AVANCES EN DIABETOLOGÍA

REVISIÓN

GLP-1 signaling and the regulation of pancreatic β-cells mass/function

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KEYWORDS
Incretins;
Glucagon-like
peptide-1;
Dipeptidyl-
peptidase 4;
Pancreatic β-cell;
Apoptosis;
Insulin secretion

Abstract   Insulin resistance and relative insulin deficiency contribute to the pathogenesis of type 2 diabetes. Defective insulin secretion from pancreatic β-cells results from the progressive deterioration of pancreatic β-cell mass and function. Glucagon-like peptide 1 (GLP-1), an incretin hormone secreted by intestinal L cells in response to a meal, improves glycemic control in patients with type 2 diabetes by addressing both the insulin secretion defect as well as the decline in β-cell mass. These observations fostered the development of new therapeutic agents targeting GLP-1 signaling. This review gives an overview our current knowledge of the molecular mechanisms by which GLP-1 enhances β-cell mass and function.

PALABRAS CLAVE
Incretinas;
Péptido similar al
glucagón tipo 1;
Di-peptidil-
peptidasa-4;
Célula β;
Apoptosis;
Secreción de insulina

La señalización de GLP-1 y la regulación de la masa/función de las células pancreáticas β

Resumen   La resistencia a la insulina y la deficiencia relativa de insulina contribuyen a la patogénesis de la diabetes mellitus tipo 2. La secreción defectuosa de insulina de las células pancreáticas β resulta del deterioro progresivo de la masa y la función de las células pancreáticas β. El péptido similar al glucagón 1 (GLP-1), una hormona incretina secretada por las células intestinales L en respuesta a la ingesta de comida, mejora el control glucémico en pacientes con diabetes mellitus tipo 2 abordando ambos, la deficiente secreción de la insulina, así como el decline de la masa en células β. Estas observaciones fomentan el desarrollo de nuevos agentes terapéuticos orientados a la señalización de GLP-1. Esta reseña resume nuestro actual conocimiento de los mecanismos moleculares por los cuales GLP-1 mejora la masa y función de las células β.

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The pivotal role of β-cells in the etiology of type 2 diabetes

The incidence of type 2 diabetes, a metabolic disorder often associated with obesity, is increasing at an alarming rate[1,2]. Type 2 diabetes results from the combination of both insulin resistance and progressive deterioration of β-cell mass and function[3]. In insulin resistant states, β-cells initially compensate for the increased physiological demand for insulin by increasing insulin secretion to efficiently maintain normoglycemia[4]. Long-standing evidence gathered from rodent models and autopsies in humans indicates that, during this initial stage, β-cell mass is also increased. This may represent an adaptive mechanism to help cope with the metabolic burden. However, β-cell compensation is transient and β-cell mass/function eventually declines in some individuals, thereby causing impaired glucose tolerance or impaired fasting glucose, two hallmarks of pre-diabetic states. It is hypothesized that the resulting postprandial hyperglycemic episodes may accelerate β-cell demise, a concept called «glucotoxicity»[5]. When β-cell mass reaches a critical threshold and normal glucose levels can no longer be maintained, type 2 diabetes develops. Indeed, morphometric analyses of pancreases from cadaveric donors demonstrate that β-cell mass is reduced by >50% in individuals with type 2 diabetes compared to control subjects[6]. Altogether, these observations illustrate the pivotal role of β-cells in the etiology of diabetes. New approaches for diabetes treatment should aim at the preservation and the enhancement of pancreatic β-cell mass/function[7].

The incretin hormone GLP-1: an anti-diabetes medication

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by intestinal L cells in response to a meal[8]. The incretin effect refers to the greater insulin response observed after an oral glucose load compared to a comparable intravenous glucose challenge[9]. It is estimated that the incretin effect could account for up to 60% of the insulin secretory response in healthy subjects[10]. Importantly, the incretin response is hampered in patients with type 2 diabetes. This could be attributed to reduced GLP-1 secretion[11] and/or GLP-1 receptor (GLP-1R) expression[12]. The observation that GLP-1 treatment can restore glycemic control in patients with type 2 diabetes[13] has rapidly fostered the development of new therapeutic agents targeting GLP-1 signaling for diabetes treatment.

The rapid degradation of native GLP-1 by dipeptidyl peptidase 4 (DPP4)[14] represents a limitation to its use as an anti-diabetes medication. Thus, long-lasting GLP-1 analogs that are resistant to the action of DPP4 were developed and characterized as a way to circumvent this major obstacle. The most notorious example is Exendin4, a GLP-1R agonist isolated from the salivary glands of the venomous Gila monster lizard. Another promising therapeutic approach is to prolong the physiological action of endogenous GLP-1 using small molecule inhibitors of DPP4. Because several of these compounds are in various stages of development or already on the market, GLP-1 mimetics and enhancers represent a novel class of anti-diabetes medications with a major impact in the treatment of type 2 diabetes mellitus[15].

Anti-diabetic actions of GLP-1

GLP-1 exerts numerous beneficial effects that improve glycemic control in diabetic subjects. As mentioned above, the stimulation of β-cell insulin secretion is a prominent action of GLP-1[16,17]. GLP-1 also stimulates insulin gene expression and insulin biosynthesis[18], at least in part via increased expression and activity of the β-cell specific transcription factor pancreatic and duodenal homeobox gene-1 (Pdx1)[19,20]; restores glucose competence in non-responsive β-cells[21]; and promotes β-cell mass expansion by stimulating cellular proliferation, survival and differentiation. Thus, GLP-1 addresses both the decline in β-cell mass and the deterioration of β-cell function, two defects that contribute to the etiology of type 2 diabetes. Moreover, GLP-1 has been shown to diminish glucagon secretion[13]. Noteworthy, the actions of GLP-1 on insulin and glucagon secretion are glucose-dependent, thus only occurring at elevated glucose concentrations. This considerably lowers the risk for hypoglycemia and represents a great advantage over other diabetes medications. Notable extra-pancreatic actions of GLP-1 include[8]: delay of gastric emptying, which slows the absorption of glucose and nutrients from the gut; inhibition of food intake, which promotes weight loss; and an insulin-mimetic action in peripheral tissues, although the presence of an active GLP-1R remains to be demonstrated in peripheral tissues.

GLP-1R

GLP-1R is a G-protein-coupled receptor (GPCR) of the B-class subfamily[22]. It was initially cloned from rat pancreatic islet cells[23] and subsequently from a human pancreatic islet library[24]. The rat and human GLP-1R show a 95% amino acid homology. GLP-1R is coupled to Gs and activates adenylate cylcase to stimulate cAMP production. Canonical downstream effectors of cAMP include protein kinase A (PKA) and cAMP-regulated guanine nucleotide exchange factors of the Epac family. In β-cells, GLP-1 triggers Ca^{2+} signaling and insulin secretion via both PKA and Epac[25-27].

Despite several attempts to precisely define the expression pattern of GLP-1R, its tissue distribution remains debated. In pancreatic islets, GLP-1R expression has been shown to be restricted to β-cells in some studies[28,29] and to be present in all islet types by others[30]. Similarly, GLP-1R expression in duct cells is also controversial. The conflicting results could be due to differences in the experimental approaches employed to study GLP-1R expression (western blot, immunohistochemistry, in situ hybridization, and radio-labeled ligand), the specificity/affinity of different GLP-1R antibodies, or variations in GLP-1R expression between species. Besides in pancreas, GLP-1R is found in a small selection of tissues including brain, lung, kidney, heart, and digestive tract[28,29].

GLP-1 signaling and insulin secretion

GLP-1 stimulates insulin secretion at elevated glucose concentrations that are physiologically observed in the postprandial state (>5 mM)[21]. This unique property increases its therapeutic value since it prevents hypoglycemia, a side effect of other blood glucose lowering agents. Although the precise mechanism is not fully elucidated, the glucoincretin action of GLP-1 has been studied extensively. It was established that GLP-1 facilitates glucose-dependent mitochondrial ATP production[31] and promotes the opening of voltage-dependent Ca^{2+} channels[21,27]. GLP-1 also increases cAMP levels[32], an effect linked to the mobilization of intracellular Ca^{2+} stores via both the cAMP-binding protein Epac[36,33] and PKA[31].

The glucoincretin action of GLP-1 is well complemented by its ability to increase insulin biosynthesis[18]. GLP-1 stimulates *Insulin* gene expression via increased expression and activity of the transcription factor Pdx1[19,20]. Other transcription factors such as NFAT[34] and CREB[35] could also participate in the process. Increased insulin synthesis and

storage is thought to enhance the potential for secretion since it helps maintaining a significant pool of insulin available for exocytosis.

GLP-1 signal transduction and β-cell proliferation

GLP-1 acts as a growth factor for the pancreatic β-cell by promoting cellular proliferation and survival. GLP-1 has been initially shown to promote β-cell replication *in vitro*[20,36,37] as well as *in vivo* in a partial pancreatectomy rat model of type 2 diabetes[19]. The molecular mechanisms by which GLP-1 promotes β-cell mass expansion have been studied extensively (fig. 1). It was shown that the action of GLP-1 on β-cell mass requires proteolytic maturation of betacellulin by membrane-bound metalloproteinases[37]. The release of betacellulin, a member of the EGF family, induces transactivation of the epidermal growth factor receptor (EGFR)[37], subsequent activation of PI3K signaling[20] and the concerted action of its downstream effectors Akt[38-40], PKC$_\zeta$[36], and p38 MAPK[36].
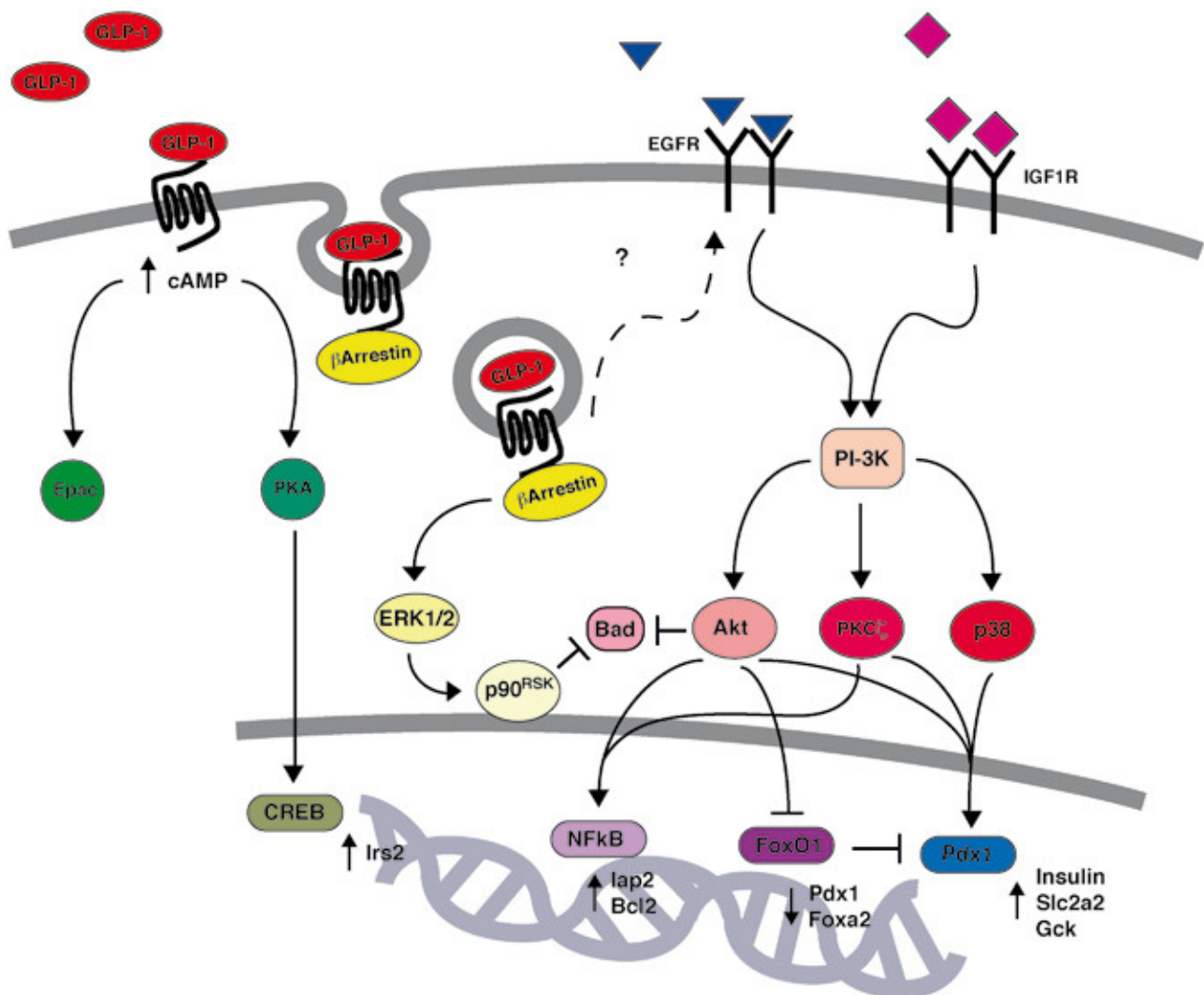

Figura 1 Schematic representation of the signaling pathways activated by GLP-1 to promote β-cell mass expansion.

GLP-1 activation of PI3K/Akt signaling has been shown to regulate two prominent β-cell transcription factors: Pdx1 and FoxO1. On the one hand, as mentioned previously, GLP-1 increases both the expression and activity of Pdx1[20]. GLP-1-induced activation of Pdx1 is essential for its proliferative and anti-apoptotic effects[41]. On the other hand, GLP-1 inhibits the Forkhead transcription factor FoxO1 via nuclear exclusion[42]. Inhibition of FoxO1 by GLP-1 relieves a constraint on β-cell mass expansion as well as *Pdx1* expression[42]. Thus, the Pdx1/FoxO1 tandem unequivocally plays a pivotal role in GLP-1 action.

GLP-1 signaling and β-cell apoptosis

The action of GLP-1 on cellular proliferation dovetails with its effect on survival. Indeed, GLP-1 and its analogs have been shown to prevent β-cell apoptosis *in vivo* in several rodent models as well as *in vitro* in response to a variety of environmental stresses. Exendin4 has been shown to delay the onset of diabetes in *db/db* mice via attenuation of β-cell apoptosis and, consequently, preservation of β-cell mass[43]. Infusion of native GLP-1 in Zucker diabetic rats promotes β-cell proliferation and prevents apoptosis via caspase-3 inhibition[44]. Mice with disruption of the *Glp1r* gene exhibit enhanced β-cell death and more severe hyperglycemia following administration of the β-cell toxin, streptozotocin[45].

The precise mechanism by which GLP-1 exerts its anti-apoptotic action has been shown to implicate both cAMP/PKA as well as PI3K signaling pathways[46]. Thus, GLP-1 has been shown to rapidly increase production of the second messenger cAMP to induce PKA-mediated activation of the transcription factor CREB. In turn, CREB enhances expression of *Irs2*, which acts as a survival factor in β-cells[47,48]. GLP-1 has also been shown to prevent glucotoxicity as well as lipotoxicity in freshly isolated human islets via PI3K/Akt signaling[38]. This observation is of great clinical importance since it suggests that GLP-1 could protect β-cells from hyperglycemia and dyslipidemia, two abnormalities that contribute to the development of type 2 diabetes. The proposed mechanism implicates Akt-dependent activation of NF-kB and up-regulation of the anti-apoptotic genes *Iap2* and *Bcl2*[38]. Whereas acute activation of Akt could involve EGFR transactivation[37], a new study suggests that prolonged stimulation of Akt could be triggered by an autocrine loop implicating insulin growth factor-2 (IGF-2) secretion and insulin growth factor-1 receptor (IGF-1R) activation[49]. A recently published study by the Dalle laboratory demonstrated that GLP-1 could also prevent glucotoxicity via barrestin1-ERK1/2-p90RSK-dependent phosphorylation of Bad[50]. In this model, barrestin1 serves as a docking molecule and creates a signaling complex that favors the sustained activation of ERK1/2. GLP-1 has also been shown to protect β-cells from cytokine-induced cell death[41], thereby suggesting a potential therapeutic value of GLP-1 in the treatment of type 1 diabetes. Finally, GLP-1 has been reported to attenuate endoplasmic reticulum (ER) stress in β-cells[51,52]. ER stress, also called unfolded protein response, designates a cellular stress response related to the endoplasmic reticulum. The underlying mechanisms[52] are subject to extensive research and have attracted much

interest since the original observation by Yusta et al[51] that diabetes is associated with the development of ER stress in β-cells and that GLP-1 signaling prevents ER stress.

Conclusion

GLP-1 analogs and enhancers, through their complementary ability to restore and preserve functional β-cell mass, have great therapeutic value in the treatment of type 2 diabetes. Despite being the subject of extensive studies, several questions remain about the biology of incretin hormones. What are the causes of the diminished incretin effect in patients with type 2 diabetes?[53]. What are the physiological actions of GLP-1 metabolites generated by DPP-4 cleavage of intact GLP-1?[54]. Furthermore, the elucidation of the precise molecular mechanisms by which GLP-1 enhance β-cell mass and function could lead to the design of new therapeutic agents in diabetes treatment. We can predict that this sizzling field of investigation will continue to keep us entertained in years to come.

Acknowledgements

Conflict of interest

The authors have no conflict of interest to declare.

References

1. Zimmet PZ, Alberti KG. Introduction: Globalization and the non-communicable disease epidemic. Obesity (Silver Spring). 2006;14:1-3.
2. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature. 2001;414:782-7.
3. Weir GC, Bonner-Weir S. Five stages of evolving Beta-cell dysfunction during progression to diabetes. Diabetes. 2004;53 (Suppl 3):S16-21.
4. Weir GC, Laybutt DR, Kaneto H, Bonner-Weir S, Sharma A. Beta-cell adaptation and decompensation during the progression of diabetes. Diabetes. 2001;50(Suppl 1):S154-9.
5. Nolan CJ, Prentki M. The islet beta-cell: fuel responsive and vulnerable. Trends Endocrinol Metab. 2008;19:285-91.
6. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes. 2003;52:102-10.
7. Moller DE. New drug targets for type 2 diabetes and the metabolic syndrome. Nature. 2001;414:821-7.
8. Drucker DJ. The biology of incretin hormones. Cell Metab. 2006;3:153-65.
9. Perley MJ, Kipnis DM. Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic sujbjects. J Clin Invest. 1967;46:1954-62.
10. Ritzel R, Schulte M, Porksen N, Nauck MS, Holst JJ, Juhl C, et al. Glucagon-like peptide 1 increases secretory burst mass of pulsatile insulin secretion in patients with type 2 diabetes and impaired glucose tolerance. Diabetes. 2001;50:776-84.

11. Ranganath LR, Beety JM, Morgan LM, Wright JW, Howland R, Marks V. Attenuated GLP-1 secretion in obesity: cause or consequence? Gut. 1996;38:916-9.

12. Xu G, Kaneto H, Laybutt DR, Duvivier-Kali VF, Trivedi N, Suzuma K, et al. Downregulation of GLP-1 and GIP receptor expression by hyperglycemia: possible contribution to impaired incretin effects in diabetes. Diabetes. 2007;56:1551-8.

13. Gutniak M, Orskov C, Holst JJ, Ahren B, Efendic S. Antidiabetogenic effect of glucagon-like peptide-1 (7-36)amide in normal subjects and patients with diabetes mellitus. N Engl J Med. 1992;326:1316-22.

14. Hansen L, Deacon CF, Orskov C, Holst JJ. Glucagon-like peptide-1-(7-36)amide is transformed to glucagon-like peptide-1-(9-36)amide by dipeptidyl peptidase IV in the capillaries supplying the L cells of the porcine intestine. Endocrinology. 1999;140:5356-63.

15. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet. 2006;368:1696-705.

16. Nauck MA, Heimesaat MM, Orskov C, Holst JJ, Ebert R, Creutzfeldt W. Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. J Clin Invest. 1993;91:301-7.

17. Kreymann B, Williams G, Ghatei MA, Bloom SR. Glucagon-like peptide-1 7-36: a physiological incretin in man. Lancet. 1987 2:1300-4.

18. Fehmann HC, Habener JF. Insulinotropic hormone glucagon-like peptide-I(7-37) stimulation of proinsulin gene expression and proinsulin biosynthesis in insulinoma beta TC-1 cells. Endocrinology. 1992;130:159-66.

19. Stoffers DA, Kieffer TJ, Hussain MA, Drucker DJ, Bonner-Weir S, Habener JF, et al. Insulinotropic glucagon-like peptide 1 agonists stimulate expression of homeodomain protein IDX-1 and increase islet size in mouse pancreas. Diabetes. 2000;49:741-8.

20. Buteau J, Roduit R, Susini S, Prentki M. Glucagon-like peptide-1 promotes DNA synthesis, activates phosphatidylinositol 3-kinase and increases transcription factor pancreatic and duodenal homeobox gene 1 (PDX-1) DNA binding activity in beta (INS-1)-cells. Diabetologia. 1999;42:856-64.

21. Holz GG, Kuhtreiber WM, Habener JF. Pancreatic beta-cells are rendered glucose-competent by the insulinotropic hormone glucagon-like peptide-1(7-37). Nature. 1993;361:362-5.

22. Brubaker PL, Drucker DJ. Structure-function of the glucagon receptor family of G protein-coupled receptors: the glucagon, GIP, GLP-1, and GLP-2 receptors. Receptors Channels. 2002;8:179-88.

23. Thorens B. Expression cloning of the pancreatic beta cell receptor for the gluco-incretin hormone glucagon-like peptide 1. Proc Natl Acad Sci USA. 1992;89:8641-5.

24. Thorens B, Porret A, Buhler L, Deng SP, Morel P, Widmann C. Cloning and functional expression of the human islet GLP-1 receptor. Demonstration that exendin-4 is an agonist and exendin-(9-39) an antagonist of the receptor. Diabetes. 1993;42:1678-82.

25. Holz GGt, Leech CA, Habener JF. Activation of a cAMP-regulated Ca(2+)-signaling pathway in pancreatic beta-cells by the insulinotropic hormone glucagon-like peptide-1. J Biol Chem. 1995;270:17749-57.

26. Kang G, Chepurny OG, Holz GG. cAMP-regulated guanine nucleotide exchange factor II (Epac2) mediates Ca2+-induced Ca2+ release in INS-1 pancreatic beta-cells. J Physiol. 2001;536(Pt 2):375-85.

27. Gromada J, Bokvist K, Ding WG, Holst JJ, Nielsen JH, Rorsman P. Glucagon-like peptide 1 (7-36) amide stimulates exocytosis in human pancreatic beta-cells by both proximal and distal regulatory steps in stimulus-secretion coupling. Diabetes. 1998;47:57-65.

28. Bullock BP, Heller RS, Habener JF. Tissue distribution of messenger ribonucleic acid encoding the rat glucagon-like peptide-1 receptor. Endocrinology. 1996;137:2968-78.

29. Campos RV, Lee YC, Drucker DJ. Divergent tissue-specific and developmental expression of receptors for glucagon and glucagon-like peptide-1 in the mouse. Endocrinology. 1994;134:2156-64.

30. Heller RS, Kieffer TJ, Habener JF. Insulinotropic glucagon-like peptide I receptor expression in glucagon-producing alpha-cells of the rat endocrine pancreas. Diabetes. 1997;46:785-91.

31. Tsuboi T, Da Silva Xavier G, Holz GG, Jouaville LS, Thomas AP, Rutter GA. Glucagon-like peptide-1 mobilizes intracellular Ca2+ and stimulates mitochondrial ATP synthesis in pancreatic MIN6 beta-cells. Biochem J. 2003;369(Pt 2):287-99.

32. Widmann C, Burki E, Dolci W, Thorens B. Signal transduction by the cloned glucagon-like peptide-1 receptor: comparison with signaling by the endogenous receptors of beta cell lines. Mol Pharmacol. 1994;45:1029-35.

33. Chepurny OG, Hussain MA, Holz GG. Exendin-4 as a stimulator of rat insulin I gene promoter activity via bZIP/CRE interactions sensitive to serine/threonine protein kinase inhibitor Ro 31-8220. Endocrinology. 2002;143:2303-13.

34. Lawrence MC, Bhatt HS, Easom RA. NFAT regulates insulin gene promoter activity in response to synergistic pathways induced by glucose and glucagon-like peptide-1. Diabetes. 2002;51:691-8.

35. Skoglund G, Hussain MA, Holz GG. Glucagon-like peptide 1 stimulates insulin gene promoter activity by protein kinase A-independent activation of the rat insulin I gene cAMP response element. Diabetes. 2000;49:1156-64.

36. Buteau J, Foisy S, Rhodes CJ, Carpenter L, Biden TJ, Prentki M. Protein kinase Czeta activation mediates glucagon-like peptide-1-induced pancreatic beta-cell proliferation. Diabetes. 2001;50:2237-43.

37. Buteau J, Foisy S, Joly E, Prentki M. Glucagon-like peptide 1 induces pancreatic beta-cell proliferation via transactivation of the epidermal growth factor receptor. Diabetes. 2003;52:124-32.

38. Buteau J, El-Assaad W, Rhodes CJ, Rosenberg L, Joly E, Prentki M. Glucagon-like peptide-1 prevents beta cell glucolipotoxicity. Diabetologia. 2004;47:806-15.

39. Wang Q, Li L, Xu E, Wong V, Rhodes C, Brubaker PL. Glucagon-like peptide-1 regulates proliferation and apoptosis via activation of protein kinase B in pancreatic INS-1 beta cells. Diabetologia. 2004;47:478-87.

40. Trumper K, Trumper A, Trusheim H, Arnold R, Goke B, Horsch D. Integrative mitogenic role of protein kinase B/Akt in beta-cells. Ann N Y Acad Sci. 2000;921:242-50.

41. Li Y, Cao X, Li LX, Brubaker PL, Edlund H, Drucker DJ. beta-Cell Pdx1 expression is essential for the glucoregulatory, proliferative, and cytoprotective actions of glucagon-like peptide-1. Diabetes. 2005;54:482-91.

42. Buteau J, Spatz ML, Accili D. Transcription factor FoxO1 mediates glucagon-like peptide-1 effects on pancreatic beta-cell mass. Diabetes. 2006;55:1190-6.

43. Wang Q, Brubaker PL. Glucagon-like peptide-1 treatment delays the onset of diabetes in 8 week-old db/db mice. Diabetologia. 2002;45:1263-73.

44. Farilla L, Hui H, Bertolotto C, Kang E, Bulotta A, Di Mario U, et al. Glucagon-like peptide-1 promotes islet cell growth and inhibits apoptosis in Zucker diabetic rats. Endocrinology. 2002;143:4397-408.

45. Li Y, Hansotia T, Yusta B, Ris F, Halban PA, Drucker DJ. Glucagon-like Peptide-1 Receptor Signaling Modulates beta Cell Apoptosis. J Biol Chem. 2003;278:471-8.

46. Hui H, Nourparvar A, Zhao X, Perfetti R. Glucagon-like peptide-1 inhibits apoptosis of insulin-secreting cells via a cyclic 5'-adenosine monophosphate-dependent protein kinase A- and

a phosphatidylinositol 3-kinase-dependent pathway. Endocrinology. 2003;144:1444-55.

47. Park S, Dong X, Fisher TL, Dunn S, Omer AK, Weir G, et al. Exendin-4 uses Irs2 signaling to mediate pancreatic beta cell growth and function. J Biol Chem. 2006;281:1159-68.

48. Jhala US, Canettieri G, Screaton RA, Kulkarni RN, Krajewski S, Reed J, et al. cAMP promotes pancreatic beta-cell survival via CREB-mediated induction of IRS2. Genes Dev. 2003;17: 1575-80.

49. Cornu M, Yang JY, Jaccard E, Poussin C, Widmann C, Thorens B. Glucagon-like peptide-1 protects beta-cells against apoptosis by increasing the activity of an IGF-2/IGF-1 receptor autocrine loop. Diabetes. 2009;58:1816-25.

50. Quoyer J, Longuet C, Broca C, Linck N, Costes S, Varin E, et al. GLP-1 mediates antiapoptotic effect by phosphorylating Bad through a beta-arrestin 1-mediated ERK1/2 activation in pancreatic beta-cells. J Biol Chem. 2010;285:1989-2002.

51. Yusta B, Baggio LL, Estall JL, Koehler JA, Holland DP, Li H, et al. GLP-1 receptor activation improves beta cell function and survival following induction of endoplasmic reticulum stress. Cell Metab. 2006;4:391-406.

52. Tsunekawa S, Yamamoto N, Tsukamoto K, Itoh Y, Kaneko Y, Kimura T, et al. Protection of pancreatic {beta}-cells by exendin-4 may involve the reduction of endoplasmic reticulum stress; in vivo and in vitro studies. J Endocrinol. 2007;193:65-74.

53. Meier JJ, Nauck MA. Is the diminished incretin effect in type 2 diabetes just an epi-phenomenon of impaired beta-cell function? Diabetes. 2010;59:1117-25.

54. Holst JJ. The physiology of glucagon-like peptide 1. Physiol Rev. 2007;87:1409-39.