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ORIGINAL INVESTIGATION

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The effects of chronic administration of hydrocortisone on cognitive function in normal male volunteers

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Abstract *Rationale*: Corticosteroids are elevated in certain neuropsychiatric disorders and this may contribute to the neuropsychological impairments reported in these disorders. *Objective*: To examine the effects of hydrocortisone on learning, memory and executive function. *Methods*: Hydrocortisone 20 mg was administered twice daily for 10 days to normal male volunteers in a randomized, placebo control, crossover, within-subject design. Learning, memory and executive function were measured using selected subtests from the Cambridge Neuropsychological Test Automated Battery. *Results*: Hydrocortisone caused impairments of visuo-spatial memory. These included increased within search errors and impaired use of strategies on the spatial working memory subtest. In addition, administration of hydrocortisone was associated with more errors in the paired associate learning subtest, although no effect was found on the Tower of London. Hydrocortisone speeded response latencies in certain tests (pattern and spatial recognition memory). *Conclusion*: These results indicate that chronic administration of hydrocortisone leads to deficits in certain tests of cognitive function sensitive to frontal lobe dysfunction and may contribute to the cognitive impairment reported in certain neuropsychiatric disorders.

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Introduction

Prolonged exposure to elevated corticosteroids may cause deficits in cognition, particularly learning and memory, which may be mediated in part by effects on hippocampal neurones (Sapolsky 1992). Much of the evidence to date has been derived from animal experimentation; for example, chronic corticosterone administration to rats has been shown to impair acquisition of a Morris water maze place navigation task (Bodnoff et al. 1995). In addition, corticosteroids have also been shown to affect hippocampal long-term potentiation (Diamond et al. 1992; Pavlides et al. 1995), which is thought to be an electrophysiological correlate of synaptic plasticity and appears to be closely linked with the initial stages of memory formation.

Despite this evidence from animal work and the potential relevance for both normal human ageing and neuropsychiatric disorders, little work directly examining the cognitive effects of corticosteroids has been done in man. There is, however, some evidence to suggest that corticosteroids may impair cognition in man: for example it has been reported that stress-induced cortisol levels correlate negatively with performance in delayed recall, a test of explicit (or declarative) memory (Kirschbaum et al. 1996). Similarly, Lupien et al. (1994) showed that cortisol levels correlated negatively with explicit, but not implicit (or procedural) memory performance in healthy elderly subjects and have also shown recently that there is a relationship between elevated cortisol levels in ageing, hippocampal atrophy and memory deficits (Lupien et al. 1998). Cortisol or dexamethasone administration is associated with explicit memory impairments in immediate and delayed recall (Wolkowitz et al. 1990; Newcomer et al. 1994; Kirschbaum et al. 1996) and mental rotation but does not affect implicit memory in a word stem priming

task (Kirschbaum et al. 1996). Subjects suffering from Cushing's disease, an endocrine disorder characterised by corticosteroid overproduction, perform poorly on tasks of explicit (episodic) memory. In addition to this, depressed patients with evidence of pituitary-adrenal disinhibition, and consequent hypercortisolaemia, are also impaired in explicit memory (Wolkowitz et al. 1990). From evidence such as this, it has been postulated that the increased corticosteroid activity seen in depression contributes to the cognitive deficits found in this disorder (Barden et al. 1995; McAllister-Williams et al. 1998).

The purpose of this study was to examine the effects on cognition in normal volunteers of prolonged exposure to elevated levels of corticosteroids. We employed a regimen of administration of hydrocortisone (cortisol) which has previously been shown to produce elevated levels of steroid similar to that found in severe depressive illness (Young et al. 1994, 1998) and examined the effects of this on neuropsychological function. To evaluate neuropsychological function, we used the Cambridge Neuropsychological Test Automated Battery (CANTAB; Robbins et al. 1996); this is a suite of computerised tests employing a touch-sensitive screen, which has been used to examine differential patterns of cognitive deficit in various patient populations including those with organic brain lesions (Owen et al. 1997) and the clinically depressed (Abas et al. 1990; Beats et al. 1996; Elliott et al. 1996). The present study employs several tests taken from the CANTAB battery that have been shown to be impaired in depressed patients relative to controls (Abas et al. 1990). In particular, visuo-spatial learning and memory has been shown to be impaired in the depressed state (O'Brien et al. 1993; Elliott et al. 1996) and this persists upon clinical recovery (Abas et al. 1990). The effects of chronic administration of hydrocortisone on visuo-spatial learning and memory, as well as aspects of executive function, were examined.

Materials and methods

Design

A within-subjects, placebo-controlled, counterbalanced cross-over design was used (Hills and Armitage 1979). Both the subject and the investigator were blind to the nature of pretreatment. Twenty healthy male volunteers were recruited and all were entirely free of other medication and had no history of medical or psychiatric disorder. The mean age was 33 years (range 21–44). All subjects gave informed consent to the study which had been approved by the local psychiatric ethics committee. Subjects underwent treatment with hydrocortisone (20 mg) or placebo capsules twice daily for 10 days. The alternative treatment (hydrocortisone/placebo) was then administered after a washout period of at least 3 weeks (giving at least 4 weeks between neuropsychological testing). Twenty-four hour urinary cortisol levels were collected in all subjects on the last day prior to cognitive testing.

Neuropsychological tests

Computerised psychological tests were given to subjects on an IBM PS/2 Model 30 286 personal computer, with a high resolution Taxan 770+ colour monitor fitted with an Intasolve touch-sensitive screen for the CANTAB tests.

Spatial working memory

This is a self-ordered search task tapping functions not only of the "visuospatial sketchpad" component of Baddeley's theory of working memory, but also which incorporates a strategic search component to tax "central executive" function (Owen et al. 1990). Subjects have to search through a number of "boxes" (four, six or eight) for a hidden "token" without returning to a box which they have already examined on the same trial (to avoid "within search" errors) or which has already contained a token on the previous trial (to avoid "between search" errors). The task is scored according to the number of each type of error at each level of difficulty and an overall index of strategy is also recorded, which has been shown to be associated with superior performance in normal subjects (Owen et al. 1990). Higher scores for this strategy index indicate less use of the strategy.

Paired associates learning

This is a test of visual pattern and visuospatial memory and learning, which contains aspects of a delayed response procedure and a conditional learning task (Sahakian et al. 1988). The subject has initially to remember the location of six stimuli over a short delay within a maximum of ten trials. The task is then repeated with eight stimuli. The computer records memory for number of stimuli correctly identified on the first trial, the total number of trials needed to reach criterion (i.e. all stimuli correctly located) and total errors.

Pattern and spatial recognition (Sahakian et al. 1988)

Pattern recognition. Subjects are presented with a series of abstract coloured visual patterns in the centre of the computer screen. Each stimulus is presented for 3 s, and there are two blocks of 12 stimuli each. Five seconds after the end of each block, the subjects are required to choose between a pattern they have already seen and a novel pattern, and point to the pattern they recognise. The two choices differ in shape but not in colour, and are simultaneously presented on the screen. Visual feedback is provided for correct and incorrect responses.

Spatial recognition. Subjects are shown a sequence of open white squares at five different positions on the computer screen, with each square being presented for 3 s. There are four blocks of five stimuli each, and no location is used more than once. Five seconds after the end of each block, the subject is presented with two white squares in different locations, only one of which the subject had seen before. The subject is required to identify which of the locations has been used before.

Tower of London (Owen et al. 1990)

This is a test of planning which taxes central executive function, based on the test by Shallice (1982) and McCarthy. Subjects must compare two different arrangements of "balls" in "socks or pockets" (one presented on the top half of the screen, the other on the bottom) and rearranging the balls in the lower half of the screen such that their positions match the "goal" arrangement in the upper half. After six practice trials, there are two, three, four and five move problems, and subjects are asked to plan out the solution to the problem prior to their first move. Number of moves required by the subject to rearrange the balls, and selection and movement latencies for both the first and subsequent moves were recorded. For each test problem, a "yoked control" condition was employed to provide baseline measures of motor initiation and execution times in milliseconds. In this condition, the actual solutions the