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Sommario/riassunto

The discovery of the negative feedback of thyroid hormones on pituitary thyroid-stimulating hormone (TSH) secretion, a classical endocrine feedback control system, has shaped diagnosis and treatment of thyroid disease for the last decades. Based on this concept, a unique diagnostic category of subclinical thyroid disorders was introduced, being defined exclusively by an abnormal TSH response in the presence of thyroid hormone concentrations within the reference range. Although this approach was able to deliver a conceptually straightforward disease definition problems surfaced in clinical practice as neither the diagnostic reference range nor the appropriate threshold for initiating substitution treatment are universally agreed upon for subclinical thyroid disorders. The situation is further aggravated by the so-called syndrome T, which comprises a substantial but heterogeneous group of L-T4 treated patients with hypothyroidism with reduced quality of life despite "normal" TSH values. A limited understanding of the physiological relationships between TSH and thyroid hormones may be a main reason for clinical difficulties in dealing with the causes of syndrome T and tailoring substitution therapy for hypothyroid patients with subclinical thyroid disorders. Feedback regulation has recently been shown to be much more complex than previously assumed. The concept of homeostatic control has also been extended to include the lesser known but equally important allostatic thyroid regulation.The

latter aims at adaptive homeostasis or stability through changing setpoints and modulating structural parameters of feedback control, as may be appropriate to adapt to a vast array of conditions spanning from fetal life, aging, pregnancy, exercise, starvation, obesity, psychiatric disorders to the severe non-thyroidal illness syndrome. A better understanding of homeostatic and allostatic mechanisms, which govern the behaviour of pituitary-thyroid feedback control, is on the horizon. This promises to improve the diagnostic utility of laboratory methods, laying the foundation for personalised methods to optimise dosage and modality of substitution therapy. The emerging new world of thyroid physiology is reflected on the side of clinical medicine in a new, relational paradigm for diagnosis and treatment. Considerable progress has been made in this respect in the following key areas: • the significance of complementary information processing structures within the feedback loop, in particular ultrashort feedback of TSH on its own secretion and the action of a TSH-T3 shunt unburdening the thyroid from T4 synthesis in imminent thyroid failure, • the unravelling of spatio-temporal dynamics of hormone concentrations ranging from ultradian to circannual rhythms and including hysteresis effects, • the emergence of "non-canonical" mechanisms of thyroid hormone signalling beyond transcriptional control of gene expression, • the physiological actions of thyronine metabolites, which have been previously regarded as biologically inactive, such as thyronamines and iodothyroacetates, • the characterisation of distinct patterns in the adaptive processes to stress and strain and their conclusive explanation through reactions to type 1 and type 2 allostatic load. This collective volume contains the contributions to the Research Topic "Homeostasis and Allostasis of Thyroid Function", which was originally published by the journal Frontiers in Endocrinology. Authored by an international team of experts from three continents , the book provides a comprehensive overview on thyroid control from recent research in basic, computational and clinical thyroidology. Many aspects addressed here can be expected to stimulate future research. A more comprehensive view and better integration of in-vitro, in-silico and in-vivo investigations will be invaluable in paving the way to this new world of thyroidology.