J. Steroid Biochem. Molec. Biol. Vol. 39, No. 5B, pp. 867–872, 1991
Printed in Great Britain.

0960-0760/91 $3.00 + 0.00

ADRENAL STEROID ENDOCRINOLOGY—SOME UNSOLVED PROBLEMS

V. H. T. JAMES
Department of Chemical Pathology, Unit of Metabolic Medicine, St Mary's Hospital Medical School, London W2 1PG, England

Summary—Although we now have a good understanding of some of the mechanisms which control pituitary–adrenal activity in human subjects, there are several important problems which still require a solution. The mechanism which controls the diurnal rhythym of aldosterone secretion is not yet identified, and although ACTH is clearly an important factor in the control of adrenocortical activity, it does not account for the pattern of these changes, or for the changes which occur in adrenal androgen secretion. Corticosteroids are well known to have suppressive effects on the release of ACTH, but the retention of pituitary–adrenal responsiveness in patients receiving ACTH therapy, and the prolonged suppression of the system caused by cortisol-secreting tumours, are not well explained by the model currently used, which needs further refinement.

The steroid secretory products of the adrenal cortex play a fundamental role in controlling numerous aspects of metabolism, interacting with neuroendocrine, immunological, and other physiological control systems. Unravelling these control mechanisms is important for a better understanding both of normal physiology and abnormal pathologies and this area of research has attracted a considerable degree of investigative effort. We have recognized for some years the major control mechanisms which govern adrenal cortical secretion, and Fig. 1 is a simple model which illustrates them. There are nevertheless, still many aspects of this system which are not understood, and several observations which this model does not explain.

The secretion of cortisol is controlled directly by adrenocorticotrophic hormone (ACTH), which increases the level of steroidogenesis and mediates glandular growth. Three major systems are recognized which influence and control ACTH release. Diurnal activity, stress, and negative feed-back systems all influence ACTH secretion and can thus modulate adrenal cortical activity. What is less clear though, is how these systems interact.

Diurnal activity is characterized by a number of ACTH secretory episodes, mostly nocturnal, and in normal subjects, these occur in a fairly reproducible manner [1]. In an individual subject, the pattern of secretion is similar from one day to the next, and even over longer periods this similarity is maintained [2] (Fig. 2). However, we do not know what is the stimulus for ACTH release or what advantage if any, such a physiological system confers on the organism. Nor is it clear how this adrenal cortical control mechanism is compatible with the negative feed-back system which operates between cortisol and ACTH. Administration of physiological amounts of cortisol reduces the activity of the adrenal cortex by inhibiting ACTH release, and conversely, a reduction of cortisol level in the plasma is compensated for by an increase in ACTH secretion. During a 24 h period in a normal subject, ACTH and cortisol levels fluctuate over a wide range and this pattern of events is difficult to reconcile with a responsive physiological negative feed-back system.

ACTH seems to play a very minor role in controlling aldosterone secretion, which responds primarily to changes in the concentration of angiotensin II and potassium in the plasma. It is therefore surprising that there is a diurnal variation in plasma aldosterone levels [3] which in many subjects follows that of cortisol very closely (Fig. 3). Since ACTH can in some circumstances cause the secretion of aldosterone, it is obviously tempting to postulate that this is the mechanism which controls ACTH release under basal conditions, but since the diurnal rhythm of aldosterone persists after ACTH secretion has been suppressed by the administration of dexamethasone (Fig. 4), and

Proceedings of the Symposium on Recent Advances in Steroid Endocrinology, held in honour of Professor V. H. T. James, London, England, 1 November 1990.

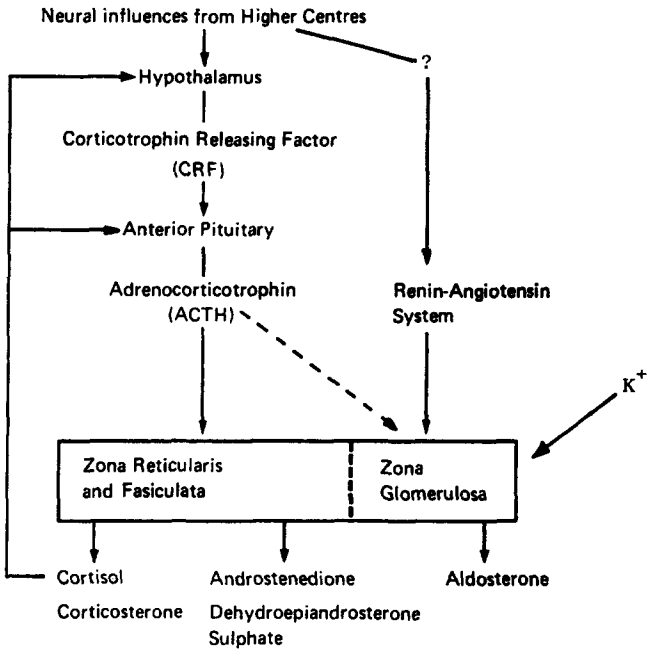

Fig. 1. Diagramatic representation of the mechanisms controlling adrenocortical secretion.

also occurs in hypophysectomized patients, ACTH is clearly not involved. A common stimulus is thus an unlikely explanation for this phenomenon and one must assume that, whatever is the stimulus to diurnal aldosterone secretion (and it is still not established what this is) it must be closely coupled to ACTH release. Again, the physiological purpose or advantage of these diurnal patterns is unclear.

The simple model shown in Fig. 1 suggests that ACTH is the stimulus to the secretion of both cortisol and the adrenal androgens. However, there is a considerable amount of evidence to suggest that this is not always the case. Under basal conditions, the plasma concentrations of cortisol, androstenedione and dehydroepiandrosterone (DHA) follow each other very closely (Fig. 5), in line with the supposition that

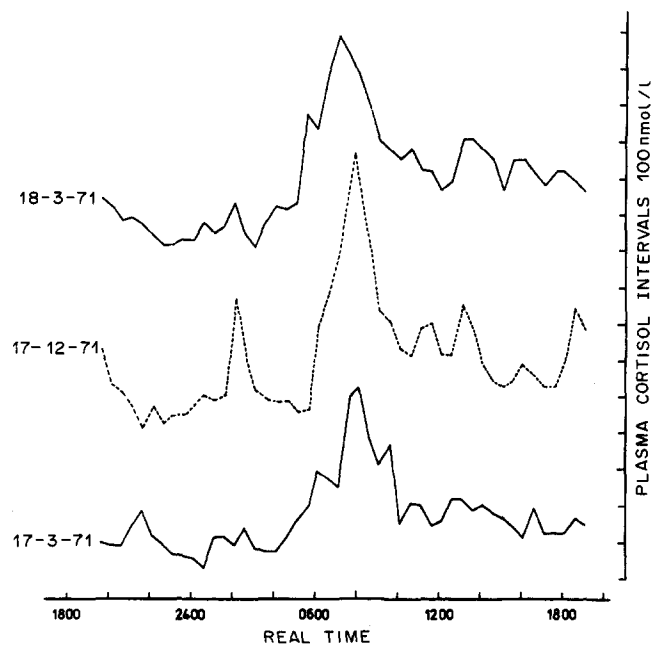

Fig. 2. Diurnal changes in plasma cortisol in the same control subject through 3 separate 24 h periods.

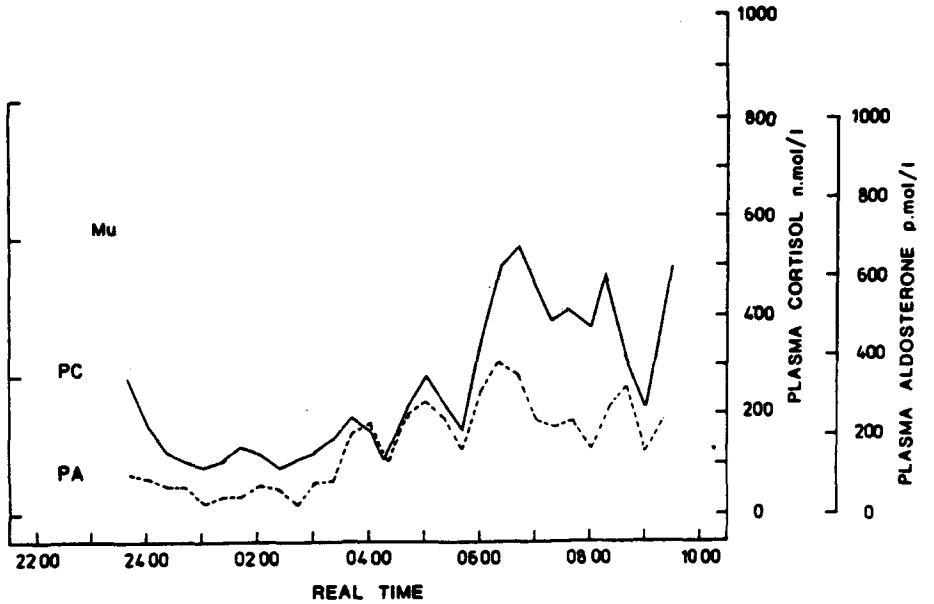

Fig. 3. Diurnal variation of plasma aldosterone and cortisol in a normal subject.

their secretion is driven by ACTH. Furthermore, administration of ACTH at physiological levels increases the secretion of all three steroids, and their threshold stimulation levels are closely similar. However, DHA sulphate, a major adrenalcortical secretory product, appears to follow a different pattern of secretion, and plasma levels are poorly related to those of the other adrenal steroids (Fig. 5). There are no obvious secretory episodes matching those of cortisol, androstenedione, and DHA, and even allowing for the very different half-life of DHA sulphate compared with the other steroids, it is difficult to believe that it is ACTH solely which is driving the secretion of DHA sulphate. DHA sulphate levels are reported to be elevated in patients with hyperprolactinaemia, although not all groups have found this. Plasma prolactin and DHA sulphate concentrations in these patients are correlated (Fig. 6), but it seems unlikely that prolactin is a physiological promoter of DHA sulphate secretion since there is no correlation between plasma levels of prolactin and DHA sulphate in normal subjects.

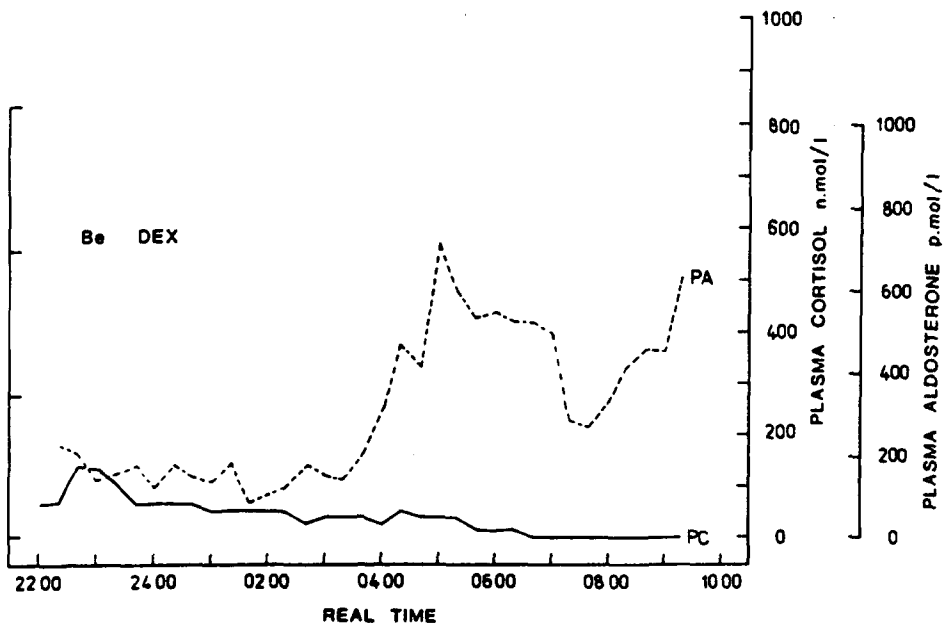

Fig. 4. Diurnal variation of plasma aldosterone and cortisol during administration of dexamethasone.

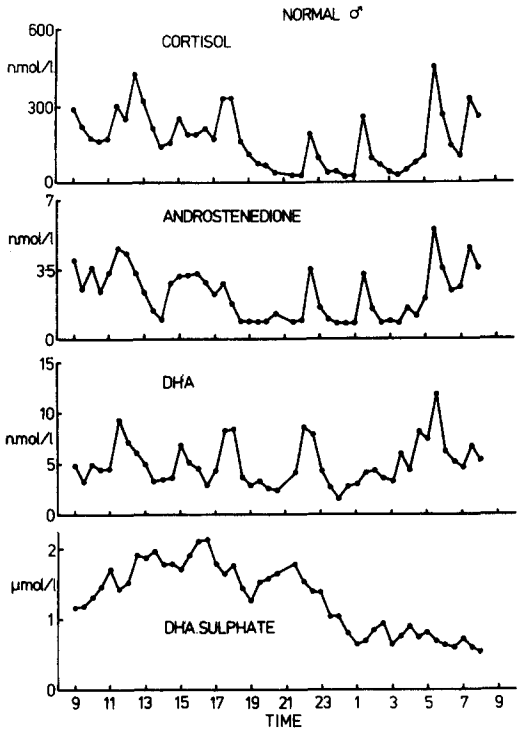

Fig. 5. Diurnal variation of plasma cortisol, androstenedione, DHA, and DHA sulphate in a normal subject.

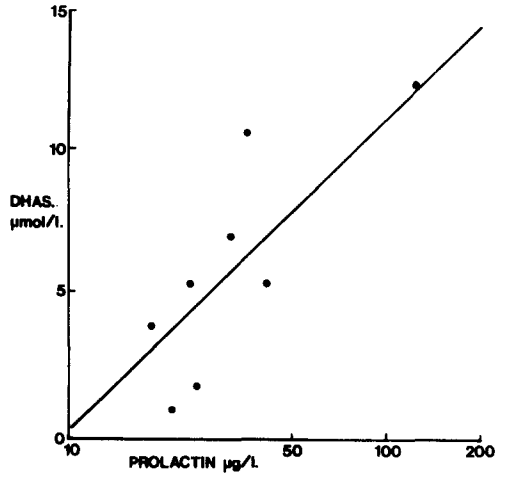

Fig. 6. The relationship between DHA sulphate (DHAS) and prolactin in patients in hyperprolactinaemia.

The problem of what it is that is driving DHA sulphate secretion remains unsolved. Nevertheless, it is clear that factors other than ACTH are involved in the control of the secretion of the adrenal androgens.

Although there appears to be a very close correspondence between cortisol and androstenedione secretion in normal subjects, the relationship becomes much less clear in other circumstances. Figure 7 shows plasma levels of cortisol and androstenedione in a patient who had had a pituitary tumour removed. Although relatively normal cortisol rhythms are maintained, there is no longer the close correspondence of cortisol and androstenedione levels which is seen in normal subjects. What effect pituitary surgery has had is unclear, but the results suggest some factor other than ACTH may be involved in modulating adrenal androgen secretion.

The negative feed-back system responds to an increase in circulating glucocorticoid levels by diminishing the secretion of ACTH. Administration of exogenous glucocorticoid therefore reduces plasma cortisol levels and also diminishes the ability of the pituitary–adrenal system to respond to stress—a side effect which is well recognized by clinicians. This effect can be observed and quantified by using insulin hypoglycaemia as a test stimulus and such studies have shown that even relatively very small doses of glucocorticoid given on a daily basis will produce some inhibition of pituitary adrenal response to stress (Fig. 8), and larger doses lead to marked, and sometimes, long standing inhibition [4, 5]. Following such therapy, reversal of the concomitant adrenal cortical atrophy can be achieved by the administration of ACTH. But even if adrenal cortical integrity is achieved in this way, suppression of ACTH release is still present and this takes some time to resolve. These observations are, of course, compatible with the model of negative feed-back illustrated in Fig. 1.

It is therefore puzzling that patients who are treated with ACTH demonstrate a very different pattern of response when tested by insulin hypoglycaemia. ACTH given chronically maintains elevated circulating levels of cortisol, which are therapeutically just as effective as exogenous glucocorticoid in patients with steroid sensitive disorders such as asthma. It would therefore be predicted from the model that endogenous ACTH release would be suppressed by ACTH therapy and just as with exogenous steroid administration, pituitary responsiveness to stress would be inhibited. But this is not so. Patients given long-term ACTH therapy generally maintain an excellent response to stress as measured by insulin hypoglycaemia [6], contrary to what would be predicted (Fig. 9). Thus, in some way, ACTH administration appears to protect the hypothalamic system from steroid suppression. The mechanism is not known, but the therapeutic implications of a better understanding of this phenomenon are clear.

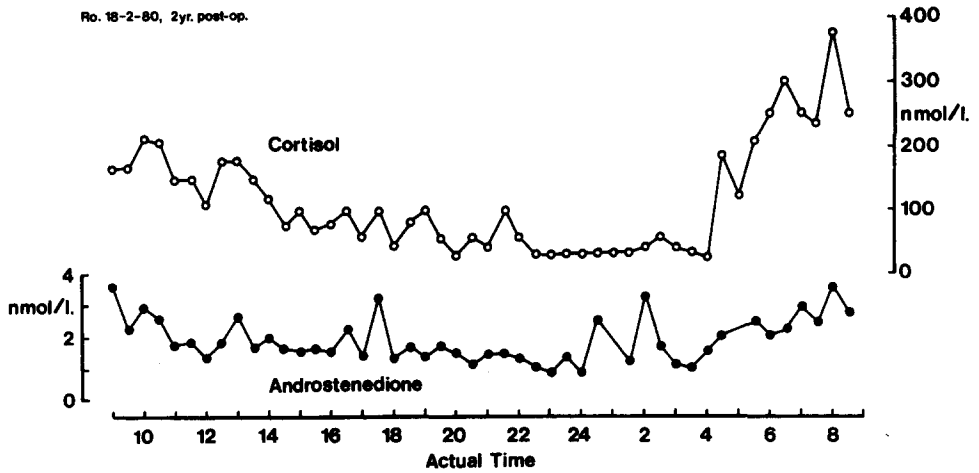

Fig. 7. Diurnal changes in plasma cortisol and androstenedione levels in a patient in whom a pituitary tumour has been removed.

One of the best known disorders of adrenal cortical secretion is Cushing's disease. It is characterized by autonomous cortisol secretion—a situation in which the negative feedback system is no longer capable of maintaining pituitary–adrenal activity within normal limits. The pathophysiology of this process is still not well understood, but it is characteristic of patients with Cushing's disease that they no longer show the fall in plasma cortisol levels in response to the administration of exogenous glucocorticoid which is seen in control subjects. Indeed, the dexamethasone suppression test has become the key diagnostic procedure in the investigation of suspected Cushing's disease. The test is usually performed by administering dexamethasone orally and then observing the change in the level of plasma cortisol or in the amount of cortisol metabolites excreted into the urine. As an alternative, dexamethasone may be given i.v. and plasma cortisol levels followed by sampling at frequent intervals over a period of about 2 h [7]. This procedure in normal subjects causes a smooth and steady fall in cortisol levels as shown in Fig. 10. When patients with Cushing's disease are studied in this way it is possible to observe the blunted

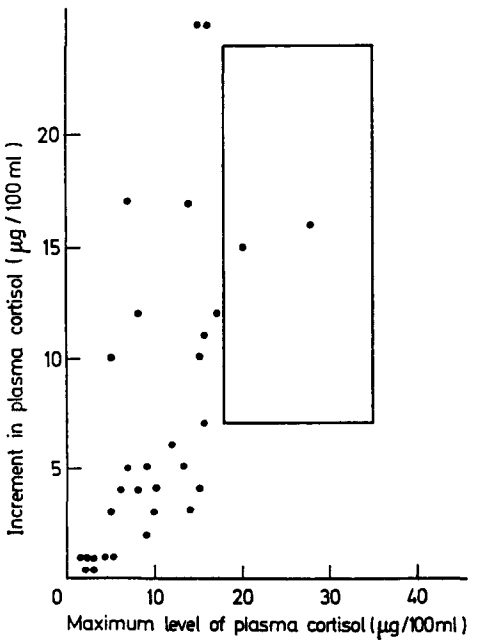

Fig. 8. The results of insulin stress tests in a group of patients receiving daily steroid therapy. The data showed the maximum plasma cortisol level achieved and the increment. The rectangle indicates the limits found in control subjects.

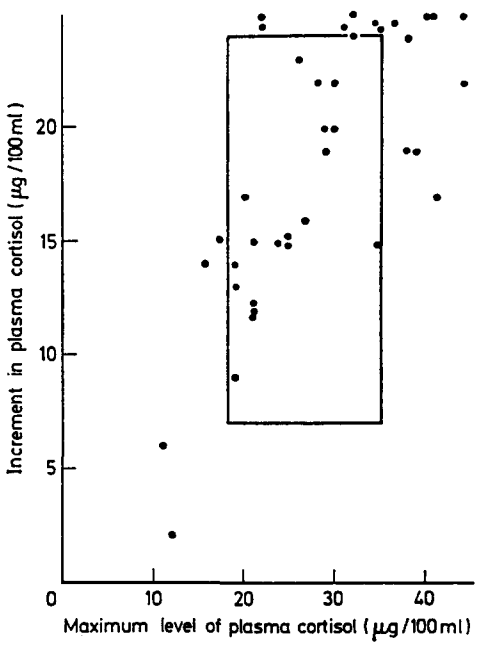

Fig. 9. Results of insulin stress tests in a group of patients receiving daily corticotrophin therapy. The details are as for Fig. 8.

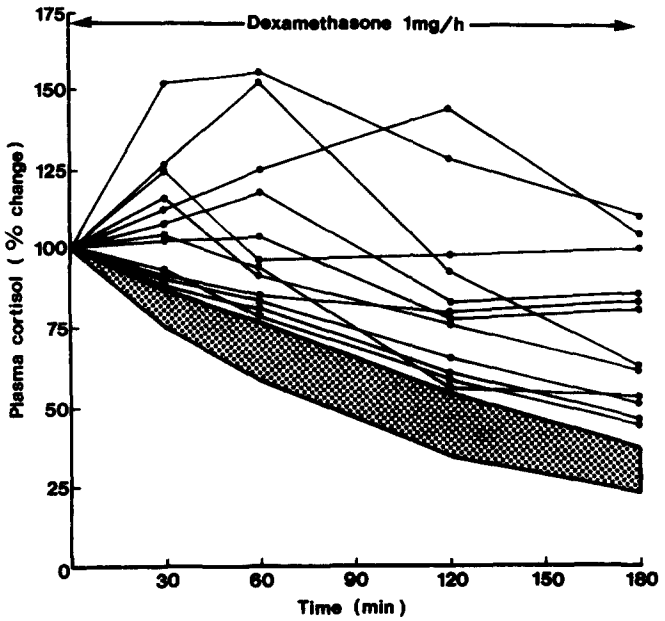

Fig. 10. Plasma cortisol levels, expressed as a percentage of the resting level, in control subjects (dotted area) and 12 patients with Cushing's disease (●——●), during the infusion of dexamethasone.

effect on pituitary adrenal activity, since the plasma cortisol levels decline in concentration at a rate which is much slower than that seen in normal subjects. However, not only is the response blunted in these patients but in the majority of subjects with Cushing's disease studied in this way, dexamethasone initially causes an increase in plasma cortisol levels, thus demonstrating an apparent positive feed-back effect (Fig. 10). Possibly this is revealing some fundamental abnormality in Cushing's disease, and one which may, if explored further, enlarge our understanding of the aetiology of this disorder.

Cushing's syndrome may also be due to the autonomous secretion of cortisol by an adrenal cortical tumour. As predicted by the model in Fig. 1, ACTH secretion is suppressed in response to the elevated cortisol levels. After removal of a unilateral tumour, there is, as expected, marked depression of pituitary adrenal function. This is similar to that seen in patients who have received long courses of treatment with a glucocorticoid, but in contrast to these patients, who will eventually recover pituitary adrenal function, patients with Cushing's syndrome with adrenal cortical tumours appear to suffer a marked degree of suppression [5] which in some cases seems to be irreversible. Why there should be such a marked contrast in these two groups of subjects in response to steroid suppression is unclear, but again, the observation demonstrates our lack of complete understanding of how cortisol and neuroendocrine control mechanisms interact.

Modern techniques of steroid biochemistry have opened many new vistas, especially in the area of molecular biology, and our knowledge of hormonal events at the cellular level has widened considerably. A combination of up-to-date *in vitro* techniques, together with further *in vivo* studies should help solve the problems outlined in this paper.

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