

## **RETHINKING STEADY STATE GLUCOSE INSULIN RELATIONSHIP**

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**Purpose:** The fasting steady state level of glucose is assumed to be mainly determined by insulin signaling although other neuronal and hormonal mechanisms that regulate glucose are known. However this assumption has not been critically evaluated. **Methods:** We examine whether glucose and insulin levels affect each other in a fasting steady state using a multitude of approaches including (i) mathematical model (ii) insulin receptor knock-out experiments in rodents (iii) insulin suppression and insulin raising experiments in rodents and humans (iv) human population data on glucose and insulin during fasting and GTT in type 2 diabetic and non-diabetic subjects. **Results:** (i) In mathematical modeling the set of assumptions that allow insulin signaling to determine fasting glucose levels, does not allow an insulin resistant hyperinsulinemic, normoglycemic state. The classical insulin centric model and clinical picture of type 2 diabetes and prediabetes are mutually incompatible. (ii) Muscle, fat, beta cell and liver specific insulin receptor knockouts have failed to give compensatory hyperinsulinemia and long lasting fasting hyperglycemia (iii) In all insulin suppression experiments in rodents as well as humans, the apparent insulin sensitivity increased after insulin suppression and fasting glucose remained normal. Disabling insulin degrading enzyme increased fasting insulin levels but did not decrease fasting glucose. (iv) Fasting glucose and insulin are poorly correlated in human data and their relationship is not explained by the classical pathway. **Conclusions:** There is no evidence that the fasting glucose levels are determined by insulin signaling and the classical pathway of glucose homeostasis needs to be re-examined.