Editorial: “Homeostasis and Allostasis of Thyroid Function”

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Editorial on the Research Topic

Homeostasis and Allostasis of Thyroid Function

CURRENT CHALLENGES IN THYROIDOLOGY

A basic understanding of thyroid control involving pituitary thyrotropin (TSH) has become a cornerstone for the contemporary diagnosis of thyroid disorders. However, long-held simplistic interpretations of the classical feedback concept fall short of the elusive goal of a universally applicable and reliable diagnostic test. Diagnostic ambiguities may arise from the dynamic nature of thyroid homeostasis. Concentrations of TSH and T3 are governed by circadian (1) and, additionally for TSH, ultradian rhythms (2). Plasticity of the hypothalamic–pituitary–thyroid axis in form of adaptive responses may promote misdiagnosis, especially in pregnancy and critical illness (3, 4). Diagnosis of subclinical dysfunction is also dependent on the mode of statistical analysis (5–9).

Consequently, the clinical care of thyroid patients faces major challenges, foremost ill-defined reference ranges for TSH and thyroid hormones (THs), and persistently poor quality of life in a substantial subset of treated hypothyroid patients (10). Divergent criteria by guidelines for defining thyroid disease and guiding therapeutic intervention have further added to the confusion. It remains unclear, if patients with subclinical hypothyroidism benefit from treatment and which are sensible targets of substitution therapy (11, 12).

By addressing predictive adaptation, the rather new theory of allostasis complements the established concept of homeostasis. In situations of strain and stress, allostasis ensures stability through change by modifying setpoints and parameters of feedback control (13–15). Despite being a basically beneficial reaction allostasis may also expose the organism to a new kind of strain referred to as allostatic load, which may result in even life-threatening diseases.

This research topic focusing on homeostasis and—still understudied—allostasis of thyroid function was initiated with the goal that deeper physiological insights in pituitary–thyroid feedback control may aid in solving the aforementioned problems. A series of articles summarizes the state of current scientific knowledge, and delivers new perspectives, as significant progress has been made in that regard.

THYROID HOMEOSTASIS—UNEXPECTED COMPLEXITIES IN A CLASSIC ENDOCRINE FEEDBACK LOOP

A review article by the editors (Hoermann et al.) provides an overview of homeostatic mechanisms in the light of recent research. The classical “short feedback” structure (Astwood-Hoskins loop) (16) is now complemented by additional motifs, an “ultrashort” autocrine loop, where TSH inhibits its own
secretion, and a TSH-T3 shunt relaying stimulation from pituitary to intrathyroidal step-up deiodinases. Although documented for decades on a biochemical level (17, 18), the clinical importance of the TSH-T3 shunt has only recently been recognized (19–23).

Newly identified non-classical processing structures add to the complexity of the control system. They explain both pulsatile thyrotropin release and significant deviations from a log-linear relationship between FT4 and TSH concentrations [Hoermann et al.; (24–26)]. In onset hypothyroidism, rising TSH concentrations stimulate T3 formation (22), thereby maintaining thyroid signaling and unburdening the thyroid from T4 synthesis (Hoermann et al.).

A balancing concept for TSH, FT4, and FT3 is introduced under the term relational stability [Hoermann et al.; (22)]. Importantly, it is lacking in athyreotic patients and suspended when treatment with L-T4 reduces TSH concentration—an important argument against universal L-T4 substitution in subclinical hypothyroidism.

The novel clinical concepts feed back to theory. Berberich et al. describe an expanded physiology-based mathematical model of thyroid homeostasis that incorporates the rediscovered TSH-T3 shunt. This model extends a rich tradition of related “parametrically isomorphic” models (27–35), demonstrating that circadian variations of FT3 concentrations are well explained by TSH action and shedding a fresh light on the evolution of subclinical thyroid diseases (Berberich et al.).

Interpretation of thyroid function tests can be severely affected by homeostatic time constants resulting in hysteresis effects (36), as reviewed by Leow, extending implications to antithyroid treatment and LT4 substitution.

TECHNOLOGICAL ADVANCEMENTS AND NOVEL DIAGNOSTIC TOOLS

Although sensitive for primary hypothyroidism, TSH measurement has low specificity and is unable to detect dysfunctions of central origin. Isolated TSH measurements may be misleading in certain physiological (37) and allostatic conditions (38), including non-thyroidal illness (39).

In a short perspective article, we summarize methodological principles and clinical trial results (Dietrich et al.) for novel diagnostic approaches based on mathematical modeling, such as functional thyroid reserve capacity and step-up deiodinase activity. These calculated parameters deliver estimates for “hidden” structure parameters of thyroid homeostasis and provide early indicators of thyroid failure. Reconstructing the individual equilibrium point (the so-called set point) of thyroid homeostasis is facilitated by new tools and may prove useful as a personal target for L-T4 dosage titration (40, 41). Mathematical modeling can further improve interpretation of L-T4 absorption tests (42).

THE ENIGMATIC ROLE OF NON-CLASSICAL TH

The world of THs is composed of more than T4 and T3. Today, we know 27 metabolites derived from the thyronine skeleton, some of them being hormonally active [Hoermann et al.; (43)]. Thyronamines have received special attention, binding to trace amine-associated receptors (44) and acting as functional antagonists of iodothyronines (45, 46).

Glossmann et al. critically appraise suggested pharmacological uses of 3-monooiodothyronamine (3-T1AM), e.g., for therapy of stroke or in long-lasting space flights. Based on its pleiotropic effects they question if 3-T1AM can be a safe cryogenic drug. Some of the inconsistencies in reported serum concentrations may result from plasma protein binding, potential role of gut microbiota in the formation of thyronamines from iodothyronines or conversion of 3-T1AM to 3-iodothyroacetic acid (3-TA1), a possible major mediator of thyronaminergic signaling (47).

HYPOTHALAMUS–PITUITARY–THYROID AXIS—AN OPEN AND DYNAMIC SYSTEM

The traditional view of pituitary–thyroid feedback control holding T4 plasma concentration constant close to a fixed set point (48) has been challenged by variable concentrations of TSH and THs in certain physiological situations beyond thyroid disease (38, 49–55). Thyroid allostasis delivers a unified theory for a plethora of adaptive processes spanning from fetal life, pregnancy, starvation, exercise, obesity, aging, and general severe illness to psychiatric disorders. In strain and stress, type 1 and type 2 allostasis affect thyroid function in different ways, creating each distinctly recognizable patterns (Chatzitomaris et al.).

PROSPECTUS

Deeper insights in the physiology of thyroid function and its homeostatic control warrant a rethinking of diagnostic practice. The old paradigm employing TSH in the center of diagnostic work-up has to be replaced by a relational concept, where TSH is interlocked with FT4 and FT3, and multivariable distributions represent homeostatic equilibria (9, 30). This new approach allows for personalized interpretation of thyroid function and understands physiological influences as constituents of homeostatic/allostatic control modes (Hoermann et al.).

AUTHOR CONTRIBUTIONS

JD, JM, and RH wrote some of the papers in this Research Topic and participated as guest editors for manuscripts, where they were not coauthors themselves. All authors listed have made a substantial, direct, and intellectual contribution to this editorial and approved it for publication.

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REFERENCES

1. Weeke J, Gundersen HJ. Circadian and 30 minutes in serum TSH and thyroid hormones in normal subjects. Acta Endocrinol (Copenh) (1978) 89:69-72. doi:10.1530/acta.0.0890039

2. Bénard G, Pranz K, Ranft U, Bergmann P, Schermer T, Hesch RD, et al. Circadian and pulsatile TSH secretion under physiological and pathophysiological conditions. Horm Metab Res Suppl (1990) 23:12–7.

3. Dietrich JW, Stachon A, Klein HH. Thyroid and thyrotropic agonists: key actors in thyroid homeostasis. J Thyroid Res (2012) 2012:351864.

4. Dietrich JW, Landgraфе G, Fotiadou EH. TSH and thyrotropic agonists: key actors in thyroid homeostasis. J Thyroid Res (2012) 2012:351864.

5. Dickey RA, Wartofsky L, Feld S. Optimal thyrotropin level: normal ranges and reference intervals do not appear to be equivalent. Thyroid (2005) 15:1035–9. doi:10.1089/thy.2005.15.1035

6. Inal TC, Serteser M, Coşkun A, Özpinar A, Ünsal I. Indirect reference intervals of plasma and glandular regulation of triiodothyronine production by thyrotropin in untreated and thyroxine-treated subjects. Horm Metab Res (2015) 47:674–80. doi:10.1055/s-0034-1398816

7. Arzideh F, Wosniok W, Haeckel R. Indirect reference intervals of plasma and serum thyrotrin (TSH) concentrations from intra-laboratory data bases from several German and Italian medical centres. Clin Chem Lab Med (2011) 49:659–64. doi:10.1515/CCLM.2011.114

8. Larisch R, Giacobino A, Eckl W, Wahl H-G, Midgley JEM, Hoermann R. Thyroid hormone conversion: evidence for a functional ultrashort feedback loop from fractal analysis. Cybrn Syst (2004) 35:315–31. doi:10.1080/01969720490443354

9. Han SX, Eisenberg M, Larsen PR, DiStefano J. THYROSIM app for education and research predicts potential health risks of over-the-counter thyroid supplements. Thyroid (2016) 26:489–98. doi:10.1089/thy.2015.0373

10. Lumen A, Mattie DR, Fisher JW. A biologically based dose-response model of the human thyroid. Math Biosci (2008) 212:22–53. doi:10.1016/j.mbs.2007.10.009

11. Leow MKS. A mathematical model of pituitary-thyroid interaction to provide homeostatic modelling of the relationship between thyrotropin and free thyroxine. Toxicol Sci (2013) 133:320–41. doi:10.1093/toxsci/kft078

12. DíStefano JJ, Stear EB. On identification of hypothalamo-hypophysial control and feedback relationships with the thyroid gland. J Theor Biol (1968) 19:29–50. doi:10.1016/0022-5193(68)90003-9

13. Dietrich JW, Tesche A, Pickardt CR, Mittendorf U. Thyrotropic feedback control: implications of mathematical modeling and consequences for thyrotropin (TSH) and free thyroxine (FT4) reference ranges. Bull Math Biol (2014) 76:1270–87. doi:10.1007/s11538-014-9955-5

14. Lumen A, McNally K, George N, Fisher JW, Loizou GD. Quantitative global sensitivity analysis of a biologically based dose-response pregnancy model for the thyroid endocrine system. Front Pharmacol (2015) 6:107. doi:10.3389/fphar.2015.00107

15. Leow MKS. A mathematical model of pituitary-thyroid interaction to provide an insight into the nature of the thyrotropin-thyroid hormone relationship. J Theor Biol (2007) 248:275–87. doi:10.1016/j.jtbi.2007.05.016

16. Benvena S, Di Bari F, Granese R, Antonelli A. Serum Thyrotropin and Phase of the Menstrual Cycle. Front Endocrinol (2017) 8:250. doi:10.3389/fendo.2017.00250

17. Petrovyan L. Relationship between high normal TSH levels and metabolic syndrome components in type 2 diabetic subjects with euthyroidism. J Clin Transl Endocrinol (2015) 2:110–3. doi:10.1016/j.jtcet.2015.02.004

18. Papi G, Corsello SM, Pontecorvi A. Clinical concepts on thyroid emergencies. Front Endocrinol (2014) 5:102. doi:10.3389/fendo.2014.00102

19. Leow MKS, Goede SL. The homeostatic set point of the hypothalamus-pituitary-thyroid axis – maximum curvature theory for personalized...
euthyroid targets. *Theor Biol Med Model* (2014) 11:35. doi:10.1186/1742-4682-11-35
41. Goede SL, Leow MKS, Smit JW A, Dietrich JW. A novel minimal mathematical model of the hypothalamus-pituitary-thyroid axis validated for individualized clinical applications. *Math Biosci* (2014) 249:1–7. doi:10.1016/j.mbs.2014.01.001
42. Eisenberg M, Distefano JJ III. TSH-based protocol, tablet instability, and absorption effects on L-T4 bioequivalence. *Thyroid* (2009) 19:103–10. doi:10.1089/thy.2008.0148
43. Senese R, Cioffi F, de Lange P, Goglia F, Lanni A. Thyroid: biological actions of “nonclassical” thyroid hormones. *J Endocrinol* (2014) 221:R1–12. doi:10.1530/JEO-13-0573
44. Qatato M, Szumska J, Skripnik V, Rijntjes E, Köhrle J, Brix K. Canonical TSH Regulation of Cathepsin-Mediated Thyroglobulin Processing in the Thyroid Gland of Male Mice Requires Taar1 Expression. *Front Pharmacol* (2018) 9:221. doi:10.3389/fphar.2018.00221
45. Hoefig CS, Zucchi R, Köhrle J. Thyronamines and derivatives: physiological relevance, pharmacological actions, and future research directions. *Thyroid* (2016) 26:1656–73. doi:10.1089/thy.2016.0178
46. Piehl S, Hoefig CS, Scanlan TS, Köhrle J. Thyronamines – past, present, and future. *Endocr Rev* (2011) 32:64–80. doi:10.1210/er.2009-0040
47. Laurino A, Raimondi L. Commentary: Torpor: The Rise and Fall of 3-Monoiodothyronamine from Brain to Gut—From Gut to Brain? *Front Endocrinol* (2017) 8:206. doi:10.3389/fendo.2017.00206
48. Reichlin S, Utiger RD. Regulation of the pituitary-thyroid axis in man: relationship of TSH concentration to concentration of free and total thyroxine in plasma. *J Clin Endocrinol Metab* (1967) 27:251–5. doi:10.1210/jcem-27-2-251
49. Sterling K, Lazarus JH. The thyroid and its control. *Annu Rev Physiol* (1977) 39:349–71. doi:10.1146/annurev.ph.39.030177.002025
50. Fontes KN, Cabanelas A, Bloise FF, Andrade CBV, Souza LL, Wilieman M, et al. Differential Regulation of Thyroid Hormone Metabolism Target Genes during Non-thyroidal Illness Syndrome Triggered by Fasting or Sepsis in Adult Mice. *Front Physiol* (2017) 8:828. doi:10.3389/fphys.2017.00828
51. Lesmana R, Iwasaki T, Iizuka Y, Amano I, Shimokawa N, Kobuchi N. The change in thyroid hormone signaling by altered training intensity in male rat skeletal muscle. *Endocr J* (2016) 63:727–38. doi:10.1507/endocr.16-0126
52. Wajner SM, Maia AL. New insights toward the acute non-thyroidal illness syndrome. *Front Endocrinol* (2012) 3:8. doi:10.3389/fendo.2012.00008
53. Van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. *Thyroid* (2014) 24:1456–65. doi:10.1089/thy.2014.0201
54. Dietrich JW, Müller P, Schiedat F, Schömisch M, Strauch J, Chatzitomaris A, et al. Nonthyroidal illness syndrome in cardiac illness involves elevated concentrations of 3,5-diiodothyronine and correlates with atrial remodeling. *Eur Thyroid J* (2015) 4:129–37. doi:10.1159/000381543
55. Flies E, Kalsbeek A, Boelen A. Mechanisms in endocrinology: beyond the fixed setpoint of the hypothalamus-pituitary-thyroid axis. *Eur J Endocrinol* (2014) 171:R197–208. doi:10.1530/EJE-14-0285

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