INVITED COMMENTARY

Dynamics of thyroid hormone suppression of serum thyrotropin: an invited commentary

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The insensitivity of the early TSH radioimmunoassays limited investigations of thyroid hormone action on pituitary TSH secretion to studies of hypothyroid rats and humans (1, 2). Now that more sensitive TSH immunometric assays are able to measure serum TSH concentrations in the subnormal range (3), it is possible to study thyroid hormone inhibition of pituitary TSH secretion in euthyroid human subjects. In the well-designed study of Sydow et al. (4), groups of euthyroid male volunteers were given different oral doses of thyroxine (25–150 μg q.i.d.) for 10 days, during which the relationships between the thyroxine dose and the resultant suppression of serum TSH and thyroglobulin (TG) concentrations were studied. The data showed that both serum TSH and Tg concentrations fell over time with single monoexponential suppression patterns. Further, the rates of decline for both serum TSH and serum Tg were proportional to the thyroxine dose administered. It should be emphasized that this study was conducted under non-steady-state conditions whereby neither serum TSH nor TG concentrations reached their nadirs during the 10-day observation period.

The Sydow study (4) emphasizes three important concepts concerning the negative feedback of thyroid hormones on pituitary TSH secretion. Firstly, some suppression of serum TSH was detected even at a low T₄ dose (25 μg) that did not produce a measurable change in serum free T₄ (FT₄) concentrations. The exquisite sensitivity of the pituitary to minor excursions in the FT₄ concentration shows that the log/linear serum TSH/FT₄ relationship found at a steady state (5) is also seen during periods of disequilibrium. Secondly, serum TSH suppression was seen without an elevation in the serum FT₃I concentration. In fact, a detectable rise in the serum FT₃I was only seen on the 10th day following the administration of the largest T₄ dose (150 μg). This emphasizes the work of Larsen and others (6) showing that it is local T₃, generated from T₄ within the pituitary by the 5' deiodinase enzyme system(s), that mediates thyroxine’s negative feedback on pituitary TSH secretion. Thirdly, the failure of serum FT₃I concentrations to rise in parallel with the rise in FT₄I is in accord with the concept that the 5'-deiodinase enzyme systems are autoregulated, such that a normal circulating T₃ concentration is “defended” in the face of changes in circulating FT₄ (7).

We reported recently on the use of third- and fourth-generation TSH assays to study serum TSH suppression responses following the administration of a single large inhibitory dose of T₃ (263 μg), T₄ (2 mg) or triac (2 mg) to euthyroid human subjects (8). This study showed that when log TSH (percentage control) was plotted against the log of time, serum TSH suppression was characterized by three temporally distinct linear phases. The first acute phase (phase 1) had an onset time of about 1 h and lasted for 10–20 h before a slower phase of suppression (phase 2) developed. When high-dose thyroid hormone was administered chronically, serum TSH concentrations plateaued at a 0.001–0.01 mIU/l nadir (phase 3) after several weeks. Replotting this data as the log TSH/linear time function used in the current study (4) reveals not a single monoexponential but a curvilinear function (8). The difference between the suppression dynamics of the two studies has mechanistic implications and most likely arises from differences in study design.

The single monoexponential relationship found for log TSH versus linear time seen by Sydow et al. (4) suggests that thyroid hormone feedback inhibitions on pituitary TSH secretion conforms to a linear system (9) based on classical homeostatic principles. In such a system, the magnitude of a response is predictable and proportional to the changes in the individual components (9). This contrasts with the triphasic log TSH/log time relationship that we reported (8), which suggests that thyroid hormone suppression of TSH follows non-linear power law dynamics (9). Non-linear systems do not respond predictably or proportionally to changes in any one component because the effects of the various components influencing the system are coupled (9). Indeed, even if thyroid hormone inhibition and TRH stimulation are dominant mediators of TSH secretory control, the multiplicity of peripheral hormones and hypothalamic factors that have been shown to influence the physiological control of serum TSH (10) is more consistent with a non-linear system.

Differences in protocol design are also likely to influence the temporal TSH suppression patterns observed. Neither study was conducted at a steady state. Our study was designed to produce maximum
suppression from the onset of hormone administration by use of a single high-dose thyroid hormone IV bolus injection. In contrast, the present study used the daily administration of a range of thyroxine doses. Although the data are not shown, this regimen would be expected to produce a gradual rise in serum FT4 concentration throughout the 10 days of study, reflecting the progressive augmentation of the body’s T4 pool. No TSH nadir was reached during the course of the study, as would be expected given a thyroxine half-life of 7 days. In fact, a new steady-state equilibrium between serum TSH and FT4 would not be reached for 3–4 weeks, which is approximately the same time needed to establish the phase 3 nadir of maximal suppression described in our study (8). The gradual initiation and progressive increase in the magnitude of T4-mediated TSH suppression resulting from the daily dosing regimen is likely to be the major factor responsible for the monoeXponential TSH suppression pattern seen in the current study.

Sydow et al. also found that serum Tg concentrations decreased monoeXponentially as a function of time and T4 dose; however, the magnitude of suppression of Tg was less than that observed for TSH. This is in accord with other studies showing that a 99% suppression in serum TSH is only associated with a 60% suppression in serum Tg concentrations (8). The lower ultimate magnitude of suppression, together with the half-life differences between TSH (~60 mins) and Tg (~4 days), are most likely responsible for the shallower Tg suppression slope. Appropriately, Sydow et al. studied serum TSH concentrations in specimens drawn around the time of the daily TSH nadir (13.00 h). Despite this, the intrasubject coefficients of variation in serum TSH seen in the control subjects were significantly greater that the intrasubject variations in serum Tg. As the authors pointed out, this would be expected from the ultradian and diurnal variation of pituitary TSH secretion; however, the half-life differences previously mentioned also dictate that the ambient serum Tg concentration will reflect the integrated 24 h TSH secretory profile.

These data have clinical implications for patients receiving thyroxine therapy. The data of Sydow et al. (14) show that when a daily dosing regimen is used, the time needed to lower serum TSH in patients with primary hypothyroidism, or resuppress TSH following thyroid hormone withdrawal, is a function of the T4 dose. Our data (11) show that a T4 loading dose followed by chronic therapy would be needed to produce the most rapid TSH suppression in patients with differentiated thyroid cancer who have undergone thyroid hormone withdrawal for radioiodine imaging. However, even with a loading dose regimen it takes a considerable amount of time (weeks) for the basal TSH and TRH-stimulated TSH responses to become maximally suppressed to phase 3 levels (< 0.01 mU/l) (8, 11). The lag in achieving maximal suppression presumably reflects the time needed to inhibit TSH biosynthesis and deplete thyrotroph TSH content. Interestingly, a reciprocal response is seen during the restoration of a normal basal and TRH-stimulated TSH response following successful treatment of Graves’ thyrotoxicosis (11). This lag in normalization of TSH concentrations presumably reflects the time needed to reinitiate TSH biosynthetic processes and repelte the thyrotroph TSH content.

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References

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