Modeling Type 2 Diabetes Pathogenesis

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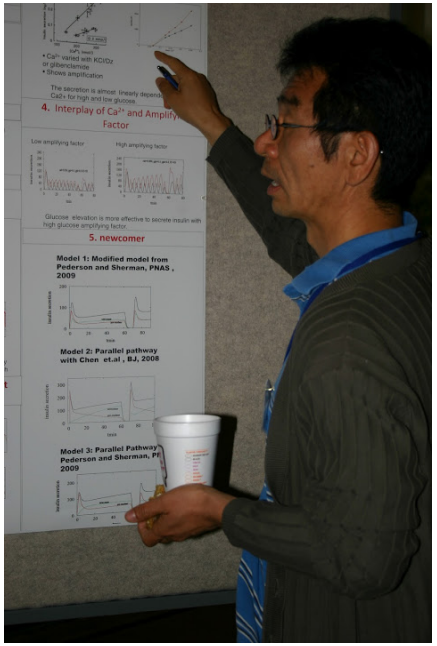
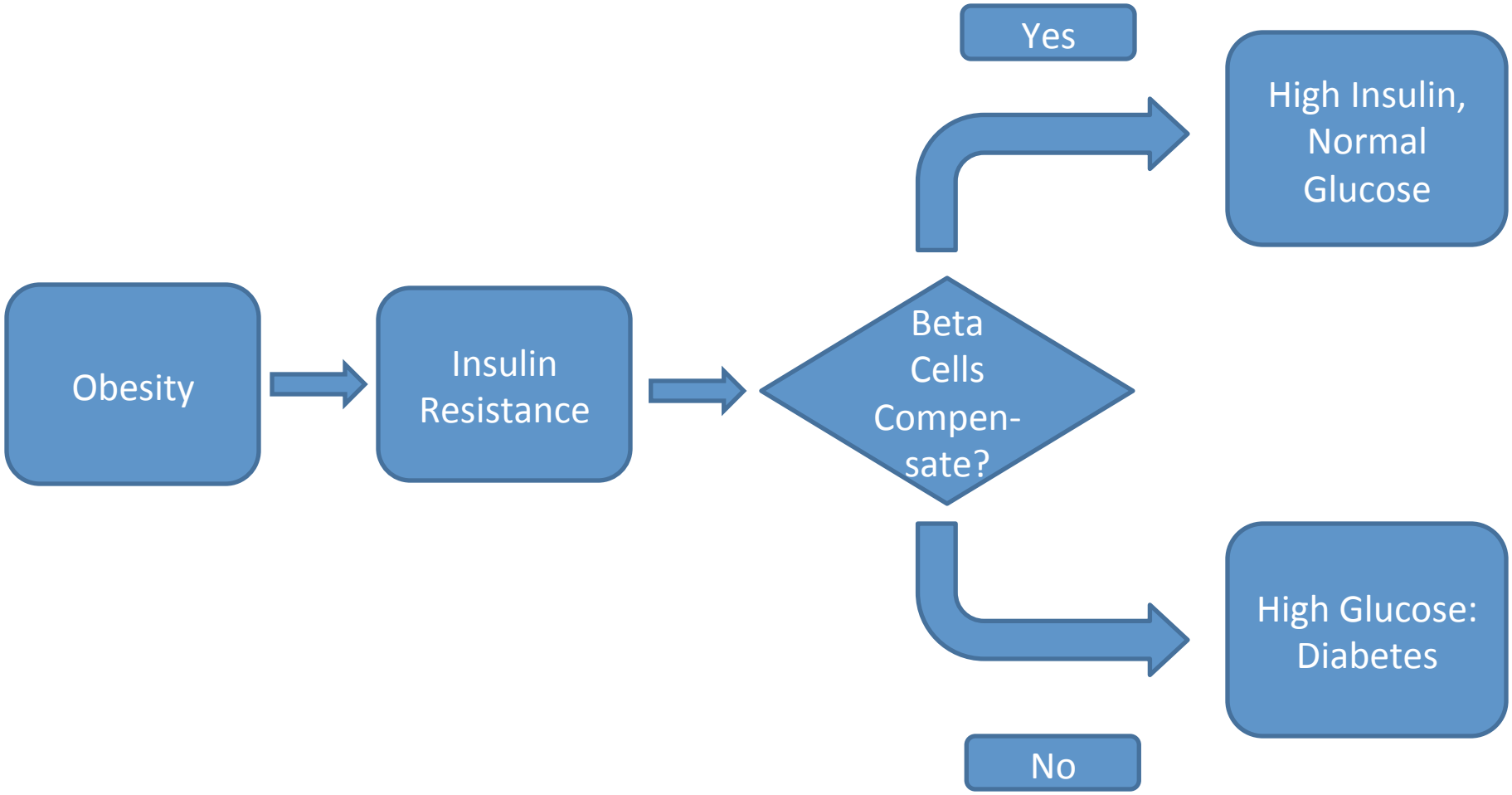


Joon Ha

The Main Question

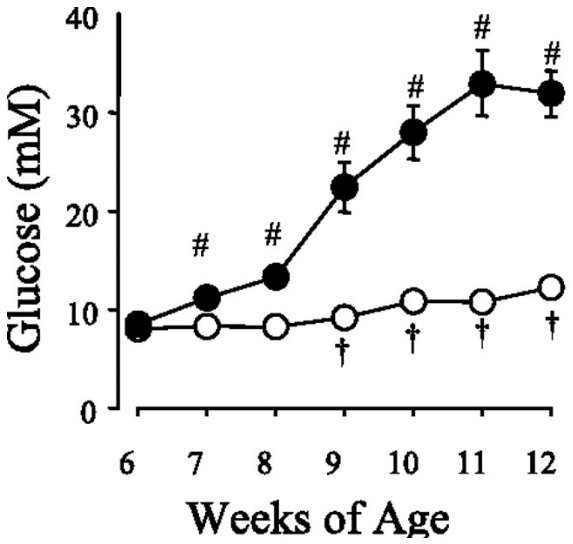
- Why do people get type 2 diabetes (T2D)?
- Most people with T2D are obese.
- But most obese people do not have T2D.
- What distinguishes the two?

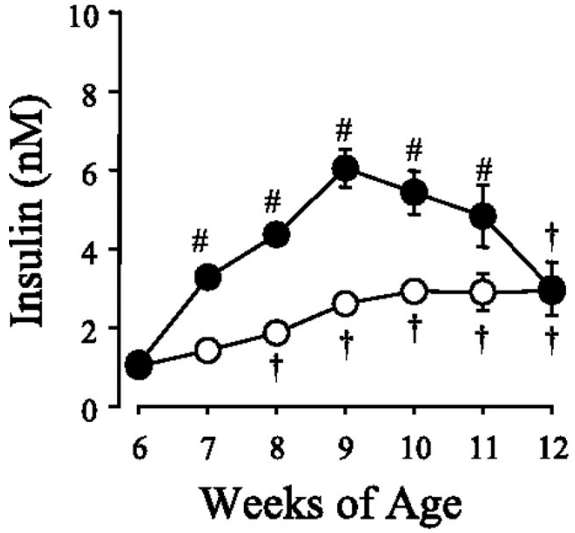
The Standard Model for Pathogenesis of T2D



What about Insulin?

Case Study: ZDF Rats





LF-fZDF (○)

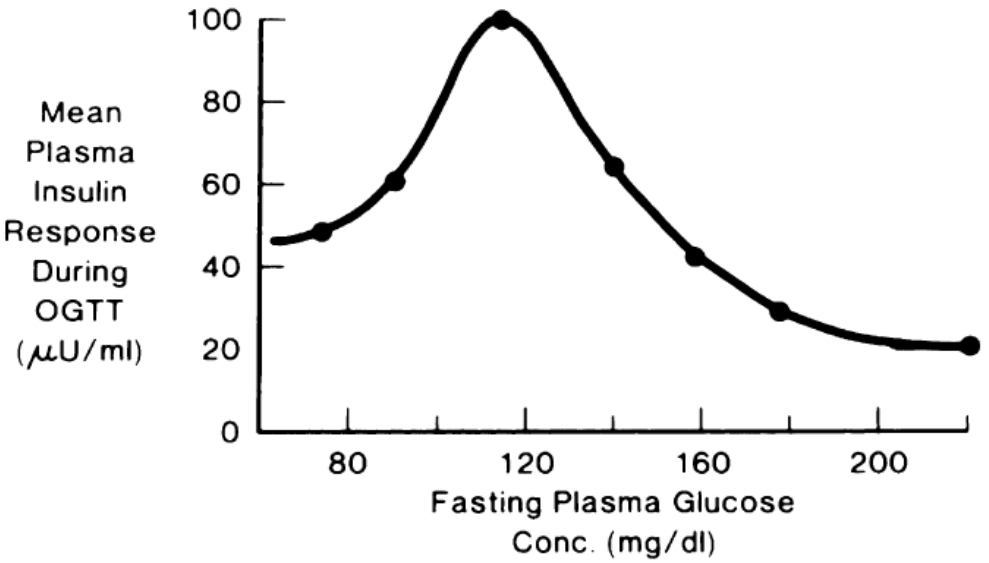
HF-fZDF (●)

"Starling's Law of the Pancreas"

Topp BG et al. Am J Physiol Endocrinol Metab 2007;293:E1730-E1735

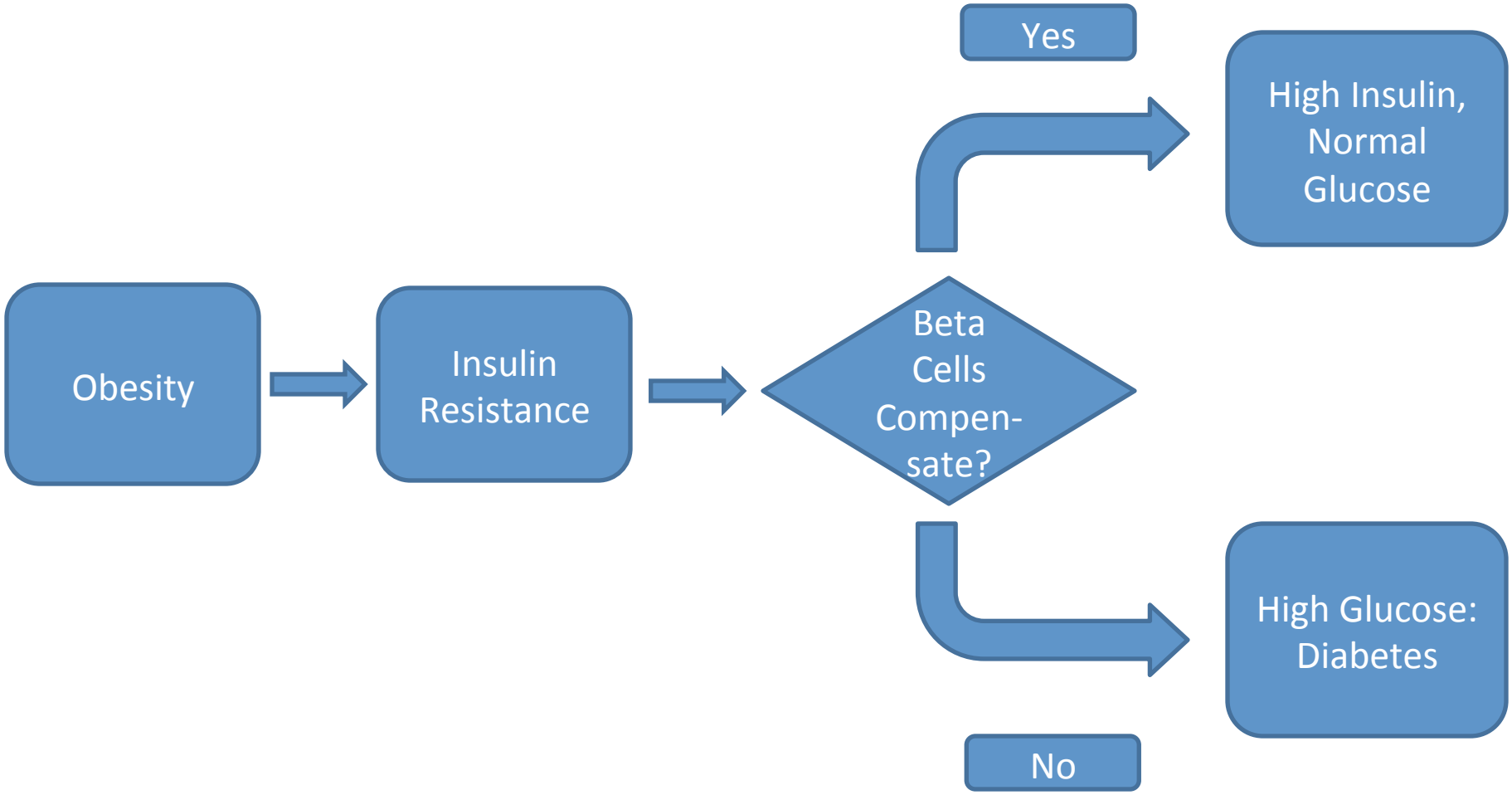
Starling's Law in Humans

Humans

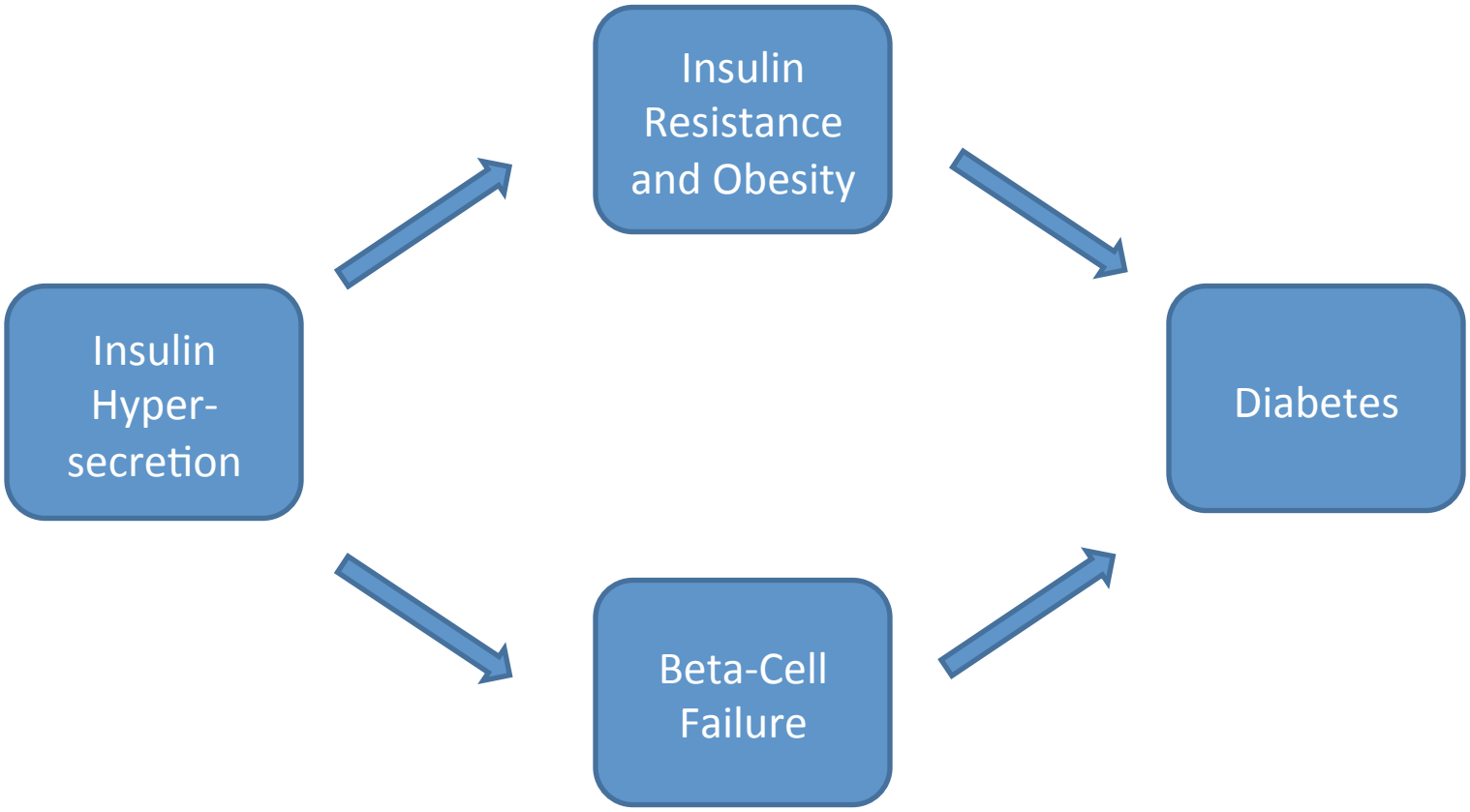


DeFronzo, Diabetes 37:667 1988 (Lilly Lecture)

The Standard Model for Pathogenesis of T2D



An Alternate Model for Pathogenesis of T2D



Two Hypotheses for Pathogenesis of T2D

- The "Standard Model":
  - Insulin resistance appears
  - Insulin secretion increases to compensate
  - If secretion is adequate, hyperinsulinemia persists but diabetes is avoided
  - If secretion is inadequate, diabetes develops
- The "Alternate Model":
  - Hypersecretion is the primary defect
  - Insulin resistance develops to compensate
  - If beta cells fail, diabetes develops

Basic Glucose-Insulin Homeostasis

$$\frac{dG}{dt} = HGP + Meals - Uptake$$

$$\frac{dI}{dt} = Secretion - Clearance$$

To maintain normal glucose:

- If *Uptake* decreases or *HGP* increases,
  Secretion must increase or *Clearance* must decrease
- If *Secretion* increases,
  HGP must increase or *Uptake* must decrease

More Specifically

Equations adapted from the Bergman-Cobelli Minimal Model

$$\frac{dG}{dt} = HGP + Meal - (E_{G0} + S_I I)G$$

$$\frac{dI}{dt} = \frac{\beta\sigma}{BV} R_{IS}(G) - kI$$

- If S_I decreases but I increases proportionally G remains the same.
- As $S_I I$ goes down, G rises, leading to T2D (Disposition Index).
- I can be increased by increasing mass (β) or function (σ) or reducing clearance (k).

The βIG-Topp Model

Fast

$$\frac{dG}{dt} = R_0 - (E_{G0} + S_I I)G$$

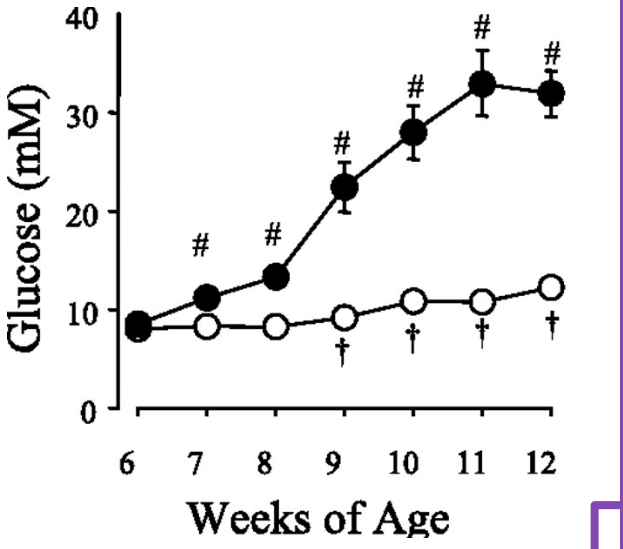
$$\frac{dI}{dt} = \frac{\beta\sigma}{BV} R_{IS}(G) - kI$$

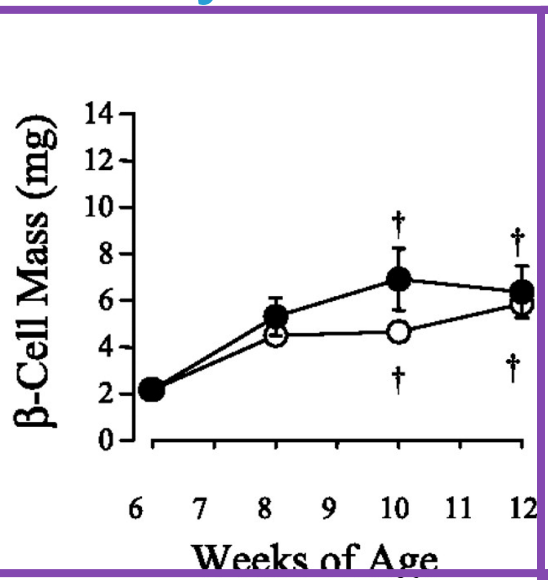
Slow

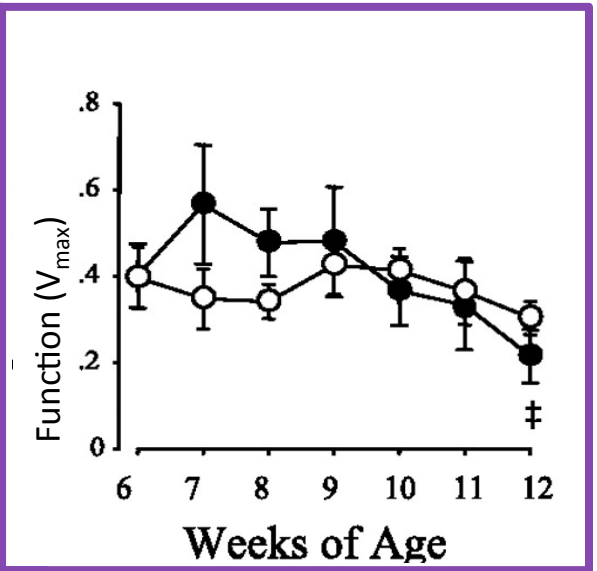
$$\frac{d\beta}{dt} = \frac{[P(G) - A(G)]\beta}{\tau_\beta}$$

Topp … de Vries … Miura … Finegood, J. Theor. Biol. 206:605 2000

Case Study: ZDF Rats

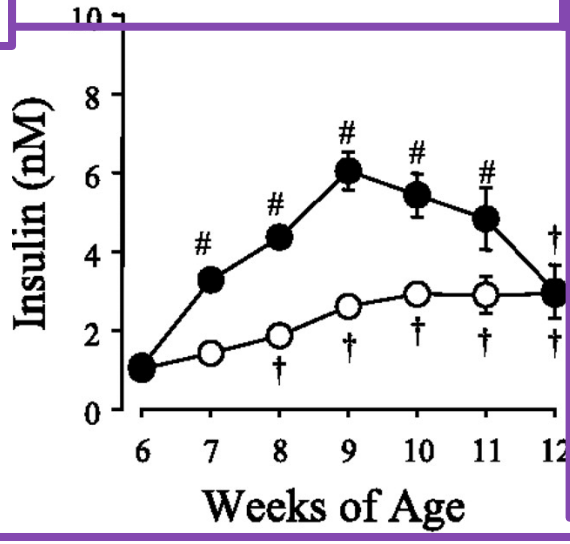


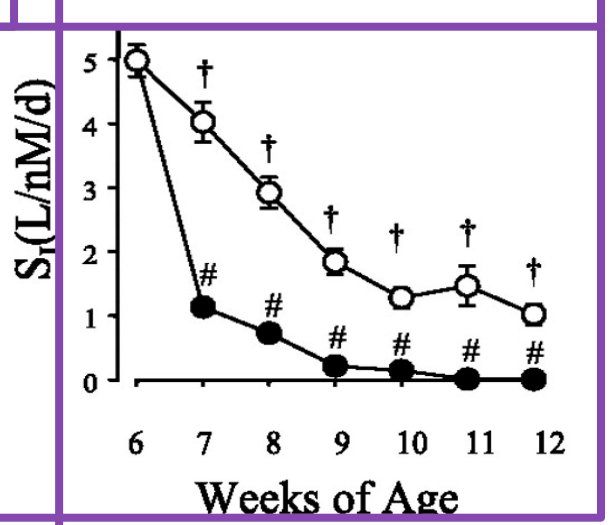




LF-fZDF (○)

HF-fZDF (●)





Topp BG et al. Am J Physiol Endocrinol Metab 2007;293:E1730-E1735

Hierarchy of β-cell Responses

Our Equations

Fast

$$\frac{dG}{dt} = R_0 - (E_{G0} + S_I I)G$$

$$\frac{dI}{dt} = \frac{\beta\sigma}{BV} R_{IS}(G;\gamma) - kI$$

Slow

$$\frac{d\beta}{dt} = \frac{[P(G) - A(G)]\beta}{\tau_\beta}$$

Intermediate

Our Equations

Fast

$$\frac{dG}{dt} = R_0 - (E_{G0} + S_I I)G$$

$$\frac{dI}{dt} = \frac{\beta\sigma}{BV} R_{IS}(G;\gamma) - kI$$

Intermediate

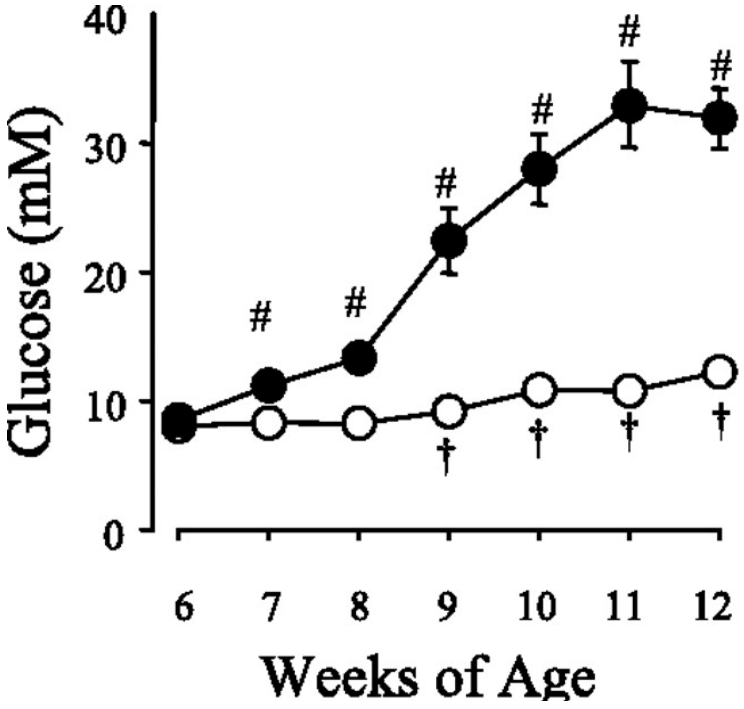
$$\frac{d\gamma}{dt} = \frac{\gamma_\infty(G) - \gamma}{\tau_\gamma}$$

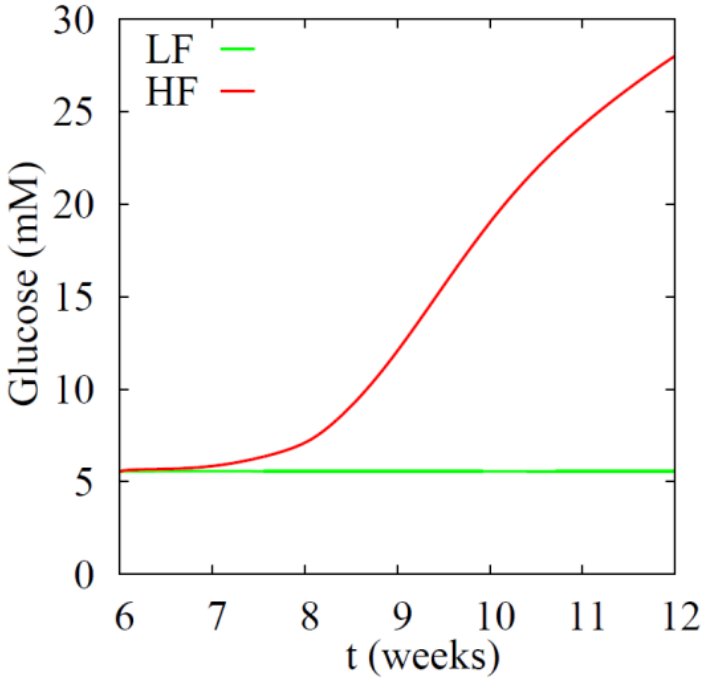
Slow

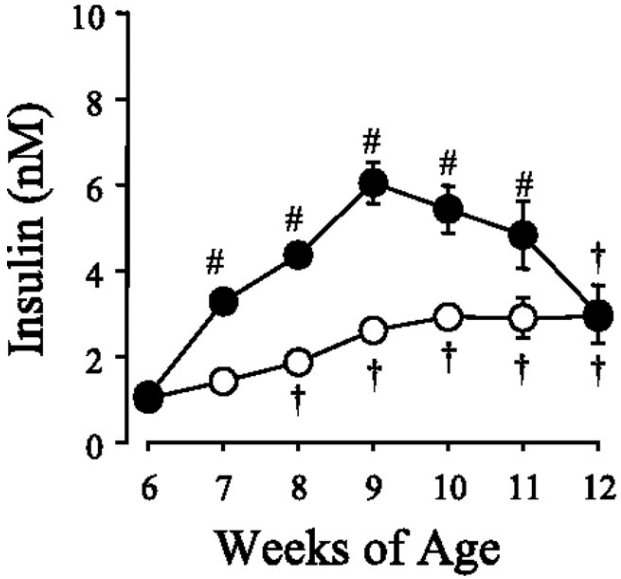
$$\frac{d\sigma}{dt} = \frac{\sigma_\infty(G) - \sigma}{\tau_\sigma}$$

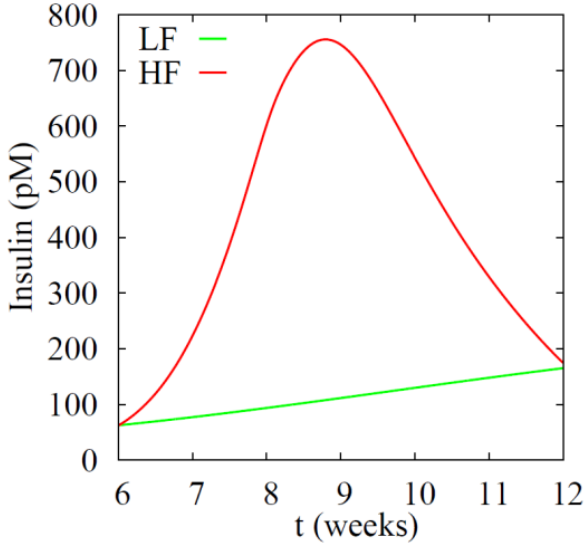
$$\frac{d\beta}{dt} = \frac{[P(G) - A(G)]\beta}{\tau_\beta}$$

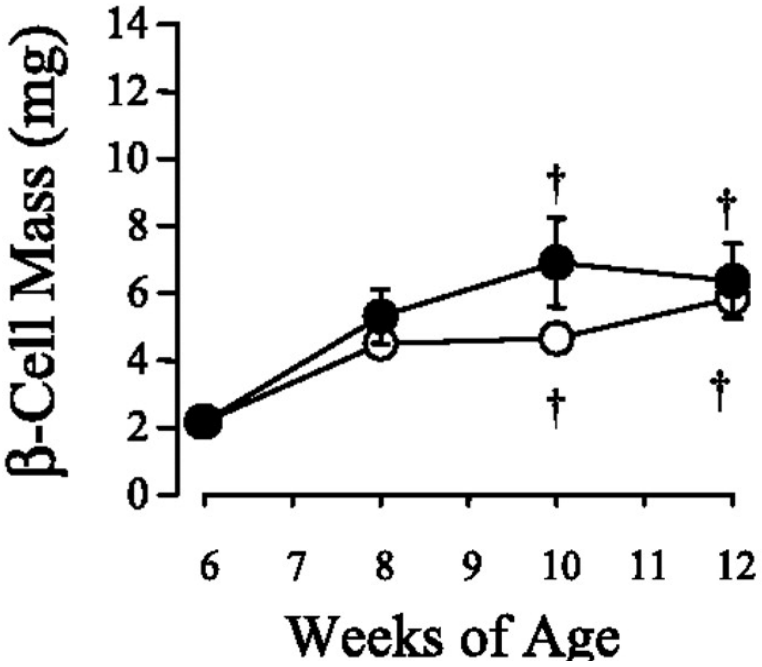
Ha et al, Endocrinology, 157:624 2016

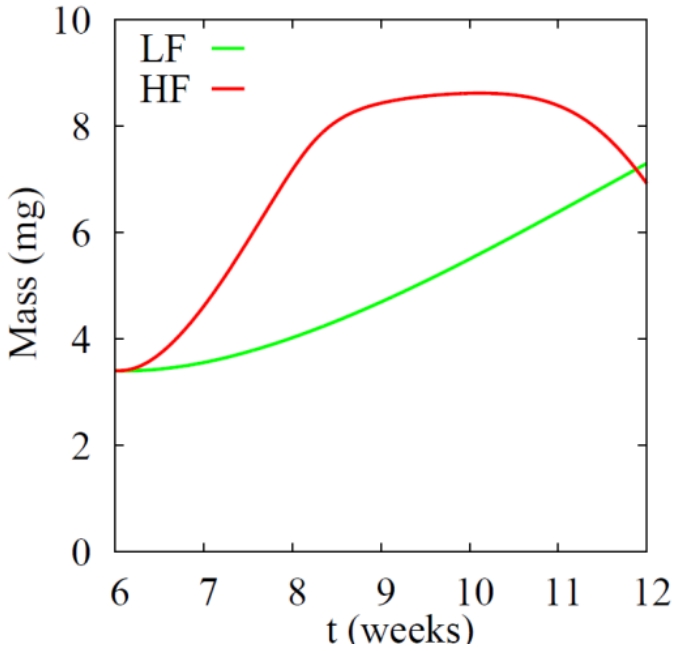

Glucose (mM)
0
10
20
30
40
6
7
8
9
10
11
12
Weeks of Age
#
†

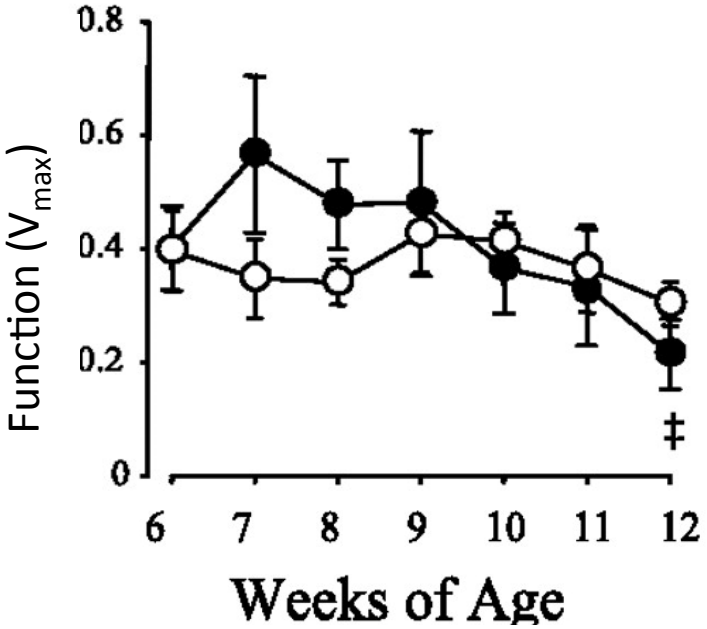

Glucose (mM)
0
5
10
15
20
25
30
6
7
8
9
10
11
12
t (weeks)
LF
HF

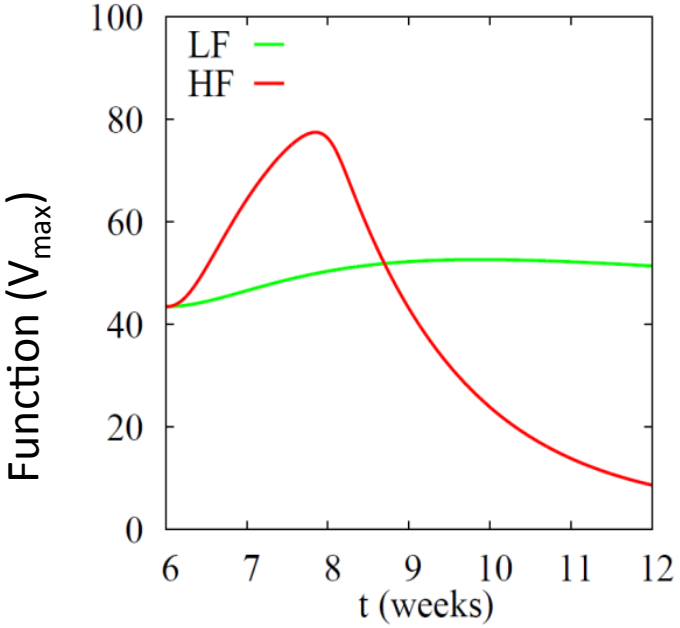

Insulin (nM)
Weeks of Age
0
2
4
6
8
10
6
7
8
9
10
11
12
#
†

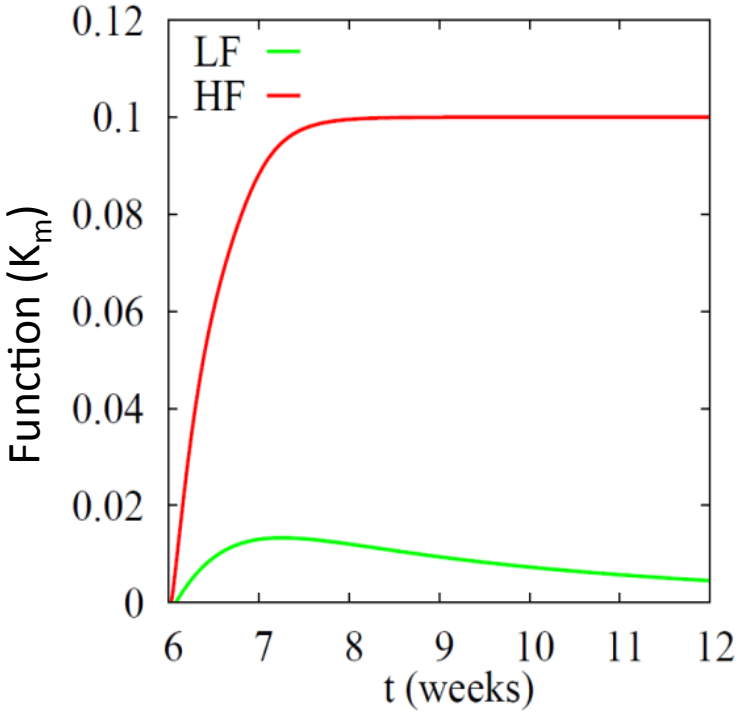

Insulin (pM)
t (weeks)
LF
HF
0
100
200
300
400
500
600
700
800
6
7
8
9
10
11
12


β-Cell Mass (mg)
14
12
10
8
6
4
2
0
†
†
†
†
6
7
8
9
10
11
12
Weeks of Age

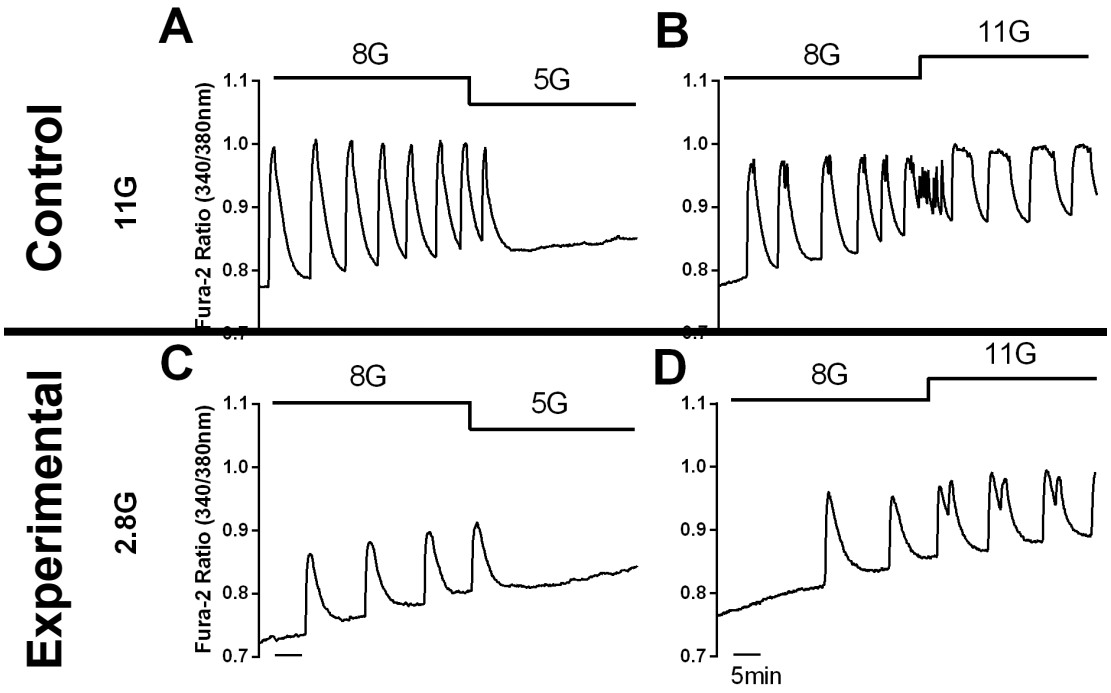

10
8
6
4
2
0
LF
HF
Mass (mg)
6
7
8
9
10
11
12
t (weeks)

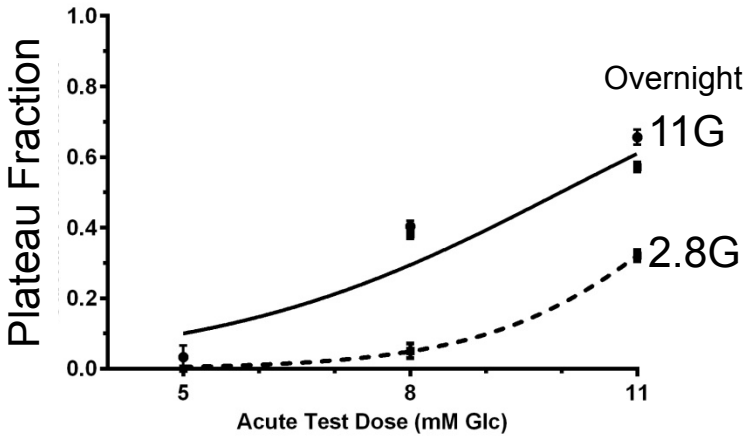

Function (V_{max})
0.8
0.6
0.4
0.2
0
6
7
8
9
10
11
12
‡
Weeks of Age


Function (V_{max})
100
80
60
40
20
0
LF
HF
6
7
8
9
10
11
12
t (weeks)


0.12
0.1
0.08
0.06
0.04
0.02
0
Function (K_m)
LF
HF
6
7
8
9
10
11
12
t (weeks)

Confirmation: Overnight High G Shifts Dose Response Left





Glynn et al, Endocrinology, 157:611 2016

What About Us Humans?

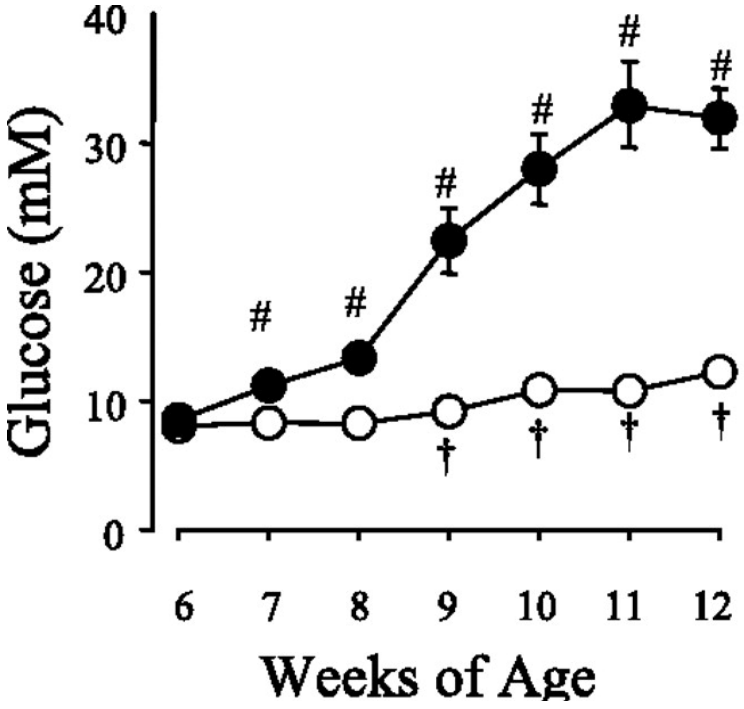
Humans are large, long-lived rodents:
Joon Ha MS 25

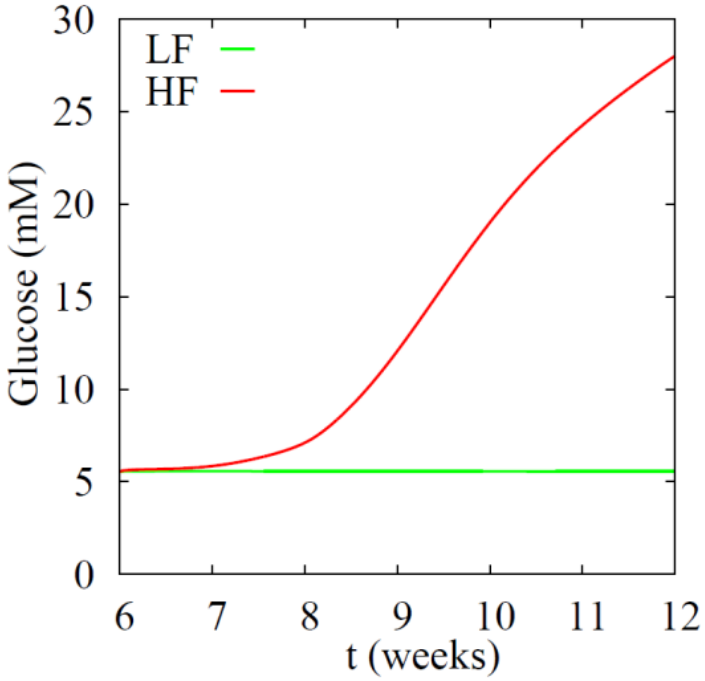
Standard Model vs. the Alternate Model

- The Standard Model:
  - Insulin resistance leads to beta-cell failure
- The Alternate Model:
  - Hypersecretion leads to insulin resistance and beta-cell failure
  - Pranay Goel MS 25 (JTB 384:131 2015)

Argument 1 for the Alternate Model:

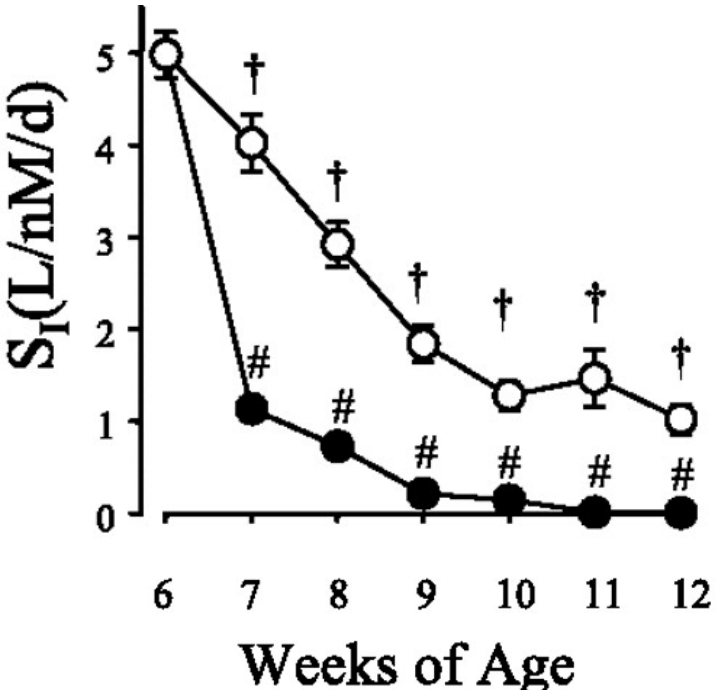
“Hyperinsulinemia appears long before glucose rises.”

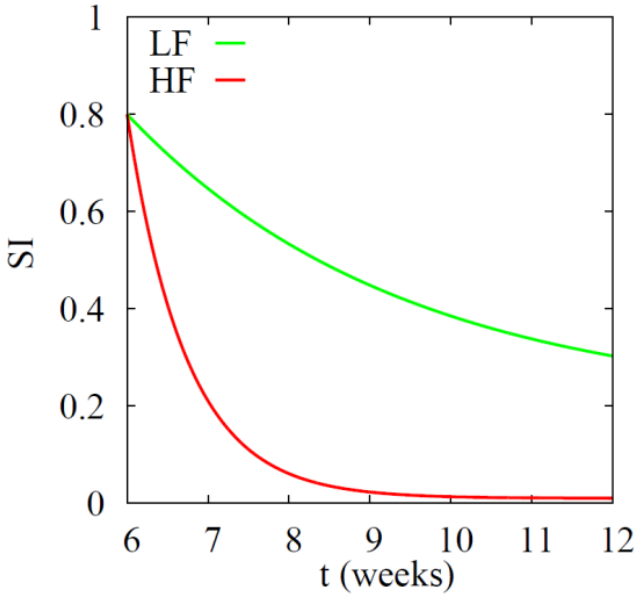

Glucose (mM)
0
10
20
30
40
6
7
8
9
10
11
12
Weeks of Age
#
†


Glucose (mM)
0
5
10
15
20
25
30
6
7
8
9
10
11
12
t (weeks)
LF
HF

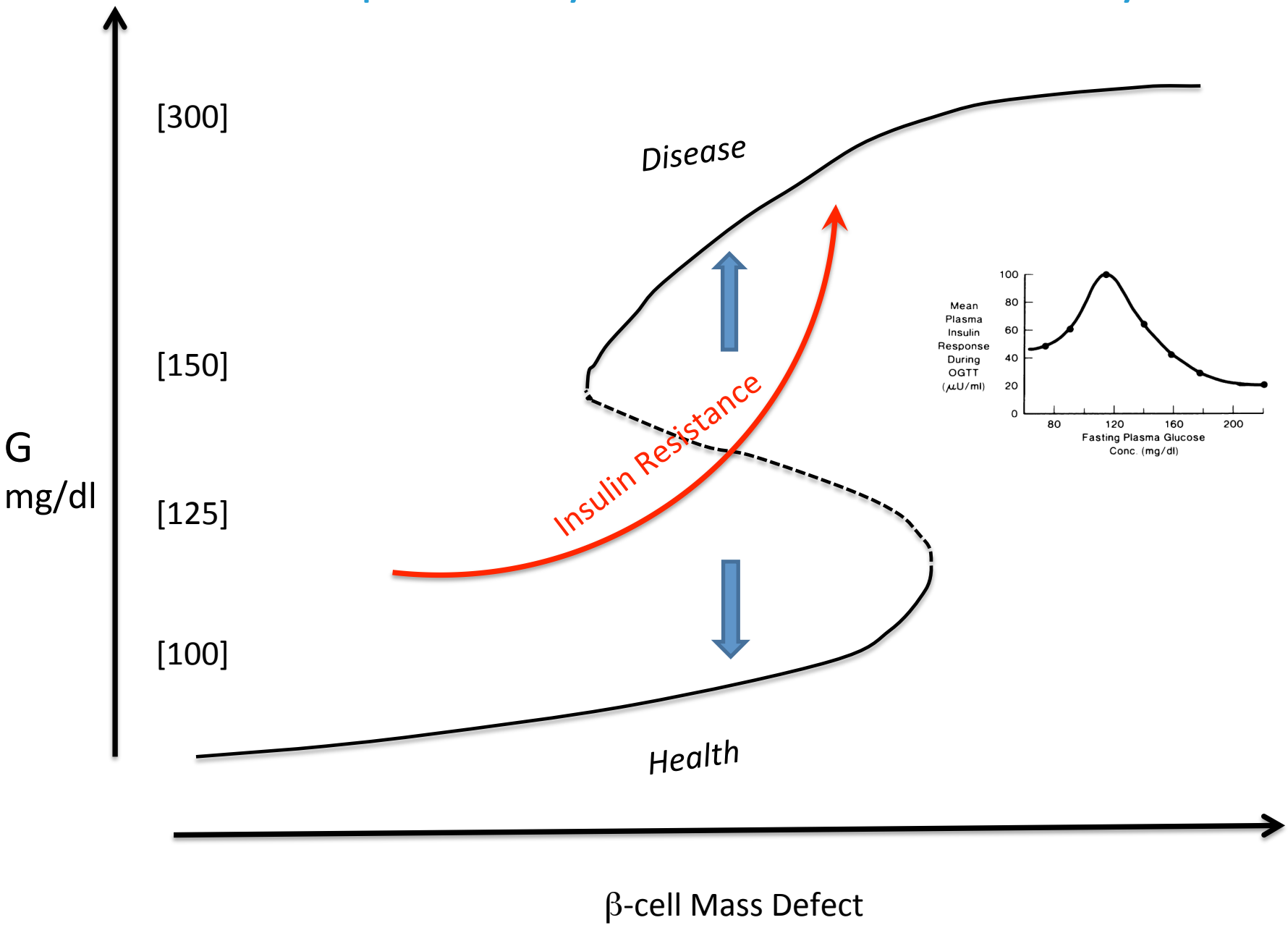
Argument 2 for the Alternate Model:

“Insulin-resistance does not change much immediately preceding diabetes.”


S_I(L/nM/d)
5
4
3
2
1
0
†
#
6
7
8
9
10
11
12
Weeks of Age


SI
1
0.8
0.6
0.4
0.2
0
LF
HF
6
7
8
9
10
11
12
t (weeks)

Both Explained by Threshold and Bistability



Argument 3 for the Alternate Model:

“Induced hyperinsulinemia causes insulin resistance.”

Reducing Insulin Improves Insulin Sensitivity and Promotes Weight Loss

Dz

Beneficial effect of diazoxide in obese hyperinsulinemic adults.

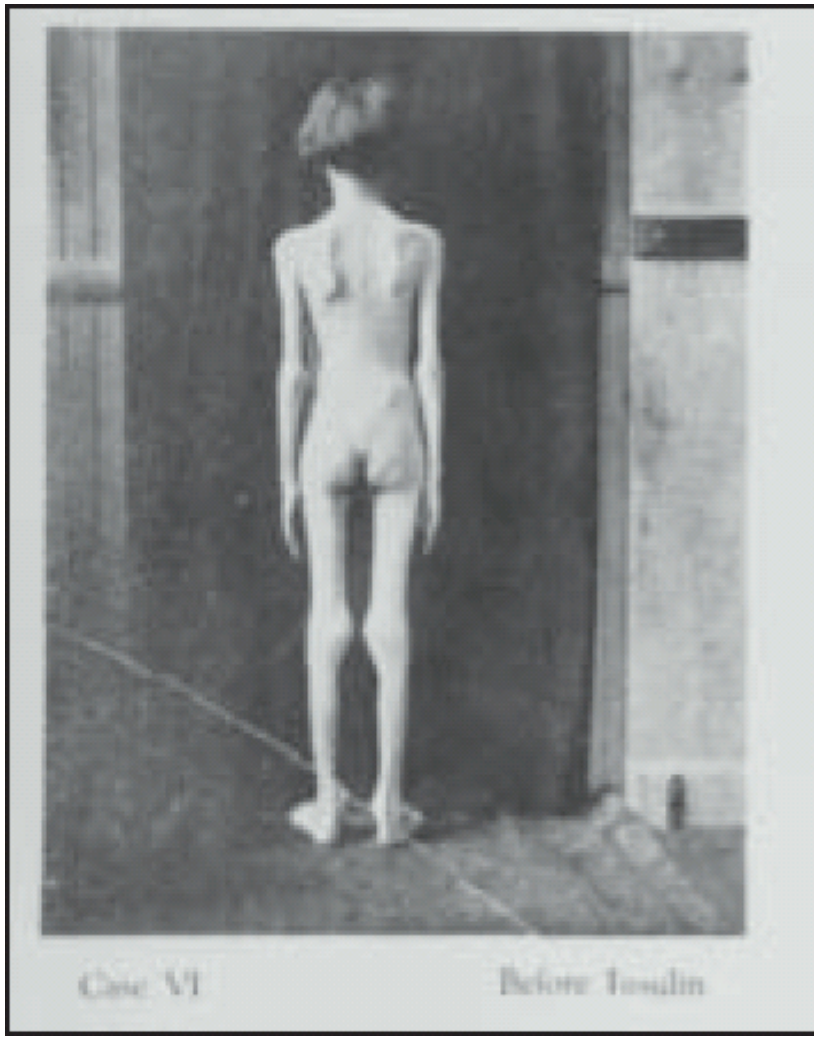
Alemzadeh R, Langley G, Upchurch L, Smith P, Slonim AE.

J Clin Endocrinol Metab. 1998 Jun;83(6):1911-5.

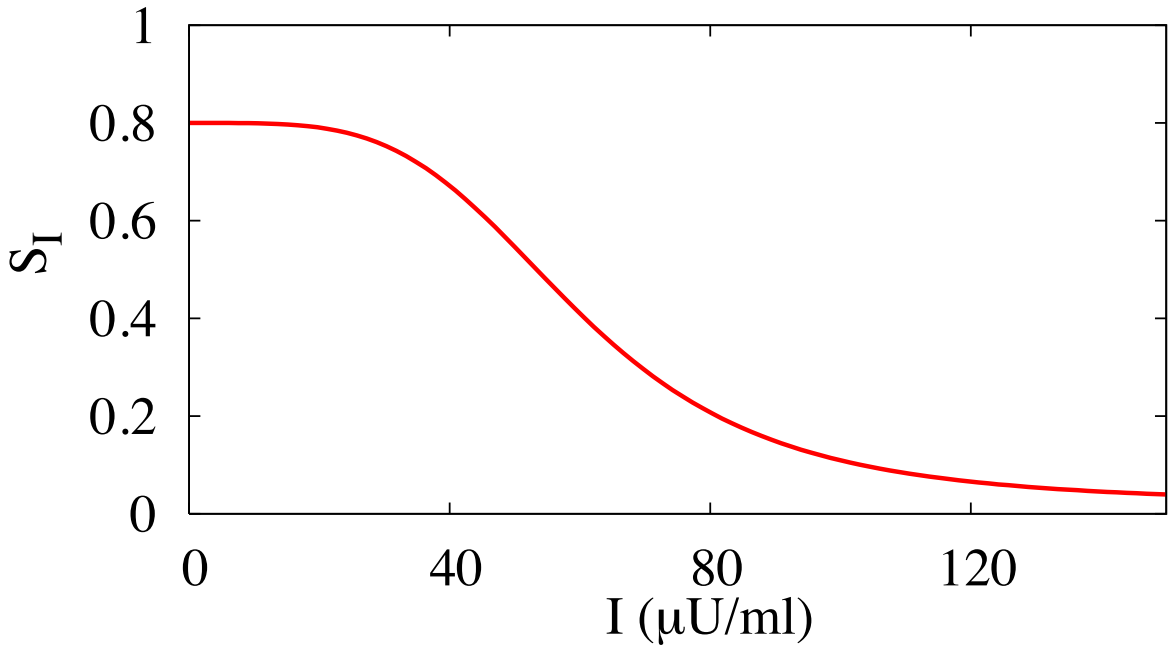
PMID: 9626118

Insulin Does Cause Weight Gain

Courtesy of Eli Lilly and Company Archives



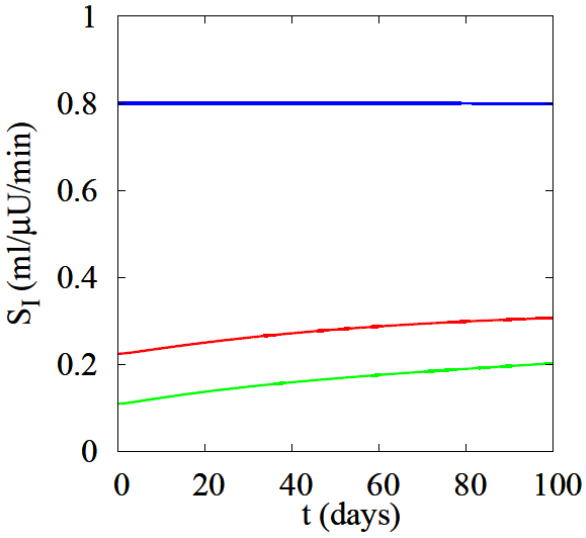
Need One More Assumption: S_I Decreases with Insulin



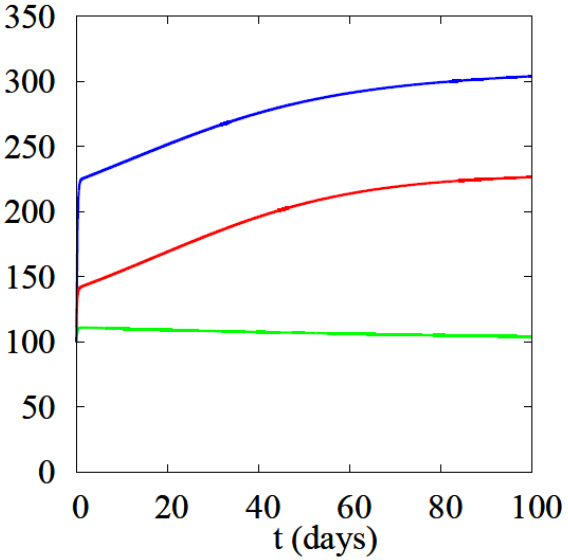
Analogy to friction: The higher *I* is, the more resistance is generated
If *I* is reduced, resistance goes away, as observed experimentally

Effect of Dz on Glucose Tolerance Depends on S_I

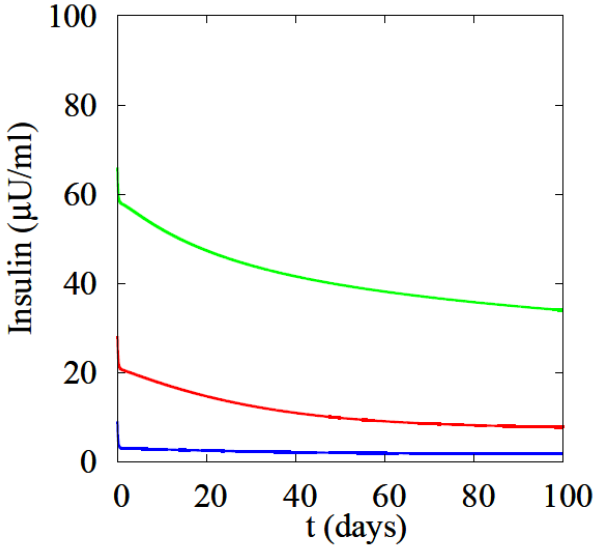
Insulin Sensitivity



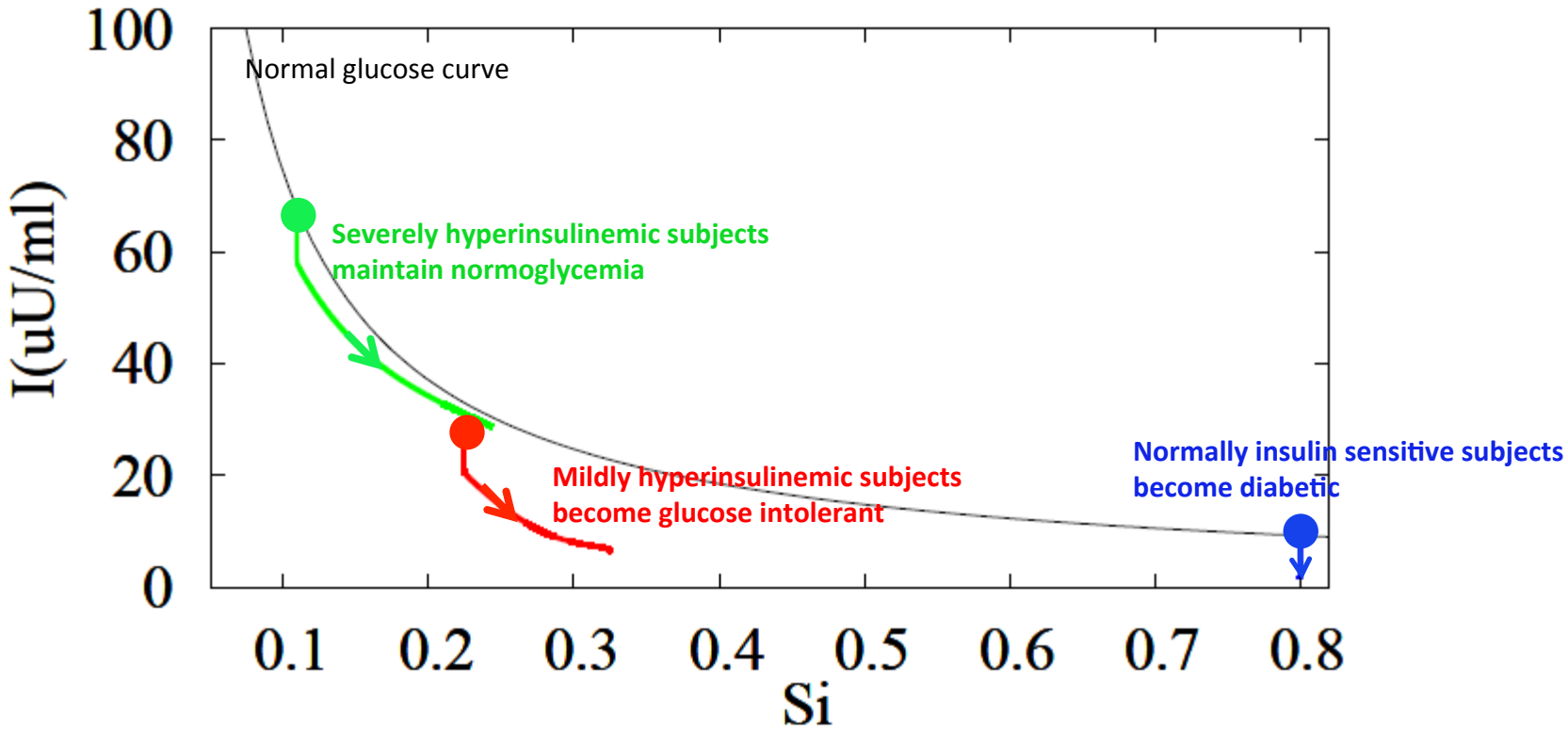
Glucose



Insulin

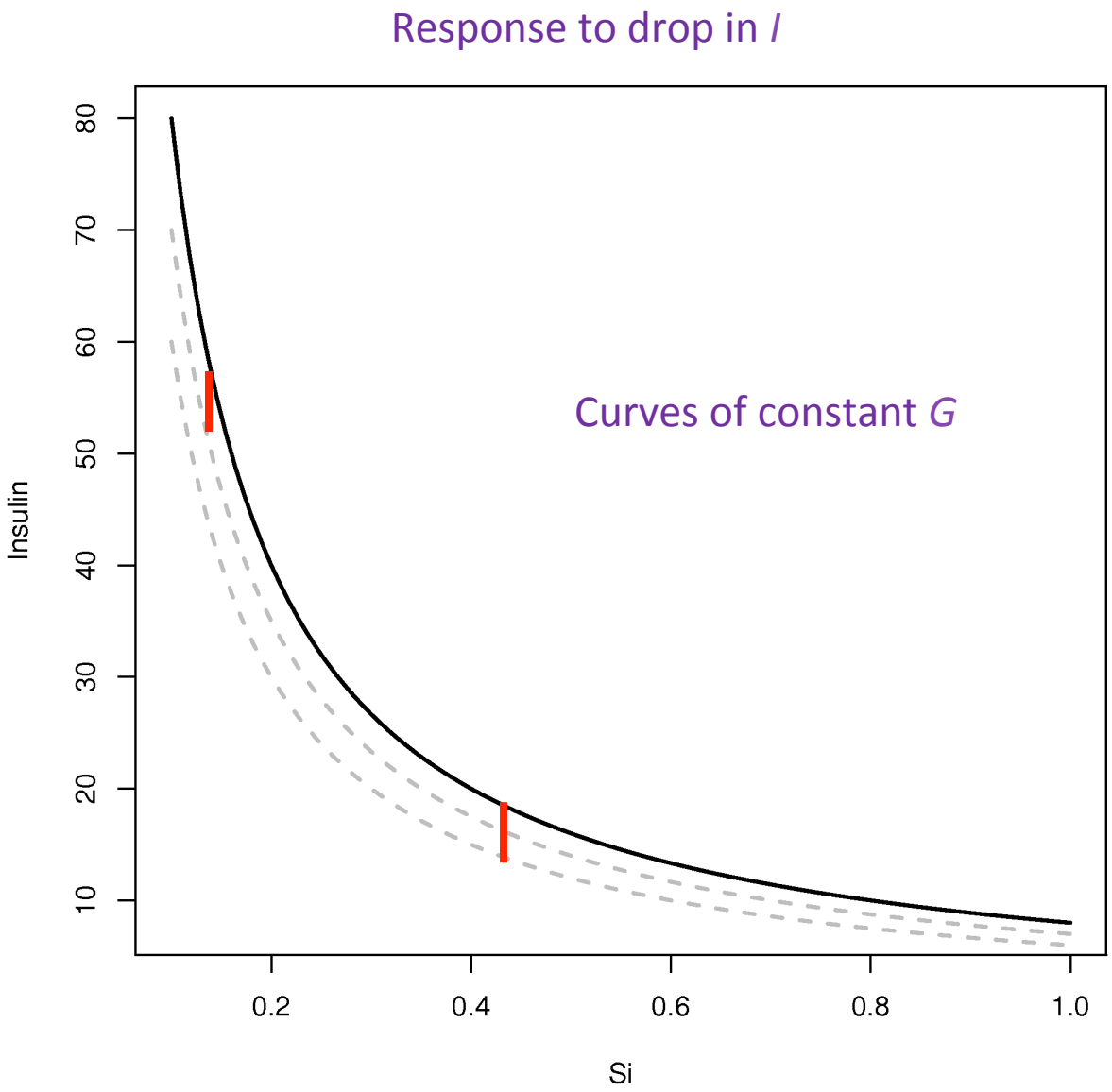


Dz Effect on Glucose Tolerance – model simulations

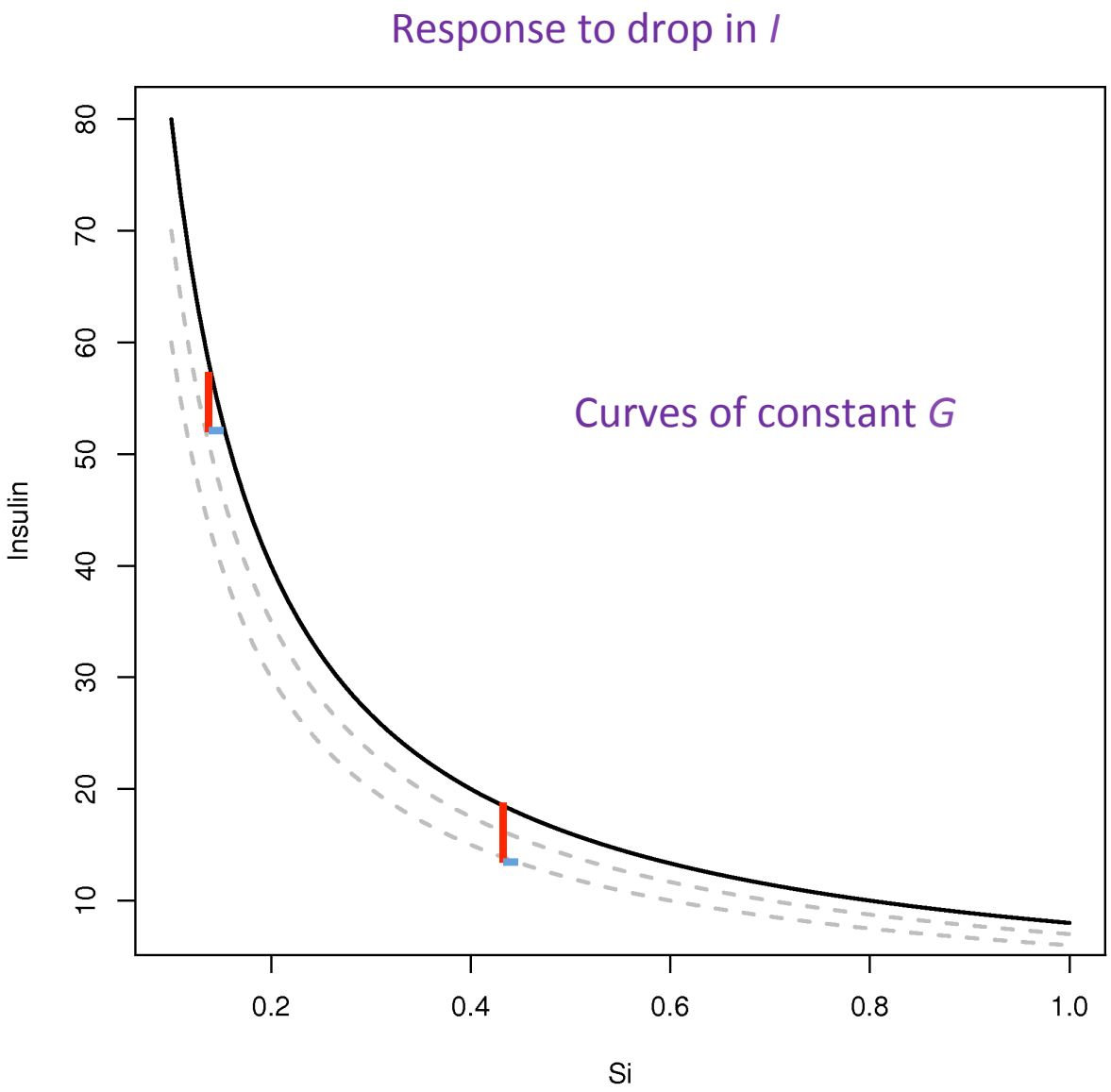


- Dz is only beneficial for severely obese, normoglycemic subjects (upper left corner in I-S_I plane).
- Upper left: A large change in I causes a small change in G
- Lower right: A small change in I causes a large change in G

As S_I Decreases, Increment in G Decreases



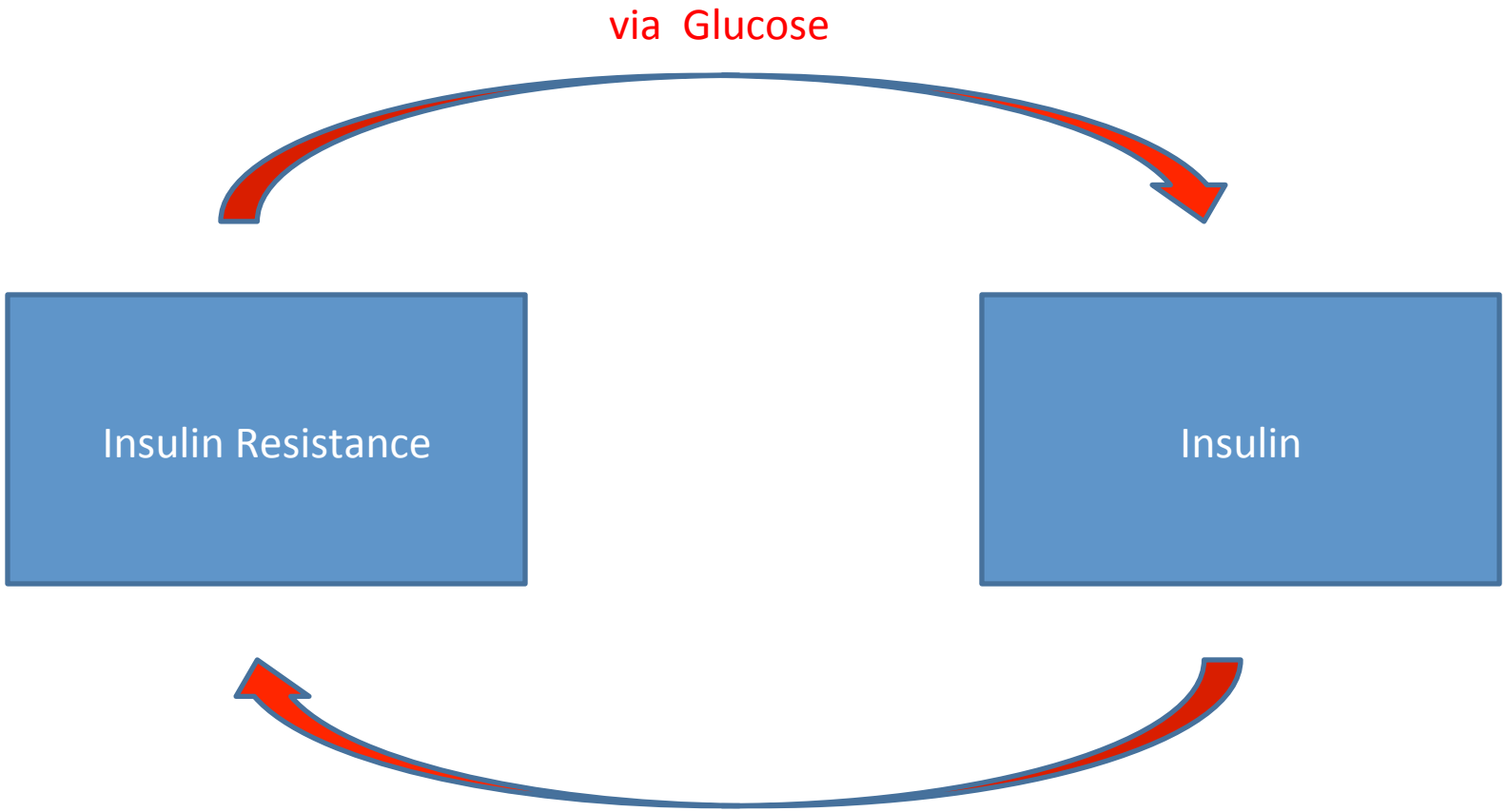
… and same improvement in S_I lowers G more



Conclusion: They picked their subjects carefully (or were lucky)

- Highly insulin-resistant individuals are at least risk for hyperglycemia from reducing insulin
- They experience the greatest gain in insulin sensitivity
- Others would suffer

Combined Model: Closed Loop



Possibility of either self-limiting process or runaway positive feedback
So far, we see only self-limiting, marginal effect

Summary

- We have shown that much of the data used to support the Alternate Model is consistent with the Standard Model
  - Insulin rises before glucose
  - Insulin resistance saturates before T2D appears
- If add frictional insulin resistance
  - Improvement in insulin sensitivity when reduce insulin secretion
  - But this is a marginal effect in typical T2D cases
  - Argues for avoiding excessive use of insulin
- Hypersecretion can also cause beta-cell failure
  - Can explain progression from hypoglycemia to hyperglycemia in cases of extreme, congenital hyperinsulinism
  - Again marginal in typical T2D cases

Argument 4 for the Alternate Model:

“Hyperinsulinemia appears years before insulin resistance is detected.”

This is not possible, unless subjects are hypoglycemic

Hyperinsulinemia and insulin resistance have to appear in tandem

Argument for the frictional model vs. hypersecretion as the driver of insulin resistance:

Insulin sensitizer given to an insulin-resistant, normoglycemic person would leave *I* high but lower *G*. The opposite happens.