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Short Communication

Sex differences in effects of cigarette smoking and 24-hr abstinence on plasma arginine vasopressin

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ABSTRACT

The present study examined plasma arginine vasopressin (AVP) levels in 18 smokers (10 men, 8 women) and in 22 non-smokers (12 men, 10 women). Non-smokers came to the laboratory once, whereas smokers came twice: while smoking freely and following 24-hr abstinence. Plasma was collected for AVP assessment; salivary cotinine and expired carbon monoxide levels confirmed smoking status. Among non-smokers, men had higher AVP levels than did women ($p<0.05$). Among smokers, however, women displayed higher AVP levels than did men both while smoking and following abstinence (p's<0.05). Among men, smoking resulted in lower AVP levels compared to non-smoking men. In contrast, women who smoked displayed higher AVP levels compared to their non-smoking counterparts. AVP levels were not affected by 24-hr abstinence among smokers, regardless of sex, which suggests that dysregulation in AVP levels in tobacco smokers continues even following 24-hr abstinence. Findings are consistent with previous reports of elevated Th1/Th2 immune function among female smokers compared to male smokers and to male and female non-smokers. Data suggest sex-dependent AVP changes during smoking that could contribute to negative impact of smoking on cardiovascular health.

1. Introduction

Tobacco use continues to be the most preventable cause of illness and death in the United States (CDC, 2008). Among its many effects, nicotine, the psychoactive ingredient in tobacco, acutely induces vasodilation (Uchida & Hotta, 2009). However, when coupled with carbon monoxide inhaled in cigarette smoke, the vasodialating properties of nicotine are diminished because carbon monoxide contributes to atherosclerosis-induced occlusion of blood vessels (Song & Ovbiagele, 2009). Ultimately, cigarette smoking leads to the development of atherosclerosis and thrombosis, which in turn leads to an increase in heart rate, vascular resistance, and blood pressure (USDHHS, 2004b). These detrimental cardiovascular effects increase the risk of coronary heart disease (CHD), congestive heart failure, hypertension, and stroke (USDHHS, 2004a). Smokers have two to four times the risk of developing CHD, and are twice as likely to develop a stroke compared to non-smokers (USDHHS, 2004b). From 2000 to 2004, about 443,000 U.S. deaths were attributed each year to cigarette smoking (CDC, 2008). Furthermore, of those deaths per year, about 128,000 deaths were due to cardiovascular diseases such as ischemic heart disease and atherosclerosis (CDC, 2008).

Nicotine-induced release of neuroendocrine hormones such as oxytocin and arginine vasopressin (AVP), as well as stress hormones [e.g., corticotrophin releasing hormone (CRH), adrenocorticotropic hormone (ATCH), cortisol] impacts the cardiovascular system (Chiodera et al., 1993; Dietz, Schomig, Kusterer, Dart, & Kubler, 1984; Fuxe, Andersson, Eneroth, Harfstrand, & Agnati, 1989; Rowe, Kilgore, & Robertson, 1980). The release of AVP from the posterior lobe of the pituitary gland is stimulated by nicotine through activation of nicotinic cholinergic receptors found in the supraoptic and paraventricular nuclei of the hypothalamus and ventral side of the medulla (Castro De Souza & Silva, 1977; Fuxe et al., 1989). AVP has two inter-related sites of action in the peripheral nervous system: the kidneys and the cardiovascular system. In the kidneys, AVP acts to stimulate water retention (Boone & Deen, 2008) which directly increases blood volume and blood pressure. In the cardiovascular system, AVP is thought to have three additional functions. First, AVP indirectly increases blood pressure by inducing the release of stress hormones (i.e., CRH, ACTH, cortisol) and catecholamines (i.e., epinephrine, norepinephrine) that elevate heart rate and vasulcar resistance as part of the "fight-or-flight" response (Matta, Singh, & Sharp, 1990; Stalke et al., 1992). Secondly, AVP in supraphysiological concentrations directly acts as a vasoconstrictor, restricting blood flow through arterioles, leading to an increase in blood pressure (Waeber, Nussberger, Hofbauer, Nicod, & Brunner,

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1986). Lastly, AVP has been found to cause blood platelet aggregation, which can lead to a clot or thrombosis (Erne & Pletscher, 1985).

With regard to tobacco use, earlier studies suggest that the cardiovascular effects of nicotine can be explained through the release of stress hormones as well as AVP. In animal models, intravenous (IV) nicotine administration leads to increased plasma AVP levels (Bisset, Feldberg, Guertzenstein, & Silva, 1975; Castro De Souza & Silva, 1977; Fuxe et al., 1989). When nicotine is administered IV in humans, this AVP increase occurs only when the toxic effects of nicotine are induced such as nausea, vomiting and hypotension (Rowe et al., 1980). Other studies report that nicotine delivered through cigarette smoke, but not intravenously, increases plasma AVP levels in humans (Husain, Frantz, Ciarochi, & Robinson, 1975; Pullan, Clappison, & Johnston, 1979; Rowe et al., 1980). These findings led Rowe et al. (1980) to conclude that nicotine causes an increase in plasma AVP in humans through a mechanism involving the lungs. Together, these studies suggest that the ability of nicotine (delivered via cigarette smoking) to stimulate the production of AVP, coupled with AVP's ability to cause blood pressure to rise and blood platetlets to aggregate, may set the stage for the development of cardiovascular disease (CVD) in tobacco smokers.

The present study took these studies one step further and examined differences in AVP levels among male and female non-smokers and among smokers both while smoking freely and following a 24-hr abstinence period. Based on previous data that suggest males have more AVP neurons and AVP availability compared to females (De Vries & Boyle, 1998; De Vries, Buijs, & Van Leeuwen, 1984; Rhodes, Kennell, Belz, Czambel, & Rubin, 2004; Rhodes, O'Toole, Czambel, & Rubin, 2001; Rhodes & Rubin, 1999), we hypothesized that men would display higher AVP levels than would women, regardless of smoking status. We also hypothesized that smokers would display higher levels of AVP compared to non-smokers based on previous reports that AVP increases in reponse to smoking (Narkiewicz et al., 1998; Waeber et al., 1984).

2. Materials and methods

2.1. Participants

Twenty-two healthy nonsmokers (12 males, 10 females) and 18 smokers (10 males, 8 females), aged 19–41 years (23.48 ± 0.81 years) were recruited for a separate study reported elsewhere (Klein, Corwin, & Ceballos, 2004; Whetzel, Corwin, & Klein, 2007). Participants were screened by telephone to determine eligibility which included no history of medical or mental illness and no over-the-counter or prescription drug use. Cigarette smokers were included if they smoked at least 11 cigarettes/day and smoked their first cigarette within 30 minutes of waking (Heatherington, Kozlowski, Frecker, & Fagerstrom, 1991; Kozlowski, Porter, Orleans, Pope, & Heatherton, 1994). To reduce the possible confounds of a recent attempt to quit smoking, smokers were included only if they reported no prior quit attempts. Nonsmoker participants reported no history of cigarette smoking, tobacco use, or over-the-counter nicotine use for at least 5 years prior. Women were included if they were not currently taking oral contraceptives, had regular menstrual cycles, were not pregnant within the last year, and did not have premenstrual mood disorder. Women participated during the late luteal phase of their menstrual cycle to reduce possible hormone influence on the outcomes of the study (Perkins et al., 2000). Smokers and nonsmokers were similar in age (22.28 ± 0.95 years vs. 24.65 ± 0.92 years, respectively) and body mass index (BMI) (24.87 ± 0.92 kg/m^2 vs. 24.46 ± 1.23 kg/m^2, respectively). Men and women were similar in age (24.59 ± 1.29 years vs. 22.11 ± 0.80 years, respectively). However, BMI among men was higher compared to women, regardless of smoking status (26.06 ± 0.88 kg/m^2 vs. 23.14 ± 0.83 kg/m^2, respectively) [$F(1,39) = 5.06$, $p = <0.05$]. The ethnic distribution of participants was: 75% ($N = 30$) Caucasian, 5% ($N = 2$), 20% ($N = 8$) were self-described as "other." All participants had at least a high school education. The Pennsylvania State University's Institutional Review Board reviewed and approved all study procedures.

2.2. Procedure

Smokers came into the lab in the morning for 2 different sessions: 1) while smoking freely and 2) following a 24-hr smoking abstinence period. Sessions were counterbalanced across smoking participants and gender. Nonsmokers came to the laboratory for one session. All participants gave informed consent at the beginning of the study and were paid for their time. Smoking status was confirmed by expired carbon monoxide (CO; Vitalograph, Lenexa, Kansas) and salivary cotinine measurements (Salimetrics, LLC, State College, PA) for each participant; abstinence was defined as CO levels <10 ppm. Among smokers, expired CO and salivary cotinine levels were significantly higher during smoking compared with abstinence [$t(17) = 4.28$, $p<0.01$ and $t(17) = 5.33$, $p<0.01$, respectively], which confirmed their smoking status (see Table 1). CO and salivary cotinine levels were nearly undetectable among non-smokers [0.59 ± 0.15 ppm and 0.03 ± 0.00 ng/mL, respectively].

Sessions were scheduled between 0800 and 0900 hrs and lasted approximately 1 hr. Following informed consent, participants were instructed to sit quietly for 5 minutes and complete questionnaires regarding health status and mood as part of a larger experiment (e.g., Corwin, Klein, & Rickelman, 2002; Klein, Corwin, & Stine, 2003). At the end of the session, participants provided a saliva sample via cotton Salivette (Sarstedt, Carey, NC) and blood samples were collected into chilled plasma collection tubes containing EDTA via antecubital venous puncture. Plasma samples immediately were centrifuged at 1500×g, aliquoted, and stored at −80 °C for later AVP assessment. Plasma AVP and salivary cotinine levels were determined using a commercially available enzyme linked immunosorbent assay kits (Assay Designs, Inc., Ann Arbor, MI and Salimetrics LLC, State College, PA, respectively). Plasma AVP and salivary cotinine levels were normally distributed.

2.3. Data analysis

Two non-smoking and 1 smoking male participant had insufficient plasma levels for AVP assessment; thus, they are not included in the AVP analyses. Two, separate 2-way analyses of variance (ANOVAs), with sex and smoking status (i.e., non-smoker, smoker) as the independent variables and AVP as the dependent measure, were used to examine sex by smoking status interactions on AVP concentrations.

Table 1
Salivary cotinine (ng/mL), expired carbon monoxide (ppm), systolic blood pressure (mmHg), diastolic blood pressure (mm Hg), and heart rate (beats per minute) among male and female non-smokers and smokers while smoking and following 24-hr smoking abstinence (means ± SEM).

	Non-smokers		
	Men ($N = 12$)	Women ($N = 10$)	Total ($N = 22$)
Cotinine (ng/mL)	0.03 ± 0.00	0.03 ± 0.00	0.03 ± 0.00
Carbon monoxide (ppm)	0.54 ± 0.24	0.65 ± 0.18	0.59 ± 0.15
	Cigarette smokers		
	Men ($N = 10$)	Women ($N = 8$)	Total ($N = 18$)
After Smoking Freely			
Cotinine (ng/mL)	361.34 ± 45.40	227.10 ± 44.33	301.68 ± 35.04
Carbon monoxide (ppm)	16.35 ± 3.98	14.69 ± 5.45	15.61 ± 3.18
After 24-hr Abstinence			
Cotinine (ng/mL)	188.33 ± 36.19	122.03 ± 23.89	158.87 ± 23.53
Carbon monoxide (ppm)	5.85 ± 2.38	3.31 ± 0.85	4.72 ± 1.37