J. Steroid Biochem. Molec. Biol. Vol. 39, No. 2, pp. 239–244, 1991
Printed in Great Britain.

0960-0760/91 $3.00 + 0.00

TREATMENT OF MAJOR DEPRESSION WITH STEROID SUPPRESSIVE DRUGS

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Summary—The hypercorticism frequently observed in major depression, unaccompanied by signs of Cushing's syndrome, is still poorly understood. One suicidal young woman, with very high cortisol levels and unusual resistance to dexamethasone suppression, is described. She was successfully treated with steroid suppressive drugs (aminoglutethimide, metyrapone), had a prompt and complete remission and has remained well for more than two years on no medication. This success prompted an on-going clinical trial of this therapy. The available drugs and a working hypothesis of their action are discussed.

Excessive cortisol levels in some types of mental patients were demonstrated as long ago as the early 1960s, but their significance remains obscure [for review, see Ref. 1]. Increases have been observed in serum, saliva, urinary and cerebrospinal fluid cortisol, and also in urinary 17-hydroxycorticoids. In the late 1960s it was noted that such patients also tended to be resistant to suppression of cortisol by dexamethasone, and this was particularly true of patients with endogenous depression.

The dexamethasone suppression test (DST) was taken up with enthusiasm and hundreds of papers documenting abnormalities were published during the 1970s. However, in no group, were all the individuals found to be affected. The mechanism of this lack of suppression after dexamethasone administration is still not understood. It is usually considered to be due to a "disinhibition" of the hypothalamic–pituitary–adrenal axis but while levels of corticotropin-releasing factor are slightly elevated, ACTH levels tend to be depressed. The data have been summarized by Arana and Mossman [2a] (Table 1).

Apart from ensuring that such subjects do not have Cushing's syndrome, endocrinologists have taken relatively little interest in these observations, while few psychiatrists are familiar with the intricacies of steroid metabolism. Only relatively recently has there been a tendency for the disciplines of endocrinology and psychiatry to come together, at meetings such as those of the International Society of Psychoneuroendocrinology and the World Congress of Biological Psychiatry.

SIGNIFICANCE OF HYPERCORTICOIDISM IN DEPRESSION

The significance of the high cortisol levels in depression and their resistance to suppression is not understood. Why should these phenomena occur in only some depressed patients and not all? If the high cortisol levels are really important, why is it that there have been a few cases reported of major depression even in adrenalectomized patients on replacement therapy?

Although patients with endogenous depression do not develop Cushing's syndrome despite high cortisol levels, patients with true Cushing's syndrome, of either pituitary or adrenal origin, are often (70–80%) severely depressed, and occasionally acute psychosis may be the presenting symptom. Does this mean that possibly these states represent a continuum and that eventually severely depressed patients would develop signs of Cushing's syndrome? This seems unlikely because when major depression improves, spontaneously or with treatment, the hypercortisolism of endogenous depression reverts to normal; Cushing's syndrome, on the other hand rarely remits spontaneously. Thus, although hypercortisolism is associated with both diseases, the etiology would seem to be different. However might the mechanism of the depression be the same in both, and be related to the hypercortisolism? This question remains to be answered.

Proceedings of the Symposium on Psychoendrocrinology, in honour of Professor Marion Krantz Birmingham, Allan Memorial Institute of McGill University, Montreal, Canada, 11 November 1989.
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Table 1. Rates of non-suppressor responses in various psychiatric disorders

Subject group	No. of subjects	Non-suppressors (%)
Controls:		
Normal	1130	7
Normal + non-psychiatric patients	1269	8
Bereavement	NS	10
Major depression:		
All	4411	43
Elderly (>60 years)	183	64
Melancholic	583	50
Psychotic	150	67
Mixed bipolar (manic depressive)	41	78
Other psychiatric disorders:		
Anxiety disorders	74	8
Schizophrenia	260	13
Minor depression	238	23
Acute psychoses	69	34
Dementia	174	41
Mania	137	41

NS, not stated. As modified from Arana and Mossman [2b].

PSYCHIATRIC EFFECTS IN IATROGENIC CUSHING'S SYNDROME

It is of interest that the administration of pharmacological amounts of glucocorticoids tends to result in euphoria (about 80%), and only occasionally in depression [1]. However spontaneous Cushing's syndrome is only rarely associated with euphoria. The reasons for this are not clear.

CASE REPORT

My own interest in psychoendocrinology came about accidentally, and entirely through Dr Marion Birmingham, as mentioned in the Foreword. In studying patients with endogenous depression as a comparison group in a study of cortisol levels in the premenstrual syndrome, one patient was of particular interest.

This 31-year-old woman had remarkably high cortisol levels (documented over several months) with little diurnal variation and extreme resistance to dexamethasone—her cortisol level remained above 140 nM/l even after 8 mg dexamethasone the night before (i.e. eight times the usual dose). In fact, had I not myself observed her slim appearance and her low B.P., I would have expected her to be frankly Cushingoid. Her electrolytes, abdominal ultrasound and CAT-scan of the brain were normal.

She had been well until 10 months previously at which time the 5-year relationship with her boyfriend deteriorated. She was also distressed when an acquaintance committed suicide. Six months previously, she was admitted to hospital after she herself made a suicide attempt. She was placed on chlorpromazine and hydroxyzine, and released after two weeks. One month later she was readmitted after taking an overdose of various pills and was treated with desipramine and lorazepam; she was released after a week. A month later, when her response to these drugs was unsatisfactory, nortriptyline and trifluoperazine were tried. Two months before our study began, she was again admitted with an overdose. On this third admission, high cortisol levels and unusual resistance to dexamethasone suppression were noted (see Table 2). She denied having had any significant previous illnesses, and had been working as a psychologist until the onset of her illness. Her family history was remarkable in that her father had died of lung cancer, her mother of endometrial cancer and one sister of cervical cancer. Her remaining sister is well. Her weight was 53 kg, B.P. 90/60, pulse 90 and regular. No physical abnormalities were found. Laboratory examinations including hemogram, routine biochemistry and thyroid function tests, were normal. Her psychiatrist, Dr R. Keller, felt that her prognosis was poor.

Having used medical steroid suppression in the treatment of patients with Cushing's syndrome and in patients with metastatic breast cancer, it seemed to me that the logical question was whether such steroid suppressive therapy might benefit this patient. Although this approach appears to be obvious, a search of the literature revealed not a single case of major depression in the absence of Cushing's syndrome having been treated in this way. The possibility of such treatment had, however, been suggested by Howlett *et al.* [3] who had observed striking improvement in the depression seen in some patients with Cushing's syndrome when medical suppression therapy was given.

Since there was little other treatment to offer this patient, her written informed consent was obtained for a trial of steroid suppressive therapy. Her previous medications were gradually withdrawn and she was started on aminoglutethimide 250 mg twice a day along with 20 mg cortisol to ensure that the cortisol levels would not drop too low. Blood pressure, pulse and temperature were monitored four times a day during her hospital stay and remained normal. On the third day of treatment she reported that her mind felt clear for the first time in months, and that she had more energy. The nurses stated that she laughed more and was less anxious. On the fourth day she was allowed to go home and she was followed

weekly as an out-patient. After one week the dose of aminoglutethimide was increased to 250 mg three times a day. B.P. rose slightly to an average of 110/70. Dehydroepiandrosterone (DHAS) and cortisol were monitored once or twice weekly (see Fig. 1). By the third day the DHAS had fallen to 1.0 μM/l. It remained low for four weeks when it rose despite therapy to 5.5 μM/l. At this point she was readmitted for one week, the aminoglutethimide was increased to 250 mg four times a day, and after a further one week metyrapone 250 mg four times a day and 9α-fluorocortisol 0.05 mg daily were added. Treatment was continued as an out-patient for a total of eight weeks, following which the drugs were gradually withdrawn. Two weeks after stopping all medications, a 1 mg dexamethasone suppression test was performed. All post-treatment laboratory values were normal (Table 2).

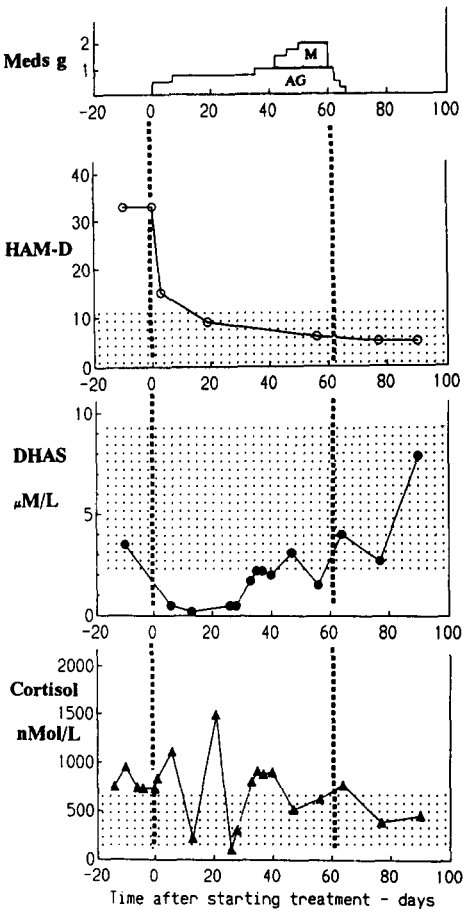

Fig. 1. Clinical course of first case of major depression treated with steroid suppression therapy. Meds g: Medications-grams; Ham-D: Hamilton Depression rating; M: metyrapone; AG: aminoglutethimide; and DHAS: dehydroepiandrosterone sulfate. Dotted areas indicate normal ranges.

Subjective improvement in mood occurred within 48 h of starting the aminoglutethimide and persisted throughout. Hamilton Depression Scale ratings, performed by my clinical assistant Dr Veena Dhar and by psychiatrist Dr Missagh Ghadirian, fell to the normal range during treatment and remained low following therapy. She has remained off all medication for two and one-half years and continues well. After being unemployed for almost a year, she has been working full-time for the past two years.

CLINICAL TRIAL

Because of this striking response, a formal clinical trial of steroid suppressive therapy in major depression (as defined by the American Psychiatric Association [4]) was undertaken. The results for the second patient, a 63-year-old man with a nine-year history of severe depression, admitted with severe self-inflicted stab wounds to his arms and abdomen, were almost as dramatic as the first patient, and he has also remained well for more than two years on no medication. The results for the first ten patients are in the process of publication [5] and it is planned to complete studies of twenty patients using these drugs. After the first four patients had been treated, ketoconazole was also tried and appears to be equally effective.

Since this is an open study, one must consider the possibility that there may be a placebo effect. However this seems unlikely to account for the results since all of these patients had failed at least two trials of adequate amounts of conventional antidepressants, and also in many cases electro-convulsive therapy. While only a few responses have been as dramatic as those of the first two patients, about 2/3 of the patients have responded (a drop of $>50\%$ in the Hamilton Depression Scale) while on treatment, and 1/3 have remained well for at least 8 months after stopping the treatment, i.e. they achieved a remission.

Side effects are not negligible, however; they include mainly lethargy, fatigue and headaches, and occasionally a rash which usually subsides with symptomatic therapy; less commonly there may be significant alterations in liver function tests. Thus efforts to find better steroid-suppressive agents must continue.

AGENTS AVAILABLE FOR STEROID SUPPRESSION

Three agents are in common use to suppress steroid production in Cushing's syndrome: aminoglutethimide, metyrapone and ketoconazole.

Aminoglutethimide, which has also been used (along with cortisol and/or 9α-fluorocortisol) to treat patients with metastatic carcinoma of the breast, blocks steroid biosynthesis particularly at the cholesterol side chain cleavage, and at the C11, C21 and C18 hydroxylation steps [6]; metyrapone, mainly the C11 hydroxylation [7]. The pattern of inhibition of ketoconazole is similar to that of aminoglutethimide; however while aminoglutethimide also inhibits estrogen synthesis, ketoconazole spares estrogen synthesis but effectively blocks androgen synthesis [8, 9]. Ketoconazole is also known to bind to the glucocorticoid receptor [8], but does not act as an agonist; thus it acts both as an inhibitor of biosynthesis and as an antagonist at the receptor.

In addition to their effects on biosynthesis, aminoglutethimide and ketoconazole also affect peripheral metabolism of steroids. Although Fishman *et al.* [10] showed as long ago as 1967 that aminoglutethimide altered the extra-adrenal metabolism of cortisol so that urinary 17OHCS excretion is disproportionately low compared to cortisol secretion and plasma cortisol levels, the mechanism of this effect has never been elucidated. They demonstrated that in Addisonian patients treated with a constant dose of cortisol before, during and after treatment with aminoglutethimide, there was a 35–45% decrease in urinary 17OHCS although plasma cortisol levels were unaffected. They also showed that aminoglutethimide is more effective in lowering aldosterone secretion than cortisol secretion; they attributed the maintenance of the cortisol levels to increases in plasma ACTH.

Because of its use as a means of 'medical adrenalectomy' in breast cancer, the effects of aminoglutethimide on estrogen metabolism have been studied. Lonning *et al.*[11, 12] have shown that aminoglutethimide has a variety of effects on peripheral steroid metabolism. It inhibits aromatase, stimulates estrogen 16-hydroxylases in the liver, and enhances the rate of estrone sulfate metabolism. Horky *et al.* [13] also showed a pronounced effect on the peripheral degradation of testosterone in men, again presumably by affecting the enzyme systems in the liver. Feldman [14] has reviewed the effects of ketoconazole on hepatic enzymes—there was potent inhibition of 6β-, 16β-, and 16α-hydroxylase activity but no inhibition of 5α-reductase.

Other inhibitors of biosynthesis, such as mitotane (o,p'DDD) have been used to treat adrenal tumors because they cause a selective necrosis of the adrenal cortex [15].

RU 486, which is a glucocorticoid antagonist, is also being used as a means of decreasing adrenocortical function [16, 17]. Suramin, used for the treatment of human trypanosomiasis, has recently been shown to have effects similar to those of ketoconazole [18]. Other potential agents are the corticostatic peptides, both synthetic [19] and naturally-occurring [20], which compete with ACTH at adrenal receptor sites.

WORKING HYPOTHESIS

If some cases of major depression do truly remit in response to steroid suppressive therapy—and double blind studies will be required to prove this unequivocally—how does this come about? Our working hypothesis is that in major depression there is adrenocortical excess but that what matters is not so much cortisol itself but its metabolites, which are also elevated in depression, i.e. that an *alteration in*

Table 2. Laboratory data

	Units	Normal range	Before	During	After
Cortisol	nmol/l	a.m. 190–690	752, 744, 986	1500–640	450
	nmol/l	p.m. 50–410	942, 729, 429	1030–315	394
	1 mg Dex	≤136	a.m. 986		103
			p.m. 429		74
	8 mg Dex	≤136	a.m. 167		
			p.m. 133		
DHAS	μmol/l	2.2–9.2	10.6, 8.8, 3.5	0.2–3.1	3.1–8.0
ACTH	pmol/l	≤20	13	4, 5, 4, 7	2
FSH	IU/l	5–40	17, 13	10, 11	—
LH	IU/l	4–30	120, 6, 20, 18	28, 41	—
Prolactin	μg/l	5–25	16	10	15
Hamilton Depression Scale		≤10	33–43	15, 9, 6	5

steroid metabolism is the important feature. Possibly in chronic stress, and possibly influenced by genetic factors, a peptide other than ACTH may be produced, which alters cortisol metabolism, and that the abnormal metabolites produced cause an abnormal feedback which tends to perpetuate the process. A corollary of this is that if one suppresses the abnormal metabolites, the process might be reversed, and a remission induced. While the emphasis has been on abnormal cortisol levels, the many other steroids produced by the adrenal and those produced via metabolism in the liver have been almost completely ignored. However we know from the early studies that the metabolites are increased as well. What we do not know is to what extent the *pattern* is altered.

Although steroid metabolites are usually regarded as being inactive, Hans Selye[21] showed in the 1940's that there are many steroid metabolites which are powerful anaesthetics. About half of the more than 20 metabolites of progesterone are known to have anaesthetic properties and some of these are among the most powerful anaesthetics ever discovered. Metabolites of desoxycorticosterone are also known to be active. If such steroids when injected as a bolus can cause unconsciousness within seconds to minutes (the rapidity of action ruling out a genomic mechanism) then what do they do to the brain in physiological amounts?

Our own studies of some of these compounds administered to rats in silastic capsules, suggest that in low doses (which do not make the animals sleepy) they may affect motor activity either increasing it or decreasing it [22]. These observations may have significance for depression, where motor activity is usually decreased.

Drs Holzbauer and Birmingham and their colleagues have shown that substantial amounts of such compounds are produced by the rat adrenal [23, 24]. Being highly fat-soluble, they are almost certainly present in high concentrations in the brain. It is also possible that these steroids are produced there, since it has been established that progesterone can be converted to its 5-dihydro and 3,5-tetrahydro metabolites in brain tissue [23]. It is of interest that one of these metabolites, 3α-hydroxy,5α-pregnane-20-one, can act as a barbiturate-like modulator of γ-aminobutyric acid (GABA) [25]. However little is known of the concentrations in either serum or brain, or of the possible effects of these steroids in the brain in health or mental disorders. One reason is that they are extremely difficult to measure; another is that there are so many of them.

The amounts and proportions of such substances are presumably altered by steroid suppressive drugs. Our encouraging results of the use of these drugs in depressed patients unresponsive to conventional antidepressant therapy suggest that the effects of these steroids on the brain merit intensive exploration.

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