Glucagon therapeutics: in diabetes and heart function (by Young H. Lee)

Abstract

Glucagon plays an important role in normal glucose homeostasis and in metabolic abnormalities. Glucagon excess, rather than insulin deficiency, is essential for the development of diabetes. Beta cell destruction in glucagon receptor null mice does not cause diabetes unless mice are administered adenovirus encoding the glucagon receptor. In rodent studies, treating diabetes by suppression of glucagon, with either leptin or antibody against the glucagon receptor, normalized glucose level, without glycemic volatility, and HbA1c to non-diabetic normal level. Suppression of glucagon in T1D or T2D have superior control of the metabolic abnormalities than that with insulin monotherapy.

The pathophysiology of T2D differs strikingly from T1D. T2D is characterized by the insulin resistance and cardiac abnormalities. Insulin resistance of T2D is due to the paracrinopathy, not by insulin deficiency as in T1D, but by α-cell resistance to paracrine action of insulin, such as resistance to insulin-stimulated glucagon suppression. Another leading theory for the mechanism driving insulin resistance is attributed to ectopic deposition of lipid, such as ceramide or di-acyl-glycerol, in various target organs. Ceramides, bioactive lipids derived from saturated fats, contribute to lipid-induced apoptosis and dysfunction of insulin-producing beta cells. The consequence of ceramides or lipotoxicity in pancreatic alpha cells caused increased glucagon secretion and insulin resistance. Cellular elimination of ceramides by overexpression of acid ceramidase locally within the mature alpha cell reverses hyperglycemia and insulin resistance in T2D diabetic mice mode, i.e. high fat induced, *ob/ob* and *db/db* mice.

Congestive heart failure has long been an associated risk factor of both type 1 and 2 diabetes, and the elevated glucagon levels of diabetes might be crucially involved in the development of diabetes-induced heart dysfunction. The role of lipid metabolism in glucagon-mediated cardiac alterations evaluated ny blocking glucagon signaling with Glucagon receptor antibody (REMD 2.59). Cardiac-specific ablation of glucagon receptors protects against cardiac damage and improves cardiac function. These improvements coincide with a reduction in lipid accumulation that is induced by an increase in AMP-activated protein kinase (AMPK) mediated lipid oxidation. Suppressing glucagon signaling by Glucagon receptor antibody promotes overall heart function by increasing lipid oxidation and decreasing of insulin desensitizing lipid intermediates, ceramide.

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