Thyrotropin (TSH) and, consequently, thyroid hormone secretion (thyroxine (T\textsubscript{4}) and tri-iodothyronine (T\textsubscript{3})) is regulated by a negative feed-back mechanism which is exerted by T\textsubscript{3} binding to its own receptor, located in the nucleus of the thyrotrope cells of the anterior pituitary gland. Thyroid hormone receptors (TRs) are known to mediate T\textsubscript{3} suppression of TSH β-subunit gene (TSH\textbeta) expression, acting at specific thyroid-hormone response elements (TREs) near the transcription start site in the promoter region, and involving interaction with nuclear cofactors, such as the retinoid X receptors (RXRs), coactivators and corepressors (1).

RXRs belong to the family of ligand-dependent transcription factors, encompassing 3 distinct isoforms – RXR-alpha, -beta, and -gamma – which are closely related to each other in their DNA- and ligand-binding domains. RXRs function as both 9-cis-retinoic acid (9-cis-RA) ligand-dependent receptors and heterodimeric partners for the vitamin D receptor, retinoic acid receptor (RAR), and TRs (2). Mangelsdorf et al. (3) have demonstrated that RXRs and RXR\textbeta mRNAs are widely expressed in developing embryo and adult murine tissues, while RXR\textgamma mRNA is more restricted in its distribution, being abundant in the thyrotropes within the pituitary gland.

RXRs are recognized as the major TR-associated proteins in many positively regulated target genes (4–6). However, their role on negatively regulated promoters remains to be clarified. Recently, it has been reported that RXR\textgamma represents the receptor isoform involved in negative regulation of TSH\textbeta gene promoter (7).

In vitro studies using thyrotrope-derived tumor cells (TtT-97) demonstrated that the binding of T\textsubscript{3} and 9-cis-RA to TRs and RXR\textgamma respectively, is able to suppress the promoter activity of the TSH\textbeta gene acting at distinct response elements. Moreover, they seem to function cooperatively as demonstrated by the fact that the combination of the two ligands suppresses TSH\textbeta gene expression more efficiently than either alone (7). These data suggest that in mice retinoids binding to RXR\textgamma can mediate the reduction of TSH secretion independently of T\textsubscript{3}.

According to these in vitro results, several papers reported that the administration in vivo to euthyroid or hypothyroid rats of pharmacological amounts of retinoic acid, an active metabolite of vitamin A, reduces both basal and thyrotropin-releasing hormone (TRH)-stimulated TSH secretion, independently of the thyroid status of the animals. This effect seems to be mediated by the binding of the retinoid acid to RXR\textgamma and does not result in the appearance of clinical hypothyroidism (7–9).

In the last few years, several RXR-selective retinoids have been designed and synthesized for the treatment of human cancers (10). Their efficacy and safety have been investigated by experimental studies in animals with different types of tumors and by in vitro investigations. These studies demonstrated that RXR-selective retinoids possess a relevant antiproliferative effect on tumor cells and may induce apoptosis (11–14).

Very recently, Sherman and coworkers (15) assessed thyroid function in a cohort of patients with cutaneous T-cell lymphoma who were receiving high doses of a specific RXR\textgamma-selective ligand, bexarotene (Targretin). About 70% of the patients (19/27) treated with bexarotene (daily dose >300 mg/m\textsuperscript{2} of body surface area) had symptoms and signs of hypothyroidism, particularly fatigue and cold intolerance. The biochemical picture was characterized by the reduction of the mean serum TSH from 2.2 mU/l at base line to 0.05 mU/l during treatment with bexarotene. Similarly, the mean serum free thyroxine concentration declined from 12.9 pmol/l to 5.8 pmol/l during bexarotene administration. The degree of suppression of TSH secretion tended to be greater in patients treated with higher doses of bexarotene. In all the patients symptoms improved after the initiation of l-thyroxine (l-T\textsubscript{4}) replacement therapy and euthyroidism was achieved when bexarotene was discontinued, strongly suggesting that the clinical and biochemical hypothyroidism was due to a direct central effect of bexarotene. To correlate these observations with a potential molecular mechanism, TtT-97 thyrotope tumor cells were transiently transfected with a murine TSH\textbeta-promoter-luciferase reporter plasmid and incubated with T\textsubscript{3}, 9-cis-RA and different concentrations (1 \textmu mol/l and 5 \textmu mol/l) of bexarotene. The authors found that the activity of the TSH\textbeta-subunit gene promoter was suppressed by as much as 50% by all three agents. Thus, they concluded that bexarotene can suppress TSH secretion, resulting in central hypothyroidism.

These relevant findings are in contrast to those observed in the animals (7–9) and in a clinical trial by...
Miller and coworkers (16) who demonstrated that in patients with different types of cancers, encompassing 9 cutaneous T-cell lymphomas, bexarotene therapy did not affect the pituitary–thyroid axis. Such discrepancy could be due to the fact that in this trial the dose of bexarotene given to the patients was 20–50% lower than that used by Sherman et al. (15).

Although further studies are necessary to determine whether hypothyroidism is a constant clinical consequence of tumor treatment with RXR-selective ligands or whether its appearance is related to a dose-dependent mechanism, the study of Sherman et al. (15) describes a new cause of central hypothyroidism which can easily be prevented by L-T4 replacement therapy.

References

4. Murray MB & Towle HC. Identification of nuclear factors that enhance binding of the thyroid hormone receptor to a thyroid hormone response element. *Molecular Endocrinology* 1989 3 1434–1442.
5. Lazar MA & Berrodin TJ. Thyroid hormone receptors form distinct nuclear protein-dependent and -independent complexes with a thyroid hormone response element. *Molecular Endocrinology* 1990 4 1627–1635.