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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.

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 (HPA) 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

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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 (Fig. 1). 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 min and 30 min 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 interest 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 $p < 0.0167$ 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 × period × 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 ($F(1,71.3) = 19.34$, $p < 0.001$), diastolic blood pressure ($F(1,71.1) = 7.95$, $p = 0.006$) and plasma epinephrine ($F(1,62) = 7.39$, $p = 0.008$) 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 × 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 × lab effects were found for plasma epinephrine, norepinephrine or cortisol concentrations. No period × sex × lab effects meeting our threshold for significance were found for any