Crossing the Hurdles of Thyroid Hormone Receptor-α Activation

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Thyroid hormone acts in virtually every biological system in vertebrates by controlling the expression of different sets of genes. To achieve this, thyroid hormone interacts with two receptors (TR), TRα and TRβ, located in the nucleus of its target cells, which turn gene transcription on or off and thus mediate the biological effects associated with the thyroid secretion (1, 2). The distribution of TRα and TRβ among different target tissues is not homogeneous: TRα pathways are implicated in the brain, skeletal muscle, heart, and bone, whereas the TRβ pathways play a metabolic role in liver and adipose tissue (3). Together both TR isoforms control a vast network of biological processes that includes critical roles in development, growth, and metabolic homeostasis (4).

The determination of the TR structure made it clear that differences in the ligand binding pocket of the receptors would allow for the development of small molecules with a reasonable degree of binding selectivity (5). This was achieved in the late 1990s and GC-1, the first of such molecules to exhibit TRβ selectivity, was tested in cell systems and in animals (6). Today an array of TRβ-selective ligands exists, expanding not only our understanding of thyroid hormone action but also the exciting possibility of pharmacological intervention in disease states (7).

That different TR isoforms control separate biological processes became clear from a series of studies in mice with inactivation or mutation of different TR isoforms as well as studies in patients with the syndrome of resistance to thyroid hormone (3). However, a landmark in this field was established with the demonstration that treatment of hypothyroid rats with GC-1 normalizes serum cholesterol and triglycerides through TRβ activation in the liver without increasing heart rate or expression of typical T3 target genes in the heart, all TRα-dependent processes (11). Later an additional key observation was made: that chronic treatment with GC-1 in euthyroid female rats lowered serum cholesterol by approximately 20% and spared bone mass as assessed by histomorphometry and dual-x-ray bone absorptiometry (12). Further studies illustrated that a substantial degree of TRβ selectivity could be achieved with GC-1, even in tissues with active TRα and TRβ pathways, such as the brown adipose tissue (BAT). In hypothyroid mice, treatment with GC-1 normalized BAT uncoupling protein-1 expression (a highly T3 responsive...
gene) but failed to normalize the responsiveness to adrenergic stimulation (13, 14). Thus, two distinct thyroid-dependent pathways were identified in BAT, a TRβ-mediated stimulation of uncoupling protein-1 and a TRα-mediated amplification of the adrenergic signaling, the latter being applicable for the heart as well.

Prompted by animal studies showing that TRβ-selective thyromimetics stimulate cholesterol elimination through low-density lipoprotein and high-density lipoprotein pathways without eliciting identifiable side effects (15, 16), investigators took the concept of TRβ-selective activation to clinical trials. A selective thyromimetic (KB2115) was used in moderately overweight and hypercholesterolemic human subjects and found to be safe and well tolerated, without measurable cardiac effects (17). Its use caused up to a 40% lowering of total and low-density lipoprotein cholesterol after 14 d of treatment through stimulation of bile acid synthesis. These extraordinary results strengthened the idea that the pharmacological TR selectivity observed in animal models successfully translates to humans. The next major break was the demonstration in rabbits, monkeys (18), and humans (19) that selective thyromimetics provide additional (~30%) cholesterol-lowering activity when given to patients receiving treatment with statins.

At the same time that the lipid-lowering effects of TRβ-selective thyromimetics were being investigated, these molecules were also found to accelerate energy expenditure in rats and to lower body weight in primates without affecting the heart (15). This implies that the known thyroid hormone effects on energy expenditure are largely mediated via the TRβ pathway. Furthermore, the acceleration in the metabolic rate induced by GC-1 over a period of 6 wk in rats was followed by a decrease in fat but not lean mass (20). Remarkably, contrary to treatment with T₃, food consumption is not increased by GC-1 (20). Subsequently, administration of TRβ-selective thyromimetics was reported to protect against diet-induced obesity and the associated glucose intolerance in rats through activation of a series of thermogenically related genes in the BAT (21, 22). Thus, liver and BAT are bona fide metabolic targets of TRβ-selective thyromimetics, a relevant finding, given the demonstration that BAT contributes to energy homeostasis in adult humans (23). Altogether these data indicate that the potential for metabolic control provided by this new class of drugs goes well beyond lowering serum cholesterol.

A logical concern is whether treatment with selective thyromimetics interferes with any aspects of thyroid economy such as the TRH/TSH feedback mechanism, for example. Indeed, patients treated with TRβ-selective thyromimetics exhibit a small but significant drop in serum T₄ (total and free) without the expected increase in serum TSH (17, 19). This is to be expected, given that TRβ is expressed in the hypothalamus and pituitary gland and is known to play a key regulatory role in the negative TSH feedback mechanism (24). Patients on TRβ-selective thyromimetics remain essentially euthyroid because serum levels of the biologically active thyroid hormone T₃ are not affected.

Luckily, other parts of the brain, however, are much less sensitive to TRβ-selective thyromimetics. Despite being able to cross the blood-brain barrier, GC-1 has only limited activity in brain because of the TRα predominance in the cerebrum and cerebellum (25). Furthermore, Grijota-Martínez et al. (9) now report that even the few genes in the brain that were previously found to be GC-1 sensitive, i.e., the striatal Rasd2 and cerebellar Rln, are not affected by treatment with GC-24. This illustrates that, just like the heart and the bone, the brain can in fact be spared from potential sides effects of the TRβ-selective thyromimetics.

The principle of selective TR activation is now well established. Cholesterol lowering is just one of the multiple potential applications of TRβ-selective thyromimetics, which could also be used in a number of other settings. For example, treatment with such drugs should be able to activate BAT and thus accelerate energy expenditure and treat obesity, particularly because activation of the TRβ pathway does not increase appetite. Similarly, TRβ-selective thyromimetics seem particularly suitable in the TSH suppression of patients with differentiated thyroid cancer, given the concern that life-long suppressive doses of levothyroxine can unnecessarily increase the risk of cardiac arrhythmias and bone fractures. At the same time, obtaining a molecule that selectively activates the TRα pathway should also be potentially rewarding. For example, thyroid hormone has been used to improve cardiac function after cardiopulmonary bypass (26) and as an adjuvant to treat depression (27), both effects likely to be mediated by the TRα pathway. For the time being, however, it seems that for the TRα-selective thyromimetics, it is back to the drawing board.

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