

β -Cell Dysfunction under Hyperglycemic Stress: A Molecular Model

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Abstract

Background:

Pancreatic β cells respond to chronic hyperglycemia by increasing the synthesis of proinsulin (the precursor molecule of insulin). Prolonged stimulations lead to accumulation of misfolded proinsulin in the secretory track, delayed insulin secretion, and release of unprocessed proinsulin in the blood. The molecular mechanisms connecting the state of endoplasmic reticulum overloading with the efficiency of proinsulin to insulin conversion remain largely unknown.

Method:

Computer simulations can help us to understand mechanistic features of the β -cell secretory defect and to design experiments that may reveal the molecular basis of this dysfunction. We used molecular crowding concepts and statistical thermodynamics to dissect possible biophysical mechanisms underlying the alteration of the secretory track of β cells and to elucidate the chemistry aspects of the secretory dysfunction. We then used numerical algorithms to relate the degree of biophysical alteration of these secretory compartments with the change of proinsulin to insulin conversion rate.

Results:

Our computer simulations suggest that overloading the endoplasmic reticulum initiates downstream molecular crowding effects that affect protein translational mechanisms, including proinsulin misfolding, delayed packing of proinsulin in secretory vesicles, and low kinetic coefficient of proinsulin to insulin conversion.

Conclusions:

Together with previous experimental data, the present study can help us to better understand chemistry aspects related to the secondary translational mechanisms in β cells and how hyperglycemic stress can alter secretory function. This can give a further impetus to the development of novel software to be used in a clinical setup for prediction and assessment of diabetic states in susceptible patients.

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Abbreviations: (ER) endoplasmic reticulum, (CP) C-peptide, (GA) Golgi apparatus, (I) insulin, (IAPP) islet amyloid polypeptide, (P) proinsulin, (PC) proinsulin convertase, (PP) preproinsulin, (SV) secretory vesicle, (T1DM) type 1 diabetes mellitus, (T2DM) type 2 diabetes mellitus

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