

HYPOTHALAMUS AND GROWTH HORMONE RELEASE*

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For a long time the anterior pituitary was thought to be the bandmaster of the endocrine orchestra. But the beginning of our modern concept of hypothalamic hypophyseal information transfer system can be traced to the studies of Rainer, a pathologist in Bucharest who in 1927 observed the plexus of vessels surrounding the pituitary stalk. Later his pupil Popa described the connections of this plexus and the brilliant studies of Harris and others (2) led to the development of new subspeciality-Neuroendocrinology.

The methods generally used to determine and demonstrate the hypothalamic influence of the endocrine influence of the anterior pituitary are depicted in Table I. It is then clear that to demonstrate changes in the secretion of pituitary hormones it should be possible to estimate the hormone levels in serum which is difficult for most of the pituitary hormones. But the effect of Gonadotrophin release can be easily perceived by observing ovulation and the changes in corticotrophin levels can be detected by studying the target gland—the adrenal cortex. Thus the hypothalamic control was first discovered with respect to gonadotrophins and later with respect to corticotrophin (7) In the case of corticotrophin the releasing factor, the release mechanism, various feedback systems have been studied in great details and the corticotrophin releasing hormone of the hypothalamus has been isolated in nearly pure form. Thyrotropin releasing factor has also been postulated but its detection and characterization have been delayed perhaps due to the fact that thyrotropin release is not normally influenced by hypothalamus to any great extent.

TABLE I

Methods used to establish hypothalamic control

I. To study changes in hormone levels after;

- (a) Pituitary stalk section
- (b) Injury to the specific areas in the hypothalamus
- (c) Stimulation of certain areas of the hypothalamus
- (d) Transplantation of the pituitary
- (e) Incubation of the isolated pituitary glands and studying the effects of hypothalamic extracts.

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II. Characterisation of various hormone releasing factors.

III. To measure the release of hormones in response to the releasing factors

On the basis of the present knowledge, following facts emerge :

- (1) Gonadotrophin release is probably entirely under the hypothalamic control, and the physiological feedbacks probably act at that level.
- (2) Corticotrophin release is largely under hypothalamic control and the feedbacks normally act at that level but certain stimuli and the feedbacks have been shown to affect anterior pituitary directly.
- (3) Thyrotropin can be released in response to hypothalamic releasing factor but pituitary gland is capable of releasing thyrotropin in its absence.

In the case of growth hormone till recently there was no sensitive method for the measurement of serum hormone levels. Neither is there any target organ to study the effects in an acute experiment. Therefore very little was known regarding the factors causing release of growth hormone and its mechanisms. But recently radioimmune assay has been developed for the measurement of serum growth hormone (1) and this has made it possible to study the release mechanisms for this hormone. What follows is the product of personal experience and review of literature.

Radioimmune assay of Growth hormone : The method essentially is as follows :

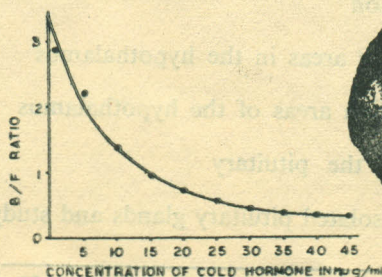
Pure Growth Hormone is tagged with radioactive Iodine (I-131)

A specific antibody is produced to react with human Growth Hormone.

Tagged Growth Hormone and the antibody are incubated in buffer with serial concentrations of cold Growth Hormone.

Antibody bound (B) and free Growth Hormone (F) are separated by chromatography or by second antibody or by adsorption of charcoal. B/F ratios are calculated for each concentration of cold hormone and a graph is plotted (Fig. 1).

ANTISERUM 1:100,000 DILUTION



B/F ratio obtained with serum added in place of cold growth hormone gives the concentration of hormone in the serum which is expressed as mug/ml.

Using this method for serum growth hormone assays, following factors have been shown to cause release of growth hormone from the pituitary :

- (a) Hypoglycemia
- (b) Exercise
- (c) Amino acid infusion—Arginine
- (d) Pyrexia and other kinds of stress.

Hypoglycemia as a stimulus for growth hormone release : Insulin administered intravenously causes growth hormone release (6) which can be shut off by infusion of glucose intravenously or by perfusion of hypothalamic areas with glucose solution. Berson and Yallow in 1963 demonstrated that influences of hypo and hyperglycemia on growth hormone release were subnormal in obese patients. Roth *et. al.* (6) have reported that hypoglycemia was much less effective after pituitary stalk section.

Obesity is being increasingly thought to be due to hypothalamic aberration and it is tempting to infer that failure of hypothalamus to transfer this information of hypoglycemia to the anterior pituitary may be the cause of obesity, for growth hormone causes mobilisation of fat and also helps to maintain adequate blood glucose level thus preventing excessive hunger stimulation.

Exercise and amino acid infusion have both been shown to cause release of growth hormone independent of blood glucose levels and in some cases despite hyperglycemia (3) Both these stimuli are more effective in females than in males. Male sensitivity can be increased by prior administration of stilboestrol. Oestrogens have been shown to get bound to certain areas in the hypothalamus and it is possible that they sensitise the hypothalamus to these stimuli. Whether it is oestrogens or lack of androgens which is responsible for this sensitisation is being actively studied by my colleague Dr. Neila Nichani. From the preliminary studies it appears to be oestrogen dependent.

Pyrogens are known to produce stimulation of hypothalamopituitary—adrenal axis (Wexler *et. al.* 1965). Recently it has been demonstrated that pyrogens cause release of growth hormone from the anterior pituitary (5) and the seat of action is suggested to be hypothalamo-hypophyseal axis. Talahasi *et. al.* (9) have postulated that growth hormone rise that occurs in sleep is not related to hypoglycemia but is associated with the phase of passing into deep sleep. And very recently some progress has been made towards isolation and characterisation of the growth hormone releasing hormone of the hypothalamus (Schally *et. al.* 1968).

Thus it can be concluded that there is sufficient evidence to suspect that a growth hormone releasing factor is liberated from the hypothalamus in response to many stimuli and that this factor causes release of growth hormone from the anterior pituitary though the demonstration and characterisation of this factor remain for the future.

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