Chronic Caffeine Consumption and the Dexamethasone Suppression Test in Depression

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Abstract. Acute caffeine administration increases cortisol and converts the dexamethasone suppression test (DST) to nonsuppression in normal humans; data concerning chronic administration as well as effects in depressed patients are minimal. To determine whether caffeine intake influenced DST results in depression, we retrospectively studied the relationship between regular daily caffeine consumption and pretreatment DST status in major depressives. Daily intake was not correlated with either post-DST cortisol levels or symptom ratings. These data suggest that chronic caffeine use is unlikely to be a major factor in dysregulation of the hypothalamic-pituitary-adrenal axis in depression, perhaps because of the development of tolerance.

Key Words. Caffeine, dexamethasone suppression test (DST), depression.

Acute caffeine administration increases cortisol in animals (Spindel et al., 1983) and humans (Spindel et al., 1984; Uhde et al., 1984; Charney et al., 1985). Uhde et al. (1985) reported the conversion of dexamethasone suppression test (DST) suppressors to nonsuppressors by giving oral caffeine 1.5 to 2 hours before 4 p.m. post-DST blood sampling in a small sample of depressed patients and normal controls.

Greden et al. (1978) reported that more severely depressed patients used more caffeine, possibly to elevate depressed mood. Therefore, if regular caffeine ingestion also affects the hypothalamic-pituitary-adrenal (HPA) axis in the same way that acute administration does, daily caffeine intake might influence DST findings in depression. However, a study in animals (Spindel et al. 1983) showed that with chronic caffeine administration tolerance developed to caffeine's cortisol-stimulating effect. Also, higher doses of caffeine seemed to be required to stimulate cortisol release (Spindel et al., 1984) than doses that produce behavioral changes (Snyder and Sklar, 1984) or catecholamine release (Robertson et al., 1981) in humans.

Thus, we examined the relationship between pretreatment DST status and retrospective self-report of daily caffeine consumption in a large sample of people with major depression. If chronic caffeine use influences DST status, we might expect higher caffeine use in DST nonsuppressors.

Methods

One hundred and twenty-one major depressives, defined according to Research Diagnostic Criteria (RDC) (Spitzer et al., 1978) (mean ± SD age = 40.0 ± 13.4 years; range 20-83 years; 42 males; 90 unipolars; 45 inpatients), completed a caffeine questionnaire (Victor et al., 1981) and the State-Trait Anxiety Inventory (Spielberger et al., 1970). Experienced clinicians evaluated all patients with the 17-item version of the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960). Anxiety was evaluated because many depressed patients report symptoms of anxiety, and anxiety has been shown to influence caffeine intake (Lee et al., 1985); thus, anxiety might be a relevant factor in interpreting results. The caffeine questionnaire assessed amount of daily caffeine intake from approximately 25 sources, and also inquired about subjective symptom responses to ingesting one cup of coffee, as well as use of other drugs such as minor tranquilizers, antidepressants, hypnotics, and diet pills. Caffeine consumption was determined on the basis of usual daily use outside of the hospital. Although coffee and tea were freely available in the hospital setting, it is possible that caffeine use changed during hospitalization; therefore, inpatients were compared to outpatients (below).

Pretreatment DSTs were done with 1 mg of dexamethasone administered orally at 11 p.m., and blood sampling for plasma cortisol levels at 8 a.m., 4 p.m., or 11 p.m. the next day. At least two blood samples were drawn from each patient; levels of plasma cortisol $> 5 \mu g/dl$ in at least one sample constituted DST nonsuppression. Plasma cortisol was assayed by the competitive protein binding method (Murphy, 1967); interassay and intra-assay coefficients of variation were 7.2% and 7.0%, respectively.

Depressives were divided into two groups according to DST outcome (suppressor or nonsuppressor). Caffeine intake was compared across all patients; patients were also divided into three groups on the basis of their caffeine intake: low (0-249 mg/day), moderate (250-749 mg/day), and high ($\geq$ 750 mg/day) (Victor et al., 1981). Possible relationships between caffeine intake with post-DST cortisol levels and symptom severities were examined. Reports of subjective symptom responses to caffeine intake were compared between groups. Because of positive skewness of the distributions, log-transformed values were used for caffeine consumption and post-DST cortisol values. Statistical tests included χ^2, Pearson product-moment correlations, and analyses of variance and covariance.

Results

Mean (± SD) daily caffeine consumption for all subjects was reported to be 393 ± 415 mg/day (range: 6-2289 mg); 49.6% were low consumers, 31.4% were moderate consumers, and 19.0% were high consumers. There were no significant correlations between caffeine intake and actual cortisol levels at any postdexamethasone time point, either for the total sample or for any of the three caffeine intake groups. There was no significant difference in percentage of subjects in the three caffeine intake groups between DST suppressors ($n = 85$) and nonsuppressors ($n = 36$), whether calculated on the basis of postdexamethasone 4 p.m. level or on the basis of maximum postdexamethasone determination (Table 1). However, after removing by covariance differences in age and depression (HRSD) scores that have been reported to influence caffeine intake (Greden et al., 1978), there was a trend toward increased

caffeine intake in DST suppressors (adjusted means: 412 mg vs. 349 mg, $p < 0.07$). There were no differences in use of other drugs between groups. DST suppressors were significantly younger than nonsuppressors (means: 37.9 vs. 47.0 years, $p < 0.001$).

Table 1. Dexamethasone suppression test (DST) percentages positive and negative at different caffeine intakes

	Daily caffeine intake (mg from all sources)		
	Low ($<$ 250)	**Moderate (250-749)**	**High ($>$ 750)**
DST negative (%)	45.9 ($n = 39$)	36.5 ($n = 31$)	17.6 ($n = 15$)
DST positive (%)	61.1 ($n = 22$)	16.7 ($n = 6$)	22.2 ($n = 8$)

by χ^2, $p = 0.096$ (highest postdexamethasone cortisol level)

DST negative (%)	46.0 ($n = 40$)	34.5 ($n = 30$)	19.5 ($n = 17$)
DST positive (%)	62.5 ($n = 20$)	18.8 ($n = 6$)	18.8 ($n = 6$)

by χ^2, $p = 0.203$ (1600h postdexamethasone cortisol level)

DST suppressors were somewhat less depressed than nonsuppressors, as indicated by the HRSD (means: 18.0 vs. 20.02) but somewhat more anxious, as indicated by the trait part of the Spielberger inventory (means: 59.4 vs. 54.0); state anxiety showed no difference. There were no differences in depression or anxiety (state or trait) across the three caffeine intake groups. There were no significant associations between reported daily caffeine intake and any symptom ratings, either in the total sample or separately for suppressors and nonsuppressors (see Table 2 for list of symptoms).

In response to ingesting a cup of coffee, 43.3% of suppressors but only 21.6% of nonsuppressors reported experiencing anxiety (χ^2 test, $p < 0.02$). Suppressors also reported more of the other symptoms including "lightheadedness" ($p < 0.05$) and "tachycardia" ($p < 0.01$) (Table 2). There were no significant differences in caffeine's mood-elevating ("cheer up," "less depressed," "well being") effect between the two groups (Table 2).

Because all subjects were instructed to rate themselves on the caffeine questionnaire based on an average day outside of the hospital over an unspecified period of time, and caffeine intake might have changed during hospitalization, all inpatients were compared to all outpatients. Inpatients had a higher percentage of nonsuppressors, based on the maximum postdexamethasone level (42.2% vs. 22.4%, by χ^2 test, $p < 0.03$) or based on the 4 p.m. level (40.9% vs. 18.7%; by χ^2 test, $p < 0.01$), and inpatients were significantly older (means: 44.9 vs. 36.8 years, $p < 0.001$). However there were no differences in caffeine intake or in depression or anxiety scores, and only a small proportion of the symptoms (12%) differed significantly between the groups.

Discussion

Daily caffeine intake in major depressives was similar to intake previously reported

Table 2. Percentages of dexamethasone suppression test (DST) suppressors and nonsuppressors reporting subjective symptoms in response to ingestion of one cup of coffee

	DST suppressors ($n = 85$)	DST nonsuppressors ($n = 36$)	p values
Anxiety	43.3%	21.6%	< 0.02[1]
Diarrhea	12.2	8.1	NS
Diuresis	80.0	69.4	NS
Headache	5.6	0.0	NS
Lightheadedness	16.7	2.7	< 0.05[2]
Palpitation	18.9	10.8	NS
Stomachache	15.6	18.9	NS
Spot in front of eye	2.2	2.7	NS
Tachycardia	32.2	10.8	< 0.01[3]
Tachypnea	5.6	2.7	NS
Tremulousness	22.5	19.4	NS
Cheer up	16.7	10.8	NS
Less depressed	17.8	16.7	NS
Well-being	33.7	24.3	NS

1. $\chi^2 = 5.86$.
2. $\chi^2 = 5.36$.
3. $\chi^2 = 7.04$.

in medical (Victor et al., 1981) and psychiatric (Greden et al., 1978) inpatients. Contrary to prediction, on the basis of retrospective reports, DST suppressors tended to use more caffeine than nonsuppressors, but the difference was small. These results suggest that chronic caffeine use produces tolerance to the acute effects of caffeine on the HPA axis, and thus that chronic caffeine use does not strongly influence DST status in depressed patients.

The data collected in this study allowed us also to address the issue of the relationship between anxiety and the DST in depressed individuals. There have been conflicting results in prior studies—either higher anxiety in nonsuppressors, or no difference (Jimerson et al., 1983; Klein et al., 1984; Sangal et al., 1984; Kocsis et al., 1985; Roy et al., 1986; Grunhaus et al., 1987), which might be due in part to the use of different instruments to measure anxiety. Our finding of no difference in state anxiety between suppressors and nonsuppressors is consistent with the report of Sangal et al. (1984), who used the same state anxiety measure. The small increase in this study in trait anxiety *in suppressors* also suggests that there is no substantial difference between suppressors and nonsuppressors. Thus, the results of this study support the view that there is no difference in anxiety between suppressors and nonsuppressors.

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