Novel insights into the importance of insulin degradation in glucose metabolism

Rebecca Baillie, Christina Friedrich, James Bosley, Tristan Maurer, David Tess, Danny Chen. Rosa & Co, San Carlos, CA, USA. Pfizer, Groton, CT, USA.

In recent clinical trial data, the insulin/c-peptide ratio increased significantly (2-7 fold) during a mixed meal tolerance test (MMTT) in some individuals, suggesting large changes in insulin degradation. Inhibition of insulin degradation could be an important modulator of both insulin concentrations and glucose metabolism. A review of the literature and trial data suggested at least three potential mechanisms for an increase in insulin degradation: increased insulin binding to low affinity receptors with recycling, insulin receptor down-regulation or regulation of the insulin receptor by an additional gastrointestinal (GI) hormone released during the MMTT.

We developed and used a large scale mathematical model of insulin and glucose metabolism to investigate these potential mechanisms and evaluate their impact on glucose regulation. A cohort of virtual diabetic patients (VPs; n=100) was used to test each hypothesis. The hypotheses were tested individually and in combinations as either synergistic or additive functions.

Incorporating recycling of receptors in the model did not alter the insulin/c-peptide ratio. Both receptor down regulation and regulation by a GI hormone increased insulin/c-peptide ratio and are reasonable hypotheses to explain the observed changes in insulin degradation seen in some individuals. Regulation of plasma insulin degradation could be a potential therapeutic approach to increase plasma insulin concentrations and lower plasma glucose. Mathematical modeling generated testable hypotheses and gave insight into potentially important mechanisms of insulin degradation in diabetes.