Regulation of biphasic and pulsatile insulin secretion

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Optimal glucose homeostasis requires that b-cells secrete insulin at the right moment, at an appropriate speed and in adequate amounts. Alterations in timing and amplitude of insulin secretion are both implicated in the pathogenesis of type 2 diabetes or may cause hypoglycaemia.

Cellular pathways controlling insulin secretion

Nutrient metabolism by pancreatic b-cells underlies the main control of insulin secretion through a dual mechanism. A *triggering* or K_{ATP} *channel-dependent pathway* produces the necessary increase in cytosolic $[Ca^{2+}]_c$ to trigger exocytosis of insulin granules. Thus, glucose-induced changes in the concentration of nucleotides lead to closure of K_{ATP} channels, membrane depolarization, Ca^{2+} influx through voltage-activated Ca^{2+} channels, and rise in $[Ca^{2+}]_c$. Independently of its action on K_{ATP} channels, glucose also activates a *metabolic amplifying pathway* that augments the amount of insulin released without further increasing $[Ca^{2+}]_c$ (Fig. 1). This metabolic amplification is distinct from the *neurohormonal amplifying pathways* set in operation by ligand-activated membrane receptors that transduce the parasympathetic and incretin-mediated potentiation of insulin secretion during meals.

The metabolic amplifying pathway was originally identified during pharmacological clamping of b-cell $[Ca^{2+}]_c$ at an elevated level. Its role could also be demonstrated by using b-cells lacking K_{ATP} channels owing to a knockout of either *Sur1* or *Kir6.2,* the two subunits of the channels. Moreover, recent studies have shown that the pathway is also operative during glucose-potentiation of insulin secretion induced by non-metabolized secretagogues (arginine or sulfonylureas) or during stimulation of insulin secretion by glucose alone. In fact, the two pathways are hierarchical and not completely independent: the amplifying pathway does not manifest itself unless the triggering Ca^{2+} signal is produced, and its contribution augments with the magnitude of the triggering signal. The amplifying pathway is thus physiologically relevant, but its molecular and cellular mechanisms have not yet been completely identified.

Role of the two pathways in temporal control of insulin secretion

When the concentration of glucose is abruptly and steadily augmented, insulin secretion occurs with a *biphasic time-course*, both in vivo and vitro. The characteristics of this biphasic response somewhat vary with the experimental conditions and the species.

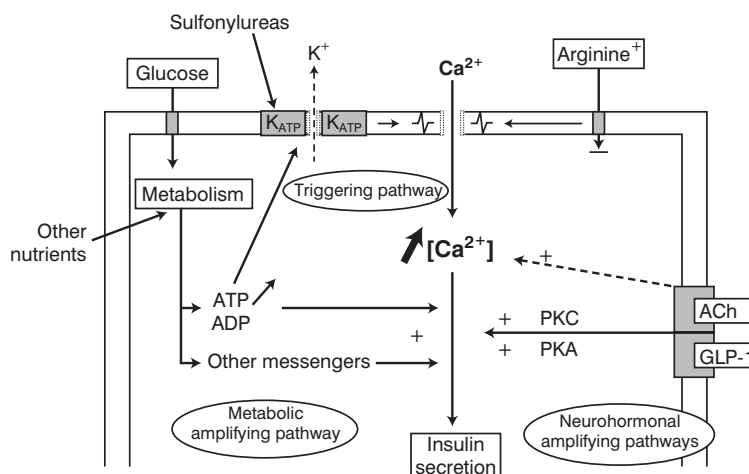**Professor of Endocrinology and Metabolism, University of Louvain Faculty of Medicine, Brussels, Belgium**

Fig. 1. *The mechanism of inuslin secretion.*

Whereas plasma insulin levels increase during second phase of a hyperglycemic clamp in all studied species, second phase insulin secretion in vitro (perfused pancreas or perifused islets) increases in the rat but is flat in mice and humans. The interest for this peculiar biphasic kinetics stems from clinical observations that impaired first phase insulin secretion in response to glucose is an early sign of b-cell dysfunction in type 2 diabetic patients. Two major models have been proposed to explain the phenomenon at the islet/b-cell level. One model is based on the distribution of insulin granules in different pools. It proposes that first phase corresponds to exocytosis of a small pool of docked and primed (readily releasable) granules, whereas second phase requires granule translocation from a reserve pool and their docking and priming. The second model suggests that biphasic secretion results from the biphasic time-course of signals stimulating exocytosis.

It is undisputed that the triggering Ca^{2+} signal is necessary for first and second phases of glucose-induced insulin secretion since both phases are abrogated when the $[Ca^{2+}]_c$ rise is prevented by whatever means. In contrast, the general view is that amplifying signals produced by glucose are necessary for second phase but are not involved in first phase, which is attributed to Ca^{2+}-induced depletion of the pool of readily releasable granules. However, comparisons of $[Ca^{2+}]_c$ and insulin secretion changes during stimulation of mouse islets with either glucose or tolbutamide, or with various glucose concentrations, show dissociations that point to a contribution of the amplifying pathway also to first phase. In summary, the mechanism triggering first phase is relatively simple: the sudden change in glucose concentration induces a synchronous augmentation of $[Ca^{2+}]_c$ in all b-cells of every islet, and the amplitude of the response depends on the magnitude of this $[Ca^{2+}]_c$ rise and on amplifying signals. Moreover, the length and shape of first phase are determined by the time course of the triggering Ca signal.

Even when the concentration of glucose is stable, the membrane potential of b-cells oscillates during second phase, due to the interplay of possible metabolic oscillations and opening and closure of ionic channels. As a result, oscillations of $[Ca^{2+}]_c$ are generated, which induce pulses of insulin secretion by individual islets. This pulsatility requires synchronization of the triggering signal in all b-cells. Whereas $[Ca^{2+}]_c$ oscillations are asynchronous between isolated b-cells, they are well synchronized throughout each islet, owing to electrical coupling of b-cells. When this coupling is abolished, the islets no longer display oscillations of $[Ca^{2+}]_c$ and insulin secretion. The magnitude of insulin pulses increases with the glucose concentration whereas that of Ca oscillations hardly chanes, in contrast to their duration. Temporal regulation of insulin secretion is thus achieved by the triggering Ca^{2+} signal, and amplitude of the pulses is controlled by the amplifying pathway. An important pending question is how all the islets within a pancreas are synchronized to produce insulin pulsatility in vivo.

References

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