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Regulation of retinoid X receptor gamma expression by fed state in mouse liver

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ABSTRACT

Glucose metabolism is balanced by glycolysis and gluconeogenesis with precise control in the liver. The expression of genes related to glucose metabolism is regulated primarily by glucose and insulin at transcriptional level. Nuclear receptors play important roles in regulating the gene expression of glucose metabolism at transcriptional level. Some of these nuclear receptors form heterodimers with RXRs to bind to their specific regulatory elements on the target promoters. To date, three isotypes of RXRs have been identified; RXRα, RXRβ and RXRγ. However, their involvement in the interactions with other nuclear receptors in the liver remains unclear. In this study, we found RXRγ is rapidly induced after feeding in the mouse liver, indicating a potential role of RXRγ in controlling glucose or lipid metabolism in the fasting–feeding cycle. In addition, RXRγ expression was upregulated by glucose in primary hepatocytes. This implies that glucose metabolism governed by RXRγ in conjunction with other nuclear receptors. The luciferase reporter assay showed that RXRγ as well as RXRα increased SREBP-1c promoter activity in hepatocytes. These results suggest that RXRγ may play an important role in tight control of glucose metabolism in the fasting–feeding cycle.

1. Introduction

Glucose and lipid homeostasis of the liver is tightly controlled in response to the variable supply of energy. Excess carbohydrate is converted into fat through glycolysis and lipogenesis during the fed state [1,2], while gluconeogenesis is active in fasted state [3,4]. A number of signaling molecules and transcription factors tightly regulate these metabolic pathways in the liver.

Liver X receptors (LXRs) are ligand-activated transcription factors belonging to a nuclear receptor superfamily [5]. LXRs control lipogenesis by activating the transcription of sterol regulatory element-binding protein -1c (SREBP-1c) [6,7], one of the master regulator of lipogenesis, as well as by directly stimulating the transcription of lipogenic enzymes such as acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS) and stearoyl CoA desaturase-1 (SCD-1) [8,9]. LXRs form heterodimers with RXRs and bind to LXR response elements (LXREs) on the promoter of target genes, thereby regulating their expression.

RXRs have three isotypes that differ in tissue distribution; RXR alpha, RXR beta and RXR gamma [10]. RXRα is expressed predominantly in the liver, kidney, epidermis, intestine, and skin, while RXRβ is ubiquitously distributed [11,12]. RXRγ is found mainly in the muscle and brain [13–15]. In addition to its role as a heterodimeric partner of LXRs, RXRs form heterodimers with various nuclear receptors, such as peroxisome proliferator-activated receptors (PPARs), retinoic acid receptors (RARs) and farnesoid X receptor (FXR) [16,17]. These nuclear receptors are participated in glucose and lipid metabolism and some of these

Abbreviations: RXR, retinoid X receptor; PPARγ, peroxisome proliferator-activated receptor gamma; RAR, retinoic acid receptor; FXR, farnesoid X receptor; LXR, liver X receptor; SREBP-1c, sterol regulatory element-binding protein -1c; PGC-1a, peroxisome proliferator-activated receptor gamma coactivator-1-alpha; LGK, liver type glucokinase; L-PK, liver-type pyruvate kinase; G6Pase, glucose-6-phosphatase; PEPCK, Phosphoenolpyruvate carboxykinase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; ChREBP, carbohydrate responsive binding protein; LXRE, LXR response element; RT-PCR, reverse transcription-polymerase chain reaction; EMSA, electrophoretic mobility shift assay; WAT, white adipose tissue; BAT, brown adipose tissue.

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receptors have been shown to be controlled by the nutritional status [10]. However, the current understanding of the regulation and function of RXRs in the interaction with other nuclear receptors in the liver is limited.

These findings indicate a need to examine whether RXRs can be governed nutritionally. To address this possibility, this study investigates expression levels of RXRs in the mouse liver under fasted or refed condition and the potential role of RXRγ in regulating the SREBP-1c expression. The results demonstrated that refeeding and glucose stimulated RXRγ gene expression in the liver. In addition, the RXRγ/LXRα complex stimulated SREBP-1c promoter activity by binding to LXRE. Taken together, these results suggest that RXRγ is a crucial mediator of glucose, acting as a controller of the lipogenic pathway.

2. Materials and methods

2.1. Materials

Insulin, dexamethasone, 9-cis-retinoic acid (9-cis-RA) and T0901317 was obtained from Sigma. The anti-RXRα antibody and the anti-RXRγ were obtained from Santa Cruz Biotechnology. Expression vectors for human LXRα (pCMV-hLXRα), mouse RXRα (pCMV-mRXRα), mouse RXRγ (pCMV-mRXRγ) and mouse PPARγ (pCMV-mPPARγ) were gifts from Dr. David J. Mangelsdorf [13]. pSREBP1c-luc was a gift from Dr. Jae Bum Kim [18]. Plasmids containing the coding sequences for mouse RXRγ1 and RXRγ2 were constructed in the vector pcDNA 3.0 (Invitrogen).

2.2. Animals

Five-week-old male C57BL/6 or ICR mice were purchased from Orient bio and adapted to the environment for 1-week prior to experiment. Mice were raised on open formula and water ad libitum, with a 12 h light–dark cycle. Fasting group of mice was fasted for 48 h and refeeding group was fasted for 48 h and then refed for 3, 6 or 12 h. All the animal experiments were approved by the Institutional Animal Care and Use Committee of Yonsei University College of Medicine.

2.3. Isolation of mouse primary hepatocytes and cell culture

Primary hepatocytes were isolated from 8 week old male mice as described previously with modification [19] and cultured in Dulbecco's modified Eagle's medium (Invitrogen) supplemented with 10% fetal bovine serum (FBS) (Invitrogen), 100 nM insulin, 10 nM dexamethasone, 100 units/mL penicillin and 100 μg/mL streptomycin (Invitrogen) prior to transfer to 60-mm dishes about 60% confluence for 6 h for attachment. Alexander cells and 293T cells were cultured in DMEM supplemented with 10% FBS, 100 units/mL penicillin and 100 μg/mL streptomycin and maintained at 37 °C in 5% CO_2.

2.4. RNA extraction and RT-PCR analysis

Total RNA was isolated from mouse tissues or primary hepatocytes using TRIzol reagent (Invitrogen) according to the manufacturer's instructions. For each sample, total RNA (3 ug) was reverse transcribed by Superscript II reverse transcriptase (Invitrogen) with random hexamer according to manufacturer's protocol. PCR was performed to measure mRNA expression levels of RXRα, RXRβ, RXRγ, RXRγ1, RXRγ2, PPARγ, LXRα, SREBP-1c, PGC-1α, LGK, L-PK, G6Pase, PEPCK, and GAPDH. Each PCR was performed from diluted cDNA template (1:25). Forward and reverse primers used were as followed;

RXRα forward, 5′-CATTGGGCTTCGGGACTGGT-3′, RXRα reverse, 5′-CCTCGTTCTCATTCCGGTCC-3′, RXRβ forward, 5′-ATTCTCCGGGCCTGTCAGCA-3′, RXRβ reverse, 5’-ctccatccccgtctttgtcc-3′, RXRγ forward, 5′-CAGGTCTGCCTGGGAT TGGA-3′, RXRγ reverse, 5′-CCTCACTCTCTGCTCGCTCT-3′, RXRγ1forward, 5′- GAGTCATCACTTCTGCCATG-3′, RXRγ2 forward, 5′-CAACCTTCACAGCTGTACAC-3′, PPARγ forward, 5-TCCGTGATGGAAGACCACTG-3′, PPARγ reverse, 5′-CCCTTGCATCCTTCACAAGC-3′, LXRα forward, 5′-GAGAAGCTGGTGGCTGCCCA-3′, LXRα reverse, 5′-AGCTGTAG GAAGCCAGGGAG-3′, SREBP-1c forward, 5′-GGAGCCATGGATTGCACATT-3′, SREBP-1c reverse, 5′-CTGAGTGTTTCCTGGAAGG-3′, PGC-1α forward, 5′-CTCAGAACCATGCAGCAAAC-3′, PGC-1α reverse, 5′-CAGAGGAAGAGATAAAGTTG-3′, LGK forward, 5′-GGAGGCCAGTGTAAAGATGT-3′, LGK reverse, 5′-CTCTTGATAGCATC TCGGAG-3′, L-PK forward, 5′-CGCCTCAAGGAGATGATCAA-3′, L-PK reverse, 5′-TTCCGTACAAAGGAGGCAAA-3′, G6Pase forward, 5′-ACATCCGGGGCATCTACA ATG-3′, G6Pase reverse, 5′-TTACAAAGACTTCTTGTGTGTCTG-3′, PEPCK forward, 5′-TATGACAACTGTTGGCTGGC-3′, PEPCK reverse, 5′-TTACAAAGACTTCTTGTG TGTCTG-3′, GAPDH forward, 5′- ACCACAGTCCATGCCATCAC-3′, GAPDH reverse, 5′-TCCACCACCCTGTTGCTGTA-3’.

2.5. Transfection and luciferase reporter assay

Cells were plated in 6-well plates about 80% confluence. Twenty-four hours later, the cells were transfected with 500 ng of firefly luciferase reporter plasmids, 100 ng of expression vectors, or empty vector and 100 ng of pCMV-β-gal using Lipofectamine and Plus reagent (Invitrogen). Twenty-four hours after transfection, cells were treated with vehicle (ethanol) or 9-cis retinoic acid (1 uM) or T0901317 (1 uM). The cells were harvested 48 h later and analyzed for luciferase activity. The luciferase activity was measured by using Luciferase Assay System (Promega) and normalized to β-galactosidase activity.

2.6. Immunoblotting

Nuclear extracts were prepared from 293T cells transfected with LXRα, RXRα, and RXRγ, respectively, using NUN buffer as previously described [20]. Proteins were subjected to SDS-PAGE and transferred to nitrocellulose membranes. Membranes were blocked in 5% non-fat dried milk in Tris-buffered saline containing 0.1% tween 20 (TBST). Membranes were then incubated with primary antibodies, horseradish peroxidase-conjugated secondary antibodies and SuperSignal West Pico chemiluminescent substrate (Pierce) and visualized using X-ray film (Fujifilm).

2.7. Electrophoretic mobility shift assay (EMSA)

EMSA was performed as previously described [20]. The oligonucleotide probe corresponding to the LXRE in the promoter of human SREBP-1c (5′-AGTGACCG-CCAGTAACCCCA-3′) was labeled with [γ-^{32}P] ATP (PerkinElmer) using T4 polynucleotidekinase (New England Biolab). Nuclear extracts were incubated with reaction buffer containing 10 mM HEPES pH 7.6, 1 mM EDTA, 1 mM DTT, 50 ng/uL poly (dI-dC)·(dI-dC) and 7% glycerol for 25 min on ice. For supershift analysis, 1 ug of antibody against either RXRα or RXRγ was pre-incubated with the nuclear extracts for 15 min on ice prior to the addition of the ^{32}P-labeled probe. Reaction mixtures were then separated on 4.5% polyacrylamide gels in 0.25X TBE buffer for 1 h and detected by autoradiography.

3. Results

The expression of metabolic enzymes and transcription factors related to glucose and lipid metabolism is regulated by feeding status. For an analysis of nutritional effects on RXRs expression,

mRNA expressions of the mouse liver subjected to fasting for 48 h or refeeding for 3, 6 and 12 h after fasting were examined. Among the RXR isotypes, RXRγ mRNA was strongly induced after 3 h of refeeding and stayed elevated level up to 12 h after refeeding (Fig. 1A). Intriguingly, the induction of RXRγ mRNA was correlated with the elevation of SREBP-1c, LGK and L-PK mRNA levels in the refed state. By contrast, the expression of neither PPARγ nor LXRα was changed by refeeding. These results imply that the expression of RXRγ was regulated by the feeding status in the liver.

Fasting mRNA level of hepatic RXRγ was higher in ob/ob mice than in control C57BL/6 mice, and similar mRNA expression levels were observed for GK, L-PK, ACC and FAS (Fig. 1B). These finding suggests the involvement of RXRγ in the regulation of glucose and lipid metabolism in fed state.

Refeeding led to a transient increase of plasma glucose level, implying the regulation of RXRγ expression by glucose. To test this hypothesis, primary cultures of mouse hepatocytes were incubated at different concentrations of glucose (0 mM, 5.5 mM, 12.5 mM or 25 mM) after pre-incubation in 0 mM glucose for 12 h. Primary hepatocytes cultured in 5.5 mM and 12.5 mM glucose demonstrated a slight increase the mRNA level of RXRγ, whereas 25 mM of glucose had a significantly positive effect on RXRγ mRNA expression. By contrast, RXRα expression was not affected by glucose concentration (Fig. 1C). These results suggest that hepatic RXRγ expression may be regulated by glucose at the transcriptional level in a dose-dependent manner.

Next, to clarify the basal tissue distribution of the RXRγ isotype, mice were fasted for 48 h or refed for 6 h after 24 h of fasting. RT-

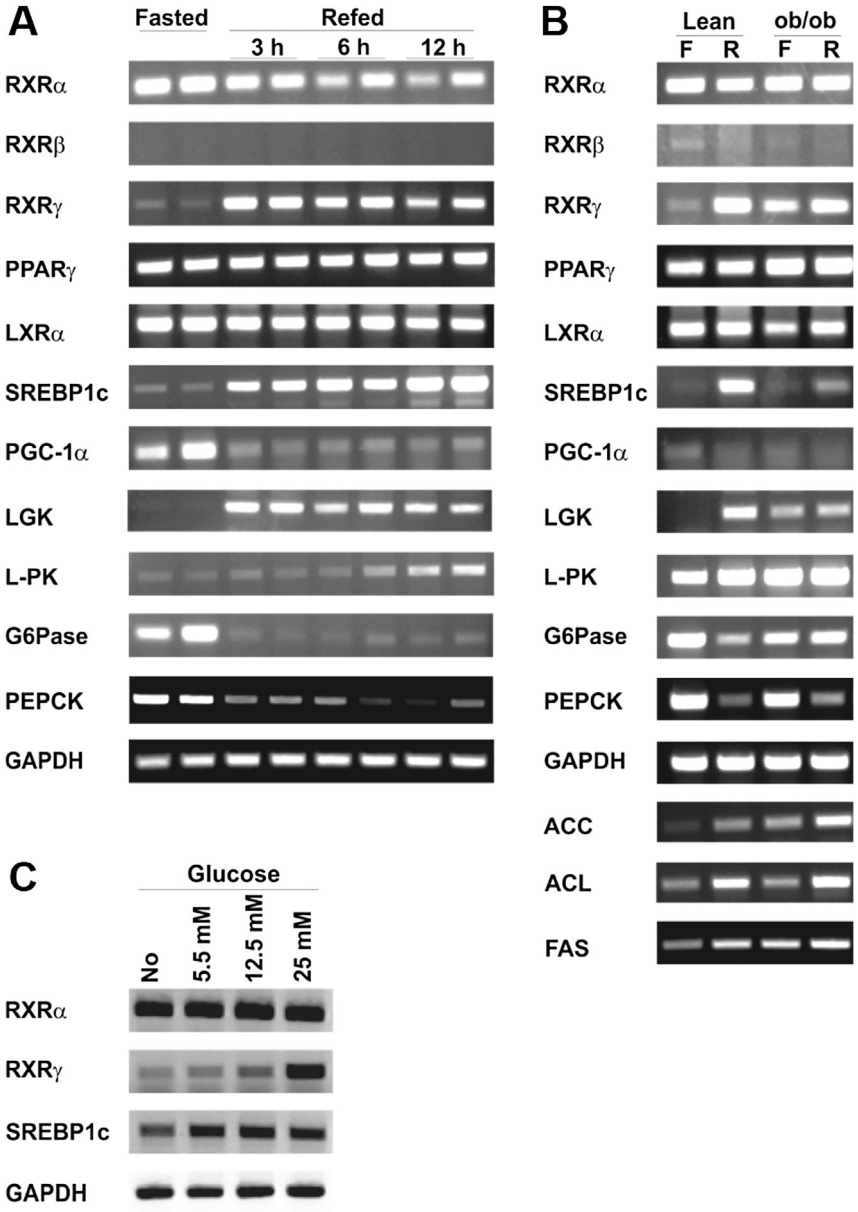

Fig. 1. Refeeding increases RXRγ expression in mouse liver (A and B) and primary hepatocytes (C). RT-PCR analysis of genes related to glucose and lipid metabolism and transcription factors in C57BL/6 mouse liver during fasting and refeeding. Mice were fasted for 48 h or refed for indicated times after fasting for 48 h. Total RNA from mouse liver was subjected to RT-PCR analysis. (A) Gene expression levels in mouse liver during fasting and refeeding. (B) Gene expression levels in liver during fasting and refeeding in C57BL/6 (lean) and ob/ob mice. (C) Mouse primary hepatocytes were cultured in the absence of glucose for 12 h followed by exposure to glucose for 24 h as indicated concentration. mRNA levels were determined by a semi-quantitative RT-PCR analysis using primers for RXRα and RXRγ.

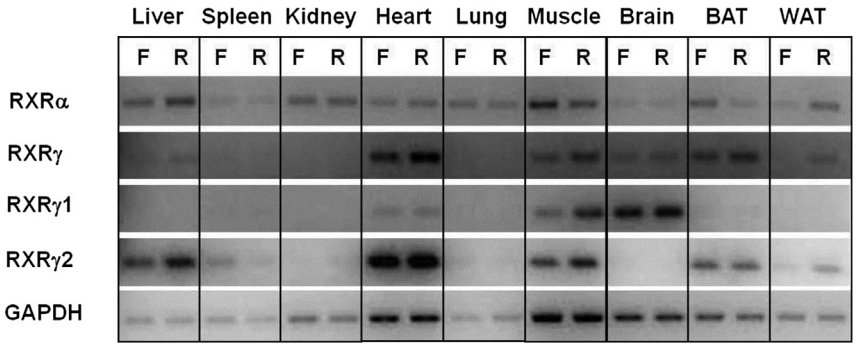

Fig. 2. Differential distribution of RXRγ1 and RXRγ2 in mouse tissues. ICR mice were fasted for 24 h and refed for 6 h after fasting. Expression levels of RXRα, RXRγ1 and RXRγ2 were determined by RT-PCR using cDNA from the mouse liver, spleen, kidney, heart, lung, muscle, brain, BAT and WAT. As a positive control, GAPDH was detected by RT-PCR.

PCR analysis was performed using liver, spleen, kidney, heart, brain, brown adipose tissue (BAT) and white adipose tissue (WAT) cDNA as templates. As shown in Fig. 2, RXRγ1 was predominantly expressed in the brain and muscle, whereas the RXRγ2 was highly expressed in liver, heart, muscle and BAT.

It is well established that LXR/RXR stimulates SREBP-1c transcriptional activity. In this regard, the potential regulation of SREBP-1c promoter activity by RXRγ was examined by luciferase assay. Alexander cells were transfected with SREBP-1c reporter plasmid and expression vectors for LXRα, RXRα or RXRγ. As shown in Fig. 3A, RXRγ led to about 4.2-fold increase in the activity of the SREBP-1c promoter, as RXRα led to 4.4-fold increase. In addition, RXRγ and LXRα cooperatively stimulated the luciferase activity (25.8-fold) as in the case of RXRα (23.2-fold), suggesting that RXRγ can also activate the SREBP-1c promoter. Furthermore, RXRγ2 increased SREBP-1c activity despite of the lack of activation domain (Fig. 3B).

To examine whether RXRγ directly interact with LXRE, we performed EMSA using nuclear extracts of 293T cells overexpressing RXRα or RXRγ. Immunoblot analysis confirmed expression of RXRα or RXRγ (Fig. 4A). Next, ^{32}P-labeled double-stranded oligonucleotide probe corresponding to LXRE (−299/-280) of the human SREBP-1c promoter (Fig. 4B) was incubated with nuclear extracts of 293T cells. As shown in Fig. 4C, RXRγ was able to form complexes with LXRE oligonucleotide. RXRγ binding to LXRE in SREBP-1c promoter was confirmed by presence of a supershift band when nuclear extract was pre-incubation with anti-RXRγ antibody (Fig. 4C, lane 5, upper arrow), demonstrating that RXRγ formed a heterodimer with LXRα and was obviously bound to LXRE on the SREBP-1c promoter.

4. Discussion

The transition from the fasted state to the fed state leads to increase glycolysis and lipogenesis in the liver. Postprandial lipogenesis is regulated mainly by glucose and insulin signaling pathways through transcription factors such as LXRα, ChREBP and SREBP-1c [21–24]. It is known that SREBP-1c and LXRs are activated by glucose at the transcription level [25,26]. However, the underlying mechanisms by which mediate glucose action are still not clearly understood. In addition, it remains controversial whether LXR is directly regulated by glucose [24,27]. On the other hand, relatively little attention has been paid to elucidate the functional role of RXRs. Thus, it is of interest to explore the effects of the fasting/refeeding or glucose on RXRs expression in the liver.

To investigate the nutritional regulation of RXR expression, mRNA levels of RXRs and metabolic genes were compared in mouse liver at fasting or feeding after fasting. Of the RXR isotypes, RXRγ mRNA expression increased in the fed state and was correlated with significant increases of glycolytic and lipogenic genes expression (Fig. 1A and B). Interestingly, the induction of RXRγ mRNA by refeeding was required a relatively short period of time (3 h), suggesting that the nutrient is a determinant of RXRγ induction and RXRγ may play a role in the regulation of glucose and

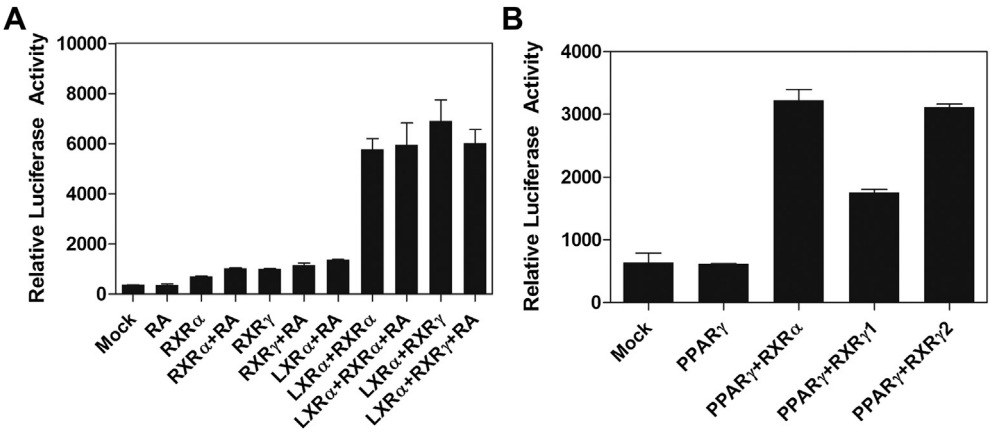

Fig. 3. RXRγ enhanced the transcriptional activity of SREBP-1c promoter. (A) pSREBP1c-Luc was transfected with LXRα, RXRα, RXRγ or control mock vector (Mock) in alexander cells. pCMV-β-gal was co-transfected to determine transfection efficiency. Twenty-four hours after transfection, T0901317 (1uM), 9-cis-RA (1 uM), or vehicle (ethanol) was added to medium and incubated another 24 h. Luciferase activity was measured in cell extracts and normalized to β-gal activity. (B) pSREBP1c-Luc was transfected with PPARγ, RXRγ1, RXRγ2 or mock vector (Mock) in 293T cells as indicated. Data are represented by means ± SEM.

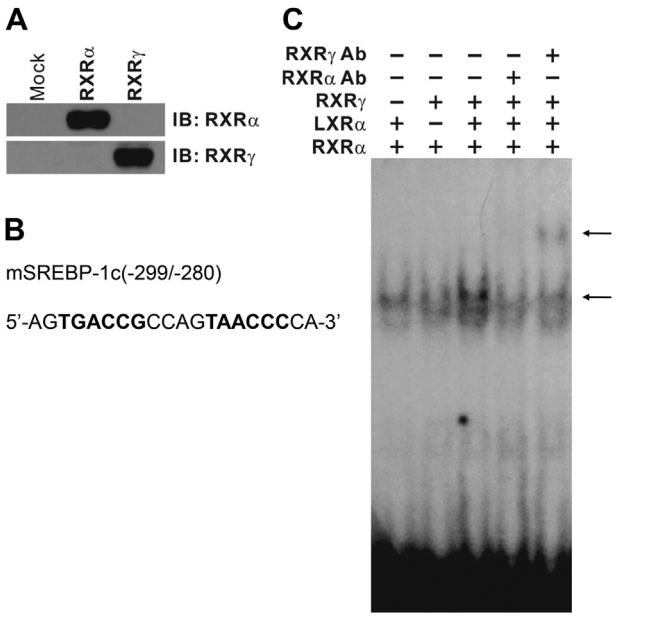

Fig. 4. RXRγ/LXRα complex binds to the LXRE on human SREBP-1c promoter. (A) 293T cells were transfected with mock vector (Mock) or expression vectors for RXRα and RXRγ. Nuclear extracts from 293T cells were subjected to Western blotting with anti-RXRα and anti-RXRγ antibodies. (B) Sequence of the LXRE derived from mouser SREBP-1c promoter. The LXRE sites are in bold type. (C) The 32P-labeled probes were incubated with nuclear extracts from 293T cells transfected with expression vectors for RXRα and RXRγ as indicated. For supershift analysis, anti-RXRα (lane 4) or anti-RXRγ antibody (lane 5) was incubated with complexes before addition of probe.

lipid metabolism in the fed state. In ob/ob mice, which are characterized by hyperglycemia, hyperinsulinemia and hepatic insulin resistance [28], fasting levels of RXRγ as well as glycolytic (LGK, L-PK) and lipogenic genes (ACC, FAS) were elevated in comparison to those in control C57BL/6 mice (Fig. 1B).

According to a recent study, RXRγ is decreased by fasting and restored by refeeding in mouse skeletal muscle [29]. However, this study showed neither glucose responsiveness of RXRγ in primary hepatocytes nor induction of RXRγ expression by refeeding in the liver. This discrepancy may be explained by differences in duration of fasting (48 h vs. 16 h) and refeeding (3–12 h vs. 16 h).

Because plasma glucose levels increased after feeding and glucose is a key modulator of gene expression in the fed state [22], it is possible that glucose may be required for the induction of RXRγ expression in refed state. In this study, glucose increased hepatic RXRγ expression in a dose-dependent manner, but had no effect on the RXRα mRNA level (Fig. 2). In addition, the induction of RXRγ occurred at the physiologic level of glucose (5.5 mM), suggesting the physiologic relevance of RXRγ. Based upon these findings, we hypothesized that RXRγ plays a role in the glucose metabolism in the liver.

Because SREBP-1c is a main target of LXR in the regulation of lipid metabolism [23,30], the potential involvement of RXRγ in the regulation of SREBP-1c was examined. According to the luciferase reporter assay and EMSA, RXRγ as well as RXRα bind to LXRE and activated the SREBP-1c promoter (Fig. 4B). Moreover, RXRγ and LXRα showed a significant synergistic effect on SREBP-1c promoter activity (Fig. 3A). These findings suggest RXRγ as a physiologic regulator of SREBP-1c transcription. In addition, RXRγ2, which lacks an activation domain, also increased SREBP-1c promoter activity (Fig. 4B), indicating that RXRγ2 activate indirectly SREBP-1c transcription probably through a direct interaction of an unidentified coactivator. Taken together, it is conceivable that RXRγ may serve as a sensor for maintaining glucose and lipid homeostasis by controlling metabolic regulators. In addition, LXRα/RXRγ may mediate the induction of SREBP-1c expression in the fed state while LXRα/RXRα may ensure a basal level of SREBP-1c expression in liver.

This study is the first to demonstrate for the regulation of RXRγ expression in the liver by feeding or glucose. In addition, RXRγ/LXRα complex bound to LXRE and trans-activated SREBP-1c promoter. Our findings provide some clues to unravel the characterization of RXRγ in the regulation of glucose and lipid metabolism. However, it still remains to be determined whether glucose or its metabolites are involved in the regulation of RXRγ expression and which factors mediate glucose-induced RXRγ expression in the liver. In addition, further investigation is needed to identify the target genes of RXRγ.

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References

[1] E.J. Parks, Dietary carbohydrate's effects on lipogenesis and the relationship of lipogenesis to blood insulin and glucose concentrations, Br. J. Nutr. 87 (Suppl. 2) (2002) S247–S253.
[2] W. Langhans, Role of the liver in the control of glucose-lipid utilization and body weight, Curr. Opin. Clin. Nutr. Metab. Care 6 (2003) 449–455.
[3] J.H. Exton, C.R. Park, Control of gluconeogenesis in liver: I. general features of gluconeogenesis in the perfused livers of rats, J. Biol. Chem. 242 (1967) 2622–2636.
[4] Hua V. Lin, D. Accili, Hormonal regulation of hepatic glucose production in health and disease, Cell. Metab. 14 (2011) 9–19.
[5] N. Zelcer, P. Tontonoz, Liver X receptors as integrators of metabolic and inflammatory signaling, J. Clin. Investig. 116 (2006) 607–614.
[6] J.R. Schultz, H. Tu, A. Luk, J.J. Repa, J.C. Medina, L. Li, S. Schwendner, S. Wang, M. Thoolen, D.J. Mangelsdorf, K.D. Lustig, B. Shan, Role of LXRs in control of lipogenesis, Genes. Dev. 14 (2000) 2831–2838.
[7] T. Yoshikawa, H. Shimano, M. Amemiya-Kudo, N. Yahagi, A.H. Hasty, T. Matsuzaka, H. Okazaki, Y. Tamura, Y. Iizuka, K. Ohashi, J.-I. Osuga, K. Harada, T. Gotoda, S. Kimura, S. Ishibashi, N. Yamada, Identification of liver X receptor-retinoid X receptor as an activator of the sterol regulatory element-binding protein 1c gene promoter, Mol. Cell. Biol. 21 (2001) 2991–3000.
[8] S.B. Joseph, B.A. Laffitte, P.H. Patel, M.A. Watson, K.E. Matsukuma, R. Walczak, J.L. Collins, T.F. Osborne, P. Tontonoz, Direct and Indirect mechanisms for regulation of fatty acid synthase gene expression by liver X receptors, J. Biol. Chem. 277 (2002) 11019–11025.
[9] Y. Zhang, L. Yin, F.B. Hillgartner, Thyroid Hormone stimulates acetyl-CoA carboxylase-α transcription in hepatocytes by modulating the composition of nuclear receptor complexes bound to a thyroid hormone response element, J. Biol. Chem. 276 (2001) 974–983.
[10] P. Lefebvre, Y. Benomar, B. Staels, Retinoid X receptors: common heterodimerization partners with distinct functions, Trends Endocrinol. Metab. 21 (2010) 676–683.
[11] D.J. Mangelsdorf, E.S. Ong, J.A. Dyck, R.M. Evans, Nuclear receptor that identifies a novel retinoic acid response pathway, Nature 345 (1990) 224–229.
[12] P. Dolle, V. Fraulob, P. Kastner, P. Chambon, Developmental expression of murine retinoid X receptor (RXR) genes, Mech. Dev. 45 (1994) 91–104.
[13] D.J. Mangelsdorf, U. Borgmeyer, R.A. Heyman, J.Y. Zhou, E.S. Ong, A.E. Oro, A. Kakizuka, R.M. Evans, Characterization of three RXR genes that mediate the action of 9-cis retinoic acid, Genes. Dev. 6 (1992) 329–344.
[14] Q. Liu, E. Linney, The mouse retinoid-X receptor-gamma gene: genomic organization and evidence for functional isoforms, Mol. Endocrinol. 7 (1993) 651–658.
[15] N.B. McDermott, D.F. Gordon, C.A. Kramer, Q. Liu, E. Linney, W.M. Wood, B.R. Haugen, Isolation and functional analysis of the mouse RXRγ1 gene promoter in anterior pituitary cells, J. Biol. Chem. 277 (2002) 36839–36844.
[16] A.I. Shulman, D.J. Mangelsdorf, Retinoid X receptor heterodimers in the metabolic syndrome, N. Engl. J. Med. 353 (2005) 604–615.

[17] P. Germain, P. Chambon, G. Eichele, R.M. Evans, M.A. Lazar, M. Leid, A.R. De Lera, R. Lotan, D.J. Mangelsdorf, H. Gronemeyer, International union of pharmacology. LXIII. Retinoid X receptors, Pharmacol. Rev. 58 (2006) 760–772.
[18] Y.S. Lee, H.H. Lee, J. Park, E.J. Yoo, C.A. Glackin, Y.I. Choi, S.H. Jeon, R.H. Seong, S.D. Park, J.B. Kim, Twist2, a novel ADD1/SREBP1c interacting protein, represses the transcriptional activity of ADD1/SREBP1c, Nucleic. Acids. Res. 31 (2003) 7165–7174.
[19] M.N. Berry, D.S. Friend, High-yield preparation of isolated RAT liver parenchymal cells, J. Cell. Biol. 43 (1969) 506–520.
[20] S.-K. Park, S.-Y. Oh, M.-Y. Lee, S. Yoon, K.-S. Kim, J.-W. Kim, CCAAT/enhancer binding protein and nuclear factor-Y regulate adiponectin gene expression in adipose tissue, Diabetes 53 (2004) 2757–2766.
[21] M. Foretz, C. Pacot, I. Dugail, P. Lemarchand, C. Guichard, X. le Liepvre, C. Berthelier-Lubrano, B. Spiegelman, J.B. Kim, P. Ferre, F. Foufelle, ADD1/SREBP-1c is required in the activation of hepatic lipogenic gene expression by glucose, Mol. Cell. Biol. 19 (1999) 3760–3768.
[22] S. Vaulont, M. Vasseur-Cognet, A. Kahn, Glucose regulation of gene transcription, J. Biol. Chem. 275 (2000) 31555–31558.
[23] G. Chen, G. Liang, J. Ou, J.L. Goldstein, M.S. Brown, Central role for liver X receptor in insulin-mediated activation of Srebp-1c transcription and stimulation of fatty acid synthesis in liver, Proc. Natl. Acad. Sci. U S A. 101 (2004) 11245–11250.
[24] P.-D. Denechaud, P. Bossard, J.-M.A. Lobaccaro, L. Millatt, B. Staels, J. Girard, C. Postic, ChREBP, but not LXRs, is required for the induction of glucose-regulated genes in mouse liver, J. Clin. Investig. 118 (2008) 956–964.
[25] A.H. Hasty, H. Shimano, N. Yahagi, M. Amemiya-Kudo, S. Perrey, T. Yoshikawa, J.-i. Osuga, H. Okazaki, Y. Tamura, Y. Iizuka, F. Shionoiri, K. Ohashi, K. Harada, T. Gotoda, R. Nagai, S. Ishibashi, N. Yamada, Sterol regulatory element-binding protein-1 is regulated by glucose at the transcriptional level, J. Biol. Chem. 275 (2000) 31069–31077.
[26] N. Mitro, P.A. Mak, L. Vargas, C. Godio, E. Hampton, V. Molteni, A. Kreusch, E. Saez, The nuclear receptor LXR is a glucose sensor, Nature 445 (2007) 219–223.
[27] M.A. Lazar, T.M. Willson, Sweet dreams for LXR, Cell. Metab. 5 (2007) 159–161.
[28] P.U. Dubuc, The development of obesity, hyperinsulinemia, and hyperglycemia in ob/ob mice, Metabolism 25 (1976) 1567–1574.
[29] Y. Kamei, S. Miura, T. Suganami, F. Akaike, S. Kanai, S. Sugita, A. Katsumata, H. Aburatani, T.G. Unterman, O. Ezaki, Y. Ogawa, Regulation of SREBP1c gene expression in skeletal muscle: role of retinoid X receptor/liver X receptor and forkhead-O1 transcription factor, Endocrinology 149 (2008) 2293–2305.
[30] D. Eberlé, B. Hegarty, P. Bossard, P. Ferré, F. Foufelle, SREBP transcription factors: master regulators of lipid homeostasis, Biochimie 86 (2004) 839–848.