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Role of pulsed endogenous insulin in type-2 diabetes therapy

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Abstract

It is argued - why the preferred method to maintain euglycemia in Type-2 Diabetes (T2D) must be simulating the physiological pulsed endogenous insulin secretion. Possible approaches leveraging this point to improve T2D therapy are suggested.

It is known, that most types of peripherally administered insulin (PAI) have drawbacks; viz. being non-native, lacking c-peptide, not mimicking physiological insulin secretion oscillations (ISO) that reduce insulin receptor saturation, contributing to weight gain (often as visceral fat). Also, PAI is far less effective in countering gluconeogenesis, a contributor to hyperglycemia, as it doesn't mimic pancreatic release of insulin into the hepatic entrance of the portal vein as triggered by feeding. Merely maintaining tight-glycemic control may not necessarily reduce endothelial dysfunction. Hence, it may be more beneficial to steer away from PAI as well as exogenous insulin.

Although, recent research demonstrates the merits of portally administered insulin, access to the portal vein is not practical. While DPP4-I/GLP-1, even with concomitant glitazones, is good therapeutic approaches, they remain insufficient to achieve tight glycemic control. They, also, fail to mimic the ISO and feeding correlated hepatic portal secretion.

Meanwhile it may be beneficial to revisit insulin secretagogues (IS) and modify traditional therapy, while improving approaches to endogenous secretion and concomitantly minimizing side effects. Dosage of sulfonylureas should be reduced to maintain a very basal secretion. This should be co-administered with a short acting IS (e.g. meglitinides) prior to feeding. This approach can be titrated to mimic native secretion. Effort should be made to find new molecules that enhance secretion efficiency while minimizing side effects. Dys-functional aspects of ISO from β-cell should be given critical consideration in the therapeutic approaches, which are likely to alleviate autocrine, paracrine and other signalling dependent secretion of glucagon, amylin and somatostatin.

To address these issues and to better understand etiology towards developing improved therapeutic approaches, a framework and protocol will be presented encompassing cellular, animal and clinical experiments. Specific therapeutic approaches targeting basal pulsed-endogenous Insulin Secretion, with postprandial enhancement will be presented.

Biography

Ravi Muppirala is a Biophysicist who has held academic appointments at TIFR, Carnegie-Mellon, Syracuse University and University of Michigan. His expertise and interests span bio-molecular structure-dynamics, origins of primitive cells and type-2 diabetes.

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