Clues to a possible new variant of thyroid hormone resistance

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Patients with thyroid hormone resistance, first described by Refetoff *et al.* in 1967 (1), usually present with goitre, elevated thyroid hormone levels and an inappropriately normal or elevated thyrotrophin (TSH) level (reviewed in 2, 3). Clinical effects of thyroid hormone resistance can include variable features of hypo- and hyperthyroidism such as tachycardia, attention deficit/hyperactivity disorder, growth retardation and hearing defects. The syndrome is known to be caused by mutations in the thyroid hormone receptor (TR) β gene, but the molecular basis of cases without mutations in this gene remains elusive, and no mutations have ever been found in the α gene of the receptor (TR α). A recent study by Wikström *et al.* (4) indicates that there may be another variant of resistance to thyroid hormones with a different clinical presentation caused by defects in TR α .

TRs are ligand-modulated transcription factors and the products of two different genes (reviewed in 5, 6). The TR β gene in chromosome 3 encodes two receptor isoforms (TR β 1 and TR β 2), which are splice variants. Proteins encoded by the TR α gene in chromosome 17 include one receptor that binds thyroid hormones (TR α 1), two isoforms that bind thyroid hormone responsive elements on DNA, but do not bind thyroid hormones (TR α 2 and TR α 3), and one structurally related orphan receptor encoded by the opposite DNA strand (rev-erbA α). The first case of thyroid hormone resistance showed an autosomal recessive pattern of inheritance and lacked not only the TR β gene, but also adjacent sequences (7). In all other familial cases there is an autosomal dominant inheritance pattern. Mutations have been demonstrated in the TR β gene resulting in a receptor with a dominant negative effect of the mutated receptor protein on normal TR function. This has also been shown in sporadic cases of thyroid hormone resistance.

It has been speculated that TR α gene mutations in humans would be incompatible with early foetal survival or give rise to clinical features not associated with the recognized form of thyroid hormone resistance. In mice, homozygous inactivation of the TR α gene, which abrogated the production of the TR α 1 and TR α 2 isoforms, led to hypothyroidism, growth arrest and death within 5 weeks after birth (8). Wikström *et al.* (4), at Björn Vennströms laboratory at the Karolinska Institute in Stockholm, wanted to identify effects of thyroid hormones specifically mediated by TR α 1. A transgenic mouse, which lacked a functional TR α 1, without losing TR α 2 and rev-erbA α expression, was developed. They demonstrated that deletion of TR α 1 did not affect viability of the mice, and there was a normal ratio between male and female offspring. Homozygous

animals survived to at least 18 months of age, and both sexes were fertile with normal litter sizes. No overt abnormalities were discovered at autopsy, and no compensatory increase in the expression of the other thyroid hormone receptors was detected in the brain. In contrast to the increase in thyroid hormone levels observed in thyroid hormone resistance, TR α 1 deficient mice had lower serum levels of free thyroxine (T₄) than the controls, whereas the levels of free tri-iodothyronine (T₃) were not statistically significantly different. In male TR α 1 deficient mice, serum TSH levels were lower than in the control mice. Northern blot analyses of pituitaries from these animals revealed that the mRNA levels of the TSH α subunit were reduced in mice without TR α 1, whereas the β subunit was increased. Although a reduction in the glycoprotein hormone α subunit mRNA was associated with a reduction in the TSH level, there was no effect on luteinizing hormone, chorionic gonadotrophin and follicle-stimulating hormone function since sexual maturation and fertility were unaffected. However, mice lacking both TR α 1 and TR α 2, became severely hypothyroid, their pituitary mRNA level of the TSH β subunit was lower than in the control mice, and their thyroid glands were hypoplastic (8). Hypothyroidism seems to induce the expression of TSH α subunit mRNA in the pituitary not only by removing a passive repression induced by thyroid hormones, but also by transcriptional activation through TR α 1. Studies of TR β deficient mice indicate that TR β 2, which is highly expressed in thyrotrophs of the pituitary, is essential for a normal inhibition of TSH production by thyroid hormones (9, 10). However, a normal feed-back regulation of thyroid hormones on TSH production also depends on a normal TR α gene. In the TR α gene knock-out mouse models a functional TR α 2 is associated with a less severe hypothyroidism (4, 8), which indicates that TR α 2 attenuates the inhibitory effects of TR β 2 on TSH production.

The syndrome of thyroid hormone resistance is often accompanied by tachycardia. In TR α 1 deficient mice, heart rate was slower than in control mice even after prolonged treatment with T₃ (4). Both TR α 1 and TR β are expressed in mouse heart (11). To some degree the effects of thyroid hormones on pacemaking functions in the heart are mediated by TR β in TR α 1 deficient mice. The molecular basis of the bradycardia induced by TR α 1 deficiency has not been revealed, but may be mediated by modulating the effects of β -adrenergic or muscarinic receptor activation in the cardiac sinoatrial node or the expression of ion channels and pumps. However, the levels of well-known myocardial target genes for thyroid hormones, such as the sarcoplasmic

Ca^{2+} -ATPase, Na^{+} - K^{+} ATPase, and β -adrenergic receptor, were not changed. Electrocardiograms corrected for the differences in heart rate revealed that the QRS-duration was prolonged. This is also observed in hypothyroid rat myocytes and in hypothyroid patients. The QT_{end} duration was also longer, which is associated with a prolonged ventricular repolarization time. The bradycardia and electrocardiographic changes indicate that there may be genes that are specifically regulated by $\text{TR}\alpha 1$ in the heart. However, the partial T_3 resistance in the $\text{TR}\alpha 1$ deficient mice heart may simply be the result of a lower total number of TRs in this tissue.

$\text{TR}\alpha 1$ deficiency was associated with a 0.5°C reduction in body temperature when compared with the control mice (4). There were no changes in locomotor activity, and the amount of brown fat was the same. After T_3 treatment the temperature increased in the $\text{TR}\alpha 1$ deficient mice, but was always lower when compared with the similarly treated controls. Both $\text{TR}\alpha 1$ and $\text{TR}\beta$ s seem to be important for thermogenesis in brown fat or in other processes regulating body temperature. As for the bradycardia, the hypothermia may depend on a lower total number of receptors rather than a specific deficiency in $\text{TR}\alpha 1$ signalling.

The mouse model created by Wikström *et al.* (4) illustrates a situation where TSH is not a good measure of thyroid hormone status. It is important that the clinician has an open mind when dealing with thyroid patients with laboratory and clinical discrepancies. A patient with slight hypothermia, bradycardia, and low serum levels of TSH and free T_4 may have a thyroid hormone resistance caused by a dysfunctional $\text{TR}\alpha 1$.

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