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Editorial

Metabolic Signal Crosstalk: Thyroid Hormone and Live X Receptor (LXR)

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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-hyroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase in cholesterol synthesis, increases the number of LDL receptors (LDLR) to uptake cholesterol and stimulates cholesterol 7α-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 transcription factors such as sterol regulatory element binding protein (SREBP)-1c, hepatic nuclear factor (HNF)-4, Fokhead protein family (FoX) and PPARγ co-factor 1 (PGC-1) to control 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 between thyroid hormone receptor (TR) and liver X receptor (LXR) focusing on regulation of mouse *CPY7A1*and *ChREBP* gene expression, 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 coactivactor 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 LXR response element (LXRE), 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) in the DAN binding domain, which recognizes sequence-specific 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 RXR for heterodimerization and for 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.

Genes	DR4 RE (consensus: AGGTCA n4 AGGTCA)	Protein function	Ref.
SREBP-1c	GGGTTA cagg CGGTCA	Fatty acid synthesis	[36,37]
FASN	GGGTTA ctgc CGGTCA	Fatty acid synthesis	[38]
ACC1	GGTTGA cccg AGGTAA	Fatty acid synthesis	[39]
PLTP	AGGTTA gtct GGGTCA	Lipid transfer	[40]
LDLR	AGACCT gccc TGACCT	Cholesterol transport	[41,42]
ABCA1	RE1: **AGGTAA** ctgt **CGGTCA** RE2: GGGTTA ctat CGGTCA	Cholesterol efflux	[43,44]
ApoE	GGGTCA ctgg CGGTCA	lipid transport	[45,46]
CYP7A1	TGGTCA ctgt AGTTCA	Bile acid synthesis	[19-27]
ChREBP	RE1: AGCTTCGGG tact AGAGGGCA RE2: AGCTTAGGC aatg AGAGGTGA	Glucose metabolism	[14-32]
Glut4	GGGTTA cttc GGGGCA	Glucose transport	[47,48]
LPL	TGACCG gtg TGACCT	lipolysis	[44-49]

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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 rodent, 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 *CYP7A1*expression 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 minimum effect on *CYP7A1*mRNA level. When mice were fed with 2% cholesterol diet, *CYP7A1*gene was significantly induced by LXRα activation. However, in euthyroid condition, cholesterol feeding or high fat diet had no significant effect on *CYP7A1*mRNA 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 immune-precipitation 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 *CYP7A1*mRNA 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 lipogensis 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-transfection of LXR and TR significantly reduced *ChREBP* mRNA level in the presence of T3 and LXR ligand T0901317 [33]. Increasing TR content prevents LXR from binding to TR binding site (LXRE2) and allows TR-mediated transcription. Vice versa, LXR dose-dependently inhibits TR binding to LXR binding site LXRE1, leading to LXR-activated the transcription [33]. This implicates the receptor concentration plays a key role in the crosstalk regulation of *ChREBP*. *In vivo* studies using TRβ$^{-/-}$ mice, T3 cannot induce *ChREBP*, which was associated with the loss of T3-induced lipogenesis in normal diet condition [33]. Under fasting/refeeding condition, ChREBP was induced in TRβ$^{-/-}$ mice, indicating glucose and other transcription factors are involved in regulation of *ChREBP* expression. Although TR is not essential regulator for *ChREBP* T3 stimulation is clearly seen and in liver and white adipose tissue (WAT) of wild type mice [33]. Similarly, *ChREBP* is highly induced by LXR ligand in wild type mice. But in LXR knockout mice, *ChREBP* mRNA level was not affected under high carbohydrate diet, demonstrating the alternative regulation by glucose [34,35]. Recently, a novel ChREBP isoform (ChREBP β has been identified [4]. In fasting/refeeding experiments using transgenic mice over-expressing glucose transporter (Glut)-4, glucose flux dramatically induces *ChREBPβ* in white adipose tissue (WAT), but has no significant effect on canonical *ChREBP α* expression. In liver, the fasting/refeeding does not affect *ChREBPβ*. The unique *ChREBPβ* induction in WAT is mediated by glucose-activated canonical ChREBPα although mechanism is not clear yet [4]. The ChREBP isoforms are transcribed using alternative promoters. The transcription starting site (TSS) for *ChREBPβ* is 17 kb upstream of *ChREBPα* TSS. It is not clear whether other transcription factors besides *ChREBα* are involved in transcription regulation of *ChREBPβ.*

CLOSING REMARKS

TR and LXR have similarity in target genes and physiological roles in metabolic homeostasis. They are distinct in pathways and ligand affinity (nM T3 for TR and in μM oxycholestrol for LXR). Understanding the gene regulation by metabolic regulators may help to developing complementary pharmacologic approaches targeting the TR and LXR to treat metabolic disorder.

REFERENCES

1. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature. 2001; 414: 799-806.

2. Uyeda K, Yamashita H, Kawaguchi T. Carbohydrate responsive element-binding protein (ChREBP): a key regulator of glucose metabolism and fat storage. Biochem Pharmacol. 2002; 63: 2075-2080.

3. Denechaud PD, Dentin R, Girard J, Postic C. Role of ChREBP in hepatic steatosis and insulin resistance. FEBS Lett. 2008; 582: 68-73.

4. Herman MA, Peroni OD, Villoria J, Schön MR, Abumrad NA, Blüher M, et al. A novel ChREBP isoform in adipose tissue regulates systemic glucose metabolism. Nature. 2012; 484: 333-338.

5. Potenza M, Via MA, Yanagisawa RT. Excess thyroid hormone and carbohydrate metabolism. Endocr Pract. 2009; 15: 254-262.

6. Brent GA. Mechanisms of thyroid hormone action. J Clin Invest. 2012; 122: 3035-3043.

7. Liu YY, Brent GA. Thyroid hormone crosstalk with nuclear receptor

signaling in metabolic regulation. Trends Endocrinol Metab. 2010; 21: 166-173.

8. Hashimoto K, Mori M. Crosstalk of thyroid hormone receptor and liver X receptor in lipid metabolism and beyond [Review]. Endocr J. 2011; 58: 921-930.

9. Cheng SY, Leonard JL, Davis PJ. Molecular aspects of thyroid hormone actions. Endocr Rev. 2010; 31: 139-170.

10. Yen PM, Feng X, Flamant F, Chen Y, Walker RL, Weiss RE, et al. Effects of ligand and thyroid hormone receptor isoforms on hepatic gene expression profiles of thyroid hormone receptor knockout mice. EMBO Rep. 2003; 4: 581-587.

11. Weiss RE, Murata Y, Cua K, Hayashi Y, Seo H, Refetoff S. Thyroid hormone action on liver, heart, and energy expenditure in thyroid hormone receptor beta-deficient mice. Endocrinology. 1998; 139: 4945-4952.

12. Mitro N, Mak PA, Vargas L, Godio C, Hampton E, Molteni V, et al. The nuclear receptor LXR is a glucose sensor. Nature. 2007; 445: 219-223.

13. Edwards PA, Kennedy MA, Mak PA. LXRs; oxysterol-activated nuclear receptors that regulate genes controlling lipid homeostasis. Vascul Pharmacol. 2002; 38: 249-256.

14. Cha JY, Repa JJ. The liver X receptor (LXR) and hepatic lipogenesis. The carbohydrate-response element-binding protein is a target gene of LXR. J Biol Chem. 2007; 282: 743-751.

15. Quinet EM, Savio DA, Halpern AR, Chen L, Schuster GU, Gustafsson JA, et al. Liver X receptor (LXR)-beta regulation in LXRalpha-deficient mice: implications for therapeutic targeting. Mol Pharmacol. 2006; 70: 1340-1349.

16. Jamroz-WiÅ›niewska A, WÃ³jcicka G, Horoszewicz K, BeÅ‚towski J. Liver X receptors (LXRs). Part II: non-lipid effects, role in pathology, and therapeutic implications. Postepy Hig Med Dosw (Online). 2007; 61: 760-785.

17. WÃ³jcicka G, Jamroz-WiÅ›niewska A, Horoszewicz K, BeÅ‚towski J. Liver X receptors (LXRs). Part I: structure, function, regulation of activity, and role in lipid metabolism. Postepy Hig Med Dosw (Online). 2007; 61: 736-759.

18. Berkenstam A, Färnegårdh M, Gustafsson JA. Convergence of lipid homeostasis through liver X and thyroid hormone receptors. Mech Ageing Dev. 2004; 125: 707-717.

19. Shin DJ, Plateroti M, Samarut J, Osborne TF. Two uniquely arranged thyroid hormone response elements in the far upstream 5' flanking region confer direct thyroid hormone regulation to the murine cholesterol 7alpha hydroxylase gene. Nucleic Acids Res. 2006; 34: 3853-3861.

20. Gullberg H, Rudling M, Forrest D, Angelin B, Vennström B. Thyroid hormone receptor beta-deficient mice show complete loss of the normal cholesterol 7alpha-hydroxylase (CYP7A) response to thyroid hormone but display enhanced resistance to dietary cholesterol. Mol Endocrinol. 2000; 14: 1739-1749.

21. Lehmann JM, Kliewer SA, Moore LB, Smith-Oliver TA, Oliver BB, Su JL, et al. Activation of the nuclear receptor LXR by oxysterols defines a new hormone response pathway. J Biol Chem. 1997; 272: 3137-3140.

22. Chiang JY, Kimmel R, Stroup D. Regulation of cholesterol 7alpha-hydroxylase gene (CYP7A1) transcription by the liver orphan receptor (LXRalpha). Gene. 2001; 262: 257-265.

23. Peet DJ, Turley SD, Ma W, Janowski BA, Lobaccaro JM, Hammer RE, et al. Cholesterol and bile acid metabolism are impaired in mice lacking the nuclear oxysterol receptor LXR alpha. Cell. 1998; 93: 693-704.

24. Hashimoto K, Cohen RN, Yamada M, Markan KR, Monden T, Satoh T, et al. Cross-talk between thyroid hormone receptor and liver X receptor regulatory pathways is revealed in a thyroid hormone resistance mouse model. J Biol Chem. 2006; 281: 295-302.

25. Chen JY, Levy-Wilson B, Goodart S, Cooper AD. Mice expressing the human CYP7A1 gene in the mouse CYP7A1 knock-out background lack induction of CYP7A1 expression by cholesterol feeding and have increased hypercholesterolemia when fed a high fat diet. J Biol Chem. 2002; 277: 42588-42595.

26. Goodwin B, Watson MA, Kim H, Miao J, Kemper JK, Kliewer SA. Differential regulation of rat and human CYP7A1 by the nuclear oxysterol receptor liver X receptor-alpha. Mol Endocrinol. 2003; 17: 386-394.

27. Drover VA, Agellon LB. Regulation of the human cholesterol 7alpha-hydroxylase gene (CYP7A1) by thyroid hormone in transgenic mice. Endocrinology. 2004; 145: 574-581.

28. Pauletzki J, Stellaard F, Paumgartner G. Bile acid metabolism in human hyperthyroidism. Hepatology. 1989; 9: 852-855.

29. Watanabe M, Houten SM, Mataki C, Christoffolete MA, Kim BW, Sato H, et al. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. Nature. 2006; 439: 484-489.

30. Poupeau A, Postic C. Cross-regulation of hepatic glucose metabolism via ChREBP and nuclear receptors. Biochim Biophys Acta. 2011; 1812: 995-1006.

31. Filhoulaud G, Guilmeau S, Dentin R, Girard J, Postic C. Novel insights into ChREBP regulation and function. Trends Endocrinol Metab. 2013; 24: 257-268.

32. Hashimoto K, Ishida E, Matsumoto S, Okada S, Yamada M, Satoh T, et al. Carbohydrate response element binding protein gene expression is positively regulated by thyroid hormone. Endocrinology. 2009; 150: 3417-3424.

33. Gauthier K, Billon C, Bissler M, Beylot M, Lobaccaro JM, Vanacker JM, et al. Thyroid hormone receptor beta (TRbeta) and liver X receptor (LXR) regulate carbohydrate-response element-binding protein (ChREBP) expression in a tissue-selective manner. J Biol Chem. 2010; 285: 28156-28163.

34. Benhamed F, Denechaud PD, Lemoine M, Robichon C, Moldes M, Bertrand-Michel J, et al. The lipogenic transcription factor ChREBP dissociates hepatic steatosis from insulin resistance in mice and humans. J Clin Invest. 2012; 122: 2176-2194.

35. Denechaud PD, Bossard P, Lobaccaro JM, Millatt L, Staels B, Girard J, et al. ChREBP, but not LXRs, is required for the induction of glucose-regulated genes in mouse liver. J Clin Invest. 2008; 118: 956-964.

36. Repa JJ, Liang G, Ou J, Bashmakov Y, Lobaccaro JM, Shimomura I, et al. Regulation of mouse sterol regulatory element-binding protein-1c gene (SREBP-1c) by oxysterol receptors, LXRalpha and LXRbeta. Genes Dev. 2000; 14: 2819-2830.

37. Hashimoto K, Yamada M, Matsumoto S, Monden T, Satoh T, Mori M. Mouse sterol response element binding protein-1c gene expression is negatively regulated by thyroid hormone. Endocrinology. 2006; 147: 4292-4302.

38. Joseph SB, Laffitte BA, Patel PH, Watson MA, Matsukuma KE, Walczak R, et al. Direct and indirect mechanisms for regulation of fatty acid synthase gene expression by liver X receptors. J Biol Chem. 2002; 277: 11019-11025.

39. Zhang Y, Yin L, Hillgartner FB. Thyroid hormone stimulates acetyl-coA carboxylase-alpha transcription in hepatocytes by modulating the composition of nuclear receptor complexes bound to a thyroid hormone response element. J Biol Chem. 2001; 276: 974-983.

40. Laffitte BA, Joseph SB, Chen M, Castrillo A, Repa J, Wilpitz D, et al. The phospholipid transfer protein gene is a liver X receptor target expressed by macrophages in atherosclerotic lesions. Mol Cell Biol. 2003; 23: 2182-2191.

41. Ishimoto K, Tachibana K, Sumitomo M, Omote S, Hanano I, Yamasaki D, et al. Identification of human low-density lipoprotein receptor as a novel target gene regulated by liver X receptor alpha. FEBS Lett. 2006; 580: 4929-4933.

42. Bakker O, Hudig F, Meijssen S, Wiersinga WM. Effects of triiodothyronine and amiodarone on the promoter of the human LDL receptor gene. Biochem Biophys Res Commun. 1998; 249: 517-521.

43. Sabol SL, Brewer HB Jr, Santamarina-Fojo S. The human ABCG1 gene: identification of LXR response elements that modulate expression in macrophages and liver. J Lipid Res. 2005; 46: 2151-2167.

44. Kern PA, Ranganathan G, Yukht A, Ong JM, Davis RC. Translational regulation of lipoprotein lipase by thyroid hormone is via a cytoplasmic repressor that interacts with the 3' untranslated region. J Lipid Res. 1996; 37: 2332-2340.

45. Benvenga S, Cahnmann HJ, Robbins J. Characterization of thyroid hormone binding to apolipoprotein-E: localization of the binding site in the exon 3-coded domain. Endocrinology. 1993; 133: 1300-1305.

46. Laffitte BA, Repa JJ, Joseph SB, Wilpitz DC, Kast HR, Mangelsdorf DJ, et al. LXRs control lipid-inducible expression of the apolipoprotein E gene in macrophages and adipocytes. Proc Natl Acad Sci U S A. 2001; 98: 507-512.

47. Dalen KT, Ulven SM, Bamberg K, Gustafsson JA, Nebb HI. Expression of the insulin-responsive glucose transporter GLUT4 in adipocytes is dependent on liver X receptor alpha. J Biol Chem. 2003; 278: 48283-48291.

48. Torrance CJ, Usala SJ, Pessin JE, Dohm GL. Characterization of a low affinity thyroid hormone receptor binding site within the rat GLUT4 gene promoter. Endocrinology. 1997; 138: 1215-1223.

49. Zhang M, Chiang JY. Transcriptional regulation of the human sterol 12alpha-hydroxylase gene (CYP8B1): roles of heaptocyte nuclear factor 4alpha in mediating bile acid repression. J Biol Chem. 2001; 276: 41690-41699.

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