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Cannabis, tobacco, and caffeine use modify the blood pressure reactivity protection of ascorbic acid

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Abstract

Cannabis, caffeine, and tobacco use are associated with increased mesolimbic dopamine activity. Ascorbic acid (AA) modulates some dopaminergic agent effects, and was recently found to decrease systolic blood pressure (SBP) stress reactivity. To examine how AA SBP stress reactivity protection varies by use of these substances, data from an AA trial (Cetebe, 3000 mg/day for 14 days; N=108) were compared by substance use level regarding SBP reactivity to the anticipation and actual experience phases of a standardized psychological stressor (10 min of public speaking and arithmetic). Self-reported never users of cannabis, persons not currently smoking tobacco, and persons consuming three or more caffeine beverages daily all exhibited AA SBP stress reactivity protection to the actual stressor, but not during the anticipation phase. Conversely, self-reported ever cannabis users, current tobacco smokers, and persons consuming less than three caffeine beverages daily exhibited the AA SBP protection during the anticipation phase, but only the lower caffeine consumption group exhibited AA protection during both phases. Covariates (neuroticism, extraversion, and depression scores, age, sex, body mass index) were all nonsignificant. Results are discussed in terms of dopaminergic effects of these substances, modulation of catecholaminergic and endothelial activity, and AA support of coping styles.

Keywords: Blood pressure; Stress; Ascorbic acid; Cannabis; Tobacco; Caffeine; Dopamine; Coping

1. Introduction

Some but not all studies of cardiovascular reactivity to psychological stress have found such reactivity to predict later tonic blood pressure increases (Brody et al., 1996; Markovitz et al., 1998). In addition, acute reactivity may place susceptible individuals at risk for cardiovascular events. In a recent randomized double-blind clinical trial, high-dose ascorbic acid (AA; Vitamin C) was found to result in less systolic blood pressure (SBP) increase in response to both the anticipation and actual experience of a standardized psychological stressor (Brody et al., 2002). These and other benefits were obtained without any discernable untoward effects, and were not due to modification of adrenal responsiveness.

AA is not only an antioxidant, but also modulates the effects of dopamine agonists and antagonists (Pierce et al., 1995; Gulley and Rebec, 1999). Caffeine (Garrett and Griffiths, 1997), tobacco (Salokangas et al., 2000), and cannabis (Markianos and Stefanis, 1982) use have all be found to be associated with increased mesolimbic dopamine activity. An examination of the possible interaction between these commonly used substances and AA stress protection would be of clinical utility, in that the differential benefits of high-dose AA supplementation would be more detailed. In addition, the study would provide more information about AA modulation of other substances (or, because of the epidemiological rather than randomized nature of substance use group membership, the personality or neurophysiological differences associated with use of these substances).

The present report examines how the palliating effects of high-dose AA (vs. placebo) on SBP reactivity to the anticipation and experience of a standardized stressor varies by self-reported consumption of these commonly used substances, controlling for several possible confounds (personality, etc.).

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2. Methods

2.1. Subjects

Subjects were recruited by means of advertisements posted at the university, a technical college, and at various shops and sports centers. Subjects were screened by telephone based on the exclusion criteria (current medication except oral contraception, vitamin supplement use during the preceding 3 months, current illnesses or pregnancy, prior experience with the standardized stressor, age over 40 or under 19, history of psychiatric disturbance, kidney stones, ulcer, cancer, asthma, cardiovascular, endocrine, or neurological disorders, known glucose-6-phosphate-dehydrogenase deficiency, body mass index >33 kg/m^2, or indications of enhanced study protocol noncompliance risk), and were then told the general details of the study. Subjects received a second screening as part of a brief medical examination at the first laboratory session (three applicants were excluded during that examination, two for medical conditions revealed during the examination, and one for fainting during cannula insertion).

2.2. Questionnaires

Subjects completed a confidential coded questionnaire at the first laboratory session, and also completed daily diaries during the trial. Among the questions were whether the subject ever used cannabis, current use of tobacco (any use in the 14 diary days, or an average of at least one cigarette weekly during the preceding 6 months), and number of servings of coffee, tea, or cola daily. Caffeine users were divided by a median split (into the high group of three or more servings of coffee, tea, or cola daily and the low group of two or less daily), cannabis users were divided on the basis of lifetime ever use, and tobacco smokers on the basis of current use. Subjects also completed the German version of the Eysenck Personality Inventory (Eysenck, 1974), which measures the two major dimensions of personality (neuroticism and extraversion), and the Beck Depression Inventory (Hautzinger et al., 1994).

2.3. Cardiovascular measure

SBP was measured with an automatic self-inflating portable sphygmomanometer (Boso Medicus PC, Bosch+Sohn, Jungingen, Germany) with the cuff placed on the upper arm and both inflation and measurement were triggered by the experimenter at prescribed times. The long-term reliability of such devices has been demonstrated (Brody et al., 1999).

2.4. Procedure and medication

Both laboratory sessions were conducted in mid-afternoon, at least one hour after eating (there was no eating or smoking during the laboratory sessions).

During the first session, subjects completed questionnaires, and each subject received 100 capsules of either a proprietary sustained-release formulation of 500 mg AA (Cetebe, preparation and coding by subject number by GlaxoSmithKline) or an identical appearing placebo. This sustained-release formula has a half-life of approximately 19 h, unlike the approximately 2 h half-life of pure AA. Subjects were instructed to consume two capsules thrice daily with ample fluid (including two doses the day of the second session) for a total of 14 days, to record the capsule use in a provided diary (in which physical symptoms were also recorded), and to return the unused capsules at the second session. Compliance was examined three ways: in addition to self-reported medication consumption, there was a pill count of unused capsules, and some statistical analyses based on change in plasma AA levels over the course of the trial (Brody et al., 2002).

On the last day of the trial, subjects attended the second laboratory session, where diaries and unused capsules were collected. After completing questionnaires and other measures, the subjects participated in the Trier Social Stress Test (TSST, Kirschbaum et al., 1993), which is a standardized psychological stress induction technique consisting of being told (following the "Time 1" [baseline] SBP measurement) that one will have to give a 5-min speech to an unknown panel (one of each sex) on personal suitability for a job in the subject's field of interest, followed by 5 min of mental arithmetic performed out loud. After 10 min of solitary preparation, the "Time 2" (preparation/anticipatory anxiety) SBP measurement is taken, and the subject enters the TSST room containing the panel of observers (one of each sex) and an obvious video camera and microphone. Pauses during the speech are dealt with by being reminded of remaining time. After 5 min, the task shifts to performing serial subtractions of 17 starting at 2023, with errors resulting in being required to return to the beginning. The "Time 3" (stressor) measurement is taken immediately at the end of the arithmetic task.

The study was approved by the State Medical Ethics Committee and by the University of Trier Ethics Committee. The study conformed to the Declaration of Helsinki principles. All subjects gave informed consent, and were informed of their ability to discontinue participation at any time. All data were coded by number for confidentiality and anonymity.

Repeated-measures analysis of variance (ANOVA) models were used for the examination of SBP reactivity. The between-subjects factors were medication group, and (in separate analyses) cannabis (lifetime ever vs. never use), tobacco (current vs. no current use), and caffeine (<3 vs. ≥ 3 doses daily). The repeated (within-subjects) factor was time (baseline, anticipation, or stressor), and the covariates in the ANOVAs were sex, age, Eysenck Personality Inventory neuroticism and extraversion scores, body mass index (measured kg/m^2), Beck Depression Inventory scores, and for the tobacco and cannabis analyses, the use of the other

substance was included as an additional covariate (this was done because of the significant [$\chi^2 = 21.3$, $P < .001$] overlap between current tobacco and ever cannabis use group membership: 74.5% of current tobacco smokers had ever used cannabis as contrasted with 30.2% of nonsmokers). Caffeine consumption group was unrelated to tobacco or cannabis group membership. Polynomial contrasts were used as described below.

In addition, multiple regression models were used to shed some light on the possible relative contributions of caffeine, tobacco, and cannabis use status to SBP reactivity protection. In separate analyses for the anticipation and actual stressor phases, the SBP change from baseline was the dependent variable. First, the medication group was entered into the equation, and then the caffeine, tobacco, and cannabis group membership, and the interaction of caffeine, tobacco, and cannabis group membership with the medication group were examined in both stepwise and forced-entry procedures.

To examine whether habitual tobacco use (and therefore abstinence during the experimental session) is related to pressor responses, Pearson correlation coefficients were calculated between the mean daily diary number of cigarettes consumed (over the 14-day period preceding the stressor) and SBP reactivity to both the anticipation and actual stressor (for the current tobacco smoker group).

All analyses were two-tailed with an alpha level of .05. Greenhouse–Geisser corrected P values are presented for the interaction of the repeated measure (time) and other variables. Only observed (no imputed) values were analyzed. Data were analyzed with SPSS statistical software. At a two-tailed alpha of .05, the study had a 77% power to detect a medium size (Cohen's $f = .25$) medication effect with the total sample size of 120, and a 73% power with the analyzed sample size of 108. Following data entry, the data were checked twice by two other persons.

3. Results

Although there were no dropouts from the study, 12 of the 120 subjects (six from each group) were excluded from analyses: four who reported unusual stress earlier on the TSST day (thereby precluding valid resting baseline values), four who were known to a member of the TSST panel (thereby possibly mitigating the stress), one who was found to have recently taken corticosteroids as part of another study, one for suspected substance use the day of the TSST, one for a pill count indicating < 80% of the required dose had been taken, and one (in the placebo group) for fainting during the TSST (Brody et al., 2002).

Baseline characteristics were similar for members of the placebo (mean age 24.4 [S.D. 4.1], 30 females, mean body mass index 22.7 [S.D. 2.8] kg/m^2) and AA (mean age 24.6 [S.D. 4.2], 36 females, mean body mass index 22.9 [S.D. 2.9] kg/m^2) groups (the means and distributions did not significantly differ by group); over the course of the trial, plasma AA levels increased significantly for the verum but not the placebo group, and at a group level, subjects were unable to discern in which group they were (further details in Brody et al., 2002). There were 27 persons (19 females) with a history of cannabis use in the verum and 26 (14 females) in the placebo group; 24 (12 females) higher caffeine users in the placebo group and 26 (16 females) in the verum group; and 32 (16 females) tobacco users in the placebo group and 23 (15 female) in the verum group (the distributions did not significantly differ by group).

For cannabis use, there was a significant effect of time interacting with medication group [($F(2,180) = 3.3$, $P = .041$], and a significant interaction of time interacting with group by cannabis use [$F(2,180) = 3.8$, $P = .028$; Greenhouse–Geisser epsilon = 0.93]. Contrasts ($df = 1$) revealed this was due solely to a quadratic effect (a significant difference in the ''bend'' of the reactivity lines in Fig. 1; $F = 5.7$, $P = .019$). As depicted in Fig. 1, the groups did not differ at baseline, but at Time 2 (preparation or anticipatory anxiety) the AA verum group (for both cannabis ever and never users) had less SBP increase than did the cannabis users who received placebo. At Time 3 (immediately after the stressor), the cannabis nonusers in the AA verum group had less SBP increase than did the placebo group (regardless of cannabis use status).

For tobacco use, there was a significant effect of time interacting with group [$F(2,180) = 3.7$, $P = .028$], and of time interacting with group by tobacco use group [$F(2,180) = 3.2$, $P = .048$; Greenhouse–Geisser epsilon = 0.93]. As depicted in Fig. 1, the pattern of results was similar to that in the cannabis analysis: among current tobacco smokers, t tests revealed that there was a protective effect of high-dose AA at Time 2, as well as a significant effect of high-dose AA at Time 3 for nonsmokers only. Contrasts ($df = 1$) revealed this was due solely to a quadratic effect ($F = 4.0$, $P = .049$). An additional ANOVA examining the reported number of cigarettes daily revealed the covariate to be nonsignificant.

For caffeine use, there was a significant effect of time interacting with group [$F(2,182) = 4.0$, $P = .024$], and a significant interaction of time interacting with group by caffeine use [$F(2,182) = 4.2$, $P = .02$; Greenhouse–Geisser epsilon = 0.91]. Contrasts ($df = 1$) revealed this was due solely to a quadratic effect ($F = 9.3$, $P = .003$). As depicted in Fig. 1, the groups did not differ at baseline, but at Time 2, the lower caffeine/AA verum subgroup had less SBP increase than did the lower caffeine/placebo and both higher caffeine subgroups. At Time 3, the lower caffeine/AA verum subgroup had less SBP increase than did the placebo group (regardless of caffeine use status), and the higher caffeine/AA verum subgroup had less SBP increase than the higher caffeine/placebo subgroup.

None of the covariates reached significance in any of the ANOVA analyses.

In the multiple regression analysis of SBP reactivity to the anticipation phase, only caffeine group membership (interacting with medication group [standardized $\beta = 1.131$,

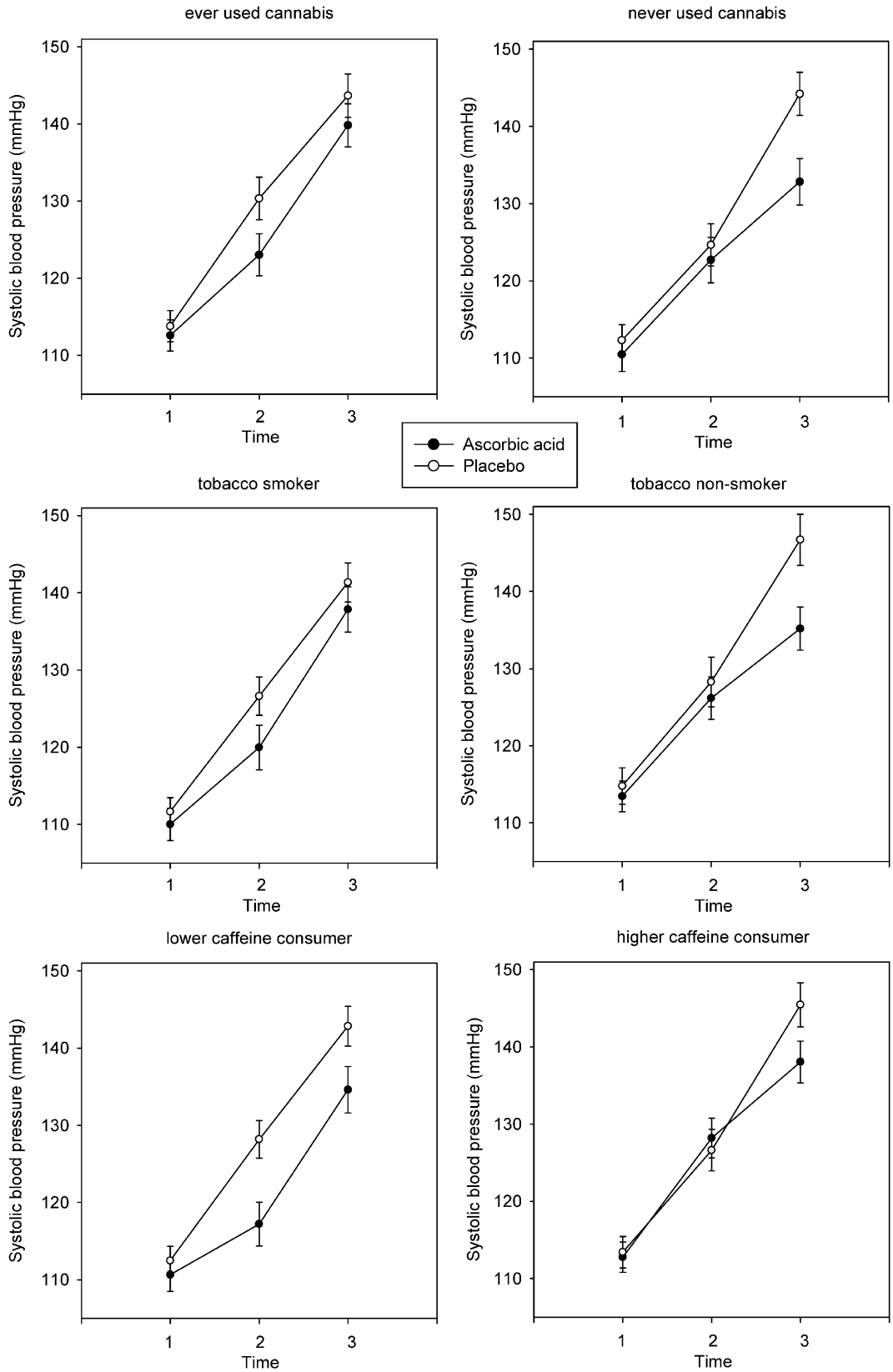

Fig. 1. SBP at Time 1 (baseline), Time 2 (anticipation of and preparation for the psychological stressor), and Time 3 (immediately following the stressor) as a function of trial group assignment (AA or placebo), and self-reported cannabis use (ever or never), tobacco use (current use or not), and caffeine consumption (<3 or >2 doses daily). Means with standard error bars are depicted. Values are adjusted for age, sex, body mass index, depression, neuroticism, and extraversion scores, and for tobacco and cannabis use of the other substance.

$t=2.7$, $P=.008$], and then as a main effect [standardized $\beta=-0.66$, $t=2.2$, $P=.03$]) made a significant contribution to the equation after medication group. This was the case for both stepwise and forced-entry models. In the multiple regression analysis of SBP reactivity to the actual stressor, only current tobacco smoking status interacting with medication group [standardized $\beta=0.26$, $t=2.2$, $P=.03$] made a significant contribution to the equation after medication group (however, cannabis group membership interacting with medication group approached significance [$t=1.7$, $P=.09$], and was not significantly less related to the criterion variable). This was the case for the stepwise model (in the forced entry model, none of the predictor variables entered the equation).

Daily cigarette consumption (mean 5.9 cigarettes/day, S.D. 7.6, maximum 30) was unrelated to SBP response to either the anticipation or the actual stressor phase (this was the case for all smokers, as well as for the two medication groups considered separately).

4. Discussion

For persons self-reporting a history of cannabis use, high-dose AA produced less SBP increase during the preparation/anticipatory anxiety phase, but did not confer significant protection during the actual stressor. For persons denying a history of cannabis use, high-dose AA led to less SBP increase during the actual stressor, but no significant protection from SBP increases during the preparation/anticipatory anxiety phase.

The pattern of results in the tobacco current/not current user analysis was quite similar to the cannabis analysis.

Among persons in the lower caffeine consumption group, high-dose AA conferred protection from both preparatory/anticipatory anxiety SBP increases and also from actual stress SBP increases. It also attenuated SBP increase during actual stress for higher-dose caffeine users, but not during the preparatory/anticipatory anxiety phase.

Inspection of Fig. 1 reveals a noteworthy similarity between users of nominally quite different substances in their differential response to AA modification of SBP response to stress. The magnitude of the effects is not only of heuristic interest, but potentially of physiological importance (given the frequency of comparable stressors in daily life): high-dose AA attenuated SBP increase during the stressor by approximately 10 mmHg, and the cannabis–AA interaction during preparation/anticipation had a magnitude of approximately 6 mmHg. It might be argued that from a prophylactic standpoint, never users of cannabis, current nonsmokers of tobacco, and consumers of more than two cups of caffeine beverages daily might derive greater SBP reactivity benefits from high-dose AA supplementation, because their protection occurs at greater SBP levels. However, a counterargument might be developed based on the finding that anticipatory blood pressure increases may be associated with the development of left ventricular hypertrophy (Kamarck et al., 2000). In either case, the magnitude of the SBP reactivity protection effect is comparable to that associated with parental history of hypertension (al'Absi et al. 1995), or aerobic fitness (Bond et al., 1999), and far greater than that of beta-blocker antihypertensive medication (Mills and Dimsdale, 1991). It is not known whether the obtained effects would be achieved with a formulation other than the sustained-release preparation used in this trial.

Not surprisingly, there was a considerable overlap between the tobacco and the cannabis group (this association might possibly be stronger in Europe than in the USA, in part because of some preference for blending hashish with tobacco in self-made cigarettes, rather than the tendency to use marijuana leaves alone as in the USA). Although cannabis use was covaried for the tobacco use analysis and vice versa, there is a possibility of residual confounding. The multiple regression approach suggested that caffeine group membership is most important for the anticipation phase, whereas current tobacco smoking status is most important for the actual stressor effect. However, given the only modest stability of multiple regression models, the near-significance of the cannabis group might still have an independent effect.

Daily cigarette consumption was unrelated to SBP response to either the anticipation or the actual stressor phase, a finding consistent with earlier work (Pauli et al., 1993) that depriving smokers of tobacco for brief periods such as the duration of this experiment does not result in alteration of cardiovascular indices. The result argues against an offset effect of tobacco.

Another issue is that although AA group was assigned in a true experimental manner, membership in cannabis, tobacco, and caffeine groups suffers from the usual vagaries of epidemiological research, including self-report biases and confounding with unmeasured factors. A shortcoming of the study is that the substance use variables are not parallel, as the cannabis criterion is ever use, tobacco is of recent use, and caffeine level is of current use (using an intrinsically arbitrary median split). Further details of use are not available. Thus, caffeine level might reflect the residual influence of the substance during the stressor, with tobacco as a possible marker (for personality and neurophysiological differences) function, and cannabis presumably acts only as a historical influence. Although blood pressure was measured immediately following the stressor, it is possible that there was a slight decline from the peak, and therefore the peak stress reactivity may have even been greater.

There are several possible interpretations of the results. In addition to an effect of relaxing the endothelium (Wilkinson et al., 1999; Gokce et al., 1999), AA modulates central catecholaminergic (notably dopaminergic) activity. High-dose AA may interact with enduring differences in receptor activity and sensitivities associated with historical

cannabis use and/or the personality features associated with its use (other than those examined as covariates, which were not significant). Similar explanations may be offered for the effects by level of caffeine use (except that the cannabis use group is more similar to the lower caffeine use group), and perhaps for tobacco users.

Solitary anticipation of a stressor combined with mental preparation for the task differs from the stress itself. In addition to the motor component of speech, the stressor has an interpersonal component, which may trigger different patterns of brain activity. High-dose AA might facilitate disengagement or at least palliate the stress from a distal stressor (preparation/anticipatory anxiety) among persons with a personality or psychopharmacological inclination to do so (cannabis users, tobacco smokers, and persons not stimulated by higher caffeine doses). For example, tobacco smokers appear to derive maximum utility from tobacco when dealing with a distal stressor (Gilbert, 1995). Similarly, high-dose AA might facilitate coping with the actual stressor for those (nonusers of cannabis and tobacco, consumers of higher doses of caffeine) with a more active and less avoidant coping style (or those seeking a higher level of arousal). In this conceptualization, AA supports an individual's neurophysiological predisposition, much in the same way that AA potentiates some effects of haloperidol and amphetamine (Pierce et al., 1995; Gulley and Rebec, 1999).

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References

al'Absi M, Everson SA, Lovallo WR. Hypertension risk factors and cardiovascular reactivity to mental stress in young men. Int J Psychophysiol 1995;20:155–60.

Bond V, Mills RM, Caprarola M, Vaccaro P, Adams RG, Blakely R, Roltsch M, Hatfield B, Davis GC, Franks BD, Fairfax J, Banks M. Aerobic exercise attenuates blood pressure reactivity to cold pressor test in normotensive, young adult African-American women. Ethn Dis 1999;9:104–10.

Brody S, Veit R, Rau H. Neuroticism but not cardiovascular stress reactivity is associated with less longitudinal blood pressure increase. Pers Individ Differ 1996;20:375–80.

Brody S, Veit R, Rau H. Four-year test–retest reliability of self-measured blood pressure. Arch Intern Med 1999;159:1007–8.

Brody S, Preut R, Schommer K, Schürmeyer TH. A randomized controlled trial of high dose ascorbic acid for reduction of blood pressure, cortisol, and subjective responses to psychological stress. Psychopharmacology 2002;159:319–24.

Eysenck HJ. Eysenck Persönlichkeits Inventar. Göttingen: Verlag für Psychologie, 1974.

Garrett BE, Griffiths RR. The role of dopamine in the behavioral effects of caffeine in animals and humans. Pharmacol, Biochem Behav 1997;57:533–41.

Gilbert DG. Smoking: individual difference, psychopathology, and emotion. Washington (DC): Taylor and Francis, 1995.

Gokce N, Keaney JF, Frei B, Holbrook M, Olesiak M, Zachariah BJ, Leeuwenburgh C, Heinecke JW, Vita JA. Long-term ascorbic acid administration reverses endothelial vasomotor dysfunction in patients with coronary artery disease. Circulation 1999;99:3234–40.

Gulley JM, Rebec GV. Modulatory effects of ascorbate, alone or with haloperidol, on a lever-release conditioned avoidance response task. Pharmacol, Biochem Behav 1999;63:125–9.

Hautzinger M, Bailer M, Worall H, Keller F. Beck-Depressions-Inventar (BDI). Bern: Huber, 1994.

Kamarck TW, Eranen J, Jennings JR, Manuck SB, Everson SA, Kaplan GA, Salonen JT. Anticipatory blood pressure responses to exercise are associated with left ventricular mass in Finnish men: Kuopio Ischemic Heart Disease Risk Factor Study. Circulation 2000;102:1394–9.

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.

Markianos M, Stefanis C. Effects of acute cannabis use and short-term deprivation on plasma prolactin and dopamine-beta-hydroxylase in long-term users. Drug Alcohol Depend 1982;9:251–5.

Markovitz JH, Raczynski JM, Wallace D, Chettur V, Chesney MA. Cardiovascular reactivity to video game predicts subsequent blood pressure increases in young men: the Cardia study. Psychosom Med 1998;60:186–91.

Mills PJ, Dimsdale JE. Cardiovascular reactivity to psychosocial stressors. A review of the effects of beta-blockade. Psychosomatics 1991;32:209–20.

Pauli P, Rau H, Zhuang P, Brody S, Birbaumer N. Effects of smoking on thermal pain threshold in deprived and minimally deprived smokers. Psychopharmacology 1993;111:472–6.

Pierce RC, Rowlett JK, Rebec GV, Bardo MT. Ascorbate potentiates amphetamine-induced conditioned place preference and forebrain dopamine release in rats. Brain Res 1995;688:21–6.

Salokangas RK, Vilkman H, Ilonen T, Taiminen T, Bergman J, Haaparanta M, Solin O, Alanen A, Syvalahti E, Hietala J. High levels of dopamine activity in the basal ganglia of cigarette smokers. Am J Psychiatry 2000;157:632–4.

Wilkinson IB, Megson IL, MacCallum H, Sogo N, Cockcroft JR, Webb DJ. Oral vitamin C reduces arterial stiffness and platelet aggregation in humans. J Cardiovasc Pharmacol 1999;34:690–3.