Middle Articles

GROWING POINTS

Hormones and the Endocrine System

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The 15 years since 1950 have seen the discovery of aldosterone, calcitonin, and a long-acting thyroid stimulator, and the development of sensitive and specific assay methods for many of the hormones in plasma. Our understanding of many endocrine diseases has greatly increased, even though treatment has not changed dramatically. In this article I propose to deal with some of the more important of these advances.

Pituitary

Anatomically the pituitary gland can be divided into two parts, the anterior lobe and the posterior lobe. At least six hormones are secreted by the cells of the anterior lobe—growth hormone, adrenocorticotrophic hormone (A.C.T.H.), thyrotrophic hormone (T.S.H.), prolactin, follicle-stimulating hormone (F.S.H.), and luteinizing hormone (L.H.). Classically, it has always been considered that two hormones—vasopressin (antidiuretic hormone, or A.D.H.) and oxytocin—are produced by the posterior lobe. But the posterior lobe of the pituitary is merely part of a larger group of structures known as the neurohypophysis, which comprises the median eminence (situated in the floor of the third ventricle), the infundibular stem, and the posterior lobe proper. The neurohypophysis is controlled by the hypothalamus (which itself receives nervous impulses from other parts of the brain), which sends fibres from its nuclei to the hypophysis, forming the hypothalamo-hypophyseal tract. It is now believed that the two posterior pituitary hormones are synthesized in nuclei in the hypothalamus and passed along the nerve fibres to the neurohypophysis, where they are either stored or released into the circulation.

Control of the Anterior Pituitary

The hypothalamus is thought to play a considerable part in the control of the anterior pituitary as well. Thus, destroying localized areas of the hypothalamus has been found to result in absence of the secretion of A.C.T.H., T.S.H., or L.H. Conversely, electrical stimulation of these areas induces the release of these hormones, though direct stimulation of the pituitary itself does not always have this effect. In disease, lesions of these parts of the hypothalamus may give rise to deficient secretion of these hormones. Lesions of other parts of the hypothalamus, on the other hand, may result in the excessive production of hormones by the anterior pituitary—for example, of prolactin. It is thus particularly interesting that cases of spontaneous lactation have been described after operative section of the stalk in man. Hence stimuli from the hypothalamus may have a dual role, in exciting the secretion of

some anterior pituitary hormones and inhibiting that of others.

The pathway of control by the hypothalamus was first described by Popa over 30 years ago. Popa described a miniature portal system of blood-vessels related to the hypothalamus and the pituitary. There are three components to this portal system, two sets of capillaries and the intervening blood-vessels. The proximal set of capillaries is situated around the median eminence and is intimately related to the nerve fibres that make up the hypothalamo-hypophyseal tract. The intervening blood-vessels are clustered around the pituitary stalk, while the second capillary network is situated within the substance of the anterior pituitary gland. The mechanism of control, therefore, seems to be as follows: substances are secreted by the cells of the median eminence or of the hypothalamic nuclei; these then pass downwards in the pituitary portal blood-stream to the cells that secrete the hormones (Fig. 1). Two sets of experiments support this suggestion.

FIG. 1.—Pathway of hypothalamic control of the function of the anterior pituitary.

* Strictly speaking the term "Posterior Lobe" refers to the infundibular process (neural lobe) and its pars intermedia; while the term "Neurohypophysis" refers to the infundibular process, the infundibular stem, and the median eminence.

In the first the anterior pituitary was transplanted to areas outside the skull, and more or less complete deficiencies of some of the hormones resulted. If, however, the gland was removed and then reinserted within or near the sella turcica it usually resumed functioning, the degree of which was correlated roughly with the amount of revascularization of the gland by the portal blood-vessels. The second set of experiments has been concerned with identifying the nature of the hormone-releasing substances. Extracts of tissue from the median eminence and the hypothalamus have been shown to be capable of causing the release of A.C.T.H., T.S.H., and L.H. Analysis has shown that the substances are polypeptides in nature, the A.C.T.H.-releasing factor being very similar in structure to vasopressin.

The other way in which hormone secretion is controlled is by a "feedback" mechanism. Thus raised levels of hydrocortisone in the plasma depress secretion of A.C.T.H. by the pituitary, and raised levels of thyroid hormone that of T.S.H. Again, it seems likely that quite often this mechanism works

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through the hypothalamus and not directly on the pituitary. For example, implants of hydrocortisone in the median eminence suppress the release of A.C.T.H., but implants in the anterior pituitary itself do not. Implants of thyroxine, on the other hand, suppress the release of thyroid-stimulating hormone whether they are placed in the hypothalamus or the anterior pituitary.

Growth Hormone

The presence of a substance in animal pituitary glands that stimulated growth was demonstrated over 40 years ago. Studies on its effects in animals showed that there were three main individual metabolic effects: first, *retention of protein*; second, *loss of body fat*; and, third, *impairment of carbohydrate tolerance*—sometimes to the point of frank diabetes mellitus, which was permanent. In man, however, preparations of animal growth hormones were found to be inactive, though extracts from human pituitary glands had potent metabolic effects. Subsequently it was found that there was a species difference between growth hormones, those from primates being similar, so that monkey growth hormone was also effective in man.

The concentration of growth hormone in the plasma can be measured by an "immuno-assay" method, similar to that originally devised for the assay of insulin and subsequently for parathyroid hormone, A.C.T.H., and glucagon. In this method human growth hormone which has been labelled with radioactive iodine is mixed with an antiserum to growth hormone prepared in animals. The test plasma or standard containing known quantities of growth hormone is now added. The radioactively labelled growth hormone will then compete with the unlabelled hormone (whether in the test plasma or in the standard solution) for binding sites on the antiserum. The result is that the higher the amount of unlabelled growth hormone present the lower will be the amount of labelled hormone bound by the antiserum—and this can be measured in several ways.

The use of the assay of human growth hormone has already shed light on its physiological role. Hypoglycaemia, exercise, and fasting (situations tending to diminish the supply of glucose to the cells) all produce a rise in the level of the hormone in the blood, whereas the administration of glucose causes it to fall.

The administration of human growth hormone to man produces many of the expected metabolic effects. Thus, there is retention of protein (as evidenced by a fall in the urea concentrations in blood and urine), mobilization of fat (as shown by a rise in the ketone bodies in the blood and urine), and an impairment of carbohydrate tolerance—though this is not usually gross. A rather surprising result is an increase in the excretion of calcium in the urine, a finding that explains the hypercalciuria often found in patients with acromegaly. Furthermore, as is seen in the case of other hormones, the effect of growth hormone is more pronounced in patients with deficiency of the hormone than in normal subjects, and this response can therefore be used in the diagnosis of deficiency states. The immuno-assay method is also valuable for assessing possible deficiency states—for example, in the investigation of dwarfism. In normal subjects the concentration of growth hormone in the plasma may be so low that it is impossible to detect. But if the person's blood-sugar level is lowered, by the administration of insulin or tolbutamide, the concentration of the hormone rapidly rises. This rise is not seen, however, in patients with dwarfism due to hypopituitarism—an uncommon though well-recognized cause of the condition.

Unfortunately the supply of human or monkey growth hormone is very limited, and this has restricted work on its use in treatment. Nevertheless, there is now considerable evidence to show that, given as twice- or thrice-weekly injections, it can

produce a pronounced increase in the rate of growth in hypopituitary dwarfs. Its use in other forms of dwarfism still has to be evaluated. Unlike sex hormones—which increase the rate of growth but also produce premature closure of the epiphyses—growth hormone does not have a disproportionate effect on bone age. Human growth hormone does not have any effect on sexual development in children with hypopituitarism, so that in treatment it is ultimately necessary to use sex hormones as well.

Thyroid

By means of thyrotrophic hormone (T.S.H.) the pituitary exerts a dominant controlling influence on the thyroid. Removal of the pituitary is followed by complete, or nearly complete, cessation of thyroid function. T.S.H. is measured by biological assay in animals, usually mice. The animals are given a preliminary dose of radio-iodine, which is taken up by the thyroid. The serum under test is then injected into the animals and the amount of radio-iodine that is discharged from the thyroid into the plasma is measured. In most normal subjects T.S.H. activity is hardly detectable by this method. In patients with primary thyroid failure, on the other hand, raised levels of T.S.H. are present in the serum, reflecting the increase in pituitary secretion that is secondary to the reduced concentration of thyroid hormone in the blood.

Most patients with thyrotoxicosis have normal levels of serum T.S.H. The implication of this—that in general thyrotoxicosis is not due to excessive T.S.H. secretion—is supported by several case reports of thyrotoxicosis occurring in patients with spontaneous failure of the pituitary, or after surgical removal of the gland.

Long-acting Thyroid Stimulator

In 1956 a new substance was found to be present in the sera of patients with thyrotoxicosis. This was called "long-acting thyroid stimulator" (L.A.T.S.), since, when it was tested by the assay method for T.S.H., its maximum effect in releasing radio-iodine into the circulation was found to be about 16 hours after injection (compared with 2–3 hours for T.S.H. itself). Like T.S.H., it was shown to produce true activation of the thyroid, as evidenced by the characteristic histological changes of activity in the gland. In nature, L.A.T.S. has been shown to be a gamma-globulin, though its source is unknown. The similarities and differences between L.A.T.S. and T.S.H. are summarized in the Table.

Characteristics of T.S.H. and L.A.T.S.

	T.S.H.	L.A.T.S.
Release of radio-iodine from animal thyroid	+	+
Time of maximum release in hours	2–3	About 16
Site of production	Pituitary	Unknown, but not pituitary
Nature	α_2 -Globulin	γ -Globulin
Half-life after injection	10–20 min.	7½ hours
Neutralization by T.S.H.-antiserum	+	–
Suppressibility by administration of thyroid hormone	+	–

The finding of L.A.T.S. in most patients with thyrotoxicosis has led to the suggestion that it is directly responsible for stimulating the excessive thyroid activity. It may also be present in patients whose thyroid function has been rendered normal by surgery or radio-iodine, possibly because there are no longer sufficient cells in the thyroid to respond excessively to it. The transfer of L.A.T.S. across the placenta has been invoked to explain the rare condition of congenital thyrotoxicosis, which affects infants of mothers with present or past

thyrotoxicosis. Congenital thyrotoxicosis usually subsides within about three months of birth—a finding which is compatible with the known rate of disappearance of maternal gamma-globulin from the infant's circulation.

Parathyroids

Removal of the parathyroid glands produces a profound lowering of the concentration of calcium in the blood and tetany. Injection of extracts of parathyroid reverses these effects, and the hormone responsible is called parathyroid hormone or parathormone. Analysis has revealed that it is a polypeptide, and studies in man and animals have shown that it has three main actions. The first, and most important, is a *direct action on bone*, releasing the calcium in the blood. Secondly, it *acts on the small intestine*, enhancing the absorption of calcium there. Thirdly, it *acts on the renal tubules*, promoting reabsorption of calcium and excretion of phosphate. The control of parathyroid secretion is probably dependent almost entirely on the level of ionized calcium in the blood, a rise in this suppressing the secretion, and vice-versa.

Calcitonin

Studies in animals have shown that parathyroid hormone has a relatively slow action on the serum-calcium level, suggesting that it was unlikely to be the only mechanism for maintaining the level constant. It was therefore of particular interest when Copp found that, when the parathyroids in dogs were perfused with blood of high calcium content, a substance with a calcium-lowering action was liberated. Subsequently this new hormone was called calcitonin. Its site of production is still, however, controversial. Copp himself suggested that it is produced by the parathyroid glands, but other workers think that it is made by the thyroid. Though the role of calcitonin is poorly understood at present, the possibility of calcitonin-secreting tumours in patients with persistent hypocalcaemia must be remembered. Already one case report has been published of a patient with hypocalcaemia and clear-cell hyperplasia of the parathyroids in whom an excess secretion of calcitonin may have been responsible for the hypocalcaemia.

Adrenals

Aldosterone

In the original work on the isolation of steroids from the adrenal gland, extracts were prepared by shaking chopped-up gland with solvents such as benzene. After the extraction processes an "amorphous fraction" remained, which could be shown to affect sodium and potassium metabolism when injected into animals. In 1952 Simpson, Tait, and Grundy succeeded in isolating a substance with such "mineralocorticoid" activity from the amorphous fraction. At first this was called electrocortin, and subsequently aldosterone; its chemical structure was soon determined and later it was successfully synthesized. The most pronounced effects of the hormone are on the renal tubules, stimulating reabsorption of sodium and secretion of potassium; this results in retention of sodium and loss of potassium.

The body responds to deprivation of salt by reducing the content of sodium in the urine. This is associated with an increased secretion of aldosterone, though the precise stimulus for the latter is uncertain. When possible mechanisms are considered, the pituitary probably has little control over aldosterone secretion, as patients who have had a total hypophysectomy may conserve salt normally when deprived of it in the diet. In animals the level of potassium in the blood passing through

the adrenal affects aldosterone secretion—a rise in potassium level increasing aldosterone secretion—but this mechanism is probably relatively unimportant in man. A known potent stimulus for secretion of aldosterone in man, however, is a fall in the volume of fluid within the blood-vessels. Such a fall might stimulate sensitive receptors either in the blood-vessels or in the kidneys.

Renin

The hormone renin, which produces hypertension when injected into animals, was isolated at the end of the last century. Renin is now known to act on a substrate circulating in the plasma to produce a substance known as angiotensin I (Fig. 2). In its turn angiotensin I is converted into angiotensin II, which is the most powerful pressor substance known. Recently it has been shown that angiotensin II will stimulate the secretion of aldosterone—even when given in doses too small to affect the blood-pressure. Renin is now thought to be manufactured in

FIG. 2.—Mechanism of the renin effect on aldosterone secretion.

the "juxtaglomerular apparatus"—a system composed of specialized cells of the afferent renal arterioles and of the distal convoluted tubules. This apparatus might be sensitive to changes of intravascular volume or pressure. A fall in intravascular volume would cause renin to be released, and eventually the secretion of aldosterone to be increased. This hypothesis has been supported by the finding of raised levels of renin in the plasma when the subject is deprived of salt, and vice versa.

Hyperaldosteronism

There are two types of hyperaldosteronism—primary and secondary. The primary type was first described by Conn in 1955. It is a relatively rare condition due to autonomous overactivity of the adrenal, usually a tumour of the cortex, which gives rise to the production of excess amounts of aldosterone. Thus the features of the condition are those of excessive retention of sodium (such as mild hypertension and a raised level of sodium in the blood) and loss of potassium (such as a reduced level of potassium in the blood, muscle weakness, and defective concentration by the kidneys, leading to polyuria). These effects are usually reversed when the adrenal tumour is removed.

Secondary hyperaldosteronism is the name given to the raised levels of aldosterone secreted in diseases characterized by oedema—such as cirrhosis of the liver and the nephrotic syndrome, when the adrenals are themselves normal. The excessive amount of aldosterone itself is unlikely to be the sole cause of the oedema. Therapeutically, however, a very dramatic diuresis can sometimes be obtained in patients with such secondary hyperaldosteronism by giving drugs that antagonize the effects of aldosterone on the renal tubules, such as spironolactone.

Raised levels of aldosterone and lowered blood levels of potassium are also found in many patients with hypertension due to ischaemia of one kidney and with malignant hypertension. Both findings may become normal with successful treatment—for example, by removing an area of renal-artery stenosis in patients with unilateral renal ischaemia.