MODERN TRENDS IN

HUMAN REPRODUCTIVE PHYSIOLOGY-1

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FOREWORD

The production of this book, the first of its kind in British literature, is evidence of the intense interest which has recently developed in the physiology of reproduction in the human. As knowledge of the disease processes of pregnancy advances, more and more are exposed the tremendous lacunae in our knowledge of the basic physiology of gestation and birth. Obstetrics in this respect has tended to lag behind the other major branches of medicine, and, especially in the sphere of reproductive endocrinology, new vistas are constantly opening up which need critical appraisal.

The Editor (himself a contributor) has always taken an active personal interest in the physiological aspects of reproduction and has assembled in this book a variety of topics of current importance, presented by authors who have themselves contributed materially to their particular field.

Thus the opinions expressed are knowledgeable and authoritative, rather than didactic, and the book as a whole covers those fields of the physiology of reproduction in which progress has been rapid in the last 15 years or so.

A review of this kind is of considerable assistance not only to the advanced student but also to the teacher and the research worker, for whom a vast and polyphonic literature is brought into focus.

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February, 1963

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CHAPTER 1

HYPOTHALAMIC CONTROL OF PITUITARY FUNCTION

Ross Wilson Hawker

THE BASIC CONTROLLING MECHANISMS

The nervous and endocrine systems are regulatory systems which play a major role in homoeostasis. They are intimately related and mutually influence each other. The hypothalamus is in a key position for integrating patterns of emotional behaviour and endocrine activity. It controls posterior pituitary activity by hormones which pass down the nerve fibres of the pituitary stalk. The anterior lobe of the pituitary is regulated by humoral agents which are derived from the hypothalamus and transported to the anterior pituitary via the portal vascular system in the pituitary stalk.

THE ANTERIOR PITUITARY

Hormones of the Adenohypophysis

The anterior pituitary gland produces six hormones: (1) Follicle stimulating hormone (FSH); (2) Luteinizing hormone (LH); (3) Lactogenic hormone (Prolactin or Luteotrophic hormone) (LTH); (4) Thyrotrophic hormone (TSH); (5) Adrenocorticotrophic hormone (ACTH); (6) Growth hormone.

The secretion of these hormones is modulated by the hypothalamus to a varying degree.

FSH and LH secretion is entirely dependent on hypothalamic control (Harris, 1955; Greer, 1957), while TSH and ACTH secretion is largely dependent on hypothalamic activity (Brown-Grant, Harris and Reichlin, 1957; Greer, 1960). On the other hand, the secretion of LTH by the pituitary is probably autonomous (Everett, 1954; 1956).

Functional Anatomy

The anterior pituitary contains three main types of cells: (1) Acidophil; (2) Basophil; (3) Chromophobe.

(*a*) Growth hormone and LTH are simple proteins and are formed by the acidophil (or alpha) cells.

Periodic-acid-Schiff (PAS) stains carbohydrate in fixed tissues, but as growth hormone and LTH do not contain carbohydrate, the acidophil cells give a negative staining reaction with PAS.

(*b*) The basophils (or beta cells) give a positive staining reaction with PAS because FSH, LH and TSH which are produced by basophils are glycoproteins.

(1) Gonadotrophins are made by oval or round basophils; (2) thyrotrophin by angular, polyhedral basophils; (3) ACTH by lightly granulated basophils.

Nerve Supply of the Anterior Pituitary

The adenohypophysis has no significant nerve supply, yet paradoxically, it is largely controlled by the central nervous system. The claim that parasympathetic and sympathetic fibres supplied the gland has not been substantiated and silver stains, which impregnate reticular connective tissue fibres as well as nerve fibres, confused the early investigators. More recently electron microscopy, which clearly differentiates between these two types of fibres, has failed to detect any nerve elements in the anterior pituitary.

Vascular Supply of the Anterior Pituitary

Anatomy of the Vascular System

The vascular system of the gland is derived from two sources: a systemic arterial supply, which stems from the internal carotid artery, and a portal blood supply. The venous blood drains into surrounding venous sinuses in the dura or the sphenoid bone.

The hypophysial portal supply was first noted by Professor Rainer in Bucharest and described in detail by Popa and Fielding in the early 1930's. Their findings in the human have been universally confirmed in vertebrates, and microphotographs of these have been published. The mammalian system originates in a plexus of vessels lying between the pars tuberalis and median eminence of the hypothalamus from which capillaries penetrate into the nervous tissue of the median eminence to form the primary plexus of the portal vessels. The capillaries then coalesce to form trunks of the portal vessels which run down the infundibular stalk into the sinusoids of the adenohypophysis. This peculiar vascular system is significant because it is necessary for the optimal functioning of the anterior pituitary.

Function of the Hypophysial Portal Mechanism

The theory currently favoured for the central control of adenohypophysial secretions postulates that nerve fibres from the hypothalamus release into the capillaries of the primary plexus in the median eminence a humoral substance(s) which, carried in the portal blood, modulates the activity of the chromophils of the anterior pituitary gland.

This unique neuro-vascular system thus mediates the hypothalamic control over anterior pituitary function.

Evidence for this Theory

The hypophysial portal vessels are remarkable for their phylogenetic constancy and it is significant that the direction of blood flow is always from the tuber cinereum to the sinusoids of the anterior pituitary.

It is well known that environmental stimuli, for example light, temperature, the presence of a mate and so on affect reproductive activity in some animals. It has been clearly shown for instance that a reflex release of gonadotrophic hormones occurs in some species in response to light stimulus.

Electrical stimulation or destruction of various areas of the hypothalamus has indicated that it is most important for the regulation of anterior pituitary function. These hypothalamic regions influencing the secretion of trophic hormones appear to be discreetly located, but their extent has not been clearly defined. Electrical stimulation of the pituitary itself is without effect on the release of its hormones.

Stalk section has yielded conflicting results, which may now be explained by varying degrees of regeneration of the portal vessels.

Heterotopic transplants of the pituitary re-establish connection with the systemic vascular system, but lose all or most of their original activity. However, if the gland is transplanted to the region of its normal site below the median eminence, the tissues become revascularised by the portal system and recover their normal function.

The Neurohumoral Agents (Neurohumors)

Vasopressin

There is some experimental evidence which suggests that the hypothalamic-hypophysial tract releases vasopressin (antidiuretic hormone) into the portal vessels, and that this neurohumor helps regulate the release of trophic hormones.

Oxytocin

The secretion of lactogenic hormone by the anterior pituitary is evoked by the action of the other neurohypophysial hormone, oxytocin.

Other humoral transmitters such as adrenaline, acetylcholine, 5-hydroxytryptamine and histamine have been suggested from time to time, including a corticotrophin releasing factor (CRF) described by Saffran, Schally and Benfey (1955), but the evidence for their mediation is equivocal and incomplete. The unknown neurohumor has not been identified with certainty.

Control of Anterior Pituitary Activity by 'Feedback Mechanisms'

Not only does the central nervous system modulate adenohypophysial activity, but there are also strong indications that the hormones secreted by the adenohypophysial target glands react back on to the hypothalamus (as well as directly on the anterior pituitary). This has come to be called a 'feed-back' or 'servo' control mechanism. As the concentration of a particular hormone rises in the blood, the hypothalamus in some way contrives to inhibit the release of the appropriate trophic hormone from the anterior pituitary until the target gland hormone blood concentration falls below a critical level. The hypothalamus then permits the release of trophic hormones once more and the cycle repeats itself. In this way homoeostasis is maintained.

Methods of Investigating Hypothalamic Control of Anterior Pituitary

This phenomenon has been studied in several ways: by pituitary stalk section and transplantation, hypothalamic lesions and by electrical stimulation of the hypothalamus.

Pituitary Stalk Section

It is now an established fact that after simple stalk section, the hypophysial portal vascular system regenerates across the site of section in most animals, including the monkey. However, stalk section (tractotomy) does interfere with anterior pituitary function in most instances and two explanations of this have been offered. Tractotomy (i) induces an ischaemic necrosis and atrophy with subsequent loss of functional activity of the gland, (ii) prevents a specific neurohumor(s), derived from the hypothalamus and transported through the portal blood, from acting on the chromophils of the adenohypophysis.

Since normal functional activity of the anterior pituitary persists following ablation of as much as 70 per cent of the pars distalis it is not likely that the functional deficiency after tractotomy results from ischaemic atrophy of the gland.

Pituitary Transplantation

If the adenohypophysis is transplanted to a site other than near its natural position, its functional activity is markedly reduced. Everett (1954, 1956) claims that under these circumstances some secretion of LTH only occurs. On the other hand, transplantation of the gonads, adrenal cortex or thyroid to remote parts of the body results in little loss of functional ability. This strongly suggests that the gonads, thyroid and adrenal cortex are normally stimulated by trophic hormones mediated through the general circulation, whereas the anterior pituitary is activated by a humoral agent transmitted to the glandular cells via the hypophysial portal circulation.

Hypothalamic Lesions

Small, bilateral lesions produce differential effects on hormone secretion by the adenohypophysis, whereas lesions, large enough to transect functionally the pituitary stalk, markedly decrease pituitary function.

Hypothalamic Stimulation

Electrical excitation of various regions of the hypothalamus shows that localized areas are concerned with the secretion of the different trophic hormones. Direct stimulation of the gland itself, provided there is no spread of the stimulus, is without effect.

Hypothalamic Control of Secretion of Trophic Hormones

The hypothalamus would appear to be the focal point of convergence of neural pathways mediating the secretion of trophic hormones by the anterior pituitary gland.

Gonadotrophic Hormones

The pituitary gland may be ' denervated ' by cutting the pituitary stalk and inserting a plate between the hypothalamus and the gland or by transplanting it to a heterotopic region. The reproductive capacity of stalk-sectioned animals can be correlated with the degree of regeneration of the hypophysial portal vessels (Harris, 1950; Fortier, Harris and McDonald, 1957).

The study of pituitary grafts placed in contiguity with the hypothalamus of hypophysectomized animals has yielded two interesting pieces of evidence (Harris and Jacobsohn, 1952). (i) By transplanting male pituitary tissue under the tuber cinereum of hypophysectomized female rats, it was found that anterior pituitary tissue retains pluripotential functional capacity and that its pattern of activity in either sex depends on the stimulus emanating from the male or female hypothalamus, and is therefore dependent on the sexual differentiation of the central nervous system. (ii) By grafting the pituitary of an infant animal under the tuber cinereum of a hypophysectomized adult of the same species, it was found that the onset of puberty could not be attributed solely to the degree of maturation of cells in the gonads or anterior pituitary but is probably regulated by the maturation of a neural mechanism within the hypothalamus. Cases of precocious puberty occurring in association with localized tumours of the hypothalamus lend support to this concept.

Profound atrophy of the testes and ovaries occurs when the pituitary is transplanted to a distant site in the body, although the testes in rats may be maintained possibly by the continuous release of LTH (Goldberg and Knobil, 1957).

Hypothalamic lesions may affect the secretion of gonadotrophic hormones and thereby gonadal activity as shown by cessation of sexual cycles, genital atrophy, precocious puberty, or a state of persistent oestrus. The latter condition is brought about by the continuous release of FSH and failure of the rhythmic secretion of LH and is probably due to the lesion destroying in the anterior hypothalamus (below the paraventricular nuclei and behind the optic chiasma) an area which normally inhibits the secretion of FSH through the hypophysial portal mechanism. It is possible that oestrogens inhibit FSH secretion by acting on this hypothalamic region (Flerko and Szentagothai, 1957). Lesions in the median eminence are frequently associated with marked sexual atrophy and cessation of gonadal secretion consequent upon reduction of FSH release.

Electrical stimulation in the region of the median eminence evokes discharge of LH and ovulation in the rabbit and lends further credence to the concept of a neurohumoral agent.

Adrenocorticotrophic Hormone

In considering the influence of the hypothalamus over the secretion of ACTH it should be remembered that both the anterior pituitary and adrenal cortex have an autonomous basal level of secretion. The evidence suggests that the integrity of the hypothalamo-hypophysial unit is essential for the release of ACTH in response to neurogenic stimuli, whereas systemic stresses, such as trauma or changes in the composition of the systemic blood, may evoke ACTH secretions in pituitary tissue isolated by transplantation or stalk section: the effect of such stresses, nevertheless, may in part be mediated by the hypothalamus.

Lesions in the posterior part of the tuber cinereum, in the mammillary bodies, or in the anterior part of the median eminence will markedly depress the augmented release of ACTH that occurs normally in response to stress, but whether or not they affect the resting rate of secretion of ACTH has yet to be proved. Adrenaline appears to elicit ACTH release by an action on neural elements in the median eminence and lesions in this region inhibit the release of ACTH after administration of adrenaline, oxytocin, 5-hydroxytryptamine and histamine. Electrical stimulation of these regions induces lymphopenic and eosinopenic responses, decreased adrenal ascorbic acid, increased corticoids in adrenal vein blood and other evidences of increased adrenal cortical activity.

Thyrotrophic Hormone

The hypothalamus appears to maintain the normal secretion of TSH and to modify the rate of secretion during conditions of stress. Emotional stimuli which normally inhibit TSH release, and exposure to a cold environment which enhances the production of TSH, are ineffective when the pituitary is ‘ denervated ’. Complete stalk section and translocation of the pituitary remote from the hypophysial portal vessels reduce the basal level of thyroid activity which, however, is not so low as in the hypophysectomized animal. This residual activity of the thyroid when the pituitary is disconnected from the hypothalamus may result from autonomous function by its cells or represent TSH secretion by the ‘ denervated ’ pituitary.

Micro-injections of thyroxine into a localized region of the anterior hypothalamus depress TSH secretion from intact pituitary tissue, as will intrapituitary injection, indicating a direct action of thyroxine on the anterior pituitary as well as an effect mediated by the hypothalamus.

The normal resting rate of TSH secretion is undoubtedly reduced by lesions in the anterior hypothalamus placed between the paraventricular nuclei and the median eminence. The effects range from complete atrophy to mere reduction in ^{131}I uptake.

An increase in thyroid activity, which may be assessed by the rate of release of thyroidal ^{131}I and the blood concentration of protein-bound ^{131}I, is observed following electrical stimulation in the region of the supra-opticohypophysial tract.

Lactogenic Hormone

The available data suggest that LTH may be under less central control than FSH and LH. The effect of stalk section on LTH secretion is not clear. Some workers contend that it causes failure of lactation, others maintain that it does not. Dandy (1940) has described the case of a young woman in whom stalk section was followed by normal menstrual cycles, pregnancy, labour and lactation, but since regeneration of the hypophysial portal vessels may have occurred the results are equivocal.

When pituitary grafts are placed beneath the median eminence of the tuber cinereum in hypophysectomized lactating animals, there is a posterior pituitary deficiency which leads to failure of the milk-ejection reflex, that is milk is produced but cannot be delivered. Everett (1954, 1956) reported augmented release of LTH from pituitary transplants in rats which may maintain luteal function.

There is persuasive evidence that suckling and coitus evoke LTH release, suggesting the intermediation of a central nervous mechanism.

THE POSTERIOR PITUITARY

Anatomy

The neurohypophysis is composed of three parts: (i) the median eminence of the tuber cinereum, (ii) the infundibular stem or neural stalk, and (iii) the infundibular process or neural lobe.

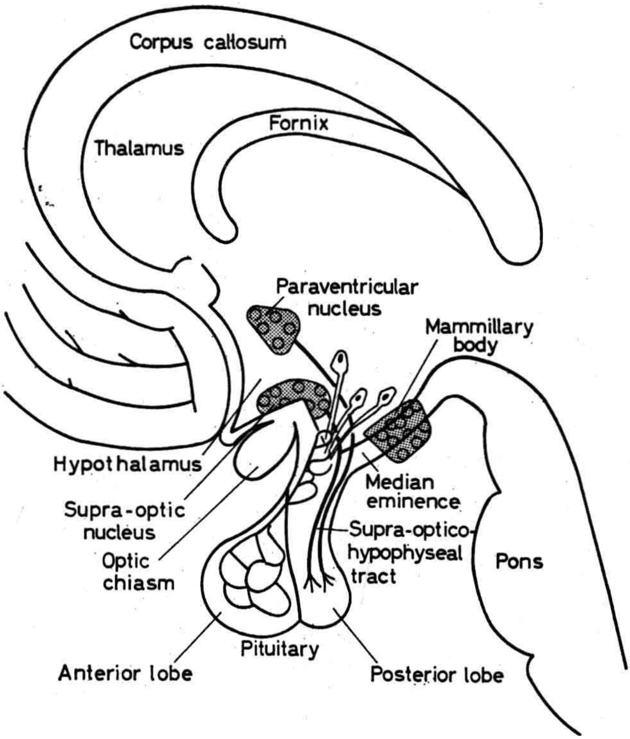
The neural stalk, with its sheath of portions of the pars glandularis, is designated the hypophysial stalk. The neuro-hypophysial tissue is uniform throughout and differs from hypothalamic tissue. It is innervated by the supra-opticohypophysial tract (about 100,000 fibres in man), originating in the paraventricular and supra-optic nuclei in the hypothalamus.

Hormones of the Neurohypophysis

Two hormones have been extracted from the neurohypophysis: (1) Vasopressin (Antidiuretic hormone ADH), (2) Oxytocin.

Vasopressin is a polypeptide amide consisting of 8 amino-acids arranged in peptide linkage to form a ring of 5 amino-acids and a side chain of 3 amino-acids (Du Vigneaud, Lawler and Popenhoe, 1953a). There are two vasopressins: arginine vasopressin is secreted in man, and lysine vasopressin has been isolated from hogs.

Oxytocin is also an octapeptide amide (Du Vigneaud and colleagues, 1953b) and it differs from vasopressin only in two of its amino-acids. As might be expected, therefore, from the close structural similarity of the hormones they possess overlapping biological activities. Synthetic vasopressin possesses certain oxytocic (uterotonic) and milk-ejecting (galactogogue) activities and pure oxytocin exerts some slight vasopressor and antidiuretic effects (Van Dyke, Adamsons and Engel, 1955). The molecular weight of each is about 1,000 and each has been extracted from the hypothalamus as well as the neurohypophysis.



'Portal System' of vessels running from the Hypothalamus to the Anterior Pituitary

Figure 1

(Reproduced from Mazer and Israel's *Diagnosis and Treatment of Menstrual Disorders and Sterility*, 4th ed., by courtesy of Paul B. Hoeber)

Analogues of oxytocin, for example oxypressin and vasotocin, have been synthesized but there is no evidence that they are naturally produced in the human.

Theory of Neurosecretion

It has been known since Loewi's (1921) classical experiments that peripheral nerve endings release chemical mediators which transmit impulses from the nervous system to the effector organ. The evidence accumulated over recent years strongly suggests that the neurohypophysial hormones might likewise be a product of nervous elements. This production of hormones in the central nervous system is called neurosecretion.

The prevailing concept is that the hormones of the posterior pituitary gland are synthesized within the perikaryon of the neurones of the supra-optic and paraventricular nuclei, and then migrate along the axoplasm of the axons of the supra-opticohypophysial tract to be stored in the three parts of the neurohypophysis, or liberated into the blood in response to various stimuli. The fibres of the supra-opticohypophysial tract, which link the hypothalamus and neurohypophysis into a functional unit, have the triple function of conducting nerve impulses, transporting neurosecretory material and regulating the release of hormones into the blood.

The accumulation of neurosecretion above a cut in the supra-opticohypophysial tract points to the centrifugal streaming of the neurosecretory material.

The paraventricular nuclei and the supra-optic nuclei are among the most highly vascularized nuclei in the brain. In view of this fact, it would seem more feasible that the hormones formed in these nuclei should be discharged directly into the surrounding capillaries, without depending on the nerve tracts. If this were so, then section of the supra-opticohypophysial tract at a level between the nuclei and the median eminence of the neurohypophysis would not be expected to result, as it does, in diabetes insipidus, failure of the milk-ejection reflex, etc. There are three possible explanations of this observation: (i) section of the tract causes retrograde degeneration of the paraventricular and supra-optic nuclei, hence the signs of glandular deficiency are due to a paucity of secreting cells in the nuclei; (ii) the nuclear capillaries may be impermeable to the polypeptide (or larger) molecules comprising the hormones; (iii) the hormones are not fully 'matured' until they pass along the axons of the supra-opticohypophysial tract (Gerschenfeld, Tramezzani and De Robertis, 1960).

The histological termination of the fibres of the supra-opticohypophysial tract is obscure, but they have in common perivascular endings throughout the neurohypophysis. The exact mechanism of release of posterior lobe hormones, as well as the role of the pituicytes, awaits further investigation. Although it is almost certain that the pituicytes do not synthesize the posterior lobe hormones, they might be involved in some way in the mechanism of hormone release. Electron microscopy studies by Gerschenfeld, Tramezzani and De Robertis (1960) have revealed neurosecretory granules in the axoplasm of axons of the preopticoneurohypophysial tract and infundibular process in toads. At the endings of the axons synaptic vesicles have also been observed. These investigators have postulated that the synaptic vesicles elicit the release of the hormones from the