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Activation of G Protein-Coupled Receptor 43 in Adipocytes Leads to Inhibition of Lipolysis and Suppression of Plasma Free Fatty Acids

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G protein-coupled receptor 43 (GPR43) has been identified as a receptor for short-chain fatty acids that include acetate and propionate. A potential involvement of GPR43 in immune and inflammatory response has been previously suggested because its expression is highly enriched in immune cells. GPR43 is also expressed in a number of other tissues including adipocytes; however, the functional consequences of GPR43 activation in these other tissues are not clear. In this report, we focus on the potential functions of GPR43 in adipocytes. We show that adipocytes treated with GPR43 natural ligands, acetate and propionate, exhibit a reduction in lipolytic activity. This inhibition of lipolysis is the result of GPR43 activation, because this effect is abolished in adipocytes isolated from GPR43 knockout animals. In a mouse *in vivo* model, we show that the activation of GPR43 by acetate results in the reduction in plasma free fatty acid levels without inducing the flushing side effect that has been observed by the activation of nicotinic acid receptor, GPR109A. These results suggest a potential role for GPR43 in regulating plasma lipid profiles and perhaps aspects of metabolic syndrome. (*Endocrinology* 149: 4519–4526, 2008)

THE SUPERFAMILY OF G protein-coupled receptors (GPCRs) is one of the largest families of proteins in the mammalian genome and shares a conserved structure composed of seven transmembrane helices. The natural ligands of this receptor superfamily are extremely diverse, comprising biogenic amines, amino acids, peptides, proteins, glycoproteins, lipids, phospholipids, fatty acids, nucleotides, odorants, ions, and light (1). Historically, the discovery of drugs acting on GPCRs has been extremely successful, with 50% of all recently launched drugs against GPCR targets and annual worldwide sales exceeding 50 billion dollars (2). Due to their involvement in diverse biological processes that affect all major disease areas combined with their druggability, GPCRs represent a very attractive family of proteins for biopharmaceutical research.

GPR43 belongs to a subfamily of related GPCRs, including GPR40 and GPR41, that have recently been identified as receptors for fatty acids (3). The three family members share about 30–40% sequence identity with specificity toward different fatty acid carbon chain length, with short-chain fatty acids (SCFAs; six carbons molecules or shorter, <C6) activating GPR41 and GPR43, and medium- and long-chain fatty acids activating GPR40 (4). Although both GPR43 and GPR41 are activated by SCFAs, they show differences in SCFA specificity, intracellular signaling, and tissue localization. GPR43 can couple to both Gi and Gq, whereas GPR41 couples only to Gi (5–7). In addition, C2 (acetate) and C3 (propionate) are the most potent activators of GPR43, whereas C2 is not as potent as C3, C4, or C5 in activating GPR41 (5, 6).

GPR43 expression level has been reported previously to be highest in immune cells, particularly in the polymorphonuclear cells (5–7). Given the well established effects of SCFAs on leukocytes, it has been suggested that GPR43 may play a role in various immune and inflammatory responses (5–7). However, GPR43 is also expressed in a number of other tissues including adipocytes. It is induced during the adipocyte differentiation process and increased during high-fat feeding in rodents, suggesting that GPR43 may affect adipocyte functions as well (8). Indeed, it has recently been reported that acetate and propionate may stimulate adipogenesis via GPR43. In addition, small interfering RNA results hinted that acetate and propionate may inhibit lipolysis in adipocytes via GPR43 activation (8). Given that GPR43 can couple to Gi/o, this suggests that GPR43 in adipocytes may activate the Gi/o pathway to inhibit lipolysis. It is interesting to note that the effects of acetate on reducing plasma free fatty acid (FFA) levels has been documented in humans (9, 10). Whether these observed effects are mediated through GPR43 and whether activation of GPR43 will lead to suppression of plasma FFA levels need to be further addressed.

Here, using GPR43 knockout (KO) animals, we demonstrate that activation of GPR43 in adipocytes will lead to inhibition of lipolysis and result in the reduction of plasma FFA levels *in vivo*. Furthermore, we show that the observed effects of acetate on lipolysis and FFA levels are the result of direct activation of GPR43. These results suggest a potential role for GPR43 in regulating plasma lipid profiles and perhaps aspects of metabolic syndrome.

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Abbreviations: FFA, Free fatty acid; GPCR, G protein-coupled receptor; HDL, high-density lipoprotein; KO, knockout; LD, laser-Doppler; LPL, lipoprotein lipase; PTX, pertussis toxin; SCFA, short-chain fatty acid.

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Materials and Methods

Lipolysis assay in differentiated 3T3-L1 cells

3T3-L1 cells (ATCC CL-173) were cultured in DMEM with 10% fetal calf serum on Corning CellBind 96-well plates. Upon confluence, differentiation was induced by adding 250 nM dexamethasone, 500 μM isobutylmethylxanthine, 1 μg/ml insulin, 2 nM T_3, and 0.3 μM Rosiglitazone into basic culture medium for 2 d. The cells were then cultured in DMEM with 10% fetal calf serum with 1 μg/ml insulin, 2 nM T_3, and 0.3 μM Rosiglitazone for 2 d and maintained in basic culture medium thereafter. Fifteen days after induction, differentiated adipocytes were preincubated with Krebs-Ringer bicarbonate 25 mM HEPES (KRH buffer, Sigma K4002; Sigma Chemical Co., St. Louis, MO) with 0.01% fatty-acid-free BSA (Sigma) and 1 U/ml adenosine deaminase (Biocatalytics Inc., Pasadena, CA; ADA-101) for 2 h. Cells were then treated with short-chain fatty acids, isoproterenol, insulin, or pertussis toxin (PTX) in KRH buffer for 4 h. PTX (Biomol, Plymouth Meeting, PA) was used as indicated at 100 ng/ml. Glycerol released from lipolysis during treatment was measured by Free Glycerol Reagent (Sigma F6428).

Preparation of mice primary adipocytes and lipolysis assay

Adipocytes were released from mouse epididymal fat pads by collagenase (Sigma C2674) digestion similar to previously described methods. Cells were then washed four times with KRH buffer (Sigma K4002) with 3% fatty-acid-free BSA (Sigma) and 1 U/ml adenosine deaminase (Biocatalytics; ADA-101). The primary adipocytes harvested from 15 mice (no fasting) were plated on 24-well plates. Cells were incubated with short-chain fatty acids, isoproterenol, or insulin in 24-well plates at 37 C with mild shaking. Aliquots were collected from centers of wells hourly for glycerol assay using free glycerol reagent (Sigma F6428).

Generation of GPR43-deficient mice

GPR43-deficient mice were generated at Lexicon Genetics, Inc. (The Woodlands, TX). The entire coding region from the GPR43 gene, contained in one exon, was substituted for a 5.3-kb *neo* cassette in the GPR43 targeting vector, along with a total of approximately 7.8 kb of homology: about 6.8 kb 5′ arm and about 1 kb 3′ arm. The targeting vector was

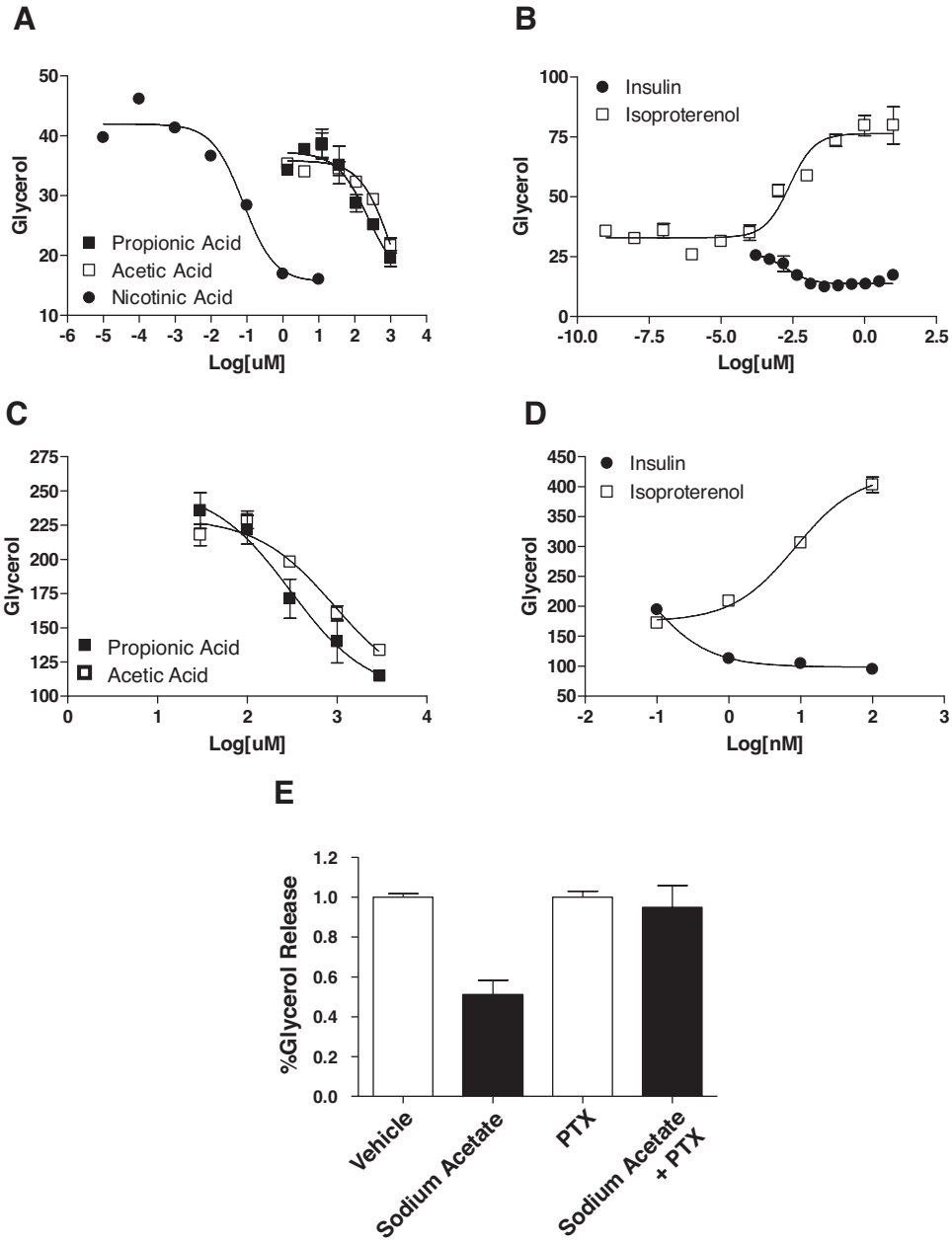

FIG. 1. GPR43 ligands, propionate and acetate, inhibit lipolysis in adipocytes via Gi coupled pathway. Differentiated 3T3-L1 cells (A and B) and primary adipocytes (C and D) were treated with acetate, propionate, nicotinic acid, insulin, and isoproterenol. Lipolysis was measured by the release of glycerol in the culture medium. Both propionate and acetate treatments lead to inhibition of lipolysis up to 50% in cultured adipocytes and in primary adipocytes. E, Sodium acetate-induced inhibition of lipolysis in 3T3-L1 cells is sensitive to PTX treatment.

introduced into embryonic stem cells derived from the 129SvEvBrd mouse strain. The integration of the targeting events on the 3′ end were confirmed by Southern blot analysis of embryonic stem cell genomic DNA after digestion with *Bgl*II, using a probe located downstream of the arms of homology. Targeted embryonic stem cell clones were injected into host blastocysts, and resulting chimeric mice were bred to C57BL/6J albino mice to generate F1 heterozygotes. F1 heterozygotes were backcrossed to C57BL/6J mice for one generation. The resulting N1F1 heterozygotes were intercrossed to generate F2 homozygous mice. Mice were subsequently backcrossed to C57BL/6J to congenicity as confirmed using microsatellite markers and then bred to homozygosity.

The genotypes of wild-type and mutant mice were identified by triplex PCR analysis of genomic DNA from tail biopsies. The wild-type specific primer pair (a/b) produced a product of 571 bp, and the KO specific primer (c/b) pair produced a product of 325 bp. The following primers were used: a, 5′-GCTACGAGAACTTCACCCAAGAG; b, 5′-CTCAGGAGCTCT-GCTAACCAGAC; c, 5′-GCAGCGCATCGCCTTCTATC.

Acetate treatment in mice

Aged matched C57BL/6 or *ob/ob* (Jackson Laboratory, Bar Harbor, ME) mice were used in all the studies. Mice were starved overnight before the experiment. Sodium acetate or vehicle (PBS) was injected ip into mice at stated concentration the next morning. Blood was collected at different time points after injection by tail bleeding. Plasma FFA and acetate were measured according to the following.

Lipoprotein lipase (LPL) enzyme assay

Epididymal fat pad was removed from age-matched wild-type or GPR43 KO mice, weighed, and homogenized in LPL lysis buffer (0.25 M sucrose, 50 mM Tris buffer, and 80 U heparin/ml with pH adjusted to 8.5; 4 ml/g tissue) using a pestle homogenizer (11). The homogenate was centrifuged at 10,000 × *g* for 30 min at 4 C. The upper-level fat cake was removed, and the clear supernatant was used to measure the LPL activity. The lipase activity was measured using a LPL assay kit according to the manufacturer's instruction (Roar Biomedicals, New York, NY; RB-LPL2) (12). LPL activities were calculated by subtracting the non-LPL activity measured in 1 M NaCl assay buffer from the total lipase activity measured in 0.1 M NaCl assay buffer (13).

Measurement of plasma FFA and acetate level

Plasma FFA level was measured using Wako HR Series NEFA-HR (2) kit following the manufacturer's instructions. Plasma acetate level was measured using an enzymatic kit (R-Biopharm, Darmstadt, Germany; catalog item 148261). To use 96-well plates instead of plastic cuvettes, the measured volume is reduced proportionally to 160 μl for each measurement. The measurement steps and calculation were performed according to the manufacturer's protocol.

Measurement of flushing

To determine cutaneous vasodilation in the mouse ear, we employed laser-Doppler (LD) flowmetry (PeriFlux System 5000; Perimed, Stockholm, Sweden). Male C57BL/6 mice at the age of 8–10 wk were anesthetized by ip injection of 60 mg/kg pentobarbital (Ovation, Dearfield, IL) and placed on their left sides on a controlled heating pad (Gaymar Industries Inc., Orchard Park, NY) to maintain their body temperature. Using adhesive strips (PF 105-3; Perimed) on PH 07-5 miniature probe holder (Perimed), a small straight LD probe (No. 407-1; Perimed) was attached to the dorsal surface of the right ear over a first-order branch of the ear artery. LD flux was continuously recorded by a LDPM Unit-PF 5010 monitor (Perimed) connected to a PC. After a 10-min stabilization period, 200 mg/kg nicotinic acid and 500 mg/kg sodium acetate were injected ip in a volume of 10 mg/kg body weight [solutions were freshly prepared in 5% (2-hydroxypropyl)-β-cyclodextrin, and the pH was adjusted to 7.0–7.3 with 1 N NaOH].

Results

Activation of GPR43 by natural ligands, propionate and acetate, results in the inhibition of lipolysis in adipocytes in vitro

Similar to previous reports, we have also observed that GPR43 is expressed in adipose tissue and highly induced during the adipocyte differentiation process (8) (data not shown). We therefore explored potential GPR43 activity on adipocyte function and lipid metabolism. Cultured 3T3-L1 cells can be differentiated into adipocytes and are used widely as an *in vitro* model to study adipocyte function. To test the effects of GPR43 activation on adipocyte lipolysis, differentiated 3T3-L1 adipocytes were treated with GPR43 natural ligands, propionate and acetate, and the rate of lipolysis was accessed by measuring the release of glycerol in the culture medium. Both propionate and acetate were able to inhibit lipolysis with an IC_{50} value in the 100- to 300-μM range. The extent of the inhibition or efficacy is similar to what was observed for nicotinic acid in the same assay, although with lower potency (Fig. 1A). The effects of propionate and acetate on lipolysis in primary adipocytes isolated from mice were also tested. Similar to the effects on 3T3-L1 differentiated adipocytes, propionate and acetate were also able to inhibit lipolysis in primary adipocytes in a dose-dependent manner (Fig. 1C). The potency of the two

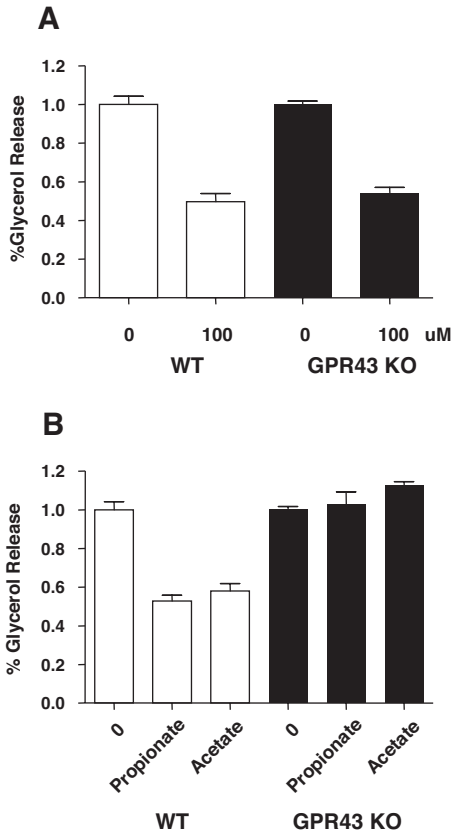

FIG. 2. GPR43 ligands, propionate and acetate, inhibit lipolysis in adipocytes through GPR43. A, Primary adipocytes from GPR43 KO mice and wild-type controls (WT) were treated with nicotinic acid, or with (B) propionate and acetate. In the absence of GPR43, both propionate and acetate failed to inhibit lipolysis.

ligands on primary cells is slightly less than in 3T3-L1 cells, with IC_{50} in the range of 300–500 μM. Although these values are much less potent than what were reported previously (8), they are much more consistent with the reported EC_{50} values of these ligands on receptor functional assays in FLIPR and GTPγS formats (5, 7). As a control for the abilities of the adipocytes to respond to other stimuli, the effects of insulin and isoproterenol were also tested. As expected, both 3T3-L1 and primary adipocytes increased lipolysis upon isoproterenol treatment, and insulin inhibited lipolysis from these cells (Fig. 1, B and D). The effects of acetate and propionate on isoproterenol-induced lipolysis were also performed. Although the fold (or window) of inhibition was smaller, acetate and propionate were able to inhibit isoproterenol-induced lipolysis similar to the data obtained in the absence of isoproterenol treatment shown in Fig. 1 (data not shown).

To test whether the inhibition of lipolysis by acetate and propionate is mediated by the activation of Gi-coupled GPCR, the effects of PTX (at 100 ng/ml) on glycerol release was tested. As shown in Fig. 1E, in 3T3-L1 adipocytes, acetate-induced lipolysis was inhibited by the addition of PTX, suggesting that the effects are mediated by Gi signaling pathway.

To test whether the observed effects of propionate and acetate on lipolysis is the result of activation of GPR43, we used primary adipocytes isolated from GPR43 KO mice. The GPR43 KO animals did not show any gross developmental defects under normal chow-fed conditions (data not shown). The adipocytes isolated from the GPR43 KO animals also responded similarly to adipocytes isolated from wild-type animals in their responses to nicotinic acid-induced inhibition of lipolysis via activation of GPR109 (Fig. 2A). This suggests that adipocytes from GPR43 KO animals are not grossly defective and can respond to Gi stimulation and suppress adipocyte lipolytic activities. In contrast to their response to nicotinic acid, the adipocytes isolated from GPR43 KO animals no longer respond to propionate and acetate, whereas both ligands are still effective on adipocytes isolated from wild-type littermates in suppression of lipolysis (Fig. 2B). These results strongly suggest that the observed anti-lipolytic activities of propionate and acetate are mediated through GPR43, and therefore, activation of GPR43 in adipocyte can result in inhibition of lipolysis.

Activation of GPR43 by acetate in vivo leads to suppression of plasma FFA levels

Plasma FFA plays a key role as an energy substrate and in regulating a number of metabolic processes. The FFA level in plasma is primarily determined by the lipolysis rate of triacylglycerols in adipocytes. To study the *in vivo* consequences of activating GPR43 on plasma FFA level, sodium acetate was injected ip into mice at 500 mg/kg, and plasma acetate and FFA levels were measured at different time points after injection. As shown in Fig. 3A, ip injection of sodium acetate leads to a significant rise in plasma acetate levels at 15 min after injection. This rise in acetate level is very transient; by 60 min, the plasma acetate levels have returned to baseline. The plasma FFA levels of the same animals were also measured. As shown in Fig. 3B, vehicle injection had no effect on plasma FFA levels during the time course of the experiment. Animals injected with acetate showed more than 30% reduction in plasma FFA levels, but only at 15 min after injection, which coincided

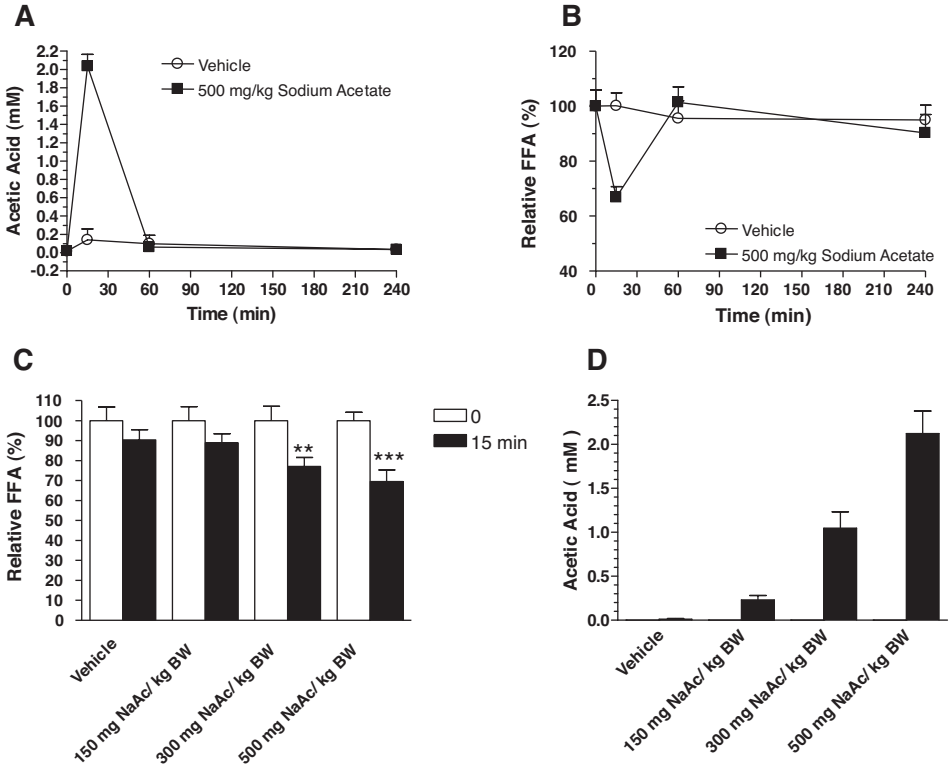

FIG. 3. Acetate treatment decrease plasma FFA levels *in vivo*. For A and B, sodium acetate (500 mg/kg) or vehicle (PBS) was ip injected into age-matched C57BL/6 mice after overnight starvation (n = 10). Plasma acetate levels (A) and FFA levels (B) were measured using the same plasma sample before and after injection. For C and D, sodium acetate at different dose or vehicle (PBS) was ip injected into age-matched C57BL/6 mice after overnight starvation (n = 10). Plasma FFA levels (C) and acetate levels (D) were measured using the same plasma sample before and 15 min after injection.

with the rise in plasma acetate levels (Fig. 3, A and B). This suggests that acetate is able to reduce plasma FFA levels *in vivo*. A dose response of acetate was carried out to determine the minimum concentration of acetate that is required to produce the effect on plasma FFA levels. As shown in Fig. 3, C and D, a minimum dose of between 150 and 300 mg/kg, which translates to plasma exposure of 0.23–1.05 mM acetate levels, is required to cause a reduction in plasma FFA levels.

To demonstrate whether the effect of acetate on plasma FFA level *in vivo* is the result of activation of GPR43, we once again used GPR43 KO animals. Both age-matched wild-type and GPR43 KO animals were treated with either vehicle or 500 mg/kg acetate, and plasma FFA levels were measured 15 min after injection. As shown in Fig. 4, A–D, acetate injection was able to lower plasma FFA levels in both male and female wild-type mice; however, these effects were completely abolished in GPR43 KO animals. The GPR43 KO animals responded similarly to wild-type animals in their responses to nicotinic acid-induced inhibition of plasma FFA levels via activation of GPR109, another Gi-coupled receptor expressed in adipocytes (Fig. 4E). In addition, the LPL activity of the adipocytes from the wild-type and GPR43 KO animals were also compared, and no differences were observed (Fig. 4F). These results suggest that the lack of response to acetate treatment in GPR43 KO animals is not the result of general defects in either the Gi signaling pathway or defects in total lipolysis in these animals. Therefore, these results strongly suggest that the observed *in vivo* effects of acetate are mediated through GPR43, and activation of GPR43 can lead to suppression of plasma FFA levels.

Given that dyslipidemia occurs predominantly in obesity, diabetes, and insulin-resistant conditions, the ability of GPR43 activation in a diseased state to regulate plasma FFA levels was also explored. Similar to wild-type conditions, GPR43 natural ligand, acetate, was able to suppress plasma FFA levels in *ob/ob* obese mice (Fig. 5, A and B). The body weights of the *ob/ob* animals were significantly higher than wild-type controls (Fig. 5C); at the age of about 8 wk used in this study, these animals typically have already developed glucose intolerance and insulin resistance. Therefore, these results suggest that GPR43 is still able to function in diseased conditions.

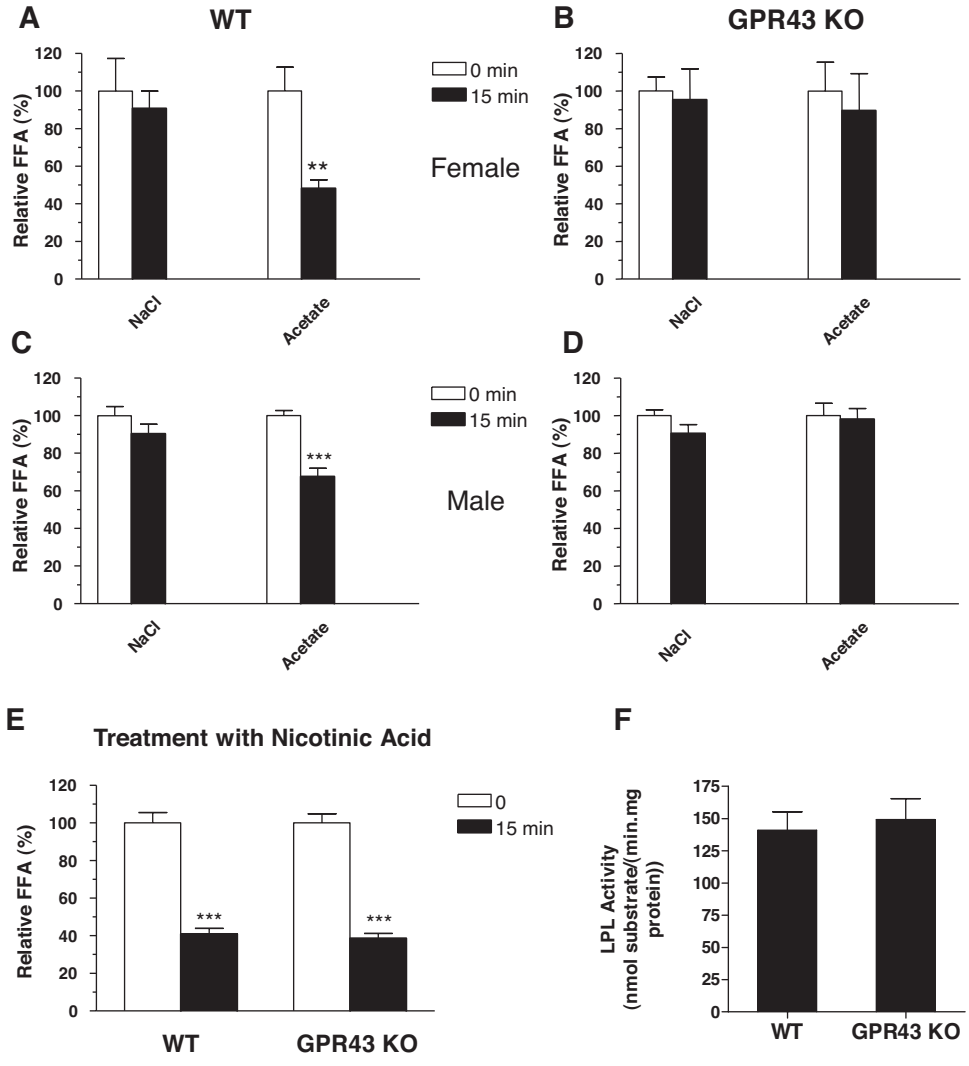

FIG. 4. The *in vivo* plasma FFA-lowering activities of acetate is mediated through activation of GPR43. A–D, Mice were divided into four age-matched groups: WT male, WT female, GPR43 KO male, and GPR43 KO female (n = 10). Sodium acetate, niacin, or vehicle (PBS) was ip injected at different concentrations after overnight starvation. Plasma FFA was measured before and 15 min after injection. E, Plasma FFA levels were measured before and 15 min after nicotinic acid injection in WT and GPR43 KO male mice (n = 10). F, LPL activities of adipocytes isolated from wild-type and GPR43 KO animals.

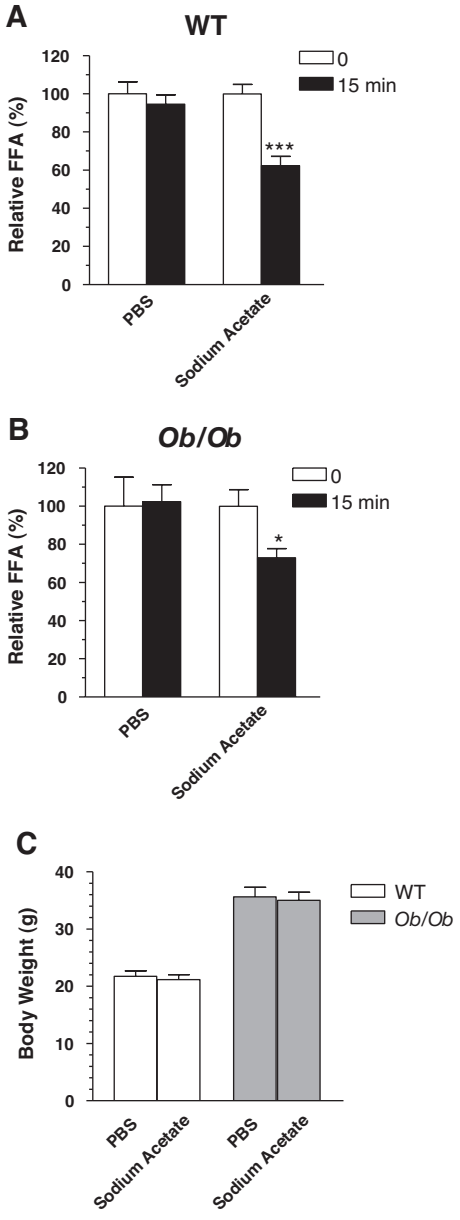

FIG. 5. Acetate treatment decreases plasma FFA levels *in vivo* in *ob/ob* model. Sodium acetate (500 mg/kg) or vehicle (PBS) was ip injected into approximately 8-wk-old, age-matched wild-type C57BL/6 or *ob/ob* mice after overnight starvation (n = 10). A and B, Plasma FFA levels were measured before and 15 min after injection. Results are expressed as percent change over PBS group; the actual FFA levels range from about 900–1600 μM at time 0 before acetate injection in both wild-type and *ob/ob* mice. C, Body weight measurements of wild-type and *ob/ob* mice.

GPR43 activation does not induce flushing side effect

Treatment with nicotinic acid results in flushing side effects due to activation of its receptor, GPR109A, in epidermal Langerhans cells via the release of prostaglandins (14, 15). Because GPR43 is also highly expressed in immune cells, we wanted to determine whether activation of GPR43 will cause the same flushing effect as nicotinic acid. The flushing side effect can be detected in the mouse model using LD flowmetry by measuring cutaneous vasodilation in the mouse ear

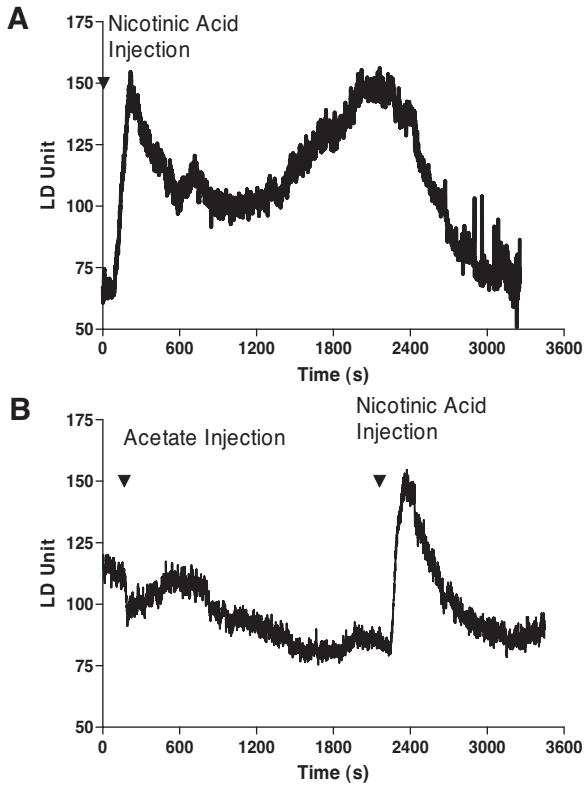

FIG. 6. Activation of GPR43 does not induce flushing response in the mouse external ear. Original recordings are shown of the LD flux signal in the ear artery. Nicotinic acid (A and B) or sodium acetate (B) were injected ip in doses of 200 and 500 mg/kg at the time points indicated by *arrows*. Shown are representative recordings of three experiments.

(14–16). Similar to these previous reports, bolus injection of nicotinic acid ip resulted in a transient increase in blood flow as detected by LD (Fig. 6A). The first peak was observed 3–4 min after administration and a second peak about 40 min after injection. In contrast, administration of acetate at 500 mg/kg, which was shown to reduce plasma FFA levels (Fig. 2), resulted in no LD, indicating no vasodilation within 30 min of treatment. The same animal that was injected with acetate was given a second injection of nicotinic acid 35 min after acetate injection. These animals still responded to nicotinic acid, and the same flushing effect could be observed (Fig. 6B). These results suggest that GPR43 activation does not induce a similar flushing side effect to one observed with nicotinic acid receptor GPR109A.

Discussion

In this report, we extend previous studies on the potential functions of GPR43 activation in adipocytes. We show that GPR43 natural ligands, acetate and propionate, can inhibit lipolysis in both *in vitro* differentiated 3T3-L1 adipocytes as well as in primary adipocytes isolated from mice (Fig. 1, A and C). Using adipocytes isolated from GPR43 KO animals, our results demonstrate that the anti-lipolytic activities of acetate and propionate are mediated through the activation of GPR43 (Fig. 2). Furthermore, we show that acetate can suppress plasma FFA levels *in vivo*. Once again using GPR43

KO animals, our results show that the reduction of plasma FFA by acetate is mediated through activation of GPR43 (Figs. 3 and 4). All of these results suggest that GPR43 is able to couple to the Gi pathway in adipocytes, and activation of GPR43 in adipocytes can lead to inhibition of lipolysis and suppression of plasma FFA levels.

The effects of GPR43 on adipocyte lipolysis and plasma FFA levels are very similar to what has been observed for the activation of another adipocyte-expressed Gi-coupled receptor, GPR109A, the receptor for nicotinic acid (17–19). Nicotinic acid has been used for the treatment of dyslipidemia for over 50 yr. The drug improves multiple cardiovascular risk factors, including elevation of high-density lipoprotein (HDL) and reduction of very low-density lipoprotein, low-density lipoprotein, lipoprotein(a), and triglycerides, that overall results in a reduction in mortality (20). Although the precise mechanism of action for nicotinic acid is unknown, GPR109A-mediated inhibition of lipolysis in adipocytes via activation of the Gi pathway resulting in a reduction in plasma FFA levels is postulated to play a central role in the improvement of plasma lipid parameters (21, 22). Given that GPR43 can also couple to the Gi signaling pathway in adipocytes and activation of GPR43 also results in the inhibition of lipolysis and reduction in plasma FFA, we speculate that activation of GPR43 has the potential utility in modulating plasma lipid profiles. Despite its great efficacy in improving plasma lipid parameters, nicotinic acid treatment results in a number of undesirable side effects, including flushing in the face and upper body and gastrointestinal upset. Recently, it was reported that in rodents, the activation of GPR109A in the epidermal Langerhans cells via the release of prostaglandins mediates the flushing side effect of nicotinic acid (14, 15). It is interesting to note that although GPR43 is also expressed in the immune cells, activation of GPR43 does not appear to induce the flushing effects that had been observed for nicotinic acid treatment, at least in a mouse model (Fig. 6). This suggests that targeting GPR43 may have improved side effects over nicotinic acid treatment as well.

Excessive chronic alcohol consumption is causally associated with more than 60 different medical conditions (23). However, moderate to low alcohol consumption has been associated with many beneficial effects; in particular, a link to increased plasma HDL levels and reduced rate of coronary heart disease have been reported (24, 25). A number of different compounds that have been extracted from various alcohols, for example, complex polyphenolic substances such as resveratrol and quercetin from red wine, have been shown to have protective effects against atherosclerosis (25). However, given the supraphysiological doses of nonalcoholic constituents that are required to observe these beneficial effects and the apparent health benefit that is not limited to any one form of alcohol, this may suggest that ethanol could directly affect the changes in the observed plasma lipid parameters. The primary fate of ethanol metabolism by the liver is the conversion and release of acetate into circulation. Plasma levels of acetate could increase up to 20-fold and into millimolar concentrations after alcohol ingestion (26, 27). It is interesting to speculate that perhaps the observed lipid effect of ethanol is, at least in part, mediated through its conversion to acetate and activation of GPR43. Given the observed beneficial effects of raising HDL associated with alcohol consumption, the similar effects of nicotinic acid receptor and GPR43 on adipocytes, and the proposed mechanism for HDL raising activities of nicotinic acid, the possible utility of GPR43 as a potential target for the treatment of dyslipidemia should be further explored in the future.

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