Ελληνικά Διαβητολογικά Χρονικά 22, 2: 108-109, 2009

Glucolipotoxicity and b-cells in type 2 diabetes: targets for durable therapy?

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Type 2 diabetes mellitus (T2DM) is a heterogeneous, progressive disease characterized by relentless decline of b-cell function, associated with loss of b-cell mass, against a background of obesity-related insulin resistance. The UKPDS has shown that, regardless of the therapy used, b-cell function declines at a rate of approximately 4% per year.

The normal pancreatic b-cell response to a chronic fuel oversupply and obesity-associated insulin resistance is compensatory insulin hypersecretion in order to maintain normoglycemia. Compensation involves expansion of b-cell mass, enhanced insulin biosynthesis, and increased responsiveness of nutrient-secretion coupling. T2DM only develops in subjects that are unable to sustain the b-cell compensatory response.

The likely mechanisms of early b-cell dysfunction include mitochondrial dysfunction, oxidative stress, endoplasmic reticulum (ER) stress, dysfunctional triglyceride/non-esterified fatty acid (TG/NEFA) cycling, and glucolipotoxicity. Once hyperglycemia has developed, additional processes linked to glucotoxicity and the diabetic state, including islet inflammation, O-linked glycosylation, and amyloid deposition, accelerate b-cell failure, resulting in severe b-cell phenotypic alterations and loss of b-cell mass by apoptosis.

Currently, blood-glucose lowering therapies are being evaluated for their b-cell protecting properties. Metformin was shown to enhance meal-related levels of the incretin glucagon-like-peptide (GLP-)1. Activation of GLP-1 receptors on b-cells stimulates meal-related insulin secretion and biosynthesis and has an additional anti-apoptotic effect on rodent-islets. GLP-1 receptor agonists and inhibitors of the incretin-degrading enzyme dipeptidyl peptidase (DPP-)4 improved b-cell function in T2DM patients. Thiazolidinediones ameliorated b-cell function, possibly through improvements in glycemia, dyslipidemia, insulin resistance and inflammation. At present, however, it is unclear whether these therapies can durably improve b-cell function in human T2DM, and favorably change the progressive course of the disease.

Therefore, novel compounds targeting the causal mechanisms of progressive b-cell decline and loss of functional b-cell mass, such as glucolipotoxicity, inflammation and apoptosis, are eagerly awaited.

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