ORIGINAL ARTICLE

Decreased Memory Performance in Healthy Humans Induced by Stress-Level Cortisol Treatment

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Background: Glucocorticoids (GCs) can regulate hippocampal metabolism, physiologic functions, and memory. Despite evidence of memory decreases during pharmacological GC treatment, and correlations between memory and cortisol levels in certain disease conditions, it remains unclear whether exposure to the endogenous GC cortisol at levels seen during physical and psychological stress in humans can inhibit memory performance in otherwise healthy individuals.

Methods: Randomized, double-blind, placebo-controlled comparison of 2 fixed oral doses of cortisol (40 mg/d and 160 mg/d using split doses to approximate circadian rhythm) given for 4 days to matched groups of healthy subjects (n = 51). Lower-dose treatment approximated cortisol exposure during mild stress, whereas the higher dose approximated cortisol exposure during major stress. Cognitive testing and plasma sampling were done at baseline, after 1 and 4 days of treatment, and after a 6-day washout period, hypothesizing dose-dependent decreases in verbal declarative memory.

Results: Cortisol treatment at the higher dose produced reversible decreases in verbal declarative memory without effects on nonverbal memory, sustained or selective attention, or executive function. A significant interaction between time and treatment condition for paragraph recall was explained by treatment-induced differences in performance after 4 treatment days, with lower immediate and delayed recall performance during higher-dose cortisol treatment compared with lower-dose treatment and placebo.

Conclusions: Several days of exposure to cortisol at doses and plasma concentrations associated with physical and psychological stress in humans can—similar to pharmacological GC treatment—reversibly decrease specific elements of memory performance in otherwise healthy individuals.

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GLUCOCORTICOIDS (GCs), which are produced by the stress-responsive hypothalamic-pituitary-adrenal axis, can regulate neuronal metabolism, physiologic functions, and gene expression in the brain, particularly the hippocampus. A range of evidence[1] supports the role of the hippocampus in declarative memory performance, with recent interest[2] in a role for hippocampal synaptic plasticity as a memory substrate. Glucocorticoid actions on the hippocampus include involution of the dendritic processes of hippocampal neurons,[3] inhibition of activity-dependent synaptic changes such as long-term potentiation,[4] site-preferential inhibition of glucose transport in vitro,[5] and glucose metabolism in humans in vivo.[6] Type 2 GC receptors have a lower affinity for the endogenous human GC cortisol than do type 1 receptors and thus tend to be activated by peak levels associated with stress rather than by basal GC concentrations.[7] Effects on glucose transport[5] and suppressant effects on neuronal excitability[8] are also mediated by type 2 receptors.

Investigators[9-12] reported adverse effects of GC exposure on cognitive functions associated with hippocampal integrity in the rodent, including recent evidence[13] for GC-induced impairments in the retrieval of learned material. Investigators[14-16] also reported dose-dependent facilitating effects of GC treatment on elements of memory function. However, the implications of these findings for memory performance in humans is complicated by varying species, dose level and timing, and variable task characteristics across the studies. In humans, case-control study designs indicate decreased memory performance during prednisone treatment of asthmatic children[17] and decreased verbal declarative memory in prednisone-treated patients vs matched medical control subjects.[18] Investigators[19-29] also reported inverse correlations between memory performance and plasma concentrations of cortisol in patients with Cushing syndrome, dementia of the Alzheimer type, schizophrenia, and depression. Various cognitive impairments have been reported in Cushing syndrome, with preferential involvement of memory func-

SUBJECTS AND METHODS

SUBJECTS

All subjects gave written informed consent for their participation in a protocol approved by the Washington University School of Medicine Human Studies Committee, St Louis, Mo. Subjects aged 18 to 30 years were recruited using local advertisements and were screened for general medical health, including psychiatric disorders, using the Diagnostic Interview for Genetic Studies.[49] Subjects were excluded for the presence of clinically significant medical or psychiatric disease, including (1) type 1 or 2 diabetes mellitus, hypertension, any major surgery within the previous 6 months, any cardiac condition causing documented hemodynamic compromise, any respiratory condition causing documented or clinically recognized hypoxia, fever, dehydration, nausea, epilepsy, other endocrine disease, body weight less than 80% ideal body weight, any other medical condition requiring more than 7 days of hospitalization in the past 4 weeks, pregnancy or higher-dose estrogen therapy, narcotic therapy, corticosteroid or spironolactone therapy, and psychotropic therapy; (2) any Axis I psychiatric disorder, including any substance use disorders; and (3) mental retardation as determined by *DSM-IV* criteria. Twenty-five men and 26 women were assigned to the higher-dose cortisol (7 men and 8 women), lower-dose cortisol (8 men and 8 women), and placebo (10 men and 10 women) groups. Complete data were available for most of the cognitive analyses for all 51 subjects, with complete plasma data for 50 of them at baseline and 49 of them over all sampling times. Clinical characteristics of the sample were as follows (mean ± SD): age, 22.2 ± 2.8 years; body mass index (calculated as weight in kilograms divided by the square of the height in meters, 23.0 ± 3.9; and education, 15.5 ± 1.96 years. No significant differences across treatment groups were detected for age ($F_{2,48} = 0.003$; $P = .99$); body mass index ($F_{2,48} = 1.03$; $P = .36$); education ($F_{2,48} = 0.49$; $P = .61$); Wechsler Adult Intelligence Scale–Revised information ($F_{2,48} = 0.65$; $P = .53$), vocabulary ($F_{2,48} = 0.75$; $P = .48$) and block design ($F_{2,47} = 0.33$; $P = .72$) subscale scores; handedness ($F_{2,47} = 0.66$; $P = .52$); or baseline cortisol ($F_{2,47} = 1.30$; $P = .28$), insulin ($F_{2,47} = 0.007$; $P = .99$), or glucose ($F_{2,47} = 0.04$; $P = .96$) plasma concentrations.

PROCEDURE

This study was a randomized, double-blind, placebo-controlled comparison of 2 fixed oral doses of cortisol (hydrocortisone), 160 mg/d and 40 mg/d, given over 4 days. All subjects received 1 of the 2 oral hydrocortisone doses or placebo using matched capsules given in divided doses (7 AM and 7 PM), with an approximately 3:2 dose ratio (higher dose, 100:60 mg; lower dose, 25:15 mg) to approximate circadian changes in endogenous cortisol secretion. As in a previous study with dexamethasone,[32] plasma sampling and blinded cognitive testing were performed at baseline (day 0), after 1 and 4 days of treatment (days 1 and 4), and after a 6-day washout period (day 10). All assessments were performed at approximately 4 PM, with no food intake after 1 PM. Plasma samples were stored at –70°C before assay. Plasma cortisol[50] and insulin[51] levels were measured by radioimmunoassay. Plasma glucose level was measured with a glucose oxidase method (Beckman Glucose Analyzer 2; Beckman Instruments, Fullerton, Calif).

COGNITIVE MEASURES

Paragraph recall was used as a valid[52] and sensitive measure of verbal declarative memory[53,54] that has also proved to be sensitive to GC effects in previous reports.[32] Additional tasks were used to explore the effect of cortisol on other elements of cognitive function, as described in the following paragraph. Different versions of each cognitive task, matched for difficulty, were administered on each study day. In addition, 2 different sets of the task battery that offered the different task versions in 2 different orders across study days were counterbalanced across subjects within each treatment group to avoid any nonrandom bias from affecting

tions.[24,30,31] However, the interpretation of these results is limited by nonrandomized treatment assignments, noncausal associations, or additional disease factors that can decrease performance.

Results of double-blind, randomized, placebo-controlled experiments with healthy humans indicate that use of pharmacological doses of the preferential type 2 GC receptor ligands dexamethasone and prednisone can decrease verbal declarative memory performance.[32,33] However, the interpretation of dexamethasone or prednisone treatment effects as a model of cortisol effects or human stress remains problematic. This is because of uncertainty about whether treatment-induced impairments result from increased brain GC receptor binding or from an alternate possibility: that treatment-induced suppression of cortisol secretion, combined with the slow entry of dexamethasone and prednisone into the brain (in contrast to the rapid availability of cortisol),[34,35] could result in decreases in brain GC receptor binding. Based on the results of animal studies noted previously[14-16] suggesting that GC agonists may sometimes enhance memory performance, decreases in hippocampal GC receptor binding might alternatively underlie the decreased performance observed during dexamethasone or prednisone treatment. This uncertainty, and differences in the binding of dexamethasone vs cortisol to type 1 vs type 2 hippocampal GC receptors, limits the utility of dexamethasone and similar ligands in modeling the effects of cortisol or stress in humans.

Previous efforts to directly study the effects of cortisol on memory performance in humans have been limited to brief (60 minutes), single-dose (10- to 50-mg) treatments.[36-38] These study designs do not model the longer duration of hypercortisolemia relevant to most stress- and disease-related human events and prevent an assessment of memory performance over the time course expected for genomic GC actions. These earlier studies produced mixed or negative results for immediate recall or, in one report, decreases in delayed recall, raising questions about the contribution of non-GC effects to these variable changes in performance. This background motivated the present study, in which we hypothesized that 4 days of randomized, double-blind, placebo-controlled cortisol (hydrocortisone) treat-

study results. The tasks were presented in a fixed order in both sets: paragraph recall (immediate), delayed match to sample, modified Stroop color-word task, continuous performance task, paragraph recall (delayed), verbal fluency, spatial delayed response, and delayed match to sample.

Immediate and delayed paragraph recall are dependent on cognitive abilities such as encoding, retrieval, and organizational and learning strategies. Subjects hear recorded short narratives that were constructed using an established method used for the Wechsler Memory Scale–Revised Logical Memory Test,[55] with 44 pieces of information followed by audiotaped immediate and delayed (30 minutes) verbatim recall. Two paragraphs are given during each test session, with all paragraphs comparable in recall difficulty. Scores for correct verbatim recall and commission errors (ie, intrusions or confabulations) are tabulated, based on a modification of established scoring methods.[56] A computerized delayed match to sample task was used to measure nonverbal recognition performance based on previous work on animals[57,58] and humans with hippocampal lesions.[59] Subjects see 10 consecutive presentations of 2 geometric line drawings (a total of 20 drawings) followed by a 3½-minute delay filled with a digit span task. After the delay, subjects are presented with 10 recognition trials with 1 target and 2 distracter drawings per trial. Number of correct responses per total possible responses and reaction time were calculated for analysis. A multiple version modification of the Stroop color-word task[60] was used as a measure of selective attention. Total time to complete each condition and number of incorrect responses per condition were analyzed. Sustained attention was measured using a computer-generated continuous performance task that presents a rapid, continual sequence of letters. Subjects must press a key whenever a specific letter appears on the screen. Accuracy and reaction time are measured. A word list generation (verbal fluency) task was used as a measure of verbal executive function.[61] The total number of correct responses was analyzed. A spatial delayed response task was used to measure nonverbal spatial recall at 5 and 120 seconds. Memory for spatial location has been well researched in primates, and this method was modified for use with humans, as previously described.[62] In general, delays longer than 15 to 30 seconds on similar tasks may be sensitive to medial temporal dysfunction.[63-65] Mean error (distance from a target on a computer screen) was calculated for each subject at each type of trial (5-second delay, 120-second delay, and cue-present [no recall] trials).

ANALYSIS

Comparability of the different treatment groups (ie, age and body mass index) was tested using analysis of variance (ANOVA). The main hypothesis concerning treatment effects on verbal declarative memory performance was tested using ANOVA to evaluate the repeated measures of paragraph performance across baseline and both treatment days, including a between-subject factor for treatment condition and a within-subject factor for recall condition (eg, immediate vs delayed). Treatment effects on plasma cortisol concentrations (and other plasma variables) were similarly tested to confirm the anticipated treatment effects on plasma cortisol level and to evaluate possible confounds to the primary analysis. Because of sex differences in plasma cortisol concentrations (see "Results" section), sex was added as a between-subject factor to the ANOVA testing the main hypothesis (including or excluding sex from this model did not alter the significance of the primary results), and a subsequent analysis of the covariance model included plasma cortisol concentrations. Treatment effects on other cognitive measures were similarly tested to evaluate secondary hypotheses concerning the specificity of treatment effects for verbal declarative memory. To adjust for any nonhomogeneity of covariance for the repeated within-subject effects, we used *P* values that were adjusted using the Huynh-Feldt (H-F) method; all tests required little or no adjustment. Significant effects (critical $P = .05$) were further evaluated using comparisons across individual treatment days and individual treatment conditions as appropriate. Analyses were performed using statistical software programs (Statview and SuperAnova; SAS Institute Inc, Cary, NC).

ment—modeling the hypercortisolemia associated with stress in humans—could produce dose-dependent decreases in verbal declarative memory performance.

Total daily oral cortisol doses for this study were selected to approximate 24-hour cortisol secretion during mild to maximal physiologic stress, based on data from medical and surgical populations.[39-44] In general, oral cortisol doses required to produce targeted secretion levels are somewhat higher than measured endogenous secretion, caused by incomplete bioavailability associated with first-pass hepatic metabolism. Lower-dose treatment was selected to approximate cortisol output in the range between mild physiologic stress (eg, laparoscopy)—producing approximately 25-mg/d cortisol per day—and moderate physiologic stress (eg, nonlaparoscopic cholecystectomy)—producing approximately 50-mg/d cortisol per day. Higher-dose treatment was selected to approximate cortisol output during major physiologic stress (eg, colectomy or aortobifemoral bypass)—producing approximately 100- to 150-mg/d cortisol per day, with maximal levels of 200 to 300 mg/d per day. The targeted range of plasma cortisol concentrations for this study was similarly based on previously observed values associated with various physical and psychological stressors, for example: 276 to 828 nmol/L (10-30 ug/dL) for minor surgical procedures[41,45]; 690 nmol/L (25 ug/dL) for the Trier Social Stress Test[46]; 828 to 1104 nmol/L (30-40 ug/dL) for more extended surgical procedures such as nonlaparoscopic cholecystectomy or hysterectomy[41]; and 1104 to 1517 nmol/L (40-55 ug/dL) for severe sepsis, multiple trauma, or following major abdominal surgery.[41,47,48]

RESULTS

Cortisol treatment produced reversible decreases in verbal declarative memory performance. The initial ANOVA testing the main hypothesis indicated a significant interaction between time and treatment condition for paragraph recall performance ($F_{4,94} = 2.49$; $P < .05$ by H-F) (**Figure 1**). Although an expected main effect of recall condition (immediate vs 30-minute delayed: $F_{1,47} = 180.3$; $P < .001$ by H-F) was detected, there was no significant

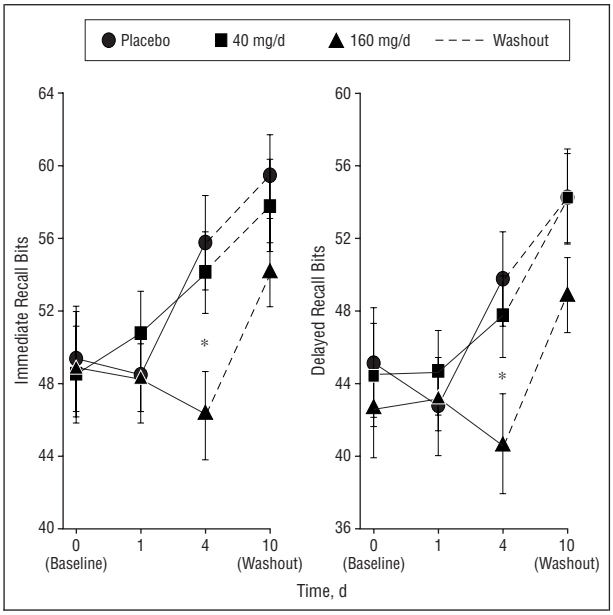

Figure 1. *Cortisol-induced decreases in verbal memory performance (n = 51). A similar effect of treatment conditions over time was observed for immediate and delayed paragraph recall. Recall performance differed across treatment groups after 4 days in the immediate and delayed recall conditions (asterisk indicates comparison point $F_{2,48} = 4.04$; P = .02 and $F_{2,48} = 3.29$; P = .05, respectively), with decreased immediate and delayed recall performance in the high-dose treatment group compared with the lower-dose ($F_{1,48} = 4.54$; P = .04 and $F_{1,48} = 3.34$; P = .07, respectively) and placebo ($F_{1,48} = 7.50$; P = .009 and $F_{1,48} = 6.26$; P = .02, respectively) groups. Error bars represent SE.*

interaction between recall condition, treatment condition, and time ($F_{4,94} = 0.77$; $P = .55$ by H-F). These results indicate that the significant effect of treatment on paragraph performance similarly affected immediate and delayed recall over time (Figure 1). Total recall performance differed across groups after 4 treatment days ($F_{2,48} = 3.82$; $P = .029$), with lower performance on higher-dose dose treatment compared with lower-dose treatment ($F_{1,48} = 4.09$; $P < .05$) and placebo ($F_{1,48} = 7.19$; $P = .01$). No difference in recall performance was detected across treatment groups at baseline ($F_{2,48} = 0.06$; $P = .94$) or after 1 treatment day ($F_{2,48} = 0.25$; $P = .78$). The addition to the model of a covariate term for plasma cortisol concentrations increased the strength of interaction between time and treatment condition ($F_{4,91} = 3.15$; $P = .018$ by H-F), reflecting the additional contribution of plasma cortisol level variance within each treatment condition to overall paragraph performance.

Inspecting the paragraph recall performance of individual subjects in the higher-dose cortisol treatment group relative to the mean performance of the placebo group, 14 of 15 individuals (93%) taking higher-dose cortisol experienced a decrease in performance below placebo levels between 1 and 4 days of treatment (mean decrease from placebo level at day 4, 21.9±16.6 bits of paragraph data, in which each bit is 1 "content" word, eg, noun, verb, adjective, or adverb). No similar effects of treatment were observed on any other cognitive task in our test battery, including tests of sustained and selective attention, verbal executive function, nonverbal object recognition, and nonverbal spatial recall at 5 and 120 seconds (**Table**). No difference in paragraph performance was detected across treatment groups after a 6-day treatment washout ($F_{2,48} = 1.44$; $P = .25$) (Figure 1), indicating a reversible effect on performance. In the placebo and lower-dose cortisol treatment groups, similar to results with placebo in our previous studies, paragraph performance increased over time because of predicted practice effects or procedural learning.

Cortisol treatment also produced expected stable increases in 4 PM plasma cortisol concentrations in the higher-dose treatment condition, resembling levels associated with moderate surgical stress and the psychological stress of the Trier Social Stress Test (**Figure 2**). Plasma cortisol concentrations were higher overall in women (main effect of sex: $F_{1,43} = 7.53$; $P = .009$), without sex differences in response to treatment conditions (sex × treatment condition × time: $F_{4,86} = 1.15$; $P = .34$ by H-F). No sex differences were detected in overall paragraph recall performance (main effect of sex: $F_{1,47} = 1.87$; $P = .18$) or in the effect of cortisol treatment conditions on recall performance (sex × treatment condition × time: $F_{4,90} = 1.71$; $P = .16$ by H-F). However, this may reflect a type II error related to the relatively small female sample size within each treatment group. No main effect of, or relevant interactions with, plasma cortisol concentrations on paragraph performance was detected. Cortisol treatment produced a mild increase in plasma glucose concentrations (treatment condition × time: $F_{4,90} = 7.51$; $P < .001$ by H-F). However, this was explained by a peak increase in glucose concentrations on study day 1 in the 160-mg/d condition only, without a temporal relationship to the memory effect. Plasma glucose concentrations varied across study days 0, 1, and 4 in the 160-mg/d condition ($F_{2,26} = 12.64$; $P < .001$ by H-F; mean±SD, 4.8 ± 0.4 [86.5 ± 7.1], 5.9 ± 1.0 [106.8 ± 17.6], and 5.5 ± 0.7 mmol/L [98.7±12.5 mg/dL], respectively). Plasma glucose concentrations did not change over repeated sampling in either the placebo ($F_{2,36} = 1.43$; $P = .25$ by H-F) or the 40-mg/d ($F_{2,30} = 0.62$; $P = .54$ by H-F) condition. Plasma insulin concentrations did not vary significantly across the different treatment conditions (treatment condition × time: $F_{4,92} = 1.55$; $P = .20$). Testing the effect of plasma glucose and insulin concentrations on paragraph performance, no significant interaction between treatment condition, time, and either plasma glucose level or insulin level was detected.

COMMENT

The results of this study indicate that several days of exposure to cortisol at doses and plasma concentrations associated with physical and psychological stress in humans can reversibly decrease verbal declarative memory function in otherwise healthy humans. The results extend previous studies[32] in humans using pharmacological GC treatments such as dexamethasone, and previously reported associations[19-29] between memory performance and plasma cortisol concentrations in patients with Cushing syndrome, dementia of the Alzheimer type, schizophrenia, and depression. The results are directly relevant to the interpretation of decreased memory performance during periods of extended stress in humans, in which plasma cortisol elevations are present

Performance on Cognitive Measures During Placebo-Controlled Cortisol Treatment in 51 Healthy Adults*

Variable	Treatment Group	Day 0 (Baseline)	Day 1	Day 4	Day 10 (Washout)
Commission errors					
Immediate	Placebo	0.7 ± 0.9	0.6 ± 0.9	9.7 ± 1.0	0.6 ± 0.8
	40 mg	0.8 ± 1.1	1.0 ± 0.9	0.7 ± 0.9	0.8 ± 1.3
	160 mg	0.7 ± 1.0	0.6 ± 0.8	0.9 ± 0.8	0.3 ± 0.5
Delayed	Placebo	1.1 ± 1.1	1.7 ± 1.2	1.0 ± 1.5	1.2 ± 1.4
	40 mg	1.7 ± 1.2	1.9 ± 1.6	1.2 ± 1.1	1.4 ± 0.4
	160 mg	1.0 ± 1.0	1.7 ± 1.4	1.5 ± 1.2	0.9 ± 0.2
Delayed match to sample					
Accuracy	Placebo	0.72 ± 0.13	0.76 ± 0.23	0.76 ± 0.18	0.81 ± 0.19
	40 mg	0.70 ± 0.16	0.76 ± 0.17	0.71 ± 0.17	0.83 ± 0.14
	160 mg	0.64 ± 0.13	0.73 ± 0.16	0.71 ± 0.10	0.77 ± 0.17
Spatial delayed response task					
Error, mm (5-s delay)	Placebo	7.8 ± 2.4	8.8 ± 4.2	6.9 ± 2.0	7.8 ± 3.0
	40 mg	8.8 ± 3.0	8.7 ± 2.7	8.8 ± 3.5	8.2 ± 3.6
	160 mg	7.4 ± 1.4	8.4 ± 2.4	7.9 ± 2.1	9.0 ± 2.9
Error, mm (120-s delay)	Placebo	14.6 ± 7.8	13.4 ± 4.7	13.4 ± 9.5	14.9 ± 8.5
	40 mg	11.9 ± 3.7	14.4 ± 7.4	13.3 ± 7.6	16.1 ± 12.4
	160 mg	13.4 ± 6.2	17.0 ± 9.7	12.1 ± 5.3	16.1 ± 10.3
Sustained attention					
Reaction time, ms	Placebo	432 ± 29	434 ± 33	425 ± 37	435 ± 36
	40 mg	436 ± 56	433 ± 55	434 ± 50	422 ± 49
	160 mg	437 ± 40	438 ± 45	440 ± 57	447 ± 56
Accuracy	Placebo	0.98 ± 0.02	0.99 ± 0.01	0.98 ± 0.02	0.99 ± 0.01
	40 mg	0.99 ± 0.01	0.98 ± 0.02	0.95 ± 0.10	0.98 ± 0.03
	160 mg	0.99 ± 0.01	0.98 ± 0.02	0.98 ± 0.02	0.98 ± 0.02
Stroop color-word task					
Time, s	Placebo	36.9 ± 5.9	30.1 ± 6.7	30.0 ± 5.6	26.9 ± 3.7
	40 mg	34.6 ± 9.4	28.9 ± 7.4	30.6 ± 8.3	26.8 ± 6.8
	160 mg	38.3 ± 7.3	33.2 ± 6.5	31.6 ± 5.4	27.9 ± 4.5
Errors	Placebo	1.0 ± 1.3	0.4 ± 0.5	0.5 ± 0.9	0.6 ± 0.8
	40 mg	1.1 ± 0.2	0.6 ± 1.1	0.6 ± 1.1	0.5 ± 0.6
	160 mg	1.6 ± 1.6	1.7 ± 2.2	1.2 ± 1.4	1.1 ± 1.4
Verbal fluency					
Correct	Placebo	29.5 ± 7.2	32.0 ± 8.7	33.3 ± 8.6	31.3 ± 6.3
	40 mg	31.9 ± 6.9	34.3 ± 6.2	39.0 ± 8.1	37.2 ± 9.0
	160 mg	30.0 ± 5.4	32.6 ± 9.0	33.9 ± 7.5	31.0 ± 7.1

**Data are given as mean ± SD.*

throughout memory encoding and retrieval processes. Memory performance was decreased only by a cortisol treatment condition resembling moderate to maximal stress levels—not mild stress—suggesting that cortisol-induced memory decreases may not occur in most individuals under mildly stressful circumstances. Future studies should carefully define the dose or plasma concentration threshold for cortisol-induced memory impairment in healthy humans.

The mean cortisol-induced memory decrease, approximating a 1-SD reduction from placebo-level performance, is clinically relevant. Similar 1-SD changes in performance on the Logical Memory passages (paragraph recall) of the Wechsler Memory Scale–Revised would lower an individual's age-normalized classification of paragraph recall performance by 1 level (eg, high-average decreased to average or low-average decreased to borderline).[55] The results of this study indicate a reversible effect of increased GC exposure on memory performance under such treatment conditions, consistent with previous results using dexamethasone.[32] The preferential effect of treatment on immediate and delayed verbal declarative memory performance, without effects on other differentiated elements of cognitive function, also replicates the previous results with dexamethasone, suggesting preferential GC effects on encoding processes or retrieval mechanisms involved in immediate and delayed recall.[13] However, results of this study and the previous study with dexamethasone indicate a GC treatment effect that may also block the practice effect or procedural memory effect observed in both studies in the placebo conditions, in addition to decreasing performance for treated groups below baseline levels. We did not in either study attempt to disentangle the effects on procedural memory vs elements of declarative memory performance, leaving some open questions about exactly which elements of memory function are altered by GC treatment. Although most previous reports in humans concerning GC effects on cognitive function have involved verbal declarative memory—usually for paragraphs or semantically related word lists—other nonverbal tasks with a declarative memory component that were used in this study did not detect GC-induced changes. This may reflect a preferential GC effect on verbal memory processes or may be caused by differing task sensitivity.

Although the cortisol doses used and the measured plasma cortisol concentrations obtained were all within

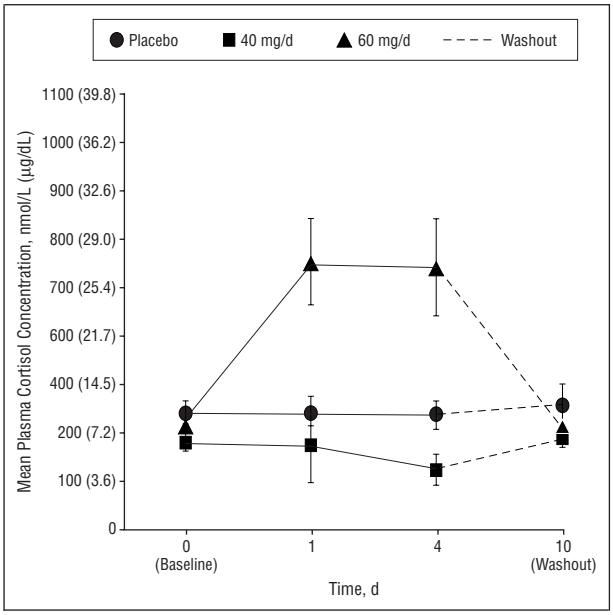

Figure 2. *Treatment-induced changes in plasma cortisol concentrations (n = 49). Treatment conditions resulted in stable stress-level elevation of plasma cortisol concentrations (time × treatment condition: $F_{4,86} = 10.72$; P<.001 by Huynh-Feldt), explained by differences after 1 ($F_{2,48} = 8.62$; P≤.001) and 4 ($F_{2,47} = 13.46$; P<.001) treatment days, with higher concentrations in those taking 160 mg/d compared with those taking 40 mg/d and placebo (P<.002, both days, by Bonferroni and Dunn tests). Error bars represent SE.*

the range associated with the human stress response, the twice-daily oral dosing regimen may have produced postdose peak levels that were higher than those measured at 4 PM and perhaps higher than those associated with stress. However, carefully derived human pharmacokinetic data for a 5-mg dose of oral deuterium-labeled cortisol[66] indicates a peak plasma cortisol concentration of 55 nmol/L (2 µg/dL) (30 minutes after ingestion), suggesting that our highest 7 AM cortisol dose of 100 mg (20×5 mg) would produce a peak plasma cortisol concentration of approximately 1100 nmol/L (40 µg/dl), which is 20 times higher than the previously reported peak plasma cortical concentration.[66] As detailed in the introduction, this is well within the range of plasma cortisol concentrations observed after moderate to major medical or surgical stress. This study was limited by the use of a single plasma sampling time on each study day, which prevented the measurement of cortisol levels throughout the entire dosing interval. Although our cortisol dosing schedule simulated a morning peak and some daily circadianlike variation in plasma levels, the study was limited by the use of only 2 dosing times to approximate physiologic cortisol secretion, with larger-than-ideal peaks and troughs in plasma cortisol levels. One such trough in plasma cortisol concentration occurred at 4 PM in the 40-mg/d dosing condition, in which levels were no longer increased above placebo levels (Figure 2). However, the biologic (vs plasma elimination) half-life of cortisol is 8 to 12 hours.[67] Indeed, the lower-dose condition remained biologically active, as evidenced by negative feedback on endogenous cortisol production (eg, mean 4 PM cortisol concentration numerically lower than that for placebo) and by treatment-induced increases in plasma leptin levels.[68] These observations suggest that cortisol effects on memory function, if present at this dose level, could similarly persist throughout the dosing interval.

The study was also limited by not measuring other potentially cognitively active compounds, such as epinephrine, norepinephrine, corticotropin, and corticotropin-releasing factor, which could be relevant to cognitive impairments in various neuropsychiatric disorders. However, the time course for our treatment effect on memory, the similar memory impairment induced by stress and exogenous cortisol in a previous report,[38] and the cortisol-related memory impairments noted in clinical populations all argue against a role for catecholamines or treatment-induced decreases in corticotropin or corticotropin-releasing factor levels in the explanation of our results. Nevertheless, this study provides only a partial experimental model for conditions such as pituitary Cushing disease or depression. Future studies should test the effects of altered exposure to corticotropin, corticotropin-releasing factor, and other relevant elements of the stress response, alone and in combination.

In summary, several days of exposure to cortisol at doses and plasma concentrations associated with physical and psychological stress in humans can reversibly decrease specific elements of memory performance in otherwise healthy individuals. The results suggest that a clinically significant impairment in human memory performance can occur during extended periods of moderate to severe physiologic stress. Future studies will be needed to define the plasma concentration threshold and duration of exposure required to produce this impairment in healthy and clinical populations. The results are relevant to identifying adverse physiologic conditions that can be targeted by future treatments or prevention approaches. Future research in this area can make important contributions to our understanding of the complex role of GCs and other factors regulating memory function in the human brain.

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