COMMENTARY

Secrets of insulin and IGF-1 regulation of insulin secretion revealed

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There has been ongoing controversy over the respective roles of insulin-like growth factor-1 receptors and insulin receptors in controlling insulin release from β -cells of the pancreas. An acute knock-down experiment exploiting small interfering RNA

approaches provides a resolution: both are required.

Key words: glucose metabolism, insulin, insulin-like growth factor-1 (IGF1), pancreatic β -cells.

Insulin release from the β -cells of the islets of Langerhans is a necessary step for the appropriate control of whole-body glucose and lipid homeostasis. The secretion of insulin can be induced by a number of agents including fatty acids, ionophores, amino acids, and pharmaceutical agents targeting the sulphonylurea receptors, but the physiologically most important secretagogue is glucose. It is currently accepted that insulin release can be regulated by increasing cellular ATP levels which arise from glucose metabolism. This is achieved via an ATP-sensitive K^+ channel and subsequent stimulation of Ca^{2+} influx [1]. It is equally important that there is an appropriate restoration of insulin stores in the β -cells, and it is clear that rising glucose levels also result in increased expression of the insulin gene [2]. However, the assumption that glucose is the primary regulator of insulin secretion and insulin synthesis has been clouded by a range of studies in recent years that suggest roles for insulin in both insulin secretion and expression of the insulin gene [2,3]. It is currently not clear exactly which effects of glucose are a consequence of its ability to stimulate insulin release. The potential importance of insulin as a means for regulating insulin secretion and for restoring cellular insulin reserves has sparked a great number of studies in recent years but these have provided conflicting results, with studies showing insulin has both positive and negative effects on insulin release from β -cells [3]. Obviously it is important to know what contribution insulin and IGF-1 (insulin-like growth factor-1) play in this process because, if they are playing important roles, defects in the process could well be a major contributor to the impairments of β -cell function that are so closely implicated in the development of Type II diabetes.

Insulin acts through insulin receptors which comprise two identical extracellular α subunits and two transmembrane receptor-tyrosine-kinase-containing β subunits ($\alpha_2\text{IR}\beta_2\text{IR}$). The sequence of the insulin receptor is very closely related to that of the IGF-1 receptor and, indeed, they share many of the same intracellular signalling pathways [4]. Traditionally insulin has only major effects in cells expressing significant numbers of insulin receptors, as, in many cell types, insulin receptor levels are much lower than those of IGF-1 receptors and most of the insulin receptors become associated with IGF-1 receptors to form a hybrid tetrameric receptor ($\alpha\text{IR}\beta\text{IR}\alpha\text{IGFR}\beta\text{IGFR}$). These hybrid receptors behave more like IGF-1 receptors in that they are not activated by the picomolar levels of insulin normally observed in the circulation, but are activated by similar concentrations of IGF-1 to those that activate IGF-1 receptor tetramers ($\alpha_2\text{IGFR}\beta_2\text{IGFR}$). It is clear that β -cells do respond to low doses of insulin, indicating that

functional insulin receptors are indeed present and that β -cells will certainly respond to the insulin that they themselves secrete. It is also evident that β -cells express the IGF-1 receptor and therefore almost certainly contain a population of hybrid receptors. There is no evidence of acute modulation of IGF-1 levels in the islets, so it is assumed that the IGF receptors are mediating a trophic effect on the cells. However, local concentrations of insulin surrounding the β -cells almost certainly rise to levels well in excess of those seen in peripheral tissues, so it is possible that insulin may have secondary effects through the IGF-1 and hybrid receptors. Given that these can activate different responses in the cell, this could provide a mechanism by which the β -cell could give different responses to low and high insulin concentrations.

The advent of gene knock-out strategies in recent years offered the possibility of dissecting the role of insulin- and IGF-receptor-mediated signalling pathways in mediating feedback regulation in response to secreted insulin. Using CRE (cAMP response element) expressed under an insulin promoter, mouse models have been created in which either the insulin receptor or the IGF-1 receptor have been deleted specifically in β -cells [5,6]. Both these models show defects in insulin secretion, but it has been difficult to fully interpret the mechanisms involved as pancreatic development appears to be impaired in these models. Consequently, it is difficult to determine whether these defects, or whether loss of acute signalling pathways, are responsible for the observed effects.

The very recent availability of siRNA (small interfering RNA) techniques has made it possible to achieve *in vitro* knock-downs of genes that allows studies of more acute reductions in gene levels. In this issue of the *Biochemical Journal*, da Silva-Xavier et al. [7] report just such an approach to directly compare the effects of knocking down expression of the insulin receptor and IGF-1 receptor genes in the MIN-6 β -cell line. Their studies are consistent with the findings of the knock-out mouse models, but the *in vitro* nature of the system allows a more detailed comparison of the role each receptor plays, highlighting the value of the siRNA approach to complement and extend animal knock-out models. Surprisingly, loss of either receptor caused a total loss of glucose-mediated insulin secretion but not that mediated by depolarizing agents. This could be explained if hybrid IGF–insulin receptors were required for glucose-induced secretion but there is currently no precedence for this. It is more plausible that insulin and IGF-1 receptors have distinct roles in maintaining the capability of β -cells to secrete insulin. Indeed, the study identifies such differences. Firstly, lack of IGF-1 results in a

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dysregulation of mechanisms controlling cellular ATP levels, which would clearly impact on the ability of glucose to bring about insulin secretion. Loss of insulin receptors, on the other hand, does not have such a drastic effect on cellular ATP levels, but does have a dramatic effect on the ability of glucose to regulate expression of key glucoregulatory genes, an effect not seen in IGF-1 receptor knock-downs. These studies reinforce the importance of both of these receptors in regulating glucose-dependent effects in the β -cell. The studies will also help to ease the controversy that has dogged this area by clearly establishing interdependent roles for the IGF-1 and insulin receptors in maintaining glucose-responsive insulin secretion. Undoubtedly, the siRNA system described will provide a framework for studies to more closely dissect the exact mechanisms used by insulin and IGF receptors to achieve these effects. The study also highlights the promise of the siRNA-based approach to dissect the intricate web of signalling mechanisms that regulate the β -cell and thus provide a rapid route to understanding the secrets of insulin secretion.

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REFERENCES

- 1 Henquin, J. C. (2000) Triggering and amplifying pathways of regulation of insulin secretion by glucose. *Diabetes* **49**, 1751–1760
- 2 Rutter, G. A. (1999) Insulin secretion: feed-forward control of insulin biosynthesis? *Curr. Biol.* **17**, R443–R445
- 3 Leibiger, I. B., Leibiger, B. and Berggren, P. (2002) Insulin feedback action on pancreatic β -cell. *FEBS Lett.* **532**, 1–6
- 4 Siddle, K., Urso, B., Niesler, C. A., Cope, D. L., Molina, L., Surinya, K. H. and Soos, M. A. (2001) Specificity in ligand binding and intracellular signalling by insulin and insulin-like growth factor receptors. *Biochem. Soc. Trans.* **29**, 513–525
- 5 Kulkarni, R. N., Holzenberger, M., Shih, D. Q., Ozcan, U., Stoffel, M., Magnuson, M. A. and Kahn, C. R. (2002) β -Cell-specific deletion of the Igf1 receptor leads to hyperinsulinemia and glucose intolerance but does not alter β -cell mass. *Nat. Genet.* **31**, 111–115
- 6 Kulkarni, R. N., Bruning, J. C., Winnay, J. N., Postic, C., Magnuson, M. A. and Kahn, C. R. (1999) Tissue-specific knock-out of the insulin receptor in pancreatic β -cells creates an insulin secretory defect similar to that in type 2 diabetes. *Cell* **96**, 329–339
- 7 da Silva-Xavier, G., Qian, Q., Cullen, P. J. and Rutter, G. A. (2004) Distinct roles for insulin and insulin-like growth factor-1 receptors in pancreatic β -cell glucose sensing revealed by RNA silencing. *Biochem. J.* **377**, 149–158