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10-oxo-12(*Z*)-octadecenoic acid, a linoleic acid metabolite produced by gut lactic acid bacteria, potently activates PPARγ and stimulates adipogenesis

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ABSTRACT

Our previous study has shown that gut lactic acid bacteria generate various kinds of fatty acids from polyunsaturated fatty acids such as linoleic acid (LA). In this study, we investigated the effects of LA and LA-derived fatty acids on the activation of peroxisome proliferator-activated receptors (PPARs) which regulate whole-body energy metabolism. None of the fatty acids activated PPARδ, whereas almost all activated PPARα in luciferase assays. Two fatty acids potently activated PPARγ, a master regulator of adipocyte differentiation, with 10-oxo-12(*Z*)-octadecenoic acid (KetoA) having the most potency. In 3T3-L1 cells, KetoA induced adipocyte differentiation via the activation of PPARγ, and increased adiponectin production and insulin-stimulated glucose uptake. These findings suggest that fatty acids, including KetoA, generated in gut by lactic acid bacteria may be involved in the regulation of host energy metabolism.

1. Introduction

The rising prevalence of obese individuals is one of the most serious health problems of the world because obesity leads to metabolic disorders such as insulin resistance, type-2 diabetes, coronary heart disease, high blood pressure, and some forms of cancer [1,2]. Obesity is caused by an imbalance between energy intake and energy expenditure, and many genetic and environmental factors have been shown to affect the development of the condition [1,3].

Recent studies have shown that gut microbiota alterations exert profound effects on host physiology and metabolism, as well as obesity and obesity-related diseases [4,5]. The gut microbiota has been shown to affect host energy metabolism by several mechanisms, including an increased capacity for energy harvesting and

Abbreviations: PPAR, peroxisome proliferator-activated receptor; aP2, adipocyte fatty acid-binding protein; LPL, lipoprotein lipase; LCFA, long-chain fatty acid; SCFA, short-chain fatty acid; TG, triglyceride; LA, linoleic acid; CLA, conjugated linoleic acid; CLA1, 9(*Z*),11(*E*)-octadecadienoic acid; CLA2, 9(*E*),11(*E*)-octadecadienoic acid; CLA3, 10(*E*),12(*Z*)-octadecadienoic acid; OA, oleic acid; *t*10-18:1, 10(*E*)-octadecenoic acid; HYA, 10-hydroxy-12(*Z*)-octadecenoic acid; HYB, 10-hydroxy-octadecanoic acid; HYC, 10-hydroxy-11(*E*)-octadecenoic acid; KetoA, 10-oxo-12(*Z*)-octadecenoic acid; KetoB, 10-oxo-octadecanoic acid; Keto C, 10-oxo-11(*E*)-octadecenoic acid.

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interference with gut barrier function [5,6]. Specific metabolites of the gut microbiota might be involved in the regulation of host energy metabolism. For example, the gut microbiota of individuals with obesity and type 2 diabetes mellitus is characterized by a lower abundance of short-chain fatty acids (SCFAs) such as acetate, propionate and butyrate [7], which are utilized for the de novo synthesis of lipids and glucose, the main energy sources for the host [8]. In addition to energy sources, SCFAs have been shown to activate two orphan G-protein-coupled receptors, GPR41 and GPR43 as signaling molecules [9]. The SCFA-mediated activation of GPR41 and GPR43 has been reported to act as a gut-microbiota-related energy sensor in the sympathetic nervous system and in white adipose tissue, respectively [10–12].

Recently, we showed that gut lactic acid bacteria generated particular fatty acids including hydroxy fatty acids, oxo fatty acids, conjugated fatty acids, and partially saturated *trans*-fatty acids from polyunsaturated fatty acids such as linoleic acid (LA) [13]. Both the plasma and intestinal levels of several hydroxy fatty acids were much higher in specific pathogen-free mice than in germ-free mice, indicating that these fatty acids are generated through the polyunsaturated fatty acid metabolism of gastrointestinal microorganisms [13]. Although these findings suggested that lipid metabolites from gastrointestinal microbes can affect the host's fatty acid composition and metabolism, not only in the gastrointestinal tract but also in other organs, the bioactivities of these gut lactic acid bacteria-mediated fatty acids are largely unknown.

Long-chain fatty acids (LCFAs) work both as essential nutrients and signaling molecules [14,15]. Several molecules have been identified to work as fatty acid receptors including nuclear receptors and G-protein-coupled receptors, many of which have been shown to play an important role in the regulation of whole-body energy metabolisms physiologically [14,15]. Peroxisome proliferator-activated receptors (PPARs; PPARα, PPARγ, and PPARδ) are members of the nuclear receptor superfamily of transcription factors that are activated by the binding of small hydrophilic ligands, including LCFAs [14,16–18]. In mammals, PPARα is highly expressed in organs that have a high catabolic capacity of fatty acids, such as the liver and brown adipose tissue. PPARγ is predominantly expressed in white adipose tissue, whereas PPARδ is expressed ubiquitously [18]. PPARs govern whole-body energy metabolism both physiologically and pharmacologically [14,16–18]. Activators of PPARs are known to ameliorate obesity-related metabolic disorders. Specifically, fibrates (PPARα agonists) and thiazolidinediones (PPARγ agonists) have been clinically used for the management of hypertriglyceridemia and insulin resistance, respectively [16–18].

In this study, we investigated the effects of LA-derived fatty acids produced by gut lactic acid bacteria on the activation PPARs. Our findings suggest that certain fatty acids generated by gut lactic acid bacteria might be involved in the regulation of host energy metabolism.

2. Materials and methods

2.1. Materials

10-Hydroxy-12(*Z*)-octadecenoic acid (HYA), 10-hydroxyoctadecanoic acid (HYB), 10-hydroxy-11(*E*)-octadecenoic acid (HYC), 10-oxo-12(*Z*)-octadecenoic acid (KetoA), 10-oxo-octadecanoic acid (KetoB), 10-oxo-11(*E*)-octadecenoic acid (KetoC), 9(*Z*),11(*E*)-octadecadienoic acid (CLA1), 9(*E*),11(*E*)-octadecadienoic acid (CLA2), 10(*E*),12(*Z*)-octadecadienoic acid (CLA3), and 10(*E*)-octadecenoic acid (t10-18:1) were produced as described previously [13]. Unless otherwise indicated, all other chemicals used were purchased from Sigma (St. Louis, MO, USA), Nacalai Tesque (Kyoto, Japan), or Wako (Osaka, Japan), and were guaranteed to be of reagent or tissue culture grade.

2.2. Cell culture

Monkey CV1 kidney cells (American Type Culture Collection (ATCC), Manassas, VA, USA) and NIH-3T3 murine fibroblasts (ATCC) were cultured as described previously [19–21]. 3T3-L1 murine preadipocytes (ATCC) were cultured and induced differentiation as described previously [19,20]. Cell viability was determined using CellTiter 96 (Promega, Madison, WI, USA). Adiponectin levels in the conditioned medium were determined using an ELISA kit (R&D Systems, Minneapolis, MN, USA).

2.3. Luciferase assay

The luciferase assay was performed as previously described [19–21]. Briefly, for the assay using the GAL4 chimera system, we transfected p4xUASg-tk-luc (a reporter plasmid), pM-hPPARs (an expression plasmid for a chimera protein for the GAL4 DNA-binding domain and human PPAR ligand-binding domain), and pRL-CMV (an internal control for normalizing transfection efficiencies) into CV1 cells. For assays using a PPARγ full-length system, pDEST-hPPARγ (a human PPARγ expression vector), p3xPPRE-tk-luc (a reporter plasmid), and pRL-CMV were transfected into NIH-3T3 cells. Luciferase activities were measured using the dual luciferase system (Promega).

2.4. Lipid analysis

Eight days after differentiation induction, Oil Red O staining was performed as described previously [19]. To determine intracellular triglyceride (TG) amounts, lipids were extracted with hexane-isopropyl alcohol (3:2, v/v). Aliquots were evaporated under reduced pressure. Samples were resuspended in 10% TritonX-100 in isopropyl alcohol and the TG amounts were measured with triglyceride G-test Wako (Wako).

2.5. RNA preparation and real-time fluorescence monitored RT-PCR

To quantify the mRNA expression, real-time RT-PCR was performed using SYBR Green fluorescence signals, as described previously [19–22]. To compare mRNA expression levels among the samples, the copy numbers of all transcripts were divided by that of mouse 36B4. All mRNA expression levels were presented as the ratio relative to the mRNA expression level of the control in each experiment.

2.6. 2-Deoxy-D-glucose uptake assay

Ten days after differentiation induction, 2-Deoxy-D-glucose uptake assay was performed, as described previously [19].

2.7. SDS-polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotting

To investigate the multimerization of adiponectin in conditioned medium in 3T3-L1 adipocytes, SDS-PAGE was performed as previously described [22].

2.8. Statistical analysis

The results were expressed in terms of the mean and SEM. The statistical significance of differences was evaluated using the Student's t-test or ANOVA and Tukey–Kramer test. Differences were considered significant at $P < 0.05$.

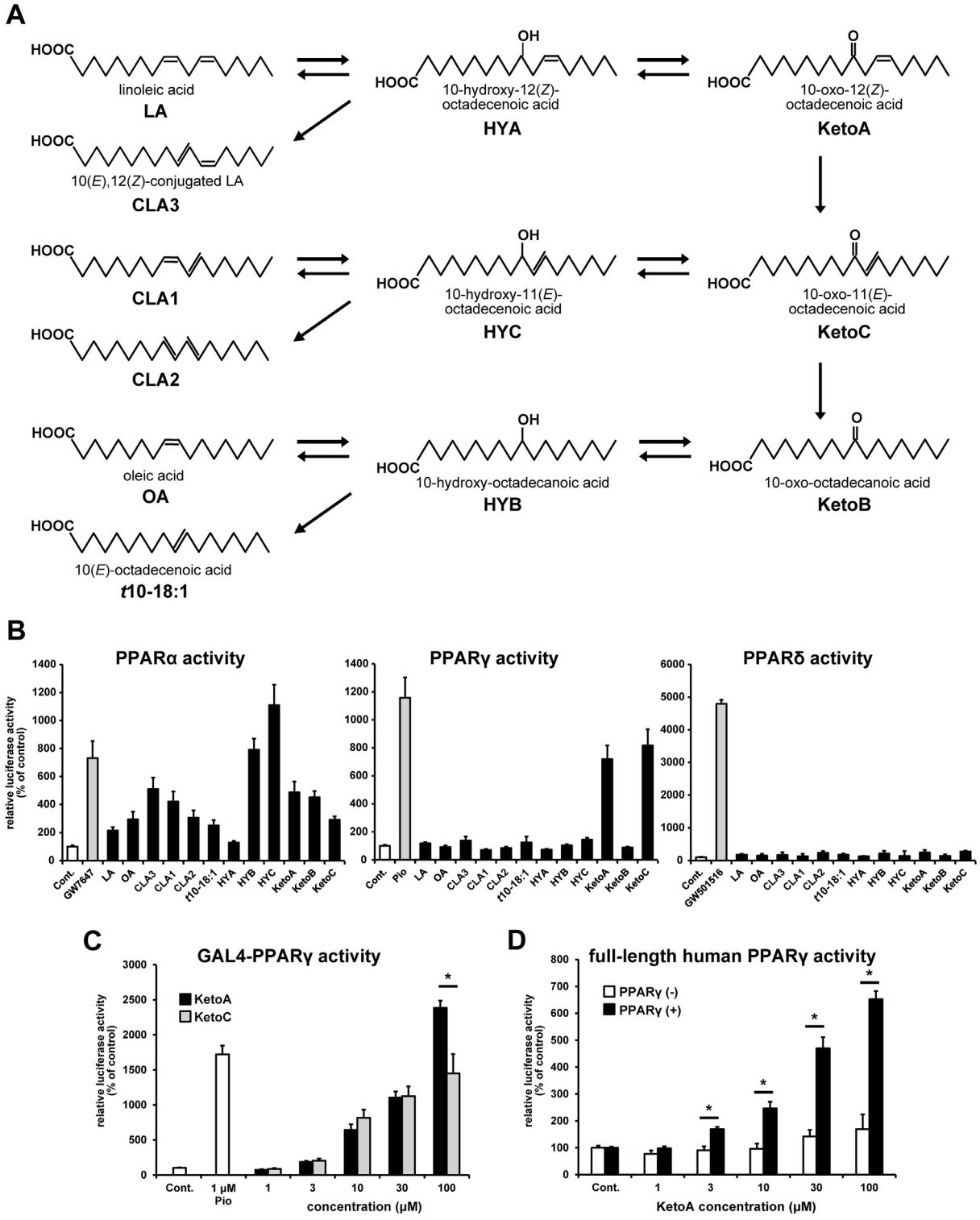

Fig. 1. Linoleic acid-derived fatty acids generated by gut lactic acid bacteria modulated PPARs activities in luciferase reporter assays. A: Pathway of linoleic acid-metabolism of gut lactic acid bacteria. B–D: Effects of fatty acids on human PPARs activity in a luciferase reporter assay using the GAL4/PPARs chimera system (B, C) or full-length human PPARγ system (D). The transfected cells were incubated in medium with or without fatty acids (10 μM in B and indicated concentrations of KetoA or KetoC in C and D) or synthetic agonists of each PPAR (10 nM GW7647, 1 μM pioglitazone (Pio), and 1 μM GW501516 for PPARα, PPARγ, and PPARδ, respectively) for 24 h. All the values are means ± SEM (n = 5). $^{*}P < 0.05$. Cont, control.

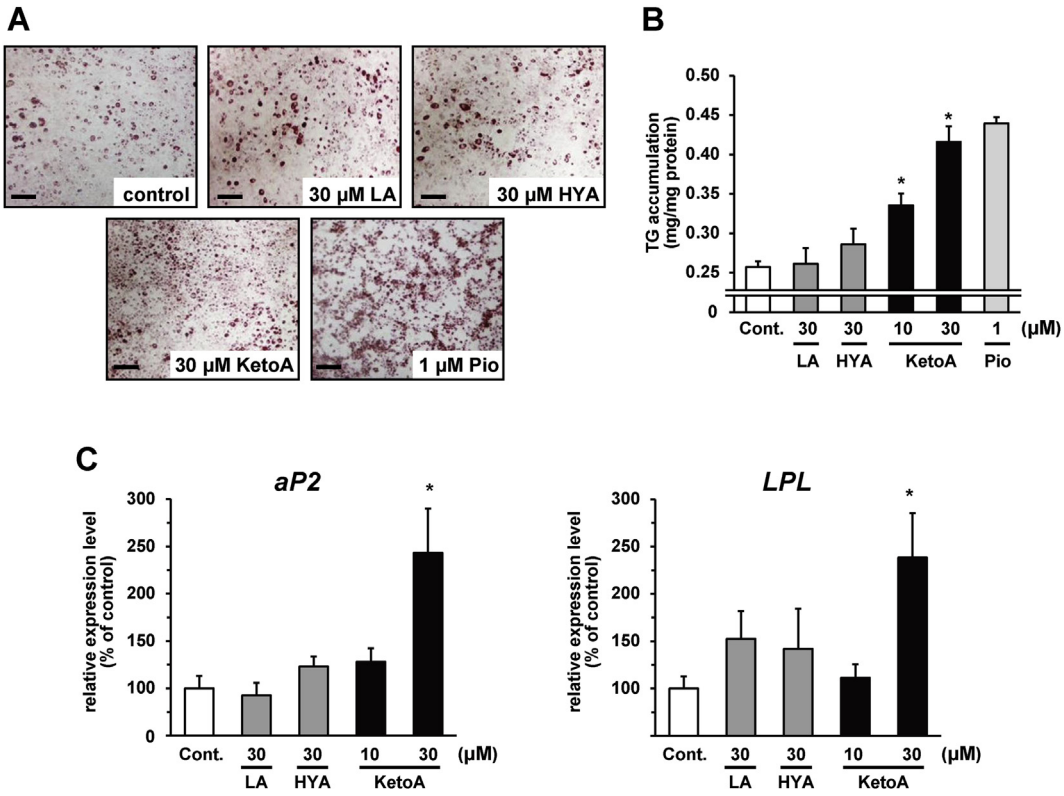

Fig. 2. KetoA treatment induced adipocyte differentiation in 3T3-L1 cells. 3T3-L1 cells were induced to differentiate with or without fatty acids (linoleic acid (LA), 10-hydroxy-12(*Z*)-octadecenoic acid (HYA), and 10-oxo-12(*Z*)-octadecenoic acid (KetoA)) or pioglitazone (Pio). A: Microscopic views of representative 3T3-L1 cells. The cells were stained with Oil Red O. Scale bars in panels represent 100 μm. B: Enzymatic determination of intracellular triglyceride (TG) contents. The TG contents were normalized to the cellular protein contents. C: Total RNA isolated and analyzed by real-time fluorescence monitored RT-PCR. The mRNA expression level of each gene was normalized to the expression level of the ribosomal 36B4 gene. All the values are means ± SEM (n = 3–4). $^{*}P < 0.05$ compared with the control (Cont).

3. Results

3.1. Linoleic acid-derived fatty acids produced by gut lactic acid bacteria showed various PPAR ligand activities

Our recent study showed that gut lactic acid bacteria generated various kinds of fatty acids from polyunsaturated fatty acids, including LA (Fig. 1A) [13]. To investigate the effects of these 12 fatty acids on the activity of PPARs, which are activated by various fatty acids and govern whole-body energy metabolism [16,17], we performed luciferase reporter assays using a chimera protein for the GAL4 DNA-binding domain and human PPAR ligand-binding domain (PPARα, PPARγ, and PPARδ). As shown in Fig. 1B, at the concentration of 10 μM, almost all the fatty acids (including LA and OA) enhanced PPARα activity. Many fatty acids had a more robust PPARα activation potency than their starting material (LA), especially HYB and HYC. On the other hand, none of the fatty acids activated PPARδ at 10 μM (Fig. 1B). As concerns PPARγ, the two oxo fatty acids KetoA and KetoC were the only fatty acids to potently activate PPARγ (Fig. 1B), showing similar levels of activity at concentrations from 3 to 30 μM (Fig. 1C). At 100 μM, however, the KetoA activity was more potent than KetoC. In the luciferase reporter assay using full-length human PPARγ in NIH-3T3 cells, KetoA induced luciferase activity in a dose-dependent manner, depending on the presence of PPARγ (Fig. 1D).

3.2. KetoA induced lipid accumulation and the mRNA expression of adipogenic PPARγ target genes during adipocyte differentiation in 3T3-L1 cells

Next, we focused on the PPARγ ligand activity of KetoA. Because PPARγ is well known to play a central role in adipocyte differentiation [18], we investigated whether KetoA affects adipocyte differentiation using 3T3-L1 murine preadipocytes. In this study, we used LA (the starting material) and HYA (a precursor of KetoA in which a ketone group in KetoA is substituted with a hydroxyl group; Fig. 1A) as the control fatty acids. The test compounds were added at the time of differentiation induction and kept in the medium throughout the differentiation period (days 0–8). Similar to the synthetic PPARγ agonist pioglitazone, the addition of KetoA induced triglyceride (TG) accumulation in a dose-dependent manner, whereas 30 μM of LA and HYA showed no changes in TG accumulation levels compared with the vehicle control (Fig. 2A and B). We did not observe any changes in 3T3-L1 cell viability at the concentrations of fatty acids and pioglitazone used in this study (data not shown). The potency of increase in lipid accumulation levels in 3T3-L1 cells correlated with that of PPARγ ligand activity. Thus, we next assessed the effects of these fatty acids on the mRNA expression levels of PPARγ target genes, aP2 and LPL. As shown in Fig. 2C, the mRNA expression levels of aP2 and LPL were up-regulated during adipocyte differentiation in the presence of 30 μM KetoA, but were unchanged in the presence of LA and HYA.

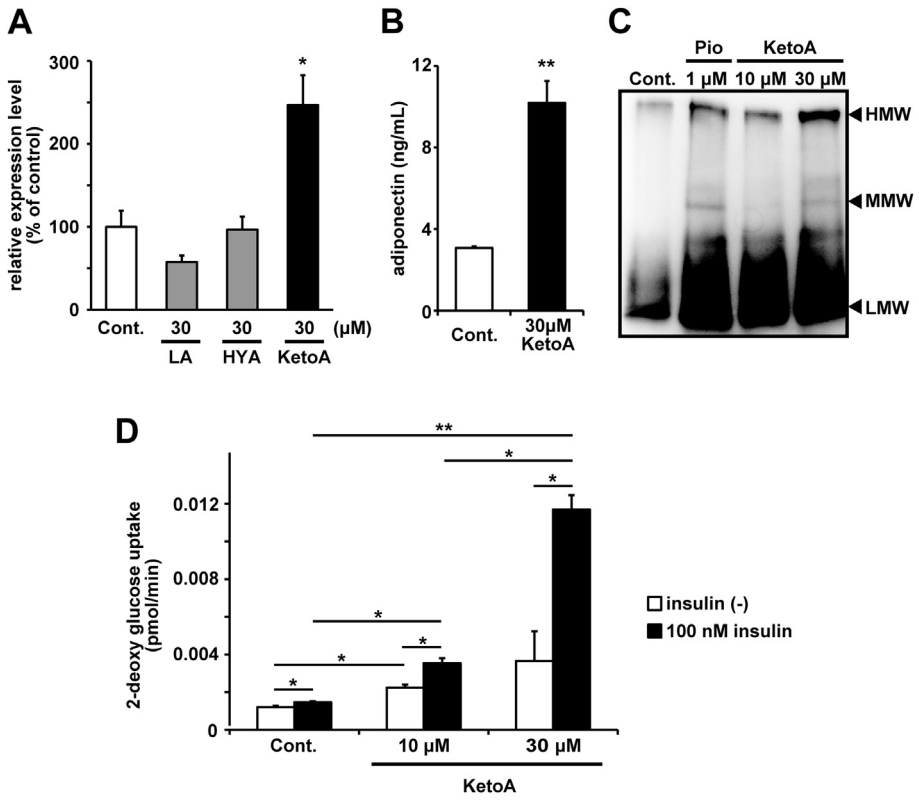

Fig. 3. KetoA treatment increased adiponectin mRNA expression and secretion and glucose uptake in 3T3-L1 cells. 3T3-L1 cells were induced to differentiate with or without fatty acids or pioglitazone (Pio). A: Total RNA was isolated and analyzed by real-time fluorescence monitored RT-PCR, and adiponectin mRNA expression was analyzed. B, C: At day 6, the conditioned medium of 3T3-L1 cells was collected and subjected to analysis of the adiponectin secretion level from days 4–6 (48 h) (B) and adiponectin multimerization (C), measured by an ELISA kit and immunoblotting, respectively. HMW, high-molecular-weight; MMW, medium-molecular-weight; LMW, low-molecular-weight. D: The ability of cells to take up 2-deoxy-D-glucose (2-DG) on day 6, in the presence (100 nM) or absence of insulin, was measured. The values are means ± SEM (n = 3–4). $^{*}P < 0.05$, $^{**}P < 0.01$ compared with the control (Cont) (A and B).

These results indicate that KetoA induces adipocyte differentiation in 3T3-L1 cells.

3.3. KetoA treatment increased mRNA expression and secretion levels of adiponectin and enhanced glucose uptake in 3T3-L1 cells

We investigated whether KetoA treatment would increase the mRNA expression and secretion level of adiponectin (an anti-atherosclerotic and anti-diabetic hormone specifically derived from adipocytes [23]) in 3T3-L1 cells. The mRNA expression level of adiponectin was significantly increased by 30 μM KetoA but not by LA and HYA (Fig. 3A). Similar to the increased mRNA level, the secretion level of adiponectin was also up-regulated in the presence of KetoA (Fig. 3B). SDS-PAGE under non-reducing and non-heat-denaturing conditions revealed that KetoA treatment, as in the case of pioglitazone, markedly increased high-molecular-weight (HMW) adiponectin, which has been shown to be able to activate AMP kinase most potently (Fig. 3C). Moreover, KetoA treatment during adipocyte differentiation led to an increase in insulin-stimulated 2-deoxy-D-glucose uptake which is enhanced during adipocyte differentiation (Fig. 3D). These results indicate that KetoA treatment increases useful functions of adipocytes, such as adiponectin production and glucose uptake, via the stimulation of adipocyte differentiation.

3.4. KetoA-induced enhancements of lipid accumulation and adipogenic PPARγ target gene expression were inhibited in the presence of a PPARγ antagonist.

To clarify the role of PPARγ in KetoA-induced adipocyte differentiation, we tested the effect of the synthetic PPARγ antagonist GW9662 on TG accumulation during adipocyte differentiation induced by KetoA. GW9662 significantly suppressed KetoA-induced TG accumulation in 3T3-L1 cells (Fig. 4A and B). We did not observe any changes in the viability of 3T3-L1 cells treated with KetoA and/or GW9662 at the concentrations used in this study (data not shown). Similar results were obtained in the case of the KetoA-induced adipogenic aP2 and adiponectin mRNA expression levels, which were significantly attenuated in the presence of GW9662 (Fig. 4C). At a concentration of 1 μM, GW9662 almost completely diminished the KetoA-induced lipid accumulation and mRNA expression (Fig. 4A–C). These results indicate that KetoA induces adipocyte differentiation via the activation of PPARγ.

4. Discussion

Long-chain fatty acids have been reported to have various physiological functions and they seem to be related to the obesity-induced pathophysiological condition [14,15,24–26]. It has been reported that ablation of elongation of the long-chain fatty acids family member 6 causes significant changes in the fatty acid composition in liver and plasma, leading to the amelioration of insulin resistance, diabetes, and cardiovascular risks [24]. Palmitoleic acid produced in the adipose tissue has been shown to improve metabolic responses in the liver and skeletal muscle [25]. Moreover, Yore et al. recently reported that a type of branched fatty acid ester of hydroxy fatty acids synthesized in adipose tissue improved glucose tolerance and stimulated glucagon-like peptide-1 secretion [26]. These reports strongly indicate that several specific fatty acids and/or changes in fatty acid composition play important roles in the maintenance of whole-body lipid and

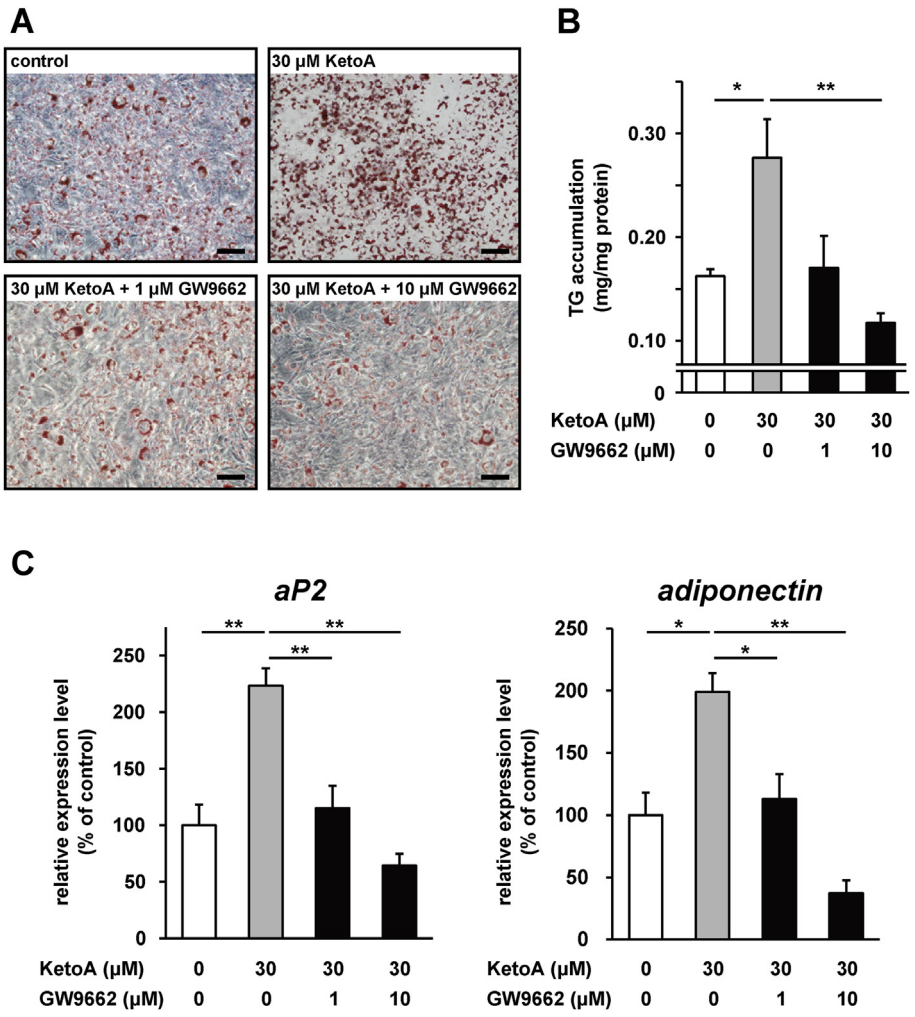

Fig. 4. KetoA-induced enhancements of lipid accumulation and the mRNA expression of adipogenic genes were attenuated in the presence of a PPARγ antagonist. 3T3-L1 cells were induced to differentiate with or without 30 μM KetoA and/or 1 or 10 μM GW9662 (a PPARγ antagonist). A: Microscopic views of representative 3T3-L1 cells. The cells were stained with Oil Red O. Scale bars in panels represent 100 μm. B: Intracellular TG contents were determined enzymatically. C: Total RNA was isolated and analyzed by real-time fluorescence monitored RT-PCR. The values are means ± SEM (n = 3–4). $^{*}P < 0.05$, $^{**}P < 0.01$ compared with 30 μM KetoA without GW9662. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

carbohydrate metabolism. Our previous study indicated that gut lactic acid bacteria produced various fatty acids during fatty acid metabolism, some of which existed at much higher levels in the some organs and plasma of specific pathogen-free mice than in those of germ-free mice, indicating that fatty acid metabolism by gut lactic acid bacteria affects the host fatty acid composition [13]. These results suggest that fatty acids, including KetoA, produced by the gut microbiota might be important for the regulation of host energy metabolism via the modulation of the activity of host fatty acids receptors, including PPARs.

A number of compounds, both synthetic and endogenous, have been reported to bind to and activate PPARs with varying specificity. Although the identities of the functional endogenous ligands of PPARs are open to debate, LCFAs have emerged as strong candidates [14]. In our luciferase reporter assays, the PPAR ligand activities of tested fatty acids were dependent on the PPAR subtypes. At the concentration of 10 μM, almost all tested fatty acids showed ligand activity for PPARα, whereas very limited and no fatty acids activated PPARγ and PPARδ, respectively. These results are consisted with a previous report, in which the binding affinities of various LCFAs to these three PPAR subtypes, as determined by their ability to compete with radioligands, were the strongest toward PPARα [27]. In that report, the authors also showed that the binding affinities of saturated LCFAs to PPARγ and PPARδ were approximately-same, but many unsaturated LCFAs bound to PPARγ relatively more potently than to PPARδ [27]. In this present study, two oxo fatty acids (KetoA and KetoC) produced by gut lactic acid bacteria showed PPARγ ligand activity. Hydroxy fatty acids (HYA and HYC), in which a ketone group in KetoA and KetoC is substituted with a hydroxyl group (Fig. 1A), did not have PPARγ ligand activity. Unlike KetoA and KetoC, KetoB (an oxo fatty acid with a saturated acyl chain) did not show any PPARγ ligand activity. These results indicate that oxo fatty acids that have unsaturated acyl chain have PPARγ ligand activity. Previous reports showed α,β-unsaturated ketone to be a core moiety of natural ligands for covalent binding to Cys-285 in human PPARγ [28–30]. Among our tested compounds, only KetoC has an α,β-unsaturated ketone, suggesting that the binding pattern of the keto fatty acids to PPARγ might be different.

Emerging evidence on the gut microbiome suggests that metabolic diseases including obesity are associated with an altered gut microbiota profile [4,5]. The gut microbiome plays an important role in metabolism and caloric extraction from dietary sources. Several studies on the relationship between the gut microbiota and

PPARγ activity in colonic cells have been reported. *Enterococcus faecalis* isolated from newborn babies possessed the ability to regulate PPARγ activity through phosphorylation in colonic epithelial cells [31]. Secreted factors from *Lactobacillus paracasei* ssp. *paracasei* F19 (a gram-positive, non-spore-forming bacterium initially isolated from human small intestine) up-regulated angiopoietin-like protein 4 expression via the activation of PPARγ in colonic cells [32]. The molecular mechanisms underlying PPARγ activation in colonic cells by gut microbiota might be partly related to SCFA-induced activation of PPARγ [33]. PPARγ has been reported to be comparatively highly expressed in the epithelium of the proximal colon [34]. Therefore, KetoA and KetoC, which activate PPARγ, identified in this study might have physiological importance in colonic cells though we investigated the effects of these fatty acids in adipocytes in this study.

In conclusion, LA-derived fatty acids produced by gut lactic acid bacteria have a variety of PPAR ligand activity. Interestingly, two types of oxo fatty acids potently activated PPARγ. KetoA, which had the most potent PPARγ ligand activity, induced adipocyte differentiation via the activation of PPARγ in 3T3-L1 cells. These findings raise the possibility that fatty acids, including KetoA, generated by gut lactic acid bacteria might be involved in the regulation of host energy metabolism. Therefore, probiotic modulation of the capacity to produce these fatty acids in gut microbiota might be an attractive target to regulate whole-body energy metabolism.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

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