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# Acute cortisone administration impairs retrieval of long-term declarative memory in humans

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Stress triggers a cascade of physiological events including glucocorticoid secretion from the adrenal cortex, which can influence memory function[1–13]. Exogenous glucocorticoids impair human declarative memory performance[1,4,5], and hypercortisolemia associated with depression, Cushing's syndrome and old age is associated with memory impairments in humans[3,6,7]. Whereas treatments used in previous studies generally affect more than one memory phase and therefore cannot detect possible differential effects of glucocorticoids on the distinct phases of acquisition, consolidation and retrieval, here we show that treatment of healthy humans with cortisone at acute-stress levels specifically impaired retrieval of declarative long-term memory for a word list.

Healthy human (18 female and 18 male) volunteers aged 20–40 years (mean ± s.d., 28.8 ± 5.5) participated in the study. Subjects gave written informed consent, and the experiments were approved by the ethical committee of the University of Basel. We used a double-blind, placebo-controlled, within-subject design. On day 1, subjects viewed a series of 60 unrelated German nouns each presented for 4 s on a computer screen with the explicit instruction to learn them for immediate and delayed recall (24 hours after learning memory tests). For the free-recall test, subjects were asked to write down all the words they remembered. For the recognition test, subjects were asked to identify the originally presented words from a larger list with 60 additional words. Cortisone (25 mg; Novartis Pharma, Switzerland) or placebo (25 mg mannite) was administered once orally. Each group received doses at one of three different times (one hour before the retention test, one hour before word presentation or immediately after word presentation). Cortisone is quickly absorbed and transformed into hydrocortisone (cortisol). Significantly elevated salivary concentrations of cortisol one hour after the pharmacological treatment were similar to cortisol levels induced by major psychological or physiological stress[1] (**Table 1**). After a 2-week interval, the procedure was repeated in the same individuals with another set of 60 words, but subjects received the treatment they had not received in the first experiment. Word sets and treatment order were balanced across subjects.

Cortisone administered 1 hour before the delayed free-recall test significantly impaired recall performance as compared with placebo treatment on tests given 2 weeks apart to the same individuals ($p < 0.005$, paired $t$-test; **Fig. 1**). Cortisone did not alter the number of confabulative errors (mean ± s.e. placebo, 1.7 ± 0.6; cortisone, 1.5 ± 0.6; $p > 0.8$, paired $t$-test). Cortisone also did not affect recognition memory (mean ± s.e. correctly recognized words/mean ± s.e. errors for placebo, 49.4 ± 2.4/11.0 ± 1.5; for cortisone, 49.5 ± 2.6/11.8 ± 2.0; $p > 0.9$/$p > 0.6$, paired $t$-tests). These findings indicate that cortisone impaired free recall of verbal material but left recognition unaffected. Furthermore, cortisone did not affect performance on an immediate free-recall test for an additional set of 20 words presented at the end of the delayed recall session (mean ± s.e. placebo, 11.5 ± 0.8; cortisone, 11.0 ± 0.7; $p > 0.4$, paired $t$-test), in agreement with previous findings[3]. Cor-

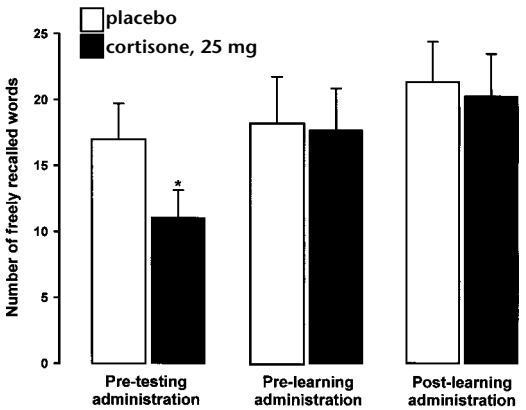


**Fig. 1.** Effects of administering a single oral dose of cortisone (25 mg) on distinct memory phases. Cortisone administered 1 h before the delayed retention test (24 h after word presentation) significantly impaired the number of words freely recalled. Cortisone administration one h before or immediately after word presentation did not impair delayed free recall. *$p < 0.005$ as compared with placebo treatment. Error bars represent s.e.; $n = 12$ per group.

**Table 1. Effects of 25 mg cortisone on saliva cortisol levels**

| Group | Treatment | Before administration | 1 h after administration |
|---|---|---|---|
| Pre-testing | placebo | 11.3 ± 1.6 | 7.3 ± 0.8 |
| Pre-testing | cortisone | 8.5 ± 1.0 | 55.8 ± 15.3** |
| Pre-learning | placebo | 7.5 ± 0.8 | 7.9 ± 1.1 |
| Pre-learning | cortisone | 7.6 ± 1.1 | 39.8 ± 10.5** |
| Post-learning | placebo | 8.9 ± 1.8 | 5.5 ± 0.8 |
| Post-learning | cortisone | 8.4 ± 1.8 | 42.8 ± 10.8** |

Data are presented as means ± s.e. in nmol per l. **$p < 0.01$ as compared within group with cortisol concentration 1h after placebo.

tisone also did not affect the subjective rating of stressfulness one hour after treatment on a scale from 1 to 10 (mean ± s.e. placebo, 4.4 ± 0.5; cortisone, 4.6 ± 0.7; $p > 0.8$, paired *t*-test) and none of the subjects reported having experienced any adverse effects of the treatment. This pattern of selective interference with delayed recall, and not immediate recall or recognition memory, excludes non-specific effects of cortisone on cognitive or intellectual function. The results are consistent with previous reports indicating that cortisol does not affect attention, verbal executive function or vigilance[4,10]. The present findings are remarkably similar to previous findings that glucocorticoids impair rats' retrieval of long-term memory[8], suggesting that this is a broadly general phenomenon.

To examine whether the same dose of cortisone influenced acquisition or consolidation processes, cortisone or placebo was given either one hour before or immediately after word presentation in two additional experimental groups. Cortisone administration an hour before word presentation for learning did not affect immediate free recall (mean ± s.e. placebo, 13.4 ± 0.7; cortisone, 13.0 ± 1.0; $p > 0.5$, paired *t*-test) and also did not affect delayed free recall ($p > 0.8$, paired *t*-test; **Fig. 1**) Cortisone administration immediately after word presentation did not affect delayed free recall ($p > 0.7$, paired *t*-test; **Fig. 1**). Neither pre- nor post-learning cortisone administration changed recognition memory. Although memory is impaired in humans by pre-learning administration of cortisol[1,4], a crucial difference may be that glucocorticoid levels remain elevated at the time of retention testing in these experiments. Thus it is possible that such results reflect impaired memory retrieval rather than altered memory acquisition or consolidation. In the present study, cortisol levels returned to baseline well before the time of retention testing, 24 hours after treatment. The delayed recall following pre- or post-learning administration of cortisone was therefore not confounded by any effects of cortisol on retrieval processes. Studies in animals indicate that glucocorticoid treatment that impairs memory retrieval when given before testing[8] can enhance memory consolidation with a dose–response relationship resembling an inverted 'U' when given after training[9,12,13]. Based on these findings, we expected administration of cortisone before or after learning to enhance later retention performance in the present study. As we found no evidence of such an enhancement, the cortisone dose used may have been too low or too high to influence memory consolidation. Moreover, animal studies clearly demonstrate that enhancement of memory consolidation by glucocorticoids critically depends on co-activation of peripheral and/or central adrenergic mechanisms[12,13]. Because the learning conditions in the present experiments were non-arousing, the conditions probably did not activate adrenergic mechanisms enabling the memory-enhancing effects of glucocorticoids.

Beside providing a future research tool for elucidating the biological mechanisms underlying the multiple effects of glucocorticoids on cognitive performance, the present findings have several direct and important implications. Short-term, everyday stressors can induce acute adrenocortical activation[1], and retrieval of declarative memory may well occur under conditions of elevated glucocorticoid levels. On the basis of our results, it seems probable that elevated glucocorticoid levels may induce retrieval impairments in such stressful conditions as examinations, job interviews, combat and courtroom testimony. Additional experiments are required to evaluate whether glucocorticoid effects on memory retrieval also contribute to the memory deficits found in human subjects with sustained elevations of glucocorticoid levels. Prolonged hypercortisolemia may induce changes in adrenal steroid receptors and neurotransmitter systems and can cause functional and structural changes in the hippocampus[14,15] that may impair memory storage. However, the findings of the present study suggest that cortisol-induced retrieval impairments may add significantly to the memory deficits found under prolonged hypercortisolemia.

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