Thyroid hormone plays a role in both lipogenesis and lipolysis. Liver is the primary tissue for cholesterol synthesis and glucose metabolism. Thyroid hormone regulates critical steps of cholesterol synthesis, uptake and excretion. Thyroid hormone stimulates rate limiting enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase in cholesterol synthesis, increases the number of LDL receptors (LDLR) to uptake cholesterol and stimulates cholesterol 7a-dydroxylase (CYP7a1) gene expression to enhance cholesterol conversion to bile acid. Liver is also the main stores for glucose in the form of glycogen used for fast release in response to tissue demand. Hepatocyte glucose metabolism is mainly regulated by insulin that stimulates carbohydrate responsive element-binding protein (ChREBP). ChREBP functions as a sensor of hepatic glucose and controls hepatic glycolysis and fatty acid metabolism flux has been recognized as an important regulatory signal for the glucose synthesis and utilization [1]. Besides insulin, glucose flux has been recognized as an important regulatory signal for hepatic glycolysis and fatty acid metabolism via activation of carbohydrate responsive element-binding protein (ChREBP). ChREBP functions as a sensor of hepatic glucose and controls transcription of lipogenic genes in response to nutritional and hormonal inputs [2-4]. Increasing thyroid hormone level is associated with increasing hepatic glucose output, decreasing glucose stores in the liver and skeletal muscle and altered bile acid synthesis [5]. The details of the mechanism of thyroid hormone action have been summarized in a recent review [6]. Thyroid hormone interacts with a range of nuclear receptor signals in modulating of lipid and glucose homeostasis, which has been reviewed elsewhere [7-9]. This article is a brief on crosstalk signals in modulating of lipid and glucose homeostasis, which has compiling evidence of the crosstalk.

Metabolic effect of thyroid hormone, in part, is by direct regulation of rate-limiting enzymes at gene level. This action is accomplished by TR binding to thyroid hormone response element (TRE) in the form of heterodimer with RXR. In the presence of triiodothyronine (T3), TR recruits coactivator for transactivation or repressor for transcriptional repression. The consensus TRE for positive regulation by thyroid hormone is characterized as direct repeat with 4 nucleotides spacing (DR4). There are two TR isoforms (TRα and TRβ). Although both isoforms are expressed in liver TRβ plays the primary role in gene regulation in liver [10,11] LXR, a hydroxylcholesterol-activated nuclear receptor regulates a range of key genes controlling glucose uptake and lipid metabolism [12,13] LXR-mediated transcription requires LXR heterodimerization with RXR and binding to LXRE response element, which is also a DR4 configuration. LXR isoforms, α and β are equally important for lipid metabolism in liver [14-17] Emerging evidence strongly support TR crosstalk with LXR in mediation of metabolic genes involved in glucose uptake, lipogenesis, and cholesterol metabolism (Table 1) [7,8]. Molecular basis of the crosstalk is based on the common features of the nuclear receptors. TR and LXR are ligand-activated transcription factors. They have identical P-box (CEGCKGFFRR) of the nuclear receptors. TR and LXR are ligand-activated transcription factors. They have identical P-box (CEGCKGFFRR) DNA binding site such as consensus DR4 response element (AGGTCA n4 AGGTCA) [18]. In addition, both receptors require RXR as an obligatory partner for optimal DNA binding and transcription activation. The crosstalk between TR and LXR could be due to competing for DNA binding or DNA binding site. The data from in vitro and in vivo studies favors the mechanism of competing for DNA binding site.

**Table 1: LXR-TR crosstalk regulation of metabolic genes.**

<table>
<thead>
<tr>
<th>Genes</th>
<th>DR4 RE (consensus: AGGTCA n4 AGGTCA)</th>
<th>Protein function</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SREBP-1c</td>
<td>GGGTCA cagg CGGTCA</td>
<td>Fatty acid synthesis</td>
<td>[36,37]</td>
</tr>
<tr>
<td>FASN</td>
<td>GGGTCA ctgc CGGTCA</td>
<td>Fatty acid synthesis</td>
<td>[38]</td>
</tr>
<tr>
<td>ACC1</td>
<td>GGGTCA cctg AGGTAA</td>
<td>Fatty acid synthesis</td>
<td>[39]</td>
</tr>
<tr>
<td>PLTP</td>
<td>AGGTTA gcct GGGTCA</td>
<td>Lipid transfer</td>
<td>[40]</td>
</tr>
<tr>
<td>LDLR</td>
<td>AGACCT gccc TGACCT</td>
<td>Cholesterol transport</td>
<td>[41,42]</td>
</tr>
<tr>
<td>ABCA1</td>
<td>RE1: AGGTTA cttg CGGTCA RE2: GGGTTA ctat CGGTCA</td>
<td>Cholesterol efflux</td>
<td>[43,44]</td>
</tr>
<tr>
<td>ApoE</td>
<td>GGGTCA ctgg CGGTCA</td>
<td>lipid transport</td>
<td>[45,46]</td>
</tr>
<tr>
<td>CYP7A1</td>
<td>TGGTTA cttg AGGTCA</td>
<td>Bilirubin synthesis</td>
<td>[19-27]</td>
</tr>
<tr>
<td>ChREBP</td>
<td>RE1: AGGTCCGGG tacc AGAGGGCA RE2: AGGTTAAGG aagt AGAGGGTA</td>
<td>Glucose metabolism</td>
<td>[14-32]</td>
</tr>
<tr>
<td>Glut4</td>
<td>GGGTCA ctgc GGGGCA</td>
<td>Glucose transport</td>
<td>[47,48]</td>
</tr>
<tr>
<td>LPL</td>
<td>TGACCG tgt TGACCT</td>
<td>Lipolysis</td>
<td>[44-49]</td>
</tr>
</tbody>
</table>

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Crosstalk Regulation of CYP7A1 in Rodents

Hepatic bile acid synthesis is the important mechanism of cholesterol catabolism. Bile acids promote intestine fat absorption and cholesterol excretion from the body. In rodents, cholesterol CYP7A1, a rate limiting enzyme for cholesterol conversion to bile acids, is regulated by TR and LXR at gene level through the DR4 response element. CYP7A1 gene expression in mouse is highly inducible by T3. In hypothyroid mice, CYP7A1 mRNA level is not detectable. Treatment with triiodothyronine (T3) restored CYP7A1 mRNA level [19]. In TRβ−/− mice, CYP7A1 does not response to T3 stimulation [20]. The TRE is located in 5’-flanking region (−3132 to −3008) of CYP7A1 gene. This region, however, does not mediate LXR-mediated transcription [19]. The LXR-mediated CYP7A1 transcription is through LXRE located at −74 to −53 in the promoter [21,22] LXRα−/− mice showed impaired CYP7A1expression and bile acid synthesis during cholesterol feeding, resulted in failed cholesterol excretion and rapid accumulation of cholesterol in the liver [15-23]. The crosstalk between TR and LXR in regulation of CYP7A1 was well-demonstrated using TRβ−/− and TRβ mutant (Δ337T) mouse models [20-24]. In these models, T3 treatment had either no effect or minimal effect on CYP7A1mRNA level. When mice were fed with 2% cholesterol diet, CYP7A1gene was significantly induced by LXRα activation. However, in euthyroid condition, cholesterol feeding or high fat diet had no significant effect on CYP7A1mRNA level, suggesting T3 may be a primary regulator. In functional assays using LXRE reporter construct, TR dose-dependently inhibits LXR-mediated transcription. That TR competes with LXR for DNA binding site was confirmed by chromatin immuneprecipitation assay [19-23]. In human, CYP7A1 gene promoter lacks of LXRE and is not directly regulated by LXR [25,26]. With regard to T3 regulation, two negative TREs were identified in human CYP7A1 promoter [27]. In transgenic mice expressing human CYP7A1 gene, treatment with T3 reduces CYP7A1mRNA level [27]. In patients with hyperthyroidism, the bile acid level is distinct lower compared to with euthyroid condition [28]. The reduction of bile acids is also associated with reduction of cholesterol level. Suppressing bile acid synthesis by T3 may be a mechanism controlling the hepatic bile acid level. On the other hand, bile acids reabsorption stimulates cAMP-activated type II deiodinase (D2), increase local conversion of T4 to T3 and promotes intracellular thyroid hormone action. This leads to increased oxygen consumption and energy expenditure [29].

Crosstalk Regulation of Chrebp by TR and LXR

ChREBP is a glucose sensor controlling glucose-induced lipogenesis in liver. At transcription level, Chrebp is regulated by several transcription factors including LXR, TR and SREBP1, and a mechanism direct influence by glucose is also suggested [30,31]. After translation, ChREBP protein is activated by glucose-induced phosphorylation. In terms of the regulation by LXR and TR, two functional DR4 REs (LXRE1 and LXRE2) were identified in mouse Chrebp promoter region (−2431 to −2393). LXR and TR are able to bind to both LXREs [14-32]. However, LXR stimulates Chrebp only via LXRE1. TR stimulates Chrebp via LXRE2. Either ligand alone is sufficient to induce Chrebp. The crosstalk between TR and LXR is by occupying each other’s binding site, LXRE1 and LXRE2, which are 8 bp apart. Co-

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