Bistability of Beta-Cell Mass in Type 2 Diabetes

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What is Insulin?

• A key hormone to regulate fuel use
  – Cells can use carbohydrate (glucose), fat or protein
• Secreted by pancreatic beta cells
• Allows muscles to consume glucose
• When fasting, muscles use fat
• When fed, muscles use glucose, fat stored in fat cells
Insulin is Secreted by b-cells in Islets in the Pancreas
What is Diabetes?

• Absolute or relative lack of insulin
• Absolute: Type 1 diabetes – loss of beta cells
• Relative: Type 2 diabetes - insulin resistance; associated with
  – Obesity
  – Age
  – Lack of exercise
• Inability to consume glucose results in hyperglycemia
• Organ damage and premature death
What We Know

• Obesity causes insulin resistance
• If beta cells compensate, no diabetes
What We Don’t Know

• How do beta cells compensate?
  – Function (secretion/cell)?
  – Mass (number of cells)?

• What is the signal for compensation?
  – Glucose?
  – Insulin?
The Natural History of Diabetes:
Starling’s law of the pancreas

Humans

DeFronzo, Diabetes 37:667 1988 (Lilly Lecture)
What We Want to Simulate: ZDF Rat

Topp BG et al. Am J Physiol Endocrinol Metab 2007;293:E1730-E1735
The Critical Experiment: Islet Transplantation

Mass homeostasis is regulated by workload, not glucose

Dadon et al, Diabetes, Obesity and Metabolism 14 Suppl 3:101-8, 2012
Hypothesis:
Mass homeostasis is regulated by workload
(secretion per cell)
Secretion is Stimulated by Glucose Metabolism
The Model (1)

\[
\begin{align*}
\frac{dG}{dt} &= R_0 - (E_{G0} + S_I I)G \\
\frac{dI}{dt} &= \frac{\beta \sigma}{M_{body}} \text{ISR}(M) - kI
\end{align*}
\]

Adapted from Bergman-Cobelli Minimal Model

Conclusions:

If $S_I$ decreases, normal fasting $G$ can be maintained by proportionally increasing $I$ and $b$.

It is difficult to disentangle $b$ and $s$. 
The Model (2)

\[
\begin{align*}
\frac{dG}{dt} &= R_0 - (E_{G0} + S_I I)G \\
\frac{dI}{dt} &= \frac{\beta \sigma}{M_{body}} ISR(M) - kI \\
\frac{d\beta}{dt} &= \frac{(P - A) \beta}{\tau_\beta}
\end{align*}
\]

Fast

Slow

Proposed Hierarchy of b-Cell Response

• Post-prandial G rise: Travel up the dose response curve.
• Persistent high G (days – rodent, weeks - human):
  – Shift the dose response curve to the left (higher Ca; g)
  – Increase efficacy of Ca (amplification factor; s).
• Persistent high workload: Proliferate.
The Model (3)

Fast

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

\[
\frac{dI}{dt} = \frac{\beta \sigma}{M_{\text{body}}} \quad ISR(M; \gamma) - kI
\]

Intermediate

\[
\frac{d\gamma}{dt} = \gamma_\infty (G) - \gamma \quad \tau\gamma
\]

Slow

\[
\frac{d\beta}{dt} = (P - A)\beta \quad \tau\beta
\]
The Auxiliary Functions

Graphs showing the relationship between ISR and M, showing curves for different values of S and γ.
Compensation for Insulin Resistance

$S_i$ stepped down from 0.8 to 0.4

Note: Increase in G is ~10%, increase in ISR ~100%.
How Compensation Happens

• Homeostatic control of workload leads naturally to homeostatic control of $G$ via increased mass
• Workload is a more sensitive indicator of demand for insulin than $G$
• Can also compensate by increased function ($s$)
Case Study: ZDF Rats

LF-fZDF (○)

HF-fZDF (●)

Insulin peaks before mass: Function (s) must decline

Topp BG et al. Am J Physiol Endocrinol Metab 2007;293:E1730-E1735
The Model (4)

\[ \frac{dG}{dt} = R_0 - (E_{G_0} + S_I I)G \]

\[ \frac{dI}{dt} = \frac{\beta \sigma}{M_{\text{body}}} \text{ISR}(M; \gamma) - kI \]

\[ \frac{d\gamma}{dt} = \gamma_\infty(G) - \gamma \]

\[ \frac{d\tau}{dt} = \tau_\gamma \]

\[ \frac{d\sigma}{dt} = \sigma_\infty(M, \text{ISR}) - \sigma \]

\[ \frac{d\beta}{dt} = (P - A)\beta \]
Proposed Mechanism for Function Defect

![Graph showing the relationship between sigma and glucose levels.](image)
Hypothesis: The only difference between LFD and HFD rats is rate and extent of fall in $S_i$
Simulations of ZDF Rats

Note: Insulin peaks before mass
How Failure Happens

- Increased workload increases mass
- If mass fails to increase rapidly enough, function declines
- Decline of function leads to beta-cell death
- To maintain normoglycemia, need b to increase as fast as $S_1$ falls
Starling’s law of the pancreas

Humans

Rats (Simulation)
Recall: The Fast G-I Subsystem

Adapted from Bergman-Cobelli Minimal Model

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

\[
\frac{dI}{dt} = \frac{\beta \sigma}{M_{body}} ISR(M) - kI
\]
Progressive Reduction of $S_I$

Curves of constant $G$

Slow reduction of $S_I$: 
- $b$ increases, $G$ mildly elevated (constant disposition index)

Rapid reduction of $S_I$: 
- Eventually decreases, $G$ rises (decreased disposition index)
Falling off the DI curve corresponds to the Starling peak.
Reversing Diabetes: Look Ahead Trial

• Goal: Lose 7% of body weight through moderate calorie reduction and exercise
• Only about 10% experienced remission first year, many relapsed over the next few years
• In contrast, a similar intervention in pre-diabetes reduced conversion to diabetes 56%

Gregg et al, JAMA 308:2489 2012
Intensive Lifestyle Intervention: Early and Rapid Succeed, Late Fails
Bariatric Surgery

Roux-en-Y stomach bypass: large portion of stomach and duodenum are bypassed

Rapid Reversal of DM by Bariatric Surgery

Increase $S_i$, reduce $R_0$, increase $s$
The Central Principle

ISR-based homeostasis plus a threshold explains everything
Lifestyle Intervention: Must be Early and Rapid
Rapid Reversal of DM by Bariatric Surgery
The Heart of the Model: Threshold and Bistability

The diagram illustrates the relationship between glucose concentration (G, mg/dl) and b-cell mass defect. The graph shows the transition from health to disease states through processes such as weight gain and typical weight loss. Acute caloric restriction is also depicted as a possible route to disease states. The thresholds and bistability points are key in understanding the model's dynamics.
Important:

$S_i$ can’t change $b, G$ steady states but can shift the trajectory across thresholds
The Heart of the Model: Threshold and Bistability

The diagram shows the relationship between glucose concentration (G in mg/dl) and b-cell mass defect. It illustrates the transition between health and disease states under different conditions of weight gain and acute caloric restriction. The graph highlights the thresholds and bistable states in glucose homeostasis.
Is There Evidence for a Threshold?
Longitudinal Two-Hour Glucose Measurements in 55 Pima Indians

Mason et al., Diabetes 2007;56:2054-2061
Is There Evidence for Bistability?
Partial Pancreatectomy Results in Bimodal Glycemia

Experiment, Laybutt et al, JBC, 2003

Simulation

Model tells us: Bimodality results from Bistability
Monostable Model

No rapid reversal of diabetes
Conclusions

• No one cause, but dynamic balance of mass, function and insulin resistance
• Workload, not G per se, drives compensation to insulin resistance
• Diabetes results when resistance worsens faster than secretion rises
• Model is bistable with a threshold:
  – Below threshold, mass increases; above, mass decreases
  – Peak in “Starling’s law of the pancreas” corresponds to crossing the threshold
  – Explains why prevention is easier than cure
  – Explains why bariatric surgery works: Improves insulin sensitivity rapidly
Don’t Pop the Champaign Cork Yet

• Model reinforces emphasis on prevention – but we don’t have drugs safe enough to give to people who are not yet sick.

• Clinical researchers want to know what molecules to target – model can’t tell them that.

• Concern that it doesn’t apply to humans.
Five Stages of b-Cell Dysfunction

1 Compensation – normal G
2 Stable Adaptation – reduced mass and function, G starts to rise
3 Transient Decompensation – G rises rapidly
4 Stable Decompensation – frank diabetes
5 Severe Decompensation – irreversible
<table>
<thead>
<tr>
<th>Stage 5 - Decompensation - T1 DM - Ketosis</th>
<th>400</th>
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<tbody>
<tr>
<td>β-cell mass - Severe reduction</td>
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| Stage 4 - Decompensation - Type 2 DM, Early T1 DM | 300 |
| β-cell mass - Reduction                        |     |

| Stage 3 - Decompensation - Transient          | 200 |
| β-cell mass - Borderline                       |     |

| Stage 2 - Adaptation - IGT, Pre-Type 1, Islet Tx | 100 |
| β-cell mass - Borderline                        |     |

| Stages 0 ("Normal") and 1 (Compensated)        | 0   |
| β-cell mass - Normal or increased (Insulin resistance/obesity) |     |

Weir G C, and Bonner-Weir S Diabetes 2004;53:S16-S21