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Novel thyroid hormone analogues, enzyme inhibitors and mimetics, and their action

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ABSTRACT

Thyroid hormones (THs) play key roles in modulating the overall metabolism of the body, protein synthesis, fat metabolism, neuronal and bone growth, and cardiovascular as well as renal functions. In this review, we discuss on the thyroid hormone synthesis and activation, thyroid hormone receptors (TRs) and mechanism of action, applications of thyroid hormone analogues, particularly the compounds that are selective ligands for TRβ receptors, or enzyme inhibitors for the treatment of thyroidal disorders with a specific focus on thyroid peroxidase and iodothyronine deiodinases. We also discuss on the development of small-molecule deiodinase mimetics and their mechanism of deiodination, as these compounds have the potential to regulate the thyroid hormone levels.

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1. Introduction

Thyroid gland, situated at the lower front part of the neck, secretes thyroid hormones (THs), which play a crucial role in controlling the overall metabolism of the body, protein synthesis, fat metabolism, neuronal and bone growth, and cardiovascular as well as renal functions. The production of thyroid hormone from the thyroid gland is tightly regulated by the action of hypothalamus and pituitary gland, which secretes thyrotropin releasing hormone (TRH) and thyroid stimulating hormone (TSH), respectively, through a classical negative feedback mechanism (Chiamolera and Wondisford, 2009; Brent, 2012; Mondal et al., 2016; Yen, 2001). The combined action of hypothalamus, pituitary and thyroid gland to control the TH concentration in the blood serum is called as hypothalamic-pituitary-thyroid (H-P-T) axis. L-Thyroxine (3,5,3′,5'-tetraiodothyronine, T4), the major prohormone secreted by the

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thyroid gland, is carried to several target organs by three serum transport proteins, thyroxine binding globulin (TBG), transthyretin (TTR) and human serum albumin (HSA). The internalisation of THs into the cell is mediated by various transmembrane proteins, such as monocarboxylate transporter 8 (MCT8) and 10 (MCT10) as well as organic anion transporter 1c1 (OATP1C1) (Mondal et al., 2016; Bernal et al., 2015). The biologically active metabolite, 3,5,3'-triiodothyronine (T3) is produced by regioselective deiodination of T4 at the phenolic ring by the mammalian selenoenzymes, iodothyronine deiodinases type 1 (DIO1) and type 2 (DIO2) (Schweizer and Steegborn, 2015a; Behne et al., 1990). Three isoforms of DIOs (DIO1, DIO2 and DIO3) exhibit different regioselectivities of the deiodination. While DIO1 and DIO2 catalyses the activation of T4 to T3 by phenolic ring deiodination, DIO3 catalyses the tyrosyl ring deiodination of T4 and T3 to produce the biologically inactive metabolites 3,3′,5'-triiodothyronine (rT3) and 3,3'-diiodotyronine (3,3′-T2), respectively. The active metabolite, T3 binds to nuclear thyroid hormone receptor α (TRα) and β (TRβ) to regulate the gene expression with the help of various co-activator and co-repressor proteins (Yen, 2001).

Various thyroid-related disorders, such as hyperthyroidism, hypothyroidism, hypercholesterolemia, cardiovascular dysfunctions, atherosclerosis and diabetes are known. While hyperthyroidism and hypothyroidism directly result from the excess and insufficient circulating TH concentrations, respectively, alterations in the TH levels contribute to the pathology of the other diseases (Mondal et al., 2016; Yen, 2001). Severe forms of hyperthyroidism can be associated with an increase in heart rate (tachycardia), atrial arrhythmias, heart failure, muscle wasting, and osteoporosis in post-menopausal women. However, excess TH has also beneficial effects on lowering the serum low density lipoprotein (LDL)-cholesterol and body fat (Webb, 2004; Baxter et al., 2001; Cooper, 2003). Therefore, uncoupling of the deleterious effects from the beneficial effects provides an excellent opportunity to develop novel drugs for atherosclerosis, dyslipidaemia and obesity. In the last few decades, several TH analogues or thyromimetics, which reduce the serum LDL-cholesterol and body fat without affecting the heart rate, bone and muscle catabolism by selectively targeting the TRβ, are developed and many of them have entered clinical trials (Baxter and Webb, 2009; Meruvu et al., 2013).

Hyperthyroidism is often treated with the antithyroid drugs, which irreversibly inhibit thyroid peroxidase (TPO), an important enzyme involved in the biosynthesis of THs, and therefore, block the biosynthesis of THs in the thyroid gland. Antithyroid drugs also inhibit the biological activation of T4 to T3 by DIO1 and DIO2, and iodide transport by Na+/I symporter (NIS) (Mondal et al., 2016; Manna et al., 2013). An alternative way to control the TH concentrations, without inhibiting TPO or DIO1, is controlling the activation and inactivation of THs. Inspired by the amino acid sequences of the active site of DIOs, that catalyse the activation and inactivation of THs (Bianco et al., 2002; Köhrle, 2002; Kuiper et al., 2005; Visser and Schoenmakers, 1992; Köhrle, 1999; Köhrle et al., 2005), several organo-sulphur or selenium compounds have been developed in the last decade to mimic the activity of DIOs. Their chemical and biochemical behavior has also contributed significantly to understand the mechanism of deiodination of THs by DIOs. In this review, we discuss the novel TH analogues for the treatment of atherosclerosis and dyslipidaemia, enzyme inhibitors and deiodinase mimics that are used to control the TH production and to understand the mechanism of deiodination by DIOs.

2. Thyroid hormone receptors (TRs) and mechanism of action

The action of THs on the transcriptional regulation is mediated by two highly homologous receptors – thyroid hormone receptor α (TRα) and β (TRβ). These two receptors, encoded by genes *TRα* and *TRβ*, respectively, are members of the nuclear receptor (NR) superfamily, which alters the gene transcription with the help of various co-activator and co-repressor proteins in response to the hormone binding (Yen, 2001; Zhang and Lazar, 2000). Differential splicing of the two TR-encoding genes generates multiple alternative splice products, such as TRα1, TRα2, TRα3, TRβ1, TRβ2 and TRβ3. The Expression of TR m-RNA is observed to be highly tissue-specific: TRα1 is predominantly expressed in heart, brain and skeletal muscle; TRβ1 is specific for liver, brain, and kidney; TRβ2 is highly expressed in brain, inner ear and retina; TRβ3 has the highest expression in the kidney, liver and lung. While TRα1 is mainly associated with the maintenance of the cardiovascular functions, TRβ1 controls the overall metabolism of cholesterol and lipoproteins. Both the receptors are known to be involved in the cartilage and bone formation and remodelling (Williams, 2013). TRβ1 and TRβ2 also control the circulating TH concentration in the body by the negative feedback mechanism involving H-P-T axis.

The tertiary structures of TRs contain four domains: N-terminal A/B domain (NTD), DNA-binding domain (DBD), C-terminal ligand-binding domain (LBD), and a linker or hinge between LBD and DBD (Mondal et al., 2016; Yen, 2001; Zhang and Lazar, 2000). Various domains of TRs have their individual roles in the gene expression and regulation pathways. DBD recognises the presence of specific nucleotide sequence (thyroid response elements or TREs) on the promoter region of their target genes and the NTD alters the rate of transcription of nearby genes by recruiting co-regulator complexes (Umesono et al., 1991; Tsai and ÓMalley, 1994). LBD is responsible for the binding of biologically active hormone T3 as well as the co-regulator proteins. LBD also mediates the formation of TR homodimer and the heterodimer between TR and retinoid X receptors (RXRs). The binding of T3 to LBD of TRs alters the positive and negative effects on the gene regulation exhibited by the unliganded TRs. At the positively regulated genes, unliganded TRs represses the gene expression by recruiting co-repressor complexes, whereas the binding of T3 promotes the dissociation of the co-repressors as well as sequential association of various co-activators to enhance the transcription (Glass and Rosenfeld, 2000). Conversely, at the negatively regulated genes, unliganded TRs activates the transcription, whereas T3 represses the transcription with the help of co-repressor proteins.

3. Thyroid hormone analogues

Thyroid hormones are particularly useful to reduce body weight by increasing the basal metabolic rate (BMR), oxygen consumption, body temperature and β-oxidation of fatty acids. Obesity is a major medical concern in the western countries and it increases the risk of developing heart attacks, strokes and type 2 diabetes mellitus (Grundy, 2000). Low density lipoprotein (LDL)-cholesterol also increases the risk of developing heart attack, stroke as well as hypercholesterolemia and cardiovascular diseases, which are presently treated with statins or hydroxymethyl-glutaryl-coenzyme A (HMGCo-A) reductase inhibitors. THs play an important role in the lipid metabolism in liver. THs lower the plasma LDL, which is responsible for the deposition of cholesterol in the arterial walls in the form of atherosclerotic plaques, by enhancing the expression of LDL receptors in the liver. THs also promote the expression of HDL receptors and biosynthesis of HDL by enhancing the production of apolipoprotein A1 (APOA1), a component of HDL particle. THs enhance the excretion of cholesterol in the form of bile acids by increasing the expression of cholesterol 7-a-hydroxylase (CYP7A1), an enzyme associated with the conversion of cholesterol to bile acids.

However, an excess of circulating THs, which may result from an

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