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Leptin-stimulated K_{ATP} channel trafficking

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

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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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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.

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

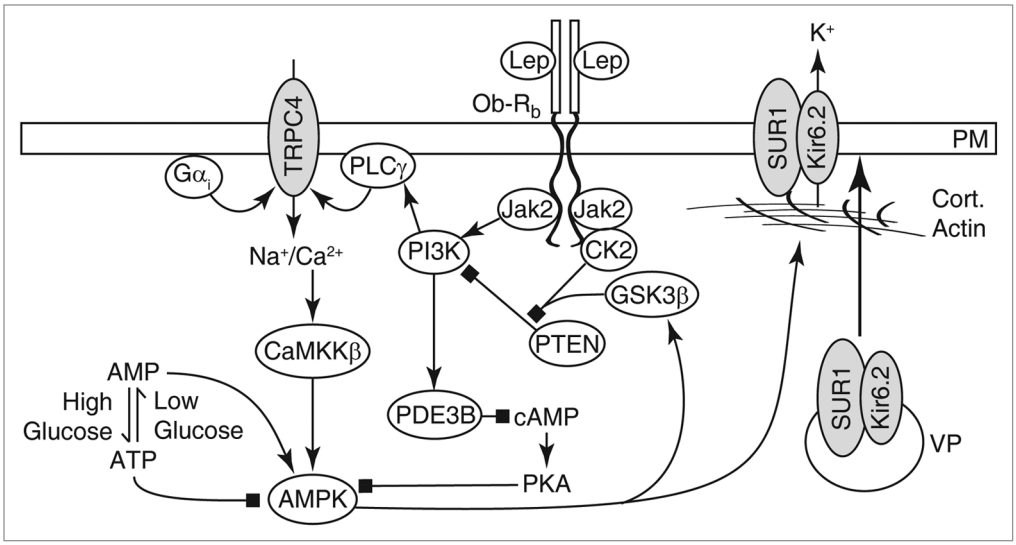

Figure 1. Park et al. propose that binding of leptin (Lep) to its receptor (Ob-R_b) on β-cells activates TRPC4 cation channels.[7] This action of leptin might be mediated by a Jak2-PI3K-PLCγ pathway, as is reported to be the case for hypothalamic neurons.[44] Park et al. also propose that Ca^{2+} influx 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.

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