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HYPOTHALAMIC REGULATORY HORMONES: PHYSIOLOGICAL AND CLINICAL IMPLICATIONS

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Summary

The hypothalamic regulatory hormones used for clinical studies are TRH, Gn-RH and somatostatin. In addition, as dopamine appears to be a physiological PIF, the dopamine agonists such as bromocriptine, could be considered as functional analogues of PIF. Gn-RH can be used to study the hypothalamic-pituitary gonadal relationship and to test the secretory reserve capacity of the gonadotrophs in disease states. Unfortunately Gn-RH testing discriminates between pituitary and hypothalamic diseases only poorly. However gonadotrophin deficient men or women may be successfully treated with long-term Gn-RH with induction of puberty, potency, spermatogenesis and ovulation. Somatostatin has multiple actions in inhibiting endocrine and exocrine secretion but its actions are still being explored in diabetes. Bromocriptine, a long acting dopamine agonist (a functional analogue of PIF), suppresses prolactin and is highly effective in treating many hypogonadal states since hyperprolactinaemia is common. It also lowers growth hormone in acromegaly. TRH has provided a major, accurate, sensitive and safe test of thyroid function.

Zusammenfassung

Die für klinische Zwecke brauchbaren hypothalamischen Regulationshormone sind TRH, Gn-RH und Somatostatin. Zusätzlich werden auch Dopaminagonisten, wie z.B. Bromocriptin verwendet, weil Dopamin ein physiologischer PIF zu sein scheint. Gn-RH kann verwendet werden für die Untersuchung des hypophysären Gonadotropin-Systems und für die Bestimmung der sekretorischen Reservekapazität dieses Systems bei krankhaften Zuständen. Leider vermag die Gn-RH Bestimmungsmethode nur ungenau zwischen hypothalamischen und hypophysären Störungen zu unterscheiden. Jedoch können Gonadotropindefekte männlicher oder weiblicher Patienten durch Langzeitapplikation von Gn-RH günstig beeinflusst werden und

Table 1. Hypothalamic hormones of known structure used clinically in their synthetic form. Commonly used abbreviations are shown.

1) Thyrotrophin releasing hormone	TRH
2) Gonadotrophin releasing hormone	Gn-RH LH/FSH-RH LH-RH
3) Growth hormone release inhibiting hormone or somatostatin	GHR-IH GIF SRIH, SRIF
4) Prolactin release inhibiting hormone	? DOPAMINE PRIH PIF

zwar zur Induktion der Pubertät, der Potenz, der Spermatogenese und der Ovulation. Somatostatin hat vielfache Wirkungen bei der Hemmung von endokrinen und exokrinen Sekretionsvorgängen, jedoch wird seine Wirkung beim Diabetes noch weiter erforscht. Bromocriptin als Langzeit-Dopaminagonist unterdrückt Prolactin und ist hochwirksam bei hypogonadalen Zustandsbildern, bei denen Hyperprolactinaemie häufig vorkommt. Es vermindert auch das Wachstumshormon bei Acromegalie. TRH bildet einen wichtigen, empfindlichen und genauen Test für die Schilddrüsenfunktion.

Earlier chapters have dealt with the nature and synthesis of hypothalamic regulatory hormones and some of their actions on the secretion of pituitary and other hormones. In this section I would like to review the predominantly human actions of these brain hormones and to comment on their significance in normal and pathological physiology. The explosive advances in understanding in this area have occurred since the structure of the first hypothalamic regulatory hormone was established in 1969 as a direct consequence of the bioassay work of Geoffrey Harris.

Hypothalamic hormones available for human studies

These are shown in Table 1. TRH and Gn-RH have been used in clinical investigation and to assess endocrine function in patients for 6 to 7 years and have achieved valued places in routine and research practice. Somatostatin however has such varied and widespread actions that it has not achieved any clear place as an investigational clinical weapon but study of its actions in normals has led to new concepts in our understanding of the control of the endocrine system. Although there may be peptide prolactin release inhibiting factors (PIFs) the direct action of the neurotransmitter dopamine on the pituitary cells which secrete prolactin is now widely accepted and there is a considerable body of evidence to support the view that

dopamine is a physiologically important PIF (1). If this is the case then the drugs which are long-acting dopamine agonists, used to lower prolactin secretion and growth hormone in acromegaly, should be considered as functional analogues of PIF.

The gonadotrophin releasing hormone (Gn-RH)

This decapeptide releases both gonadotrophins in a dose related manner when administered intravenously in doses between 25 and 500 μg (2). Although there is usually a simultaneous increase in circulating LH and FSH levels following an intravenous bolus injection, infusions of Gn-RH have shown that in normal men FSH secretion precedes that of LH by a few minutes, that circulating levels are pulsatile and that the LH and FSH fluctuations in concentration are asynchronous (3). This suggests that there are times when the pituitary gonadotroph is refractory to the action of the releasing hormone. As well as the different time course of release of the gonadotrophins, the pattern of response alters with age. In prepubertal children the FSH response is similar to that of the adult, but the LH response is slight and smaller than that of FSH; as the patient passes through puberty, the LH response increases to reach the adult pattern with a greater LH than FSH release (4). It would seem likely that the mechanisms involved in initiation of puberty produce increasing exposure of the relatively inactive prepubertal gonadotroph to Gn-RH. If patients with severe gonadotrophin deficiency due to such conditions as Kallman's syndrome or anorexia nervosa are treated with long-term exogenous Gn-RH then FSH secretion is induced alone initially followed by low secretory levels of LH which progressively increase until the LH responses are greater than FSH and the normal adult pattern is reached. Thus with Gn-RH treatment the sequence of events seen through puberty is followed (5, 6).

In women with a normal menstrual cycle pituitary sensitivity alters with the phase of the cycle. The greatest gonadotrophin response to Gn-RH is seen at the time of ovulation, and is greater in the luteal than the follicular phase (7, 8). These changes in pituitary responsiveness appear to be the result of feedback effects of changes in circulating oestrogen and progesterone levels. It appears that once the gonadotrophins have induced follicular development it is the ovary which controls the menstrual cycle by modulation of the pituitary LH and FSH responses to Gn-RH through the negative and positive feedback mechanisms of the gonadal steroids. The ovary is "conducting" the pituitary-ovarian orchestra during the menstrual cycle whereas the hypothalamus is providing the driving force to produce gonadotrophin secretion. Apart from alteration in pituitary responsiveness there is also evidence of an increase in hypothalamic secretion of endogenous Gn-RH as a result of gonadal steroid feedback at mid cycle and this may be measured in the circulation by radioimmunoassay

(9, 10). Our own observations show that immunoreactive Gn-RH secretion occurs in brief pulses producing circulating levels which range between <0.2 and 2.5 pg/ml. The effect of oestrogen in combination with progesterone in the second half of the cycle diminishes pituitary responsiveness rather than diminishing Gn-RH level (10).

In men, the effect of oestrogen is different in that there is no clear evidence of positive feedback at either the pituitary or hypothalamic level. Instead the administration of oestrogen in normal males results in the suppression of basal gonadotrophin levels and the pituitary response to Gn-RH (11). The effect of testosterone on hypothalamic-pituitary function is not clear in the male since there is in vivo conversion to oestrogen (12). However, it would appear that any feedback effects of testosterone are less suppressive on pituitary function than are similar increases in oestrogen levels. Dihydrotestosterone probably has little if any inhibitory effect on pituitary function. Gn-RH does not affect the secretion of other pituitary hormones although it may cause GH release in acromegalics (13). Presumably this indicates the presence on the pituitary tumour cells of abnormal TRH sensitive receptors in acromegaly.

Gn-RH has considerably facilitated the investigation of patients with hypothalamic-pituitary-gonadal dysfunction. A single bolus of the releasing hormone given intravenously produces a dose-dependent release of both LH and FSH. With a $100\text{ }\mu\text{g}$ dose the peak LH and FSH response occurs between 20 and 30 minutes and this is the basis of the standard test (2, 14).

Hypothalamic Disease: Patients with isolated gonadotrophin deficiency usually show an LH and FSH response after Gn-RH demonstrating that they are deficient in the releasing hormone and not gonadotrophin. Some patients require a larger dose ($500\text{ }\mu\text{g}$) or several applications of Gn-RH to produce a response. In patients who have organic hypothalamic diseases and who are hypogonadal, impaired or absent LH and FSH responses are usually seen, but they may be entirely normal if the pituitary gonadotrophs contain hormone. Since many patients with hypothalamic disease but intact pituitary glands fail to show LH/FSH responses to Gn-RH unless this is repeatedly given, it is clear that Gn-RH promotes synthesis as well as release of "readily-releasable" gonadotrophin. Indeed in such patients long-term treatment with Gn-RH promotes normal gonadal function in both men and women (5, 15).

Pituitary Disease: In one series of 31 patients with functionless pituitary tumours 25 were clinically hypogonadal. Despite this there was some FSH and LH secretion after Gn-RH in all except one patient. However, in 19 patients the LH response was impaired in contrast to only 3 patients who had impaired FSH responses (16). This suggests that in these patients the ability to secrete LH is lost before FSH.

It is evident that the Gn-RH test cannot distinguish between primarily hypothalamic and pituitary disease because absent, impaired or normal responses may be seen in either group (14). It does however establish the "functional residual capacity" of the pituitary for gonadotrophin secretion, i.e. the amount of readily available gonadotrophin in the gonadotroph cells. If the response is absent or impaired initially when Gn-RH is given, normal gonadotrophin responses can be obtained after regular injections of this material if the pituitary cells are intact, indicating that Gn-RH can promote synthesis as well as release of gonadotrophins. Such recovery of secretory capacity mimics progress through normal puberty in terms of the relative LH and FSH responses (5).

Patients who are post-menopausal or who have primary gonadal failure after the age of normal puberty and therefore deficient in the feedback effects of gonadal steroids at the hypothalamic or pituitary level (such as Turner's syndrome or patients with Klinefelter's syndrome and low circulating testosterone levels) have excessive gonadotrophin responses to the releasing hormone. Patients with apparent primary gonadal failure who do not have an excessive response should be suspected of hypothalamic or pituitary disease. Although gonadal steroids clearly effect gonadotrophin feedback mechanisms it appears that a further substance, "inhibin", produced during spermatogenesis may also be involved in the regulation of FSH secretion. Patients with oligo- or azoospermia but normal testosterone levels and virilization will often show a normal LH response to Gn-RH but an excessive FSH response indicating the diminished negative feedback effect of inhibin at the pituitary level. Patients who have azoospermia with normal testosterone levels and LH and FSH responses to the releasing hormone may have blocked vasa deferentia and require investigation.

Gn-RH therapy: Since hypopituitary patients with impaired or absent gonadotrophin responses to initial testing with 100 µg of the releasing hormone may be made to release gonadotrophins after repeated stimulation with higher doses, Gn-RH has been used in the treatment of hypogonadotrophic hypogonadism resulting either from hypothalamic or pituitary diseases. Studies of the time course of action of the synthetic decapeptide have shown that it is equally effective in promoting gonadotrophin secretion whether given intravenously, intramuscularly or subcutaneously, although the intranasal route is far less effective (17, 18). When sufficient supplies of the material became available doses of 500 µg were given subcutaneously, eight hourly to four infertile males with craniopharyngioma, acromegaly or "isolated gonadotrophin deficiency". All these patients were treated for up to 24 months. Potency increased within 3-16 days of starting treatment despite only small changes in testosterone levels. During therapy sperm counts increased from zero (or 6000,000 dead sperms in the craniopharyngioma patient who had received intramuscular gonadotrophin therapy up to 4 months

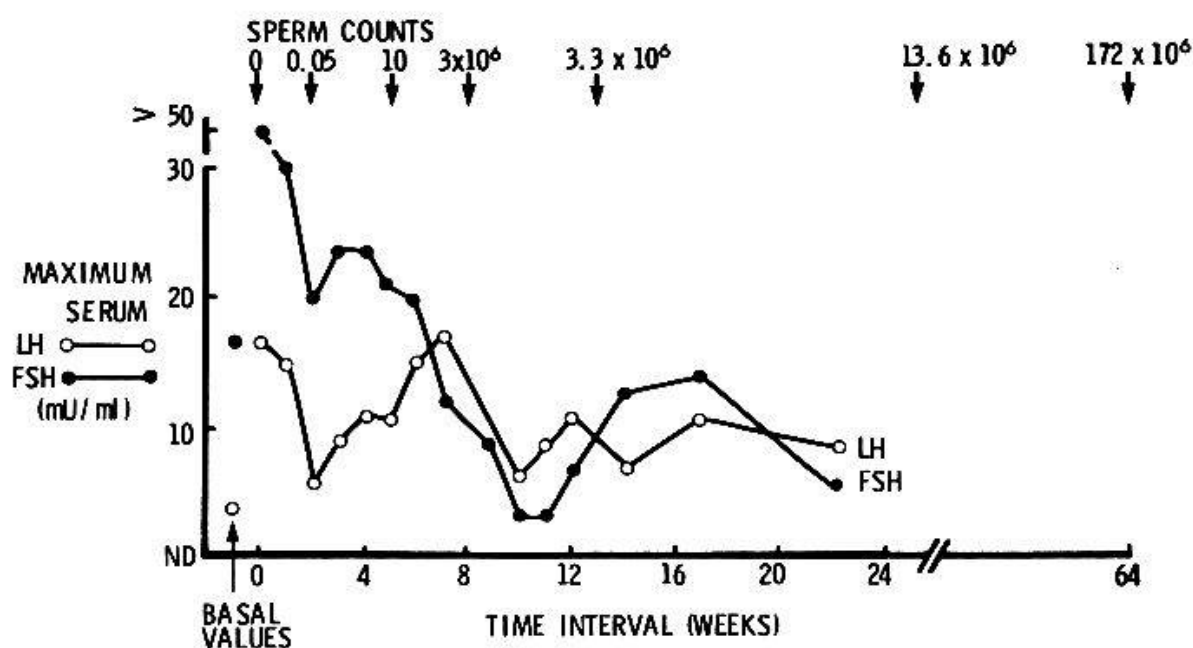


Fig. 1. Gonadotrophin responses and changes in sperm counts in hypogonadal patient with treated acromegaly managed on long term gonadotrophin releasing hormone therapy, 500 μ g subcutaneously each eight hours.

before) to maximum total counts of 432, 170, 66 and 7.8 millions respectively with 40-75 % motility. The initial results in the acromegalic patient are shown in Fig. 1. This patients' wife became pregnant after he had been on therapy for 16 months when the total sperm count was in the region of 132 millions, and has since delivered a normal boy (5). It remains to be seen whether patients with oligospermia due to primary gonadal disease or FSH deficiency can be made fertile. However, since LH and FSH release can be promoted and maintained over long periods in patients who may show no gonadotrophin secretion before treatment, it is clear that Gn-RH stimulates the synthesis as well as the release of gonadotrophins. Subcutaneous Gn-RH in a dose of 500 μ g 8 hourly has also been used for ovulation induction. Four patients with anorexia nervosa and clomiphene-unresponsive secondary amenorrhoea of 5-7 years duration were treated by us. Two were at their ideal body weight and two 3.8 and 5.8 kgs below this. During initial treatment for 1-7 and then 12-14 days each showed a rise in 24hr urinary oestrogens to between 62 and 135 μ g/24hrs and one patient menstruated although none ovulated. There was evidence of spontaneous LH and FSH release on days 18-28 despite being off therapy indicating that there had been positive feedback of the rise in circulating oestrogens at the hypothalamic-pituitary-level. It seemed that the hypothalamus, pituitary and gonads were no longer functioning in isolation but the normal feedback cycle of gonadal steroids on the hypothalamic-pituitary system was operating. Two of these patients were then retested with clomiphene 12-14 weeks later and both had now

become responsive with a rise in serum gonadotrophins and 24hr urinary oestrogens together with ovulation and menstruation. The other two patients were not retested with clomiphene but received a further course of 14 days Gn-RH therapy. Both showed a rise in 24hr urinary oestrogens and a rise in plasma progesterone before the human chorionic gonadotrophin (HCG) had been given suggesting ovulation had occurred before hand. One of these patients then received 28 days of continuous Gn-RH therapy together with HCG on day 14 and became pregnant. Ovulation has also been achieved by other workers with Gn-RH (20, 21). It may be that Gn-RH therapy will become the treatment of choice replacing gonadotrophin therapy as the gonadotrophin and oestrogen levels produced during treatment remain within the physiological range since the normal gonadal-pituitary feedback mechanisms and cyclicity operate and hyperstimulation and multiple births should be avoided. The interesting observation that cyclic gonadotrophin and oestrogen secretion occurs despite continuous Gn-RH therapy supports the view that the feedback by ovarian hormones controls the pattern of menstrual cyclicity as discussed earlier.

Apart from pituitary gonadotrophin stimulation Gn-RH may have other effects. MOSS and MCCANN (22) and PFAFF (23) have noted a marked increase in sexual activity in ovariectomised and hypophysectomised rats. This work indicated that Gn-RH was exerting a direct central stimulatory effect on sexual behaviour which was independent of gonadotrophin or gonadal steroid secretion. The implications of these effects in psychogenic impotence in men requires further investigation. Preliminary data suggest that although some behavioural changes do occur after Gn-RH in man, these effects are weak and insufficient to be effective in psychogenic impotence (24).

Further analogues more resistant to enzymatic degradation are currently being developed and assessed in order to provide practical and possibly intranasal therapy for male and female infertility.

Somatostatin (growth hormone release inhibiting hormone)

This tetradecapeptide was isolated by GUILLEMIN and his colleagues in 1973 (25). It suppresses growth hormone secretion in man after all known stimuli but also inhibits TSH, insulin, glucagon, gastric inhibitory polypeptide, gastric acid, pepsin, vasoactive intestinal polypeptide, gastric motility, motilin, cholecystokinin-pancreozymin, secretin, salivary amylase and renin (for review see GOMEZ-PAN and HALL (26)). The interpretation of the significance of this dazzling variety of secretion-inhibiting activities was further confounded when somatostatin was found not only in the hypothalamus but also in other parts of the central nervous system as well as in the gut and pancreatic islet D cells.

A general viewpoint is growing that these multiple inhibiting activities depend on a physiological role of somatostatin as a local modulator of humoral or exocrine secretion, developed possibly from a more primitive peptide neurotransmitter function. Such a local modulator function has been termed "paracrine" since local diffusion rather than systemic circulation to a distant part is required in contrast to the endocrine secretions.

The multiplicity of actions of somatostatin has meant that to date little clinical therapeutic or routine investigational function has been established. Extensive studies have been performed in diabetes since it was hoped that suppression of excessive glucagon and growth hormone secretion might allow for easier stabilisation, prevention or cure of ketoacidosis and even prevention of the vasculopathy. Certainly somatostatin administration together with insulin has resulted in lower blood sugar levels and improvement of postprandial hyperglycaemia (27, 28) and reduced insulin requirements by 50 % as assessed by the artificial pancreas (29) but it has yet to be convincingly shown to be a significant advance in management. Although somatostatin can prevent developing ketoacidosis it cannot reverse the established derangement (30, 31). It is too early to obtain evidence concerning its role in management or prevention of vasculopathy.

Dopamine and its functional analogues

Prolactin: Hypothalamic dopamine, acting as a prolactin inhibiting factor (PIF), tonically inhibits pituitary prolactin secretion (32). Hyperprolactinaemia will occur during treatment with drugs which deplete the brain of dopamine or which block pituitary dopamine receptors, or with a pituitary stalk or hypothalamic lesions since PIF will not reach the pituitary; there is therefore release from the normal hypothalamic inhibition of pituitary prolactin secretion. However small or large pituitary tumours may secrete prolactin in excess and in the absence of obvious radiological changes in the pituitary it is important to be able to identify them by endocrine investigation.

Stimulation of prolactin release by TRH is thought to occur by an action directly on the pituitary. Until recently the secretagogue actions of neuroleptics such as the phenothiazines, metoclopramide and sulpiride, by which are dopamine receptor blocking agents, were thought to occur by mechanisms operating at the hypothalamic level. Observation of the differences between the responses to TRH and the neuroleptics were used in attempts to distinguish hypothalamic from pituitary causes of hyperprolactinaemia. However recent evidence shows that all these agents work by blocking dopamine receptors at the pituitary level even though they may also work within the mid brain (1, 34). Clearly, as these drugs and TRH may both work at the same site on the pituitary, this type of diagnostic is invalid.

Hyperprolactinaemia is a common clinical endocrine problem causing infertility and amenorrhoea or menstrual abnormalities in women and impotence in men. The hypogonadism may be accompanied by galactorrhoea. The cause of the gonadal dysfunction in hyperprolactinaemia appears to be a peripheral blockade of the actions of the gonadotrophins at the gonadal level since in the human, unlike the rat, gonadotrophin secretion is not reduced when prolactin rises (34). The presence of secretion-inhibiting dopamine receptors on the prolactin secreting cells of the pituitary is of great clinical significance since long acting dopamine agonists such as bromocriptine, lergotriple, lisuride and piribedil may be used to lower the circulating prolactin levels and normalize the gonadal function in any cause of hyperprolactinaemia. Bromocriptine (2 bromo- α -ergokryptine) is the only agent to have had extensive clinical trials and is highly successful (34, 35, 36). In a sense it is a functional analogue of the prolactin inhibiting factor.

Growth hormone: Excess secretion causing acromegaly or gigantism is usually associated with pituitary tumours but it is still far from clear whether the primary defect is hypothalamic or pituitary. Evidence in favour of a hypothalamic cause is the abnormal hypothalamic glucostatic control of GH in acromegaly - many patients show a rise in GH with hyperglycaemia, while normal subjects show a fall. However primary defects in the pituitary are suggested by the abnormal GH response to the direct pituitary acting TRH and Gn-RH; such a GH response is not seen in normals.

Dopamine and other dopamine agonists produce a rise in GH in normal subjects but there is frequently a paradoxical fall in GH in acromegaly and gigantism (37, 38). There must presumably be an abnormality of the dopaminergic mechanisms either in the median eminence (outside the blood brain barrier for dopamine) or more probably in the pituitary itself in acromegaly, as well as altered receptors to TRH and Gn-RH. The inhibitory action of dopamine agonists on GH in acromegaly is of great clinical value since the use of the dopamine agonist bromocriptine has provided the first medical treatment for this disease. We find that 80 % of patients respond well (39, 40).

Thyrotrophin releasing hormone (TRH)

This has been extensively covered in an earlier chapter. Since a rise in circulating thyroid hormone levels impair the pituitary responses to exogenous TRH, and is augmented when thyroid hormone levels are low, it is evident that a main site for physiological negative feedback control of the thyroid is at the pituitary. One presumes that TRH secretion is also altered but the evidence for this is insubstantial (see review by BURGER and PATEL (41)).

TRH is of great value as a test of thyroid function. The test has been described by ORMSTON et al. (42) and HALL (43). The TSH response to TRH may be normal, absent, impaired or delayed. The response to TRH will be impaired in patients on pharmacological doses of corticosteroids or replacement therapy with triiodothyronine or thyroxine. Primary hypothyroidism is associated with an excessive response and in thyrotoxicosis the response is absent. The typical pattern in hypothalamic disease is a delayed rise in TSH (43), whether or not hypothyroidism is present; although this response is characteristic it is not diagnostic and may also be seen in patients with pituitary disease. Patients with pituitary (secondary) hypothyroidism typically show an impaired or absent response, but this too may be normal. In acromegaly, the response to TRH may appear impaired even though the patient is euthyroid. The frequency of deviation from the typical pattern is so high that the TRH test is often of little value in investigating pituitary and hypothalamic diseases. It does however indicate how much functioning pituitary thyrotroph tissue remains. Diagnosis is further helped since any hypothyroid patient who fails to show an excessive TSH response to TRH will not have primary thyroid disease and the defect must lie in the hypothalamic-pituitary system. TRH has no therapeutic indication except perhaps to augment endogenous TSH levels in association with radioiodine treatment of carcinoma of the thyroid (44).

The significance of the prolactin-secretoagogue actions of TRH are not understood. Most workers doubt that the prolactin releasing hormone is TRH since TSH and prolactin secretion can be readily dissociated, for example during suckling, thyrotoxicosis, and during circadian secretion. However the hyperprolactinaemia often encountered in hypothyroidism may be due to elevated TRH levels in that condition but this has not been established.

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