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Sex Differences in Physiological Response to the Combination of Stress and Smoking

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Abstract

Stressful situations are among the most commonly cited smoking triggers. Smoking and stress exposure each individually increase cardiovascular and hypothalamic-pituitary-adrenal measures with larger increases occurring when stress and smoking are combined. In this analysis, sex differences in the physiological response to the combination of stress and smoking are examined. Smokers (36 males; 34 females) completed a laboratory session in which systolic (SBP) and diastolic blood pressure (DBP), heart rate (HR), plasma epinephrine (Epi), norepinephrine and cortisol concentrations were measured at rest, while smoking a cigarette, during a speech task occurring immediately after smoking and at several time-points following the stressor. Significant period by sex effects were observed for HR, SBP, DBP and EPI but not for cortisol or norepinephrine concentrations. For SBP ($p=0.002$), the increase between resting and speech were larger in men than in women, primarily due to a larger increase between smoking and speech occurring in men. A similar pattern was observed for DBP and Epi with a significantly larger EPI increase from smoking to speech observed in men than in women ($p=0.016$). A different pattern emerged for HR - the total increase was larger in women ($p<0.001$), due to a larger rest to smoking increase ($p<0.001$). In most measures therefore, overall increases were greater in men than women, primarily due to larger smoking to speech increases. Additional research is needed to determine the clinical implications of these results as they apply to sex difference in smoking cessation success rates and in the cardiovascular risks of smoking.

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Declaration of Interest

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Keywords

Sex differences; mental stress; smoking; blood pressure; heart rate; catecholamines

1. Introduction

Cigarette smoking has been well established as a significant cause of cardiovascular morbidity and mortality (USDHHS, 2010). One of the mechanisms by which smoking is thought to be detrimental to cardiovascular health is through chronic sympathetic activation as demonstrated by the acute increases in plasma epinephrine concentrations, blood pressure and heart rate that occur after smoking (USDHHS, 2010). Exposure to stressful events leads to an increase in sympathetic activity (reflected by increases in blood pressure, heart rate and plasma epinephrine concentrations) and activation of the hypothalamic-pituitary-adrenal axis (reflected by increases in cortisol concentrations) (Brotman et al., 2007; Chrousos, 2009; Foley and Kirschbaum, 2010; Kotlyar et al., 2017). Exposure to the combination of stress and smoking leads to larger increases in cardiovascular measures compared to exposure to stress or smoking individually (Kotlyar et al., 2013; MacDougall et al., 1983). Since stress is consistently cited as among the most common smoking triggers, stress and smoking likely frequently occur in close proximity to each other (Shiffman et al., 1996). The large increase in sympathetic activity that occurs as a result has been suggested as a potential mechanism by which smoking increases the risk of cardiovascular disease (Epstein and Perkins, 1988).

There is conflicting data regarding differences between men and women in the magnitude of the physiological response to stress (Back et al., 2008) and there has been limited research evaluating differences between men and women in the physiological response to smoking (Hering et al., 2008) and particularly in the physiological response to the combination of stress and smoking. Smoking attributable risk of cardiovascular disease is larger in women than men (Huxley and Woodward, 2011) and differences between men and women have been reported for a number of smoking cessation outcomes. For example, women are less likely to successfully quit smoking than men and stress may have a greater deleterious effect on the ability to quit smoking for women than men (McKee and Weinberger, 2015; Smith et al., 2015). Data regarding differences between men and women in the physiological response to the combination of stress and smoking are therefore needed in order to better understand sex difference in smoking attributable cardiovascular risk and in smoking cessation outcomes so as to provide targets for smoking cessation treatment. The purpose of the current analysis was to determine sex differences in the blood pressure, heart rate, plasma catecholamine and plasma cortisol response to the combination of stress and smoking.

2. Methods

2.1. Study Design & Subjects

Design details of this study have been described previously (Kotlyar et al., 2013). In brief, physiological responses to a stressful situation that was presented immediately after smoking a cigarette were tested in generally healthy individuals between the ages of 18 and 65 who

smoked at least 10 cigarettes per day over the previous year. Exclusion criteria included having an unstable or serious medical condition at the time of screening, use of medication that could interfere with measures being studied (e.g., psychoactive medications, antihypertensives) and psychiatric diagnosis as assessed by the PRIME-MD (Spitzer et al., 1994). Subjects were recruited through flyers and newspaper advertisements. As the primary aim of the study was to assess the effects of paroxetine on the physiological response to the combination of stress and smoking, this was a double-blind cross-over study in which one laboratory period occurred after participants had been taking paroxetine for a four week period (10 mg daily for 1 week followed by 20 mg daily) and the other occurred after participants had been taking matching placebo. The order of placebo vs. paroxetine administration was randomized.

2.2 Procedures

Each laboratory session occurred after overnight abstinence from smoking. Upon arrival, an indwelling catheter was inserted into an arm vein and a cuff from an automated sphygmomanometer was attached to the other arm. A 30 minute rest period started after catheter and blood pressure cuff placement. Other studies assessing stress response have used rest periods of similar duration after the insertion of an intravenous catheter (Gordon and Girdler, 2014; Kotlyar et al., 2008), and in this study was likely of sufficient duration for cardiovascular measures to return to resting levels. Indeed measures observed during this 30 minute period were not higher than those observed during the final relaxation period by which time any physiological effects of catheter insertion would have likely worn off (figure). Following the relaxation period, participants smoked one cigarette of their usual brand over a 5 minute period. Participants then completed two stressful tasks which consisted of delivering a 3 minute speech describing how they would handle a hypothetical scenario involving an interpersonal conflict followed by a 3 minute mental arithmetic task. These tasks were based on a modified Trier Social Stress Test (Kirschbaum et al., 1993; Kotlyar et al., 2013). A final 30 minute rest period followed the stress tasks. Blood pressure and heart rate were measured, using an automated sphygmomanometer, at 2 minute intervals during the rest periods and at 1 minute intervals during the stress tasks. Venous blood was drawn following the initial rest period, while smoking the cigarette, during the speech task, during the math task and twice during the final rest period at time-points corresponding to 15 minutes and 30 minutes following the conclusion of the math task. Blood was assayed for plasma epinephrine, plasma norepinephrine and plasma cortisol concentrations. All laboratory sessions occurred in the morning after overnight smoking abstinence (confirmed via exhaled carbon monoxide concentration <8 ppm). Written informed consent was obtained from all subjects and this study was approved by the University of Minnesota Institutional Review Board.

2.3 Statistical Analysis

The primary analysis included data from the laboratory session occurring after subjects took placebo for 4 weeks (n=70). Although paroxetine did decrease blood pressure response to the combination of stress and smoking (Kotlyar et al., 2013), no significant sex by treatment effects were found. Therefore in order to maximize the number of observations available for analysis, we conducted a supplemental analysis in which we included data from both the

laboratory session occurring after subjects took placebo for 4 weeks and the laboratory session occurring after subjects took paroxetine for 4 weeks ($n=62$). The primary measures of interests for blood pressure, heart rate and plasma catecholamines were the physiological response that occurred between the initial rest period and during delivery of the speech. We only report on the speech stressor in this study because the physiological response to the speech stressor was larger than to the math stressor indicating that it was a more stressful challenge and the speech stressor was in closer temporal proximity to the math stressor and therefore more relevant to assessing physiological response to the combination of stress and smoking. Since cortisol response to stress is typically delayed, the primary measure of interest was sex differences in changes in cortisol concentrations across the entire session.

In order to model the nested and hence correlated nature of the data (multiple assessments from within individuals) we employed a mixed effects approach (SPSS V.19) examining overall change in response to the stress task as well as differences by sex and the interactions between sex and period. The model was fitted with a random intercept (subject level) and sex, period and their interaction terms as fixed effects. The initial analysis examined period by sex effects for the entire session. For variables for which a significant overall effect was found, separate follow-up period by sex analyses were conducted for each segment of interest (i.e. rest to stress, rest to smoking, smoking to stress). The significance threshold was adjusted to $p<.0167$ to adjust for these 3 post-hoc analyses. An additional analysis to look for habituation effects was conducted in which the various interactions between sex, period and lab (i.e., first lab vs. second lab) were examined. The significance threshold for the sex $\times$ period $\times$ lab analysis was adjusted to $p<0.01$ to adjust for the 5 post-hoc analyses. Because the percentage of African American subjects was significantly different between men and women, race (black vs. other) was included as a covariate in these analyses.

3. Results

A total of 70 subjects completed the laboratory session after receiving placebo for 4 weeks and were included in the primary analysis. Sixty-two subjects completed both laboratory sessions and were included in the supplemental analysis in which data from both laboratory sessions was included. One additional subject completed both laboratory sessions but did not have usable cardiovascular measures and was not used in the analysis. Among the subjects in the primary analysis, 48.6% ($n=34$) were women. Significant differences in baseline demographic characteristics between male and female subjects were found only in the proportion of participants who were African American (27.8% of men vs. 2.9% of women) (Table 1).

A significant sex effect was observed for systolic blood pressure ($F(1,71.3)=19.34$, $p<.001$), diastolic blood pressure ($F(1,71.1)=7.95$, $p=.006$) and plasma epinephrine ($F(1,62)=7.39$, $p=.008$) concentrations with higher overall values reported in men than in women. These differences are generally consistent with other studies in the literature (Kotlyar et al., 2006; Reckelhoff, 2001). Significant period $\times$ lab effects were found for heart rate, systolic blood pressure and diastolic blood pressure (p values <0.001) with smaller responses observed in the second laboratory session than in the first. No significant period $\times$ lab effects were found for plasma epinephrine, norepinephrine or cortisol concentrations. No period $\times$ sex $\times$ lab

effects meeting our threshold for significance were found for any measures suggesting that the degree to which heart rate and blood pressure response were smaller in the second laboratory session (relative to the first) did not differ by sex.

After receiving placebo for 4 weeks, significant period x sex effects across all measurement points were observed for heart rate ($F(1,2574.4)=12.26$; $p<0.001$), systolic blood pressure ($F(1,2574.5)=6.59$, $p<.001$), diastolic blood pressure ($F(1,2574.4)=8.47$, $p<.001$) and plasma epinephrine concentrations ($F(1,333)=4.38$, $p=.001$) (figure). No significant period x sex effect was observed for plasma norepinephrine concentrations or for plasma cortisol concentrations (figure). The increase between measures observed during the initial rest period and measures observed during speech were significantly larger in men than in women for systolic blood pressure ($F(1,1167.4)=9.98$, $p=.002$), were numerically larger in men than in women for diastolic blood pressure ($F(1,1167.2)=4.42$, $p=.036$) and for plasma epinephrine concentrations ($F(1,65.9)=2.57$, $p=.11$) but were significantly larger in women than men for heart rate ($F(1,1167.3)=12.52$, $p<.001$). In all of these measures, the increase between smoking and speech was numerically larger in men than in women but only reached our adjusted threshold of statistical significance ($p<0.017$) for plasma epinephrine concentrations ($F(1,66.3)=6.06$, $p=.016$) (figure). The increase in measures that occurred between rest and smoking were similar between men and women for all measures except for heart rate in which the response was greater in women than in men ($F(1,1151.4)=47.2$, $p<.001$).

Repeating this analysis using both laboratory sessions for subjects that completed the entire study led to a similar pattern of response although greater statistical significance in several measures due to the reduced standard errors resulting from the greater number of data points. The increase between measures observed during the initial rest period and measures observed during speech were significantly larger in men than in women for systolic blood pressure ($F(1,2148.1)=29.9$, $p<0.001$), diastolic blood pressure ($F(1,2148.1)=9.28$, $p=0.002$) and plasma epinephrine concentrations ($F(1,178.8)=7.14$, $p=0.008$). The increase in measures between those observed during smoking and those observed during stress were significantly larger in men than in women for heart rate ($F(1,631.6)=12.71$, $p=0.001$) and plasma epinephrine concentrations ($F(1,176.6)=8.65$, $p=0.004$). The increases were also numerically larger for SBP ($F(1,632.1)=4.23$, $p=0.04$) and DBP ($F(1,632.0)=5.15$, $p=0.024$) but did not reach our threshold for statistical significance. Similarly to the previous analysis, the increase in measures that occurred between rest and smoking were not significantly different for any measures except for heart rate in which the response was greater in women ($F(1,2119.3)=38.89$, $p<0.001$). Similar to the primary analysis, significant period x lab effects were found for heart rate, systolic blood pressure and diastolic blood pressure (p values <0.001) with smaller responses observed in the second laboratory session than in the first. No period x sex x lab effects were found for any measure.

4. Discussion

This study found that when a stressful situation is presented immediately after smoking a cigarette, the resultant cardiovascular response is larger in men than in women in many measures. This difference in response appears to be due to a larger incremental increase that

occurs between the measures observed during cigarette smoking and those observed during the stressor although larger studies are needed to confirm if this is the case. Since attenuated physiological responses to stress has been found to be associated with increased smoking cessation relapse rates (Lemieux and al'Absi, 2016), it is necessary to determine if these findings are relevant to the lower smoking cessation rates reported for women during unassisted quit attempts.

Previous research has not extensively assessed if cardiovascular response to smoking differs between men and women. One study that did address this issue (Hering et al., 2008) found that, in contrast to our study, women exhibited a larger increase in SBP during smoking than did men. Consistent with our study, a larger increase in HR was also found in women than in men. Reasons for the discrepant finding for SBP are not clear, although one difference between studies is the number of cigarettes smoked (1 in our study vs. 2 in the previous study) suggesting that some sex differences may depend on the amount smoked. Since acute response to smoking has been suggested as one mechanism by which smoking causes cardiovascular disease and since smoking increases cardiovascular disease in women to a greater extent than in men (Huxley and Woodward, 2011), further research is needed to clarify differences between men and women in the cardiovascular response to smoking. Studies assessing sex differences in physiological response to stress have reported inconsistent results with some studies indicating a larger response in men and others finding a larger response in women (Back et al., 2008). Reasons for these differences are not clear but are likely due (at least in part) to differences among studies in the methods used (e.g. type of stressor used) and the populations included (e.g. smokers vs non-smokers) (Back et al., 2008). Although studies have shown that cardiovascular response to the combination of stress and smoking is larger than to either individually (MacDougall et al., 1983), it is not known if there are sex differences in the magnitude of the combined response. Our findings therefore extend the existing literature by demonstrating that the combination of stress and smoking results in a larger overall increase in blood pressure and possibly plasma epinephrine concentrations in men than in women. It is not known if our findings of no significant sex differences in cortisol and norepinephrine concentrations were due to the greater variability observed in these measures (therefore necessitating a larger sample size to see significant effects) or differences in how these two measures respond to the combination of stress and smoking. Due to its delayed response (peak response occurring approximately 10 to 30 minutes after stress exposure) (Foley and Kirschbaum, 2010), interpretation of the cortisol data is difficult as it is not possible to separate the effects of smoking from those of stress. Additionally, although we attempted to minimize the effect of circadian rhythms on cortisol concentrations by conducting all laboratory sessions in the morning, there may nonetheless have been differences between subjects in time since waking as this data was not collected.

Data suggest that smaller responses to stress during the tobacco withdrawal period are associated with greater relapse (Lemieux and al'Absi, 2016). For example, a study in which physiological response to a stressor was assessed after 24 hours of abstinence found that attenuated DBP and cortisol response was associated with higher smoking cessation relapse rates at 4 weeks (al'Absi et al., 2005). Research is needed to determine if the lower cardiovascular responses to the combination of stress and smoking observed in women in the

current study are related to the lower smoking cessation success rates reported for women in previous studies.

Studies suggest that the decreases observed in the physiological response to a speech stressor upon repeated presentations of the task (i.e., habituation) occur to a greater extent in HPA axis measures than in sympathetic nervous system measures (al'Absi et al., 1997; Allen et al., 2014; Gerra et al., 2001; Jonsson et al., 2010; Schommer et al., 2003). Our results are consistent with previous analyses in that no habituation was found for plasma catecholamine concentrations (Schommer et al., 2003) but differs from previous analyses in our finding of no habituation in cortisol response. It is not known if these differences from previous studies are due to the population studied (i.e., smokers vs. non-smokers) or to other differences in the methods of this study compared to previous studies. There is limited data regarding sex differences in habituation, particularly in smokers. Our results however are generally consistent with a study that found no sex differences in blood pressure or heart rate to a repeated computerized stressor task in smokers (in contrast to finding differences in diastolic blood pressure response in non-smokers) (Hughes and Higgins, 2010). The significance of these results requires further study.

There are several limitations to the current study. One limitation is that menstrual cycle phase was not controlled for in this study and therefore it is not known the extent to which it impacts physiological response to stress when occurring after smoking a cigarette. Although information on menstrual cycle phase was collected, dividing the sample into menstrual cycle phases yielded too few women in each group to yield interpretable results. This is an issue that merits additional study since research has shown that cardiovascular response to smoking may be affected by menstrual cycle phase (Masson and Gilbert, 1999) and the cycle phase during which a quit attempt occurs may influence smoking success rates (Weinberger et al., 2015). Another limitation includes the fixed order in which stress and smoking occurred. Although stress and smoking occurred within several minutes of each other in the study, it is not known if the pattern of response would have been different had the order of tasks been reversed. In this study, participants smoked one of their usual brand cigarettes with no instruction provided regarding how it should be smoked (e.g., the number or durations of puffs). This approach was selected in order to more closely mimic the physiological response that occurs when individuals smoke in the natural environment, however a limitation of this approach is that variations in the rate of inhalation or nicotine content of cigarettes may have affected the results. As most of the differences between men and women were found in the physiological response that occurred between smoking and stress rather than between rest and smoking, this limitation is unlikely to have affected many of the findings of this analysis. The absence of a non-smoking session and a non-smoking control group means that it is not possible to determine if the sex differences in stress responses found in this study would occur in non-smokers or in the absence of smoking. Future studies with these control groups are needed to confirm the current findings. Despite these limitations, the data showed across several measures that the observed response was greater in men and then women.

In summary, we found that when exposed to a stressor shortly after smoking a cigarette, blood pressure increases were greater in men than women which appeared to be primarily

due to larger increases in the response to the stress task that occurred after smoking a cigarette rather than to smoking a cigarette. For plasma epinephrine concentrations, a significantly larger response was observed in men (compared to women) during this same period (i.e. increase from smoking to stress). Additional research is needed to determine the clinical implications of these results as they apply to the cardiovascular risks of smoking and to sex differences in smoking cessation efficacy.

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References

- al'Absi M, Bongard S, Buchanan T, Pincomb GA, Licinio J, Lovallo WR. Cardiovascular and neuroendocrine adjustment to public speaking and mental arithmetic stressors. *Psychophysiology*. 1997; 34:266–275. [PubMed: 9175441]
- al'Absi M, Hatsukami D, Davis GL. Attenuated adrenocorticotrophic responses to psychological stress are associated with early smoking relapse. *Psychopharmacology (Berl)*. 2005; 181:107–117. [PubMed: 15834539]
- Allen AP, Kennedy PJ, Cryan JF, Dinan TG, Clarke G. Biological and psychological markers of stress in humans: focus on the Trier Social Stress Test. *Neurosci Biobehav Rev*. 2014; 38:94–124. [PubMed: 24239854]
- Back SE, Waldrop AE, Saladin ME, Yeatts SD, Simpson A, McRae AL, Upadhyaya HP, Contini Sisson R, Spratt EG, Allen J, Kreek MJ, Brady KT. Effects of gender and cigarette smoking on reactivity to psychological and pharmacological stress provocation. *Psychoneuroendocrinology*. 2008; 33:560–568. [PubMed: 18321653]
- Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. *Lancet*. 2007; 370:1089–1100. [PubMed: 17822755]
- Chrousos GP. Stress and disorders of the stress system. *Nat Rev Endocrinol*. 2009; 5:374–381. [PubMed: 19488073]
- Epstein LH, Perkins KA. Smoking, stress, and coronary heart disease. *J Consult Clin Psychol*. 1988; 56:342–349. [PubMed: 3294259]
- Foley P, Kirschbaum C. Human hypothalamus-pituitary-adrenal axis responses to acute psychosocial stress in laboratory settings. *Neurosci Biobehav Rev*. 2010; 35:91–96. [PubMed: 20109491]
- Gerra G, Zaimovic A, Mascetti GG, Gardini S, Zambelli U, Timpano M, Raggi MA, Brambilla F. Neuroendocrine responses to experimentally-induced psychological stress in healthy humans. *Psychoneuroendocrinology*. 2001; 26:91–107. [PubMed: 11070337]
- Gordon JL, Girdler SS. Mechanisms underlying hemodynamic and neuroendocrine stress reactivity at different phases of the menstrual cycle. *Psychophysiology*. 2014; 51:309–318. [PubMed: 24397365]
- Hering D, Somers VK, Kara T, Jazdzewski K, Jurak P, Kucharska W, Narkiewicz K. Heightened acute circulatory responses to smoking in women. *Blood Press*. 2008; 17:141–146. [PubMed: 18608198]
- Hughes BM, Higgins NM. Habituation-sensitization of cardiovascular reactivity to repeated stress in smokers and non-smokers: an anthropometrically matched trial. *Int J Psychophysiol*. 2010; 76:34–39. [PubMed: 20144664]
- Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet*. 2011; 378:1297–1305. [PubMed: 21839503]

- Jonsson P, Wallergard M, Osterberg K, Hansen AM, Johansson G, Karlson B. Cardiovascular and cortisol reactivity and habituation to a virtual reality version of the Trier Social Stress Test: a pilot study. *Psychoneuroendocrinology*. 2010; 35:1397–1403. [PubMed: 20451329]
- Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier Social Stress Test'--a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology*. 1993; 28:76–81. [PubMed: 8255414]
- Kotlyar M, al'Absi M, Thuras P, Vuchetich JP, Adson DE, Nowack AL, Hatsukami DK. Effect of paroxetine on physiological response to stress and smoking. *Psychosom Med*. 2013; 75:236–243. [PubMed: 23504241]
- Kotlyar M, Brauer LH, al'Absi M, Adson DE, Robiner W, Thuras P, Harris J, Finocchi ME, Bronars CA, Candell S, Hatsukami DK. Effect of bupropion on physiological measures of stress in smokers during nicotine withdrawal. *Pharmacol Biochem Behav*. 2006; 83:370–379. [PubMed: 16581115]
- Kotlyar M, Donahue C, Thuras P, Kushner MG, O'Gorman N, Smith EA, Adson DE. Physiological response to a speech stressor presented in a virtual reality environment. *Psychophysiology*. 2008; 45:1034–1037. [PubMed: 18778321]
- Kotlyar M, Lindgren BR, Vuchetich JP, Le C, Mills AM, Amiot E, Hatsukami DK. Timing of nicotine lozenge administration to minimize trigger induced craving and withdrawal symptoms. *Addict Behav*. 2017; 71:18–24. [PubMed: 28235705]
- Lemieux A, al'Absi M. Stress psychobiology in the context of addiction medicine: from drugs of abuse to behavioral addictions. *Prog Brain Res*. 2016; 223:43–62. [PubMed: 26806770]
- MacDougall JM, Dembroski TM, Slaats S, Herd JA, Eliot RS. Selective cardiovascular effects of stress and cigarette smoking. *J Human Stress*. 1983; 9:13–21.
- Masson CL, Gilbert DG. Cardiovascular and mood responses to quantified doses of cigarette smoke in oral contraceptive users and nonusers. *J Behav Med*. 1999; 22:589–604. [PubMed: 10650538]
- McKee SA, Weinberger AH. Innovations in translational sex and gender-sensitive tobacco research. *Nicotine Tob Res*. 2015; 17:379–381. [PubMed: 25762746]
- Reckelhoff JF. Gender differences in the regulation of blood pressure. *Hypertension*. 2001; 37:1199–1208. [PubMed: 11358929]
- Schommer NC, Hellhammer DH, Kirschbaum C. Dissociation between reactivity of the hypothalamus-pituitary-adrenal axis and the sympathetic-adrenal-medullary system to repeated psychosocial stress. *Psychosom Med*. 2003; 65:450–460. [PubMed: 12764219]
- Shiffman S, Paty JA, Gnys M, Kassel JA, Hickcox M. First lapses to smoking: Within-subjects analysis of real-time reports. *Journal of Consulting and Clinical Psychology*. 1996; 64:366–379. [PubMed: 8871421]
- Smith PH, Kasza KA, Hyland A, Fong GT, Borland R, Brady K, Carpenter MJ, Hartwell K, Cummings KM, McKee SA. Gender differences in medication use and cigarette smoking cessation: results from the International Tobacco Control Four Country Survey. *Nicotine Tob Res*. 2015; 17:463–472. [PubMed: 25762757]
- Spitzer RL, Williams JB, Kroenke K, Linzer M, deGruy FV 3rd, Hahn SR, Brody D, Johnson JG. Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *JAMA*. 1994; 272:1749–1756. [PubMed: 7966923]
- USDHHS. How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: a report of the Surgeon General. Dept. of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; Atlanta, GA: 2010.
- Weinberger AH, Smith PH, Allen SS, Cosgrove KP, Saladin ME, Gray KM, Mazure CM, Wetherington CL, McKee SA. Systematic and meta-analytic review of research examining the impact of menstrual cycle phase and ovarian hormones on smoking and cessation. *Nicotine Tob Res*. 2015; 17:407–421. [PubMed: 25762750]

Highlights

- Blood pressure, heart rate, plasma catecholamine concentrations and plasma cortisol concentrations were measured at rest, while smoking a cigarette and during a speech task which occurred immediately following smoking
- Systolic blood pressure increases occurring between rest and the speech task were larger in men than in women whereas the heart rate increase was larger in women than in men
- The larger increase in blood pressure was due primarily to an larger response in men (vs. women) occurring between the measures observed during smoking and those observed during the speech
- A larger increase in plasma epinephrine concentrations was observed in men (vs. women) between the measures obtained during smoking and those obtained during speech

Figure.

Systolic blood pressure (A), diastolic blood pressure (B), heart rate (C), plasma epinephrine concentrations (D), plasma norepinephrine concentrations (E), and plasma cortisol concentrations (F) (mean [standard error of the mean]) in participants who completed a laboratory session after receiving 4 weeks of placebo. p values are provided for the period within bracket (i.e. rest to smoking, smoking to speech and rest to speech). For Epinephrine, Norepinephrine and cortisol concentrations “Math+15” and “Math+30” refer to samples collected during a rest period at time-points corresponding to 15 minutes and 30 minutes following the conclusion of the math task

Table 1

Baseline demographics for Men and Women (n = 70)

	Men (N=36)	Women (N=34)	P value
Age (mean $\pm$ SD)	42.2 (12.6)	38.8 (12.6)	0.27
Race			
Caucasian (%)	58.3	73.5	0.18
Black (%)	27.8	2.9	0.004
Number of cigarettes per day (means $\pm$ SD)	19.4 (6.8)	17.6 (7.1)	0.31