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Leptin-stimulated K_{ATP} channel trafficking

A new paradigm for β-cell stimulus-secretion coupling?

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Insulin secretion from pancreatic β-cells is initiated by the closure of ATP-sensitive K^+ channels (K_{ATP}) in response to high concentrations of glucose, and this action of glucose is counteracted by the hormone leptin, an adipokine that signals through the Ob-R_b receptor to increase K_{ATP} channel activity. Despite intensive investigations, the molecular basis for K_{ATP} channel regulation remains uncertain, particularly from the standpoint of whether fluctuations in plasma membrane K_{ATP} channel content underlie alterations of K_{ATP} channel activity in response to glucose or leptin. Surprisingly, newly published findings reveal that leptin stimulates AMP-activated protein kinase (AMPK) in order to promote trafficking of K_{ATP} channels from cytosolic vesicles to the plasma membrane of β-cells. This action of leptin is mimicked by low concentrations of glucose that also activate AMPK and that inhibit insulin secretion. Thus, a new paradigm for β-cell stimulus-secretion coupling is suggested in which leptin exerts a tonic inhibitory effect on β-cell excitability by virtue of its ability to increase plasma membrane K_{ATP} channel density and whole-cell K_{ATP} channel current. One important issue that remains unresolved is whether high concentrations of glucose suppress AMPK activity in order to shift the balance of membrane cycling so that K_{ATP} channel endocytosis predominates over vesicular K_{ATP} channel insertion into the plasma membrane. If so, high concentrations of glucose might transiently reduce K_{ATP} channel density/current, thereby favoring β-cell depolarization and insulin secretion. Such an AMPK-dependent action of glucose would complement its established ability to generate an increase of ATP/ADP concentration ratio that directly closes K_{ATP} channels in the plasma membrane.

Keywords: leptin, glucose, K_{ATP} channel, AMPK, F-actin, ion channel translocation

Abbreviations: AMPK, AMP-activated protein kinase; F-actin, filamentous actin; GLP-1, glucagon-like peptide-1; GSIS, glucose-stimulated insulin secretion; GSK3β, glycogen synthase kinase isoform 3-beta; K_{ATP}, ATP-sensitive K^+ channel; PDE3B, cyclic nucleotide phosphodiesterase isoform 3B; PI3K, phosphatidylinositol 3-kinase; PIP_3, phosphatidylinositol (3,4,5)-trisphosphate; PTEN, phosphatase and tensin homolog

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Leptin, a product of the LEP/Ob gene, is an "obesity hormone" secreted from adipocytes in direct proportion to body fat mass.[1] Leptin stimulates the activity of ATP-sensitive K^+ channels (K_{ATP}) in pancreatic β-cells,[2] insulin-secreting cell lines,[2,3] and hypothalamic glucose-responsive neurons.[4] As expected for a hormone that reduces β-cell excitability, leptin also inhibits insulin secretion from the islets of Langerhans.[2,5,6] Although the stimulatory action of leptin at β-cell K_{ATP} channels was first discovered by Kieffer and coworkers in 1997,[2] uncertainty exists concerning exactly how this effect is achieved. New insights are now provided by the report of Park and coworkers in which leptin stimulates trafficking of K_{ATP} channels from cytosolic vesicles to the plasma membrane of β-cells.[7] This unexpected action of leptin produces increased K_{ATP} channel activity as measured using the patch clamp technique, and its existence provides a new "K_{ATP} trafficking" paradigm for our understanding of β-cell stimulus-secretion coupling (**Fig. 1**).

Prior to the report of Park et al. it was generally assumed that leptin binds β-cell Ob-R_b receptors in order to exert a stimulatory effect at K_{ATP} channels present

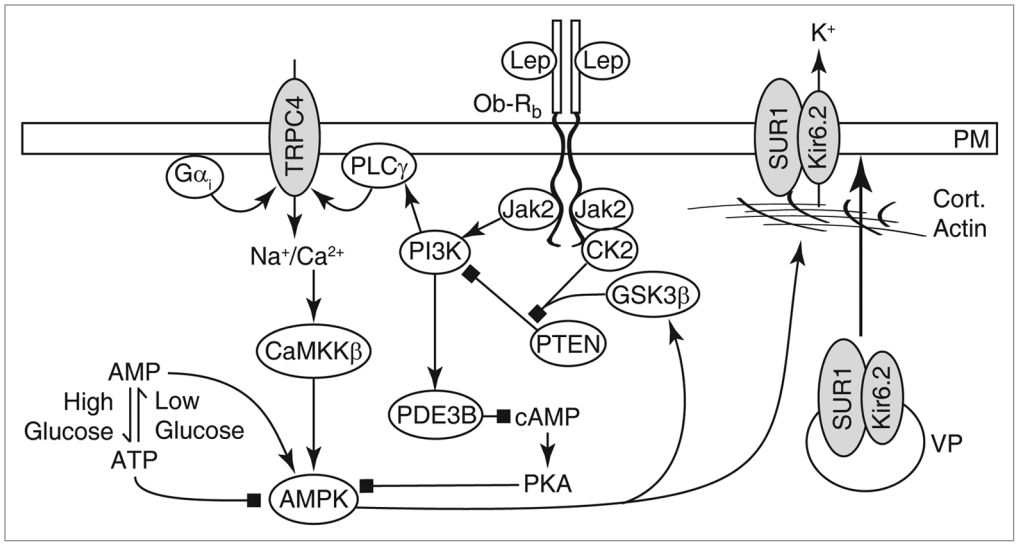

Figure 1. Park et al. propose that binding of leptin (Lep) to its receptor (Ob-R_b) on β-cells activates TRPC4 cation channels.[7] This action of leptin might be mediated by a Jak2-PI3K-PLCγ pathway, as is reported to be the case for hypothalamic neurons.[44] Park et al. also propose that Ca^{2+} influx through TRPC4 activates CaMKKβ in order to phosphorylate and stimulate AMP-activated protein kinase (AMPK).[7] We propose that the stimulatory action of leptin at AMPK might be counteracted by cAMP-elevating agents such as GLP-1 since PKA inhibits AMPK catalytic activity in some cell types.[45] Note that by activating AMPK, leptin stimulates trafficking of a vesicular pool (VP) of K_{ATP} channels to the plasma membrane (PM). Similar to epithelial cells,[27] this trafficking might be stimulated by a CaMKKβ-AMPK pathway that regulates cortical actin dynamics and cytoskeletal remodeling in the β-cell. Abbreviations: CaMKKβ, calmodulin-regulated kinase kinase β, CK2, protein kinase CK2; Cort. Actin, cortical actin barrier; $G\alpha_i$, inhibitory heterotrimeric G protein α subunit; Jak2, janus kinase 2; Kir6.2, pore-forming subunit of K_{ATP} channels; PDE3B, cyclic nucleotide phosphodiesterase 3B; PI3K, phosphatidylinositol 3-kinase; PKA, protein kinase A; PLCγ, phospholipase Cγ; PTEN, phosphatase and tensin homolog; SUR1, sulfonylurea receptor 1. Arrows at ends of lines indicate stimulatory effects. Solid squares at ends of lines indicate inhibitory effects.

in the plasma membrane.[8-10] This effect of leptin might be explained by its ability to increase plasma membrane levels of phosphatidylinositol (3,4,5)-trisphosphate (PtdIns(3,4,5)P_3), a polyphosphoinositide that exerts a direct stimulatory action at K_{ATP} channels.[11-13] Additional actions of leptin potentially relevant to K_{ATP} channel regulation are its abilities to lower levels of cytosolic ATP,[14] to stimulate intracellular phosphotransfer networks,[15] to activate cyclic nucleotide phosphodiesterase 3B (PDE3B),[16] and to promote cytoskeletal remodeling.[13,14,17] What was unexpected is that leptin exerts a stimulatory effect on β-cell vesicular transport so that K_{ATP} channels within these vesicles will traffic to the plasma membrane.

This trafficking action of leptin is measurable using cell surface immunochemical or biotinylation assays that detect the Kir6.2 or SUR1 subunits of β-cell K_{ATP} channels.[7] It occurs with a characteristic delay and is partially reversible due to retrieval of K_{ATP} channels via endocytosis. Notably, the time course of leptin-induced K_{ATP} channel trafficking is in agreement with prior patch clamp measurements of single K_{ATP} channel activity in which an *ca.* 4 min delay was measured between administration of leptin and the detection of increased K_{ATP} channel activity in cell-attached patches of β-cell plasma membrane.[2] Importantly, the vesicles that undergo trafficking in response to leptin do not correspond to insulin-containing secretory granules. Rather, Park et al. report that they contain a marker (EEA1) for early endosomes,[7] so they may participate in endosome recycling.[18]

Recently, Chen et. al[19] confirmed the findings of Park et al.,[7] and both groups agree that trafficking of K_{ATP} channels to the plasma membrane results from an ability of leptin to stimulate the activity of AMP-activated protein kinase (AMPK). Such findings are remarkable in view of a prior report that AMPK mediates K_{ATP} channel trafficking under conditions in which β-cells are chronically exposed to low levels of glucose.[20] Thus, an inhibition of insulin secretion may result from long-term effects of leptin and low glucose to promote AMPK-mediated trafficking of K_{ATP} channels to the plasma membrane (**Fig. 1**).

The current "consensus" model of β-cell stimulus-secretion coupling proposes that when β-cells are exposed to low levels of glucose, K_{ATP} channels already present in the plasma membrane act as metabolic sensors to detect a low cytosolic ATP/ADP concentration ratio. Under these conditions the channels open in order to suppress insulin secretion.[21] When β-cells are exposed to high levels of glucose, resultant glucose metabolism generates an increase of cytosolic ATP/ADP concentration ratio that is detected by K_{ATP} channels in order to directly promote their closure.[21] K_{ATP} channel closure at high levels of glucose initiates β-cell depolarization, action potential generation, and Ca^{2+} influx that triggers insulin exocytosis.[22] However, since AMPK is inhibited by high levels of glucose,[23,24] it is conceivable that K_{ATP} channel closure induced by high glucose also results from a shift in the balance of β-cell membrane cycling such that the rate of K_{ATP} channel endocytosis exceeds that of K_{ATP} channel insertion into the plasma membrane. In this manner, retrieval of K_{ATP} channels from the plasma membrane might produce a decrease of K_{ATP} channel density, thereby reducing whole-cell K_{ATP} channel currents (**Fig. 1**).

Analysis of the effects of leptin on β-cell K_{ATP} channel trafficking provides additional insights concerning how AMPK might serve as a metabolic sensor for the control of glucose-stimulated insulin secretion (GSIS). Chen et al. report that leptin induces AMPK-dependent depolymerization of filamentous actin (F-actin).[19] This finding implies that remodeling of the cortical actin barrier allows vesicles containing K_{ATP} channels

to approach and insert into the plasma membrane (**Fig. 1**). What is unclear is whether high levels of glucose counteract this AMPK-dependent actin remodeling in order to favor endocytosis over vesicle insertion of K_{ATP} channels. Intriguingly, the actin-binding protein cofilin is capable of either depolymerizing or polymerizing actin in order to remodel cortical actin.[25] Since cofilin is regulated by AMPK in various cell types,[26,27] cofilin might mediate K_{ATP} trafficking in response to leptin and/or glucose (**Fig. 1**).

When evaluating the recently published findings concerning K_{ATP} trafficking, several uncertainties remain. Park et al. report that leptin activates TRPC4 cation channels in order to promote Ca^{2+} influx that activates AMPK in a Ca^{2+}/calmodulin kinase kinase-β (CaMKKβ) dependent manner (**Fig. 1**).[7] However, no such Ca^{2+}-elevating action of leptin was observed in prior studies of β-cells.[2,28] In a more recent report, Park et al. also propose that AMPK activates glycogen synthase kinase 3-β (GSK3β) in order to stimulate K_{ATP} channel trafficking, yet how this effect is achieved is not defined.[29] Furthermore, AMPK signaling through GSK3β is proposed to inhibit the phosphatase and tensin homolog PTEN in order to stimulate trafficking of K_{ATP} channels.[29] Mutational analysis of PTEN reveals that its protein phosphatase activity is important to K_{ATP} channel trafficking, yet the substrate protein dephosphorylated by PTEN remains unknown.[29] Since PTEN is also a lipid phosphatase that dephosphorylates PtdIns(3,4,5)P_3, and since PtdIns(3,4,5)P_3 stimulates K_{ATP} channel activity in β-cells,[12-14] a situation may exist in which AMPK-mediated inhibition of PTEN by leptin allows leptin to exert a dual effect—it may promote K_{ATP} channel trafficking to the plasma membrane while also activating K_{ATP} channels already in the plasma membrane.

When evaluating whether leptin exerts a vesicular trafficking-independent effect to activate K_{ATP} channels, Chen et al. report that leptin pretreatment does not alter the ATP or ADP sensitivity of K_{ATP} channels in excised inside-out patches of plasma membrane.[19] This finding is interpreted to indicate that leptin has no membrane-delimited action to directly stimulate K_{ATP} channel activity, a conclusion that is seemingly at odds with prior studies of the Ashford laboratory in which plasma membrane PtdIns(3,4,5)P_3 activates K_{ATP} channels.[11-13,15,17] However, assays of K_{ATP} channel activity in excised inside-out patches are complicated by "wash-out" phenomena in which intracellular factors important to K_{ATP} channel regulation diffuse away or become inactive when the cytosolic face of a patch is exposed to a bath solution. For this reason, a membrane-delimited action of leptin to stimulate K_{ATP} channel activity, and to possibly modulate the channel's ATP and/or ADP sensitivity, cannot be excluded.

It is interesting to note that Chen et al. find that K_{ATP} trafficking is stimulated not simply by leptin, but also by the cAMP-elevating agent forskolin in β-cells.[19] This finding is counterintuitive in view of the fact that leptin activates PDE3B in order to reduce levels of cAMP.[16] Since a knockout of leptin receptor gene expression raises levels of cAMP in β-cells while also enhancing GSIS,[30,31] it seems unlikely that cAMP would reproduce the action of leptin to increase K_{ATP} channel expression in the plasma membrane. In fact, cAMP-elevating agents such glucagon-like peptide-1 (GLP-1) synergize with glucose metabolism to inhibit K_{ATP} channel activity, to raise levels of Ca^{2+}, and to potentiate GSIS.[32-40] Thus, leptin and GLP-1 are normally considered to be counter regulatory hormones for the control of insulin secretion.[9,41] These considerations raise an important issue – how could it be that cAMP-elevating agent forskolin reproduces the K_{ATP} trafficking action of leptin, yet unlike leptin, forskolin stimulates insulin secretion rather than inhibits it? Clearly, new studies are warranted in order to determine if the K_{ATP} trafficking stimulated by leptin and cAMP-elevating agents is of physiological significance to the control of insulin secretion.

Finally, it should be noted that an earlier study of Yang and coworkers provides evidence for a cAMP and Ca^{2+} dependent action of high glucose to stimulate K_{ATP} channel trafficking to the plasma membrane of β-cells.[42] This trafficking involves dense core vesicles that are chromogranin-positive but insulin-negative.[42] Although a role for AMPK in support of this vesicle trafficking was not evaluated, such a surprising observation is clearly at odds with the findings of Park et al.[7,29] and Lim et al.[20] and Smith et al.[43] demonstrating vesicular K_{ATP} channel trafficking in response to low glucose. Despite these multiple uncertainties, it seems clear that the hormonal and metabolic regulation of K_{ATP} channel trafficking constitutes an emerging field of potentially high significance to β-cell biology.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Author Contributions

Holz GG wrote the manuscript. Chepurny OG and Leech CA edited the manuscript. Leech CA created Figure 1.

References

1. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature 1998; 395:763-70; PMID:9796811; http://dx.doi.org/10.1038/27376
2. Kieffer TJ, Heller RS, Leech CA, Holz GG, Habener JF. Leptin suppression of insulin secretion by the activation of ATP-sensitive K^+ channels in pancreatic β-cells. Diabetes 1997; 46:1087-93; PMID:9166685; http://dx.doi.org/10.2337/diab.46.6.1087
3. Harvey J, McKenna F, Herson PS, Spanswick D, Ashford ML. Leptin activates ATP-sensitive potassium channels in the rat insulin-secreting cell line, CRI-G1. J Physiol 1997; 504:527-35; PMID:9401961; http://dx.doi.org/10.1111/j.1469-7793.1997.527bd.x
4. Spanswick D, Smith MA, Groppi VE, Logan SD, Ashford ML. Leptin inhibits hypothalamic neurons by activation of ATP-sensitive potassium channels. Nature 1997; 390:521-5; PMID:9394003; http://dx.doi.org/10.1038/37379
5. Emilsson V, Liu YL, Cawthorne MA, Morton NM, Davenport M. Expression of the functional leptin receptor mRNA in pancreatic islets and direct inhibitory action of leptin on insulin secretion. Diabetes 1997; 46:313-6; PMID:9000710; http://dx.doi.org/10.2337/diab.46.2.313
6. Kulkarni RN, Wang ZL, Wang RM, Hurley JD, Smith DM, Ghatei MA, Withers DJ, Gardiner JV, Bailey CJ, Bloom SR. Leptin rapidly suppresses insulin release from insulinoma cells, rat and human islets and, in vivo, in mice. J Clin Invest 1997; 100:2729-36; PMID:9389736; http://dx.doi.org/10.1172/JCI119818

7. Park SH, Ryu SY, Yu WJ, Han YE, Ji YS, Oh K, Sohn JW, Lim A, Jeon JP, Lee H, et al. Leptin promotes K(ATP) channel trafficking by AMPK signaling in pancreatic β-cells. Proc Natl Acad Sci U S A 2013; 110:12673-8; PMID:23858470; http://dx.doi.org/10.1073/pnas.1216351110
8. Kieffer TJ, Heller RS, Habener JF. Leptin receptors expressed on pancreatic β-cells. Biochem Biophys Res Commun 1996; 224:522-7; PMID:8702421; http://dx.doi.org/10.1006/bbrc.1996.1059
9. Kieffer TJ, Habener JF. The adipoinsular axis: effects of leptin on pancreatic β-cells. Am J Physiol Endocrinol Metab 2000; 278:E1-14; PMID:10644531
10. Covey SD, Wideman RD, McDonald C, Unniappan S, Huynh F, Asadi A, Speck M, Webber T, Chua SC, Kieffer TJ. The pancreatic β cell is a key site for mediating the effects of leptin on glucose homeostasis. Cell Metab 2006; 4:291-302; PMID:17011502; http://dx.doi.org/10.1016/j.cmet.2006.09.005
11. Harvey J, McKay NG, Walker KS, Van der Kaay J, Downes CP, Ashford ML. Essential role of phosphoinositide 3-kinase in leptin-induced K(ATP) channel activation in the rat CRI-G1 insulinoma cell line. J Biol Chem 2000; 275:4660-9; PMID:10671495; http://dx.doi.org/10.1074/jbc.275.7.4660
12. Ning K, Miller LC, Laidlaw HA, Burgess LA, Perera NM, Downes CP, Leslie NR, Ashford ML. A novel leptin signalling pathway via PTEN inhibition in hypothalamic cell lines and pancreatic β-cells. EMBO J 2006; 25:2377-87; PMID:16675953; http://dx.doi.org/10.1038/sj.emboj.7601118
13. Ning K, Miller LC, Laidlaw HA, Watterson KR, Gallagher J, Sutherland C, Ashford ML. Leptin-dependent phosphorylation of PTEN mediates actin restructuring and activation of ATP-sensitive K^+ channels. J Biol Chem 2009; 284:9331-40; PMID:19208634; http://dx.doi.org/10.1074/jbc.M806774200
14. Lam NT, Cheung AT, Riedel MJ, Light PE, Cheeseman CI, Kieffer TJ. Leptin reduces glucose transport and cellular ATP levels in INS-1 β-cells. J Mol Endocrinol 2004; 32:415-24; PMID:15072548; http://dx.doi.org/10.1677/jme.0.0320415
15. Beall C, Watterson KR, McCrimmon RJ, Ashford ML. AMPK modulates glucose-sensing in insulin-secreting cells by altered phosphotransfer to KATP channels. J Bioenerg Biomembr 2013; 45:229-41; PMID:23575945; http://dx.doi.org/10.1007/s10863-013-9509-9
16. Zhao AZ, Bornfeldt KE, Beavo JA. Leptin inhibits insulin secretion by activation of phosphodiesterase 3B. J Clin Invest 1998; 102:869-73; PMID:9727054; http://dx.doi.org/10.1172/JCI3920
17. Harvey J, Hardy SC, Irving AJ, Ashford ML. Leptin activation of ATP-sensitive K^+ (KATP) channels in rat CRI-G1 insulinoma cells involves disruption of the actin cytoskeleton. J Physiol 2000; 527:95-107; PMID:10944173; http://dx.doi.org/10.1111/j.1469-7793.2000.00095.x
18. Grant BD, Donaldson JG. Pathways and mechanisms of endocytic recycling. Nat Rev Mol Cell Biol 2009; 10:597-608; PMID:19696797; http://dx.doi.org/10.1038/nrm2755
19. Chen PC, Kryukova YN, Shyng SL. Leptin regulates KATP channel trafficking in pancreatic β-cells by a signaling mechanism involving AMPK and PKA. J Biol Chem 2013; PMID:24100028
20. Lim A, Park SH, Sohn JW, Jeon JH, Park JH, Song DK, Lee SH, Ho WK. Glucose deprivation regulates KATP channel trafficking via AMP-activated protein kinase in pancreatic β-cells. Diabetes 2009; 58:2813-9; PMID:19720793; http://dx.doi.org/10.2337/db09-0600
21. Nichols CGK. KATP channels as molecular sensors of cellular metabolism. Nature 2006; 440:470-6; PMID:16554807; http://dx.doi.org/10.1038/nature04711
22. Henquin JC. Triggering and amplifying pathways of regulation of insulin secretion by glucose. Diabetes 2000; 49:1751-60; PMID:11078440; http://dx.doi.org/10.2337/diabetes.49.11.1751
23. Salt IP, Johnson G, Ashcroft SJ, Hardie DG. AMP-activated protein kinase is activated by low glucose in cell lines derived from pancreatic β cells, and may regulate insulin release. Biochem J 1998; 335:533-9; PMID:9794792
24. da Silva Xavier G, Leclerc I, Varadi A, Tsuboi T, Moule SK, Rutter GA. Role for AMP-activated protein kinase in glucose-stimulated insulin secretion and preproinsulin gene expression. Biochem J 2003; 371:761-74; PMID:12589707; http://dx.doi.org/10.1042/BJ20021812
25. Ghosh M, Song X, Mouneimne G, Sidani M, Lawrence DS, Condeelis JS. Cofilin promotes actin polymerization and defines the direction of cell motility. Science 2004; 304:743-6; PMID:15118165; http://dx.doi.org/10.1126/science.1094561
26. Lee YM, Lee JO, Jung JH, Kim JH, Park SH, Park JM, Kim EK, Suh PG, Kim HS. Retinoic acid leads to cytoskeletal rearrangement through AMPK-Rac1 and stimulates glucose uptake through AMPK-p38 MAPK in skeletal muscle cells. J Biol Chem 2008; 283:33969-74; PMID:18927084; http://dx.doi.org/10.1074/jbc.M804469200
27. Miranda L, Carpentier S, Platek A, Hussain N, Gueuning MA, Vertommen D, Ozkan Y, Sid B, Hue L, Courtoy PJ, et al. AMP-activated protein kinase induces actin cytoskeleton reorganization in epithelial cells. Biochem Biophys Res Commun 2010; 396:656-61; PMID:20438708; http://dx.doi.org/10.1016/j.bbrc.2010.04.151
28. Seufert J, Kieffer TJ, Leech CA, Holz GG, Moritz W, Ricordi C, Habener JF. Leptin suppression of insulin secretion and gene expression in human pancreatic islets: implications for the development of adipogenic diabetes mellitus. J Clin Endocrinol Metab 1999; 84:670-6; PMID:10022436; http://dx.doi.org/10.1210/jc.84.2.670
29. Park SH, Ho WK, Jeon JH. AMPK rgulates KATP channel trafficking via PTEN inhibition in leptin-treated pancreatic β-cells. Biochem Biophys Res Commun 2013.
30. Morioka T, Asilmaz E, Hu J, Dishinger JF, Kurpad AJ, Elias CF, Li H, Elmquist JK, Kennedy RT, Kulkarni RN. Disruption of leptin receptor expression in the pancreas directly affects beta cell growth and function in mice. J Clin Invest 2007; 117:2860-8; PMID:17909627; http://dx.doi.org/10.1172/JCI30910
31. Morioka T, Dishinger JF, Reid KR, Liew CW, Zhang T, Inaba M, Kennedy RT, Kulkarni RN. Enhanced GLP-1- and sulfonylurea-induced insulin secretion in islets lacking leptin signaling. Mol Endocrinol 2012; 26:967-76; PMID:22474124; http://dx.doi.org/10.1210/me.2011-1306
32. Holz GG 4th, Kühtreiber 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; PMID:8381211; http://dx.doi.org/10.1038/361362a0
33. Barnett DW, Pressel DM, Chern HT, Scharp DW, Misler S. cAMP-enhancing agents "permit" stimulus-secretion coupling in canine pancreatic islet β-cells. J Membr Biol 1994; 138:113-20; PMID:7529322; http://dx.doi.org/10.1007/BF00232639
34. He LP, Mears D, Atwater I, Kitasato H. Glucagon induces suppression of ATP-sensitive K^+ channel activity through a Ca^{2+}/calmodulin-dependent pathway in mouse pancreatic β-cells. J Membr Biol 1998; 166:237-44; PMID:9843597; http://dx.doi.org/10.1007/s002329900465
35. Ding WG, Kitasato H, Matsuura H. Involvement of calmodulin in glucagon-like peptide 1(7-36) amide-induced inhibition of the ATP-sensitive K^+ channel in mouse pancreatic β-cells. Exp Physiol 2001; 86:331-9; PMID:11429650; http://dx.doi.org/10.1113/eph8602173
36. Light PE, Manning Fox JE, Riedel MJ, Wheeler MB. Glucagon-like peptide-1 inhibits pancreatic ATP-sensitive potassium channels via a protein kinase A- and ADP-dependent mechanism. Mol Endocrinol 2002; 16:2135-44; PMID:12198249; http://dx.doi.org/10.1210/me.2002-0084
37. Bode HP, Moormann B, Dabew R, Göke B. Glucagon-like peptide 1 elevates cytosolic calcium in pancreatic β-cells independently of protein kinase A. Endocrinology 1999; 140:3919-27; PMID:10465260; http://dx.doi.org/10.1210/en.140.9.3919
38. Holz GG, Leech CA, Heller RS, Castonguay M, Habener JF. cAMP-dependent mobilization of intracellular Ca^{2+} stores by activation of ryanodine receptors in pancreatic β-cells. A Ca^{2+} signaling system stimulated by the insulinotropic hormone glucagon-like peptide-1-(7-37). J Biol Chem 1999; 274:14147-56; PMID:10318832; http://dx.doi.org/10.1074/jbc.274.20.14147
39. Tsuboi T, da Silva Xavier G, Holz GG, Jouaville LS, Thomas AP, Rutter GA. Glucagon-like peptide-1 mobilizes intracellular Ca^{2+} and stimulates mitochondrial ATP synthesis in pancreatic MIN6 β-cells. Biochem J 2003; 369:287-99; PMID:12410638; http://dx.doi.org/10.1042/BJ20021288
40. Dzhura I, Chepurny OG, Kelley GG, Leech CA, Roe MW, Dzhura E, Afshari P, Malik S, Rindler MJ, Xu X, et al. Epac2-dependent mobilization of intracellular Ca^{2+} by glucagon-like peptide-1 receptor agonist exendin-4 is disrupted in β-cells of phospholipase C-ε knockout mice. J Physiol 2010; 588:4871-89; PMID:21041529; http://dx.doi.org/10.1113/jphysiol.2010.198424
41. Seufert J. Leptin effects on pancreatic β-cell gene expression and function. Diabetes 2004; 53(Suppl 1):S152-8; PMID:14749281; http://dx.doi.org/10.2337/diabetes.53.2007.S152
42. Yang SN, Wenna ND, Yu J, Yang G, Qiu H, Yu L, Juntti-Berggren L, Köhler M, Berggren PO. Glucose recruits K(ATP) channels via non-insulin-containing dense-core granules. Cell Metab 2007; 6:217-28; PMID:17767908; http://dx.doi.org/10.1016/j.cmet.2007.08.002
43. Smith AJ, Partridge CJ, Asipu A, Mair LA, Hunter M, Sivaprasadarao A. Increased ATP-sensitive K+ channel expression during acute glucose deprivation. Biochem Biophys Res Commun 2006; 348:1123-31; PMID:16904639; http://dx.doi.org/10.1016/j.bbrc.2006.07.170
44. Qiu J, Fang Y, Rønnekleiv OK, Kelly MJ. Leptin excites proopiomelanocortin neurons via activation of TRPC channels. J Neurosci 2010; 30:1560-5; PMID:20107083; http://dx.doi.org/10.1523/JNEUROSCI.4816-09.2010
45. Hurley RL, Barré LK, Wood SD, Anderson KA, Kemp BE, Means AR, Witters LA. Regulation of AMP-activated protein kinase by multisite phosphorylation in response to agents that elevate cellular cAMP. J Biol Chem 2006; 281:36662-72; PMID:17023420; http://dx.doi.org/10.1074/jbc.M606676200