Caffeine May Potentiate Adrenocortical Stress Responses in Hypertension-Prone Men


The effect of caffeine on blood cortisol levels and blood pressures was examined during rest and in response to a challenging psychomotor task in men with a low versus high risk of essential hypertension. Thirty-four healthy men ages 21-35 years were selected such that 17 were at high risk for hypertension (positive parental history and screening blood pressures of 135/85-155/95 mm Hg) and 17 were at low risk (negative parental history and no pressures above 132/84 mm Hg). Testing consisted of quiet rest (20 minutes); oral placebo (grapefruit juice) or caffeine administration (3.3 mg/kg in grapefruit juice); rest during a postdrug absorption period (40 minutes); work on an unsignalled simple reaction time task (15 minutes); and quiet rest (20 minutes). Blood pressures were recorded at 2-minute intervals, and blood samples were withdrawn via an indwelling catheter at the end of the baseline, drug absorption, task, and recovery periods. The combination of task plus caffeine produced the highest blood pressures in men at risk for hypertension. Cortisol levels were found to be sustained during rest in members of the high risk group after they had consumed caffeine, whereas members of the low risk group showed a modest decline. The high risk subjects also showed a significant rise in cortisol during (+3.7 μg/dl) and after (+4.0 μg/dl) work on the reaction time task after caffeine consumption. In the low risk group, cortisol responses to caffeine were smaller (+2.2 μg/dl or less) when compared with responses to the task after caffeine consumption. The results suggest that these men at high risk for hypertension were sensitive to caffeine and that caffeine combined with a demanding psychomotor challenge produced neuroendocrine signs of stress. These findings point toward the need for studies of the role of caffeine in modifying stress responses of targeted groups such as those at risk for hypertension. (Hypertension 1989;14:170-176)
In view of caffeine's role as a central nervous system stimulant, its effects on vascular resistance at rest, and its enhancement of cardiac activity during stress, we have initiated studies on the effects of caffeine in men at risk for development of essential hypertension. A key factor in the early stages of the development of hypertension is an enhanced neurogenic drive. Cortisol is capable of potentiating release of and receptor affinity for the catecholamines. It is, therefore, important to understand the actions of agents, such as caffeine, that may interact directly or indirectly with the enhanced neurogenic function associated with development of hypertension.

The present data form part of a larger study of the effects of caffeine on cardiovascular and neuroendocrine functions in healthy young men who vary in risk for development of essential hypertension. We report here that the elevation of cortisol secretion by caffeine during psychomotor challenge is especially pronounced in men with a parental history of hypertension who also show high normal resting blood pressures (high risk) when compared with responses of men with a negative parental history and low normal resting pressures (low risk).

Subjects and Methods

The subjects involved in this report were 34 Caucasian men, of whom 17 were designated high risk for essential hypertension and 17 were designated low risk. Risk classification was based on parental hypertension and resting blood pressures as follows: high risk, report of essential hypertension in either or both parents verified by physician and two or more resting blood pressures in the range of 135 mm Hg systolic or 85 mm Hg diastolic, to 155 systolic or 95 mm Hg diastolic, inclusive; low risk, report of a negative history of hypertension in both parents and no screening pressures above 132 mm Hg systolic or 84 mm Hg diastolic.

Inclusion criteria were as follows: age 21-35 years, weight within 20% of normal as defined by Metropolitan Life Insurance Company norms, normal health defined by absence of self-reported major illnesses, no prior treatment for essential hypertension and no current use of any prescription medication, usual caffeine consumption equivalent to 1–5 cups of coffee/day with no reported intolerance or negative side effects to caffeine, and smoking of less than 10 cigarettes/day and alcohol consumption of less than 15 drinks/week.

All volunteers signed a consent form approved by the Institutional Review Board of the University of Oklahoma Health Sciences Center and Veterans Administration Medical Center and were paid for their participation.

Screening procedures consisted of two phases. Phase 1 involved a visit to the laboratory for blood pressure screening and medical history review. Blood pressure screening consisted of taking three automated blood pressure measurements in 5 minutes after the subject had been seated upright at rest for 5 minutes. A second set of three readings was taken over 5 minutes after 15 minutes seated at rest.

The subject was then interviewed for his personal medical history and his parents' hypertension history. Consent was then obtained from the parents to get hypertension-related information (hypertensive diagnosis, previous blood pressures, and medications) from their physicians. A second screening was scheduled, pending confirmation of parents' blood pressure status.

Phase 2 of screening consisted of a return visit to the laboratory for a physical exam; determination of height, weight, and percent body fat by skinfold thickness; and symptom-limited exercise tolerance test using the Bruce protocol. Normal results from physical exam and treadmill test were required for further testing. Table 1 shows the characteristics of the final subject sample.

Each subject was then assigned at random to one of two caffeine-placebo test orders. Test sessions were scheduled two or more days apart at the same time of day, usually 9:00 AM. Subjects were instructed to abstain from alcohol for 24 hours, from caffeine for 18 hours, and to maintain a fasting state for 12 hours before testing.

The test procedure was as follows: After having been fitted with a blood pressure cuff and a heparinized intravenous catheter placed in a forearm vein, the subject sat in a semirecumbent position in a recliner chair. Testing included quiet rest and baseline period (20 minutes), caffeine or placebo drink and drug absorption period (40 minutes), task instructions and psychomotor task period (15 minutes), and recovery period (20 minutes). The subject was allowed to read general interest reading materials during rest, drug absorption, and recovery periods.

Caffeine (USP, anhydrous; Amend Drug and Chemical Co., Irvington, New Jersey) was administered in a 3.3 mg/kg dose mixed with 6 oz unsweetened grapefruit juice (Texsun, Weslaco, Texas). Placebo consisted of the grapefruit juice alone.

The psychomotor test consisted of an unsignalled, simple reaction time task with 60 trials spaced at randomly chosen intertrial intervals ranging from 4 to 30 seconds with a mean interval of 15 seconds. Programming used digital logic apparatus (Med Associates, East Fairfield, Vermont). The subject was instructed to watch a red light placed at eye level and was told that the light would flash on at unpredictable intervals. The subject was then shown a response key mounted near his right hand and told to press the key as rapidly as possible after detecting the light and that each "very rapid" response (less than 270 msec) would result in his earning a $.50 bonus. The number of bonuses earned was displayed continuously on a counter placed next to the stimulus light.

Blood pressure was measured at 2-minute intervals with a Critikon (Tampa, Florida) Dynamap oscillometric monitor. These were averaged over
The study used a double-blind, placebo-controlled, crossover design that was the basis for a 2 risk group (low vs. high risk) × 2 test order (placebo vs. caffeine) × 2 test day (first, second) analysis of variance (ANOVA) with a repeated measure on the last factor. The effect of caffeine versus placebo is identical to the test order by test day interaction term and will be referred to as the caffeine or drug effect.

Risk group characteristics were compared using Student's t test. Blood levels of caffeine were compared for the risk groups and across postdrug sampling periods on the caffeine day by using a 2 group (low vs. high risk) × 3 period (drug absorption, post task, recovery) ANOVA. Rewards earned during the task were analyzed using a 2 risk group × 2 drug (placebo vs. caffeine) ANOVA.

Caffeine effects on cortisol concentrations at rest were tested using a 2 risk group × 2 drug × 2 period (baseline vs. drug absorption) ANOVA and a 2 risk group × 2 drug analysis of covariance in which the predrug values were used as covariates. Caffeine influences on cortisol response to the reaction time task were tested first with a 2 risk group × 2 drug × 2 period (task and recovery) analysis of covariance in which cortisol levels at the end of drug absorption served as the covariates. This ensured that tests of differences between groups in cortisol concentrations during and after the task were not enhanced by group differences existing before the task. A second test of the effect of caffeine on cortisol changes to the task involved averaging task and recovery cortisol values and conducting a 2 risk group × 2 drug (placebo vs. caffeine) ANOVA.
Blood pressures were analyzed using a 2 risk group×2 drug×4 period (baseline, drug absorption, posttask, recovery) ANOVA. Appropriate risk group × caffeine interactions were further examined using simple effects tests.\(^{14}\) When error terms for \(F\) ratios contained heterogeneous sources of variance, degrees of freedom for tests of significance in simple effects tests were calculated using Satterthwaite’s approximation.\(^{14}\) All ANOVAS were conducted using the program BMDP, P2V (University of California at Los Angeles, Los Angeles, California). A criterion of \(p<0.05\) was adopted for statistical significance.

**Results**

Comparison of the risk groups’ characteristics revealed that the two were similar in height, percent body fat, and aerobic fitness. The high risk subjects were somewhat heavier and had a greater weight-to-height ratio\(^{15}\) (See Table 1).

Examination of plasma caffeine concentrations revealed good compliance with pretest restriction of caffeine intake on both days of testing and that all caffeine and placebo doses were administered correctly. Average placebo-day concentrations were very low at all sample points (less than 0.07 \(\mu\)g/ml). On the caffeine days, predrug mean was 0.0 \(\mu\)g/ml, whereas samples drawn postdrug, during the task, and after recovery were substantially higher (mean±SEM, 4.86±0.37, 5.27±0.22, and 5.15±0.15 \(\mu\)g/ml, respectively). These proved not to vary significantly over the three postingestion periods \([F(2,64)=1.59, p>0.21]\), and not to differ between low and high risk groups [4.84 and 5.35 \(\mu\)g/ml, respectively, \(F(1,32)=1.96, p>0.16\)]. These plasma caffeine concentrations agree with those reported elsewhere using comparable doses.\(^{16}\) One low risk subject showed residual plasma caffeine concentrations (less than 2.2 \(\mu\)g/ml) in each plasma sample from his placebo day. This person’s data were retained in the analysis because this concentration of caffeine was considered negligible for present purposes. Animal studies have indicated that low doses of caffeine alone do not accelerate cortisol production,\(^{7}\) and these residual levels were less than half those produced by the dose of caffeine used in this study.

Rewards earned on the task were increased on the caffeine day relative to the placebo day [30 and 24, respectively; \(F(1,29)=6.69, p<0.02\)]. This effect was equivalent for both risk groups.

Cortisol did not increase from baseline during the 40-minute postdrug absorption period for the subject sample as a whole [\(F(1,32)=0.91, p>0.30\)], indicating that the dose used was not capable of enhancing cortisol synthesis at rest in a group of men heterogeneous for risk of hypertension. Inspection of Figure 1 and Table 2 indicates that low risk men had comparable predrug cortisol concentrations on caffeine and placebo days that showed a downward trend over the 40-minute postdrug period.

Although this downward trend was also evident for the high risk group on their placebo day, these subjects showed a slight upward trend in cortisol levels on their caffeine day. At 40-minutes postdrug, these caffeine-day cortisol concentrations were significantly higher than the corresponding placebo-day values [14.1 vs. 11.3 \(\mu\)g/dl, respectively; \(F(1,47)=4.10, p<0.05\)]. After correction for predrug baseline differences, this comparison showed a nonsignificant trend \([F(1,31)=3.33, p=0.083]\). The low risk group had comparable task-related cortisol concentrations on both placebo and caffeine days, whereas the high risk group had significantly higher levels on their caffeine day [groups by caffeine interaction, \(F(1,31)=5.21, p<0.03\)]. This effect of caffeine on the high risk subjects was evident at both the end of the task and 20 minutes later \([F(1,29)>11.90, p<0.005]\). Finally, comparison of pretask cortisol values with values averaged over task and recovery again revealed that the caffeine-related cortisol rise for high risk subjects was significantly greater than that for the low risk subjects \([F(1,32)=4.32, p<0.05]\). Separate comparisons showed that the cortisol rise in response to the task in the presence of caffeine was significant in the case of the high risk subjects only [14.10 to 17.96 \(\mu\)g/dl, \(F(1,11)=8.26, p<0.025\)], the latter group showing a 27% rise.
In general agreement with the cortisol results, the highest blood pressures were seen among the high risk men during the reaction time task on the caffeine day (Table 2). Caffeine was associated with higher systolic and diastolic pressures across all periods \( F^2s(1,32)>31.00, p^2<0.0001 \), and high risk subjects showed higher pressures than low risk subjects \( F^2s>26.00, p^2<0.0001 \). The size of the baseline blood pressure difference between the risk groups was maintained after caffeine consumption and during the task plus caffeine \( F^2s(1,32)>28.00, p^2<0.0001 \). The blood pressure rise in response to caffeine was equivalent for both groups, and the blood pressure rise in response to the task was enhanced by caffeine equivalently in both risk groups. Caffeine was, therefore, shown to exert an additive effect on blood pressure during the task, and this increment was similar in both risk groups, resulting in task blood pressures on the caffeine day among high risk men of 137/80 mm Hg compared with 128/68 mm Hg among low risk men.

### Discussion

The above results contain three findings of particular interest. First, during the period of activation associated with work on the psychomotor task, the high risk men showed an exaggerated cortisol rise in the presence of caffeine relative to their low risk counterparts. This difference in cortisol response was not associated with any apparent difference in effort on the task because both groups earned a similar number of rewards. Second, the high risk subjects showed a tendency toward sensitivity to caffeine while at rest, as indicated by their sustained cortisol concentrations over the 40-minute postdrug period after ingestion of caffeine. Third, caffeine increased blood pressure equivalently in both risk groups during rest and during the psychomotor task. The additive effects of task plus caffeine resulted in the high risk men having the highest pressures with this combination \( 137/80 \) vs. \( 128/68 \) mm Hg in the low risk group. This suggests that caffeine, in combination with behavioral stress, can have implications for hypertension development and treatment. The increment in blood pressure caused by caffeine \( (\text{approximately} 6/6 \text{ mm Hg}) \) could raise pressures into the borderline hypertension range in men with otherwise marginally elevated levels and could counteract the effects of antihypertensive medication in patients receiving such therapy.

These findings are consistent with our prior studies of the effect of caffeine on the cortisol response to behavioral stressors. We have reported that the reaction time task alone does not produce a significant rise in cortisol above baseline when monetary reward is used as the incentive, but that cortisol does increase to the task when aversive incentives are used. This difference in the adrenocortical response to aversive and nonaversive conditions is consistent with formulations by Mason and Frankenhaeuser that view adrenocortical mechanisms as coming into play when the individual is faced with threatening or unpleasant challenges. The reaction time task with monetary bonuses, as used here, would normally be characterized as stimulating or activating but not as threatening or distressing.

The present results are also consistent with our prior work in showing that caffeine does not provoke a rise in cortisol in unselected groups of persons who are resting quietly. Studies of rats have also shown that caffeine in low to moderate doses does not elevate corticosterone but may do so at high doses. At least one study, however, has shown a cortisol rise after administration of caffeine in a dose comparable with that used here. Although low risk men in the present sample showed a downward cortisol trend from baseline to 40 minutes after caffeine consumption, the lack of decline in the high risk subgroup argues that the men at risk for hypertension were more sensitive to caffeine than those in the low risk group.

In contrast to its minimal effects on resting persons, caffeine appears to be capable of evoking an adrenocortical response during behavioral stress in subject samples unselected for hypertension risk. The present study, as well as our prior work wherein...
the same reaction time task was used, showing that caffeine may produce a rise in plasma cortisol during work demanding vigilance and effort. Caffeine is capable of increasing cortisol levels when taken in an occupational setting during periods of either low or high work stress. Together, these findings suggest that caffeine is capable of enhancement of neuroendocrine responses to behavioral stressors and, indeed, may produce a significant cortisol response when one would otherwise be minimal or absent. The present finding that caffeine selectively potentiated cortisol rises in men at risk for hypertension is of particular significance. Cortisol is known to enhance the synthesis of catecholamines, to inhibit the usual degradation of catecholamines by catechol-o-methyl-transferase, to increase 

\[\beta\]-receptor synthesis in arterial smooth muscle cells, and to increase sensitivity of catecholamine receptors. Therefore, the exaggeration of cortisol responses in the high risk group may have widespread secondary consequences.

The source of the potentiation of the cortisol response by caffeine merits examination. In the normal chain of events, neurosecretory cells of the hypothalamus release corticotropin releasing factor (CRF) into the portal circulation, which carries this substance to the anterior pituitary. CRF causes the division of a precursor molecule (pro-opiomelanocortin) to yield adrenocorticotropic hormone (ACTH) and \n
\[\beta\]-endorphin. It is now well established that epinephrine may also cause this precursor to divide and give rise to ACTH and \n
\[\beta\]-endorphin and may also potentiate the CRF-induced route of ACTH production. The hypothalamus and adrenal medulla, therefore, form important links by which the pituitary–adrenocortical system is integrated into the total neuroendocrine response to stress.

Caffeine is capable of producing the release of cortisol and \n
\[\beta\]-endorphin into the circulation. This implies that ACTH is also released because \n
\[\beta\]-endorphin and ACTH share an identical mode of regulation. This also implies that caffeine may not produce direct release of cortisol from the adrenal cortex but acts on the hypothalamus or pituitary. There is also evidence that caffeine does not act directly on the pituitary to produce ACTH release but that it can increase CRF production by the hypothalamus. Caffeine has also been shown to increase urinary excretion rates of norepinephrine and epinephrine and to cause the release of epinephrine from the adrenal medulla. Doses comparable with those used here may increase plasma epinephrine concentrations by 258% in resting, normotensive men.

The foregoing indicates that caffeine may enhance cortisol secretion by acting at the hypothalamus, or indirectly by stimulation of epinephrine release from the adrenal medulla. The existence of these dual modes of action has important implications for the ability of caffeine to interact with behavioral stress, as seen here. Caffeine has been shown to interact with behavioral stress in mice to produce large increases in corticosterone secretion. We have also observed a potentiation of inotropic effects on the heart when caffeine is combined with the visual reaction time task used here.

Caffeine, therefore, appears capable of altering neuroendocrine and cardiovascular responses to behavioral challenges. Tasks that alone may elicit behavioral and cardiovascular activation unaccompanied by an adrenocortical response may, in the presence of caffeine, function as neuroendocrine stressors accompanied by rises in cortisol concentrations. This caffeine-mediated cortisol effect assumes increased significance in view of its possible selective enhancement in men at risk for essential hypertension. Future studies should be directed to replication of these results and should also examine CRF, ACTH, and epinephrine responses accompanying stimulation of cortisol secretion by caffeine.

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