodes et al., 2001, 2004; Skwara et al., 2012) and continuous delivery (Faraday et al., 2005) of this drug. In an *in vitro* perfusion system, the presence of nicotine increased CRF and ACTH levels to a greater extent in hypothalamic tissue that was collected from female versus male rats (McKlveen et al., 2010; Moidel et al., 2006). Overall, these studies suggest that the behavioral and biological effects of nicotine on stress systems are greater in females as compared to males.

Another factor that is important to consider with regard to tobacco use initiation is the direct reinforcing effects of nicotine. Indeed, much work has shown that there is sex differences in the rewarding effects of nicotine that likely contribute to tobacco use initiation in females. For example, previous work has demonstrated that female rats display higher nicotine self-administration rates (Chaudhri et al., 2005; Lynch, 2009; Rezvani et al., 2008) and they acquire nicotine self-administration at lower doses of nicotine than males (Donny et al., 2000; Lanza et al., 2004). In addition, adult female rats display place preference following conditioning with a wider dose range of nicotine than males (Torres et al., 2009). These findings are consistent with other studies demonstrating that female rats (Edwards et al., 2014; Lenoir et al., 2015) and mice (Kota et al., 2007, 2008) display a more robust place preference produced by nicotine than males. Female rats also display greater oral consumption of nicotine than males (Klein et al., 2004; Nesil et al., 2011). However, we also recognize one report showing that male rats display greater place preference produced by nicotine than females (Yararbas et al., 2010). Taken together, the majority of the literature suggests that the strong rewarding effects of nicotine likely promote tobacco use initiation in females. Thus, the possibility exists that the strong rewarding effects of nicotine and the greater contribution of stress are additive factors that together promote tobacco use vulnerability in women.

7. The contribution of stress in promoting withdrawal during abstinence in females

Clinical studies have shown that during smoking abstinence, women report more negative mood states, such as depression, anxiety, and intense craving than men (al'Absi, 2006; Schnoll et al., 2007; Xu et al., 2008). Women smokers also report more often than men that the anxiety-reducing effects of cigarettes are the main reason for relapse (Perkins and Scott, 2008; Perkins et al., 2009, 2012a, 2012b; Piper et al., 2010). Importantly, women also display higher levels of cortisol during smoking abstinence relative to men (Hogle and Curtin, 2006). These findings suggest that the strong aversive effects of withdrawal contribute to greater vulnerability to relapse behavior in women as compared to men.

In rodent studies, nicotine withdrawal has been widely studied using chronic nicotine administration via subcutaneous osmotic minipumps for at least 5-7 days (Kenny and Markou, 2001; Malin et al., 2001). Withdrawal from nicotine is produced via removal of the nicotine pump (spontaneous withdrawal) or administration of a nicotinic receptor antagonist (precipitated withdrawal). Using either spontaneous or precipitated methods, nicotine withdrawal produces a behavioral profile comprised of both physical and affective components. The negative affective properties of nicotine withdrawal have been studied in procedures that assess anxiety-like behavior in rodents (Bruijnzeel et al., 2012). Studies comparing sex differences produced by nicotine withdrawal have revealed that female adult rats display more physical signs of nicotine withdrawal relative to males (Hamilton et al., 2009). Also, female adult rats display elevated plasma ACTH and corticosterone levels during nicotine withdrawal relative to their male counterparts (Gentile et al., 2011). Consistent with these findings, Skwara et al. (2012) also demonstrated that plasma ACTH and corticosterone levels are increased in female rats following precipitated nicotine withdrawal as compared to males. Work in our laboratory revealed that females display greater anxiety-like behavior, plasma corticosterone, and CRF gene expression in NAcc during nicotine withdrawal compared to male rats (Torres et al., 2013). There were no sex differences in CRF gene expression in the amygdala or hypothalamus, suggesting that sex differences during nicotine withdrawal are likely modulated within the local circuits of the NAcc. Taken together, these studies provide pre-clinical evidence suggesting that nicotine withdrawal elicits greater stress responses in females versus males.

8. Age differences in the contribution of stress to tobacco initiation and withdrawal in females

Our hypothesis that stress plays a central role in promoting tobacco use in females is supported by a recent pre-clinical study showing that administration of a pharmacological stressor (yohimbine) increased nicotine self-administration in adolescent female, but not male rats (Li et al., 2014). With regard to the direct anxiolytic effects of nicotine; however, there appears to be an important distinction between the pattern of results between female and male rats of different ages. As described above, nicotine administration produces direct anxiolytic effects that are greater in female versus male adult rodents. Based on this work, we suggest that the anxiolytic effects of nicotine likely promote tobacco use initiation in adult females. However, studies comparing the anxiolytic effects of nicotine during adolescence have produced a different pattern of results. Namely, the anxiolytic effects of nicotine are greater in male versus female adolescent rats (Cao et al., 2010) and mice (Damaj, 2001). Adolescent male mice also display a greater activation of the PVN following an injection of nicotine as compared to females (McCormick and Ibrahim, 2007). These findings suggest that nicotine may produce greater anxiolytic effects in adolescent males as compared to females. During adolescence, we suggest that there may be other factors such as the effects of nicotine on social behavior that may also play a role in promoting tobacco use. This is based on the finding that nicotine increases social rewards in adolescent male rats (Thiel et al., 2009). With regard to sex differences, female adolescent rats display a greater increase in social interaction behavior following administration of a low dose of nicotine as compared to males (Cheeta et al., 2001). This work suggests that nicotine may promote social interaction in a manner that enhances tobacco use in young females.

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Much research has suggested that nicotine withdrawal is reduced during the adolescent period of development in rodents (for a review see O'Dell, 2009). With regard to sex differences, the majority of literature suggests that there are no differences in nicotine withdrawal in female and male rodents during adolescence. For example, the physical signs of nicotine withdrawal are similar in adolescent female and male mice (Kota et al., 2007, 2008) and rats (Hamilton et al., 2010; Torres et al., 2013). There are also no sex differences in plasma corticosterone levels produced by nicotine withdrawal (Torres et al., 2013). It may not be surprising that there are no sex differences in nicotine withdrawal during adolescence, given the preponderance of evidence suggesting that nicotine withdrawal does not appear to play a major role in promoting tobacco use in adolescents.

9. Ovarian hormones modulate tobacco use

Clinical reports have shown that there is a relationship between tobacco use and ovarian hormones in women. With regard to nicotine reward, it is thought that high levels of estrogen are positively correlated with enhanced sensitivity to the rewarding effects of nicotine in women (Lynch and Sofuoglu, 2010). Also, during smoking abstinence, women display enhanced nicotine craving and increased relapse rates during the follicular-phase when estrogen levels are highest (Allen et al., 2009). There are also reports showing an accelerated metabolism of nicotine in women who use oral contraceptives that enhance estrogen levels (Benowitz et al., 2006; Dempsey et al., 2002). Thus, estrogen may promote tobacco use via a mechanism involving accelerated nicotine metabolism. Taken together, these studies suggest that estrogen likely promotes the various phases of tobacco use in women. However, the role of progesterone appears to be opposite to that of estrogen. For example, high levels of progesterone are correlated with a diminished urge to smoke in women (Schiller et al., 2012). Moreover, progesterone treatment attenuates the urge for tobacco use in female smokers (Sofuoglu et al., 2001, 2009). Women also report lower subjective effects of nicotine in the luteal phase of the menstrual cycle when progesterone levels are higher than estrogen (DeVito et al., 2014). However, the literature on smoking rates during different phases of the menstrual cycle are not consistent, as there are reports showing that women smoke more cigarettes during the luteal phase (Sakai and Ohashi, 2013) and display less craving for cigarettes during the follicular-phase (Franklin et al., 2004).

Pre-clinical studies in our laboratory have examined the role of ovarian hormones in modulating nicotine reward and withdrawal using ovariectomy (OVX) procedures in rats. With regard to nicotine reward, our initial studies revealed that OVX females displayed reduced place preference produced by nicotine as compared to intact females (Torres et al., 2009). Other laboratories have also found that ovarian hormones are necessary for the rewarding effects of other drugs of abuse. For example, OVX female rats are less likely to acquire cocaine self-administration (Lynch et al., 2001) and to reinstate cocaine-seeking behavior following extinction (Larson et al., 2005) relative to intact females. In addition, OVX female rats display longer acquisition of heroin self-administration (Roth et al., 2002) and diminished place preference produced by morphine (Mirbaha et al., 2009). With regard to nicotine withdrawal, we recently observed that intact females display higher levels of anxiety-like behavior and increased expression of several stress-associated neuropeptide genes including CRF and UCN in the NAcc (Torres et al., 2015). Interestingly, the latter effects were absent in OVX females. These studies imply that ovarian hormones are crucial for the manifestation of withdrawal produced by nicotine. Taken together, these studies suggest that ovarian hormones play an important role in modulating drug abuse, consistent with a recent review paper summarizing pre-clinical work in this area of research (Bobzean et al., 2014).

Recently, we posited that estradiol is an important ovarian hormone that promotes the effects of stress on nicotine reward and withdrawal in females (see O'Dell and Torres, 2014). Our hypothesis is based on studies demonstrating that estradiol potentiates stress in females. For example, activation of the beta estradiol receptor has been shown to increase anxiety-like behavior in female rats (Morgan and Pfaff, 2001; Walf and Frye, 2005). In addition, studies comparing CRF levels across the 4-day estrous cycle in female adult rats have found that the highest levels of CRF are observed during the proestrus phase, where estradiol levels are highest (Bohler et al., 1990; Nappi et al., 1997). Other work has also shown that direct activation of estradiol-beta receptors increase CRF mRNA expression *in vitro* (Chen et al., 2008; Lalmansingh and Uht, 2008; Zhu and Zhou, 2008). Estradiol has also been shown to promote gene expression of stress-associated neuropeptides (Kageyama et al., 2011; Sanchez et al., 2010; Vamvakopoulos and Chrousos, 1993). Collectively, these studies suggest that estradiol enhances stress responses via facilitating CRF systems. Thus, estradiol may be an important hormone that modulates sex differences produced by nicotine. A recent review has described the modulatory role of ovarian hormones on neurotransmission in different regions of the brain (Barth et al., 2015). However, there remains a knowledge gap with regard to the mechanisms by which estradiol promotes CRF mechanisms and anxiety-like behavior in a region-dependent manner. We also recognize that other ovarian hormones, such as progesterone may also play an important role in modulating tobacco use in females (see Anker and Carroll, 2010; Carroll and Anker, 2010; Lynch and Sofuoglu, 2010)."

10. Stress promotes poly drug use in females

Converging lines of evidence suggest that anxiety is a key factor that promotes addiction to a variety of drugs in women. For example, more women with a prior anxiety-related disorders report alcohol use than men (Landheim et al., 2003). Other clinical reports have shown that women with chronic anxiety produced by a traumatic event, are more likely than men to use alcohol and have polydrug use problems (Jaquier et al., 2014; Peters et al., 2012; Weiss et al., 2014). Consistent with this, women veterans diagnosed with PTSD have a higher risk for poly drug use (Dobie et al., 2004). Furthermore, women report greater anxiety and guilt after cocaine use than men (Kennedy et al., 2013). Clinical findings also suggest that anxiety management techniques are beneficial in reducing drug use in women (Wu et al., 2014). These studies suggest that anxiety contributes to the addiction to a variety of abused substances in women.

A review of the pre-clinical literature suggests that stress has profound effects on the rewarding effects of drugs of abuse other than nicotine (Aguilar et al., 2013). Work focused on other drugs of abuse is consistent with pre-clinical studies that have compared sex differences with nicotine. For example, female rats show greater reinstatement of cocaine-seeking behavior as compared to males after intracerebroventricular infusions of CRF (Buffalari et al., 2012) or intraperitoneal injections of yohimbine (Anker and Carroll, 2010; Feltenstein et al., 2011). Additionally, female rats self-administer more heroin on a food restriction paradigm that induces stress than males (Carroll et al., 2001). Stressed female rats also display a longer-lasting enhancement of cocaine-induced increases in dopamine levels in the NAcc as compared to stressed males (Holly et al., 2012). However, we acknowledge other reports showing that chronic stressors may not induce sex-differences in cocaine intake (Haney et al., 1995) and cocaine-induced increases in NAcc dopamine levels (Shimamoto et al., 2011).

11. Other factors that promote tobacco use in females

There are a variety of factors other than stress that may also promote tobacco use in females. First, women are more likely to use tobacco products as a tool to control appetite and decrease weight than men (Austin and Gortmaker, 2001; Kaufman and Augustson, 2008;

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Pomerleau and Snedecor, 2008). Second, genetic factors may play an important role in promoting tobacco use susceptibility in women. For example, Colamussi et al. (2007) showed that women with first-degree relatives who smoke display higher levels of stress-induced cigarette craving as compared to their male counterparts. In addition, a meta-analysis found that in comparison to males, females with a twin who smokes are more likely to engage in smoking behavior (Li et al., 2003). Although sociocultural factors also play a role in smoking initiation among female twins (Hamilton et al., 2006), nicotine dependence has been mostly closely attributed to hereditary and genetic factors among female twins (Kendler et al., 1999). Clinical studies have also highlighted the importance of other external factors such as having a friend who smokes (Oh et al., 2010; Holahan et al., 2012), lower socioeconomic status (Wewers et al., 2012) and educational level (Kandel et al., 2009) as strong predictors of nicotine use in women. Taken together, these studies imply that there are important factors other than stress that also contribute to tobacco use in women.

12. Clinical implications

The literature suggests that as compared to males, females experience stronger rewarding effects of nicotine and greater negative effects during withdrawal from this drug. Given that both reward processing and withdrawal contribute to tobacco use, we suggest that stronger effects in both domains contribute to greater vulnerability to tobacco use in females. The present review posits that a major factor that promotes tobacco use in females is stress produced by withdrawal. These observations suggest that female smokers may require specialized medications that help to alleviate intense stress experienced during abstinence. Future work is needed to help guide the development of novel therapeutic agents that may be more useful in smoking cessation in women. Given that most smoking cessation medications focus on alleviating withdrawal, one approach might include CRF antagonists in combination with other treatments, such as NRT or partial nicotinic receptor agonists. In fact, a previous review suggested that CRF receptor antagonists might be useful medications for alleviating negative mood states produced by drug withdrawal (Logrip et al., 2011). Future studies are needed to understand the complex interactions in the brain that modulate sex differences in to tobacco use. Recent research has made important advances in our understanding of the underlying circuitry that promotes tobacco use. The recent literature suggests that CRF systems within key structures of the mesolimbic pathway, including the VTA (Grieder et al., 2014), NAcc (O'Dell and Torres, 2014), and amygdala (Bruijnzeel, 2012; George et al., 2012) play an important role in orchestrating the behavioral effects of nicotine and withdrawal from this drug. Future studies are needed to elucidate the underlying neurochemical systems within these structures that promote tobacco use. Ultimately, this work is important towards elucidating the role of stress in promoting smoking behavior and reducing health disparities produced by chronic tobacco use in women.

Acknowledgements

The authors would like to thank Dr. Luis M. Carcoba, Joseph A. Pipkin and Rodolfo J. Flores for their helpful comments in the preparation of this review paper. The authors also appreciate the support that was provided from The National Institute on Drug Abuse (R01-DA021274, R24-DA029989 and R25-DA033613) and the National Institute of Minority Health Disparities (G12MD007592) as part of the UTEP Border Biomedical Research Center. This work was also partially supported by funds from the Intramural Research Program of the NIDA Scientific Director's Fellowship for Diversity in Research (OVT). The authors declare no conflicts of interest.

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Please cite this article as: Torres OV, O'Dell LE, Stress is a principal factor that promotes tobacco use in females, Prog Neuro-Psychopharmacol Biol Psychiatry (2015), http://dx.doi.org/10.1016/j.pnpbp.2015.04.005

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Please cite this article as: Torres OV, O'Dell LE, Stress is a principal factor that promotes tobacco use in females, Prog Neuro-Psychopharmacol Biol Psychiatry (2015), http://dx.doi.org/10.1016/j.pnpbp.2015.04.005

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Please cite this article as: Torres OV, O'Dell LE, Stress is a principal factor that promotes tobacco use in females, Prog Neuro-Psychopharmacol Biol Psychiatry (2015), http://dx.doi.org/10.1016/j.pnpbp.2015.04.005

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Please cite this article as: Torres OV, O'Dell LE, Stress is a principal factor that promotes tobacco use in females, Prog Neuro-Psychopharmacol Biol Psychiatry (2015), http://dx.doi.org/10.1016/j.pnpbp.2015.04.005