This is a very exciting time for the development of novel compounds that affect thyroid hormone signaling pathways. Compounds have been developed that function as tissue selective thyroid hormones, inducing thyroid hormone action in certain tissues but not in others. Two such compounds are currently being used in human clinical trials for the treatment dyslipidemia. In other recent developments, a class of novel thyroid hormone metabolites with unique biological activity has been discovered. These compounds, called thyronamines, are proving useful as probes of thyroid hormone function and may also find a role in therapeutic use. The latest developments in the area of novel thyroid hormone analogues will be discussed in this presentation.

In 1998, the selective thyroid hormone agonist GC-1 was first reported. The chemical structure of GC-1 differs from that of 3,5,3'-triiodothyronine (T3) in that the iodines are replaced by hydrocarbon residues, the biaryl ether linkage is replaced by a methylene unit and the alanine side chain is replaced by an oxyacetic acid side chain (Fig. 1). GC-1 has selective actions compared to T3. GC-1 binds to the beta subtype of the thyroid hormone receptor (TRβ) about 10 times more tightly than it binds to the alpha subtype (TRα). In addition, GC-1 stimulates TR-mediated target gene transcription more potently with TRβ than with TRα. This in vitro selectivity is also observed in various in vivo systems. In tadpole metamorphosis for example, GC-1 strongly stimulates TRβ-mediated activation of genes involved in gill and tail resorption, whereas little stimulation of TRα-mediated genes involved in limb bud growth and development is seen. In rodents, GC-1 potently reduces serum cholesterol, a thyroid hormone mediated process thought to involve acceleration of reverse cholesterol transport (RCT) through the liver, an organ using predominantly TRβ. However, unlike T3, GC-1 treatment does not lead to undesired effects such as increases in heart rate, reduction in bone mineral density and skeletal muscle weakness and fatigue. Therefore, GC-1 could have potential therapeutic use for lowering cholesterol by a novel mechanism distinct from statins, the class of cholesterol lowering agents most commonly used which work as inhibitors of cholesterol biosynthesis. To explore this possibility further, GC-1 was taken into clinical development by QuatRx Pharmaceuticals. As part of this process, the name of the compound was changed to QRX-431 and most recently changed again to Sobetirome after successful completion of Phase-I clinical trials. More information on the clinical development of Sobetirome can be found at the QuatRx website (www.quatrx.com). Karo Bio is developing a selective thyromimetic, KB-2115 or Eprotirome (Fig. 1).

Another class of interesting thyroid hormone analogs that have emerged recently is the thyronamines. These compounds are deiodinated and decarboxylated derivatives of thyroxine (T4) and 3-iodothyronamine (T1AM, Fig. 2) is the best characterized of the class to date. T1AM is a potent agonist of the orphan G-protein coupled receptor trace amine-associated receptor 1 (TAAR1). In addition to TAAR1, T1AM also binds to aminergic GPCRs α-adrenergic receptor 2A and serotonin receptor 2C, although its affinity and potency for these receptors is somewhat less than for TAAR1. T1AM also is an inhibitor, but not a substrate, for the vesicular monoamine transporter (VMAT) and the dopamine (DAT) and norepinephrine (NET) plasma membrane reuptake transporters; T1AM has no activity against the serotonin plasma membrane reuptake transporter (SERT). T1AM is an
endogenous metabolite of T₄ that is found in variety of different tissues including brain, heart, liver, pancreas, skeletal muscle, smooth muscle and fat. It is also found in circulation where it is predominantly bound to a carrier protein. Administration of T₁AM to rodents leads to a number of interesting effects including, hypothermia, bradycardia, hyperglycemia and shift in fueling away from carbohydrate utilization and toward fat burning. This research area is still in its infancy and the basic biology of this new class of endogenous thyroid hormone analogues remains to be defined and better understood. However, it is conceivable that certain diseases and disorders will track with imbalances in the thyronamine axis of the thyroid endocrine system and understanding this will be important for the development of better therapeutic agents.

Further reading

Review articles on selective thyromimetics

Articles on GC-1/QRX-431/Sobetirome

**Articles on KB-2115/Eprotirome**


**Articles on Thyronamines**


