Thyroid-stimulating hormone: neuroregulation and clinical applications

PART 2

M. F. SCANLON, B. REES SMITH AND R. HALL
Endocrine Unit, Departments of Medicine and Clinical Biochemistry, Royal Victoria Infirmary, Newcastle upon Tyne, U.K.

Regulation of thyrotrophin synthesis and secretion (continued)

Role of catecholamines and serotonin

Animal studies with central neurotransmitter agonist and antagonist drugs have indicated the existence of stimulatory α-noradrenergic and inhibitory dopaminergic pathways in the control of thyrotrophin (TSH) secretion in the rat (Tuomisto, Ranta, Mannisto, Saarinen & Leppaluoto, 1975; Mueller, Simpkins, Meites & Moore, 1976; Ranta. Mannisto & Tuomisto, 1977; Krulich, Giachetti, Marchlewksa-Koj, Hefco & Jameson, 1977). However, Chen & Meites (1975), using the catecholamine precursor drug L-dopa, were unable to find any significant catecholamine effects on TSH release. Conflicting results have also been obtained with regard to the role of serotonin. Grimm & Reichlin (1973) found that the serotonin precursor 5-hydroxytryptophan inhibited the release of thyrotrophin-releasing hormone (TRH) radioactivity from mouse hypothalamic slices and suggested that serotonin was an inhibitory neurotransmitter in the control of TRH release. TSH suppression was also found after intrahypothalamic implantation of serotonin in rats (Mess & Peter, 1975). This was supported by the findings in vivo of Tuomisto et al. (1975) but conflicts with the findings in vivo of Chen & Meites (1975), who found direct evidence for a stimulatory serotonergic pathway in the control of TSH release.

Such conflicting findings are difficult to interpret and may well reflect in part the technical difficulties involved in the administration in vivo of centrally active drugs to animals in which stress itself is known to inhibit TSH release. There is also considerable variation in standardization and methodology between different laboratories, making direct comparison of results difficult. Despite this, however, the most consistent findings are in favour of stimulatory α-noradrenergic and inhibitory dopaminergic pathways, although the site of action of such putative regulators of TSH release remains to be determined.

In man, there is as yet no definite evidence of direct noradrenergic regulation of TSH release (Woolf, Lee & Schalch, 1972; Birk Lauridsen, Faber, Friis, Kirkegaard & Nerup, 1976), and the TSH suppression in hyperthyroidism is unrelated to any increase in central adrenergic activity (Epstein, Pimstone, Vinik & Meharen, 1975; Wartofsky, Dimond, Noel, Frantz & Earll, 1975). Adrenergic-receptor-blocking drugs lead indirectly to a slight elevation in basal TSH levels but this presumably reflects the known peripheral action of such drugs in reducing the conversion of T₃ and T₄ and hence the degree of negative feedback inhibition of TSH release (Wiersinga & Touber, 1977).

There is now clear evidence of a physiological inhibitory role for dopamine in the control of TSH release in man. The initial studies of Besses, Burrow, Spaulding & Donabedian (1975) demonstrated that dopamine infusion inhibited the TSH response to TRH and this has now been confirmed (Burrow, May, Spaulding & Donabedian, 1977). Furthermore, dopamine infusion lowers basal TSH levels in both euthyroid and hypothyroid subjects (Camanni, Massara, Belforte, Vergano & Molinatti, 1977; Delitala, 1977); although acute L-dopa administration has no effect on TSH levels, chronic administration to patients with Parkinsonism leads to suppression of the TSH response to TRH (Spaulding, Burrow, Donabedian & Van...
Similarly, dopamine receptor stimulation with bromocriptine lowers the elevated basal TSH levels in hypothyroid patients (Miyai, Onishi, Hosokawa, Ishibashi & Kumahara, 1974; Felt & Nedvidkova, 1977) and suppresses acutely the TSH response when administered 2 h before TRH (Garcia Centenera, Buxeda Paz, Hervas Olivieras, Perez Merida, Pozuelo Escudero & Gomez-Pan, 1977). Fusaric acid is an inhibitor of dopamine β-hydroxylase, which converts dopamine into noradrenaline. Administration of fusaric acid thus leads to a relative increase in endogenous dopamine levels and lowers the elevated basal TSH levels in patients with primary hypothyroidism (Yoshimura, Hachiya, Ochi, Nagasaka, Takeda, Hidaka, Refetoff & Fang, 1977).

Whilst such findings suggest an inhibitory role for dopamine, they provide no indication of the physiological relevance of dopaminergic pathways in the control of TSH release. In previous studies in which dopamine receptor-blocking drugs such as metoclopramide and chlorpromazine were administered to euthyroid subjects, no effect on TSH release was detected (Delitala, Masala, Alagna & Devilla, 1975; Onishi, Miyai, Izumi, Nakanishi & Kumahara, 1975; Judd, Lazarus & Smythe, 1976), suggesting that there was no significant physiological dopaminergic inhibition of TSH release in man. In the light of recent findings, such a conclusion must be regarded as invalid, since there is marked elevation in basal TSH levels after metoclopramide administration to patients with primary thyroid failure (Scanlon, Weightman, Mora, Heath, Shale, Snow & Hall, 1977; Fig. 1). Thus, in euthyroid subjects, TSH release after dopamine antagonist drugs may be masked by the dominant inhibitory effects of normal circulating levels of thyroid hormones. However, even after metoclopramide administration to euthyroid subjects, a relatively small but highly significant rise in basal TSH levels can be detected by using a sensitive and precise radioimmunoassay for human TSH and adequate control studies (Scanlon, Weightman, Shale, Mora, Heath, Snow & Hall, 1978; Fig. 2). Such findings in euthyroid subjects are in agreement with the recent reports of others (Sowers, McCallum, Hershman, Carlson, Sturdevant & Meyer, 1976; Healy & Burger, 1977).

![Fig. 1. Thyrotrophin (TSH) response to metoclopramide (10 mg orally) and placebo in hypothyroid patients. Mean values ± SEM are shown.](image1)

![Fig. 2. Thyrotrophin (TSH) response to metoclopramide (10 mg orally) and placebo in 10 euthyroid males (○) and 10 euthyroid females (●). Mean values are shown.](image2)
The TSH response to metoclopramide is significantly greater in females than in males and pretreatment with metoclopramide leads to enhancement of the TSH response to TRH (Scanlon et al., 1978; Fig. 3). In euthyroid subjects, the degree of TSH response to metoclopramide is unrelated to $T_3$ and $T_4$ levels but is inversely related to the basal TSH level (Fig. 4). This is in striking contrast to the TSH response to TRH, which is directly related to basal TSH levels (Sawin & Hershman, 1976). This finding illustrates the fundamentally different mechanism of action of TRH and dopamine antagonism in causing TSH release and suggests that the degree of TSH release after administration of dopamine antagonist drugs is not directly related to the size of the readily releasable pool of TSH. The physiological and clinical implications of this are discussed below.

Dopamine, therefore, is a physiological regulator of TSH release in man, although its site of action is unknown. It may act at a hypothalamic level to inhibit TRH synthesis and release from peptidergic neurons. Alternatively, recent evidence suggests a major pituitary site of action for dopamine. Dopamine itself, because of its high polarity, does not cross the blood–brain barrier and therefore the well-documented TSH suppression during dopamine infusion is likely to be due to a direct action of dopamine on the pituitary or median eminence, tissues which have direct connections with the systemic circulation. Furthermore, dopamine receptors have now been identified on anterior pituitary cells but not in median eminence tissue (Brown, Seeman & Lee, 1976). Further study is required to establish which pituitary cell types possess dopamine receptors.

Any role of serotonin in the control of TSH release in man is less clear. Yoshimura, Ochi, Miyazaki, Shiomi & Hachiya (1973) reported lowering of basal TSH levels in hypothyroid but not in euthyroid patients after administration of 5-hydroxytryptophan. Woolf & Lee (1977) found that t-tryptophan had no effect on basal TSH in euthyroid subjects. On the other hand, cyproheptadine, a drug which blocks serotonin receptors, produces suppression of the TSH response to TRH in euthyroid subjects (Ferrari, Paracchi, Rondena, Beck-Pecco & Faglia, 1976; Egge, Rogol, Varma & Blizzard, 1977). However, this effect on TSH is unlikely to be related to serotonin since metergoline, a more specific serotonin antagonist, has no effect on TRH-induced TSH release (Ferrari et al., 1976).

**Role of somatostatin**

Somatostatin is a cyclic tetradecapeptide found in highest concentrations in the hypothalamus. The
hormone is thought to have a physiological inhibitory control over growth hormone release. However, recent studies in vitro and in vivo suggest that somatostatin may also be a physiological inhibitor of TSH release. Administration of somatostatin antisera to cultured anterior pituitary cells causes elevation of both growth hormone and TSH levels in the medium (Tanjasiri, Kozbur & Florsheim, 1976), and administration of the antisera to intact rats produces enhanced TSH responses to both cold stress and TRH as well as elevation of basal growth hormone and TSH levels (Arimura, Gordin & Schally, 1976; Ferland, Labrie, Jobin, Arimura & Schally, 1976). Such responses after antagonist of endogenous somatostatinergic activity provide strong evidence of a physiological inhibitory role for somatostatin in the control of these two hormones. There is no such direct evidence in man, although somatostatin infusion lowers the elevated basal TSH levels in patients with primary thyroid failure (Lucke, Höfken & Von zur Muhlen, 1975), suppresses the TSH response to TRH (Siler, Yen, Vale & Guillemot, 1974); Carr, Gomez-Pan, Weightman, Roy, Hall, Besser, McNeilly, Schally, Kastin & Coy, 1975) and abolishes the nocturnal elevation in basal TSH levels (Weeke, Hansen & Lundbaek, 1975).

Other influences on thyrotrophin secretion

In the light of the neuroregulatory pathways outlined above and in Part 1 (Scanlon, Rees Smith & Hall, 1978), it is now possible to consider other factors which modify TSH secretion in man.

Circadian variation

It has now been clearly established that there is a circadian rhythm of TSH secretion in both animals (Bakke & Lawrence, 1965) and man (Nicoloff, Fisher & Appleman, 1970; Patel, Alford & Burger, 1972; Weeke, 1973). This is not entirely sleep-related since TSH levels begin to rise during the evening before the onset of sleep, reaching a peak at about 23.00 hours, when the TSH response to TRH is also enhanced. Levels remain elevated overnight and gradually decline over the ensuing morning, reaching a nadir around 11.00 hours (Weeke, 1973).

The neuroendocrine mechanisms underlying this circadian rhythm are unknown. Administration of pharmacological doses of glucocorticoids abolishes the nocturnal elevation (Nicoloff et al., 1970; Patel et al., 1972) and reduces both basal and TRH-stimulated TSH levels (Re, Kourides, Ridgway, Weintrab & Maloof, 1976; Sowers, Carlson, Brautbar & Hershman, 1977). It has therefore been suggested that the circadian TSH variation may be secondary to the circadian changes in adrenocortical function. In support of this suggestion Re et al. (1976) found a slight elevation in basal TSH levels in normal subjects treated with metyrapone, which lowers plasma cortisol levels by blocking 11-hydroxylation. This finding requires confirmation but does suggest that physiological levels of glucocorticoids can suppress TSH release. However, Patel, Baker, Burger, Johns & Ledinek (1974) did not find any close correlation between circadian cortisol and TSH rhythms.

There is little, if any, circadian variation in basal TSH levels in patients with severe hypothyroidism (Weeke & Laurberg, 1976) and the dopaminergic inhibition of TSH release also decreases with increasingly severe hypothyroidism (Scanlon et al., 1977). Again, both the circadian rhythm of TSH secretion and the TSH response to dopamine receptor blockade are restored after partial thyroid hormone treatment of severely hypothyroid patients (Weeke & Laurberg, 1976; M. F. Scanlon, unpublished work). Furthermore, in euthyroid subjects, the degree of TSH response to dopamine receptor blockade is inversely related to basal TSH levels (Fig. 4), suggesting that dopamine may be a determinant of low daytime TSH levels and is thus implicated in the circadian rhythm of TSH secretion. Whether the nocturnal elevation in TSH levels reflects reduced dopaminergic inhibition of TSH or the activity of another stimulus to TSH secretion remains to be determined.

Effects of cold stress

Environmental cooling is a potent stimulus to TSH release in both laboratory animals (Itoh, Hiroshige, Koseki & Nakatsugawa, 1966; Tuomisto, Ranta, Saarinen, Mannisto & Leppaluoto, 1973) and human neonates (Fisher & Odell, 1969; Wilber & Baum, 1970). The TSH response to cold stress in adult man is much less striking (Odell, Vanslager & Bates, 1968; Tuomisto, Mannisto, Lamberg & Linnoila, 1976).

Reichlin (1966) has suggested that, in rats, cold stress causes release of TRH since the effect could be abolished by appropriately placed hypothalamic lesions. More recent studies based on urinary TRH measurements in cold-exposed animals have provided conflicting results (Emmerson & Utiger, 1975; Montoya, Seibel & Wilber, 1975). However, in a recent report Muller, Franco,
Reichlin & Jackson (1977) have described suppression of the TSH response to cold stress in rats by pretreatment with antibodies to TRH. Such a finding provides the most direct evidence for a physiological role for TRH in the TSH response to cold.

On the basis of animal studies it seems likely that cold stress leads to increased α-noradrenergic activity (Kruilich et al., 1977) and consequent TRH release (Mueller et al., 1977). Serotonergic pathways appear to have an inhibitory effect on the TSH response to cold, possibly through inhibition of TRH release (Tuomisto et al., 1975). The neurotransmitter pathways involved in the slight TSH release (Mueller et al., 1974) following environmental cooling in adults are unknown.

Effects of calorie restriction

Calorie restriction in man leads to impaired peripheral conversion of T₄ into T₃, resulting in low total and free T₃ levels and normal or slightly elevated free T₄ levels (Portnay, O'Brian, Bush, Vagenakis, Azizi, Arky, Ingbar & Braverman, 1974; Vagenakis, Burger, Portnay, Rudolph, O'Brian, Azizi, Arky, Nicod, Ingbar & Braverman, 1975; Croxson, Hall, Kletzky, Jaramillo & Nicolaou, 1977). Furthermore it has recently been reported that in rats starvation also decreases the nuclear T₃ receptor content (Schussler & Orlando, 1978). In addition, short-term fasting produces suppression of basal and TRH-stimulated TSH levels (Vinik, Kalk, McLaren, Hendricks & Pimstone, 1975; Croxson et al., 1977), although TSH responsiveness after more prolonged fasting over 3-4 weeks is normal or only minimally decreased (Rothenbuchner, Loos, Kiessling, Birk & Pfeiffer, 1973; Portnay et al., 1974). The initial fall of TSH and the subsequent failure of the response to TRH in the face of low levels of T₃ suggests inhibition of TSH release. Croxson et al. (1977) could detect no alteration in the daily excretion of 17-hydroxycorticosteroids or urinary cortisol, or in the diurnal pattern of serum cortisol. Furthermore, metyrapone administration did not reverse the inhibitory effects of fasting on TSH release. It seems unlikely, therefore, that glucocorticoids mediate the TSH suppression of fasting. The possible role of dopamine in this context is currently being investigated.

The pattern of TSH response to TRH varies in different types of calorie restriction: in protein-calorie malnutrition the TSH response to TRH is enhanced (Becker, Vinik, Pimstone & Paul, 1975), whereas patients with anorexia nervosa frequently show a delayed or 'hypothalamic pattern' of TSH response to TRH (Miyai, Yamamoto, Azukizawa, Ishibashi & Kumahara, 1975). The reason for this difference is unknown. However, there is increasing evidence of TSH suppression in some patients with anorexia nervosa leading to decreased thyroid release of T₄. Such patients also show a loss of the diurnal rhythm of thyroidal iodide release which reflects a loss of diurnal TSH variation (Croxson & Ibbertson, 1977). This suppression could explain the low or low-normal TSH levels seen in such patients in the face of reduced serum T₃ levels, but the exact mechanism is unknown. However, in view of the recently demonstrated physiological inhibitory role of dopamine in the control of TSH release, it is tempting to speculate that one component of the anorexia nervosa syndrome may be dopaminergic hyperactivity.

Role of prostaglandins

Prostaglandins are widely distributed in the central nervous system, including the hypothalamus (Holmes & Horton, 1968) and prostaglandin E can activate pituitary adenylate cyclase (Zor, Kaneko, Schneider, McCann & Field, 1970). They may therefore be involved in the control of anterior pituitary function at either extra- or intracellular levels.

Several studies in vitro have indicated that prostaglandins can increase both basal and TRH-stimulated TSH release from anterior pituitary cells (Kudo, Rubinstein, McKenzie & Beck, 1972; Brown & Hedge, 1974). Furthermore, indomethacin, a prostaglandin synthetase inhibitor, abolished the TSH response to TRH in vitro (Dupont & Chavancy, 1972). Other workers, however, have found no effect of prostaglandins on TSH release in vivo (Ess, Szabo & Burke, 1974). Studies in vivo in animals are equally conflicting: prostaglandin E₂ had no effect on TSH release when administered intraventricularly to rats (Ess, Warberg, Mical & Porter, 1975) whereas prostaglandin E₁ given to pregnant rats caused a significant elevation in maternal TSH levels (D'Angelo, Wall & Bowers, 1975).

There is, as yet, no evidence for TSH stimulation by prostaglandins in man. Indomethacin pretreatment had no effect on TRH-stimulated TSH release in men, even though plasma prostaglandin E and F levels were significantly lowered (Ramey, Burrow, Spaulding, Donabedian, Speroff & Frantz, 1976).
In the same study, aspirin (another prostaglandin synthetase inhibitor) did suppress TRH-induced TSH release but this was probably due to its known effect in increasing the fraction of unbound thyroid hormones (Larsen, 1972). There are no reports of the effects of prostaglandin synthetase inhibitors on the elevated basal TSH levels in patients with primary hypothyroidism but the available indirect evidence does not suggest any significant action at this level.

Clinical applications of thyrotrophin measurements

Measurement of basal and TRH-stimulated TSH levels are of established value in the diagnosis of disorders of the hypothalamus–pituitary–thyroid axis, and the degree of TSH release after administration of dopamine antagonist drugs could also prove to be a more refined test of the integrity of this axis.

*Basal TSH levels*

Patients with hypothyroidism due to primary thyroid failure have elevated basal TSH levels (>6 munits/l) and this is usually sufficient evidence to confirm the diagnosis. However, hypothyroidism is a graded phenomenon and there are many patients with primary thyroid disease who have normal or low–normal thyroid hormone levels and an elevated basal TSH in the absence of any symptoms attributable to thyroid hormone insufficiency (Evered, Clark & Petersen, 1973). A variety of names have been given to such conditions, including compensated euthyroidism, pre-myxoedema (Fowler, Swale & Andrews, 1970) and subclinical hypothyroidism (Evered, Ormston, Smith, Hall & Bird, 1973). It seems likely that thyroid function is fully compensated by the increased TSH drive in some of these patients, whereas in others circulating thyroid hormone levels are suboptimal and treatment with thyroxine might be beneficial. At present there is no way of distinguishing between such patients and thyroxine replacement therapy is usually restricted to patients with mild and overt clinical hypothyroidism. Replacement therapy with L-thyroxine is generally regarded as adequate when the patient’s symptoms of hypothyroidism are relieved and the basal TSH level is reduced to the normal range (<6 munits/l).

Elevated basal TSH levels in the presence of clinical and biochemical hyperthyroidism indicate the rare condition of hypothalamic–pituitary hyperthyroidism due to excessive TSH secretion. As previously mentioned, specific TSH α-subunit measurements in such patients may serve to identify those patients with a pituitary adenoma and serial estimations of α-subunit levels may better indicate the adequacy of therapy.

Measurements of TSH in cord blood or on filter-paper spots taken some 5 days after birth have indicated that, in North America and in certain areas of Europe, the prevalence of neonatal hypothyroidism is in the region of 1/3000 to 1/6000 live births (Klein, Agustin & Foley, 1974; Dussault, Coulombe, Laberge, Letarte, Guyda & Khoury, 1975; Walfish, 1975; Illig & Rodríguez de Vera Roda, 1976). This is about two to three times the prevalence of phenylketonuria, for which there is an established screening programme based on the Guthrie spot. TSH measurements can easily be grafted on to the existing phenylketonuria screen, TSH being measured on the filter-paper spots (Illig & Rodríguez de Vera Roda, 1976). Advantages of TSH over T₄ measurements are a lower false positive rate (most cretins diagnosed so far have TSH values greater than 100 munits/l). Hypothalamic–pituitary hypothyroidism may be responsible for about 10% of cases of neonatal hypothyroidism and they would be missed by TSH measurements (Dussault, Parlow, Letarte, Guyda & Laberge, 1976). Further information is required about the frequency and severity of this variety of cretinism. It seems likely that screening programmes will be set up in most developed countries but some time will have to elapse before the probable benefits of early therapy can be demonstrated.

*TSH levels after TRH stimulation*

The standard intravenous TRH test (Ormston, Garry, Cryer, Besser & Hall, 1971) now has an established role in the diagnosis of disorders of the hypothalamus–pituitary–thyroid axis. Two hundred micrograms of TRH are given as an intravenous bolus and TSH levels are measured in blood samples taken at 0, 20 and 60 min. Basal routine thyroid-function tests (T₃, T₄, a thyroid hormone-binding test, and thyroid autoantibodies are also estimated in the 0 sample). The test is free from significant side effects, although about half the patients experience a transient metallic taste, deep urethral sensation, facial flushing and mild nausea, all of which pass off within a few minutes of the injection. Although the 60 min sample is helpful to detect delayed responses, in routine clinical practice the peak sample (20 min) is sufficient to confirm the diagnosis of thyroid disease. It is now
our practice to perform the TRH test during the initial outpatient visit when indicated. For diagnostic purposes, the greater TSH response during the follicular phase of the cycle in females, or the diurnal variations observed in a given subject, may be disregarded when the TRH test is performed at a routine clinic visit, and, in addition, the patient need not be fasting or recumbent. The TRH test can be performed in conjunction with the LHRH and insulin tolerance tests since there is no interaction between the various hormones released (Besser, Ratcliffe, Kilborn, Ormston & Hall, 1971; Mortimer, Besser, McNally, Tunbridge, Gomez-Pan & Hall, 1973). This procedure provides a test of pituitary reserve of the gonadotrophins, TSH, prolactin, growth hormone and corticotrophin.

Results in hyperthyroidism. Patients with hyperthyroidism fail to respond to TRH because of the suppressive effects of elevated circulating levels of thyroid hormones. A normal TSH response to a 200 μg dose of TRH absolutely excludes a diagnosis of hyperthyroidism. The main diagnostic application of the TRH test is the exclusion of mild or subclinical hyperthyroidism. However, it must be emphasized that an impaired or absent response to TRH is not in itself indicative of hyperthyroidism since it can be seen in patients with ophthalmic Graves' disease (Ormston, Alexander, Evered, Clark, Bird, Appleton & Hall, 1973), in multinodular goitres and autonomous thyroid adenomata (Evered et al., 1974), in some non-toxic diffuse goitres, in patients with a variety of pituitary diseases with or without hypothyroidism (Hall, Besser, Ormston, Cryer & McKendrick, 1972), in Cushing's disease and acromegaly, in states of supraphysiological replacement with T₄ or T₃ for hypothyroidism and in some subjects rendered clinically and biochemically euthyroid for several months after treatment of hyperthyroidism (Von Zur Muhlen, Hesch & Kobberling, 1975; Sanchez-Franco, Garcia, Cacicedo, Martin-Zurro, Escober Del Rey & Morreale de Escobar, 1974). This sustained delay in the restoration of a normal TSH response to TRH renders the TRH test unreliable in the follow-up and monitoring of antithyroid therapy for a period of up to 9 months after clinical remission has occurred. Although the TSH response to TRH correlates well with suppressibility by T₃ of thyroidal radioisotope uptake (Ormston et al., 1973) a number of discrepancies have been observed between the two tests, which are still not fully understood. Despite this lack of absolute correlation between these tests, the TRH test has now replaced the outdated T₃ suppression test. It is more rapid, less expensive, safer and does not require administration of radioisotopes or a potentially dangerous drug to the patient.

Results in hypothalamic–pituitary disease. The TRH test has limited value in the assessment of pituitary reserve (Hall et al., 1972). A suboptimum TSH response is associated with secondary hypothyroidism in about 40% of the cases studied. Patients with hypothyroidism due to pituitary disease usually fail to respond to TRH. Patients with hypothyroidism may show a characteristic 'delayed' response in which the 60 min TSH value is higher than that obtained at 20 min. Such a response may also be seen in patients with primary pituitary disease, although the pressure effects of the tumour or the effect of previous therapy may play a role in causing hypothalamic disturbance. In patients with anorexia nervosa, a 'hypothalamic' type of response is often seen, which returns to normal after restoration of body weight.

Results in chronic renal failure. The TRH test provides unreliable information in patients with impaired renal function. An exaggerated response may be due to poor renal clearance of TRH (Gonzalez-Barcena, Kastin, Schalch, Torres-Zamora, Perez-Pasten, Kato & Schally, 1973) and impaired, absent or delayed TSH responses during the standard TRH test may be observed in patients with chronic renal failure, without any evidence of hypothalamic–pituitary or thyroid disease (Gomez-Pan, Sachdev, Duns, Tunbridge & Hall, 1975).

TSH levels after dopamine antagonism

The finding that serum TSH levels rise after dopamine-receptor blockade in both euthyroid and hypothyroid subjects suggests that this mechanism might be of potential value as a more refined test of the integrity of the hypothalamic–pituitary–thyroid axis. It may prove possible to distinguish compensated from uncompensated thyroid function in patients who are currently labelled as mildly or subclinically hypothyroid on the basis of their degree of TSH response to dopamine-receptor blockade. Patients in this category have elevated basal TSH levels and all show an exaggerated TSH response to TRH and therefore the TRH test is of no diagnostic value in this context. However, patients whose thyroid function is truly compensated by their increased TSH drive might be expected to show no greater TSH response to dopamine-receptor blockade than a euthyroid subject, regardless of the basal TSH levels. The validity of this hypothesis depends critically on the
relationship between basal TSH and the degree of dopaminergic inhibition of TSH. The hypothesis is supported by the finding of an inverse relationship between basal TSH and the degree of dopaminergic inhibition of TSH release in euthyroid subjects in daytime hours. However, further work is required to clarify the situation in patients with mild and subclinical hypothyroidism.

Therapeutic applications of TRH

So far, no definite therapeutic applications have been described for TRH. It has already been indicated that the value of the TRH test in monitoring antithyroid therapy is limited by the delay in restoration of pituitary responsiveness to TRH after hyperthyroidism. It is of no value in the treatment of hypothalamic (tertiary) hypothyroidism, but it does not offer any advantage over thyroid hormone replacement. We have not observed any beneficial effect of TRH in regenerating thyroid remnants after surgery.

References


