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 (TRα). 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 TRα.

TRs are ligand-modulated transcription factors and the products of two different genes (reviewed in 5, 6). The TRβ gene in chromosome 3 encodes two receptor isoforms (TRβ1 and TRβ2), which are splice variants. Proteins encoded by the TRα gene in chromosome 17 include one receptor that binds thyroid hormones (TRα1), two isoforms that bind thyroid hormone responsive elements on DNA, but do not bind thyroid hormones (TRα2 and TRα3), and one structurally related orphan receptor encoded by the opposite DNA strand (rev-erbαα). The first case of thyroid hormone resistance showed an autosomal recessive pattern of inheritance and lacked not only the TRβ gene, but also adjacent sequences (7). In all other familial cases there is an autosomal dominant inheritance pattern. Mutations have been demonstrated in the TRβ 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 TRα 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 TRα gene, which abrogated the production of the TRα1 and TRα2 isoforms, led to hypothyroidism, growth arrest and death within 5 weeks after birth (8). Wikström et al. (4), at Björn Vennström’s laboratory at the Karolinska Institute in Stockholm, wanted to identify effects of thyroid hormones specifically mediated by TRα1. A transgenic mouse, which lacked a functional TRα1, without losing TRα2 and rev-erbαα expression, was developed. They demonstrated that deletion of TRα1 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, TRα1 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 TRα1 deficient mice, serum TSH levels were lower than in the control mice. Northern blot analyses of pituitary from these animals revealed that the mRNA levels of the TSH α subunit were reduced in mice without TRα1, 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 TRα1 and TRα2, 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 TRα1. Studies of TRβ deficient mice indicate that TRβ2, 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 TRα gene. In the TRα gene knock-out mouse models a functional TRα2 is associated with a less severe hypothyroidism (4, 8), which indicates that TRα2 attenuates the inhibitory effects of TRβ2 on TSH production.

The syndrome of thyroid hormone resistance is often accompanied by tachycardia. In TRα1 deficient mice, heart rate was slower than in control mice even after prolonged treatment with T3 (4). Both TRα1 and TRβ are expressed in mouse heart (11). To some degree the effects of thyroid hormones on pacemaking functions in the heart are mediated by TRβ in TRα1 deficient mice. The molecular basis of the bradycardia induced by TRα1 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 sarcomplasmic
Ca²⁺-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 QTend 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 TRα1 in the heart. However, the partial T3 resistance in the TRα1 deficient mice heart may simply be the result of a lower total number of TRs in this tissue.

TRα1 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 T3 treatment the temperature increased in the TRα1 deficient mice, but was always lower when compared with the similarly treated controls. Both TRα1 and TRβs 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 TRα1 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 T₄ may have a thyroid hormone resistance caused by a dysfunctional TRα1.

References
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