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TOBACCO (AH WEINBERGER, SECTION EDITOR)

Targeting the Brain Stress Systems for the Treatment of Tobacco/Nicotine Dependence: Translating Preclinical and Clinical Findings

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Abstract
Purpose of review Tobacco use is the leading cause of preventable mortality in the USA, and Food and Drug Administration (FDA) approved medications fail to maintain long-term abstinence for the majority of smokers.
Recent findings One of the principal mechanisms associated with the initiation, maintenance of, and relapse to smoking is stress. Targeting the brain stress systems as a potential treatment strategy for tobacco dependence may be of therapeutic benefit.
Summary This review explores brain stress systems in tobacco use and dependence. The corticotropin-releasing factor (CRF) system, the hypothalamic-pituitary-adrenal (HPA) axis, and the noradrenergic system are discussed in relation to tobacco use. Preclinical and clinical investigations targeting these stress systems as treatment strategies for stress-induced tobacco use are also discussed. Overall, nicotine-induced activation of the CRF system and subsequent activation of the HPA axis and noradrenergic system may be related to stress-induced nicotine-motivated behaviors. Pharmacological agents that decrease stress-induced hyperactivation of these brain stress systems may improve smoking-related outcomes.

Keywords Tobacco · Nicotine · Stress · CRF · HPA · Noradrenergic

This article is part of the Topical Collection on *Tobacco*

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Introduction

Tobacco use is the leading cause of preventable morbidity and mortality in the USA, with over 556,000 deaths attributable to smoking-related causes per year in the USA [1] and over 6 million deaths attributable to smoking-related reasons per year worldwide [2]. The high degree of tobacco use across the globe contributes to the well-documented magnitude of medical and financial consequences associated with smoking. Smoking increases risk for lung, oral, liver, and bladder cancers, chronic obstructive pulmonary disease (COPD), coronary heart disease, and cardiovascular disease amongst many others [3]. Correspondingly, smoking imposes an economic burden of nearly $289 billion dollars in medical expenses and lost productivity in the USA alone [4]. Despite the extensive health and economic consequences associated with smoking, smokers often fail to maintain long-term abstinence and relapse to tobacco use remains high. More than 70 % of cigarette users relapse to smoking within 1 year, even with the most efficacious treatments [5], underscoring the importance of targeting novel systems for treatment of tobacco dependence.

It is well-established that one of the principal mechanisms associated with the initiation, maintenance of, and relapse to smoking is stress [6, 7]. Cigarette users (35–100 %) self-report stress and negative affect as causal factors when recounting relapse episodes [8–10], and measures of smoking lapse behavior indicate that robust increases in negative affect were predictive of relapse to cigarette smoking [11, 12]. Acute stress has also been shown to reduce the ability to resist smoking, increase the intensity of smoking, and increase craving and physiologic reactivity in daily smokers [13].

Considering the large portion of smokers who report stress as a primary factor for maintaining and relapsing to smoking, and the fact that current Food and Drug Administration (FDA)-approved medications for smoking cessation are only

modestly efficacious in maintaining long-term smoking abstinence, targeting brain stress systems as a treatment approach for tobacco dependence is of the utmost importance. Specifically, the ability of stressors to reliably activate the corticotropin-releasing factor (CRF) system, the hypothalamic-pituitary-adrenal (HPA) axis, and the catecholaminergic system (norepinephrine, epinephrine, and dopamine) has been linked to stress-induced increases in drug-motivated behaviors [14], and in nicotine-exposed animals and humans, acute stress additively increases HPA and catecholamine activation [15]. The following sections will review the state of the literature on the influence of three brain stress systems, the CRF system, the HPA axis, and the noradrenergic system, on tobacco/nicotine dependence. Preclinical and clinical investigations targeting these stress systems as treatment strategies for stress-induced tobacco use are discussed.

The Corticotropin-Releasing Factor System and Tobacco/Nicotine Dependence

An Overview

Since the discovery of CRF, a 41 amino acid peptide, by Wylie Vale in 1981 [16], the CRF system has emerged as a key mediator of the stress response and, consequently substance use. CRF is widely distributed throughout the brain, with high concentrations of neuronal cell bodies located within the paraventricular nucleus of the hypothalamus, the basal forebrain, and the brainstem [17]. The CRF system is composed of two main receptor subtypes: CRF_1 and CRF_2. CRF_1 receptors are widely distributed the cerebral cortex and cerebellum, and in brain regions associated with stress and anxiety, including the central nucleus of the amygdala and thalamus [18]. CRF_2 receptors can be divided into $CRF_{2\alpha}$ and $CRF_{2\beta}$, and are distributed throughout the brain, including the olfactory bulb, bed nucleus of the stria terminalis, the hippocampus, and the posterior cortical nuclei of the amygdala [18].

It is established that CRF initiates the HPA axis response to stress by binding to CRF_1 receptors in the anterior pituitary [19]. As reviewed by Koob and colleagues [20], preclinical work demonstrates that CRF mimics or enhances the behavioral response to stress in rodents. In particular, CRF_1 and CRF_2 activation is related to heightened stress responsiveness [21], although CRF_2 findings are mixed with some findings indicating an opposite effect of CRF_2 receptors to those of CRF_1 [22]. Consequently, administration of CRF antagonists reduces stress-related neural activation and behavior in rodents [23].

Nicotine and the CRF System

It is thought that persistent sensitization of the behavioral stress response following chronic drug use is driven by the CRF system. Preclinical models demonstrate that nicotine activates the HPA axis via hypothalamic CRF activity [24]. Further, extracellular CRF increases in response to precipitated withdrawal from chronic nicotine in rodents, particularly in the central nucleus of the amygdala [25]. Similarly, nicotine withdrawal-induced decrements in brain reward function have been demonstrated to be mediated by CRF_1 receptors [26]. Specifically, CRF messenger RNA (mRNA) levels in the central amygdala and nucleus accumbens increase following nicotine withdrawal [27, 28•], and this increase in CRF mRNA levels during withdrawal is more pronounced in female rats relative to males [28•]. In the same study, CRF mRNA levels were higher in the amygdala during nicotine exposure in male versus female rats. Correspondingly, stress-induced effects associated with nicotine withdrawal are reversed by CRF_1 antagonists [29].

Preclinical

It is well-established that the CRF system mediates drug-motivated behaviors, and antagonists of the CRF_1 receptor reduce nicotine self-administration, stress-induced reinstatement to nicotine-seeking, and nicotine withdrawal effects in animal models of nicotine dependence. Older studies demonstrate that CRF antagonists reverse conditioned stress responses elicited by nicotine [29], reduce stress-induced reinstatement of nicotine-seeking when administered directly into extrahypothalamic brain regions [30], attenuate abstinence-induced increases in nicotine self-administration [25], and reverse deficits in brain rewards function following nicotine withdrawal in rodents [31, 32].

More recently, CRF_1 antagonist administration into the central amygdala abolished mecamylamine-induced elevations in brain reward thresholds in rodents chronically treated with nicotine [33]. CRF antagonism attenuates withdrawal-induced deficits in response to a painful thermal stimulus in nicotine-dependent rats [34]. Relatedly, blockade of CRF_1 receptors in the ventral tegmental area (VTA) blocked the aversive effects of nicotine withdrawal, and viral vector-mediated downregulation of CRF mRNA in the VTA reduced increases in nicotine self-administration induced by chronic nicotine exposure [35]. With regard to stress induction, blockade of CRF_1 receptors reduced the ability of footshock stress to facilitate nicotine conditioned place preference (CPP) acquisition [36]. Taken together, the CRF system modulates nicotine-motivated behaviors at a molecular, genetic, and behavioral level, and reduces stress reactivity to nicotine CPP.

Clinical

Although CRF activation is associated with mood regulation and depression in the clinic, very few studies in humans have examined the role of CRF mechanisms underlying tobacco

dependence and stress-related smoking lapse behavior. A recent genetic study examined the CRHR1 gene, a gene encoding for the CRF_1 receptor, and whether variants in the CRHR1 gene were associated with nicotine dependence [37]. That study demonstrated a significant association between CRHR1 single nucleotide polymorphisms (SNPs) and smoking quantity in African American individuals, and a significant association between the same SNP and smoking quantity and Fagerstrom Test for Nicotine Dependence (FTND) scores in African American and European American individuals. Despite the genetic link between CRF and nicotine dependence, human laboratory studies investigating the role of the CRF system on smoking behavior have been limited. This may be related to the limited efficacy of some CRF_1 antagonists for the treatment of depression, anxiety disorders, and alcohol dependence [38, 39], the failure of CRF_1 antagonists to reduce anxiety-potentiated startle responses in women [40], and the potential for a negative adverse event profile associated with their use [38]. Ongoing phase II clinical trials of CRF_1 antagonists for the treatment of PTSD symptoms may further elucidate the role of CRF blockade on stress-responsiveness [41].

Overall, preclinical findings support the notion that increased CRF levels in the brain mediate nicotine-motivated behaviors and stress-induced nicotine-seeking. CRF_1 antagonists reduce the anxiogenic effects of increased extracellular CRF on nicotine responding and withdrawal in rodent models of nicotine dependence. Of particular importance is the recent literature indicating a gender-sensitive role of CRF activity in the modulation of nicotine reward in female rodents. A recent review postulates that there are sex-dependent differences in CRF modulation of dopamine within the nucleus accumbens during nicotine withdrawal, and that nicotine withdrawal may produce a stronger and more sustained activation of the CRF stress system in females relative to males (see review by O'Dell and Torres) [42]. This is supported by studies demonstrating that female relative to male rats have higher numbers of CRF_1 receptors and lower levels of beta-arrestin2, an intracellular protein that internalizes CRF_1 receptors [43], indicating that female rats may be more responsive to CRF activation than males. The human literature on the relationship between CRF activity and tobacco dependence is sparse, with a single genetic study demonstrating a link between CRF encoding genes and nicotine dependence in African and European Americans. The lack of studies in human laboratory paradigms or clinical trials may be related to the limited efficacy of CRF blockade for depression, anxiety, and alcohol dependence, suggesting that findings may not be translatable from preclinical to clinical work. Continued work should focus on elucidating the role of the CRF system in stress-induced nicotine-motivated behavior in preclinical paradigms and the translational utility of CRF_1 antagonists for tobacco dependence in humans.

Hypothalamic-Pituitary-Adrenal Axis and Tobacco/Nicotine Dependence

An Overview

The HPA axis is perhaps the system most widely associated with stress and arousal. During the stress response, CRF synthesis in the paraventricular nucleus of the hypothalamus increases, and once released, CRF binds to CRF receptors in the anterior pituitary. Downstream cascade effects of CRF induce the release of adrenocorticotropin (ACTH) from the pituitary and subsequent secretion of glucocorticoids and cortisol (or corticosterone), from the adrenal glands [44]. There are two primary glucocorticoid receptors in the brain: the mineralocorticoid receptor and the glucocorticoid receptor [45]. Mineralocorticoid receptors are located in brain regions including the hippocampus and amygdala, and glucocorticoid receptors are located throughout the hippocampus and in the parvocellular neurons of the paraventricular nucleus [45]. It is established that the release of cortisol plays an important role in the modulation of the stress response, and the action of cortisol on glucocorticoid receptors during periods of stress results in a suppression of stress-induced increases in HPA axis reactivity.

Nicotine and the HPA Axis

Work originally conducted by Balfour in the 1980s demonstrated that nicotine is a potent activator of the HPA axis [46], influencing the release of ACTH and cortisol. In humans, cortisol levels tend to be higher in smokers than in non-smokers. It is largely thought that the magnitude of effects of smoking within the HPA axis depends on the number of cigarettes smoked, the nicotine content of cigarettes smoked, and smoking topography [47]. For example, there have been mixed findings regarding the influence of nicotine content in cigarettes on the release of ACTH and cortisol. Low nicotine content cigarettes have demonstrated no effect on ACTH and cortisol levels or an increase in cortisol levels in the laboratory [48–51]. In contrast, smoking higher nicotine content cigarettes reliably increases ACTH and cortisol levels in male smokers [48–50]. Dysregulated HPA activation has also been demonstrated after chronic nicotine exposure [52]. Further, smoking cessation appears to immediately decrease salivary cortisol, and this effect is maintained over a period of abstinence [47].

Preclinical

Early studies of neuroendocrine responses to nicotine and stress indicate that independent administration of nicotine or restraint stress increased corticosterone levels, and that nicotine administered in conjunction with stress enhanced this

increase in corticosterone levels [15]. Similarly, acute nicotine self-administration increased ACTH and corticosterone levels in rats, but chronic administration of nicotine resulted in an attenuated effect of nicotine on increased ACTH and corticosterone [53]. In that study, chronic nicotine self-administration increased HPA activation in response to mild footshock stress. During nicotine withdrawal, adult female rats displayed increased anxiety-like behavior and elevated plasma corticosterone in the nucleus accumbens relative to their male counterparts [28•]. Corticosterone synthesis inhibitors have shown efficacy in reducing cocaine self-administration in rodents [54, 55], but these drugs have not been investigated for nicotine until recently. A recent study examined the low-dose combination of a corticosterone synthesis inhibitor, metyrapone, and a benzodiazepine, oxazepam, on nicotine self-administration and demonstrated that low doses of these two drugs in combination decreased intravenous (IV) nicotine self-administration in rats [56].

Clinical

In early studies, smokers demonstrated blunted HPA responsiveness to stress regardless of smoking abstinence status [57], and this attenuated HPA stress response was associated with quicker time to relapse [58]. In a recent study on stress and smoking relapse in nicotine dependent men and women, lower cortisol levels predicted relapse to smoking in men, but higher cortisol levels predicted relapse in women after 48 h of abstinence [59•]. Similar work has demonstrated that smokers exhibit blunted increases in cortisol levels in response to stress following acute nicotine withdrawal [60] and acute tobacco abstinence [61]. This is consistent with the theory that chronic nicotine exposure and withdrawal dysregulate the HPA axis system, and that women may be more sensitive to stress-induced relapse to smoking than men.

Our research group has also demonstrated that stress increased HPA axis reactivity in daily smokers, and increased levels of ACTH and cortisol and tobacco craving were associated with reduced ability to resist smoking following stress [62]. Increased ACTH and cortisol levels were also associated with smoking reward and smoking satisfaction, respectively. More recently, findings from our group indicate that guanfacine, an α_2-adrenergic agonist, may help normalize a blunted stress response in nicotine-deprived smokers [63•]. In that study, nicotine-deprived smokers exhibited decreased cortisol levels, and guanfacine normalized this stress response.

Taken together, preclinical findings indicate that both nicotine and stress increase HPA activation, and that this effect is dysregulated after chronic nicotine self-administration. The same effect has been demonstrated in humans after smoking abstinence. Nicotine activates the HPA axis, but acute abstinence blunts nicotine-induced ACTH and cortisol release. In agreement with sex-difference findings in preclinical literature, a recent investigation on sex differences in HPA reactivity to smoking lapse and stress demonstrate that women have higher cortisol levels following abstinence and that this is predictive of relapse. This is consistent with other literature discussed in this review suggesting that women smokers may be more sensitive to stress-reactivity than males. With regard to medication development, guanfacine shows promise in normalizing HPA axis activation in smokers, but cortisol synthesis inhibitors may be limited in their use in humans due to aversive adrenal side effects [56].

The Noradrenergic System and Tobacco/Nicotine Dependence

An Overview

The noradrenergic system is widely known to be involved in arousal, anxiety, and more recently, substance use. The noradrenergic system is comprised of two main ascending projections within the brain: the dorsal noradrenergic bundle (DNB) and the ventral noradrenergic bundle (VNB) [64–66]. The DNB has cell bodies originating in the dorsal pons (locus coeruleus; LC) and projects from the LC, a nucleus comprised of entirely norepinephrine-containing neurons, to the cortices and hippocampus. The VNB is comprised of four noradrenergic cell groups (A1, A2, A5, and A7) and has cell bodies that originate in the brain stem (pons and medulla) and innervate the hypothalamus, basal forebrain, and amygdala [67].

This system is comprised of three main receptor subtypes, α_1 (alpha-1), α2 (alpha-2), and β (beta), to which norepinephrine binds. Alpha-1 and β adrenoceptors are primarily located postsynaptically [67, 68] in several brain regions including the LC [67, 69], olfactory bulb, cerebral cortex, amygdala, dentate gyrus, and the thalamus [67, 70], and can be further subdivided into α_{1a}-, α_{1b}-, and α_{1d}-adrenergic and β_1-, β_2-, and β_3-adrenergic receptor subtypes [67]. Alpha-2 adrenoceptors can be subdivided into α_{2a}-, α_{2b}-, and α_{2c}-adrenergic receptors, and exist both presynaptically and postsynaptically [67, 68] in regions including the LC, amygdala, and hypothalamus [67, 71]. Medications that act on these receptor subtypes by way of reducing central noradrenergic activity have historically been used for the treatment of hypertension and attention-deficit/hyperactivity disorder (ADHD), with more recent use for the treatment of drug-motivated behavior.

Nicotine and the Noradrenergic System

Nicotine primarily binds to nicotinic acetylcholine receptors (nAchRs) in the brain, and the activity of nicotine on nAchRs interacts with the noradrenergic system to enhance noradrenergic signaling and peripheral sympathetic activity [15]. Preclinical models indicate that systemic administration of nicotine increases extracellular norepinephrine levels, and that this

effect is directly mediated by the LC, the main noradrenergic-containing region in the brain [72]. Chronic nicotine exposure also increases tyrosine hydroxylase activity, a precursor for the synthesis of norepinephrine, in brain regions innervated by the noradrenergic system but not in dopamine projection areas [73].

In humans, tobacco use increases plasma levels of norepinephrine and epinephrine, and elevated baseline plasma norepinephrine and epinephrine levels in smokers decrease during long-term abstinence [74]. Chronic smoking behavior is also related to decrements in the density of noradrenergic receptors and receptor binding in the LC, and these decrements normalize with smoking abstinence [75]. Overall, it is well-established that nicotine stimulates noradrenergic activity in both rodents and humans, and noradrenergic agents that reduce noradrenergic activity or normalize noradrenergic activity have demonstrated potential as treatments for tobacco dependence.

Preclinical

Animal models indicate that exposure to acute stress induces relapse to nicotine-seeking in non-dependent and dependent rodents, and drugs that reduce noradrenergic signaling also reduce nicotine-motivated behaviors, such as stress-induced reinstatement of nicotine-seeking [76–80]. Thus, stress-induced nicotine-seeking and self-administration may be mediated by the noradrenergic system. Provocation of the noradrenergic system by yohimbine, an α_2-adrenergic antagonist and pharmacological stressor, has been reliably used in both animal and human studies to reinstate drug-seeking behaviors. Relevant to the present review, yohimbine has been found to reinstate nicotine-seeking in female and male rodents [76, 81]. Yohimbine also increased progressive ratio (PR) breakpoints for nicotine intake in male and female rats, but female rats were more sensitive than males to stress-induced responding for nicotine [77].

Correspondingly, prazosin, an α_1-adrenergic antagonist, blocked the acquisition of nicotine self-administration behavior and reduced nicotine-induced dopamine release in the nucleus accumbens (NAc), a brain region associated with reward and reward processing [82]. Subsequent studies demonstrated that prazosin dose-dependently decreased nicotine self-administration and blocked reinstatement of extinguished nicotine-seeking induced by a nicotine prime or cue [78], and decreased elevations in brain reward thresholds associated with nicotine withdrawal [79]. Propranolol, a β-adrenergic antagonist, decreased somatic signs associated with nicotine withdrawal and modestly inhibited cue-induced reinstatement of nicotine-seeking [79, 83]. With regard to stress, exposure to footshock reinstated extinguished nicotine-seeking behaviors, and the α_2-adrenergic agonist, clonidine, reduced stress-induced reinstatement of nicotine-seeking when administered directly into the central nucleus of the amygdala (CeA) [80] and when given systemically [30]. Taken together, pharmacological provocation of the noradrenergic system demonstrates increased effects on stress-induced nicotine responding in rodents, and pharmacological agents that blunt noradrenergic firing demonstrate decreased effects on nicotine-motivated behaviors.

Clinical

Noradrenergic effects on nicotine-motivated behaviors have been examined to a lesser extent in the human laboratory, although noradrenergic medications have demonstrated efficacy in reducing subjective reactivity to smoking, ad libitum smoking behavior, and withdrawal symptoms associated with smoking [63•, 84, 85]. Carvedilol, an α_1- and β-adrenergic antagonist, reduced self-reported subjective ratings of "bad effects" associated with nicotine in female and male abstinent smokers, but did not affect tobacco withdrawal symptoms [84]. However, another an α_1- and β-adrenergic antagonist, labetalol, reduced tobacco withdrawal symptoms following intravenous (IV) nicotine administration in abstinent smokers [85].

More recently, in a validated laboratory analogue of stress-precipitated smoking, stress decreased the latency to smoke and increased tobacco craving and smoking self-administration in nicotine-deprived smokers [63•]. In that study, the stress-related effects on smoking were absent or attenuated in subjects treated with guanfacine, an α_{2a}-adrenergic agonist. Specifically, guanfacine eliminated the effect of stress on time to resist smoking and ad libitum smoking, and reduced tobacco craving. Preliminary findings from our group have also found that doxazosin, an α_1-adrenergic antagonist with a longer half-life profile than prazosin, increased the ability to resist smoking following stress and reduced tobacco craving for positive and negative reinforcement (Verplaetse et al., in preparation).

Similar to preclinical work regarding stress-related sex differences on nicotine responding, in a 4-week proof-of-concept treatment period, our research group found that guanfacine may act through gender-sensitive mechanisms for smoking-related behavior. Although guanfacine reduced the number of cigarettes per day following a quit attempt in both women and men, guanfacine decreased smoking lapse, tobacco craving, and smoking self-administration following stress in women but not men [86]. Our research group has recently hypothesized that smoking activates different brain systems modulated by the noradrenergic activity in women versus men, such that noradrenergic agents that normal noradrenergic hyperarousal differentially attenuate stress reactivity in women and nicotine-related reinforcement in men [67]. This is consistent with preclinical findings in which CRF mRNA levels are increased during nicotine withdrawal in female rats relative to males, but CRF mRNA levels are increased during nicotine exposure in male versus female rats [28•].

Taken together, noradrenergic agents reduce negative subjective effects of smoking, decrease tobacco craving, and decrease smoking self-administration in adult cigarette smokers. Moreover, preclinical and clinical findings indicate that the noradrenergic system may be a sensitive to gender-sensitive effects on nicotine-related outcomes. Female rodents were more sensitive to yohimbine-induced increases in PR responding for nicotine, while guanfacine preferentially decreased smoking-related behavior following stress in women compared to men. Overall, relatively few recent studies have examined the noradrenergic system with regard to stress-induced smoking behavior. Older investigations in regular smokers demonstrated that clonidine increased smoking cessation rates, and reduced tobacco craving and withdrawal symptoms [87, 88], with particular efficacy in women versus men [89, 90]. However, significant adverse events, most notably sedation, have since limited its use as a medication option for smoking cessation [88]. Continued work is needed to further elucidate the role of the norepinephrine brain stress system on tobacco dependence, and potential gender-sensitive mechanisms underlying treatment efficacy.

Conclusions

Stress is a primary mechanism associated with tobacco use and relapse to smoking, and preclinical and clinical findings suggest that targeting the brain stress systems as a novel treatment strategy for tobacco/nicotine dependence may be promising. Substantial preclinical and clinical evidence demonstrates a role for the CRF system, HPA axis, and noradrenergic system in stress-induced smoking and relapse. Overall, nicotine-induced activation of the CRF system and subsequent activation of the HPA axis and noradrenergic system seem to be related to stress-induced nicotine-motivated behaviors, and medications that blunt CRF, HPA, and noradrenergic activity are efficacious in reducing nicotine self-administration and stress-induced reinstatement of nicotine-seeking in rodents. The translation of CRF_1 antagonist and corticosterone synthesis inhibitor use in humans has been limited due to efficacy and aversive side effects. However, agents that normalize noradrenergic signaling demonstrate efficacy for reducing smoking-related outcomes in humans while maintaining a safe side effect profile. Future work should continue to focus on the clinical utility of pharmacotherapeutic treatments targeting the brain stress systems for tobacco dependence.

Of importance, converging lines of preclinical and clinical evidence suggest that brain stress systems may be more sensitive in female smokers relative to males. It is well-established that women are more likely to smoke to reduce stress and negative affect. A considerable body of data indicates that female rats relative to males have elevated plasma corticosterone and CRF mRNA during nicotine withdrawal; female rats relative to males are more sensitive to yohimbine stress-induced nicotine responding, and in women smokers, higher cortisol levels are predictive of relapse following a period of smoking abstinence compared to men. Noradrenergic medications also preferentially act through gender-sensitive mechanism to reduce tobacco craving and smoking self-administration following stress in women but not men. Therefore, women smokers in particular may preferentially benefit from pharmacotherapeutic treatment strategies targeting the brain stress systems. Continued work in this area will determine whether CRF, HPA, and noradrenergic mechanisms hold promise for gender-sensitive medication development for smoking cessation.

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Compliance with Ethical Standards

Conflict of Interest Terril L. Verplaetse, PhD and Sherry A. McKee, PhD declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors. Terril L. Verplaetse, PhD and Sherry A. McKee, PhD contributed to studies cited in the article. An institutional research ethics board approved each of these studies, and each conformed to the ethical principles outlined in the Declaration of Helsinki.

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