Although it is more than 100 years since Addison first drew attention to the vital importance of the adrenal glands, it was not until 1930 that it became generally accepted that the cortex is their life-maintaining part. It also became evident that increased activity of the adrenal cortex is an essential part of the body's response to stress and is dependent upon stimulation of the adrenal cortices by an adrenocorticotrophic hormone (ACTH) secreted by the anterior pituitary gland. In the 1930's a remarkable stimulus to interest in the physiology of the adrenal cortex was provided by Selye's claims that various "diseases of adaptation" result from abnormal adrenocortical responses to stress. An even greater impetus to research came almost 20 years later with Hench's demonstrations of the remarkable effectiveness of adrenal cortical steroids (corticosteroids or corticoids) in the treatment of various allergic and inflammatory conditions. The foundations of Neuroendocrinology were laid when Harris showed that the release of ACTH, in addition to that of other anterior pituitary hormones, is controlled by the hypothalamus. In recent years attention has been focused on the numerous polypeptides which affect the functional activity of the pituitary gland, and our understanding of the mechanisms which control their secretion is advancing rapidly. At the same time, the frequent indiscriminate use of the many sophisticated methods, particularly those involving radioimmunoassays, which have been exploited for their investigation has often produced a considerable amount of data which have done nothing but add to our confusion!

Chemistry of the corticosteroids

Adrenocortical extracts effective in the treatment of Addison's disease were first prepared in 1930. They were believed to contain only one hormone, but chemists soon began to show that a very large number of steroids could be isolated from these extracts. However, some of these steroids were devoid of biological activity and others were artificial products of the extraction process.

It is now known that the adrenal cortex secretes mainly the corticosteroids aldosterone, cortisol and corticosterone (fig. 1) and small quantities of androgens. Most mammals secrete all three corticosteroids, but the ratio of cortisol to corticosterone varies according to the species. Man produces mainly cortisol, the rat mainly corticosterone and the dog approximately equal amounts of the two. The adrenals of a normal healthy adult man secrete approximately 25 mg of cortisol per day and the concentration of the steroid in the blood varies in a circadian pattern, associated with light-dark and sleep-wake cycles, with the lowest concentration occurring at about midnight and the highest at about 6 a.m. Much of the cortisol in the circulation is bound to a plasma protein termed transcortin. The plasma cortisol concentration may be increased enormously in
stress (heat, cold, injury, infection, emotion, etc.). It is also increased markedly in pregnancy but, in this condition, there is a corresponding increase in transcortin in blood. The daily production of aldosterone is considerably less than that of cortisol and its concentration in blood is correspondingly lower. It also exhibits a circadian pattern in its plasma concentration which appears to result mainly from alterations in posture.

The corticosteroids are synthesized from adrenal cholesterol and are released into the circulation, according to the requirement of the organism, as soon as they are synthesized. The production of cortisol takes place in the zona fasciculata and zona reticularis and is dependent upon the action of the adrenocorticotrophic hormone. The synthesis of aldosterone occurs in the zona glomerulosa, is less dependent upon ACTH and takes place partly in response to changes in blood volume and in the sodium-potassium balance. A more important factor in the control of aldosterone secretion is the renin-angiotensin mechanism. Renin, secreted by the juxtaglomerular cells of the kidney in response to changes in renal blood flow and to sympathetic stimulation of β-adrenoceptors, acts on angiotensinogen in the blood to produce the decapeptide angiotensin I, which is converted by an enzyme mainly present in the lungs to the octapeptide angiotensin II, which stimulates the production of aldosterone by the zona glomerulosa cells. The principal stages in the biosynthesis of corticosteroids are shown in figure 2. Steroids other than those depicted in figure 1 may also be formed in small amounts, for example 18-hydroxy-11 deoxycorticosterone. Some may be secreted in increased amounts in certain disorders of the adrenal cortices and the symptoms of a particular condition may even be predicted from knowledge of the physiological properties of the steroids involved.

**Physiology of the corticosteroids**

The corticosteroids appear to possess ubiquitous effects in the body and to exert intricate actions on almost every metabolic process. A simple view of their actions may be obtained from a consideration of the effects of adrenalectomy in experimental animals or adrenocortical insufficiency as in Addison’s disease. These include electrolyte metabolic defects, carbohydrate metabolic defects and susceptibility to stress. Removal of the adrenal glands results in an inability to re-absorb sodium and chloride in the distal renal tubules. The concomitant water loss results in dehydration which leads to hypotension, diminished renal blood flow and hence an increase of blood non-protein nitrogen. At the same time serum potassium concentration increases, probably as a result of inability to excrete potassium and because of the passage of potassium ions from intracellular to extracellular fluid. The salt-retain-
omized animals and Addisonian patients can be kept alive with diets containing a high sodium content. The electrolyte metabolic defects result from the absence of aldosterone which acts normally on specific receptors mainly in the distal renal tubules, but also in the sweat gland and the colon, to promote the reabsorption of sodium ions and the excretion of potassium and hydrogen ions.

The defects in carbohydrate metabolism which follow adrenocortical insufficiency are manifested by hypoglycaemia and low tissue glycogen concentrations because the peripheral utilization of glucose is accelerated and the ability of the liver to convert amino acids to glycogen is reduced. These metabolic defects result from insufficiency of cortisol which, in its effects on carbohydrate metabolism, tends to oppose those of insulin. Thus, for example, it inhibits the uptake of glucose by fat cells. It promotes increased glyconeogenesis by the liver and stimulates protein catabolism.

It is well known that adrenalectomized animals and patients with impaired adrenocortical function are very sensitive to all types of stress, such as heat, cold, injury or infection. In a patient with Addison's disease stress may precipitate an "adrenal crisis" characterized by prostration and peripheral circulatory failure. In normal animals, stress causes a rapid increase in the blood concentration of cortisol, which is accompanied by appropriate changes in carbohydrate and protein metabolism and which is essential for the organism to withstand the stress. Animals with adrenocortical insufficiency can be protected against stress by treatment with appropriate doses of cortisol, but administration of the steroid to normal animals does not appear to confer any additional resistance to a stressful stimulus.

Other effects of adrenocortical insufficiency, which can be corrected by maintenance therapy with cortisol, include muscle weakness and emotional disturbances.

The administration of corticosteroids to animals with adrenocortical insufficiency corrects the disturbed electrolyte and carbohydrate metabolism and increases their ability to withstand stress. The steroids which are not oxygenated in the C11 position (e.g. 11-deoxycorticosterone) are particularly active on electrolyte metabolism and are called "mineralocorticoids" and those oxygenated in the C11 position (e.g. cortisol) are more active on carbohydrate metabolism and in providing protection against stress and are called "glucocorticoids". This is not a very satisfactory classification because the glucocorticoids possess considerable mineralocorticoid activity and the mineralocorticoid aldosterone (which is oxygenated at C11) also possesses glucocorticoid activity. However, 11-deoxycorticosterone has no effect on carbohydrate metabolism. The administration of large doses of corticosteroids to normal animals produces pharmacological effects, many of which are exaggerations of the responses which lower doses produce in correcting adrenocortical insufficiency. Thus the corticosteroids cause retention of salt and water, hyperglycaemia and glycosuria (leading to "steroid diabetes") and a negative nitrogen balance. These effects may be seen in patients suffering from adrenocortical hyperactivity or receiving therapy with corticosteroids.

Subjection of a animal to stress results in the metabolic changes associated with increased adrenocortical activity. Stress causes hyperglycaemia, glycosuria and increased nitrogen excretion in normal but not in adrenalectomized animals. Treatment of adrenalectomized animals with very small doses of glucocorticoids causes no metabolic changes. However, subjection of corticosteroid-treated, adrenalectomized animals to stress results in the usual metabolic changes. These and other similar observations suggest that the glucocorticoids, which affect the metabolic process profoundly when given in large doses, normally play a supportive role in the body. They exert a permissive rather than a causal effect in producing stress-induced metabolic changes. In addition to their permissive role, the corticosteroids have a normalizing effect on many functions of the body. Thus, for example, the glucocorticoids promote salt retention in Addisonian patients if their salt intake is too little and salt excretion if it is too great.

Pharmacological doses of glucocorticoids, but not mineralocorticoids, inhibit the inflammatory reaction of tissue to injection, injury etc. They diminish capillary permeability and suppress the formation of granulation tissue. They inhibit wound healing and reduce anaphylactic reactions. Their mode of action in producing these effects has not been understood for many years, but it now seems clear that they work by releasing a polypeptide, termed macrocortin, from leucocytes. Macrocortin inhibits the activity of the enzyme, phospholipase A2, which catalyses the formation of arachidonic acid from phospholipids. Thus, the corticosteroids inhibit the first stage in the biosynthetic pathways leading to the production of the prostaglandins and the leuko-
triene, both of which are involved in inflammatory and allergic reactions (Flower, 1981).

The adrenocorticotropic hormone

The adrenocorticotropic hormone (corticotrophin, ACTH), which controls the functional activity of the adrenal cortices, is a comparatively simple linear polypeptide of 39 amino acid residues (fig. 3). The N-terminal 1–24 amino acid sequence is essential for biological activity, but the C-terminal 25–39 sequence is not. The amino acid composition of the C-terminal varies slightly according to the species. A synthetic polypeptide identical with the N-terminal 1–24 sequence is available commercially as tetracosactrin. The hormone is released continuously from the pituitary gland and its concentration in blood varies in a circadian pattern similar, not surprisingly, to that of blood cortisol concentration. It is released rapidly in increased amounts in conditions of stress. It stimulates receptors on the cell membranes of the adrenal cortical cells, increasing adenyl cyclase activity which, in turn, causes an increase in intracellular cyclic AMP, the "second messenger" responsible for the conversion of cholesterol to pregnenolone. Thus, its secretion is followed more slowly by the marked increase in blood cortisol concentration which appears necessary for the organism to withstand the stress. ACTH has a considerably shorter half-life in blood than do the corticosteroids and it is destroyed in a few minutes by peptidase enzymes.

ACTH is formed in specialized anterior pituitary cells called corticotrophs. It is stored as part of a large precursor molecule, pro-opiomelanocortin (POMC), from which it is liberated into the blood stream. POMC is a polypeptide containing 265 amino acids which include the ACTH sequence in addition to those of several of the endogenous opioid peptides, for example β-lipotrophin, β-endorphin and met-enkephalin (fig. 4). These are released from the anterior pituitary gland, together with ACTH, and may act not only in the modulation of pain perception, but also as co-hormones in the regulation of the adrenocortical response to stress.

Control of ACTH secretion

The physiological effects of corticotrophin depend upon its ability to stimulate the adrenal cortices to increase their output of the glucocorticoids which, in turn, are responsible for widespread metabolic effects. When an animal is subjected to stress, ACTH (released rapidly from the pituitary gland) causes increased activity of the adrenal cortices. The resulting increased blood and tissue concentrations of corticosteroids appear to be essential for the animal to withstand stress. Although it is well

\[\text{TETRACOSACTRIN 1-24}\]

\[\text{α MSH 1-13}\]

Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro-

\[1\ 2\ 3\ 4\ 5\ 6\ 7\ 8\ 9\ 10\ 11\ 12\ 13\ 14\ 15\ 16\ 17\ 18\ 19\ 20\ 21\ 22\ 23\ 24\]

Asp-Ala-Gly-Glu-Asp-Glu-Ser-Ala-Glu-Ala-Phe-Pro-Leu-Glu-Phe

\[25\ 26\ 27\ 28\ 29\ 30\ 31\ 32\ 33\ 34\ 35\ 36\ 37\ 38\ 39\]

25-33 varies with species

\[\text{HUMAN CORTICOTROPHIN}\]

1-39

Fig. 3. Structural formula of the adrenocorticotropic hormone.
known that the secretion of the adrenal cortex in response to stress is governed by the adrenocorticotrophic activity of the pituitary gland, the exact mechanisms by which the secretion of ACTH is controlled are still not fully understood. It is clear that ACTH secretion is influenced by neurohumoral transmitter(s) from the hypothalamus, the production of which may be affected by central inhibitory and excitatory nervous pathways as well as by the circulating corticosteroids. However, the chemical composition of the transmitter substance(s), the precise nature of the nervous pathways controlling its secretion and the mode and locus of action of the corticosteroids are still enigmatic.

**Role of the hypothalamus**

Figure 5 illustrates diagrammatically the nerve and blood supply to the pituitary gland. The rapidity with which ACTH is secreted in response to stress suggests the existence of a neural or neurohumoral mechanism controlling the adrenocorticotrophic activity of the pituitary gland. A direct neural mechanism is unlikely to be involved, since the adenohypophysis receives few nerve fibres. Harris and his colleagues (Harris, 1955) suggested that the secretion of ACTH is controlled by a corticotrophin releasing factor (CRF) secreted in the hypothalamus and conveyed to the adenohypophysis by the hypothalamo–hypophyseal portal blood vessels. The importance of the hypothalamus in this respect was made evident by their experimental work in small mammals in which they showed that electrical stimulation of the median basal hypothalamus causes ACTH secretion and that destruction of the same region prevents the release of the hormone in response to stress. However, there were many objections to the concept of the hypothalamus exerting a functional dominance over the adenohypophysis, mainly on the grounds that pituitary stalk section usually fails to produce any marked change in adenohypophyseal activity. Such objections were refuted and the importance of the hypothalamo–hypophyseal vessels in the control of pituitary adrenocorticotrophic activity was firmly established when Harris showed that regeneration of the vascular connections between the hypothalamus and the adenohypophysis occurs unless transection of the pituitary stalk is accompanied by the insertion of a plate to prevent revascularization. Confirmation of the existence in the hypothalamus of a corticotrophin releasing factor came when it was shown that extracts of hypothalamic tissue stimulate ACTH secretion when injected into animals with hypothalamic lesions or when incubated with pituitary tissue in vitro. Several hypothalamic hormones which control the secretion of different anterior pituitary hormones have subsequently been characterized but, although CRF was the first of these to have its existence postulated, its chemical nature is still unknown. Several substances have been isolated from hypothalamic extracts, hypophyseal portal blood or even blood from the peripheral circulation, all of which appear to be capable of releasing ACTH. Most of the active compounds are polypeptides and many have structures not unlike that of vasopressin.
At one time, it was suggested that the corticotrophin releasing factor and vasopressin are identical. Thus, rats in which the stress-induced release of ACTH has been abolished by hypothalamic lesions also exhibit diabetes insipidus. Furthermore, the release of ACTH can be elicited in these animals by the injection of vasopressin. It is now evident that vasopressin is probably not the neurohormonal transmitter responsible for ACTH secretion and there can be marked differences between the antidiuretic and the ACTH-releasing activities of hypothalamic extracts. Both hypothalamic extracts and vasopressin cause dose-related increases in ACTH production by segments of anterior pituitary tissue in vitro. From a carefully controlled study of the characteristics of the dose–response relationships in addition to those of hypothalamic extracts from rats with inherited diabetes insipidus (Brattleboro rats), Buckingham (1982) concluded that vasopressin is not the corticotrophin releasing factor, but that it acts synergistically with the hypothalamic hormone and is essential for the full expression of hypothalamo–pituitary–adrenocorticotrophic activity. A linear polypeptide containing 41 amino acid residues (CRF-41) (fig. 6) has recently been isolated (Vale et al., 1981). It appears to fulfil some of the criteria for a physiological CRF. It stimulates ACTH secretion by anterior pituitary tissue in vivo and in vitro. However, its presence in hypothalamic extracts does not account for all their activity and its action is potentiated by vasopressin. The chemical nature of the corticotrophin releasing factor remains

\[
\begin{align*}
\text{H-Ser-Gln-Glu-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-Pha-His-Leu-Leu-Arg-} \\
\text{Glu-Val-Leu-Glu-Met-Thr-Lys-Ala-Asp-Gln-Leu-Ala-Gln-Gln-Ala-His-} \\
\text{Ser-Asn-Arg-Lys-Leu-Leu-Asp-Ile-Ala-NH}_2 \\
\end{align*}
\]

Fig. 6. Corticotrophin releasing factor (CRF-41).
an enigma and progress is hampered by the lack of specificity and doubtful validity of some of the methods which are being used for its detection and estimation. Probably, it is not a single entity but a complex, containing several polypeptides, which may include CRF-41 and vasopressin acting synergistically.

Corticotrophin releasing factor is secreted by neurones in the hypothalamus which terminate on the vessels of the primary plexus of the hypophyseal portal system. Thus, the releasing factor complex is secreted directly into the portal blood. The activity of the CRF-producing neurones is under the control of afferent impulses from higher centres in the brain. The circadian rhythm in ACTH secretion is under the influence of afferent pathways different from those controlling the release of the hormone in response to stress. These afferent pathways appear to be cholinergic and the circadian periodicity in ACTH release, but not the stress response, can be abolished by drugs such as atropine which block muscarinic acetylcholine receptors (Krieger et al., 1968). Interruption of the anterior connections to the hypothalamus also obliterates the circadian rhythm without preventing the release of ACTH in response to stress, whereas cutting the dorsal, lateral and posterior connections has the opposite effect (Halasz, Slusher and Gorski, 1967).

Data from experiments involving electrical stimulation or production of lesions in discrete areas of the brain suggest that the hippocampus and the amygdala are particularly important areas from which inhibitory and excitatory stimuli emanate. Attempts to characterize the neurones which influence the secretion of CRF have been made using brain implants of various drugs. However, the results are often difficult to interpret because of the lack of specificity of action of the drugs used and their tendency to diffuse to other areas of brain. A new approach to the problem (Buckingham and Hodges, 1977; Jones, Hillhouse and Burden, 1977) was made by measuring the CRF output of rat hypothalami incubated in vitro in the presence of neurotransmitter substances. The results have provided valuable information on the nature of the hypothalamic receptors which control CRF secretion with obvious implications regarding their innervation. It now appears that central cholinergic nervous pathways stimulate and that GABA-ergic and adrenergic pathways inhibit the secretion of CRF. CRF secretion is also affected markedly by opioid substances which may act on receptors in the hypothalamus, on the neurones which supply the CRF producing cells or on higher centres in the brain. Figure 7 illustrates some of these possibilities. CRF production is also influenced by 5-hydroxytryptaminergic fibres, but whether their effect is inhibitory or stimulatory is equivocal.

Role of corticosteroids

A negative feed-back mechanism involving the blood corticosteroid concentration is believed to be of major importance in regulating the secretion of corticotrophin. Exploitation of highly sensitive, precise and specific cytochemical bioassay methods (Alaghband-Zadeh et al., 1974) has shown clearly the inverse correlation between the blood concentration of ACTH and that of cortisol in normal subjects receiving infusions of cortisol. A similar inverse relationship between the concentration of ACTH in the blood and the pituitary gland and the concentration of corticosterone in the blood has been demonstrated in intact, adrenalectomized and adrenalectomized rats treated with corticosterone (Buckingham and Hodges, 1974, 1975). There can be no doubt that the blood corticosteroids are concerned with the regulation of hypothalamo-pituitary-adrenocortical activity under basal, non-stress conditions, but the importance of a negative feedback mechanism in controlling the release of ACTH in response to stress is not clear. Sayers and Sayers (1947) suggested that stress causes increased utilization of corticosteroids by the peripheral tissues and that the resulting low blood concentration of the steroids acts as a stimulus to the pituitary gland to increase its output of ACTH. The hypothesis was advanced mainly as the result of experiments, in rats, which showed that the release of ACTH in response to stress can be inhibited by treatment with corticosteroids. It received convincing support from demonstrations that blood ACTH concentrations are increased in adrenalectomized rats and in patients with Addison's disease. Since the hypothesis implies that ACTH release follows a decrease in plasma corticosteroid concentration, it was disputed on the grounds that stress causes an increase and never a decrease in plasma corticosteroid concentration. Objections made on this basis were countered by the suggestion (Yates et al., 1961) that the immediate effect of stress is to increase the set point of the corticosteroid-sensitive controller. Thus the pituitary gland is provided with a signal similar to a decrease in blood corticosterone concentration and ACTH secretion occurs until the new set
Fig. 7. Possible relationship of opioid-peptidergic neurones to other neurones controlling CRF secretion.

point in plasma corticosteroid concentration is reached. This "variable set point" hypothesis has been tested in many laboratories, but it has not been confirmed.

It is well established that prolonged changes in the concentrations of circulating corticosteroids influence markedly the response of the hypothalamo-pituitary-adrenocortical system to stress. The release of ACTH is easily suppressed by large doses of corticosteroids. However, the degree of impairment of pituitary function which such doses produce is not directly proportional to blood corticosteroid concentration. In rats treated with corticosterone and subsequently subjected to stress, no impairment of pituitary corticotrophic function occurs when the plasma corticosterone concentration is greatest, but ACTH release is inhibited after a considerable delay and at a time when the plasma corticosterone concentration has returned to resting values. Such data suggest that a delayed, corticosteroid-sensitive, feedback mechanism is involved in the control of the secretion of ACTH. Recently a "rapid" feedback mechanism has also been implicated and it has been shown that, in rats treated with corticosterone, there is a short period of suppression of hypothalamo-pituitary-corticotrophic activity occurring almost immediately after the administration of exogenous steroid which, some workers consider, is dependent upon the rate at which the plasma corticosterone concentration increases (Jones, Brush and Neame, 1972). Hence, although it is unlikely that increased output of ACTH is a direct result of a decrease in blood corticosteroid concentration, the possibility cannot be eliminated, that the corticosteroids play some part in controlling the response of the hypothalamo-pituitary-adrenocortical system to stress. Corticosteroid-sensitive controllers of ACTH release appear to be present in many regions of the brain-hypothalamo-pituitary system. There is a considerable amount of evidence that the corticosteroids exert their inhibitory effects by acting on specific receptors in the adenohypophysis, the hypothalamus and a variety of centres in the brain. Many studies have involved work in vitro on pituitary and hypothalamic tissue or experiments in vivo.
using brain implants of corticosteroids. The former suffer from the limitation that data from experiments in vitro cannot always be translated to the situation in vivo, and the latter are often difficult to interpret because the concentration of the steroid may be unphysiologically high or it may diffuse from the site of injection. Both in vivo and in vitro work suggest that the functional activity of the hypothalamus is more sensitive to the inhibitory action of the corticosteroids than is that of the anterior pituitary gland. Perhaps the receptors in the hypothalamus represent the normal corticosteroid-sensitive controllers of ACTH release and those in the adenohypophysis and the brain are stimulated only for maximal suppression of hypothalamo-pituitary-adrenocortical activity (Buckingham, 1980).

Impairment of the hypothalamo-pituitary-adrenocortical response to stress is a hazard associated with the clinical use of the corticosteroids. For example, anaesthesia may be a life-threatening situation in a patient who has been on prolonged treatment with these compounds because of his inability to exhibit a normal adrenocortical response.
to stress. He requires adequate “cover” with large doses of corticosteroids. Suppression of adrenocortical function may last for several months. Its intensity appears to be related more to the frequency of dosage than to the duration of treatment or to the absolute amount of corticosteroid administered. The impaired activity of the system results both from a failure of the hypothalamic-pituitary-adrenocortical system and from a reduced ability of the adrenal cortex to respond to the hormone, but it is not clear which is the more important. A clearer understanding of the physiology of the hypothalamic-pituitary-adrenocortical system is still required for the solution of this and other problems associated with corticosteroid therapy.

CONCLUSION

A considerable amount of attention continues to be focused on the physiology and pharmacology of the corticosteroids and corticotrophin because of their therapeutic importance. In spite of the use of sophisticated experimental methods, the precise mechanisms controlling the secretion of ACTH, the identity of the corticotrophin releasing factor and many other aspects of hypothalamic-pituitary-adrenocortical function are still not completely understood. There are too many papers in endocrinology journals which describe the results of poorly designed, badly controlled experiments. The indiscriminate use of many radioimmunoassay methods has led to the dissemination of spurious data. So-called bioassay methods have been used without regard to the fundamental principles underlying their use. Recently, accurate, specific, sensitive and precise methods for the biological assay of ACTH and other hormones have been developed. Such methods will undoubtedly play a vital role not only in the validation of new radioimmunoassay and other assay methods, but also in the provision of important information on many aspects of endocrinology and, hence, lead to a better understanding of the physiology of the hypothalamic-pituitary-adrenocortical system.

SUMMARY

Control of the secretion of ACTH appears to involve several mechanisms. It is dependent upon the release, from neurones in the hypothalamus, of corticotrophin releasing factor, which is probably a complex including CRF-41 and vasopressin. The secretion of the complex is influenced by various central inhibitory and excitatory nervous pathways. The releasing factor is conveyed by the hypophyseal portal vessels to the adenohypophysis where it stimulates the secretion of ACTH. The corticosteroids exert a profound control over the basal secretion of ACTH, but only modulate the pituitary adrenocorticotrophic response to stress. The mechanisms which may be involved are summarized in figure 8.

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