MEDICAL PRACTICE

Occasional Survey

Hypothalamus as an Endocrine Organ*—I

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British Medical Journal, 1974, 3, 560-564

It has long been recognized that the hypothalamus has an endocrine function associated with the control of water excretion. The classical experiments of Verney showed that secretion of an antidiuretic hormone into the blood was related to the rise in tonicity of blood perfusing the brain.^{1 2} Since then the octapeptide hypothalamic hormones vasopressin and oxytocin and the associated much larger neurophysin have been identified and the structures of oxytocin and vasopressin established. Though synthesized in the cell bodies of the neurones of the supraoptic and paraventricular nuclei of the hypothalamus, these hormones pass down the neuronal axons to be stored at their terminal regions in granulated swellings within the posterior lobe of the pituitary, as was indicated by the early neuroanatomic studies of Ranson and Rasmussen and their colleagues.³⁻⁵ The process is called "neurosecretion." I do not intend to review in detail the well-described factors controlling secretion of the hormones of the posterior pituitary but to try to draw an analogy between the hypothalamic neurosecretory mechanisms concerned with the posterior pituitary hormones and those now being recognized as concerned with control of hormonal secretion from the anterior pituitary (fig. 1).

The stimuli to the synthesis and secretion of vasopressin seem to involve neurological processes, either osmolar stimulation of centres within the hypothalamus when osmoregulation is required, reflex pathways when secretion occurs in response to a fall in plasma volume, or higher centres when psychological factors such as stress are involved. The function of neurophysin

FIG. 1—Neural connexions between hypothalamus and posterior pituitary and portal vascular connections between the hypothalamus and anterior pituitary.

is uncertain; though it is secreted with vasopressin it clearly can bind the smaller hormones and may act as a carrier. While oxytocin is secreted during labour and suckling in subhuman species it has not yet been possible to relate oxytocin reliably to these functions in the human. Nevertheless, this hormone exists in the human posterior pituitary and hypothalamus of both sexes and may be secreted during stress. The observation of Chard *et al.*⁶ that the highest blood oxytocin levels in man have been seen in fetal blood at parturition has led them to speculate that the fetus, rather than the mother, might initiate the uterine contractions of labour by secreting oxytocin, which reaches the uterus via the umbilical artery and placenta.

*Based on the Goulstonian Lecture given at the Royal College of Physicians of London on 16 May 1974.

Hypothalamus and Anterior Pituitary

More recently evidence has accumulated that the hormonal secretion of the anterior pituitary is also linked to the hypothalamus though the anatomical relation is obviously different. Significant neural connexions were not found between the brain and anterior pituitary gland; instead a portal capillary system was described which was in close contact with the neurosecretory cells of the median eminence of the hypothalamus and which transversed the pituitary stalk to drain into the vascular sinusoids surrounding the cells of the anterior pituitary.

Transmitter substances were therefore thought to be neuro-secreted within the hypothalamus, stored in the region of the median eminence, and released as required into the portal capillaries to pass in the blood to act on the anterior pituitary and to control the secretion of its hormones.⁷⁻⁹ Despite the abundant experimental evidence for the existence of these hypothalamic hypophysiotropic substances, collected largely by Harris and his colleagues over some 20 years at Oxford, it was not until 1969 that the chemical structure of the first was established and a synthetic form of it produced. The early physiological experiments had been carried out largely with fractionated extracts of hypothalami, and these extracts have been shown to either stimulate or inhibit the release of individual pituitary hormones. Since the structures of the active constituents of some of these extracts have been established the term "factor" has been conventionally restricted to the activity of hypothalamic extracts, and "hormone" is used when the structure is established and the synthetic material is available. The substances as a group are called the "hypothalamic regulatory hormones."

As yet six factors which release and three which inhibit the release of anterior pituitary hormones have been shown, and for three of them the structures have been elucidated and the synthetic compounds shown to be active in man (see table). The determination of the structure of the first of these, thyrotrophin-releasing hormone (TRH), was the culmination of many years of intense work involving elaborate techniques of peptide chemistry to purify extracts of many hundreds of thousands of animal hypothalami. This achievement not only validated Harris's initially most controversial concepts but also marked a major turning point in the understanding of the control of the endocrine system and the pathogenesis of many endocrine diseases.

Hypothalamic-Pituitary Amplifier

The mechanism whereby the hypothalamus controls the anterior pituitary seems to be more subtle than merely constituting a simple sequence of chain reactions. The hypothalamic hormones are synthesized within the cell bodies of the nuclei of the hypothalamus and neurosecreted down their axons to be stored in their terminal dendrites in the region of the median eminence. The release of the stored hormone into the blood is under neurological control from higher centres involved in establishing time-dependant rhythms, responses to psychological factors such as stress, feedback control, and in reflex responses mediated by the peripheral nerves. In this way the system is entirely analogous to that related to the posterior pituitary (figs. 1 and 2).

FIG. 2—Relationships between hypothalamus, pituitary, and target organs.

The total content of hypothalamic hormone in the median eminence seems to be very small (a few nanograms, 10^{-9} g) and only minute amounts are secreted into the portal capillary blood at any one time. These substances then act on the pituitary cells to cause synthesis and release of trophic hormones in amounts which are probably a thousand or a million times greater than those of the incident hormone. In turn the pituitary hormones act on their target glands to cause them once again to produce between a thousand and a million times as much hormone. There thus seems to be a "cascading amplifier" system greatly multiplying the original hypothalamic "signal." In a sense there is an additional amplification of the signal for there are behavioural changes induced by the target organ hormones both in the subject and in his environment which can be regarded as end results of the hypothalamic hormone secretion, but these are not easily measurable.

The hormonal amplifier model may be taken further for there are at least three levels at which the amplified signals may be "sensed" and the degree of amplification modulated. Chemical feedback occurs at the pituitary cell since target organ hormone levels interfere with the actions of the hypothalamic hormones and this is one way in which the classical negative feedback mechanisms work. In addition, circulating hormonal levels alter the secretion of the hypothalamic hormones themselves. Cerebral and psychogenic factors operating through an interaction between normal sensations and conscious and subconscious mechanisms within the reticular formation and through a final common path at the median eminence of the hypothalamus clearly can alter regulatory hormone secretion, and these mechanisms may be disturbed in disease. For example, the condition of the girl with the psychogenic problems of anorexia nervosa in whom gonadal function is deficient is due to impaired secretion of the hypothalamic gonadotrophin-releasing hormone and in turn to reduced gonadotrophin release.

I shall now consider the effects of the three hormones whose structures are established and which have been used in man.

Hypothalamic Regulatory Hormones. Principal Actions are Indicated

Releasing hormone (RH) or factor (RF) for:

Thyrotrophin (TRH). Structure: pyroGLU-HIS-PROamide

Luteinizing hormone and follicle-stimulating hormone (LH/FSH-RH).

Structure: pyroGLU-HIS-TRP-SER-TYR-GLY-LEU-ARG-PRO-GLYamide

Growth hormone (GH-RF)

Corticotrophin (CRF)

Melanocyte-stimulating hormone (MSH-RF)

Prolactin (PRF)

Release-inhibiting hormone (RIH) or factor (RIF) for:

Growth hormone (GH-RIH).

Structure: H-ALA-GLY-CYS-LYS-ASN-PHE-PHE-TRP-LYS-THR-PHE-THR-SER-CYS-OH

Melanocyte-stimulating hormone (MSH-RIF)

Prolactin (PRIF)

Thyrotrophin-releasing Hormone

The structure of TRH was described by Folkers *et al.*¹⁰ and Burgus *et al.*¹¹ Human, bovine, ovine, and porcine TRH seem to have the same tripeptide structure. Intravenous injection or oral administration results in a dose-related secretion of thyroid-stimulating hormone (TSH) within a few minutes and later in transient increase of both thyroxine (T-4) and triiodothyronine (T-3) concentrations.¹²⁻¹⁴ The TSH responses to TRH are slightly greater in women than in men and during the night than by day.¹⁵⁻¹⁷ The administration of 200 µg TRH intravenously with blood sampling before and at 20 and 60 minutes afterwards for TSH has provided a safe, reliable, and simple test for primary thyroid disease, which is of great value when routine thyroid function assessment is unhelpful. Thus, in hyperthyroidism the raised thyroid hormone levels block the action of TRH on the pituitary and result in an absent TSH response to TRH whether or not the hormone in excess is predominantly T-4 or T-3, and in the latter case routine test results are often normal. Conversely mild primary hypothyroidism will be detected since an excessive TSH response will be found. A normal TRH test result excludes thyrotoxicosis or primary hypothyroidism.¹⁵

In pituitary or hypothalamic disease less valuable data are obtained since the results are variable, but if the patient is hypothyroid and the TSH response is normal or impaired then the patient has pituitary disease. If the rise is delayed, in that the 60-minute value is higher than that at 20 minutes (never seen in the normal), then hypothalamic disease is suspected.¹⁸ This test should replace T-3 suppression tests or TSH-stimulation tests since these are more dangerous, expensive, time consuming, and provide no more diagnostic information. Absent responses may be found in some euthyroid patients on replacement therapy, those on corticosteroid therapy, and those with ophthalmic Graves's disease, euthyroid patients with a reduced thyroid reserve—for example, because of thyroiditis, a thyroidectomy, or antithyroid drugs—may give excessive responses.

TSH is not the only hormone released by TRH. Marked prolactin release is also stimulated (fig. 3) but the effects on the two hormones can be dissociated; TRH does not seem to be the physiological prolactin-releasing hormone.¹⁹⁻²⁰ This phenomenon may, however, explain the galactorrhoea and hyperprolactinaemia which may be seen in association with primary hypothyroidism.²¹ In addition TRH releases follicle-stimulating hormone (FSH) in men (fig. 4) but not women, an effect which can be suppressed by small doses of oestrogen. Luteinizing hormone (LH) is usually unaffected,²²⁻²³ though Franchimont²⁴ has reported LH secretion after TRH in some normal women at the midcycle luteal peak. TRH does not normally seem to affect other hormones, but in acromegaly growth hormone (GH) secretion may be seen.²⁵ It is of great interest that the hypothalamic inhibitor of GH secretion, growth hormone release-inhibiting hormone (GH-RIH), also interferes with the TSH and FSH

FIG. 3—Serum prolactin response to infusion of TRH in normal man.

FIG. 4—Serum FSH response to infusion of TRH in normal man.

responses to TRH but not the prolactin response, suggesting that different receptor mechanisms are involved.

Gonadotrophin-releasing Hormone

The structure of the decapeptide hormone LH/FSH-RH was established and synthesized by Schally *et al.*²⁶ Though experiments with hypothalamic extracts suggested that there would be two separate gonadotrophin-releasing hormones, one for LH and another for FSH, only this one has been isolated. It releases both gonadotrophins in a dose-dependent fashion, and in the adult the LH response is much greater than that of FSH, but prepubertally the relative effects are reversed.²⁶⁻²⁹ Other pituitary hormones are not affected, but GH secretion may be seen in some acromegalic patients.³⁰ Though both gonadotrophins are released by the single decapeptide the mechanisms for each must be distinct since the time courses of the responses may be different, and the two hormones are secreted in an asynchronous and pulsatile fashion.³¹⁻³² Similarly, different gonadal steroid hormones can differentially suppress the two gonadotrophins.³³⁻³⁶ It is difficult to explain the complex changes in LH and FSH seen during the menstrual cycle on the basis of a single gonadotrophin-releasing hormone, but possibly these may be produced by an interaction between the single decapeptide and the gonadal steroids present at different phases of the cycle.

Administration of LH/FSH-RH to patients with hypogonadism has produced some unexpected results.³⁷⁻³⁸ After the menopause or when pathological gonadal failure is present excessive increases in serum LH and FSH levels are seen. In men with normal virilization and plasma testosterone concentrations but with oligospermia or azoospermia normal LH but excessive FSH responses occur. This is due to the reduction in the negative feedback effects of "inhibin," a substance of unknown constitution normally responsible for negative feedback control of FSH and produced during the last stages of spermatogenesis, LH being primarily modulated by testosterone. In patients who are hypogonadal from gonadotrophin deficiency in association with a pituitary tumour normal, impaired, or even excessive LH and FSH responses may be seen (fig. 5), so evidently in most cases the gonadotrophin-producing cells are present, either in the tumour or the surrounding compressed pituitary, and a state of functional gonadotrophin-releasing hormone deficiency exists which can be corrected with LH/FSH-RH. Here is the promise of potential therapeutic benefit. Those patients with absent or impaired gonadotrophin secretion when first tested usually may be made to respond normally with repeated administration of LH/FSH-RH.

In patients with hypothalamic tumours such as craniopharyngiomas, we know the LH and FSH responses to LH/FSH-RH are often absent even when there is evidence that the pituitary is, at least in part, intact from the ACTH responses to hypoglycaemia and TSH responses to TRH (fig. 6). However, repeated administration of the gonadotrophin-releasing hormone in these cases soon results in normal LH and FSH secretion

FIG. 5—Serum LH responses to 100 µg LH/FSH-RH given intravenously in 15 hypogonadal patients with functionless pituitary tumours. ● = Normal response. ○ = abnormal response. ND = Not detectable

FIG. 6—Serum LH responses to 100 µg LH/FSH-RH given intravenously in 10 patients with craniopharyngiomas. Seven patients were clinically hypogonadal. ● = Normal response. ○ = Abnormal response. ND = Not detectable

FIG. 7—Serum LH and FSH responses to prolonged treatment with LH/FSH-RH 500 µg given subcutaneously in man with "isolated gonadotrophin deficiency" syndrome. ND = Not detectable

(fig. 7), indicating that this hypothalamic hormone induces synthesis as well as release of the pituitary trophic hormones.³⁹

When patients with the "isolated gonadotrophin deficiency" syndrome—that is, inborn partial or complete gonadotrophin deficiency without evidence of overt pituitary or hypothalamic disease or deficiency of other pituitary hormones—are studied we find that when LH/FSH-RH is given either once or repeatedly LH and FSH secretion invariably occurs, again providing evidence that it promotes synthesis, and we can produce gonadal stimulation on prolonged treatment. Thus we presume these patients have not primary failure of the gonadotrophin cells of the pituitary, but rather deficiency of the gonadotrophin-releasing hormone due to an inborn hypothalamic defect.^{37, 38} Many of these patients also have anosmia due to olfactory bulb agenesis without more central brain defects.⁴⁰

In these and other conditions of pituitary-hypothalamic hypogonadism, such as anorexia nervosa and the galactorrhoeic states, we usually see evidence that the gonadotrophin deficiency is not owing to inability of the gonadotrophs to synthesize and release gonadotrophins but rather the lack of their stimulation to do so. Thus in a series of over 150 patients with apparent gonadotrophin deficiency we were able to stimulate the release of LH and FSH in more than 85%; in the remainder who were resistant to initial administration of LH/FSH-RH gonadotrophin secretion regularly occurred when we gave repeated doses. In these patients with apparent hypogonadotropic hypogonadism we have noted that LH levels are low more often than FSH either basally or after LH/FSH-RH.

The studies described in this review were carried out in collaboration with my many colleagues at St. Bartholomew's Hospital, Professor R. Hall and colleagues at the Royal Victoria Infirmary, Newcastle upon Tyne, Dr. S. R. Bloom of the Middlesex Hospital, and Dr. A. V. Schally of the Veterans Administration Hospital, New Orleans. The studies have been supported by the Joint Research Board of St. Bartholomew's Hospital, the Peel Medical Trust, and Ciba Laboratories Ltd.

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Outside Europe

Diagnostic Clue to Acute Splenic Torsion in the Tropics

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British Medical Journal, 1974, 3, 564-566

Summary

In three patients with acute torsion of the spleen in the tropics the presenting symptoms included an abdominal mass, pain, and vomiting. In malarious areas adults usually know that they have splenomegaly and hence this fact should be ascertained in the clinical history. In an acute abdominal catastrophe, with a palpable tumour and a history of known splenomegaly, the absence of the spleen in the normal position suggests acute splenic torsion.

Introduction

According to Maingot¹ torsion of the spleen is rare; though Bowesman² says that it is seen more frequently in the tropical areas of the world, and Davey³ points out that the diagnosis is seldom made correctly unless the tumour is situated in the upper left quadrant of the abdomen. An acute torsion presents as an abdominal catastrophe, usually requiring urgent laparotomy. Where malaria is rife, the presence of an enlarged spleen is common, and most adults with this abnormality are aware of the fact.

This paper describes three cases of acute torsion of the spleen. In two of these—patients with known splenomegaly—the absence of the spleen in its normal position was the key to diagnosis.

Case 1

A Melanesian woman aged about 30, was admitted to the Central Hospital, Honiara, British Solomon Islands, on 9 September 1969 with a four-year-old abdominal mass. She had three children, and shortly after the birth of the last child, aged 4, had noticed an abdominal swelling which had gradually increased in size. She was adamant that a spell had been cast on her and that the mass was a turtle which was growing in size and swimming around her abdominal cavity. She had had numerous attacks of malaria, was thin, and looked older than her years.

On examination the patient had a normal temperature, a pulse rate of 88, and the abdomen was soft and contained a large, hard, mobile swelling 35 cm × 15 cm. The mass could be moved into any quadrant of the abdomen easily and without pain. It could be felt both rectally and vaginally. There was no other abnormality.

Investigations showed haemoglobin level of 9.4 g/100 ml, white blood count 7,900 mm³. A blood film was negative for malaria but contained microfilarial parasites, and an ovarian cyst was diagnosed. The patient was treated with diethylcarbamazine for her filariasis and arrangements made to carry out laparotomy in due course.

On 11 September she suddenly developed constant severe, generalized abdominal pain. This was followed by copious vomiting of digested food and bile-stained fluid. Her pulse rate rose to 102 and she had a temperature of 37.4°C. There was marked guarding all over the abdomen with maximum tenderness and rebound over the mass which was now fixed in the right iliac fossa. Bowel sounds were normal. On rectal examination the tender mass was palpable. The diagnosis was now torsion of a large ovarian cyst.

An emergency laparotomy was carried out and the abdomen explored through a right lower paramedian incision. The peritoneal cavity contained a small amount of colourless free fluid and a large, congested spleen was found lying in the right iliac fossa. The splenic pedicle was long and had undergone four to five complete anticlockwise turns. The vessels in the pedicle were not thrombosed. The spleen was easily mobilized and splenectomy carried out. The abdomen was closed without drainage. The spleen weighed 2,540 g. A routine suppressive course of chloroquine was given. After the operation the patient ran an intermittent mild pyrexia of unknown origin which settled on penicillin. She was discharged 12 days after the operation, and, when last seen in February 1974, was very well despite several attacks of fever.

Case 2

A 30-year-old Melanesian plantation labourer, was admitted to hospital on 1 October 1973. He had developed a severe abdominal pain three days previously which had become progressively worse. Copious vomiting had occurred on at least three occasions. Nothing had been taken orally and his bowels had not opened. He had had many attacks of fever and admitted that he had a palpable spleen in the left hypochondrium.

He looked ill and was dehydrated. He had a temperature of 37.6°C, and a pulse rate of 106. The chest was clear; the abdomen was rigid and to the right of the umbilicus there was an abdominal mass 10 cm × 15 cm which was firm, tender, and fixed on palpation. There was definite rebound tenderness all over the abdomen and bowel sounds were absent. A spleen was not palpable in the left hypochondrium. On rectal examination the tender mass could be felt in the right iliac fossa. A routine blood film revealed no malaria parasites. The haemoglobin level was 11.2 g/100 ml, and