Beta cell Signalling
Revisited

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Editorial

The International Group on Insulin Secretion – IGIS – was established in the late 1990s by a group of academic researchers to boost interest in islet biology and insulin secretion and promote the dissemination of front-line research results to a wider medical public.

As a company with a long-standing interest in promoting research in diabetes, Servier provided IGIS with a long-term grant. Thanks to this support, a series of yearly closed symposia was initiated, each focusing on a central theme related to islet function in relation to type 2 diabetes.

Attended by senior scientists and younger researchers, these symposia were developed into high-level meetings with an emphasis on extensive interaction.

The XVIIth Servier-IGIS Symposium, held on the theme “Beta cell Signalling Revisited,” was another successful meeting where leading experts were able to interact and share their views of the subjects discussed at the meeting.

With a view of sharing the latest developments with scientists and clinicians working in the field of diabetes, the present Digest summarizes a range of topics covered at the Symposium.
Cell signalling is part of any communication process that governs and coordinates basic cellular activities and actions. The ability of cells to perceive, integrate, and respond correctly to signals from the microenvironment is the basis of development, tissue repair, and immunity as well as normal tissue homeostasis. Defective cell signalling is responsible for numerous diseases, such as cancer, autoimmunity, and diabetes. A better understanding of β cell signalling could logically lead to new therapeutic opportunities to fight both type 1 and type 2 diabetes by, at least in part, restoring insulin secretion. The 18th Servier-IGIS symposium revisited β cell signalling by focusing on new mechanisms and approaches, such as N-methyl-D-aspartate (NMDA) receptors, calcium-binding proteins, or β cell metabolomics. First, we will consider the receptors at the surface of the β cell as the first step in cell signalling. Then, we will focus on new findings about the well-known intracellular regulators, namely Ca²⁺ and cyclic AMP (cAMP), and more specifically, on how these regulators may affect β cell function and survival. Metabolic signals play a fundamental role in controlling insulin secretion, and β cell metabolomics has uncovered new regulatory pathways. Finally, this review will discuss exocytosis, the ultimate step in insulin secretion, and the importance of the islet microenvironment and organ cross talk in maintaining adequate insulin secretion.

I. Receptors at the surface of the beta cell: first step in cell signalling

A. Allosteric modulation as a unifying mechanism for receptor function and regulation

Allosteric regulation was described decades ago as the regulation of an enzyme by an effector molecule via binding at a different site than the active (orthosteric) site, ie, the allosteric site. The binding of an effector molecule results in a conformational change that affects protein dynamics; some effector molecules are allosteric activators (positive allosteric modulators) that enhance a protein’s activity, whereas others are allosteric inhibitors (negative allosteric modulators) that reduce a protein’s activity. Most allosteric effects can be explained by two models: (i) the concerted Monod-Wyman-Changeux model; and (ii) the sequential model. The Monod-Wyman-Changeux model postulates that enzyme subunits are connected in such a way that a conformational change in one subunit is conferred to all subunits (thus all subunits
are in the same conformation, ie, tensed or relaxed; Figure 1). The sequential model proposed by Koshsland et al holds that the subunits do not necessitate the same conformation. It is now accepted that protein dynamics are especially important in cell signaling, and Jean-Pierre Changeux stressed the point that allosteric proteins are not only enzymes, but also ion channels, G-protein-coupled receptors (GPCRs), nuclear hormone receptors, and tyrosine kinase receptors. He suggested that allosteric modulation is a unifying mechanism for receptor function and regulation. Indeed, the signal transduction mediated by receptors needs a "communication over a distance" between the activating site and the locus of the biological response. Changeux and Christopoulos proposed the concept that the link between activation and response is allosteric, ie, proteins are organized into symmetrical oligomers that undergo discrete cooperative changes in the quaternary structure and switched from one state to another state as described in the Monod-Wyman-Changeux model (Figure 1). The recent advances in understanding the mechanisms of allosteric receptor transition represent an important opportunity for pharmacological applications in various domains, including diabetes. In particular, the allosteric modulation of the nicotinic acetylcholine receptor, GPCRs (for which lipids are allosteric modulators), or ion channels could modulate β cell function. Allosteric antibodies that bind to the insulin receptor tyrosine kinase have been discovered recently. In addition, a database of more than 72,000 substances that could be considered as allosteric modulators (http://mdl.shsmu.edu.cn/ASD/) is promising for future applications.

**B. GPCRs as sensors of autocrine and paracrine metabolite signalling**

GPCRs are seven-transmembrane domain receptors that can detect molecules outside the cell and activate intracellular signal transduction pathways (eg, cAMP, phosphatidylinositol, and β-arrestin signaling pathways), thus leading to a cellular response. Numerous GPCRs are present at the surface of β cells (eg, GPR120 or GPR40) and involved in insulin secretion. Husted et al defines the metabolites acting on these GPCRs as extracellular signalling molecules that could be compared
with hormones and neurotransmitters. These “signalling metabolites” mainly come from nutrients, but they could also be produced by the gut microbiota, and they primarily target the gut mucosa and the liver. In contrast, metabolites from intermediary metabolism, such as acetate, propionate, or succinate, mainly act as metabolic stress-induced autocrine and paracrine signals in adipose tissue, the liver, and the endocrine pancreas (Figure 2).

In islets, GPR40 and GPR120 recognize triglyceride-derived metabolites, such as long-chain fatty acids and 2-monoacylglycerol, produced by the action of the intracapillary lipoprotein lipase action. In particular, GPR40 mediates free fatty acid–induced insulin secretion in β cells, and, currently, a partial GPR40 agonist is being tested in a clinical phase 1 proof-of-concept study in patients with type 2 diabetes. Fasiglifam (TAK-875), another selective partial GPR40 agonist that is orally available, reached phase 3 clinical trials for the potential treatment of type 2 diabetes; however, the drug development was stopped due to liver side effects. GPR142, another GPCR that is highly expressed in β cells has been recently identified as a potential glucose-stimulated insulin secretion target, and several agonists belonging to the triazole family are under close investigation.

G proteins, coupled with GPCRs, (also known as guanine nucleotide-binding protein) are a target in islet function. When they are bound to GTP, they are “on,” and, when they are bound to GDP, they are “off.” Anjaneyulu Kowluru reviewed the roles of several small G proteins in supporting glucose-induced insulin secretion (GSIS) (ie, Rac1, Cdc42, Arf6, Rab27A) by promoting cytoskeletal remodeling and in the transport and docking of insulin granules on the plasma membrane. Lipidation (farnesylation and geranylation) mediates the effects of G proteins by limiting their targeting to specific cellular compartments. For instance, defective prenylation leads to the mislocalization of G proteins, activation of stress kinases, and production of reactive oxygen species, which could ultimately lead to β cell apoptosis.

C. Sweet taste receptors and insulin secretion

Glucose is the primary stimulator of insulin secretion, which is not a matter of debate; however, Itaru Kojima questioned whether glucose solely exerts its effects on β cells through its intracellular metabolism. Indeed, glucose induces rapid Ca2+ and cAMP signalling in β cells that is independent of metabolism, which, as a proof of concept, can be reproduced with nonmetabolizable glucose analogs. Some cell surface receptors activated by glucose or glucose analogs have been discovered and named “sweet taste receptors.” In β cells, Kojima et al recently showed that taste type 1 receptor 3 (T1R3), a subunit of the sweet taste receptor, functions as a glucose-sensing receptor by forming a heterodimer with the calcium sensing subunit CaSR. This receptor is blocked, glucose metabolism is decreased and
GSIS is inhibited (Figure 3A),26 demonstrating that sweet taste receptors may play a role in the β cell response to glucose (Figure 3B).27,28

D. NMDA receptors

Pancreatic β cells and central nervous system cells have common features; in particular, they share the expression of NMDA receptors. In his lecture, Eckhard

Figure 3. Effect of glucose on islets and β cells. A. Effect of glucose on insulin secretion in islets. Islets obtained from normal and T1R3 knock-out mice were stimulated with 16.7 mM glucose, and insulin secretion was measured in a perfusion system. Values are the mean + SE for four experiments. B. Mode of action of glucose, in β cells. Glucose first activates the cell-surface GSR, thereby priming the metabolic pathway. Glucose then enters the β cell and is metabolized through the already activated metabolic pathway. Abbreviations: ATP, adenosine triphosphate; G6P, glucose 6-phosphate; GA3P, glyceraldehyde-3-phosphate; GLUT2, glucose transporter type 2; GSR, glucose-sensing receptor; KATP, ATP-sensitive potassium; T1R3, taste type 1 receptor 3; VDCC, voltage-dependent calcium channel.


Figure 4. NMDA receptor-regulated insulin release. A. Proposed mechanism of NMDA receptor-regulated insulin release. The uptake and metabolic degradation of glucose by pancreatic β cells results in the generation of ATP, closure of the KATP channel, and, ultimately, in membrane depolarization. Membrane depolarization triggers the opening of VDCCs, leading to an oscillatory increase in the intracellular Ca2+ concentration and insulin release. NMDA receptors are part of a negative feedback loop that limits GSIS at stimulatory glucose concentrations: it is expected that NMDA receptors on β cells are fully saturated with glutamate and the coagonist glycine (or serine). Therefore, depolarization of the β cell plasma membrane is the critical event for NMDA receptor activity. Upon membrane depolarization, NMDA receptors activate K+ channels, thus allowing K+ efflux and membrane repolarization, which closes the VDCCs and reduces insulin release. B. Pharmacological inhibition of NMDA receptors enhances GSIS. The NMDA receptor antagonists DXM and DXO impede the activation of K+ channels, reduce K+ efflux, and prolong the time β cells stay in a depolarized state. Consequently, the intracellular Ca2+ concentration increases in the form of Ca2+ oscillations, which increases insulin release.

Abbreviations: ATP, adenosine triphosphate; DXM, dextromethorphan; DXO, dextrorphan; GSIS, glucose-induced insulin secretion; KATP, ATP-sensitive potassium; NMDA, N-methyl-D-aspartate; VDCC, voltage-dependent calcium channel.

Lammert recapitulated the recent evidence on NMDA receptors in β cell function, and proposed that morphinan-based NMDA receptor antagonists, such as dextromethorphan, could be beneficial for insulin secretion, glucose tolerance, and islet cell survival. Figure 4 displays the proposed mechanism of physiological NMDA receptor–regulated insulin release, stating that NMDA receptors are part of a negative feedback loop that limits GSIS at stimulatory glucose concentrations (Figure 4A). The pharmacological use of dextromethorphan would allow for sustained membrane depolarization, thereby increasing insulin release (Figure 6B).

In addition to the beneficial effect of NMDA receptor antagonists in β cells, they could act on the long-term complications of diabetes, such as nephropathy, retinopathy, and neuropathy.

II. Intracellular regulators: Ca²⁺ and cAMP

A. Ca²⁺ is a key intracellular regulator of insulin secretion

In response to high glucose levels, the ATP-sensitive K⁺ (KATP) channel closes and the plasma membrane depolarizes, leading to sophisticated machinery that drives pulsatile cytosolic Ca²⁺ changes that will act as an ultimate trigger for insulin exocytosis. Guy Rutter discussed the regional calcium dynamics in β cells and islets. The use of targeted Ca²⁺ probes showed that, during each cytosolic Ca²⁺ pulse, the uptake of Ca²⁺ by the mitochondria, endoplasmic reticulum (ER), secretory granules, and lysosomes fine tunes cytosolic Ca²⁺ dynamics and controls organellar function. In this regard, the Ca²⁺ binding protein Sorcin appears to provide a link between ER Ca²⁺ levels and ER stress, which affects β cell function and survival. The same team also showed that the transcription factor Pax6 is required for Ca²⁺ dynamics in adult mouse β cells.

B. cAMP is essential for the neurohormonal amplification of insulin release and GSIS

Anders Tengholm’s lecture recalls that cAMP is generally considered to be an amplifier of insulin secretion that is triggered by Ca²⁺ elevation in β cells. Also named “second messenger,” it is one of the most important cellular signalling molecules and its actions are mediated by protein kinase A and the guanine nucleotide exchange factor Epac. cAMP levels are regulated by hormones, neural factors, and nutrients via adenylyl cyclase–catalyzed generation and phosphodiesterase-mediated degradation. Any alteration in this cAMP system in β cells is associated with diabetic features. In other words, genetic variations and metabolic conditions that compromise the cAMP signalling pathway in β cells contribute to type 2 diabetes. Indeed, a deterioration in cAMP signalling leads to a lower stimulation of insulin secretion and then to a loss of β cell mass in the long term since cAMP also protects β cells from apoptosis. The cAMP signalling system offers different potential targets for the treatment and prevention of type 2 diabetes, such as specific inhibitors of overexpressed Gαi-coupled receptors or activation of alternative pathways for cAMP generation, such as adenylyl cyclase 5.
C. Insulin secretagogues: integration of different signalling pathways toward better insulin secretion

As presented by Susumu Seino, the different drugs used to stimulate and preserve insulin secretion exert their effects via different mechanisms. Recent advances in β cell signaling studies provide a better understanding of how insulin secretagogues act and open the way for conceiving treatments with additive or synergistic actions (Figure 5A). The combination treatment of a sulfonylurea and glucagon-like peptide-1 (GLP-1) in wild-type mice augments insulin secretion (Figure 5B), whereas this synergistic effect is markedly reduced in Epac2A knockout mice. Of note, this integration of different signalling pathways in response to secretagogues also plays a role in a cells to stimulate glucagon secretion in response to hypoglycemia.

III. Metabolic signals

A. Metabolomics used as a tool to detect signals controlling insulin secretion

Metabolomics is the comprehensive profiling of metabolites at different scales (ie, cells, tissues, or whole organisms). This approach has undergone a rapid evolution during the last 20 years. When applied to β cells, it allows for the detection of signals controlling insulin secretion. The current model is that glucose induces insulin secretion via its own glycolytic and oxidative metabolism, leading to an increase in the ATP:ADP ratio, inhibition of KATP channels, activation of voltage-gated Ca2+ channels, and influx of extracellular Ca2+ to stimulate insulin granule exocytosis. However, Christopher Newgard showed that a modified version of the central model has emerged in which the KATP channel–dependent pathway is the primary mediator of the triggering (or first phase) of insulin secretion and other signals are key drivers of the more prolonged amplifying (or second phase) of insulin secretion. In particular, the new glucose/isocitrate and S-AMP pathways of GSIS are viewed as complementary to the classic KATP channel–dependent initiating pathway. Whether these newly described pathways are additive or synergistic with each other and with the canonical KATP channel–dependent mechanism in terms of physiological response remains to be determined.
B. Metabolic signals from lipid metabolism dysregulation control insulin secretion

As explained above, a number of lipid species are signalling molecules that can bind GPCRs at the β cell plasma membrane. Marc Prentki stressed the point that intracellular lipid species are also important signalling modulators that can control the biological function of β cells. Alterations in lipid homeostasis could lead to chronic pathologies, such as obesity and diabetes.46,47 Glucose and nonesterified fatty acid (NEFA) metabolism interface into the glycerolipid/NEFA cycle using its lipogenic and lipolytic arms (Figure 6). Lipolysis is mediated by the consecutive actions of (i) adipose triglyceride lipase (ATGL),9 which catalyzes the conversion of triglycerides to diacylglycerols (DAGs), (ii) hormone-sensitive lipase, which hydrolyzes DAGs to monoacylglycerols (MAGs), and (iii) monoacylglycerol lipase and α/β-hydrolase domain-containing protein 6 (ABHD6), which hydrolyze MAGs to NEFA and glycerol.48 Several MAGs are only recently being recognized as signalling lipid molecules in different tissues. In particular, recent studies indicate the importance of the ubiquitously expressed serine hydrolase ABHD6, which can hydrolyze MAGs, in both central and peripheral tissues, including in β cells.49 Zhao et al showed that deletion of the ABHD6 gene (either whole body or β cell specific) leads to an increase in GSIS that is due to the binding of MAGs to the exocytic effector Munc13-1, resulting in insulin secretion (Figure 6).49 Targeting ATGL in the islets is also of interest because β cell–specific ATGL knockout mice showed decreased insulinemia and GSIS under chow diet or a high-fat diet, which was associated with enhanced insulin sensitivity. These findings led to the conclusion that the islet β cell ATGL–lipolysis/adipose tissue axis controls energy homeostasis and body weight via insulin secretion.48

IV. The final step: insulin exocytosis

A. Insulin granules

Michele Solimena showed that the age of the insulin secretory granules has a great impact on their behavior inside the β cell and the likelihood of their secretion. Technical advances in live-cell imaging, automated image analysis, and correlative light and electron microscopy have improved our knowledge concerning the connection between the age of the insulin secretory granule, the secretory granule dynamics, the
in intracellular location, and the interactions with other proteins.\textsuperscript{56,57} Young secretory granules are highly dynamic and preferentially released, whereas old secretory granules are nearly immobile and likely to undergo intracellular degradation within multigranular bodies/lysosomes through autophagy.\textsuperscript{52} Interestingly, insulin secretory granules differ in their luminal pH; young secretory granules have a low pH around 5.5, while old secretory granules could reach a pH around 6.3.\textsuperscript{53} Michele Solimena also showed that GLP-1, which acts as an allosteric modulator, can decrease the pH of old secretory granules and activate a rescue pathway by “rejuvenating” the secretory granules.

B. SNARE-regulated exocytosis

The exocytosis underlying secretion is essential for biological processes. It relies on two protein families: Sec1p/Munc18 proteins and soluble N-ethylmaleimide-sensitive attachment protein receptor (SNARE) proteins.\textsuperscript{54} Herbert Gaisano showed that granule exocytosis involves the specific binding of vesicle (v)-SNARE–associated membrane protein with the target membrane (t)-SNARE complex, composed of the SNAP25/23 and syntaxin (Syn) proteins. In particular, Xie et al showed that, in human pancreatic β cells, Syn-4 mediates, redundantly with Syn-1A and Syn-3, and promotes the exocytosis of predocked and newcomer secretory granules, which underlies the biphasic GSIS process.\textsuperscript{55} These new insights into β cell exocytosis could lead to the development of novel SNARE replacement strategies that can restore the deficient insulin secretion in type 2 diabetic islets, although this approach is challenging both technically and conceptually. It has been shown that a slight excess in the SNARE protein Syn-1A\textsuperscript{56} (genetically overexpressed in mice) resulted in a paradoxical reduction in GSIS, perhaps as the result of the formation of nonfusion-competent SNARE complexes.\textsuperscript{57} In addition, some SNAREs could act in an inhibitory manner on insulin granule exocytosis, as it has been demonstrated for Syn-2.\textsuperscript{58}

V. Intra-islet connectivity, islet microenvironment, and organ cross talk

A. Intra-islet cell connectivity

Herbert Gaisano showed that intact islets (having functional intercellular connectivity) display distinct features from dispersed single β cells that profoundly affect insulin secretion, including plasma membrane domain-specific molecular cues that define the functional polarity of β cells, and coupling of adjacent β cells into large clusters that promote synchronized
exocytosis and pulsatile secretion. Guy Rutter proposed a model of intercellular communication across the islet between highly interconnected “hubs,” which act as a β cell pacemaker, and subservient “followers,” which ensure efficient insulin secretion (Figure 7). Loss of connectivity is a feature of type 2 diabetes, and several attempts to increase this connectivity by restoring the functionality of “hub” cells (typically 1% to 10% of the total β cells) have been made. High expression of glucokinase and low expression of Pdx1 and Nkx6.1 seem to be required for repurposing deficient hub cells.

B. Complex and integrated pancreatic islet microenvironment

Alvin Powers discussed how β cells exist in the context of a complex and integrated pancreatic islet microenvironment where they interact with other endocrine cells (mainly glucagon-secreting α cells and somatostatin-secreting δ cells), vascular endothelial cells, the extracellular matrix, neuronal projections (both sympathetic and parasympathetic fibers), and islet macrophages. Interendocrine cell interactions are critical in the pancreas for the regulation of glucose homeostasis, and include paracrine and autocrine signaling in addition to connections between endocrine cells via cell adhesion molecules (e.g., neural cell adhesion molecule [N-CAM] and cadherins), gap junctions, and ephrin receptors and ligands. For example, blocking N-CAM prevents endocrine cell types from segregating properly and leads to abnormalities in both insulin and glucagon secretion. Historically, studies on the role of immune cells in the islet microenvironment have primarily focused on the autoimmune destruction of β cells in type 1 diabetes. However, several recent studies have demonstrated an important role for islet macrophages in promoting β cell regeneration. Interactions are also seen at the whole-body scale; for example, interrupted glucagon signaling in the liver leads to α cell proliferation and hyperplasia and reveals a hepatic α-cell axis. Another example of organ cross talk is the secreted protein angiopoietin-like 4, which originates from adipose tissue and links α cell proliferation with adipose tissue triglyceride metabolism. Romano Regazzi showed that failure in the coordination between organs can lead to the appearance of metabolic disorders, such as diabetes mellitus.

C. In vitro generation of β cells for transplantation

Successful regeneration of functional β cell mass in diabetic patients via cell-based therapy would restore normal insulin secretion and cure the disease. However, developing methods to differentiate human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs) into pancreatic β cells remains a major challenge (Ludovic Vallier lecture), and the in vivo transplantation is delicate. The transdifferentiation of pancreatic cells of other lineages into β cells is also a promising approach.

D. Exosomes as new players in metabolic cross talk

Romano Regazzi presented exosomes the new players in the organs’ metabolic cross talk. Exosomes are small extracellular vesicles produced via the endosomal pathway and released from the cells upon fusion of multivesicular bodies with the plasma membrane. There is growing evidence that they are mediators of cell-to-cell communication. Exosomes transport bioactive proteins, mRNAs, and microRNAs...
that can be transferred in an active form to adjacent cells or distant organs (Figure 8). MicroRNAs are key regulators of β cell physiology because they are involved in β cell differentiation and play a key role in the acquisition of their secretory ability. Guay et al reported that exosomal microRNA horizontal transfer (ie, β cell to β cell) transduces apoptotic signals that originate from cytokines. As a proof of concept, they demonstrated that, if cel-miR-238, a Caenorhabditis elegans microRNA not present in mammalian cells, is expressed in MIN6B1 cells, a fraction of it is released in exosomes and transferred to the recipient β cell. Furthermore, incubation of untreated MIN6B1 or mice islet cells in the presence of microRNA-containing exosomes isolated from the culture media of cytokine-treated MIN6B1 cells triggers apoptosis of the recipient cells. In contrast, exosomes originating from cells not exposed to cytokines have no impact on cell survival. Romano Regazzi presented data suggesting that exosomes could be implicated in the autoimmune destruction of β cells and in type 1 diabetes, leading to the proposal that proteins essential for microRNA action represent a valuable target in the prevention of the disease. In particular, the inhibition of Ago2, a component of the RNA-induced silencing complex that is essential for microRNA action, prevented the proapoptotic effects of exosomes originating from cytokine-treated cells.

VI. Conclusions

As Susumu Seino pointed out, research on β cell signaling represents a path for improving diabetes therapy. As drug therapy is commonly given to patients with diabetes and because insulin secretagogues are widely used, a better knowledge of the mechanisms of β cell signaling will favor our understanding of how an insulin secretagogue works, help with the design of new drugs, and improve therapy.

The 18th Servier-IGIS symposium revisited β cell signaling and uncovered new mechanisms and promising approaches for the therapy of type 2 diabetes. In particular, recent advances in the understanding of the allosteric modulation of the nicotinic acetylcholine receptor, GPCRs, or ion channels and how this modulation impacts β cell function opens the way for new therapeutic strategies. The intracellular regulator (Ca²⁺ and cAMP) systems also offer potential targets for the prevention and treatment of type 2 diabetes, and metabolomics applied to β cells has uncovered new regulatory pathways. In addition, recent data suggest that exosomes—vesicles involved in both organ cross talk and β cell to β cell microRNA transfer—could transduce apoptotic signals and play a role in the autoimmune destruction of β cells and in type 1 diabetes.
Bibliography:


Lectures during the IGIS meeting

- Jean-Pierre Changeux (Paris): Allosteric interactions and cell signalling: 50 years of development
- Herbert Gaisano (Toronto): New insights into SNARE-regulated exocytosis in the beta-cell
- Klaus Kaestner (Philadelphia): Epigenetic signals for beta-cell function
- Itaru Kojima (Maebashi): Role of the glucose-sensing receptor in insulin secretion
- Anjaneyulu Kowluru (Detroit): Role of G-proteins in islet function in health and diabetes
- Eckhard Lammert (Dusseldorf): NMDA receptors as possible drug targets for diabetes treatment
- Christopher Newgard (Durham): Metabolomics applied to the beta-cell
- Alvin Powers (Nashville): Islet microenvironment and beta-cell function
- Marc Prentki (Montreal): Metabolic signals of insulin secretion
- Romano Regazzi (Lausanne): Exosomal signalling in the islet
- Guy Rutter (London): Regional calcium dynamics in beta-cells and islets
- Thue Schwartz (Copenhagen): Structure and function of metabolite receptors – from physiology to therapeutics
- Susumu Seino (Kobe): Beta-cell signalling and insulin secretagogues - A path to improved diabetes treatment
- Michele Solimena (Dresden): Aging of insulin granules
- Anders Tengholm (Uppsala): cAMP dynamics and beta-cell function
To date, 18 Servier-IGIS Symposia have been held, and the proceedings published

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