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The hypothalamo-pituitary-adrenocortical system

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I joined the Pharmacology Department at the School of Pharmacy not long after the appearance of the first reports that corticotrophin (ACTH) and the corticosteroids were remarkably effective in the treatment of rheumatoid arthritis. The publications provided an intense stimulus to research in pituitary-adrenocortical physiology and when I arrived at the Square vigorous attempts were being made by Professor G. A. H. Buttle and his colleagues to set up facilities for the biological standardization of corticotrophin. Gerald Cox and Kenneth Adam were working on the method described by Sayers, Sayers & Woodbury (1948) which depends upon the ability of the hormone to reduce the ascorbic acid content of the adrenal glands in the hypophysectomized rat. Hypophysectomy was essential to avoid the mobilization of endogenous ACTH but the technique requires considerable skill and infinite patience. At that time no-one disputed the role of the corticosteroids in the control of corticotrophin secretion and it appeared feasible to replace the hypophysectomized animals necessary for the Sayers' assay by rats in which the mobilization of endogenous ACTH had been prevented by previous treatment with corticosteroids. The task was not as easy as it appeared at first but ultimately a biological assay method was developed which obviated the need for hypophysectomy (Buttle & Hodges, 1952). Thus my interest in the hypothalamo-pituitary-adrenocortical axis began.

Corticotrophin, which controls the functional activity of the adrenal cortices, is a comparatively simple polypeptide. Chemically it consists of a straight chain of 39 amino acids the terminal 15 of which can be split off without the loss of biological activity. The composition of this terminal group varies slightly according to the species. A synthetic polypeptide with the 1–24 amino acid sequence has the same biological activity as the naturally occurring hormone and is available commercially as tetracosactrin.

The action of corticotrophin depends upon its ability to stimulate the adrenal cortices to increase their output of glucocorticoids which, in turn, are responsible for widespread metabolic effects. It is now clear that when an animal is subjected to stress ACTH is released rapidly from the pituitary gland and causes increased activity of the adrenal cortices. The resulting elevated blood and tissue concentration of corticosteroids appears to be essential for the animal to withstand the stress. It has been firmly established that the secretion of the adrenal cortex in stressful situations is governed by the adrenocorticotrophic activity of the pituitary gland but the exact mechanisms by which the secretion of ACTH is controlled are still not properly understood. Views concerning the control of ACTH secretion have varied considerably and are still changing. It is not very long since the bulk of the evidence seemed to point to the all important function of the blood corticosteroids in the control of ACTH secretion. Subsequently adrenaline appeared to play a major role and later the function of the hypothalamus became increasingly evident. Now adrenaline is apparently unimportant and it is known that ACTH secretion is controlled by the release of neurohumoral transmitter substances from the hypothalamus which, in turn, may be influenced by central inhibitory and excitatory nervous pathways as well as by the circulating corticosteroids.

The role of corticosteroids

Despite some evidence to the contrary, it is still widely believed that a negative feedback mechanism involving the blood corticosteroid concentration is of major importance in regulating the secretion of corticotrophin. In 1948 Sayers & Sayers suggested that stress causes increased utilization of corticosteroids by the peripheral tissues and that the resulting low blood level of the steroids acts as a stimulus to the pituitary gland to increase its output of ACTH.

Most of the evidence that the secretion of corticotrophin is controlled by changes in the blood level of corticosteroids has been provided by demonstration that large doses of corticoids depress the secretion of ACTH and that animals with adrenocortical insufficiency exhibit high circulating ACTH levels. The release of ACTH in response to stress can be

suppressed only by very high non-physiological doses of corticosteroids. High circulating levels of ACTH do occur in animals with adrenocortical insufficiency but only after the pituitary stores of the hormone have increased considerably. It is unlikely, therefore, that the increased output of ACTH which occurs in response to stress is controlled by variations in the blood corticoid level.

A new concept for the role of blood corticoids in controlling ACTH secretion was advanced by Yates, Leeman & others (1961). They suggested that the physiological mechanism controlling the release of ACTH does involve negative feedback by the corticosteroids in the blood and that the immediate effect of stress is to raise the set point of the controller. Thus the pituitary gland is provided with a signal similar to a drop in blood corticoids and ACTH secretion occurs until the new set point in plasma corticoid concentration is reached. This variable set point hypothesis has been tested in many laboratories and has not been confirmed. However, in most of the experimental data which appear to disprove the hypothesis, the fact has been ignored that most of the corticosteroids are bound to plasma protein and are probably without effect on pituitary activity. With this reservation, the bulk of the evidence available suggests that a negative feedback mechanism is of only minor importance in controlling pituitary adrenocorticotrophic activity.

However, a possibility that corticoids play some part in ACTH secretion cannot be excluded. Adrenalectomized rats exhibit a marked rise in circulating corticotrophin in response to mild stress stimuli which appear to produce no change in blood ACTH in intact rats (Hodges & Jones, 1964). Thus adrenalectomy results in overactivity of the adenohypophysis and this can be prevented by corticosterone treatment. Furthermore, adrenalectomy causes an initial *fall* in pituitary ACTH concentration which can also be prevented by physiological doses of corticosterone. In contrast the release of the hormone in response to stress can be prevented only by very large doses of the steroid.

The degree of impairment of pituitary function which large doses of steroids undoubtedly produce has been assumed to be directly proportional to the blood corticoid concentration. Such an assumption is incorrect and experiments in which blood corticosteroid concentrations and the degree of pituitary inhibition have been measured together have revealed that there is no direct correlation between the two. In rats treated with corticosterone and subsequently subjected to stress, no impairment of pituitary corticotrophic function occurs when the plasma steroid concentration is greatest but corticotrophin release is inhibited only after a time delay during which the plasma corticosterone concentration has returned to the resting level. Such a time lag suggests the existence of a corticoid sensitive controller of adrenocorticotrophic function in some tissue not readily accessible to the systemic circulation. The hypothalamus has often been suggested as the site of a corticoid sensitive controller. Steroid implants in the basomedial hypothalamus, like electrolytic lesions in the same region, undoubtedly inhibit ACTH secretion. However, the concentration of the steroid around the implants must be so high as to make obscure the physiological significance of such experimental data.

Until comparatively recently further advances in this field have been hampered by the lack of a sensitive method for the accurate determination of corticotrophin. Radio-immunological methods suitable for the assay of many hormones have never been entirely satisfactory for ACTH. Recently a very sensitive, precise and specific cytochemical method was developed by Chayen, Loveridge & Daly (1972) and has been exploited to investigate further the role of corticosteroids in the regulation of corticotrophin (ACTH) secretion (Buckingham & Hodges, 1974, 1975). Pituitary and plasma ACTH and plasma corticosterone concentrations were measured in bilaterally adrenalectomized and adrenal enucleated rats some of which were given replacement therapy with corticosterone. Both the increments in plasma and pituitary ACTH which occur after adrenalectomy and adrenal enucleation may be inversely correlated with the plasma corticosterone concentration but the rise which follows subjection to stress cannot. The data suggest that the corticosteroids are involved in the control of both the synthesis and the basal secretion of ACTH but that they do not affect the stress induced release of the hormone.

The role of the hypothalamus

The rapidity with which ACTH is secreted in response to stress is in accord with 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. It is now well known that the secretion of ACTH is dependent upon the functional integrity of the hypothalamus. Its importance in this respect was made evident by the work of de Groot and Harris

and Hume and Wittenstein (Harris, 1955). They showed independently 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.

Many objections were made to the idea that the hypothalamus exerts 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 by Harris (1955), who showed that regeneration of the vascular connections between the hypothalamus and the adenohypophysis occur unless transection of the pituitary stalk is accompanied by the insertion of a plate to prevent re-vascularization. Thus it became clear that the vascular connections between the hypothalamus and the adenohypophysis (i.e. the hypothalamo-hypophyseal portal vessels) are of prime importance in the control of pituitary adrenocorticotrophic activity. These blood vessels had been described about 20 years previously when it was suggested incorrectly that the blood flows from the adenohypophysis to the hypothalamus. Not until several years later was it established that the principal flow occurs in the opposite direction.

The secretion of corticotrophin in response to stress is initiated by a neurohumoral transmitter substance named corticotrophin releasing hormone or factor (CRH or CRF) secreted in the median basal hypothalamus and conveyed to the adenohypophysis by the hypophyseal portal vessels. The presence of such a factor in hypothalamic extracts and hypophyseal portal blood has often been demonstrated and several substances have been isolated which appear to be capable of releasing ACTH. Most of the active compounds are polypeptides with structures not unlike either melanophore expanding hormone or lysine vasopressin. At one time it was even suggested that CRH is identical with vasopressin. 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 (McCann & Brobeck, 1954). It is now evident that vasopressin is *not* the neurohumoral transmitter responsible for ACTH secretion and there is a marked dissociation between the antidiuretic and ACTH-releasing activities of hypothalamic extracts. However, it may play a part in the sequence of events which lead to corticotrophin release and it has been shown that vasopressin causes ACTH secretion if injected into the median eminence, but not if it is introduced directly into the adenohypophysis. Thus it may provide a stimulus for the release of CRH. The chemical nature of CRH is still not known but a method potentially useful for its identification and assay has recently been developed using pituitary tissue *in vitro*. Pituitary segments are capable of synthesizing ACTH and some of the hormone is released into the incubation medium. Of the many putative neurotransmitter substances tested so far, only arginine and lysine vasopressin increase both the pituitary ACTH content and the amount of hormone released. However, although their effects are dose related the deviation from parallelism of their dose-response lines and those of hypothalamic extracts is highly significant (Buckingham & Hodges, 1976).

The activity of the CRH-producing neurons is under the control of afferent impulses from 'higher centres' in the brain and considerable attention is now being focused on this aspect of neuroendocrinology. Many of the afferent fibres to the hypothalamus are adrenergic and others appear to release dopamine at their endings. Experiments involving either the placement of discrete lesions or the stimulation of discrete areas of the brain are being used to investigate its regulatory effect on hypothalamo-pituitary-adrenal activity. Thus it is becoming increasingly clear that the hippocampus and amygdala exert inhibitory and stimulatory influences respectively on the mechanisms controlling ACTH release.

The circadian ACTH rhythm 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 blocked by cholinoceptive receptor blocking drugs like atropine (Krieger, Silverberg & others, 1968). Similarly, interruption of the anterior connections to the hypothalamus 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 & Gorski, 1967). Furthermore, the mechanisms controlling circadian ACTH periodicity and stress-induced pituitary adrenocorticotrophic activity differ widely in their sensitivity to the inhibitory action of corticoids (Hodges & Mitchley, 1970). Since the basal hypothalamus is part of the final common pathway for ACTH release the difference in the sensitivity of the two mechanisms suggests that the site of action of the corticoids is higher in the central nervous system.

CONCLUSION

Multiple mechanisms, some more sensitive than others to the inhibitory action of the corticosteroids, appear to be involved in controlling the secretion of corticotrophin. Its secretion in conditions of stress is dependent upon the release of a corticotrophin-releasing hormone from nerve endings in the hypothalamus. This is probably a polypeptide similar to but distinct from vasopressin. It is conveyed via the hypophyseal portal vessels to the adenohypophysis where it stimulates the secretion of corticotrophin. The secretion of CRH is influenced by various central inhibitory and excitatory nervous pathways. Although the corticoids may influence corticotrophic function by effects on corticotrophin synthesis and its *basal* rate of release, stress-induced ACTH release does not appear to be initiated by either a fall in the blood corticosteroid concentration or a re-setting of a corticoid sensitive controller.

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