Psychoneuroendocrinology, Vol. 17, No. 4, pp. 343–354, 1992
Printed in Great Britain

0306–4530/92 $5.00+0.00

THE BRAIN AS A TARGET FOR ADRENOCORTICAL STEROIDS: COGNITIVE IMPLICATIONS

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(Received in final form 18 March 1992)

SUMMARY

It is well established that a reciprocal control exists between the brain and glucocorticoid hormones. The brain regulates adrenocortical function via hypothalamic corticotrophin releasing hormone-41 (CRH-41), glucocorticoids act at specific receptors in the hippocampus, thus promoting negative feedback mechanisms. Because the hippocampus is a major site for memory processes, a role for excessive/long-lasting plasma glucocorticoid levels has been suggested in conditions of mental impairment. Major depression, Cushing's disease, and dementia of the Alzheimer type are disorders which share hyperactivity of the hypothalamo-pituitary-adrenal axis, as well as symptoms of cognitive decline. Although the mechanisms leading to hypercortisolemia appear to be different in each case, the neuropsychological features of these three disorders accord with the hypothesis of glucocorticoid-associated brain damage. It therefore is important to find pharmacological strategies that will avert or reduce these potential consequences on brain function.

INTRODUCTION

OVER THE YEARS, following Selye's work, our understanding of the phenomenology of stress has been enhanced, and we have come to view different disorders as being related to the mechanisms of adaptation. Indeed, we have become familiar with the notion that the impaired ability to cope with prolonged and intense challenges may result, under particular circumstances, in pathological processes. The hypothesis put forward by Sapolsky *et al.* (1986) included brain damage among such consequences. Speculations that stress may be neurodegenerative and that the mechanisms of pathological aging might be associated with stressful events remain of considerable interest.

In neuroendocrine terms, stress refers to the hormonal response to any environmental demand, in order to minimize the excursions from homeostasis. Among the endocrine systems activated by stressors, the hypothalamo-pituitary-adrenal (HPA) axis is of extreme importance, although its physiological function remains essentially unknown. The activation of this system occurs under particular circumstances, i.e., when the individual perceives a failure to adapt or non-coping (Mason, 1968). From a psychoendocrine perspective, this means that it is not the

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stimulus *per se* that is stressful, but whether the organism considers that it can deal with it successfully. Thus, even though the stress response, according to Selye's description, is general or nonspecific (Selye, 1935), the actual or projected failure to cope with the environmental demands may activate a specific neuronal system. Corticotrophin releasing hormone-41 (CRH-41) neurons appear to be a major system that mediates an organism's response to such stressors. Inputs to this neuronal group come from the septo-hippocampal system under conditions of stress. The release of adrenocorticotrophin (ACTH) from the pituitary, however, is regulated by other peptides, including vasopressin and, most probably, other releasing factors as well (Antoni, 1986). ACTH stimulates the adrenal cortex to produce cortisol, usually considered the most fundamental stress hormone. Cortisol, in turn, produces physiological changes required to prepare the body for acute emergencies. However, since cortisol is a catabolic hormone, prolonged exposure may prove to be detrimental, resulting in pathological conditions in chronically stressed animals (Sapolsky *et al.*, 1986).

It is now widely accepted that the brain represents one of the principal targets for steroid hormones. Circulating steroids secreted by peripheral glands (such as glucocorticoids, mineralocorticoids and sex hormones) easily cross the blood-brain barrier and exert their actions in the central nervous system (CNS) at classical steroid receptors. It has become apparent that the brain itself is also able to synthesize steroids: Glial cells, and especially the oligodendrocytes, can produce pregnenolone from cholesterol, the common precursor of steroid hormones in the endocrine glands (Le Goascogne *et al.*, 1987).

CORTICOSTEROIDS, THE HIPPOCAMPUS AND COGNITION

As a consequence of these findings, the brain appears to be constantly exposed to a considerable amount of steroids, partly deriving from the uptake from the peripheral pool and partly produced locally (and hence termed "neurosteroids"). It is presently unclear, however, whether these different pools of steroids perform identical or separate functions in the brain.

As far as the HPA axis is concerned, glucocorticoids (corticosterone, or cortisol in primates) exert their actions primarily on the hippocampus, which is the brain area richest in glucocorticoid receptors. Two different classes of such receptors have been described, type I and type II, according to their affinity for different glucocorticoids (Reul & De Kloet, 1985; Arriza *et al.*, 1988). They appear to operate as a two-level recognition system in hippocampus, type I receptors being occupied at lower glucocorticoid concentrations than type II receptors. This mechanism probably helps the brain to discriminate between the two different modes of glucocorticoid secretion, *viz.*, the circadian rhythm and the stress-dependent release; in either case, the receptors ensure the shut-off of the circuit, via a negative feedback mechanism.

The hippocampus is also a region extremely vulnerable to neurological insults, especially anoxic or hypoxic stress (Siesjo, 1981). Such vulnerability has long been explained in vascular terms, the hippocampus being a watershed between different vascular beds. Nevertheless, it now appears more convincing that this phenomenon may be due to the high concentration of excitatory neurotransmitters found in this brain area (Sapolsky, 1991). Furthermore, the hippocampus is a critical site for memory, and a role for circulating levels of endogenous or exogenous glucocorticoids has been claimed in cognitive processes (Sapolsky *et al.*, 1986). Over the past few years, our understanding of human cognition has been considerably revised, several models and theories having emerged about different aspects of information, learning, memory (Cohen & Squire, 1980; Weingartner *et al.*, 1983). These models have proved to be of great help in the investigation of the cognitive implications of various diseases.

Here we briefly review recent data on the effect of glucocorticoid treatment and on the spontaneous activity of the HPA axis, with particular respect to cognitive performance.

COGNITIVE EFFECTS OF EXOGENOUS AND ENDOGENOUS STEROIDS IN HUMANS

Can stress mechanisms be neurodegenerative? Studies performed on animals have provided quite convincing evidence in favor of this theory. In populations of socially subordinate monkeys, Uno *et al.* (1988) found that some animals developed fatal gastric ulcers, and most of them showed neurodegenerative features at the hippocampal level. Indirect evidence also exists for the human. Intense psychological challenges, i.e., major life events, are clearly associated with increased release of cortisol. In subjects such as concentration camp survivors, who have faced the most stressful circumstances conceivable, the prevalence of cognitive disturbances (part of the so-called KZ syndrome) was found to be extremely high (Thuggesen *et al.*, 1970). A similar pattern was observed in the "war sailor" syndrome (Sjaastad, 1986), consisting of psychic and cognitive symptoms showed by Norwegian sailors previously involved in extremely stressful tasks during World War II. Furthermore, a CT scan investigation performed in political prisoners who had been subjected to physical torture showed cerebral atrophy with ventricular enlargement (Jensen *et al.*, 1982). The notion that stress may affect cognition has become so widely accepted that in the current classifications of dementia syndromes, stress is included among the etiological factors for the secondary types (Gottfries, 1989).

The simplest way to test the hypothesis that glucocorticoids may endanger hippocampal neurons and hence impair cognition has been to investigate the effect of corticosteroids in normal subjects. Moreover, it also seems relevant to verify whether conditions of cognitive disruption, such as dementia, are characterized by increased adrenocortical function, and vice versa, if hypercortisolemic states, such as Cushing's disease or depression, are associated with any decline in mental performance. However, in interpreting these findings it should be borne in mind that exogenous and endogenous corticosteroids may differ considerably in their action in the CNS.

Studies in normal subjects and depressed patients

It is well established that corticosteroid treatment may induce reversible psychotic conditions (so-called steroid psychosis) (Ling *et al.*, 1981) or mental disturbances resembling dementia, such as loss of memory, attention, concentration, logical thinking, or occupational performance. Varney *et al.* (1984) described a peculiar dementia-like syndrome (decreased attention, concentration, retention, and mental speed) in patients showing no concurrent psychosis who were given high doses of corticosteroids for medical illnesses not affecting the CNS. However, studies on patients have generally failed to discriminate the cognitive effects related to the treatments from those due to the underlying illnesses. It may be possible that the steroid psychosis and the dementia-like disturbances reflect different pathophysiological mechanisms; on the other hand, a pure cognitive deficit may simply represent the prodromal phase of a psychic disorder (Wolkowitz *et al.*, 1990).

The administration of exogenous corticosteroids to healthy subjects has been associated with impairment in higher brain functions. Wolkowitz *et al.* (1990) showed poor performance (errors of commission) on verbal memory tasks in normal volunteers given dexamethasone (1 mg in a single dose) or prednisone (80 mg/day for 5 days). The cognitive failure was similar to that occurring in normal aging and quite different from that observed in response to treatment with benzodiazepines or scopolamine (Caine *et al.*, 1981; Wolkowitz *et al.*, 1987). Although

the specific ways in which cognition is altered are still unclear, corticosteroids may impair selective attention, i.e., an individual's ability to discriminate relevant and important inputs from irrelevant and unimportant ones (Wolkowitz *et al.*, 1990). Moreover, according to McEwen (1982), corticosteroids may act by suppressing the activity of hippocampus, which has been suggested as the structure where stimuli are initially filtered. It also has been speculated that corticosteroids may induce a peculiar state of overarousal, resulting in impaired cognitive performance (Wolkowitz, 1990). This explanation would fulfill the Yerkes-Dodson law (Yerkes & Dodson, 1908), according to which arousal and cognition show an inverted U-shaped relationship.

A large proportion of patients suffering from major depression are characterized by increased activity of the HPA axis, as detected by estimation of circadian cortisol secretion and cortisol nonsuppression in response to dexamethasone (Carroll, 1982). Several studies have indicated that depressed patients show qualitative and quantitative cognitive deficits, such as failure in attentional tasks, verbal and visual memory, and retrieval (Weingartner *et al.*, 1981; Cohen *et al.*, 1982; Roy-Byrne *et al.*, 1986). It is indeed common that, especially at their onset, depressive disorders in the elderly can be predominantly represented by cognitive symptoms, thus resulting in so-called (depressive) pseudodementia (Caine, 1981). Moreover, in hypercortisolemic patients and in those who fail to suppress cortisol secretion following dexamethasone administration, neuropsychological deficits appear to be even more pronounced (Rubinow *et al.*, 1984; Winokur *et al.*, 1987; Sikes *et al.*, 1989). In particular, cognitive impairment seems to be more severe in situations or tasks which require sustained effort. In this respect, it has been reported that in depressed patients tests such as free recall and short-term memory are performed more poorly than tests of recognition or working memory (Roy-Byrne *et al.*, 1986). This would imply that operations for which little cognitive ability is required can be more easily accomplished by depressed patients.

The cognitive features in depression may be viewed in terms of glucocorticoid-induced cortical atrophy. Such explanation is supported by the finding that in a group of depressed patients brain ventricular size, measured with magnetic resonance imaging, was directly correlated with post-dexamethasone plasma cortisol levels (Rao *et al.*, 1989).

The dishinibition of adrenocortical activity in depression has long been considered as reflecting disrupted neurotransmitter activity in the brain. In particular, CRH-41 hypersecretion at a hypothalamic level has been suggested, possibly as a result of reduced control of inhibitory neurotransmitters (Nemeroff *et al.*, 1984). However, CRH-41 is not only the peptide which regulates pituitary-adrenocortical secretions; it also acts in the CNS as a neurotransmitter which promotes and modulates various stress-associated phenomena, possibly including cognitive changes (Koob & Bloom, 1985). Therefore, the cognitive aspects of depression should not be ascribed merely to the effect of high levels of circulating corticosteroids.

Studies in Cushing's syndrome

Cushing's syndrome (CS) is an endocrine disorder characterized by a sustained overproduction of steroid hormones, mainly cortisol, from the adrenal cortex. CS can be divided into ACTH-dependent and ACTH-independent types (Trainer & Grossman, 1991). The former includes the syndrome due to pituitary ACTH oversecretion, referred to as Cushing's disease (CD); other forms are due to ectopic ACTH production or to ACTH therapy. The ACTH-independent group consists of cortisol hypersecretion by adrenal tumors (adenoma or carcinoma) or micronodular hyperplasia, and glucocorticoid therapy. The most common cause of hypercorti-

solemia in all age groups, including the elderly, is the excessive administration of exogenous glucocorticoids, used for their anti-inflammatory effects.

Several studies have dealt with the histopathological findings in brain from patients with CS. Trethowan and Cobb (1952) described signs of limbic atrophy at autopsy, the finding being later confirmed *in vivo* by other authors (Bentson *et al.*, 1978). Although in some cases patients may have been on treatments aiming at attenuating their hormone secretion, several studies also have assessed neuropsychological parameters in CS patients. Difficulties with attention, concentration, and memory have been reported (Whelan *et al.*, 1980; Starkman & Schteingart, 1981). In one study the patients' overall impairment correlated with their plasma ACTH and cortisol levels, and an improvement occurred after the reduction of plasma cortisol levels (Starkman *et al.*, 1986). In their extensive study in 35 untreated patients, Whelan *et al.* (1980) found mild to severe neuropsychological deficits in 22 cases, the most affected being visual-ideational and visual memory functions. The pattern was similar to that found in other types of diffuse and bilateral neuropathological processes.

We conducted a study on 24 patients, 16 men and 8 women, diagnosed as having CD, to test the hypothesis that, as far as cognition is concerned, this disease may be considered as a model of memory impairment. The duration of disease was 1 yr or less in all cases. Twenty-two of the 24 patients had a pituitary adenoma; 2 had no detectable pituitary neoplasia. In all patients, psychosis, confusional states, and affective disturbances had been ruled out by adequate investigation. Patients entered the study prior to starting any therapy. Attention, memory, language, visuo-spatial, and logical abilities were evaluated with a neuropsychological battery in the patients and in a group of 24 controls matched for age, sex, and educational level. Complaint of discomfort in everyday tasks was present in about 50% of patients. As reported in Table I, a

TABLE I. NEUROPSYCHOLOGICAL EVALUATION SCORES (MEAN ± SD) OF 24 UNTREATED PATIENTS WITH CUSHING'S DISEASE (CD) AND 24 CONTROLS

	CD patients	Controls	p
LM s.t.	6.16 ± 2.25	8.17 ± 1.89	0.005
LM l.t.	7.08 ± 3.20	10.00 ± 2.54	0.001
VR s.t.	8.66 ± 3.69	11.00 ± 2.20	0.01
VR l.t.	6.50 ± 3.82	9.65 ± 2.21	0.001
DS f.	5.58 ± 1.02	5.52 ± 1.23	NS
DS b.	3.50 ± 0.83	4.10 ± 0.75	0.025
Street	7.33 ± 1.99	7.78 ± 1.24	NS
Raven Colored Matrices	26.00 ± 4.37	26.40 ± 3.78	NS
Similarities	13.41 ± 2.68	13.61 ± 3.27	NS
DSST	36.04 ± 13.87	47.29 ± 11.18	0.005
Cancellation test	53.66 ± 6.03	53.82 ± 4.60	NS
TMT	54.66 ± 18.10	50.00 ± 17.18	NS
Verbal fluency	19.00 ± 5.18	20.43 ± 4.20	NS
Age (yr)	36.16 ± 14.31	36.00 ± 14.1	NS
Education (yr)	8.75 ± 3.52	8.80 ± 3.50	NS

LM = Logic Memory; VR = Visual Reproduction; (l.t. = long-term; s.t. = short-term); DS = Digit Span (f. = forwards; b. = backwards); DSST = Digit Symbol Substitution Test; TMT = Trail Making Test.

significant impairment in the items Logical Memory and Visual Reproduction (both short- and long-term) was found in the CD patients. They also showed poor performance on the Digit Span (backwards) and on the Digit Symbol Substitution Test. Therefore, the patients showed an impairment in verbal and non-verbal episodic memory. No significant relationship was found with plasma ACTH levels, urinary free cortisol levels, or with the cortisol nonsuppression in response to dexamethasone. Seven patients were re-tested 6 mo after surgical treatment and showed a significant recovery of verbal memory (Table II). These results appear to be in substantial agreement with previous studies. Furthermore, the mnesic impairment was found to increase with age; indeed, the percentage of subjects showing a pathological score on the memory tests was higher in the older group (over 45 yr). It therefore seems reasonable to speculate that CD may represent a clinical model of early mnesic decline, possibly related to hippocampal involvement; in surgically treated patients, however, the changes may be partially reversible, at least in a restricted subgroup, suggesting the occurrence of dysfunctional brain damage in these patients.

HPA AXIS ACTIVITY AND COGNITION IN DEMENTIA OF THE ALZHEIMER TYPE

Dementia of the Alzheimer type (DAT) represents a paradigm of disrupted cognition in humans. Studies on brain tissues have demonstrated that in subjects suffering from DAT, the CRH-41 content is reduced in the frontal, temporal and occipital cortex, while a reciprocal increase in the number of CRH-41 receptors can be observed (De Souza *et al.*, 1986).

Bearing in mind the central role that CRH-41 plays in the regulation of pituitary-adrenocortical activity, this evidence strongly suggested an involvement of the HPA axis in the pathogenesis and/or evolution of degenerative dementia. Interest in this topic was further enhanced by the observation that aged rats are characterized by a hyperactivity of the HPA axis (Sapolsky *et al.*, 1986). Such findings therefore stimulated a revision, in a neuroendocrine framework, of the mechanisms underlying aging and dementia.

TABLE II. NEUROPSYCHOLOGICAL EVALUATION IN 7 PATIENTS WITH CUSHING'S DISEASE BEFORE AND 6 MONTHS AFTER SURGICAL TREATMENT

	Before	After	*p*
LM s.t.	6.00 ± 1.40	9.57 ± 2.37	0.01
LM l.t.	7.42 ± 1.90	10.71 ± 2.69	0.025
VR s.t.	11.28 ± 2.28	10.14 ± 3.02	NS
VR l.t.	8.42 ± 3.36	8.42 ± 2.29	NS
DS f.	5.57 ± 0.97	6.28 ± 1.11	NS
DS b.	3.28 ± 0.75	3.85 ± 0.38	NS
Street	8.28 ± 1.38	8.30 ± 1.38	NS
Raven Colored Matrices	28.42 ± 3.45	29.42 ± 4.11	NS
Similarities	14.71 ± 1.11	15.57 ± 0.78	NS
DSST	41.30 ± 14.72	50.00 ± 17.43	NS
Cancellation test	56.71 ± 3.14	56.42 ± 2.37	NS
TMT	45.14 ± 13.65	44.57 ± 15.08	NS
Verbal fluency	19.85 ± 5.90	20.22 ± 5.65	NS

See Table I for abbreviations.

Prolonged exposure to corticosterone in rats seems to exert noxious effects on brain neurones, by enhancing their vulnerability to endogenous or environmental toxic agents via disruption of glucose metabolism. This action, as mentioned above, is maximal in the hippocampus, whose dorsal region participates in the negative feedback mechanisms of the HPA axis, and hence in extinguishing the stress response. In fact, the hippocampus should inhibit the activity of the neurones in the paraventricular nucleus (PVN) and therefore CRH-41 release, possibly via pathways involving the fornix (Sapolsky *et al.*, 1985). Enhanced plasma levels of glucocorticoids are able to induce changes in the hippocampus which are initially of a functional type (receptor down-regulation), and subsequently of a morphological type (neuronal loss). Impairment in hippocampal function, therefore, may ultimately disrupt mechanisms of self-regulation of the HPA circuit. Indeed, aged rats show an exaggerated HPA response to immobilization stress and a delayed recovery of corticosterone levels compared to young rats (Sapolsky *et al.*, 1986). Studies thus are needed to elucidate to what extent exposure to chronic stress can affect the aging brain processes.

As far as the human is concerned, the findings of increased plasma cortisol levels (Davis *et al.*, 1986) and a high prevalence of abnormal dexamethasone suppression tests (Greenwald *et al.*, 1986) suggested a state of hyperactivity of the HPA axis in DAT patients. Consistently, it has been reported that the CRH-41 content in the hypothalamic PVN was markedly increased in histologically verified cases of DAT (Powers *et al.*, 1987). Therefore, hypercortisolemia has been proposed as a neuroendocrine marker of the pathological aging brain, and it has been speculated that a stress-adaptation failure in DAT might be of specific etiopathological significance (Deshmukh & Deshmukh, 1990).

Accordingly, in DAT patients a correlation between enhanced cortisol response to an oral glucose tolerance test and severity of hippocampal atrophy and cognitive decline has been reported (De Leon *et al.*, 1988). Other investigators found that mean 24-hr cortisol levels and scores on neuropsychological tests for memory were inversely related in DAT patients (Heuser *et al.*, 1988). Another study showed that post-dexamethasone cortisol levels in DAT were correlated with the Global Deterioration Scale (GDS) score (Oxenkrug *et al.*, 1989).

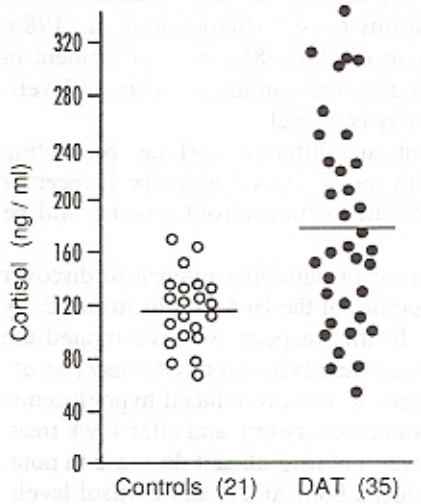


FIG. 1: Morning (0800h) plasma cortisol levels in 35 Alzheimer's patients and 21 age-matched controls. Horizontal lines = mean values; $p < 0.01$ between groups.

Our group performed an evaluation of HPA axis activity in this disease. In our first study, we found high morning (0800h) plasma cortisol and beta-endorphin (β-EP) levels in mildly demented patients (Nappi *et al.*, 1988). A more extensive investigation then was carried out in another group of 10 patients, diagnosed as suffering from probable DAT (Martignoni *et al.*, 1990). We found elevated cerebrospinal fluid (CSF) CRH-41 concentrations, high morning (0800h) cortisol levels, and an increased mesor (24-hr mean secretion) and amplitude of the cortisol circadian rhythm in this group of patients. Nonsuppression of cortisol levels to dexamethasone was shown in 6 out of the 10 patients. In the CRH test, an earlier peak of cortisol response was detected in the DAT group, without any difference in the secretory area under the curve. Interestingly, CSF CRH-41 levels were inversely correlated with the severity of cognitive impairment, as

assessed by the Mini Mental State examination. The finding of high morning plasma cortisol levels was subsequently confirmed by our group in a larger series (n=35) of DAT patients, as shown in Fig. 1 (Nappi *et al.*, 1990). In these cases, the hormone levels were correlated with the severity of cognitive decline as measured by the GDS.

In accord with our data, Maeda *et al.* (1991) found that, in a group of DAT patients, the urinary free cortisol levels were higher than in controls; moreover, they correlated with 1600h post-dexamethasone plasma cortisol levels.

Taken together, these studies indicate that abnormal HPA axis function, which is not related to a depressive state, occurs in DAT. Such dysregulation most likely reflects changes in neurotransmitter pathways at a supra-hypothalamic level. As yet, evidence that this condition may be related to functional or structural hippocampal lesions in humans is lacking. Although HPA hyperactivity cannot be considered as a marker of degenerative dementia, biological findings such as increased CSF CRH-41 levels and elevated urinary free cortisol concentrations may be of clinical usefulness in an early stage of disease.

THERAPEUTIC PERSPECTIVES

In view of the wide use of corticosteroid treatments for a number of diseases (allergic, autoimmune, rheumatologic, and neurologic), large, prospective, and more accurate studies on the possible effects of this therapy on mental performance are needed. If one considered the common use of corticosteroids in the treatment of brain tumors or in the aftermath of a stroke, it would appear that neurologists are among those particularly concerned about the brain implications of such therapy.

But what about conditions in which glucocorticoids are endogenously overproduced? Again, suggestions for possible therapeutic strategies arise from animal studies. It has been demonstrated in rat that the hippocampal damage following ischemic insults can be significantly reduced by adrenalectomy (Sapolsky *et al.*, 1986). In humans, the pharmacological reduction of glucocorticoid hypersecretion is commonly adopted in CD. Treatments with agents like mitotane and ketoconazole appear effective in this respect (Starkman *et al.*, 1986; Ravaris *et al.*, 1988). Moreover, in the study of Starkman *et al.* (1986) an improvement in attention, concentration, and memory was associated with a decrease in urinary cortisol levels. Metyrapone, which inhibits cortisol steroidogenesis, also may be useful.

Other studies have described the possibility of treatments at a different level, i.e., preventing corticosteroids from binding to hippocampal receptors with specific type I and type II receptor antagonists (Lane *et al.*, 1988). In this case, a block of the corticosteroid effect could be achieved more quickly than by inhibiting steroidogenesis.

As far as normal subjects are concerned, it would appear of particular interest to discover drugs able to control the response, or the possible overresponse, of the HPA axis to stressors, by dampening down stress-associated hormone increases. In this respect, we investigated the effects of etoperidone, an antiserotoninergic as well as an adrenolytic agent (Ramacci *et al.*, 1974). Plasma ACTH, cortisol, and catecholamine responses to insulin-induced hypoglycemia (0.15 UI/kg insulin) were evaluated in 10 young healthy volunteers before and after 1-wk treatment with etoperidone (150 mg/day orally). While there was a nonsignificant decrease in noradrenaline and adrenaline levels, etoperidone markedly reduced both ACTH and cortisol levels, compared to placebo (Figs. 2 & 3). It is our belief that this effect can be ascribed to the inhibition of serotoninergic (and possibly adrenergic) inputs which normally facilitate CRH-41 release from the hypothalamus (Nakagami *et al.*, 1986; Tsagarakis *et al.*, 1988).

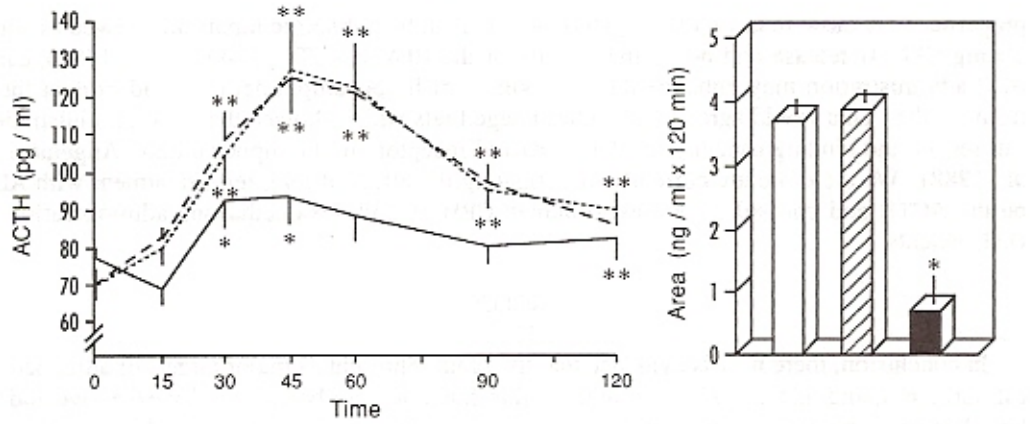


FIG. 2: Right: Mean (±SEM) plasma ACTH values during insulin tolerance test (ITT) in 10 healthy volunteers before (dotted line) and after 1-wk treatment with etoperidone (solid line) or placebo (dashed line). *$p<0.05$, **$p<0.01$ vs. time 0 values.
Left: Mean (±SEM) area of cortisol secretion during ITT before (open bar) and after (solid bar) etoperidone or placebo (hatched bar). *$p<0.01$ vs basal and placebo.

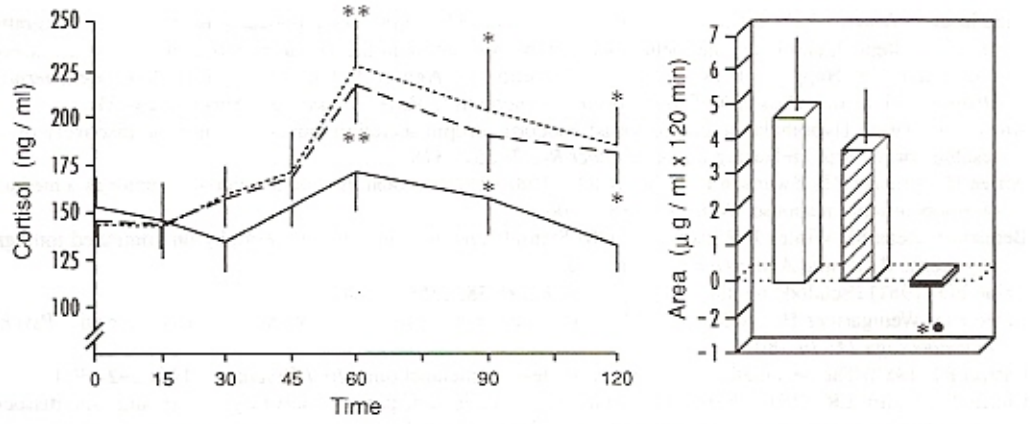
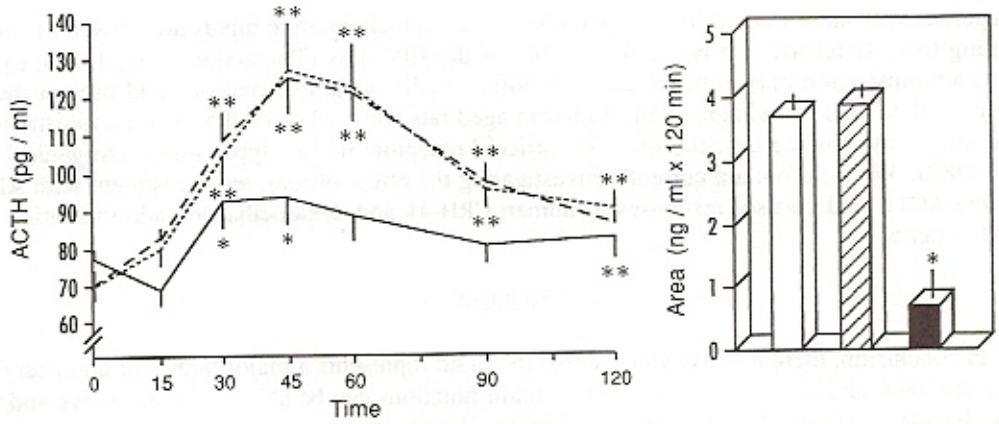


FIG. 3: Right: Mean (±SEM) plasma cortisol values during ITT in 10 healthy volunteers before (dotted line) and after 1-wk treatment with etoperidone (solid line) or placebo (dashed line). *$p<0.05$, **$p<0.01$ vs. time 0 values.
Left: Mean (±SEM) area of cortisol secretion during ITT before (empty bar) and after (solid bar) etoperidone or placebo (hatched bar). *$p<0.05$ vs. placebo and *$p<0.01$ vs. basal values.

Finally, another line of treatment might employ drugs acting at a further level, i.e., counteracting the metabolic disruption caused by corticosteroids. There is evidence that in rats supplementation of glucose or mannose to hippocampal neurons can considerably reduce the toxic effects of corticosteroids (Sapolsky, 1986). In humans, there are certain "nootropic" agents which are thought to act via their metabolic effects. For example, we have observed a normalization of plasma cortisol and β-EP levels in mild DAT patients after 3-mo administration of acetyl-L-carnitine (ALC) (Nappi *et al.*, 1988), an endogenous compound with a structure and



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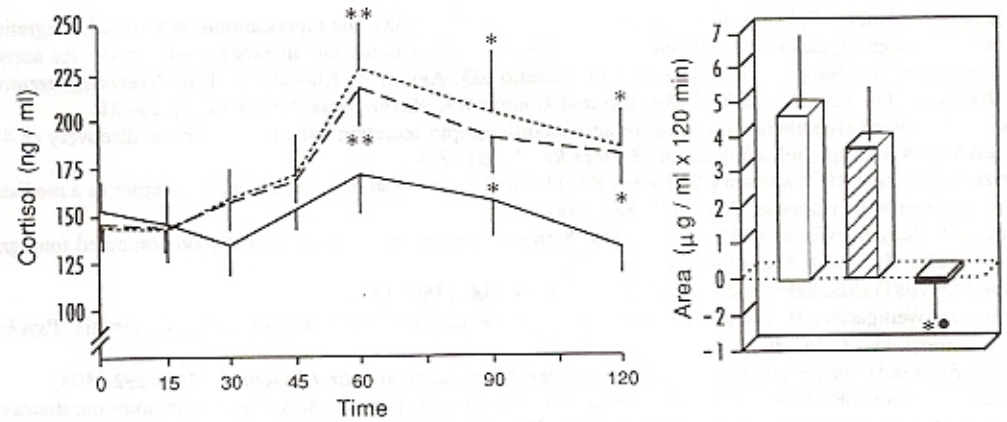

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properties very close to those of acetylcholine. Although cholinergic inputs are viewed as stimulating CRH-41 release and hence the activity of the HPA axis (Tsagarakis *et al.*, 1988), early ALC administration may enhance the metabolism of hippocampal neurons and protect them from insults. This would agree with studies in aged rats which showed that ALC administration can restore the binding capacity of glucocorticoid receptors in the hippocampus (Angelucci *et al.*, 1988). We therefore are currently investigating the effect of long-term treatment with ALC on the ACTH and cortisol responses to human CRH-41 and dexamethasone administration in DAT patients.

CONCLUSION

In conclusion, there now is evidence that the brain represents a major target for adrenocortical hormones, and that at least some higher brain functions can be affected by excessive and/or long-lasting circulating levels of glucocorticoids. Because the consequences in humans are currently uncertain, further studies are necessary to understand the precise mechanisms and the real implications of glucocorticoid effects in human brain, as well as to define rational strategies to retain these effects within physiological limits.

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