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NEWSLETTER

SIGNAL TRANSDUCTION IN TYPE 1 DIABETES MELLITUS

Plenary Lecture at the 47th Annual ESPE Meeting,

Istanbul 20-23 September 2008

by Per-Olof Berggren,

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The insulin secretory process is regulated by a sophisticated interplay between glucose and a plethora of additional factors. Besides the action of other nutrients, incretin factors, innervation and systemic growth factors, also autocrine and paracrine regulatory loops within the islet of Langerhans modulate function of the insulin-producing β -cell. Although this modulatory role is well appreciated, the underlying molecular mechanisms involved remain poorly understood.

The action of the actual factors is mediated by β -cell membrane receptors coupled to either G-proteins or tyrosine kinases, which subsequently activate respective second messenger cascades. Due to differences in cytoarchitecture between rodent and human islets, the human β -cell may be subjected to a unique extracellular milieu which may have implications for signal-transduction and thereby β -cell function and survival. Exposure of the pancreatic β -cell to stimulatory glucose concentrations leads to the activation of a chain of events, which culminates in the release of stored insulin. This complex of processes starts with the uptake of glucose by the β -cell glucose transporters and proceeds with the conversion of glucose into glucose-6-phosphate by the β -cell isoform of glucokinase. Metabolism of glucose in glycolysis and the Krebs cycle results in the generation of ATP. The coupling of glucose metabolism to electrical activity remains central in all models of β -cell stimulus-secretion coupling. The resting membrane potential of the pancreatic β -cell is set by the ATP-sensitive potassium (K_{ATP}) channel. Elevation in the ATP/ADP ratio leads to closure of K_{ATP} channels, which in turn results in depolarization of the plasma membrane. The subsequent opening of voltage-gated L-type Ca^{2+} channels leads to an increase in cytoplasmic free Ca^{2+} concentration, $[Ca^{2+}]_i$, which promotes insulin secretion. It is of interest to note that $[Ca^{2+}]_i$ is not only increasing but is actually increasing and decreasing in an oscillatory manner, which may be crucial for both β -cell function and survival. Unphysiological increases in $[Ca^{2+}]_i$ have been linked to cell death in a number of experimental systems. Ca^{2+} coming from the extracellular space, through the voltage-gated L-type Ca^{2+} -channel, is an important determinant of $[Ca^{2+}]_i$. Hence, any alterations in the capability of the voltage-gated L-type Ca^{2+} -channels to conduct Ca^{2+} -influx will have major effects on $[Ca^{2+}]_i$. We have shown that serum from patients with type 1 diabetes increases L-type voltage-gated Ca^{2+} -channel activity in insulin-producing cells. The subsequent increase in $[Ca^{2+}]_i$ is associated with DNA fragmentation typical of programmed cell death or apoptosis. These effects of the serum are prevented by adding verapamil, a blocker of voltage-gated L-type Ca^{2+} -channels. A serum-mediated increase in Ca^{2+} -influx may thus work in concert with the autoimmune reaction associated with type-1 diabetes and contribute to the destruction of β -cells in vivo and thereby aggravate the disease progression.

In this context we have shown that serum from type-1 diabetic patients contains increased concentrations of apolipoprotein CIII (apoCIII). This factor increases $[Ca^{2+}]_i$ and promotes β -cell death. The effects of type-1 diabetic serum and apoCIII on $[Ca^{2+}]_i$ and β -cell death are abolished when β -cells are co-incubated with antisera against apoCIII. Signal-transduction will be discussed in light of pancreatic β -cell function under normal conditions and how changes in this process affect the β -cell in type 1 diabetes.

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We are always in search of items of interest to the international community for inclusion in this newsletter and on the COPES website (www.COPESinternational.org). Contact the Coordinator or Vice Coordinator with your suggestions.

Upcoming Events

Dates and locations in **bold** are annual meetings of the affiliated societies.

2009

JANUARY 21 Bangalore, India	Pediatric Endocrinology Workshop – ISPAE Contact: Prof P Raghupathy E-mail: p.raghupathy@gmail.com
February 26th-28th Ottawa	Annual Scientific Meeting of CPEG
May 17-19 Villasimius, Cagliari (Italy)	Pediatric Neuroendocrinology: An update Contact: Sandro Loche sandroloche@libero.it www.sardiniameeeting.it
JUNE 23-26 Cambridge, UK	5 th International Conference of Children's Bone Health Contact: Jeremy Allgrove E-mail : Jeremy.allgrove@bartsandthelondon.nhs.uk www.ICCBH5.org
SEPTEMBER 2-5 Ljubljana, Slovenia	34th Annual Meeting of ISPAD Contact: Tadej Battelino, MD, PhD E-mail: tadej.battelino@mf.uni-lj.si www.ispad2009.com
SEPTEMBER 9-12 New York, USA	8th Joint ESPE/LWPES Meeting Contact: Paul Saenger Fax: +856.439.0525 E-mail: pksaenger@aol.com and lwpes-espe2009@ahint.com www.lwpes-espe2009.org
SEPTEMBER 29-OCTOBER 2 Vienna, Austria	44th Annual Meeting of the European Association for the Study of Diabetes (EASD) www.easd.org
OCTOBER 1-3 Tochigi, Japan	43rd Annual Meeting of the JSPE Contact: Osamu Arisaka, MD E-mail: arisaka@dokkyomed.ac.jp
November 5-7 Naples, Italy	17 th Meeting of the Italian Society of Pediatric Endocrinology and Diabetes (ISPED) Contact: Laura Perrone or Mariacarolina Salerno E-mail: laura.perrone@unina2.it or mariacarolina.salerno@unina.it
November 11–13 New Delhi, India	ISPAE-PET (Pediatric Endocrine Training program) Contact: Prof Anju Seth E-mail: anju_seth@yahoo.com
November 13–15 New Delhi, India	Biennial meeting of ISPAE Contact: Prof Sangita Yadav E-mail: sangita_yadav@hotmail.com

2010

SEPTEMBER 5-11 Buenos Aires, Argentina	35th Annual Meeting of ISPAD Contact: Olga Ramos, MD E-mail: ramoso@interlink.com.ar
SEPTEMBER 22-25 Prague, Czech Republic	49th ESPE Meeting www.espe2010.org

2011

SEPTEMBER 28-October 1 Glasgow, Scotland	50th ESPE Meeting
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For more international events, visit www.endo-society.org/apps/Events.

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The COPES newsletter publishes information on the meetings of the affiliated societies and other meetings of interest. Reports on activities of the Affiliated Societies and information on meetings, workshops, courses, fellowships, and exchange programs, as well as selected letters and brief summaries or reviews pertaining to newsworthy items are published in the Newsletter and on the website. All contributions are welcome, so please mail or fax your correspondence to the Coordinator or Vice-Coordinator.

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