

## System-Level Control to Optimize Glucagon Counterregulation by Switch-Off of $\alpha$ -Cell Suppressing Signals in $\beta$ -Cell Deficiency

Leon S. Farhy, Ph.D.<sup>1</sup> and Anthony L. McCall, M.D., Ph.D.<sup>2</sup>

### Abstract

#### Background:

Glucagon counterregulation (GCR) is a key protection against hypoglycemia that is compromised in diabetes. In  $\beta$ -cell-deficient rats, GCR pulsatility can be amplified if insulin (INS) or somatostatin (SS) are infused in the pancreatic artery and then switched off during hypoglycemia. The data indicate that these signals act by different mechanisms, and here we analyze the differences between the two switch offs (SOs) and predict the GCR-amplifying effect of their individual or combined application.

#### Methods:

A minimal control network (MCN) of  $\alpha/\delta$ -cell interactions is approximated by differential equations to explain the GCR response to a SO and test *in silico* the hypotheses: (i) INS SO suppresses basal and pulsatile, while SS SO blocks only pulsatile glucagon release and (ii) *simultaneous* application of the two switch offs will augment the individual GCR response.

#### Results:

The mechanism postulated in (i) explains the differences in the GCR responses between the SOs. The MCN predicts that simultaneous application of INS and SS decreases basal glucagon but increases post-SO amplitude, thus doubling the response of GCR achieved by each of the individual signals.

#### Conclusion:

The current analyses predict that INS and SS SOs improve defective GCR in  $\beta$ -cell deficiency through different but complementary mechanisms and suggest SO strategies to maximally enhance GCR in type 1 diabetes by simultaneous manipulation of the network control. These results are clinically relevant, as they could have application to design of an artificial pancreas by providing ways to augment GCR that would not require glucagon infusion.

*J Diabetes Sci Technol* 2009;3(1):21-33

**Author Affiliations:** <sup>1</sup>Departments of Medicine, Center for Biomathematical Technology, University of Virginia, Charlottesville, Virginia and <sup>2</sup>Departments of Medicine, University of Virginia, Charlottesville, Virginia

**Abbreviations:** (BG) blood glucose, (GCR) glucagon counterregulation, (INS) insulin, (MCN) minimal control network, (SO) switch off, (SS) somatostatin

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

**Corresponding Author:** Leon S. Farhy, Ph.D., Departments of Medicine, Center for Biomathematical Technology, Box 800735, University of Virginia, Charlottesville, VA 22908; email address [leon@virginia.edu](mailto:leon@virginia.edu)