Lipid and glucose metabolism are adversely affected by diabetes, a disease characterized by pancreatic β-cell dysfunction. To clarify the role of lipids in insulin secretion, we generated mice with β-cell-specific overexpression (βLPL-TG) or inactivation (βLPL-KO) of lipoprotein lipase (LPL), a physiologic provider of fatty acids. LPL enzyme activity and triglyceride content were increased in βLPL-TG islets; decreased LPL enzyme activity in βLPL-KO islets did not affect islet triglyceride content. Surprisingly, both βLPL-TG and βLPL-KO mice were strikingly hyperglycemic during glucose tolerance testing. Impaired glucose tolerance in βLPL-KO mice was present at one month of age, whereas βLPL-TG mice did not develop defective glucose homeostasis until approximately five months of age. Glucose-simulated insulin secretion was impaired in islets isolated from both mouse models. Glucose oxidation, critical for ATP production and triggering of insulin secretion mediated by the ATP-sensitive potassium (KATP) channel, was decreased in βLPL-TG islets but increased in βLPL-KO islets. Islet ATP content was not decreased in either model. Insulin secretion was defective in both βLPL-TG and βLPL-KO islets under conditions causing calcium-dependent insulin secretion independent of the KATP channel. These results show that β-cell-derived LPL has two physiologically relevant effects in islets, the inverse regulation of glucose metabolism and the independent mediation of insulin secretion through effects distal to membrane depolarization.

Normal secretion of insulin, the anabolic hormone central to glucose metabolism, is necessary for normal lipid metabolism. The converse may also be true; normal lipid metabolism may be necessary for normal insulin secretion. Acute exposure to fatty acids potentiates glucose-stimulated insulin secretion, whereas chronic exposure causes a muted insulin secretory response to glucose (1, 2). Pharmacological depletion of plasma fatty acids after a prolonged fast inhibits glucose-stimulated insulin secretion (3–5). The excessive delivery of lipids to the β-cell is thought to contribute to insulin secretory failure and the development of type 2 diabetes, part of a general process commonly called lipotoxicity (6).

How lipids affect insulin secretion is unknown. In most tissues, glucose and fatty acids compete for respiration. Increased provision of lipids might be expected to decrease insulin secretion by decreasing pyruvate dehydrogenase activity and glucose oxidation, known as the Randle effect (7). Reports addressing this issue are conflicting (8, 9), but it is likely that any effects on pyruvate dehydrogenase are blunted because of the high activity of pyruvate carboxylase in islets, which ultimately prevents effects on glucose oxidation by preserving cytoplasmic pyruvate (10). Fatty acids have been postulated to interfere with insulin secretion by disrupting normal mitochondrial pyruvate metabolism (11), inducing apoptosis (12), and by depleting ATP levels through the induction of uncoupling protein-2 (13,14). Fatty acids have been postulated to promote insulin secretion through the effects of long chain acyl-CoA molecules on a variety of potential targets (15), and more recently, through direct effects on the G-protein-coupled receptor GPR40 (16).

The source of lipids that modulate insulin secretion is also unknown. Fatty acids delivered to β-cell regulatory pools could be derived from circulating non-esterified fatty acids (mostly bound to albumin), intracellular triglycerides (the substrate for the intracellular enzyme hormone-sensitive lipase) (14), or circulating triglycerides traveling in lipoproteins. The relative contribution of each of these pools in β-cells to insulin secretion is unknown. In other tissues, hydrolysis of circulating lipoprotein-associated triglycerides is the principal source of fatty acids destined for metabolism (17). This process is accomplished by the extracellular enzyme lipoprotein lipase (LPL).1 LPL is regulated by hormones and nutrients in a tissue-specific manner (18). In adipose tissue, where fatty acids are stored, LPL activity is induced by feeding and suppressed by fasting. In muscle, which relies on fatty acids for energy production in the postabsorptive state, LPL activity is induced by fasting and suppressed by feeding. Insulin stimulates LPL in adipocytes and adipose tissue (19) but may inhibit LPL in heart (20). We have shown that LPL is expressed in human and rodent islets (21) where its regulation resembles that of adipocytes, because β-cell LPL expression is induced by glucose and insulin (22).

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1 The abbreviations used are: LPL, lipoprotein lipase; βLPL-KO, β-cell lipoprotein lipase knockout; βLPL-TG, β-cell lipoprotein lipase transgenic; HA, hemagglutinin; BSA, bovine serum albumin; KO, knock-out; SNARE, soluble N-ethylmaleimide-sensitive factor attachment protein receptors; tSNARE, target membrane-associated SNARE; vSNARE, vesicle-associated SNARE; TG, transgenic; WT, wild-type.
Here we describe two novel mouse models generated to define how LPL, a physiologic provider of fatty acids, affects insulin secretion. Both overexpression and inactivation of \( \beta \)-cell LPL activity cause diabetes phenotypes despite opposite effects on islet glucose metabolism. Both also cause defects in the amplifying pathway of insulin secretion, suggesting that optimal \( \beta \)-cell function requires maintenance of a discrete range of triglyceride-derived fatty acids by LPL.

**EXPERIMENTAL PROCEDURES**

**Animals**—The Washington University Animal Studies Committee approved these studies. Mice were housed in a specific pathogen-free barrier facility with unrestricted access to water and standard mouse chow containing 6% fat.

For mice with \( \beta \)-cell overexpression of LPL (\( \beta \)-PL-TG), a human LPL cDNA engineered to encode a hemagglutinin (HA) tag at the carboxyl terminus of the protein was inserted at the EcoRI site of the vector pRIP I (a gift from Dr. Bess Marshall), which contains an intron and polyadenylation signal and is known to direct expression of transgenes in mouse \( \beta \)-cells (23). The recombinant plasmid was sequenced traditionally treated with SacI and XhoI to liberate the LPL transgene and then the fragment was separated from vector DNA, and C57BL/6 x CBA hybrids (bred in the facility) were injected at the Washington University Mouse Core. Transgenic animals, identified by PCR genotyping using human LPL/HA-specific primers, were born in expected Mendelian frequencies, and all experiments were performed with littersmates.

For mice with \( \beta \)-cell-specific inactivation of LPL (\( \beta \)-PL-KO), Ins2Cre mice (The Jackson Laboratory, number 003573) were crossed with mice carrying LPL alleles flanked by loxP recombination sites (LPL\(^{lox}\)lox) (24). First generation animals homozygous for the RIP-Cre gene and bearing one “floxed” LPL allele (LPL\(^{loxlox}\) Cre\(^{+}\)) were crossed with LPL\(^{lox}\)lox animals to generate \( \beta \)-cell LPL-deficient (LPL\(^{loxlox}\) Cre\(^{+}\)) and \( \beta \)-cell LPL wild-type (LPL\(^{lox}\)lox Cre\(^{+}\)) littersmates that were used for experiments. The following primers (schematically represented in Fig. 2) were used to document LPL gene rearrangement: Primer A, 5′-GTA GGT TGT GAA TGG TCA TTT GTC AGT TCC-3′; Primer B, 5′-TTT CCA CTC CAG AGC TGT TTA GTG AGC TGG-3′; and Primer C, 5′-CCT AGT CTT CTC TAG GCA GAG AGC ACC AGA-3′. Amplification of non-rearranged DNA by primers A and B yields a product of \( \Delta 700 \) bp, whereas the amplification of appropriately rearranged DNA with primers A and C yields a product of \( \Delta 400 \) bp.

**Islet Isolation**—Islets were isolated by collagenase digestion and Ficoll step density gradient separation and then selected with a micropipette. Islets were solubilized in a buffer composed of 100 mM Tris-HCl (pH 8.5), 10 mM MgCl\(_2\), 80 mM sucrose, 50 \( \mu \)g/ml heparin, and 2 mg/ml deoxycholate. Activity was assayed as the release of radiolabeled oleate from an emulsion containing glycerol tri[1-14C]oleate (Amersham Biosciences).

Serum glucose, cholesterol, triglyceride, and non-esterified fatty acids were measured using reagents from Sigma. Islet triglycerides were determined after extraction of lipids with 2:1 (v/v) chloroform and methanol followed by sonication of the extract in reagent buffer using a Branson 250-probe-tip Sonifier. Serum insulin was assayed by enzymometric sandwich assay (Nichols Institute Diagnostics, San Juan Capistrano, CA). The assay was performed in triplicate, and the results are expressed as the mean \( \pm \) S.E. Statistical differences among means were determined by one- or two-way analysis of variance with appropriate post-hoc tests. Significance levels are described in the individual figure legends.

**RESULTS**

**Generation of \( \beta \)-PL-TG and \( \beta \)-PL-KO Mice**—For \( \beta \)-PL-TG mice, two independent founders carrying the transgene encoding an HA-tagged LPL molecule, shown schematically in Fig. 1A, were characterized and found to share the same phenotype. An HA-tagged protein of the predicted size was detected in islets from \( \beta \)-PL-TG animals but not in control islets (Fig. 1B). Certain regions of the brain, such as the hypothalamus, transiently activate the insulin promoter during embryogenesis (28). No HA-tagged LPL was detectable in brain extracts from \( \beta \)-PL-TG or control mice (Fig. 1B), and there was no difference in brain LPL enzyme activity between genotypes (data not shown). Compared with non-transgenic islets, \( \beta \)-PL-TG islets exhibited three-fold more LPL activity (Fig. 1C) in the presence of 3 mM glucose (\( \rho = 0.0019 \)) and nearly five-fold more LPL activity in the presence of 20 mM glucose (\( \rho = 0.0004 \)). Islet triglyceride content was modestly but significantly increased in the transgenic animals (Fig. 1D). Isolated islets in culture respond to elevated glucose concentrations by increasing LPL activity (22). The increased intracellular triglyceride accumulation (Fig. 1D) suggests that the increased LPL activity measured in our in vitro assay (Fig. 1C) leads to increased fatty acid flux and subsequent metabolic adaptations in vivo.

For \( \beta \)-PL-KO mice, the presence of the Cre recombinase in \( \beta \)-cells was predicted to remove exon 1 of the LPL gene (Fig. 2A). PCR reactions, including Primers A, B, and C as shown in Fig. 2A, showed the expected rearrangement of the LPL gene (as indicated by the presence of a 400 bp band) in islet DNA from Cre\(^{+}\) mice (Fig. 2B). Deletion of the 700-bp wild-type band in the KO lane is expected, as Cre is driven by a \( \beta \)-cell-specific promoter, and DNA from non-\( \beta \)-cells in islets should not be rearranged. That the conditional rearrangement of the LPL gene occurred only in the \( \beta \)-cell was shown by the presence of the wild-type product and the absence of the rearranged product in DNA from the following tissues of RIP-Cre\(^{+}\) mice: brain, heart, adipose tissue, spleen, and liver (data not shown).
LPL enzyme activity (Fig. 2C) was ~40% lower in βLPL-KO as compared with control islets in the presence of 20 mM glucose ($p = 0.0307$). Residual LPL activity detected in islets from βLPL-KO mice is likely because of the presence of non-β-cells.

Although we observed a reduction in glucose-stimulated LPL activity in βLPL-KO islets (Fig. 2C), this change in LPL activity did not alter the islet content of triglycerides in vivo (Fig. 2D).

Glucose Intolerance and Defective Insulin Secretion with Perturbations of β-cell LPL.—Neither genetic manipulation of LPL expression affected fasting serum levels of cholesterol, triglycerides, free fatty acids, or insulin (data not shown). There was also no effect of increased or decreased islet LPL activity on body mass. Weights for βLPL-TG mice at the age of 12 weeks were: TG males, $32.8 \pm 1.8$ g; WT males, $31.2 \pm 0.9$ g; TG females, $24.5 \pm 4.9$ g; and WT females, $25.5 \pm 5.0$ g. Weights for βLPL-KO mice at the age of 12 weeks were: KO males, $27.2 \pm 1.6$ g; WT males, $28.3 \pm 1.3$ g; KO females, $22.0 \pm 0.5$ g; WT females, $21.3 \pm 1.3$ g.

Insulin sensitivity as assessed by insulin tolerance testing was unaffected in both βLPL-TG and βLPL-KO mice (Fig. 3, B and D). However, βLPL-TG and βLPL-KO animals became hyperglycemic compared with their respective wild-type littermates during glucose tolerance testing (Fig. 3, A and C). The data of Fig. 3 represent males, but the same results were seen with females. To characterize in vivo insulin secretory responses, insulin was measured during glucose tolerance tests in separate cohorts. Compared with the basal state, plasma insulin nearly doubled 30 min after glucose administration in both the βLPL-TG and βLPL-KO animal models (Table I). Although βLPL-TG and βLPL-KO mice displayed significantly higher blood glucose levels 30 min after challenge, there were no significant differences in circulating insulin concentrations between these animals and their respective wild-type litter-

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**Image Descriptions**

**Fig. 1.** Increased LPL enzyme activity and triglyceride content in islets of βLPL-TG animals. A, schematic representation of the human LPL transgene. B, Western blots of islet (50 islets/lane) and brain (200 μg/lane) proteins from wild-type (wt) and littermate βLPL-TG (tg) animals using an anti-HA antibody. C, LPL activity assay of wild-type (open bar) or littermate βLPL-TG (filled bar) islet extracts. D, triglyceride content of islets isolated from wild-type (open bar) and littermate βLPL-TG (filled bar) animals. Islets and brain tissue were obtained from 5–6-month-old βLPL-TG animals and littermates. *, $p < 0.005$; **, $p < 0.05$ versus wild-type littermates under the same condition; FFA, free fatty acid.

**Fig. 2.** LPL gene rearrangement and decreased LPL enzyme activity in islets of βLPL-KO animals. A, schematic representation of the LPL gene in the absence (−) or presence (+) of Cre recombinase. B, three primer PCR screening of DNA from βLPL-KO (ko) and wild-type (wt) islets. C, LPL enzyme activity of wild-type (open bars) and βLPL-KO (filled bar) islet extracts. *, $p < 0.05$ versus wild-type littermates under the same condition; FFA, free fatty acid. D, triglyceride content of islets isolated from wild-type (open bar) and littermate βLPL-KO (filled bar) animals. Islets were isolated from 2–3-month-old βLPL-KO mice and wild-type siblings.
**β-Cell LPL and Insulin Secretion**

*Fig. 3.* βLPL-TG and βLPL-KO mice have impaired glucose tolerance but normal insulin sensitivity. A, glucose tolerance testing in βLPL-TG (filled circles) and wild-type littermate (open circles) mice. Data are reported for six males at the age of 5–6 months for each genotype. The same results were seen in two other male cohorts and with females. Glucose intolerance was also seen in males from a separate founder line. B, insulin tolerance testing in βLPL-TG (filled circles) and wild-type littermate (open circles) mice. C, glucose tolerance testing in βLPL-KO (filled squares) and wild-type littermate (open squares) mice. Data are reported for eight males at the age of 2–3 months for each genotype. D, insulin tolerance testing in βLPL-KO (filled circles) and wild-type littermate (open squares) mice. The time zero blood glucose values (mg/dl) in B were 126 ± 9 and 149 ± 8 for wild-type and βLPL-TG animals, respectively, and in D, were 130 ± 5 and 116 ± 5 for wild-type and βLPL-KO mice, respectively. *, p < 0.05; **, p < 0.005 versus wild-type littermates at the same time point.

**Table I**

*Plasma insulin and glucose concentrations before and after glucose challenge*

Blood samples were obtained from mice after fasting 4 h (time 0) or after subsequently being challenged with 50% dextrose at a dose of 2 mg/g body weight (time 30). Plasma insulin was determined by an enzyme-linked immunosorbent assay using mouse insulin for the standard curve. βLPL-TG mice and their respective littermates were 5–6 months old when tested, whereas βLPL-KO mice and wild-type siblings were 2–3 months of age when examined.

| Animal model and respective littermate control | Time after glucose injection | Insulin | Glucose | Insulin/Glucose |
|-----------------------------------------------|-----------------------------|---------|---------|----------------|
| Wild-type                                     | 0 min                       | 800 ± 265 | 244 ± 27 | 3.13 ± 0.82   |
| βLPL-TG                                       | 0                           | 868 ± 203 | 213 ± 26 | 4.22 ± 1.0    |
| Wild-type                                     | 30                          | 1775 ± 664 | 398 ± 30 | 4.40 ± 1.6    |
| βLPL-TG                                       | 30                          | 1690 ± 592 | 572 ± 16<sup>a</sup> | 2.90 ± 1.1 |
| Wild-type                                     | 0                           | 440 ± 24  | 126 ± 10 | 2.99 ± 0.35   |
| βLPL-KO                                       | 0                           | 460 ± 60  | 109 ± 5  | 4.15 ± 0.58   |
| Wild-type                                     | 30                          | 844 ± 7   | 274 ± 25 | 3.21 ± 0.34   |
| βLPL-KO                                       | 30                          | 829 ± 11  | 403 ± 35<sup>b</sup> | 2.14 ± 0.32<sup>c</sup> |

<sup>a</sup> p < 0.001 compared to wild-type littermate glucose level 30 minutes after injection.

<sup>b</sup> p < 0.005 compared to wild-type littermate glucose level 30 min after injection.

<sup>c</sup> p < 0.05 compared to wild-type littermate insulin/glucose ratio 30 min after injection.

mates. The failure to detect higher insulin levels in the setting of hyperglycemia suggests the presence of defective insulin secretion, which was confirmed using isolated islets (Fig. 4). βLPL-TG (Fig. 4A) and βLPL-KO (Fig. 4C) islets secreted less insulin than controls when stimulated with 20 mM glucose. Islet insulin content was unaffected in both models (Fig. 4, B and D).

Although both βLPL-TG and βLPL-KO mice display impaired glucose tolerance relative to their relevant wild-type littermates, the age at which this occurs differs between the two models. βLPL-TG mice and their wild-type siblings have normal glucose tolerance up to four months of age, then manifest glucose intolerance by the age of five months (data not shown). This delayed onset of glucose intolerance suggests that these animals successfully compensate for the increased delivery of fatty acids for a period of time. In contrast, βLPL-KO mice as young as one month of age, the earliest age examined, exhibit impaired glucose tolerance (data not shown), suggesting that these animals have insufficient levels of a fatty acid-derived signal required for normal insulin secretion. Because these two animal models developed impaired glucose tolerance at different ages, βLPL-TG animals were studied at 5–6 months of age, whereas βLPL-KO mice were studied at 2–3 months of age.

**Opposite Effects on Inlet Glucose Oxidation and Defects in the Amplifying Pathway of Insulin Secretion**—These genetic models of altered islet LPL expression had opposite effects on islet glucose oxidation. Glucose oxidation was decreased at 16.5 mM glucose in βLPL-TG islets relative to islets from wild-type siblings (Fig. 5A), but this decrease was unlikely to be due to lipotoxicity-induced mitochondrial dysfunction, because islet ATP content was increased (Fig. 5B). Previous studies have suggested that increased availability of fatty acids in islets can increase expression of uncoupling protein-2 (14), known to decrease insulin secretion presumably through effects on ATP generation (29). Consistent with the ATP data of Fig. 5B, there was no effect of LPL expression on islet uncoupling protein-2 mRNA levels (not shown). There was also no effect of LPL modulation on islet mRNA levels for glucokinase (not shown), a key mediator of β-cell glucose metabolism.
Glucose oxidation was increased at both 3 and 16.5 mM glucose in βLPL-KO islets as compared with islets from wild-type littermates (Fig. 5C). Qualitatively, the increased glucose oxidation as a consequence of lowered β-cell LPL expression is the opposite to that of βLPL-TG islets, which have reduced glucose oxidation. However, differences in the ages of animals studied and in their genetic backgrounds limit the validity of direct quantitative comparisons of glucose oxidation between these two models of altered LPL expression. There was no effect of β-cell LPL knockdown on islet ATP content (Fig. 5D).

Despite differing effects on glucose oxidation, βLPL-TG and βLPL-KO islets had similar defects in the amplifying pathway of insulin secretion (Fig. 6). Treatment with 250 μM diazoxide and 30 mM KCl, conditions inducing insulin secretion independent of the K<sub>ATP</sub> channel, revealed defects in insulin secretion at 3 and 20 mM glucose in βLPL-TG islets (Fig. 6A) and at 20 mM glucose in βLPL-KO islets (Fig. 6B).

**DISCUSSION**

Diabetes, a disease projected to affect 366 million people worldwide by the year 2030 (30), is characterized by two salient pathophysologies: insulin resistance and the inability of the

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### FIG. 4

**βLPL-TG and Wild-type littermates**

A, static insulin secretion at basal (3 mM) and stimulatory (20 mM) glucose levels using islets isolated from wild-type (open bars) and βLPL-TG littermate (filled bars) animals. B, insulin content of islets isolated from wild-type (open bar) and βLPL-TG littermate (filled bars) mice. C, static insulin secretion at basal (3 mM) and stimulatory (20 mM) glucose levels using islets isolated from wild-type (open bars) and βLPL-KO littermate (filled bars) mice. D, insulin content of islets isolated from wild-type (open bar) or βLPL-KO littermate (filled bar) mice. In βLPL-TG studies, islets were obtained from 5–6-month-old βLPL-TG animals and littermates. For the βLPL-KO model, islets were isolated from 2–3-month-old βLPL-KO mice and wild-type siblings. The results in A and C were each replicated in four or more experiments. The same results shown in B and D were seen in two independent experiments. *, p < 0.05 and **, p < 0.005 versus wild type under the same condition.

### FIG. 5

**Glucose oxidation is diminished in βLPL-TG islets but enhanced in βLPL-KO islets.** A, glucose oxidation at basal (3 mM) and stimulatory (16.5 mM) glucose levels using islets isolated from wild-type (open bars) and βLPL-TG littermate (filled bars) animals. B, ATP content of islets isolated from wild-type (open bar) or βLPL-TG littermate (filled bar) mice. C, glucose oxidation at basal (3 mM) and stimulatory (16.5 mM) glucose levels using islets isolated from wild-type (open bars) and βLPL-KO littermate (filled bars) animals. D, ATP content of islets isolated from wild-type (open bar) or βLPL-KO littermate (filled bar) mice. The same results for these panels were seen in 2–5 independent experiments. For the βLPL-TG experiments, islets were obtained from 5–6-month-old βLPL-TG animals and littermates. For the βLPL-KO model, islets were isolated from 2–3-month-old βLPL-KO mice and wild-type siblings. *, p < 0.005 and **, p < 0.01 versus wild type littermates under the same condition.
β-cell to secrete sufficient insulin to maintain normal levels of blood glucose. Both may be affected by abnormal lipid metabolism. By modulating β-cell expression of LPL, which is known to be altered in diabetes and critical for the physiologic delivery of fatty acids to tissues, we have identified three important roles for this enzyme in β-cell function. First, normal levels of β-cell LPL are required to maintain glucose homeostasis in an intact physiologic system, because an increase in islet LPL results in systemic glucose intolerance. Second, LPL activity inversely regulates islet glucose metabolism (35). Two independent groups have shown that glucose metabolism is impaired in mice with skeletal muscle specific knockdown of LPL (34, 35). Cardiac-specific knockdown of LPL activity increases myocardial glucose metabolism (24). Now we show that β-cell-specific overexpression of LPL decreases and β-cell-specific knockdown of LPL increases islet glucose metabolism (Fig. 5).

Surprisingly, these effects on glucose metabolism did not appear to account for defective insulin secretion in our models. Glucose oxidation was decreased in βLPL-TG islets, but ATP levels were increased (Fig. 5), and insulin secretion was decreased in the presence of KCl and diazoxide (Fig. 6), implicating an effect on events distal to membrane depolarization. Glucose oxidation was increased in βLPL-KO islets (Fig. 5), which might be expected to increase insulin secretion by increasing ATP production and decreasing K_{ATP} activity, but instead, glucose-stimulated insulin secretion was decreased in the presence of KCl/diazoxide (Fig. 6). Studies using insulinoma cells have shown that the inhibition of glucose-stimulated insulin secretion caused by the chronic exposure of free fatty acids occurs independently from the effects of those fatty acids on glucose metabolism (39, 40). Our animal models of altered β-cell LPL expression suggest that the dissociation of the effects of fatty acids on glucose oxidation and insulin secretion also occurs in vivo. Other groups have provided evidence that a lipid-coupling factor mediates a K_{ATP} channel-dependent pathway of insulin secretion (34, 35). Our data demonstrate that β-cell LPL activity is a key physiologic generator of the lipids involved in this effect.

We did not address the in vivo effects of individual fatty acids on β-cell function in this study. However, the in vitro effects of different free fatty acid species on islet function have been studied extensively. No difference between saturated and un-
saturated fatty acids, in terms of acute potentiating effects on insulin secretion, was observed by Warnotte et al. (41). Chronic stimulation by saturated fatty acids, such as palmitate, provokes β-cell apoptosis, whereas monounsaturated fatty acids do not cause apoptosis and appear to protect against palmitate-induced apoptosis by redirecting this saturated fatty acid into the triglyceride esterification pathway (32, 33). A slight preference of rat LPL for saturated fatty acid species over unsaturated ones was detected using an in vitro assay (42), but whether this difference affects LPL substrate selectivity in vivo is unclear.

A downstream event likely to be affected by LPL expression is the exocytosis of vesicles containing insulin (43). Docking and fusion of vesicles with the plasma membrane requires the assembly of a complex between tSNAREs, located on the plasma membrane, and vSNAREs, located on secretory vesicles. The tSNARE protein SNAP-25, important for insulin release (44), is palmitoylated (45), a modification that allows proteins to be associated with membranes. Palmitoylation is unclear.

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Pancreatic β-Cell Lipoprotein Lipase Independently Regulates Islet Glucose Metabolism and Normal Insulin Secretion

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