Editorial

Insulin Secretion: Movement at All Levels

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With this Second SERVIER-IGIS Symposium *Diabetes* Supplement, we, the members of the International Group on Insulin Secretion (IGIS), happily realize that we have been able to keep the promise made in the First SERVIER-IGIS Symposium (*Diabetes* 50 [Suppl. 1], 2001): we are indeed initiating a tradition, with a yearly series of state-of-the-art collections on various aspects of islet biology, with the emphasis on type 2 diabetes. Without the logistics and the generous unrestricted educational grant put at our disposal by SERVIER, Paris, it is doubtful that we would ever embark on this project, let alone succeed in producing these high-quality publications.

The Second SERVIER-IGIS Symposium dealt with the "Kinetics of Insulin Release in Health and Type 2 Diabetes." To optimally fulfill its preeminent role in glucose homeostasis, insulin secretion must not only be quantitatively appropriate, it must also follow a precise time course. It has indeed been known since the 1960s that insulin secretion is phasic; later work refined the definition of phasicity by the discovery of superimposed oscillations of varying frequencies. Many of these features are absent or disturbed in type 2 diabetic patients, sometimes before overt hyperglycemia is established. These convincing findings notwithstanding, the conditions required to demonstrate certain aspects of phasic insulin release are sometimes unphysiological. Just to mention the often used hyperglycemic clamp, in nature the β-cell is never exposed to a "jump" of the extracellular glucose concentration from 5 to 15–20 mmol/l within 2–3 min. It is therefore a legitimate question whether phasic insulin release is a bona fide biological characteristic of the β-cell. This supplement examines the question from several angles, at different levels of "magnification."

Section 1 serves as a general introduction. The characteristics of the exocytotic events in β-cells determine what the clinician eventually measures in a brachial vein; therefore, several articles deal with the cellular and molecular events that control the release phenomenon. The effector proteins involved in this extremely complex process are discussed in detail, as are the respective roles of several regulatory signals: Ca^{2+}, the triggering signal, whose cytosolic concentration in β-cells increases upon closure of K^{+}_{ATP} channels, and various messengers potentially involved in the "amplification pathway" or "K^{+}_{ATP} channel-independent" component of insulin release. It is suggested that even sulfonylureas, K^{+}_{ATP} channel-active drugs par excellence, may have such "distal" actions.

In Section 2 an "old-timer"—biphasic insulin release—is tackled, again from several angles. The phenomenon was described more than 30 years ago but its mechanism seems to resist full clarification. Several articles discuss this aspect of β-cell behavior in terms of the macrophysiology of the event, whereas others try to identify the molecular characteristics of first- versus second-phase release. There seems to emerge some degree of consensus, suggesting that the first phase is triggered by a rapid, depolarization-mediated elevation of cytosolic Ca^{2+}, while the second phase is more under the influence of metabolic factors and kinase isoforms of the PKA and PKC families, all amplifying the effects of the rise of Ca^{2+} on the exocytotic machinery. Also, it seems clear that simple compartmental models (two pools of granules, or pools of β-cells with different glucose sensitivities) are inadequate to fully account for the phasicity of insulin release under different experimental set-ups. In terms of quantitative data, it has been calculated that first-phase insulin release, which has attracted so much interest, corresponds to the discharge of only 50–100 of the more than 10,000 granules contained in a β-cell.

This tiny first-phase insulin release indeed affects the glucose metabolism of the whole organism, as analyzed in Section 3. Studies in animals and humans have shown that the liver's sensitivity to insulin makes it a prime candidate as a biological target for first-phase insulin release, allowing the closure of glucose production, a factor of paramount importance for the postprandial hyperglycemia of the type 2 diabetic patient. Also discussed in Section 3 is the evolution of phasic insulin secretion throughout the development of type 2 diabetes, including studies on so-called gluco- and lipotoxicity. Since the early 1960s, it has become something of a dogma that it is first-phase insulin secretion that is mostly affected in diabetes. There may be more heterogeneity also in this aspect, as shown by a genetic study included in this supplement.

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Oscillations characterize the functioning of most biological systems. β-cells are no exception, as discussed in detail in Section 4. Insulin secretion is not only biphasic, it is also pulsatile at both the single islet and whole pancreas levels. It has long been known that β-cells are electrically excitable and that their membrane potential typically oscillates during glucose stimulation. These repetitive depolarizations, in concert with other Ca^{2+} entry pathways, generate oscillations of cytoplasmic free Ca^{2+}, which trigger pulses of insulin secretion. Evidence is also presented that several metabolic events oscillate in glucose-stimulated β-cells, but no consensus has yet been reached on their origin: whether they reflect intrinsic properties of glucose metabolism, or are generated by subtle positive or negative feedback loops linked to Ca^{2+} oscillations remains disputed. Another debated issue is whether these metabolic oscillations only serve to entrain electrical and Ca^{2+} oscillations, or directly contribute to the oscillations of insulin secretion via the amplification pathway. Identification of the mechanisms by which all islets within the pancreas are synchronized to produce defined pulses of insulin in the portal vein is also challenging.

The confusion of plasma insulin concentration for pancreatic insulin secretion has led to many misconceptions in diabetes research; hence, the importance of the development, since the 1960s, of increasingly reliable means of extrapolating β-cell function from peripheral hormone levels, usually with the help of mathematical modeling. In Section 5 two original approaches are presented, both based on the use of a more physiological stimulus (oral glucose or multiple meals). These will certainly be of great help in larger population and patient studies. Another important message is that insulin secretion and insulin sensitivity (or resistance) are closely linked, and therefore β-cell function cannot be studied isolated from insulin action. Several articles discuss the methodology for solving this problem and present concrete examples.

The pulsatility of insulin secretion can also be studied in vivo by monitoring and adequately analyzing the concentration of the hormone in a time series of frequently drawn plasma samples, as shown in Section 6. Distinct oscillations associated with or independent of glucose changes occur with different periods, the shortest ones being close to those of pulsatile insulin secretion in vitro. In addition to the alteration of the two "classical" phases of insulin secretion, perturbations of insulin pulsatility have been identified as an early sign of β-cell dysfunction in glucose intolerance and type 2 diabetes. We should, however, realize that the exact "raison d'être" of the oscillatory behavior of β-cells is not entirely clear. Some data suggest that it serves to produce insulin with a time course ensuring the optimal response of target tissues. Alternatively, oscillations of various signals could be advantageous for the β-cell itself (not necessarily for secretion), and the oscillations of secretion could simply be an obligatory consequence thereof. Anyhow, the conclusions drawn from these clinical investigations amply justify the efforts of many basic researchers to elucidate the mechanisms controlling the kinetics of insulin secretion.

We are convinced that this supplement will provide the reader with an up-to-date overview of insulin secretion, examined at all levels, from the molecular to the physiological and clinical levels. Not only is insulin release dynamic, but so is its research, as witnessed by the impressive amount of science presented in this Second SERVIER-IGIS Symposium. It is our conviction that diabetes research, like research in other medical areas, must be indivisible and span from molecular biology to clinical investigation. We believe the present supplement is an excellent illustration of this philosophy.

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