Original Paper

GLP-1/GLP-1R Signaling in Regulation of Adipocyte Differentiation and Lipogenesis

Jicui Chen^{a,b} Huichen Zhao^c Xiaoli Ma^c Yuchao Zhang^{a,c} Sumei Lu^d
Yangang Wang^e Chen Zong^a Dandan Qin^a Yuanmei Wang^f Yingfeng Yang^a
Xiangdong Wang^a Yuantao Liu^c

^aDepartment of Cell Biology, Shandong University School of Medicine, Jinan, ^bDepartment of Blood Transfusion of Qilu Hospital, Shandong University, Jinan, ^cDepartment of Endocrinology, Qingdao Municipal Hospital, Qingdao, ^dDepartment of Laboratory Medicine, Shandong Provincial Qianfoshan Hospital, Shandong University, Jinan, ^eDepartment of Endocrinology, Affiliated Hospital of Qingdao University, Qingdao, ^fDepartment of Nephrology, the Second Hospital of Shandong University, Jinan, China

Key Words

Liraglutide • 3T3-L1 preadipocytes • Adipogenesis • FASN

Abstract

Background/Aims: The aim of this study was to determine the direct role of liraglutide (LG) in adipogenesis and lipid metabolism. **Methods:** Lipid accumulation was evaluated by oil red O staining, quantitative real-time PCR (qPCR) was performed to determine glucagon-like peptide 1 receptor (GLP-1R), fatty acid synthase (FASN) and adipose triglyceride lipase (ATGL) expression in 3T3-L1 preadipocytes, differentiated adipocytes and in adipose tissues from mice. The effects of LG on 3T3-L1 adipogenesis and lipid metabolism were analyzed with qPCR, Western Blotting, oil red O staining, immunohistochemistry (IHC) and immunofluorescence (IF). All measurements were performed at least three times. **Results:** LG increased the expression of differentiation marker genes and lipid accumulation during preadipocyte differentiation. In differentiated adipocytes, LG decreased FASN expression, and simultaneously led to CREB phosphorylation and ERK1/2 activation which were abolished by a GLP-1R antagonist, exendin (9-39). LG induced-FASN down-regulation was partially reversed by PKA and ERK1/2 inhibitors. Consistent with above *in vitro* findings, LG treatment significantly reduced FASN expression in visceral adipose tissues of *ob/ob* mice, and reduced body weight gain. **Conclusion:** LG promotes preadipocytes differentiation, and inhibits FASN expression in adipocytes. LG induced down-regulation of FASN is at least partially mediated by PKA and MAPK signaling pathways.

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Introduction

Obesity, characterized by over accumulation of adipose tissue, is becoming a major health problem worldwide [1]. A body of evidence shows that obesity is closely associated

J. Chen and H. Zhao contributed equally to this work.

Dr. Yuantao Liu
and Dr. Xiangdong Wang,

Department of Endocrinology, Qingdao Municipal Hospital, 5 Donghai Street, Qingdao 266071, Shandong (China); Department of Cell Biology, Shandong University School of Medicine, Jinan, 250012, Shandong (China)
E-Mail sduliuyuantao@163.com / xdongw@sdu.edu.cn

with the development of insulin resistance and type 2 diabetes [2-4], cardiovascular disease [5], stone disease [6], gastrointestinal (GI) diseases, gall bladder disease, hypertension, osteoarthritis and sleep apnea [7-9]. In addition, dyslipidemia is usually present in obese patients [10, 11].

Fatty acid synthase (FASN), a 270kDa cytosolic dimeric enzyme, is a key enzyme in *de novo* lipogenesis and responsible for palmitate synthesis, catalyzing the conversion of malonyl CoA into palmitate [12]. It was reported that FASN plays a role in regulation of food intake, body weight and obesity [13, 14]. Recent studies showed that FASN expression is up-regulated in a variety of cancers and is strongly correlated with a poor prognosis [15, 16]. FASN expression can be induced by insulin, thyroid hormone, carbohydrate ingestion and glucocorticoid while down-regulated by unsaturated fatty acids and glucagon [17]. Our previous study showed that PKA and MAPK signaling pathways are involved in regulation of FASN expression [18].

Adipose triglyceride lipase (ATGL), also known as patatin like phospholipase domain containing 2 (PNPLA2), is responsible for the initial step of lipolysis, converting triacylglycerols (TGs) to diacylglycerols (DGs) [19]. ATGL needs to interact with its co-activator protein, comparative gene identification-58 (CGI-58) for full hydrolytic activity [20]. Previous studies showed that ATGL expression is induced by PPAR γ agonists, fasting and glucocorticoids, while food intake, insulin and mTOR complex 1-dependent signaling suppress its expression [21, 22]. It was shown that AMP-activated kinase (AMPK) may play a role in regulation of ATGL expression [23, 24].

Glucagon-like peptide-1 (GLP-1), a peptide released from the intestinal L cells and the brain [25, 26], possesses multiple biological activities. GLP-1 stimulates insulin biosynthesis and secretion [27], improves insulin sensitivity [28, 29], inhibits glucagon secretion [30, 31]. Moreover, GLP-1 shows an effect on weight loss. The proposed mechanisms include reducing appetite and food intake [32-34], slowing gastric emptying [35]. Liraglutide as a GLP-1 receptor agonist have been approved by FDA to be used for treatment of obesity. However, it remains elusive about the direct effects of GLP-1 receptor agonist on FASN and lipid metabolism.

In this study, we aimed to explore the direct effects of GLP-1 on adipogenesis, lipogenesis and lipolysis in 3T3-L1 adipocytes and *ob/ob* mice. To explore the possible mechanisms underlying the effects of liraglutide, we will focus on its impacts on FASN expression and signaling pathways involved.

Materials and Methods

Reagents

DMEM cell culture medium was from Macgene (Beijing, China). Fetal bovine serum (FBS) and bovine serum (BS) were from GIBCO (Invitrogen, CA). Dexamethasone, 3-isobutyl-1-methylxanthine (IBMX), insulin, PD98059 and exendin(9-39) were purchased from Sigma (St. Louis, MO). H89 was obtained from Selleckchem (Houston, USA). Albumin from bovine serum was from Sangon Biotech (Shanghai, China). Liraglutide was from Novo Nordisk. Anti-ACTIVE ® MAPK antibody (V8031, 1:2000) was from Promega (Madison, WI). Anti-CREB (phospho-Ser133) (#A7053, 1:1000) was obtained from Anbo Biotechnology (Jinan, China). Anti-FASN (10624-2-AP, 1:1000), anti-ATGL (55190-1-AP, 1:1000) and anti-PPAR γ (16643-1-AP, 1:1000) antibodies were from Proteintech Group (Wuhan, China). Anti-GLP1R (ab39072, 1:1000) and anti-FABP4 antibody (ab92501, 1:1000) were Abcam product (Cambridge, UK). Anti-beta Actin (TA-09, 1:1000) was purchased from Zhongshan Goldenbridge Biotechnology (Beijing, China). Secondary antibodies conjugated to HRP (Zhongshan Golden Bridge Biotechnology, Beijing, China) were used at 1:5000 for western blotting. The UltraSYBR Mixture was purchased from ComWin Biotech (Beijing, China). PCR primers used in this study were synthesized in Genomics Institute of Sangon Biotech in Shanghai.

Cell culture and treatment

Culture, differentiation of 3T3-L1 cells and oil red O staining for lipid accumulation were conducted as previously described [18, 36]. To determine the effect of LG on adipogenesis, 3T3-L1 cells were treated

with or without LG at different concentrations along with cell differentiation until day 10, then harvest cells for western blotting. For FASN detection, when cells full differentiated, adipocytes were serum-starved in DMEM containing 0.5% BSA overnight before stimulation. Then, for dose-response of liraglutide (LG) on FASN, 3T3-L1 differentiated adipocytes were stimulated with LG at different concentration (0, 1, 10, 100, 1000nM) for 24 hours. For time effect analysis, mature adipocytes were treated by LG (100nM) for various lengths of time (0, 6, 12, 24, 48 h). When indicated, adipocytes were pretreated with 10nM exendin (9-39), 20μM H89 or 20μM PD98059 or vehicle for 1 hour before stimulation with 100nM LG for 24 hours.

Animals studies

Six-week old male *ob/ob* mice were purchased from the Beijing HFK Bioscience CO.,LTD. Animals were cared for in accordance with "Principles of Laboratory Animal Care" established by the National Institutes of Health and animal experiments were approved by the "Animal Care and Use Committee" at Shandong University. Mice were housed in laboratory cages in a temperature-controlled room under a 12 hr light-dark cycle with free access to water and high-fat diet (HFD) containing 20% fat [37-39]. Fasting blood was detected weekly using a glucometer after 7 h of fasting at 14:00 pm with food withdrawn at 7:00 am until all mice were hyperglycemic. Then, mice were divided into 2 groups randomly, and injected subcutaneously in the abdominal region with saline (NS) or LG (300ug/kg) daily for 4 weeks. Body weight was measured daily before injection during experiments. Fasting blood was measured at the onset and termination of the study. The animals were sacrificed after deep anesthesia with ether. Immediately prior to sacrifice, blood was collected to 2ml eppendorf tube through the removable eyeball and placed at room temperature for 1 hour, then centrifuged at 3000rpm for 10 min at 4°C. The obtained plasma was snap frozen in liquid nitrogen and stored at -80°C, then sent to department of laboratory medicine of Shandong Provincial Qianfoshan Hospital affiliated to Shandong University to measure serum blood glucose, triglyceride (TG), cholesterol (CHO), low-density lipoprotein-C (LDL-C) and free fatty acids (FFA). Visceral adipose tissues obtained for RNA and protein extraction were quick frozen in liquid nitrogen and stored at -80°C. Tissues for immunohistochemistry (IHC) and immunofluorescence (IF) were immediately fixed in 4% paraformaldehyde and then sent to Wuhan Goodbio Technology CO., LTD to embed, slice and stain. Paraffin sections for IHC were stained with HE, and frozen sections for IF were stained with anti-FASN or rabbit IgG antibodies using standard protocols.

RNA extraction and real-time PCR

Total RNA isolation from cultured cells and animal adipose tissue, reverse transcription PCR and quantitative real-time PCR (qPCR) were conducted as previously described. Relative gene expression was calculated by the $2^{-\Delta\Delta C_q}$ method [18, 40]. All measurements were performed at least for three times. qPCR primers were as follows:

18S rRNA-F: CGCGTTCTATTTTGTGGT;
18S rRNA-R: AGTCGGCATCGTTTATGGTC;
FABP4-F: AAGGTGAAGAGCATCATAACCCT;
FABP4-R: TCACGCCTTTCATAACACATTCC;
PPAR γ -F: TGGTGACTTTATGGAGCCTAA;
PPAR γ -R: GGCGAACAGCTGAGAGGACTCTG;
GLP1R-F: TGCAACCGGACCTTTGATGA;
GLP1R-R: TTGTAGCACACTACTGGCCC;
ATGL-F: TCCGTGGCTGTCTACTAAAGA;
ATGL-R: TGGGATATGATGACGTTCTCTCC;
FASN-F: GGAGGTGGTGATAGCCGGTAT;
FASN-R: TGGGTAATCCATAGAGCCCAG.

Western Blotting

After drug treatment, cells were washed by cold PBS containing sodium vanadate and harvested for protein extraction. Cells and about 100mg animal visceral adipose tissue were lysed in RIPA buffer (50 mM Tris pH 7.4, 150 mM NaCl, 1% tritonX-100, 1% sodium deoxycholate, 0.1% SDS, Beyotime Biotechnology) containing protease and phosphatase inhibitors, and the protein concentration was measured using the BCA Protein Assay Kit (Sangon Biotech). Samples were subjected to electrophoresis (SDS-PAGE) with equal

amounts of protein (at least 30µg, respectively). ACTIVE® MAPK, CREB (phospho-Ser133), FASN, ATGL, PPAR γ , GLP1R and secondary antibodies conjugated to HRP from ZSGB-BIO were used for western blotting. All measurements were performed in triplicate. Relative densitometry was measured by Image J software.

Statistical analysis

All data are presented as mean $\pm$ SEM. Analyses were performed using Graph Pad Prism 5.0 software. One-way analysis of variance (ANOVA) was used, followed by the Student-Newman-Keuls tests. A value of $P < 0.05$ was considered statistically significant.

Results

LG promoted 3T3-L1 preadipocytes differentiation

GLP-1R was shown to be expressed in many tissues including the adipose tissue [41, 42]. In this study, we first examined the expression profile of GLP-1R during 3T3-L1 preadipocyte differentiation with PPAR γ and FABP4 as differentiation makers. Adipocyte differentiation was also evaluated by oil-red O staining (Fig. 1A). In accordance with previous results, we confirmed that GLP-1R was expressed both in preadipocytes and mature adipocytes. Interestingly, GLP-1R expression in mRNA level was decreased along with the differentiation (Fig. 1B), while the protein expression of GLP-1R increased in the early stage of differentiation and then decreased eventually (Fig. 1C, D, E, F).

To determine the role of GLP-1 in adipocyte differentiation, 3T3-L1 preadipocytes were induced with MDI (Dexamethasone, IBMX, insulin) induction medium in the absence or presence of liraglutide (LG), a GLP-1 receptor agonist. Results showed that LG enhanced PPAR γ and FABP4 expression and increased lipid accumulation in a dose-dependent manner (Fig. 2A and B).

Fig. 1. GLP-1R expression in 3T3-L1 adipogenesis. (A) Accumulation of lipid droplets was observed with oil-red O staining by light microscopy. Magnification 100 $\times$. (B) The mRNA expression of GLP-1R was normalized to the levels of 18S rRNA, black circles = GLP-1R, black squares = PPAR γ , black triangle = FABP4. Results are shown as mean $\pm$ SEM of three independent experiments. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs. D0. (C) Representative GLP-1R protein expression during adipogenesis. (D, E, F) Densitometric analyses of the Western blots, the data show the means of three independent experiments, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs. D0.

Fig. 2. Effects of LG on adipogenesis and FASN expression. (A) Oil-red O staining at Day10 with different dose of LG treatment. Magnification 100×. (B) PPAR γ , FABP4 and GLP-1R protein expression in response to LG stimulation during adipogenesis. (C) Protein expression of FASN, ATGL and downstream molecules in response to LG stimulation at different concentrations. (D, E) mRNA expression of FASN and ATGL in response to LG stimulation at different concentrations. Results are shown as mean $\pm$ SEM of three independent experiments. $**P < 0.01$, $***P < 0.001$, vs. control. (F) FASN mRNA expression under LG stimulation at different time points. ns = no significance, $**P < 0.01$, $***P < 0.001$, vs. control. (G) Protein expression

of FASN, ATGL and downstream molecules in response to LG stimulation at different time points. (H) Effect of exendin (9-39) on LG induced FASN expression. Representative results of Western blots (n=3).

LG reduced FASN expression via GLP-1R in mature adipocytes

To explore the role of LG in lipid metabolism in mature adipocytes, we examined its effect on the expression of FASN, a key enzyme in the *de novo* lipogenesis, and ATGL, an enzyme for lipolysis. Differentiated 3T3-L1 adipocytes were treated with LG as indicated. As is shown, LG treatment significantly reduced FASN expression in both mRNA and protein levels in dose- and time course dependent manners (Fig. 2C, D, F and G), whereas LG showed no obvious effect on ATGL expression (Fig. 2C, E and G). In order to investigate whether the effect of LG was mediated by GLP-1R, we pretreated adipocytes with exendin (9-39), a specific blocker for GLP-1R. As expected, LG-induced FASN downregulation was attenuated by exendin (9-39) (Fig. 2H).

LG reduced FASN expression in adipocytes through activation of PKA and MAPK

To determine the downstream signaling pathways that may mediate the effect of LG, we examined its effects on activation of pCREB and ERK, both have been implicated in adipocytic differentiation and lipid metabolism. As shown in Figure 2C and G, LG treatment induced CREB and ERK phosphorylation in dose-dependent manner and time-dependent manners.

To further explore whether LG reduced FASN expression in adipocytes through activation of PKA and MAPK, we conducted additional experiments using specific inhibitors for PKA and ERK.

Fig. 3. Effects of PKA and MAPK inhibitors on LG induced FASN expression in 3T3-L1 adipocytes. Differentiated 3T3-L1 adipocytes were pre-treated with either 20 μ M H89 or 20 μ M PD98059 or vehicle for 1 hour, followed by treatment with 100nM LG for 24 hours. Levels of FASN, pCREB and pERK were detected by Western Blotting. (A, D) Representative results of Western blotting. (B, E) Densitometric analyses of the Western blots, the data show the means of three independent experiments, $**P < 0.01$, $***P < 0.001$ vs. Control. (C, F) Representative results of oil red O staining.

As shown in Fig. 3A, H89, a specific inhibitor for PKA, prevented LG induced FASN down-regulation and CREB activation, relative protein expression were shown in Fig. 3B. PD98059, a specific ERK inhibitor, blocked ERK phosphorylation and significantly prevented LG induced-FASN down-regulation (Fig. 3D and E). However, no obvious changes were observed in lipid droplets measured by oil red O staining (Fig. 3C and F).

LG treatment prevented mice body weight gain and adiposity

After 4 weeks, LG treated mice showed less weight gain when compared to control mice injected with saline (Fig. 4A) (7.47 ± 0.52 vs. 2.9 ± 1.25 g, $P < 0.05$). The body weight gain showed no difference in the first 3 weeks between the two groups until the 4th week (Fig. 4B). Meanwhile, the visceral fat weight and the ratio of visceral fat weight to body weight were also markedly decreased in LG injection mice when compared to control mice (Fig. 4C and D). In addition, the average size of adipocytes in the perirenal and epididymal adipose

Fig. 4. Influence of LG on body weight and adiposity in ob/ob mice. Ob/ob mice were given injection subcutaneously with saline (NS) or LG (300ug/kg) daily for 4 weeks. Body weight was measured daily before injection during experiments. Perirenal and epididymal adipose tissues were obtained for HE staining, mRNA and protein analyses (n=3 per group). (A) Body weight gain at the end of the 4-week. (B) Body weight change over 4-weeks, black circles = NS group, black squares = LG group. (C) The weight of visceral fat pads, and (D) the ratio of visceral fat weight to body weight in saline and LG treated mice. Results are presented as mean $\pm$ SEM. * $P < 0.05$, ** $P < 0.01$ vs. NS group. (E) Representative results of HE staining of perirenal and epididymal adipose tissues from saline and LG treated mice. Magnification, 100 $\times$. (F) Quantification results of HE staining. ** $P < 0.01$, *** $P < 0.001$ vs. NS.

Table 1. Serum biochemical indexes in NS and LG groups. (Glu: blood glucose; TG: triglyceride; CHO: cholesterol; FFA: free fatty acids; LDL-C: low-density lipoprotein-C). All data are expressed as the mean $\pm$ SEM. * $P < 0.05$, vs. NS. (n=3)

Indexes (mmol/L)	NS	LG
Glu	10.21 $\pm$ 0.19	7.95 $\pm$ 0.79 *
TG	0.83 $\pm$ 0.07	0.65 $\pm$ 0.06
CHO	5.67 $\pm$ 0.58	3.15 $\pm$ 0.05 *
FFA	0.79 $\pm$ 0.06	0.51 $\pm$ 0.07 *
LDL-C	0.69 $\pm$ 0.13	0.33 $\pm$ 0.01

tissues of LG treated mice was smaller when compared to control mice (Fig. 4E). Fig. 4F is semi-quantification analysis of Fig. 4E by Image J software.

LG attenuated dyslipidemia in obese mice

Since visceral fat accumulation in obese mice is generally accompanied by diabetes and dyslipidemia, we next detected blood glucose and several serum lipid biochemical indexes. Compared with control mice, LG treated mice had reduced levels of fasting blood glucose, serum cholesterol (CHO) and free fatty acids (FFA) (Table 1).

Fig. 5. Effect of LG treatment on FASN expression in mice. (A) Representative results of FASN expression in visceral adipose tissues in saline or LG treatment mice. Frozen sections of visceral adipose tissues were immuno-stained with FASN primary antibody and secondary antibody labeled with FITC, blue = DAPI, green = FASN. FASN was showed in green color in visceral adipose tissues, normal rabbit IgG (sc-2027) was used as primary antibody for control samples. The magnification is 200×. FASN mRNA expression in (B) perirenal fat tissues and (C) epididymal fat tissues. * $P < 0.05$, ** $P < 0.01$ vs. NS group. $n = 3$ per group. The protein levels of FASN in (D) perirenal fat tissues and (E) epididymal fat tissues. $n = 3$ per group. (F, G) Densitometric analyses of the Western blots, the data show the means of three mice in one group, ns = no significance, * $P < 0.05$, *** $P < 0.001$ vs. NS.

LG treatment significantly reduced FASN expression in ob/ob mice

FASN expression in perirenal and epididymal adipose tissues was analyzed by immunofluorescence staining. Results showed that FASN expression was apparently reduced in LG treated mice (Fig. 5A). In addition, we also detected FASN mRNA and protein expression by quantitative RT-PCR (Fig. 5B and C) and Western blotting (Fig. 5D and E). Consistent with cell experiments, LG treatment significantly reduced FASN expression both in perirenal and epididymal adipose tissues when compared to control mice (Fig. 5B-G).

Discussion

Obesity, a condition of body characterized by over accumulation of fat, is associated with multiple metabolic disorders, including dyslipidemia, hyperinsulinemia and impaired glucose metabolism. Obese patients often accompanied by decreased vascular flexibility, increased blood lipids and reduced insulin sensitivity. These disorders contribute to the development of diabetes mellitus, hypertension and cardiovascular disease [3, 5, 8, 11]. According to the viewpoint of energy balance, obesity develops when energy intake by an individual exceeds the rate of energy expenditure. At cellular level, obesity can be considered as a hypertrophic disease resulted from an increase in the number or size of individual adipocyte. The number of adipocytes in adults is usually invariable, therefore, adult obesity often present as the increase of adipocytes size, that is, adipogenesis.

GLP-1, an incretin hormone, is predominantly produced by L cells of the distal small intestine in response to food intake [25]. It is generally believed that the action of GLP-1 is mediated by its specific receptor (GLP-1R). GLP-1R is showed to be expressed in many tissues, including pancreas, GI system, heart, liver, kidney, muscle, adipose tissue as well as the central and peripheral nervous systems [41, 42]. To explore the possible roles of GLP-1/GLP-1R in adipogenesis and lipid metabolism, we first examined the expression profile of GLP-1R in 3T3-L1 adipocytes. Consistent with previous observations [43, 44], we confirmed the presence of GLP-1R in both preadipocytes and differentiated adipocytes. Interestingly, we found that GLP-1R expression in both mRNA and protein levels decrease along with the differentiation, which may imply that GLP-1/GLP-1R signaling could play more important roles in undifferentiated adipocytes.

Next, we determined whether GLP-1 has direct effect on adipocyte differentiation. Previous studies have revealed that adipogenesis process is orchestrated by numerous moleculars, including the products of adipocyte-specific genes *C/EBPs* and *PPARγ*. [45, 46] These transcription factors are the primary drivers of differentiation [47]. Liraglutide (LG) is a GLP-1 analog with 97% amino-acid sequence homology to native GLP-1. In this study, we demonstrated that LG treatment significantly promoted 3T3-L1 preadipocyte differentiation in a dose dependent manner as evidenced by increased *PPARγ* and *FABP4* expression and lipid accumulation. Further experiments showed that these effects of LG were abolished by specific GLP-1 receptor blocker, suggesting that these effects of LG are mediated by GLP-1 receptor. Our results are generally consistent with previous studies. However, there is a study showing that GLP-1 promoted the proliferation of human bone marrow-derived mesenchymal stem cells (hMSCs), while prevented the differentiation of these cells into adipocytic lineage [48]. It is possible that GLP-1 may have distinct effects in different stages of adipocyte differentiation and maturation. Recent studies showed that obese individuals have reduced differentiation capability of their preadipocytes, or so-called "impaired adipose tissue expandability", which may contribute to metabolic complications and insulin resistance due to ectopic deposition of excess lipid in non-adipose tissues like skeletal muscle or liver [49-51]. From this viewpoint, our findings may partially explain the beneficial effects of GLP-1 on insulin resistance and non-alcoholic fatty liver disease.

To determine the role of GLP-1 in lipid metabolism in mature adipocytes, we examined the effects of LG on the expression of *FASN* and *ATGL*. *FASN* is the key enzyme in the *de novo* lipogenesis, whereas *ATGL* is an important enzyme for lipolysis. In consistency with previous studies [11, 41, 52, 53], we found that LG treatment significantly reduced *FASN* expression in both protein and mRNA levels, but had no obvious effect on *ATGL* expression. Additional experiments showed that LG-induced down-regulation of *FASN* was accompanied with increased phosphorylation of pCREB and ERK, and specific inhibitors for PKA and ERK partially prevented LG induced *FASN* down-regulation. These findings indicate that GLP-1 negatively regulates *FASN* expression, which is at least partially mediated by PKA and MAPK pathways.

To substantiate our findings *in vitro*, we further conducted animal experiments with six-week old male *ob/ob* mice. Consistent with previous studies [33-35], our results showed

that LG treatment significantly decreased the weight gain of *ob/ob* mice after 4 weeks. Meanwhile, the visceral fat weight and the ratio of visceral fat weight to body weight were also markedly decreased in LG treated mice when compared to controls. Furthermore, the average size of adipocytes in visceral adipose tissues was markedly smaller in LG treated mice. We examined FASN expression in the perirenal and epididymal adipose tissues of *ob/ob* mice. Consistent with our findings in cell experiments, LG treatment significantly reduced FASN expression in both mRNA and protein levels. We suppose that the reduced hypertrophy of adipocytes in LG treated mice may be partially due to the inhibition of FASN expression, which may also partially account for the reduced visceral fat weight.

As we found, there was no change in the expression of ATGL *in vitro* experiments. Thus, we did not check its expression *in vivo* study.

Taken together, in this study we demonstrated that GLP-1 can directly promote preadipocyte differentiation via a GLP-1 receptor dependent mechanism. In addition, GLP-1 may inhibit lipogenesis in mature adipocytes by down-regulating FASN expression, which is at least partially mediated by PKA and MAPK pathways. Our findings reveal a direct link between GLP-1, obesity and obesity related dyslipidemia.

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Disclosure Statement

The authors state no conflict of interest.

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