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Scientific Basis of Clinical Practice

Antidiuretic and Growth Hormones

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Antidiuretic hormone (ADH) and oxytocin are thought to be secreted by the neurones in the supraoptic nucleus and the paraventricular nuclei of the hypothalamus, ADH mainly or entirely in the former and oxytocin in the latter. The neurones, and their axons which form the hypothalamico-hypophyseal tract, contain neurosecretory granules consisting of neurohypophyseal hormone bound to the protein, neurophysin. The tract terminates in the posterior lobe of the pituitary, where the nerve endings are rich in neurosecretory granules.[1] The pituitary cells (pituicytes) were formerly thought to be secretory but are now known to be a neuroglial type of cell.

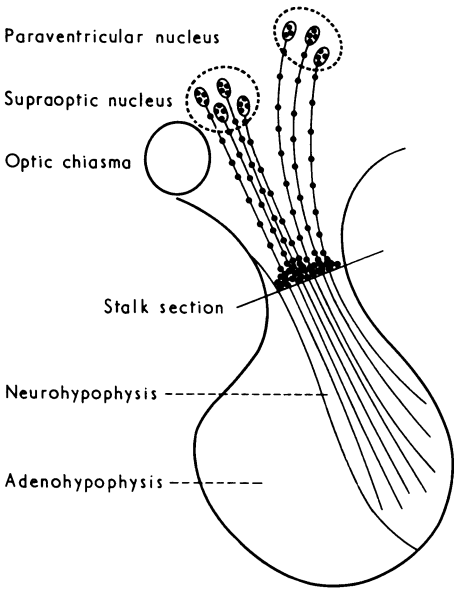

FIG. 1—Diagram showing accumulation of neurosecretory material at the proximal cut end of the hypothalamico-hypophyseal tract after section of the pituitary stalk.[2]

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In vivo the neurosecretory granules migrate down the hypothalamico-hypophyseal tract at a speed of about 3 mm per day. If the tract is cut granules accumulate above the cut and disappear below (Fig. 1[2]). Vascular reorganization can occur above the cut with subsequent release of the hormones and this is why diabetes insipidus is usually only a temporary sequel of hypophysectomy unless the greater part of the pituitary stalk has been removed together with the gland.

Stimulation of the supraoptic and paraventricular nuclei provokes action potentials in the hypothalamico-hypophyseal tract, and the resultant depolarization of the nerve endings in the neurohypophysis causes release of neurosecretory granules. Release of the neurohypophyseal hormones depends on the presence of calcium, as does the release of insulin, thyroid-stimulating hormone, luteinizing hormone, and adrenaline.

After release, the neurohypophyseal hormones become dissociated from neurophysin, which also enters the circulation.

Actions of ADH

In a person without renal disease the 15% or so of the glomerular filtrate which enters the distal convoluted tubules of the nephrons is hypotonic because sodium has been reabsorbed from the ascending limb of the loop of Henle without the reabsorption of an equivalent amount of water. In the absence of antidiuretic hormone the distal tubules and the collecting ducts are relatively impermeable to water, and hypotonic urine with an osmolarity of approximately 100 mOsm/litre (specific gravity 1·003) is formed. This occurs in severe diabetes insipidus and 20 litres or more are excreted a day.

ADH increases the permeability of the distal convoluted tubules and collecting ducts. When the hormone is present the increasing concentration of solutes in the interstitial fluid towards the tips of the renal papillae causes reabsorption of water by osmosis. If there is sufficient ADH the urine becomes isotonic with the interstitial fluid in the papillae and the osmolarity reaches about 1200 mOsm/litre (specific gravity 1·030), which is the level found in a normal subject deprived of fluid.

The effect of ADH on the kidney may be detected within two to four minutes of intravenous injection. The hormone is an octapeptide containing a cystine residue. It has been suggested that ADH binds to receptor cells by the formation of covalent linkages between the disulphide bridges of the cystine residues

and sulphydryl radicles on the cell surface.[3] It is not known how ADH exerts its effect on cell permeability, but the hormone increases the rate of formation of cyclic 3′, 5′ -AMP, and possibly this nucleotide—now implicated in the action of so many hormones—mediates the change in permeability.[4]

ADH is also known as vasopressin because pharmacological concentrations cause contraction of arteriolar smooth muscle. Nevertheless, the concentrations normally present in the circulation have no pressor action. A related effect, spasm of intestinal and uterine smooth muscle, sometimes occurs in patients treated with excessive amounts of ADH.

Control of ADH Release

The rate at which ADH is released into the circulation is determined by the crystalloid osmotic pressure of the plasma. The osmotic pressure in the deep cerebral branches of the internal carotid artery is monitored by osmoreceptors in the region of the supraoptic nucleus.[5] These osmoreceptors are very sensitive, responding to changes of less than 2 mOsm/litre. The receptor cells may or may not be the cells which secrete ADH, but they do not appear to be the osmoreceptors responsible for stimulating the sensation of thirst. Though the usual determinant of ADH release is the serum osmolarity, the most potent stimulus for release is a rapid fall in plasma volume such as occurs during a brisk haemorrhage. It is not known precisely how this effect is mediated, but there is evidence which implicates receptors in the region of the carotid bifurcation and in the left atrium.[6]

Diabetes Insipidus

When other organic disease has been excluded it is often difficult to decide whether polyuria is due to deficiency of vasopressin or to psychogenic polydipsia. The fluid deprivation test described by Dashe and colleagues[7] has proved to be a safe and satisfactory way of distinguishing between the two conditions. Results from two patients are given in the Table. Patient 1 had been treated with pitressin injections which were stopped some weeks before

Fluid Deprivation Test

Patient	Ratio of urine osmolarity to serum osmolarity after 6½ hr fluid deprivation* (mOsm/kg water)	Diagnosis
1	3·2	Psychogenic polydipsia
2	1·3	Diabetes insipidus

*Characteristically the ratio is less than 1·9 in diabetes insipidus.

she was deprived of fluid for 6½ hours. At the end of this time the ratio of urine osmolarity to serum osmolarity was normal (that is, greater than 1·9), indicating that the ADH mechanism for concentrating the urine was not impaired. Patient 2 had had a craniopharyngioma removed six years previously and had also been treated with pitressin. The low urine to serum osmolarity ratio which was found after fluid deprivation indicated the persistence of diabetes insipidus.

Most patients with diabetes insipidus are treated satisfactorily with preparations containing ADH, though paradoxically treatment with a thiazide diuretic is said to be successful in mild cases.[8] In the small proportion of patients whose kidneys are insensitive to ADH (nephrogenic diabetes insipidus) thiazide diuretics also reduce the volume of urine.

The opposite of diabetes insipidus, the rare condition in which there is excessive secretion of ADH, is most often due to the production of ADH by an oat-cell carcinoma of the bronchus. Limitation of the fluid intake may control the resultant dilutional hyponatraemia, but it may also be necessary to stimulate sodium retention by treatment with a mineralocorticoid.[9]

Chemistry of Growth Hormone

Growth hormone (GH) is a protein whose composition is different in different species. In man antibodies are formed to non-primate GH and in some cases to exogenous human GH. Unfortunately, it is not possible to obtain enough human GH from pituitary glands post mortem to treat all children with pituitary dwarfism. In man it has not yet been possible to separate GH from prolactin, though the two hormones are not chemically identical in other species.

The serum concentration of GH is now measured by radioimmunoassay.[10] In this method a known but small quantity of antibody to growth hormone is added to a mixture of a known quantity of growth hormone labelled with radioiodine and a known volume of the serum whose GH concentration is to be measured. If the concentration of GH in the test serum is high, little of the radioiodine-labelled GH forms a complex with antibody, and therefore the ratio of complexed iodinated GH to uncomplexed iodinated GH is low. On the other hand, if there is little GH in the test specimen, the ratio is high (Fig. 2.)

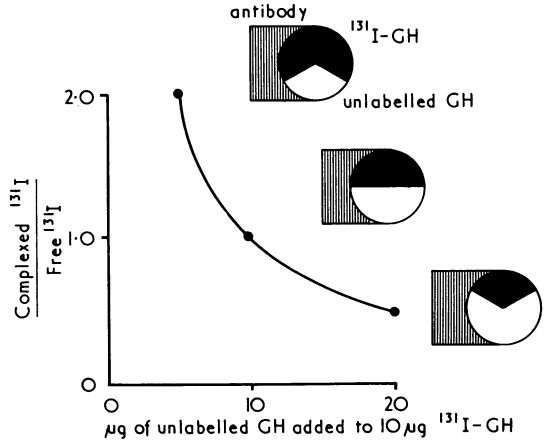

FIG. 2—Principle of radioimmunosassay.[11]

The complexed and uncomplexed iodinated GH are separated by electrophoresis or chromatography and their activity is measured in a gamma-ray counter.

Control of GH Secretion

The rate of secretion of GH appears to be related to age. The plasma level is higher in a newborn baby than in the mother and

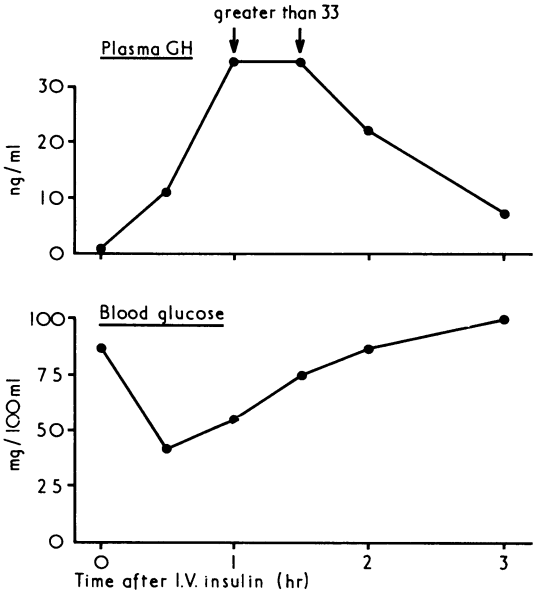

FIG. 3—Blood glucose and plasma growth hormone levels after the administration of insulin. Mean values from five normal subject (data of Roth *et al.*[13])

the level in children and adolescents two to three hours after a meal is generally ten to twenty times as high as in adults.[12]

Changes in blood glucose concentration have a very pronounced effect on plasma GH. Fig. 3 shows the rise in plasma GH concentration provoked by insulin-induced hypoglycaemia and the subsequent fall when the blood glucose level recovers. GH secretion increases after an increase in the plasma concentration of certain amino-acids and after several stressful stimuli —for example, exercise, psychological stress, or injection of pyrogen.[14] The plasma level of growth hormone itself also affects the secretion rate, a high level tending to inhibit production. Each of these factors controlling GH secretion appears to act via by the hypothalamus, where growth hormone releasing factor is secreted. This is a polypeptide hormone which passes down the pituitary portal vessels and stimulates the synthesis and release of GH by the acidophil cells of the pars distalis.[15]

GH and Metabolism

GH binds firmly to cells and then has two rapid effects on protein metabolism: firstly, the passage of certain amino-acids across the plasma membrane is stimulated; and secondly, the ratio of active to inactive ribosomes is increased.[16] GH increases RNA synthesis by increasing RNA polymerase activity. It is unlikely, however, that the hormone has a primary action on RNA, in muscle at least, because GH stimulates protein synthesis even when messenger RNA synthesis is inhibited by actinomycin. Though the plasma half-life of GH is only about 25 minutes, its effects on protein synthesis are long lasting and the growth of GH-deficient children increases in response to injections given once a week.

Whereas GH cannot stimulate protein anabolism in the absence of insulin, the effects of these two hormones together on carbohydrate metabolism are antagonistic. This antagonism accounts for the high incidence of abnormal glucose tolerance and of diabetes mellitus in acromegaly. Probably the two hormones share the same receptor sites and their binding is competitive. GH decreases glucose transport into muscle and adipose tissue and reduces phosphorylation of glucose by muscle.[17] It also stimulates gluconeogenesis and the output of glucose from the liver. These actions increase the blood glucose concentration. Hyperglycaemia, however, provokes a secretion of insulin so that the glucose concentration then falls.

Even though the actions of GH and insulin are antagonistic, the two hormones have complementary roles in the control of energy metabolism. Shortly after a meal the high blood glucose level stimulates the secretion of insulin, which promotes the storage and utilization of carbohydrate. In the fasting state, on the other hand, the low blood glucose level stimulates secretion of GH, which reduces the utilization of carbohydrate and increases the mobilization and oxidation of fat. The hyperglycaemia which occurs after GH has been injected into fasting animals is actually preceded by transient hypoglycaemia.

Recent work has suggested a way in which it is possible for growth hormone to have these opposing effects. In vitro hydrolysis of the hormone has yielded two polypeptides, one of which causes hypoglycaemia and the other hyperglycaemia.[18] If a similar reaction occurs in vivo it could account for the biphasic activity of GH. The hyperglycaemic polypeptide has been shown to interfere with glycolysis by inhibiting the glycolytic enzyme, triose phosphate dehydrogenase.[19]

Diagnosis of Pituitary Dwarfism

Among the many possible causes of short stature without disproportion, five important conditions are likely to need differentiation: consitutional delay in growth and adolescence; congenital dwarfism; pituitary dwarfism; hypothyroid dwarfism; and Turner's syndrome. Pituitary dwarfism is the only one of these which is not manifest at birth. Cases of constitutional delay and of congenital dwarfism are likely to have a family history of small stature. Puberty does not occur in Turner's syndrome and is delayed in cases of constitutional delay and in hypothyroidism. Most pituitary dwarfs have a deficiency of gonadotrophin and puberty is either delayed or fails to occur. In contrast with the delayed mental development of the hypothyroid dwarf, the intelligence of most pituitary dwarfs is said to be normal. Local manifestations, such as calcification above the sella, are frequently obvious in acquired pituitary dwarfism and in these cases there is usually also deficiency of other anterior pituitary hormones.[8]

Tests of thyroid function will confirm the diagnosis of primary hypothyroidism and will demonstrate the secondary hypothyroidism occurring in some pituitary dwarfs. Tests of adrenal cortical function may give evidence of secondary adrenal hypofunction in pituitary dwarfism and will exclude Cushing's syndrome and adrenogenital syndrome as causes of short stature. In pituitary dwarfism the definitive laboratory investigation is the assay of growth hormone, which is not detectable in the plasma even after inducing hypoglycaemia with insulin.

This article is based on a lecture given in the Birmingham course under the title "The Scientific Basis of Clinical Practice" (see B.M.J. 27 November 1971, p. 510).

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