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Biological Mechanisms Underlying the Relationship between Stress and Smoking: State of the Science and Directions for Future Work

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Abstract

Theories of addiction implicate stress as a crucial mechanism underlying initiation, maintenance, and relapse to cigarette smoking. Examinations of the biological stress systems, including functioning of the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS), have provided additional insights into the relationship between stress and smoking. To date, convergent data suggests that chronic cigarette smoking is associated with alterations in HPA and ANS functioning; however, less is known about the role of HPA and ANS functioning in smoking initiation and relapse following cessation. In order to organize existing findings and stimulate future research, the current paper summarizes the available literature on the roles of HPA axis and ANS functioning in the relationship between stress and cigarette smoking, highlights limitations within the existing literature, and suggests directions for future research to address unanswered questions in the extant literature on the biological mechanisms underlying the relationship between stress and smoking.

1. Overview

The CDC estimates that approximately 19.8% of U.S. adults currently smoke (CDC, 2008a). Moreover, cigarette smoking continues to be the leading preventable cause of death and disability in the United States accounting for approximately 1 of every 5 deaths (443,000 people) each year (CDC, 2008b). Because of its enormous public health impact, it is imperative to gain a comprehensive understanding of the mechanisms involved in the initiation, maintenance, and relapse of cigarette smoking.

In considering mechanisms within addiction, theories have emphasized the role of stress (Conger, 1956; Khantzian, 1985; Koob & Le Moal, 1997, 2001; Leventhal & Cleary, 1980; Marlatt & Gordon, 1985; Russell & Mehrabian, 1975; Sher & Levenson, 1982; Shiffman,

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1982; Sinha, 2001; Solomon, 1977; Tomkins, 1966; Wikler, 1948; Wills & Shiffman, 1985). A number of studies have provided evidence that acute and chronic stress are related to smoking across multiple stages of the addiction process including initiation (Wills, Sandy, & Yaeger, 2002; Wills, Vaccaro, McNamara, & Hirky, 1996), maintenance (McEwen, West, & McRobbie, 2008; Payne, Schare, Levis, & Colletti, 1991), and relapse to cigarette smoking (Cohen & Lichtenstein, 1990; Falba, Teng, Sindelar, & Gallo, 2005; Heishman, 1999; Hymowitz, Sexton, Ockene, & Grandits, 1991; Matheny & Weatherman, 1998; Siahpush & Carlin, 2006; Wewers, 1988).

Although there is a large body of research on the relationship between smoking and stress, this literature historically has been limited to self-report measurement (Cummings, Jaen, & Giovino, 1985; O'Connell & Martin, 1987; Shiffman, 1982; Swan et al., 1988; Wills et al., 1996; 2002) which often relies on retrospective memories of stressful events and internal experiences, and may be subject to reporter biases (e.g., Turner et al., 1998). Despite the advancements made by self-report studies of the relationship between stress and smoking, many questions remain about the complex relationship between stress and smoking. A multimodal approach may provide one strategy for gaining clarity in this complex relationship. As a compliment to self-report, biological measures of stress may provide information about potential mediators and moderators of the relationship between stress and smoking. Two biological stress systems of interest are the hypothalamic-pituitary-adrenal (HPA) axis, which can be assessed via serum/plasma and salivary cortisol concentrations, and the autonomic nervous system (ANS) which is routinely examined by measuring catecholamine levels and cardiovascular responses. Available evidence suggests that chronic cigarette smoking is associated with altered functioning in these systems, and in some cases, these alterations have been shown to increase the reinforcing effects of acute smoking, particularly in the context of stress; however, many questions remain regarding the processes through which biological stress reactivity affects the relationship between stress and smoking across the stages of addiction. Thus, the aim of the current paper is to summarize the existing literature regarding the role of HPA axis and ANS functioning in the relationship between stress and smoking at each stage of nicotine addiction, to identify limitations and gaps within the extant literature, and to suggest clear directions for future research in order to specifically address the remaining questions in the literature.

2. Acute Effects of Nicotine and Psychological Stress

Striking parallels exist between the effects of acute nicotine exposure and psychological stress on neurobiological mechanisms involved in both stress regulation and reward. These neurobiological parallels point to important processes that can function to increase the reinforcing effects of nicotine, particularly in the face of acute stress. As such, a brief overview of the neurobiological effects of both acute nicotine and psychological stress exposure is in order.

2.1 Acute effects of nicotine

Acute nicotine administration is associated with increased HPA axis activation (Rohleder & Kirschbaum, 2006). Specifically, nicotine induces the release of corticotrophin releasing hormone (CRH) by binding to cholinergic receptors in the locus coeruleus and hypothalamus (e.g., Fuxe, Anderson, Eneroth, Harfstrand, & Agnati, 1989; Matta, Fu, Valentine, & Sharp, 1998; Rosencrans and Karin, 1998). Subsequently, ACTH is released from the pituitary, followed by cortisol secretion by the adrenal glands, resulting in an overall increase in ACTH and cortisol. Indeed, research among human smokers has shown that cortisol reliably increases after smoking a minimum of two cigarettes (Caggiula et al., 1998; Kirschbaum, Wust, & Strasburger, 1992; Kirschbaum, Scherer, & Strasburger, 1994) and the magnitude of acute nicotine-induced HPA activation (as well as changes in heart

rate and positive subjective effects of smoking) appear to be dose-dependent (Gilbert, Dibb, Plath, & Hyane, 2000; Gilbert, Meliska, Williams, & Jensen, 1992; Kirschbaum et al., 1992; Meliska & Gilbert, 1991; Mendelson et al., 2005; Newhouse et al., 1990; Seyler et al., 1984; Winternitz & Quillen, 1977).

Cigarette smoking also reliably activates the autonomic nervous system (ANS), which is most frequently studied by assessing changes in plasma catecholamine levels (i.e., epinephrine and norepinephrine), as well as cardiovascular responses including systolic blood pressure (SBP), diastolic blood pressure (DSB), heart rate (HR) and heart rate variability (HRV). Specifically, acute cigarette smoking is associated with increased cardiovascular activation, which is mediated in part by catecholamine release (Cryer, Haymond, Santiago, & Shah, 1976; Grassi et al., 1994), muscle sympathetic nerve excitation (Narkiewicz et al., 1998), and nicotinic receptor stimulation (Haass & Kubler, 1997). Research on ANS functioning among smokers has contributed greatly to our understanding of the physiological effects of both acute and chronic smoking (Adamopoulos, van de Borne, & Argacha, 2008; Cryer et al., 1976; Grassi et al., 1994; Haass & Kubler, 1997; Najem et al., 2006; Narkiewicz et al., 1998), as well as the mechanisms underlying the relationship between chronic cigarette smoking and cardiovascular disease (Adamopoulos et al., 2008).

In addition to activation in stress circuits, nicotine also activates reward circuits of the brain by binding to the nicotinic acetylcholinergic receptors (nAChR) located throughout the central nervous system (Rosecrans & Karin, 1998). Animal studies suggest that nicotine activates reward circuits directly by acting on nAChRs in the mesolimbic dopaminergic system, resulting in increased dopamine release (Corrigall, Franklin, Coen, & Clarke, 1992; Nisell, Nomikos, & Svensson, 1994, 1995; Pontieri, Tanda, Orzi, & Di Chiara, 1996). Dopaminergic functioning in these regions is believed to be a key component of the brain reward systems that contribute to the reinforcing properties of drugs of abuse, including nicotine (Di Chiara & Imperato, 1988; Koob & Le Moal, 1997; Roberts, Koob, Klonoff, & Fibiger, 1980; Taylor & Robbins, 1984). At the same time, nicotine also stimulates glutamate release, triggering additional nicotine-induced dopaminergic activation indirectly (Fagan, Mansvelder, Keath, and McGehee, 2003). Taken together, acute nicotine administration is associated with increased activation in circuits within the central nervous system that are associated with both stress regulation and drug reinforcement.

2.2 Tolerance to the acute effects of nicotine

Recent evidence in nicotine-dependent humans suggests that successive cigarette smoking can lead to the rapid development of physiological and psychological tolerance to the acute effects of nicotine (Mendelson, Goletiani, Sholar, Siegel, & Mello, 2008). In this study, participants abstained from smoking for one night, and were randomized to smoke either three low-nicotine or three high-nicotine cigarettes at 60 minute intervals in a session beginning at 10:00am on the following day. The smokers in the low-dose group showed no increase in ACTH, and a significant decrease in cortisol levels after each cigarette. Conversely, smokers in the high dose group showed significant increases in ACTH and cortisol levels, but the peak hormonal responses decreased over the course of the three cigarettes. Also of note, the researchers reported increases in heart rate and positive subjective effects (e.g., ratings of “high”, “rush”, and “liking”) following each cigarette, but these responses also diminished over the course of three successive cigarettes. Findings from this study suggest that repeated smoking can lead to the rapid development of an acute tolerance to the physiological effects of acute nicotine exposure, and this physiological tolerance is also associated with a reduction in the reinforcing effects of smoking. Notably, this is the only study of its kind among human smokers, suggesting a need for independent replication of these findings.

2.3 Acute effects of psychological stress

Acute stress exposure is also associated with stimulation of the HPA axis (Selye, 1936; Tsigos & Chrousos, 2002), which is most reliably activated in response to laboratory stress paradigms involving elements of forced failure and social evaluation (Dickerson & Kemeny, 2004). The HPA axis is extremely sensitive to inputs from the limbic system and prefrontal cortex (McGewen et al., 1968; Sanchez et al., 2000), two brain areas implicated in neurobiological models of addiction (e.g., Bechara, 2005; Everitt & Robbins, 2005; Goldstein & Volkow, 2002; Koob & LeMoal, 2008; Li & Sinha, 2008; Volkow, Fowler, & Wang, 2004). Additionally, acute exposure to stress also reliably activates the ANS, resulting in increased cardiovascular and respiratory output, as well as increased secretion of catecholamines (i.e., epinephrine and norepinepherine) (Chrousos & Gold, 1992). Further, some studies have reported relationships between HPA axis functioning and ANS activation (Kizildere, Gluck, Zietz, Scholmerich, & Straub, 2003; Young, Abelson, & Cameron, 2005) suggesting that these two systems are activated in response to stress via overlapping mechanisms.

Similar to the acute effects of smoking, acute stress exposure is also associated with increases in dopaminergic neurotransmission in mesolimbic “reward” regions of the brain (Dunn, 1988; Kalivas & Duffy, 1989; Piazza & Le Moal, 1996; Prasad, Sorg, Ulibarri, & Kalivas, 1995; Thierry, Tassin, Blanc, & Glowinski, 1976). Moreover, stress has been shown to sensitize animals to the reinforcing effects of amphetamines (e.g., Goeders & Guerin, 1996), thus illustrating the relationship between stress and drug reinforcement and motivation. Taken together, the available evidence suggests that stress activates both brain stress and reward circuits simultaneously, just as acute nicotine exposure does, thereby providing the neural substrate by which exposure to acute stress may prime drug craving and enhance the reinforcing effects of drugs of abuse, including nicotine (Sinha, 2001; 2008).

3. The Biological Stress Response and Smoking Initiation and Progression

3.1 HPA axis reactivity to stress and smoking initiation

Given the highly addictive nature of cigarette smoking, one important approach to addressing this public health concern is to identify individuals at the highest risk of smoking initiation, and target prevention efforts toward these high-risk individuals. Indeed, the biological stress response, and HPA axis reactivity to stress in particular, has been studied as a potential indicator of vulnerability to substance use initiation and progression to addiction. Specific to HPA axis functioning, most of the work on substance use initiation has relied primarily on animal models using substances other than nicotine (e.g. alcohol and illicit drugs); however, a small number of studies in humans have recently emerged contributing further to this literature. The available data on smoking initiation among human subjects is extremely limited, is not specifically relevant to stress reactivity per say, is somewhat contradictory, and excludes assessments of ANS functioning, thus precluding us from drawing any major conclusions. This being said, the relevant research findings in the area of smoking initiation are highlighted below.

Regarding the available animal findings, studies largely suggest that hyperactivation of the HPA axis in response to stress may increase one’s vulnerability to substance use initiation (Piazza, Deminiere, Le Moal, & Simon, 1989, 1990; Piazza, Derouche, Rouge-Pont, & Le Moal, 1998; Piazza & Le Moal, 1996; Piazza et al., 1991). Specifically, rats who respond to stressful stimuli with prolonged secretion of the HPA stress hormone corticosterone, a cortisol equivalent in animals, as well as enhanced locomotor responses, were more likely to acquire amphetamine self-administration behavior than those with lower-level stress reactivity (Piazza et al., 1991). Moreover, administration of corticosteroids to rats who were

low level responders led to an increased risk that these rats would begin to self-administer amphetamines, suggesting a causal role of corticosteroids in drug self-administration.

Among humans, Moss and colleagues conducted a series of two studies examining the relationship between HPA functioning and subsequent substance use experimentation. First, Moss, Vanyukov, and Martin (1995) examined the roles of family history and current child externalizing problems in HPA axis functioning. Specifically, the researchers assessed cortisol reactivity to a novel neurophysiological task in 10–12 year old boys with (FH+; n = 81) and without (FH−; n = 103) a family history of alcohol and drug use. FH+ boys showed lower cortisol levels in anticipation of the task, and an attenuated decline in cortisol levels following the task compared to FH− boys, suggesting an association between blunted HPA axis functioning and a family history of alcohol and drug use. However, additional analyses revealed that the significant relationship between risk-group and cortisol reactivity to the novel task was entirely accounted for by child measures of aggressive delinquency and impulsivity, suggesting that externalizing problems may contribute to the pattern of HPA dysregulation that was seen among at-risk boys.

A subsequent study conducted with the same sample of boys showed that low anticipatory cortisol secretion at age 10–12 was the strongest predictor of experimentation with cigarettes and marijuana at age 15–16, regardless of family history (Moss, Vanyukov, Yao, & Kirillova, 1999). Although these studies provide some preliminary evidence for the role of blunted cortisol reactivity to stress in smoking initiation, there are several limitations that should be noted. First, the researchers made no deliberate attempt to induce stress or anxiety in response to the novel task; therefore, the findings herein may be better characterized as HPA axis reactivity to novelty, rather than stress in particular. Additionally, there was no control condition to allow for the examination of cortisol functioning in the absence of the novel task (i.e., basal HPA axis functioning). Finally, the authors did not directly test for the role of externalizing problems at age 10–12 (i.e., aggressive delinquency and impulsivity) in the development of subsequent experimentation with cigarettes and marijuana at age 15–16. Early externalizing problems represent a clear confounding factor that may better account for the development of substance use experimentation among at-risk boys; therefore, replication and expansion of these findings are clearly needed in order to further elucidate the causal relationships between externalizing psychopathology, biological stress reactivity, and human smoking initiation.

3.2 Basal HPA axis functioning and smoking initiation

More recently, a second group of researchers examined the complex relationships between basal HPA axis functioning, stressful life events, smoking, and depression (Rao, Hammen, London, & Poland, 2009). One hundred and fifty-one adolescents with no personal or family history of psychiatric disorders (n = 48), with no personal psychiatric history but a family history of parental depression (n = 48), and with current major depressive disorder (n = 55) provided evening salivary cortisol and nocturnal free urinary cortisol for three consecutive nights. They were then followed up at six-month intervals over the course of five years to assess smoking history, clinical course of depression and other psychiatric disorders, and stressful life events. Results indicated that higher basal cortisol levels were associated with an increased risk of smoking initiation and smoking persistence, and that exposure to stressful life events had an additive effect on smoking. Additionally, higher basal cortisol values at baseline and exposure to stressful life events during follow up partially mediated the positive relationship between smoking and subsequent depressive episodes. Overall, findings from this study suggest that high basal HPA axis functioning may be a risk factor for smoking initiation and persistence among adolescents, and stressful life events can function to further increase this risk. Additionally, high basal HPA axis functioning and stressful life events both play a mediating role in the relationship between smoking behavior

and the clinical course of depression. More prospective studies of this kind are needed to clarify the relationship between basal HPA axis functioning and smoking risk among both clinical and non-clinical samples.

3.3 HPA axis reactivity to stress and smoking progression

In addition to smoking initiation, we know of one study to date that has examined the relationship between stress reactivity and smoking progression (de Wit, Vicini, Childs, Sayla, & Terner, 2007). Forty-four light to moderate non-dependent young adult smokers were recruited and exposed to an oral dose of dextroamphatamine (20mg), an oral placebo, and a psychological stressor across three separate laboratory sessions while their heart rate, blood pressure, and salivary cortisol concentrations were monitored. Thirty-one of the participants then completed a follow-up interview 6 months later to assess alcohol and drug use, with a specific emphasis on cigarette smoking. Stress-induced changes in salivary cortisol concentrations were positively associated with cigarette smoking progression during the 6-month follow-up period. Conversely, salivary cortisol response to dextroamphatamine was not related to smoking progression, and the authors did not report on the relationships between cardiovascular reactivity and smoking outcomes. In contrast to the smoking initiation findings from Moss and colleagues, these findings are consistent with laboratory animal findings such that greater HPA axis reactivity to stress (but not dextroamphatamine) was associated with an increasing trajectory of smoking progression among regular non-dependent smokers.

3.4 Summary

Taken together, the available human findings suggest that blunted HPA axis reactivity among pre-adolescent children may serve as a risk factor for smoking initiation, while high basal HPA axis functioning among adolescents and HPA hyper-reactivity to stress among smoking-experienced young adults are both indicators of increased smoking behavior. However, these findings are all very limited given that few researchers have studied the role of HPA functioning in smoking initiation and progression. Moreover, the challenge that was used in the studies on HPA reactivity and smoking initiation was not truly a stressor, but more of a novel experience, which is not well suited for drawing firm conclusions about the relationship between cortisol reactivity to stress and smoking initiation. Additionally, to our knowledge neither line of research has reported significant effects of ANS functioning in predicting smoking initiation or progression. These limitations and remaining questions clearly highlight the need for replication and extension of findings regarding the role of biological stress reactivity in the relationship between stress, smoking initiation, and progression.

4. The Biological Stress Response and Smoking Maintenance

Neurobiological models of addiction suggest that chronic substance use is associated with neuroadaptive changes in neural circuits implicated in motivation and reinforcement, including decreased activation in brain reward systems and increased recruitment of opposing brain stress circuits (e.g., Koob & LeMoal, 2001). This combination of depressed reward circuits and elevated antireward circuits is hypothesized to be the driving force motivating continued drug seeking behavior (Koob & Le Moal, 2008). Further, elevated activation of brain stress systems is hypothesized to reduce an individual's ability to adapt or cope with additional stressors and may increase the reinforcing effects of acute nicotine exposure during abstinence, thereby contributing to the increased vulnerability to relapse brought on by stress exposure during abstinence. As such, a comprehensive examination of biological stress circuits among chronic smokers is crucial for understanding the maintenance of this highly addictive behavior.

4.1 Basal HPA axis functioning among habitual smokers

Among habitual smokers, a substantial body of research has been established examining HPA axis functioning both at rest and in response to stress. Specific to resting state functioning, evidence suggests that chronic cigarette smokers exhibit elevated cortisol concentrations throughout the day compared to nonsmokers (Baron, Comi, Cryns, Brinck-Johnsen, & Mercer, 1995; Cam & Bassett, 1984; del Arbol et al., 2000; Field, Colditz, Willett, Longcope, & McKinlay, 1994; Frederick et al., 1998; Kirschbaum et al., 1992); however, this elevation may be explained by repeated acute nicotine-induced increases in cortisol that occur throughout the day (Kirschbaum et al., 1994). As such, it is unclear whether elevated cortisol concentrations play a causal role in smoking maintenance, or if increased basal cortisol levels are merely a consequence of repeated acute exposure.

4.2 HPA axis reactivity to stress among habitual smokers

In addition to abnormalities in cortisol secretion at rest, researchers have also reported abnormal cortisol responses to stress among habitual smokers. Specifically, several studies have shown that smokers exhibit a blunted cortisol response to stress compared to nonsmokers, even after controlling for baseline cortisol concentrations (al'Absi, Wittmers, Erickson, Hatsukami, & Crouse, 2003; Baron, Comi, Cryns, Brinck-Johnsen, & Mercer, 1995; Gilbert, Meliska, & Plath, 1997; Kirschbaum, Strasburger, & Langkrar, 1993; Rohleder & Kirschbaum, 2006; Roy, Steptoe, & Kirschbaum, 1994). For example, Kirschbaum, Strasburger, and Langkrar (1993) found an attenuated cortisol response in habitual smokers (n=10) compared to nonsmokers (n=10) following a standardized public speaking task and mental arithmetic task in front of an audience. They suggested that frequent and prolonged stimulation of the HPA axis as a result of cigarette smoking leads to a reduced responsiveness of the system. This hypothesis was supported by Rohleder & Kirschbaum (2006) when they subjected 118 nonsmokers and habitual smokers (>10 cigarettes per day) to the Trier Social Stress Test (TSST) (Kirschbaum, Pirke, & Hellhammer, 1993). Although they found a significant increase in cortisol levels across all subjects in response to the stressor, this response was blunted among smokers as compared to their nonsmoking counterparts. Similar findings were reported by Childs and de Wit (2009) in an all-male sample of smokers (n=15) and non-smokers (n=20). Smokers exhibited a blunted cortisol response to the TSST and prolonged subjective ratings of agitation following the stressor as compared to non-smokers, suggesting a possible relationship between hypoactive HPA axis reactivity to stress and a prolonged time to recovery from the subjective mood altering effects of stress exposure.

A more recent study subjected daily smokers (DS; n=35), occasional smokers (OS; n=13), and non-smokers (NS; n=58) to the TSST in order to examine the effects of dependence severity, smoking habits, and cortisol reactivity to stress on smoking urges (Buchmann et al., 2010). Cortisol concentrations significantly increased following exposure to the stressor across all three groups; however, the magnitude of cortisol increase was significantly lower among DS as compared to OS and NS. There was no significant difference between the OS and NS participants. Ratings of smoking urges significantly increased following the stressor among DS and OS, and the change in smoking urge positively correlated with cortisol response to stress among DS. As such, the findings from this study provide additional evidence of a blunted cortisol response to stress among DS; however, somewhat paradoxically, cortisol reactivity to stress among DS was positively correlated with smoking urges.

To account for the finding that DS who have a more "normal" (i.e., less blunted) pattern of cortisol reactivity to stress actually report the highest stress-induced cravings, the authors proposed a new hypothesis involving a classical conditioning process. Specifically, acute

cigarette smoking is accompanied by a short burst in cortisol secretion. This repeated pairing over time leads to a classically conditioned relationship between cortisol secretion and the reinforcing effects of cigarettes. As a result, stress-induced cortisol activation in the absence of cigarette smoking may act as a conditioned stimulus, thus triggering cigarette craving. This hypothesis is supported by the fact that the positive relationship between cortisol reactivity and cigarette craving was only seen among DS who have had more regular exposure to the cortisol-activating effects of acute cigarette smoking, and thus more opportunity to develop this conditioned relationship. Additional research involving experimental manipulation of the HPA axis is needed in order to test this hypothesis, and determine whether cortisol reactivity to stress plays a causal role in triggering cigarette cravings among daily smokers.

Other researchers have found interesting moderating effects of gender in the relationship between smoking status and cortisol reactivity to stress (Back et al., 2008). Specifically, 46 participants (25 female) were exposed to the TSST and a pharmacological stressor (corticotrophin releasing hormone (CRH) administration) following two separate, but consecutive, overnight stays at the research facility. ACTH, cortisol, blood pressure, and heart rate were monitored throughout both sessions. There was no significant effect of smoking status, and no significant interaction between gender and smoking status in predicting blood pressure or heart rate, either at baseline or in response to the challenges. There was a significant interaction between gender and smoking status in predicting cortisol reactivity to stress, such that female smokers showed a lower cortisol response to both the TSST and the CRH challenge as compared to female non-smokers, but no significant difference was seen between male smokers and non-smokers. These results suggest that women may be more sensitive to the blunting effect of chronic smoking on cortisol reactivity to stress, and may help to explain the increased difficulty with smoking cessation that has been reported among women as compared to men (Borrelli et al., 2004; Sherman et al., 2005; Wileyto et al., 2005). However, the role of HPA axis functioning as a mediator in the relationship between gender and smoking cessation outcomes must be tested in future larger scale studies in order to clarify these relationships.

4.3 Combined effects of stress and smoking on HPA functioning among habitual smokers

Given that HPA axis response to stress appears to be altered among smokers, and empirical evidence suggests that stress tends to increase craving, smoking intensity, and smoking frequency among smokers (Cherek, 1985; Epstein & Collins, 1977; Mangan & Golding, 1984; Parrott, 1993; Perkins & Grobe, 1992; C. S. Pomerleau & Pomerleau, 1987; Rose, Ananda, & Jarvik, 1983; Schachter, Silverstein, & Perlick, 1977), researchers have also focused on examining the additive effects of stress and smoking on HPA axis functioning. There are a number of studies in humans which suggest that nicotine additively increases both the cortisol and sympathetic response to stress (Benwell & Balfour, 1982; Davis & Matthews, 1990; Dembroski, MacDougall, Cardozo, Ireland, & Krug-Fite, 1985; Kirschbaum, Scherer, & Strasburger, 1994; MacDougall, Musante, Howard, Hanes, & Dembroski, 1986; Perkins, Epstein, Jennings, & Stiller, 1986; O. F. Pomerleau & Pomerleau, 1990; Roy, Steptoe, & Kirschbaum, 1994). Specific to cortisol functioning, Pomerleau and Pomerleau (1990) examined both the individual and combined effects of a psychological stressor and smoking on cortisol secretion among 8 moderate smokers. Participants were exposed to a psychological stressor (a mental arithmetic task) or no stress (reading National Geographic aloud), followed by either smoking a regular cigarette or pretending to smoke an unlit cigarette. The stress task produced a significant increase in cortisol within minutes of the stressor followed by a decline in cortisol concentrations until the end of the session, while exposure to cigarettes produced a gradual increase in cortisol concentrations that continued until the end of the session. When both acute stress and

cigarette smoking were combined, the elevating effects of both manipulations on cortisol secretion were additive. This study should be interpreted with caution, however, given that it was based on a small sample of smokers (n = 8), included only males, and failed to include a control group of non-smokers. As such, it is unclear if smoking-naïve individuals would exhibit the same pattern of additive effects, and if the combined effects of smoking and psychological stress that were observed among smokers would appear blunted compared to controls.

More recently, researchers used a novel laboratory model of smoking lapse that combined psychological stress with the opportunity to smoke a cigarette in order to examine the effects of stress on the ability to resist smoking (McKee et al., 2010). Using a within subjects design, 37 daily smokers were deprived of nicotine overnight and exposed to a personalized stress or neutral imagery script on two separate days. Following imagery exposure, participants were given the option to either smoke or delay smoking initiation for up to 50 minutes in exchange for small monetary reinforcements. Upon initiating the first cigarette (or after 50 minutes for those who resisted smoking for the entire delay period), participants were allowed a 1-hour ad libitum smoking session. Exposure to the stress imagery script significantly increased cortisol concentrations, negative emotions, smoking craving, and sympathetic response relative to the neutral condition. Additionally, cortisol concentrations continued to increase as participants commenced the ad libitum smoking period, and higher cortisol and ACTH concentrations at these later time points were associated with a reduced ability to resist the first cigarette following stress, and with higher ratings of smoking satisfaction and reward. These findings suggest that stress and acute nicotine exposure may additively increase cortisol concentrations among habitual smokers, and that cortisol reactivity to cigarette smoking in the context of stress may increase the reinforcing effects of nicotine thus driving continued smoking maintenance.

4.4 ANS functioning among habitual smokers

In addition to dysregulated HPA axis functioning, convergent research suggests that chronic cigarette smoking also results in altered ANS functioning. Regarding sympathetic nervous system (SNS) functioning, chronic nicotine exposure appears to decrease, or even completely abolish, the sensitivity of nicotinic receptors (Gentry & Lukas, 2002) and smoking-induced catecholamine release (Niedermaier et al., 1993), resulting in reduced sympathetic response to acute cigarette exposure among smokers as compared to non-smokers (Grassi et al., 1994; Najem et al., 2006; Niedermaier et al., 1993). In the absence of acute cigarette smoking, chronic smokers exhibit increased sympathetic activation at rest as compared to non-smokers, as measured by resting muscle sympathetic nerve activity (Hering, Kucharska, Kara, Somers, & Narkiewicz, 2010) and basal plasma norepinephrine levels (Jensen, Espersen, Kanstrup, & Christensen, 1996). Thus, habitual smoking appears to chronically elevate basal SNS arousal, and reduce SNS reactivity to acute cigarette smoking.

A substantial body of research has also examined the relationship between chronic cigarette smoking and heart rate variability (HRV), which is thought to reflect the balancing action of the SNS and the parasympathetic nervous system (PNS), which concurrently influence the heart's ability to detect and quickly respond to unpredictable challenges (Acharya, Joseph, Kannathal, Lim, & Suri, 2006). Lower HRV generally indicates a reduced ability of the heart to adapt to changing circumstances (Acharya et al., 2006). Short- and long-term cigarette smoking are both associated with increased sympathetic activity and decreased parasympathetic activity, resulting in reduced HRV (Cryer et al., 1976; Hayano et al., 1990; Tsuji et al., 1996; Yotsukura et al., 1998). Moreover, HRV is lower in smokers compared to non-smokers (Gallagher et al., 1992;), in heavy smokers compared to light smokers (Kupari et al., 1993), and in cigarette exposed fetuses relative to non-exposed fetuses (Zeskind &

Gingras, 2006). These alterations in autonomic functioning may contribute to the increased risk of cardiovascular disease associated with cigarette smoking (Pope, 2001).

4.5 Summary

Among habitual smokers, the work on HPA axis functioning generally points to elevated basal cortisol levels and a blunted HPA axis response to stress among smokers relative to nonsmokers, and indicates that cortisol reactivity to stress among smokers is positively correlated with smoking urges (Buchmann et al., 2010) and smoking satisfaction and reward (McKee et al., 2010). It is possible that chronic elevations in basal cortisol levels among habitual smokers result in altered responsivity of the HPA axis to stress, leading to blunted cortisol reactivity to stress. As was suggested by Lovallo (2006), blunted HPA axis reactivity to psychological stress may be indicative of an inability to adapt or cope in the face of distress. Impairments in adaptive coping mechanisms may then lead to an overreliance on cigarette smoking as a means to cope in times of stress, thereby driving the relationship between stress and cigarette craving and relapse (Cohen & Lichtenstein, 1990; Falba, Teng, Sindelar, & Gallo, 2005; Heishman, 1999; Hymowitz, Sexton, Ockene, & Grandits, 1991; Matheny & Weatherman, 1998; Payne, Schare, Levis, & Colletti, 1991; Siahpush & Carlin, 2006; Wewers, 1988). Additionally, the consistent finding that cortisol response to stress is related to subjective ratings of smoking urges and reward suggests that cortisol may function to increase the reinforcing effects of smoking in the context of stress, thus driving continued smoking maintenance among habitual smokers. As such, cortisol functioning may play a mediating role in the relationship between stress and smoking maintenance. However, additional research is needed to understand the extent to which cortisol functioning serves as a causal agent in maintaining smoking behavior.

The literature on habitual smokers also includes research on the ANS effects of chronic cigarette exposure. Chronic smoking is associated with decreased sympathetic activation in response to acute cigarette exposure and chronically elevated SNS arousal at rest, as well as lower HRV among habitual smokers as compared to non-smokers, suggesting an imbalance between sympathetic and parasympathetic functioning. Like chronic smoking, chronic stress also leads to alterations in autonomic system functioning, including increased sympathetic arousal as measured by blood pressure and heart rate (Weber et al., 2010), as well as decreased HRV (Chida & Hamer, 2008). Despite these clear relationships between ANS functioning, stress, and smoking, cardiovascular measures of autonomic arousal have not been associated with the ability to resist smoking (McKee et al., 2010), suggesting that stress-induced SNS activation and impaired PNS functioning may not play as big of a role in smoking motivation and reinforcement as HPA axis activation does. More research is clearly needed to determine whether or not altered sympathetic arousal or parasympathetic imbalance might play a role in smoking motivation, reinforcement, and maintenance.

5. The Biological Stress Response and Smoking Withdrawal and Relapse

Numerous studies have found that stress is an important risk factor for smoking relapse (Cohen & Lichtenstein, 1990; Shiffman et al., 1996; Wills, Sandy, & Yaeger, 2002). For example, it has been shown that smokers who failed to quit or who were early relapsers reported high levels of stress prior to initial abstinence and at one, three, and six months following cessation (Cohen & Lichtenstein, 1990). In addition, certain nicotine withdrawal symptoms such as irritability, anxiety, and some physical symptoms can resemble the physiological stress response and may contribute to stress-related enhancement of the desire to smoke (Parrott, 1995). Given the key role of stress in smoking withdrawal and relapse, biological stress reactivity may play an important role in mediating the relationship between stress and subsequent withdrawal symptoms and relapse following smoking cessation.

5.1 HPA axis functioning and smoking withdrawal

A series of studies by al'Absi and colleagues examined the role of cortisol in the relationship between stress, smoking withdrawal, and subsequent relapse in the real world (for detailed review, see al'Absi, 2006). In the first step, al'Absi, Amunrud, & Wittmers (2002) examined the effects of short term nicotine abstinence on psychophysiological activity and mood changes both at rest, and in response to a stressful task. Thirty habitual smokers participated in two laboratory sessions where they completed a mental arithmetic challenge, following either overnight abstinence or ad libitum smoking. Overnight abstinence was associated with increased withdrawal symptoms and greater urges to smoke, particularly among women, when compared to the ad libitum condition. Women also evidenced a greater increase in the desire to smoke following exposure to the challenges as compared to men. In addition, participants exhibited greater systolic blood pressure and poorer cognitive performance on the mental arithmetic challenge during abstinence compared to the ad libitum smoking condition, but no significant differences in salivary cortisol levels were reported across the two conditions. Methodological limitations, including the absence of a neutral non-stressed condition and the exclusion of a non-smoking control group, left many questions remaining.

A second study addressed these limitations by examining cortisol reactivity to a public speaking stressor compared to a resting control condition, within a sample of nicotine dependent cigarette smokers randomly assigned to either overnight abstinence (n=21) or ad libitum smoking (n=17), and a nonsmoking control group (n=32) (al'Absi, Wittmers, Erickson, Hatsukami, & Crouse, 2003). Smokers in both groups evidenced higher cortisol concentrations than non-smokers at all time points during the resting condition. During the stress condition, ad libitum smokers showed significantly greater cortisol concentrations at all time points (both pre-stress and post-stress) than the other two groups, suggesting additive effects of acute nicotine exposure and psychological stress on cortisol secretion. However, while nonsmokers evidenced the expected cortisol response to stress, there was no significant increase in cortisol response to the public speaking task in either the abstinent or ad libitum smoking groups. These results are consistent with al'Absi, Amunrud, & Wittmers (2002) and suggest that chronic smoking is associated with enhanced resting adrenocortical activity, but hyporesponsive cortisol reactivity in the face of stress.

5.2 HPA axis functioning and smoking relapse

In a third study, al'Absi, Hatsukami, & Davis (2005) examined the extent to which alterations in cardiovascular and cortisol reactivity to stress among smokers during the first 24 hours of nicotine withdrawal predicted early relapse. Seventy-two smokers who had been abstinent for 24 hours completed a series of psychological stressors including public speaking and cognitive challenges. Results indicated that men, but not women, who relapsed within four weeks evidenced attenuated ACTH and cortisol responses to stress in the first 24 hours of abstinence compared to men who did not relapse. In addition, those who relapsed showed reduced blood pressure response to stress, exaggerated withdrawal symptoms and mood deterioration. Moreover, these responses predicted relapse even when controlling for baseline smoking and psychological measures, suggesting that a hyporesponsive stress response in men, but not necessarily women, is associated with an increased vulnerability for smoking relapse above and beyond other relevant predictors.

5.3 ANS and smoking withdrawal and relapse

In addition to HPA axis functioning, there also appear to be direct effects of smoking cessation on cardiovascular measures of sympathetic arousal and parasympathetic balance (Minami, Ishimitsu, Matsuoka, 1999). Specifically, 42 male habitual smokers were randomly assigned to either one week of smoking abstinence followed by one week of their usual smoking pattern (n=19) or the reverse study design (n=23), and provided 24-hour

ambulatory measures of blood pressure, heart rate, and HRV. Plasma catecholamine levels were also assessed on the last day of each study period. Findings revealed that smoking abstinence was associated with reductions in ambulatory blood pressure and heart rate, as well as plasma norepinephrine and epinephrine levels, and increases in ambulatory HRV as compared to ad-libitum smoking. These findings highlight the immediate and substantial cardiovascular benefits of smoking cessation.

In terms of smoking relapse, al'Absi and colleagues (2005) reported a significantly lower blood pressure response to stress among recently abstinent male smokers who went on to relapse as compared to those who did not relapse. However, this is the only study to our knowledge that found a relationship between stress-induced sympathetic arousal and smoking relapse. Moreover, there is no evidence thus far that chronic smoking-related changes in other measures of sympathetic arousal and parasympathetic control, including plasma catecholamine levels, HR, and HRV are associated with smoking motivation, reinforcement, or relapse. More research is clearly needed to in order to directly examine the extent to which smoking-induced alterations in SNS functioning might influence smoking relapse.

5.4 Summary

There have been very few studies examining cortisol reactivity to stress during early abstinence from habitual smoking, thus highlighting the need for more independent replication. Despite the limited available data, findings suggest that smokers during early abstinence exhibit similar patterns of abnormal HPA axis functioning as ad libitum smokers, including elevated resting cortisol concentrations and blunted cortisol reactivity to stress. There is also evidence to suggest that the severity of HPA axis dysregulation in response to stress predicts relapse among men, but not women. Additionally, withdrawal from habitual smoking is associated with significant improvements in ANS functioning; however, this data was collected among men only, thus limiting the generalizability of these findings to women. More research may be useful for determining the relationship between biological stress reactivity and smoking relapse, and for identifying mechanisms, such as hormonal variation across the menstrual cycle, that may explain the moderating effect of gender in the relationship between cortisol reactivity to stress and smoking outcomes.

6. Future Directions

The examination of physiological measures of stress, including cortisol concentrations, SNS arousal, and HRV has provided new insights into the relationship between stress and smoking across stages. Convergent data suggests that chronic cigarette smoking is associated with elevated basal cortisol levels and a hypoactive cortisol response to stress. Far less data is available, however, regarding the role of basal and tonic cortisol functioning in smoking initiation and relapse to smoking following cessation. Additionally, research on ANS functioning among chronic smokers has provided information about the mechanisms underlying the relationship between chronic smoking and cardiovascular disease, but almost no research exists examining the role of SNS arousal or parasympathetic balance in smoking initiation, or in smoking motivation and reinforcement among current habitual smokers and chronic smokers in the early stages of abstinence. We now outline a number of clear gaps that remain in the literature, and offer suggestions for addressing these gaps in order to maximize the contribution of future work.

6.1 Future directions in research examining the role of HPA axis functioning in smoking

6.1.1 Considering both Tonic and Phasic Cortisol Functioning—First, there is a clear dearth of existing studies reporting on the relationship between baseline (i.e., tonic)

cortisol concentrations and subsequent cortisol reactivity to stress (i.e., phasicfunctioning) among chronic smokers. That is, it is possible that high tonic functioning may lead to blunted phasic cortisol reactions to stress due to a “ceiling effect”, such that chronically elevated cortisol levels may inhibit the potential for high cortisol reactivity in response to stress. Importantly, cortisol is not only involved in activating the physiological stress response, but also plays a regulatory role in terminating the stress response through negative feedback loop processes (Tsigos & Chrousos, 2002). As such, individuals who display chronically elevated cortisol levels may be vulnerable to premature stimulation of the negative feedback loop that functions to turn off the HPA axis response to stress. A significant association between higher baseline cortisol concentrations and a blunted cortisol response to stress has been reported within studies of alcohol dependent subjects (Sinha et al., 2009); however, to our knowledge, the relationship between tonic and phasic cortisol functioning has not been directly reported in smokers. There is some evidence to support a relationship between tonic and phasic functioning given that habitual and abstinent smokers consistently display both elevated tonic cortisol concentrations and blunted cortisol reactivity to stress, and limited evidence also suggests that individuals at risk for smoking initiation and progression display both elevated basal HPA axis functioning (Rao et al., 2009) and blunted reactivity to stress (De Wit et al., 2007); however, the relationship between tonic and phasic HPA axis functioning has not been directly tested at any point in the addiction process. As such, future researchers should consider assessing both tonic and phasic cortisol functioning in order to obtain a more complete picture of the role of cortisol functioning in smoking behaviors.

6.1.2 Psychopathology—Psychopathology may be an important mechanism involved in the relationship between HPA axis dysregulation and smoking. HPA axis functioning has consistently been found to be hypoactive in individuals with certain psychopathology including antisocial personality disorder (Vanyukov et al., 1993; Virkkunen, 1985) and PTSD (Yehuda, Halligan, & Bierer, 2002). Further, smoking rates are significantly higher among individuals who suffer from a number of psychological disorders as compared to healthy individuals (Lasser et al., 2000). Surprisingly, there is limited research examining the role of psychopathology as a possible mediator or moderator in the relationship between HPA axis functioning and smoking. Specific to smoking initiation, Moss and colleagues did not specifically test for the effects of early externalizing problems on subsequent experimentation with smoking; therefore, it is unclear if the reported relationship between HPA hyporeactivity and smoking initiation may be better accounted for by factors such as delinquency or impulsivity. Similarly, Rao and colleagues (2009) found that basal HPA axis functioning partially mediated the relationship between smoking and depressive episodes; however, HPA axis reactivity to stress was not assessed in this study. As such, more research is needed to determine how psychopathology fits into the relationship between HPA axis hyporeactivity and smoking initiation.

Among current smokers, work examining psychopathology has largely focused on cortisol concentrations at rest, as opposed to HPA reactivity to stress. For example, Canals, Colomina, Domingo, & Domenech (1997) noted that among smokers, psychopathology such as comorbid anxiety or depression (two forms of psychopathology that frequently co-occur with nicotine dependence; Hall, 1996; McCabe et al., 2004; Tsoh et al., 2000), can also have an effect on cortisol secretion. In a sample of 106 adolescents, they found that moderate to heavy (10+ cigarettes per day) female smokers had significantly higher mean cortisol levels than light smokers and nonsmokers; however, this difference was not significant in males, but only emerged among when male subjects with ICD-10 psychopathology (i.e. sleep, mood, and anxiety disorders) were excluded from the sample. These results show some interesting sex differences in the relationship between HPA functioning and smoking, and

suggest that psychopathology can be an important moderator in this relationship, particularly in males.

A more recent study by Olff and colleagues (2006) examined the interaction between smoking status and post-disaster psychopathology (PTSD and post-traumatic MDD) to predict circadian salivary cortisol patterns in a sample of survivors of a large fireworks disaster in the Netherlands. Researchers found that salivary cortisol levels were significantly higher in smokers throughout the day than in nonsmokers, and that survivors with post-traumatic MDD tended to smoke more cigarettes than other survivors. After controlling for quantity of smoking, researchers found differences in salivary cortisol patterns with healthy survivors and survivors with PTSD showing the usual dynamic rise and fall of salivary cortisol concentrations over the course of the day, while survivors with MDD showed a flattened circadian salivary cortisol profile. Based on these findings, the authors suggest that cigarette smoking may be an important mediator in the relationship between traumatic stress disorders and HPA axis functioning. However, it is possible that individuals with flattened circadian salivary cortisol patterns prior to the trauma may have been at a greater risk of developing post-traumatic MDD. More research is needed in order to more fully understand the directionality of these relationships.

Psychopathology may also be an important factor to consider when examining the relationship between HPA reactivity to stress and relapse. A number of studies have suggested that some forms of psychopathology, including depression in particular, are associated with an increased risk of relapse among smokers (Glassman et al., 1993; Glassman et al., 1988); however, little research has examined the role of HPA axis functioning in this relationship. The only study of this kind to date examined HPA functioning during early abstinence from smoking in a sample of 24 women with and without a history of depression (O. F. Pomerleau et al., 2004). Specifically, participants were exposed to a 5-day interval of ad libitum smoking, followed by another equal interval of abstinence from smoking. On the fourth day of each condition, participants were administered a standardized dysphoric mood induction procedure, followed by a 1mg dose of dexamethasone at 11pm. Although the depression history group showed a greater level of depression following the mood induction and higher levels of withdrawal distress than the group with no depression history, there were no differences in cortisol response to the dexamethasone suppression test between diagnostic groups. However, depression history was associated with an overall elevation in ACTH levels, as well as limited ACTH suppression during the abstinence condition. Thus, HPA axis dysregulation cannot be ruled out as a potential mechanism underlying the increased risk of relapse among individuals with a history of depression. Further research with more severe clinical populations is needed to gain additional insight about the influence of HPA functioning in the relationship between depression and smoking relapse.

6.1.3 Individual Differences—It is unclear the extent to which the role of HPA axis functioning within each stage of smoking may be better accounted for by other individual difference factors that are associated HPA axis dysregulation such as chronic stress (e.g., Li, Power, Kelly, Kirschbaum, & Hertzman, 2007; Ockenfels et al., 1995), genetic variations (Kumsta et al., 2007; Uhart, McCaul, Oswald, Choi, & Wand, 2004), childhood trauma (Heim et al., 2000; Newport, Heim, Bonsall, Miller, & Nemeroff, 2004), and nicotine exposure in utero (Schuetze, Lopez, Granger, & Eiden, 2008). It is notable that Moss and colleagues (1999) found that children whose fathers either had a current SUD, or who were only recently abstinent (within the last two years) showed the lowest cortisol responses to the stressor. The authors suggested that lower HPA axis response to stress among this subsample may be suggestive of a biological adaptation to the chronic stress of being exposed to a father with an SUD. However, an alternative explanation of the finding is that

fathers who evidence more chronic forms of SUD may confer a greater genetic load for SUD risk onto their children, and these genetic factors may represent a common mechanism underlying both HPA dysregulation and SUD risk. These two interpretations are unlikely to be mutually exclusive, and both may influence the relationship between HPA axis functioning and smoking initiation.

Regarding studies of HPA axis functioning and smoking maintenance and relapse, individual difference variables have not routinely been measured. Future researchers should aim to assess individual difference factors such as personality, chronic stress, and genetic variability in order to understand the extent to which HPA axis functioning can predict smoking outcomes above and beyond these other relevant factors.

6.1.4 Gender—Gender is another important mechanism that is in need of greater study in the relationship between HPA axis functioning and smoking outcomes. Indeed, gender differences have not always been explored in studies of HPA axis functioning and smoking, and some studies have limited their samples to only a single gender, thus precluding opportunities to explore differences. However, some notable gender differences have been reported, particularly as they relate to smoking outcomes. For example, al'Absi and colleagues (2005) reported that the severity of HPA axis dysregulation during smoking abstinence predicts relapse among men, but not women. It is possible that the limited predictive utility of HPA axis functioning among women may be due to the influence of sex hormones on cortisol reactivity to stress. Gender differences have been found, with the majority of studies reporting a smaller salivary cortisol response to psychological stress in healthy women as compared to men (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Kudielka & Kirschbaum, 2005; Rohleder & Kirschbaum, 2006).

Menstrual phase has also been shown to significantly influence HPA axis reactivity, with women in the luteal phase showing increased HPA axis response to stress as compared to the follicular phase (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Rohleder, Schommer, Hellhammer, Engel, & Kirschbaum, 2001; Tersman, Collins, & Eneroth, 1991; Wolf, Schommer, Hellhammer, McEwen, & Kirschbaum, 2001). Additionally, research suggests that HPA axis functioning tends to be more inconsistent among menopausal women and women on hormone therapy (Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004; Lindheim et al., 1992; Seeman, Singer, Wilkinson, & McEwen, 2001). As such, sex hormone related factors such as menstrual phase, menopause, and hormonal contraceptives may reduce the reliability of the HPA axis as a measurement tool, thus reducing the utility of cortisol reactivity as a predictor of smoking outcomes among women. However, more research is needed in order to test this hypothesis.

6.1.5 Causality—Despite accumulating descriptive data regarding the role of HPA axis functioning across all stages of smoking, there remain core questions regarding causality in observed relationships. As of yet, it is not clear whether cortisol is an epiphenomenon marking nicotine dependence, or whether cortisol is a causal mechanism in its own right that drives continued nicotine use and relapse. In order to answer these questions, it is necessary to conduct studies that experimentally manipulate the HPA axis, and cortisol in particular, and examine the consequences on smoking behavior and outcomes. For example, intravenous administration of corticotrophin releasing hormone (CRH) has been used to examine the relationship between HPA axis activation and drug craving among cocaine users (Brady et al., 2009). By using similar experimental manipulation of the HPA axis among smokers, future researchers may be able to provide answers regarding the extent to which cortisol is simply a marker of nicotine dependence or is a causal mechanism driving smoking behavior and outcomes. Alternatively, pharmacological and behavioral manipulation studies that experimentally decrease tonic cortisol concentrations or increase

cortisol reactivity to stress, and assess the impact of these manipulations on smoking behavior, may also provide clues on the causal role of the HPA axis, and cortisol in particular, in smoking behavior and relapse.

6.2 ANS functioning

It is clear from existing findings that chronic cigarette smoking has a significant effect on catecholamine levels, as well as cardiovascular measures of ANS functioning. The literature on the role of ANS functioning in cigarette smoking faces many of the same limitations as the HPA axis functioning literature. Clearly missing from the literature, for example, is research examining SNS and PNS functioning as predictors of smoking initiation and relapse, as well as the role of SNS functioning and parasympathetic balance in smoking motivation, reinforcement, and maintenance. That is, does ANS functioning merely serve as a marker of chronic cigarette smoking, or is it possible that smoking-induced alterations in ANS functioning might play a causal role in smoking risk? Additional research is needed to answer these questions. More research is also needed to elucidate the effects of gender, psychopathology, and individual difference factors on the relationship between ANS functioning and cigarette smoking. Moreover, future research could expand on extant findings by conducting more integrative work on HPA and ANS functioning within smoking to gain a deeper understanding of how these systems function together, and to identify the common and unique mechanisms underlying each system's relationship with chronic smoking. Taken together, there are a number of clear directions for future work examining the role of biological stress reactivity in smoking initiation, maintenance, and relapse, with many opportunities available for expanding our knowledge of these relationships.

7. Conclusions

The assessment of biological stress mechanisms, including HPA axis functioning and ANS arousal in particular, is one approach to expanding our understanding of the mechanisms underlying the relationship between stress and smoking initiation, maintenance, and relapse following cessation. Research to date suggests that chronic smoking leads to alterations in both HPA axis and ANS functioning. Despite the advances that have been made, a number of clear research gaps remain. Suggestions for addressing these research gaps include examining the relationship between basal cortisol concentrations and cortisol reactivity to stress across the diurnal cycle; isolating the role of psychopathology in the relationship between biological stress mechanisms and smoking; incorporating assessment batteries tapping a wide range of individual factors, including genetic vulnerability, personality, and environmental adversity; recruiting larger samples of both male and female smokers with more careful controls for gender-related factors (e.g., menstrual phase) that may reduce the reliability of biological measures among women; experimentally manipulating the HPA axis in order to ascertain the causal role of HPA dysfunction in smoking behaviors; and conducting more integrative research that examines the relationship between measures of HPA axis functioning and ANS activation at different stages of nicotine addiction, as well as the differential utility of these measures in predicting smoking initiation and relapse. Addressing these research gaps and limitations may be useful for developing larger integrative models that include mediators and moderators of the relationship between stress and smoking, clarifying the causal role of biological stress reactivity in smoking outcomes, and developing and evaluating treatments targeting dysregulated biological stress circuits among smokers.

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Research Highlights

- Chronic smoking is associated with alterations in biological stress reactivity.
- Altered biological stress circuits may increase reinforcing effects of smoking.
- Most extant research is in chronic smokers, more work needed in initiation.
- Future work should integrate measures of individual difference factors.
- Experimental manipulation of stress circuits needed to elucidate causal relations.