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# Models of Glucagon Secretion, Their Application to the Analysis of the Defects in Glucagon Counterregulation and Potential Extension to Approximate Glucagon Action

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## Abstract

This review analyzes an interdisciplinary approach to the pancreatic endocrine network-like relationships that control glucagon secretion and glucagon counterregulation (GCR). Using *in silico* studies, we show that a pancreatic feedback network that brings together several explicit interactions between islet peptides and blood glucose reproduces the normal GCR axis and explains its impairment in diabetes. An α-cell auto-feedback loop drives glucagon pulsatility and mediates triggering of GCR by hypoglycemia by a rapid switch-off of β-cell signals. The auto-feedback explains the enhancement of defective GCR in β-cell deficiency by a switch-off of signals in the pancreas that suppress α cells. Our models also predict that reduced β-cell activity decreases and delays the GCR. A key application of our models is the *in silico* simulation and testing of possible scenarios to repair defective GCR in β-cell deficiency. In particular, we predict that partial suppression of hyperglucagonemia may repair the impaired GCR. We also outline how the models can be extended and tested using human data to become a part of a larger construct including the regulation of the hepatic glucose output by the pancreas, circulating glucose, and incretins. In conclusion, a model of the normal GCR control mechanisms and their dysregulation in insulin-deficient diabetes is proposed and partially validated. The model components are clinically measurable, which permits its application to the study of the abnormalities of the human endocrine pancreas and their role in the progression of many diseases, including diabetes, metabolic syndrome, polycystic ovary syndrome, and others. It may also be used to examine therapeutic responses.

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**Abbreviations:** (BG) blood glucose, (GABA) γ-aminobutyric acid, (GCR) glucagon counterregulation, (GLP-1) glucagon-like peptide-1, (HGO) hepatic glucose output, ($ID_{50}$) median infective dose, (MCN) minimal control network, (STZ) streptozotocin, (TM) transfer model

**Keywords:** counterregulation, diabetes mellitus, feedback, glucagon, hypoglycemia, intrapancreatic network, mathematical model

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