J. Pharm. Pharmac., 1977, **29**, 649–656 *Received May 6, 1977*

REVIEW

The endocrine function of the hypothalamus

JULIA C. BUCKINGHAM

Department of Pharmacology, Royal Free Hospital School of Medicine, London, WC1N 1BP, U.K.

The role of the pituitary gland in the control and integration of endocrine activity was first realized over 50 years ago. However, although the nervous and endocrine systems were recognized as the two major co-ordinating mechanisms of the body, some 20 years elapsed before Harris and his colleagues demonstrated the fundamental importance of the brain, in particular the hypothalamus, in the regulation of pituitary activity. These studies naturally led endocrinologists throughout the world to study the inter-relations of the nervous and endocrine systems and consequently neuroendocrinology is now a rapidly expanding subject.This article is intended as a brief review of our current knowledge of the functional relations between the hypothalamus and the pituitary gland.

The pituary gland

The pituary gland (Fig. 1.) is a bilobed structure located in the sella turcica immediately below the median eminence area of the hypothalamus. The two lobes are derived embryologically from different sources. The anterior lobe or adenohypophysis, which is differentiated into three distinct zones, the pars distalis, pars intermedia and the pars tuberalis, is derived from ectodermal tissue of the oral epithelium. The posterior lobe or neurohypophysis is formed from nervous tissue of the diencephalon.

Although the adenohypophysis receives few if any nerve fibres it is linked to the median eminence area of the hypothalamus by a highly specialized portal vascular system from which it receives its entire blood supply. The hypothalamus is supplied with blood by a branch of the internal carotid artery which forms a capillary plexus, the primary plexus, within the median eminence. The blood flows into the hypothalamo-hypophysial portal vessels which pass down the infundibulum to the adenohypophysis where they break into sinusoidal vessels. The nervous and vascular supplies of the neurohypophysis differ markedly from those of the adenohypophysis. The neurohypophysis is well supplied with nerve fibres being connected to two prominent groups of cells in the hypothalamus, the supraoptic and paraventricular nuclei, by the well defined supraoptico-hypophysial tract. There is no vascular link between the hypothalamus and the neurohypophysis but the latter is supplied directly by a pair of posterior hypophysial arteries which originate from the internal carotid arteries.

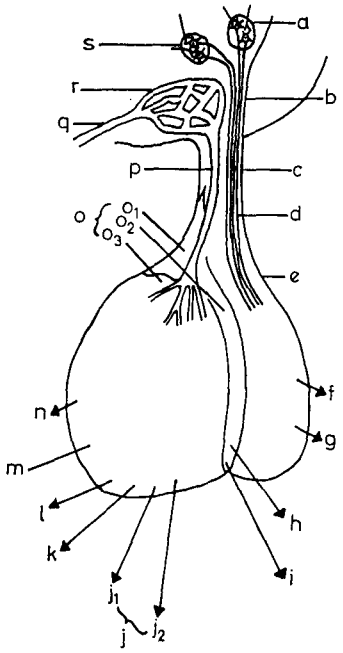

FIG. 1. The pituitary gland and its anatomical relations with the hypothalamus. a—paraventricular nucleus, b—median eminence, c—infundibulum, d—supraoptico-neurohypophysial tract, e—neurohypophysis, f—vasopressin (osmotic balance), g—oxytocin (uterine contraction, milk production), h—melanocyte stimulating-hormone (skin colour), i—corticotrophin-like intermediate lobe peptide (insulin secretion?), j—gonads (j_1—lutenizing hormone, j_2—follicle stimulating hormone), k—corticotrophin (adrenal cortex), l—thyrotrophin (thyroid gland), m—prolactin (lactation), n—growth hormone (normal growth), o—adenohypophysis (o_1—pars tuberalis, o_2—pars intermedia, o_3—pars distalis), p—hypothalamo-hypophysial portal vessels, q—internal carotid artery, r—capillary plexus, s—supraoptic nucleus.

The anterior pituitary gland is responsible for the synthesis and release of at least 8 hormones of which physiological actions are well understood. The secretions of the pars distalis include growth hormone (normal growth and development), thyrotrophin (thyroid gland activity), corticotrophin (maintenance of the adrenal cortices), prolactin (lactation), luteinizing hormone (LH) and follicle stimulating hormone (FSH) (gonadal function), while the pars intermedia produces α- and β-melanocyte stimulating hormones (α-MSH and β-MSH) (camouflage in lower vertebrates). Recent evidence suggests that the pars intermedia also secretes a substance similar to corticotrophin, the corticotrophin-like intermediate lobe peptide (CLIP), which may be associated with the control of insulin secretion. With the exception of two glycoproteins (LH and FSH) the hormones of the adenohypophysis are polypeptides. Each of the hormones is synthesized by a specific cell type randomly distributed throughout either the pars distalis or pars intermedia.

The posterior pituitary gland secretes only two hormones each of which is an octapeptide: vasopressin, the antidiuretic hormone, is concerned with osmotic balance and oxytocin with mammary milk production and uterine contractions.

Hypothalamo-neurohypophysial link

Although the nerve fibres which connect the supraoptic nucleus (SON) and paraventricular nucleus (PVN) of the hypothalamus with the posterior pituitary gland were described in 1930 it was not until the late 1940's and early 1950's that the functional relationship between these nuclei and the neurohypophysis was realized. Histological studies demonstrated that the amount of Gomori positive material in the SON and PVN can be roughly correlated with the vasopressin content of the neurohypophysis. It also became evident that the nuclear regions themselves contain material with posterior pituitary activity and that neurosecretory material tends to accumulate on the proximal side of a cut in the pituitary stalk (Green, 1966; Sloper, 1966). It is now firmly established that both oxytocin and vasopressin are synthesized within the cell bodies of the SON and PVN. Vasopressin is produced predominantly by the supraoptic nucleus and oxytocin by the paraventricular nucleus (Olivecrona, 1957) although both nuclei are capable of synthesizing either hormone. Synthesis takes place in the endoplasmic reticulum. The octapeptides immediately become associated with a carrier protein, neurophysin, and the hormone/protein complex is 'packaged' by the cell's golgi apparatus. The resulting membrane bound granules are transported by axonal flow (Sloper, 1966) to the nerve endings in the neurohypophysis. The concept of axonal flow in these neurosecretory cells is well documented and is supported by the accumulation of stainable neurosecretory material with vasopressin- and oxytocin-like activity above transections of the pituitary stalk but, as in other nerve cells, the mechanisms producing the axonal flow are not understood. Two neurophysins (neurophysin I & II) have been isolated and their amino acid sequences determined. A third neurophysin has been identified in some species but this is now believed to be merely a precursor of neurophysin I. It has been suggested, and indeed would seem logical, that one neurophysin should carry specifically oxytocin and the other vasopressin, however, the evidence available at present indicates that both octapeptides are capable of binding with either neurophysin. Neither oxytocin nor vasopressin is released immediately from the nerve endings in the neurohypophysis but are stored as membrane bound granules until required. Release of the hormone/protein complex into the blood involves a process of exocytosis during which the hormone becomes dissociated from its carrier protein.

The release of both oxytocin and vasopressin from the neurohypophysis is controlled almost entirely by nervous reflex responses which involve the passage of information from a receptor to the brain and ultimately the neurosecretory cells of the hypothalamo-neurohypophysial complex. Vasopressin production is most readily influenced by changes in either blood volume or osmotic pressure although emotional stimuli may also influence its release. Changes in blood volume are thought to be monitored through 'blood volume' receptors located in blood vessels in the thorax and by the stretch receptors in the atria of the heart. The osmoreceptors are present primarily in the hypothalamus itself although there is some evidence that in the rat such receptors are also present in the hepatic portal vessels.

Stimuli from the genitalia and mammary glands, as well as psychic influences, are important in the control of oxytocin secretion. In domestic animals oxytocin is also released during labour and presumably plays an important role in the control of uterine contractions. However, it is not agreed that parturition is precipitated by a sudden release of oxytocin and the causative factors promoting the discharge of oxytocin during labour are not fully understood.

Hypothalamic control of anterior pituitary function

(a) *The evidence*

When Harris (1937) and Brooks (1938) first suggested, perhaps rather tentatively, that the adenohypophysis may be controlled by humorally transmitted stimuli from the hypothalamus little interest was expressed in their hypothesis. This was probably mainly because at that time it was thought that the direction of blood flow in the hypothalamo-hypophysial portal vessels (which form the only anatomical link of the hypothalamus with the anterior pituitary gland) was from the adenohypophysis to the hypothalamus. The direction of flow in these vessels subsequently became a matter of controversy and it was not until 1949, after the development of an elegant technique for the direct observation of blood flow in the portal vessels of rats that Green and Harris were able to state dogmatically that the blood passes from the hypothalamus to the pituitary gland.

It is now firmly established that the synthesis and release of the hormones of the adenohypophysis are controlled by substances released from nerve endings in the hypothalamus and conveyed to the anterior pituitary gland via the portal vessels. The evidence which demonstrated the fundamental importance of the hypothalamus and the hypothalamo-hypophysial portal vessels came mainly from experiments which involved transection of the pituitary stalk, transplantation of the pituitary gland to a site remote from the sella turcica or electrical stimulation of the hypothalamus.

Transection of the pituitary stalk in rabbits is followed by gonadal atrophy (Harris, 1937) and subsequent recurrence of oestrus (Brooks, 1938). Histological studies demonstrated that, unless a wax-paper plate is inserted between the two cut ends, transection of the stalk is followed, almost invariably, by regeneration of the portal vessels and, that the degree of regeneration could be correlated with the degree of restoration of pituitary activity (Harris, 1950).

The simple experiment of removing the pituitary gland from the sella turcica to another site of the body also demonstrated the role of the hypothalamus in the control of anterior pituitary function. If the transplanted tissue is placed in a site remote from the sella turcica, for example the anterior chamber of the eye, the kidney capsule or temporal lobe of the brain, partial or complete atrophy of the ovaries, testes, reproductive tracts, thyroid gland and adrenal cortices is observed together with a reduction in the rate of body growth. If, however, the transplanted tissue is placed in the vicinity of the hypothalamus and pituitary stalk, regeneration of the hypophysial portal vessels then occurs and anterior pituitary function is restored as shown by the maintenance of reproductive, thyroid and adrenocortical activity (Harris & Jacobsohn, 1952).

As early as 1936 it was realized that diffuse electrical stimuli applied to the head or lumbar spinal cord of rabbits (Marshall & Verney, 1936) or rats (Harris, 1936) enhance adenohypophysial activity. In an attempt to delimit the neural structures involved, closely localized electrical stimuli were applied directly to regions of the hypothalamus and anterior pituitary gland of anaesthetized animals. Electrical stimulation of the pituitary gland was ineffective in causing gonadotrophin release but fully effective if applied to discreet areas of the hypothalamus (Harris, 1937; Haterius & Derbyshire, 1937; Markee, Sawyer & Hollingshead, 1946). Corresponding lesions in the hypothalamus were, however, not always effective in suppressing pituitary activity. Moreover, since the electrical stimulation of the hypothalamus was performed in anaesthetized animals the possibility existed that the endocrine activity observed was the result of a complication induced by the anaesthesia.

Harris (1947) believed it important to study endocrine function in conscious animals and, accordingly, developed an ingenious method for 'remote control stimulation' of the hypothalamus in unanaesthetized rabbits. Using this technique experiments could be performed for relatively long periods without concomitant operative trauma. Furthermore the experiments could be repeated many times in the same animal thereby reducing the chances that variable factors, such as differences in the nutritional or oestrus state of the animal, influenced the result. The method involved a preliminary operation in which a small flat coil was inserted between the skull and scalp. The inner turn of the coil was connected to an electrode implanted in the hypothalamus and the outer turn of the coil to a second electrode, the indifferent electrode. Stimulation of the hypothalamus was readily achieved by placing the animal's head in an electromagnetic field and inducing a voltage in the buried coil. The experiments which followed demonstrated clearly that stimulation of discreet areas of the hypothalamus increases markedly the activity of the reproductive system (Harris, 1948) thyroid gland (Colfer, 1949) and adrenal cortex (de Groot & Harris, 1950). It was these studies, which are now regarded as a major landmark in endocrinology by

biologists throughout the world, that led Harris to postulate, correctly, that the hypothalamus liberates chemical transmitter substances into the hypophysial portal vessels which are carried to the anterior pituitary gland to exert a specific influence over the activity of the gland.

(b) *Isolation of the hypothalamic hormones*

The realization that the hypothalamus contains substances capable of affecting pituitary activity naturally led to attempts to isolate and identify these neurohormones. It seemed unlikely that the traditional chemical transmitters of the parasympathetic and sympathetic nervous system, acetylcholine and noradrenaline, were responsible since neither influenced adenohypophysial activity when injected directly into the pituitary gland. Histamine and adrenaline were also ineffective in this respect despite their being present in considerable quantities in the hypothalamus. Attempts to separate the hypothalamic hormones, or 'releasing-hormones' as they are known, has therefore primarily involved chemical extractions of the hypothalamus. This laborious work, which has been carried out mainly in the laboratories of Schally and Guillemin, has not been without problems. Since the hypothalamus contains only minute quantities of each releasing hormone extractions were performed on large numbers of pooled hypothalami. The yields from each extraction were usually very low and the 'pure hormone' fractions, which are generally peptide in nature, sometimes contaminated and unstable. Nevertheless, several releasing hormones have now been isolated by chemical extraction techniques, and their structures determined (Fig. 2). It was originally postulated that each pituitary hormone is controlled by a single hypothalamic neurohormone but it now appears that the system is more complex. A pituitary trophic hormone may be under both excitatory and inhibitory influences from the hypothalamus and conversely a hypothalamic neurohormone may activate more than one pituitary cell type. For example, growth hormone production is controlled by both a growth hormone release inhibiting hormone, 'somatostatin', and a growth hormone releasing hormone. Prolactin is predominantly under the control of prolactin inhibiting hormone (now believed to be simply dopamine), although evidence is accumulating that there may also be a prolactin releasing hormone which is similar to, if not identical with, the thyrotrophin-releasing hormone, and the gonadotrophin-releasing hormone stimulates the release of both follicle stimulating hormone and luteinizing hormone.

One of the first postulated hypothalamic hormones was the corticotrophin releasing factor (CRF) (de Groot & Harris, 1950) but its precise chemical nature is not yet known. Chemical extraction of hypothalamic tissue has yielded several polypeptides with varying degrees of corticotrophin releasing activity. Vasopressin is the most active of these peptides but it is considerably less potent than a crude hypothalamic extract in stimulating the synthesis and release of corticotrophin from pituitary tissue both *in vivo* and *in vitro*. The use of differential bioassay techniques has provided another approach to the determination of the chemical nature of CRF. Since CRF is believed to be a polypeptide similar to vasopressin valuable information of its chemical nature may be obtained by comparison of the dose response relations of various polypeptides related to vasopressin with those of hypothalamic extracts using two or more bioassay systems for the determination of CRF activity. Many vasopressin analogues have now been tested for their ability to release ACTH using both an *in vitro* assay technique (Buckingham & Hodges, 1977a) and an *in vivo*/*in vitro* system (de Wied, 1967). Oxypressin and arginine vasotocin exhibited marked CRF activity in both assay systems and the dose response relations of the latter closely resembled those of hypothalamic extracts (Buckingham & Hodges, 1977a; Buckingham & van Wimersma Greidanus, 1977). There is no evidence that this observation has any physiological significance but, in this respect it is interesting to note that arginine vasotocin has been demonstrated in the pineal gland, cerebrospinal fluid and hypothalamus of certain mammalian species. However, as yet, no physiological role has been assigned to it.

Recently a new approach to the study of the chemical nature of CRF has been developed by Jones and his colleagues. They demonstrated that 5-hydroxytryptamine selectively stimulates the release

Thyrotrophin releasing hormone	(Pyro)Glu-His-Pro(NH_2)
Growth hormone Release inhibiting hormone	H–Ala–Gly–Cys–Lys–Asp–Phe–Phe–Trp–Lys–Thr–Phe–Thr–Ser–Cys–OH
Gonadotrophin releasing hormone	(Pyro)Glu–His–Trp–Ser–Tyr–Gly–Leu–Arg–Pro–Gly(NH_2)
Prolactin release inhibiting hormone	dopamine?

FIG. 2. Structures of some hypothalamic hormones.

of CRF but not vasopressin from hypothalamic tissue *in vitro*. They have isolated two peptide fractions with CRF activity from the incubation medium of the hypothalamus (Jones, Hillhouse & Burden, 1976). These 'hormones' appear to be rather unstable and consequently their amino acid sequence has not yet been determined. However, it is hoped that this will soon be achieved and thus that the chemical nature of the corticotrophin releasing factor(s) will finally be elucidated.

(c) *Localization of hypothalamic hormones*

Although the hypothalamus is considered the source of peptide hormones which influence the pituitary gland and other target tissues outside the brain, the specific cells which produce these hormones have yet to be isolated. Because of the extreme complexity of the cellular structure of the hypothalamus compared with other endocrine organs the precise site of production of many of the hypothalamic hormones remains obscure. Assay of even a very small piece of hypothalamus obtained by microdissection enables only the area and not the precise cells producing the hormone to be determined. More detailed information has been obtained from experiments involving the placement of electrolytic lesions in specific hypothalamic regions (Szentágothai, Flerkó & others, 1968) or by evaluation of the releasing hormone concentration in the 'hypothalamic islands' of rats submitted to hypothalamic deafferentation (Halász, 1969). However, most of our knowledge concerning the site of neurohormone production has come from histological studies. The classical work on the magnocellular neurosecretory system of the hypothalamus demonstrated the formation of neurosecretory material in the perikarya of supraoptic and paraventricular neurons and its transportation along the nerve axons to the posterior pituitary gland. However, these techniques were not sensitive enough to detect the hypothalamic releasing hormones. Recently, highly sensitive chemical immunofluorescence methods have been developed in an attempt to localize these hormones. Preliminary studies using these techniques have confirmed directly that oxytocin and vasopressin are secreted by the magnocellular system and indicated strongly that the hypophysiotrophins are synthesized within the parvicellular nuclei. The gonadotrophin releasing hormone (GnRH) and 'somatostatin' have been demonstrated in granules within axon terminals close to the portal capillaries in the median eminence suggesting that the releasing hormones are transported along the axons of the parvicellular nuclei and secreted directly into the portal blood vessels. However, direct neurosecretion from the parvicellular structures to the portal vessels may not be the only route by which the releasing hormones reach their target organs. Hypothalamic hormones have now been demonstrated both in regions of the hypothalamus outside the parvicellular and magnocellular structures and in the cerebrospinal fluid, csf) (Zimmerman, 1976). The physiological significance of these observations is not known but, recent evidence suggests that releasing hormones may also pass directly from the csf to the portal blood. Injection of thyrotrophin releasing hormone into the third ventricle causes rapid release of thryrotrophin from the pituitary gland while a similar injection of GnRH facilitates the release of the gonadotrophins. Histological examination of the ependymal cells of the median eminence has demonstrated the presence of elongated cells, the tanycytes, interposed between the csf and portal capillaries which are believed to perform a transport function. The cells have a variable number of ciliated microvilli projecting into the third ventricle and a basal process which intermingles with the perivascular basement membrane of the portal capillaries (Fig. 3). The fact that the cells are capable of absorbing endogenous peroxide from

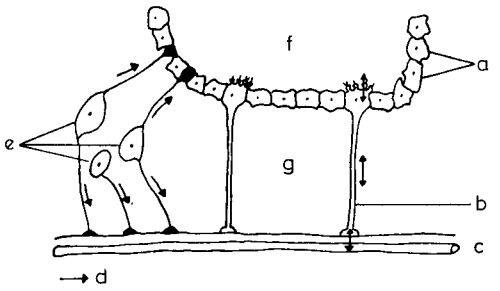

FIG. 3. Means by which hormones may be transported between the hypophysial portal blood vessels and the cerebrospinal fluid. a—ependymal cells, b—tanycyte, c—portal capillary, d—direction of transport, e—releasing hormone cells, f—third ventricle, g—median eminence.

the csf suggests that transport may occur from the csf towards the basal processes, but the possibility that transport may occur in the opposite direction cannot be disregarded. The full physiological role of the tanycytes is not understood. Clearly they may be associated with the transportation of the releasing hormones and substances which influence their production. However, they may also be concerned with the passage of substances from the systemic circulation to the cns. Indeed they may provide an

important route by which steroids and pituitary hormones enter the csf to influence the production of the hypothalamic releasing hormones by negative feed back mechanisms (see control of hypothalamic hormones).

(d) *Control of the hypothalamic hormones*

Many parts of the brain contribute to the influx of information which controls the synthesis and release of the hypothalamic hormones. The brain structures important in this regard are believed to be the septum, hippocampus, anterior thalamus, amygdala, piriform cortex and midbrain although additional areas may influence hypothalamic activity indirectly. It appears that the production of a single hormone involves the integration and differentiation of a barrage of afferent impulses, which may be either excitatory or inhibitory, from several regions of the brain. The chemical nature of the hypothalamic neurons which influence the activity of the releasing hormone cells is not yet fully understood. Many monoaminergic and cholinergic pathways can be traced through the hypothalamus and changes in the hypothalamic content of noradrenaline, dopamine, acetylcholine and 5-hydroxytryptamine can be correlated with changes in endocrine function. These observations have been confirmed by studies involving the administration of such putative transmitter agents, their agonists and antagonists both *in vivo* (van Loon, Scapagnini, & others, 1971) and *in vitro* (Jones & others, 1976). However, this work has also indicated that the production of the hypothalamic hormones may be influenced by other substances, notably γ-aminobutyric acid and glycine.

In addition to influences from higher centres of the brain, negative feedback mechanisms play an important part in the regulation of certain hypothalamic and pituitary hormones. For example, administration of thyroxine inhibits the release of thyrotrophin-releasing hormone and thyrotrophin (Kajihara & Kendall, 1969) whilst basal hypothalamic corticotrophic releasing activity and pituitary adrenocorticotrophic activity is reduced by corticosteroids (Buckingham & Hodges, 1977b). The evidence in the literature suggests that not only the target organ hormones influence the activity of the hypothalamo-hypophysial complex but that the pituitary hormones and possibly the hypothalamic hormones themselves may feed back in a similar manner. Fig. 4 summarizes the possible sites of action of these feedback effects.

The relative importance of negative feedback in the control of the functional capacity of the hypothalamo-pituitary complex is not clear. It appears that the activity of each hypothalamo-pituitary—target organ axis at any time is controlled by a fine balance between the functional state of the system and information received from higher centres of the brain.

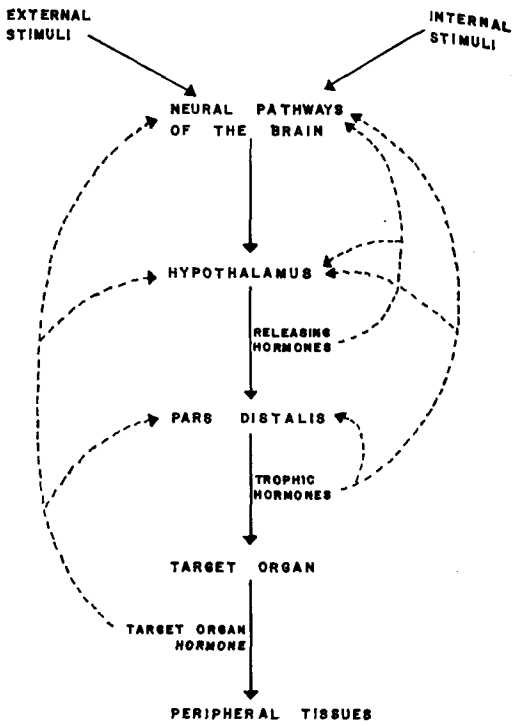

FIG. 4. Brain-pituitary-target organ control mechanisms.

(e) *Clinical uses of releasing hormones*

Until the introduction of synthetic thyrotrophin-releasing hormone (TRH) and gonadotrophin-releasing hormone (GnRH) clinical neuroendocrinology did not exist as a separate discipline. The availability of these hypothalamic regulatory hormones permits the direct evaluation of pituitary function for the first time (Besser & Mortimer, 1976). Consequently, attempts can now be made to study the capacity of the pituitary gland to produce the trophic hormones, thus enabling accurate differentiation between diseases of the pituitary gland and hypothalamus as apparent causes of pituitary dysfunction. The standard TRH test (Ormston, Garry & others, 1971) has certainly proved a useful tool in the diagnosis of thyroid disease and in the assessment of pituitary TSH reserve in patients with pituitary lesions (Hall,

Besser & others, 1972). In this test the blood TSH concentration is estimated at various times after intravenous administration of TRF. Basal triiodothyronine (T_3) and thyroxine (T_4) are also assessed. In patients with primary hypothyroidism TRH causes an exaggerated rise in the already elevated TSH concentrations while those with hypothyroidism due to pituitary disease usually fail to respond. Because of the already high circulating concentrations of T_3 and T_4, TRH is also generally ineffective in subjects with hyperthyroidism but, with this test, it is not possible to distinguish between hyperthyroidism and, for example, autonomous thyroid adenomata (Evered, Clark & Peterson, 1974). Thyrotrophin-releasing hormone also exhibits marked prolactin-releasing activity and, accordingly, it is also used in investigations of abnormal prolactin production (Giustina, Trojsi & others, 1975). A similar standard GnRH test (in which LH and FSH are estimated at various times after intravenous administration of GnRH) is also of considerable diagnostic value (Mortimer, Besser & others, 1973). Like the TRH test it provides a test for pituitary reserve and enables differentiation between brain-hypothalamic and pituitary disease. Since pure corticotrophin-releasing hormone is not available, there is no comparable test for use in the diagnosis of pituitary-adrenal dysfunction. Vasopressin has often been used as a test for pituitary ACTH reserve. However, vasopressin is not chemically identical with corticotrophin releasing hormone (Buckingham & Hodges, 1977a) and the validity of this test is doubtful.

In addition to their diagnostic usefulness the hypothalamic releasing hormones are of potential value in the treatment of hypothalamic and pituitary disease. Certainly intravenous infusion of growth hormone release inhibiting hormone is effective in reducing the excessive growth hormone levels in patients with acromegaly. However, the results of treating patients suffering from infertility with GnRH have been disappointing. Increases in sperm count and motility have been reported in patients with oligospermia but the counts later fell despite continued therapy. Attempts to induce ovulation with GnRH have also been relatively unsuccessful although Besser & Mortimer (1976) have reported some success in the treatment of secondary amenorrhea in patients with anorexia nervosa. Various GnRH analogues which cause prolonged gonadotrophin secretion (Fujino, Kobayashi & others, 1972; Coy, Schally & others, 1975) have now been synthesized. The increased activity of these analogues was believed to be associated with a higher affinity for the hormone receptor (Monahan, Amoss & others, 1973) but recent evidence indicates that these peptides are more resistant to enzymic degradation and that consequently their bio-half life is prolonged (Marks & Stern, 1974). Clinical trials are now in progress with these superactive analogues and the results look promising. In addition to analogues with enhanced activity, certain competitive inhibitors of GnRH have also been synthesized (Vale, Grant & others 1972; Coy & others, 1975). Inhibitory analogues with both a resistance to *in vivo* degradation and a high affinity for the receptor (but which interact in a way not leading to FSH and LH release) may be potentially useful as contraceptive agents (Coy & others, 1975).

The use of pharmacological agents known to influence the activity of releasing hormone cells has been effective in the treatment of some endocrine disorders. There are many reports of successful attempts to induce ovulation in patients suffering from infertility by treatment with bromocriptine, a dopamine receptor agonist. Bromocriptine also effectively reduces blood prolactin concentrations in subjects with hyperprolactinaemia and paradoxically reduces growth hormone production in acromegalic patients, while cyproheptadine, a 5-HT antagonist, has been successful in the treatment of 'hypothalamic Cushing's syndrome'. Clearly a deeper understanding is necessary of the neural pathways within the hypothalamus which influence the synthesis and release of the hypothalamic hormones so that 'releasing hormone therapy' is superceded at least to some extent, by treatment with neurotransmitter agents, their agonists and antagonists.

Concluding Remarks

While the brain is the 'master gland' controlling the endocrine system, in the last decade it has become increasingly apparent that it is also influenced by hormones. A detailed discussion of this aspect of endocrine physiology is beyond the scope of this article. However, it should perhaps be mentioned that, in addition to their 'feedback effects', certain hormones, notably the sex steroids and corticosteroids, act directly on the central nervous system to produce profound behavioural effects. This is believed to be of particular importance in the foetus and new born animal since the hormonal environment of the brain during this 'critical period' imprints a pattern of behaviour and endocrine function which persists throughout life.

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