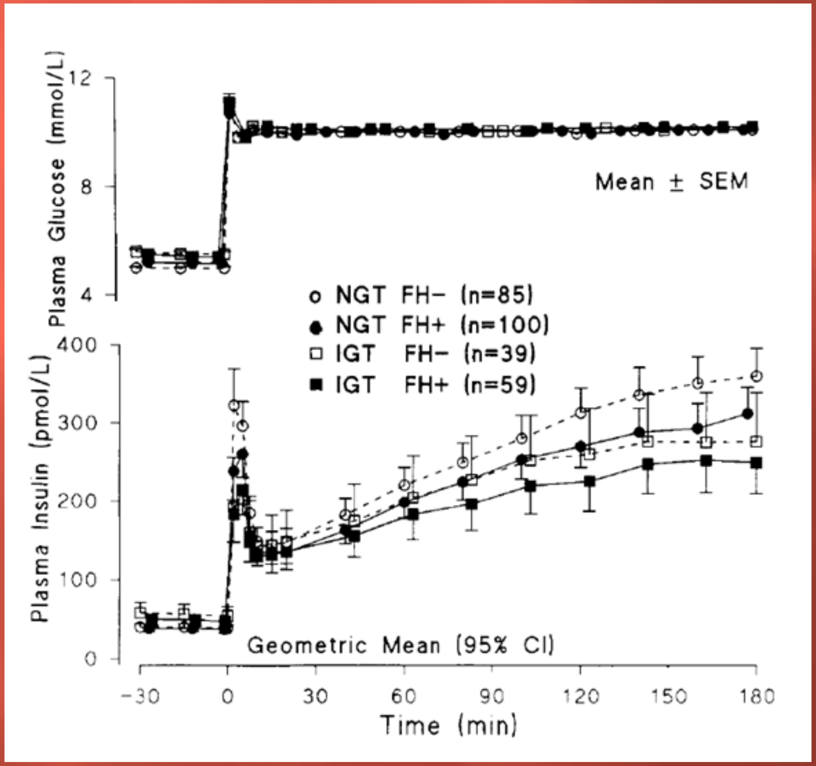
SIMPLE MODELS EXPLAIN COMPLEX PHENOMENA IN GLUCOSE METABOLISM AND INSULIN SECRETION.

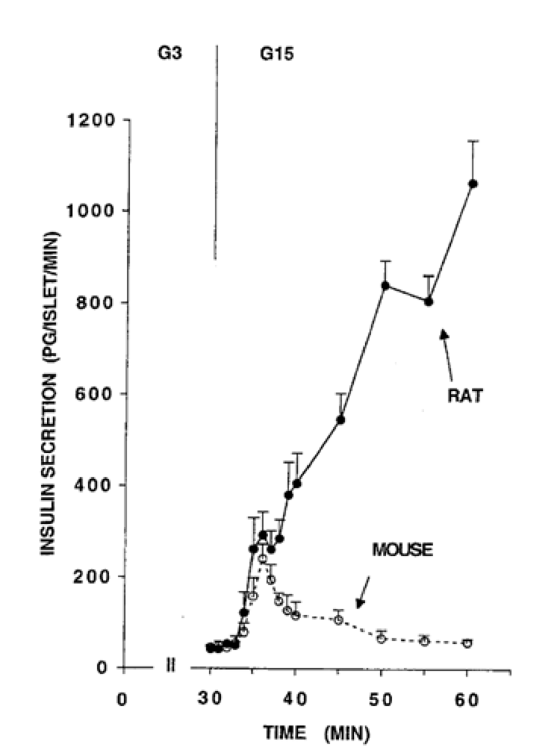
Biphasic Insulin Secretion

- Instantaneous rise in glucose



T.W. van Haeften, W. Pimenta, A. Mitrakou, M. Korytkowski, T. Jenssen, H. Yki-Jarvinen, and J.E. Gerich

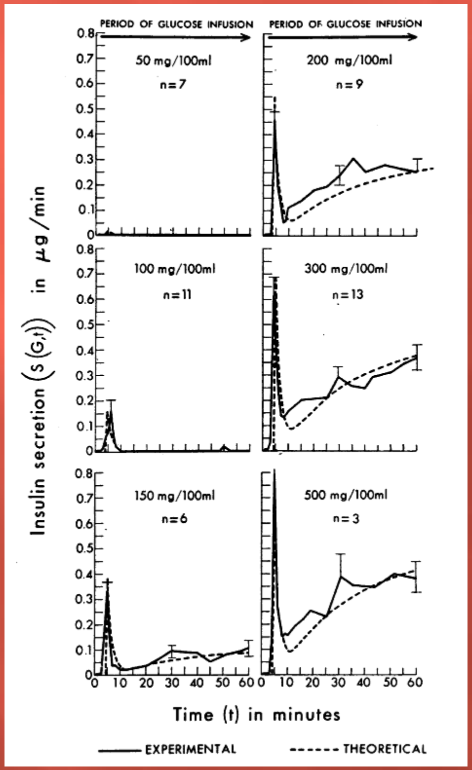
Metabolism, Vol 49, No 10 (October), 2000: pp 1318-1325

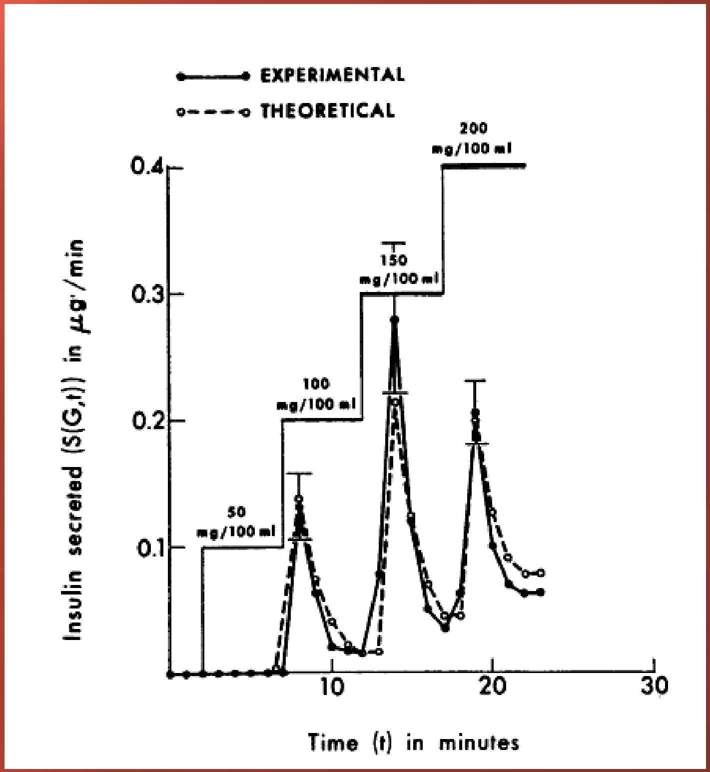


Zawalich WS and Zawalich KC. Species differences in the induction of time dependent potentiation of insulin secretion. *Endocrinology* 137: 1664–1669, 1996.

Dose-dependent Response

- Different Thresholds

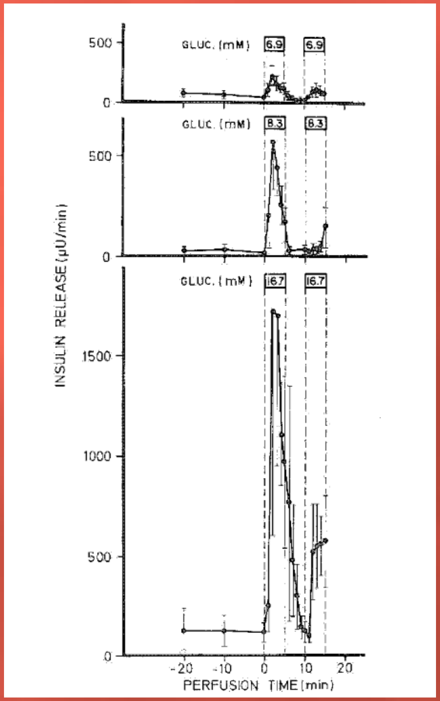




GEROLD M. GRODSKY *The Journal of Clinical Investigation Volume 51 August 1972*

Time-dependent Inhibition

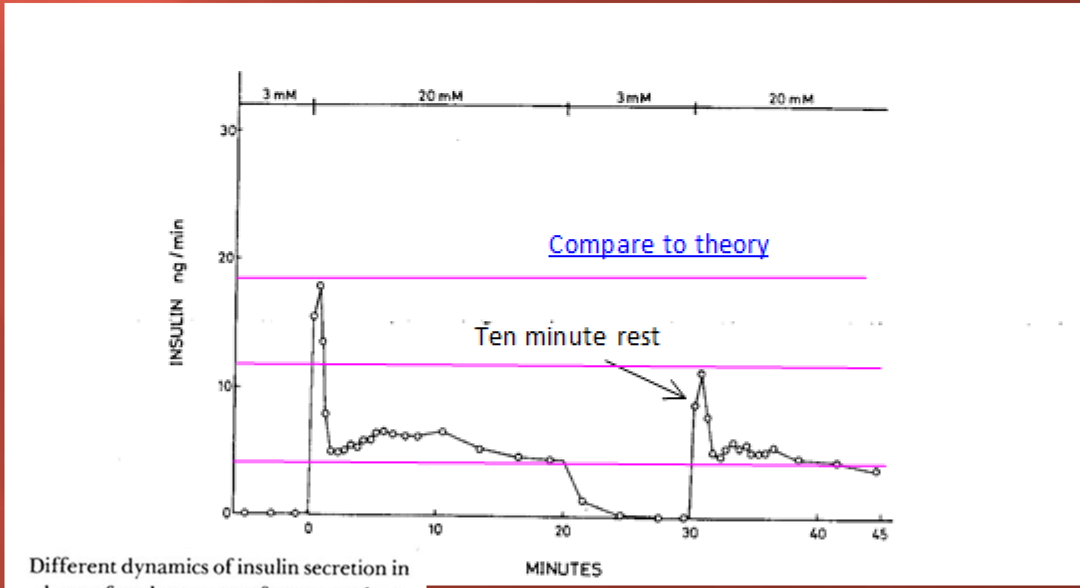
Stimulus-Rest-Stimulus



Biphasic Insulin Release as the Expression of Combined Inhibitory and Potentiating Effects of Glucose*

RAFAEL NESHER AND EROL CERASI

Mouse



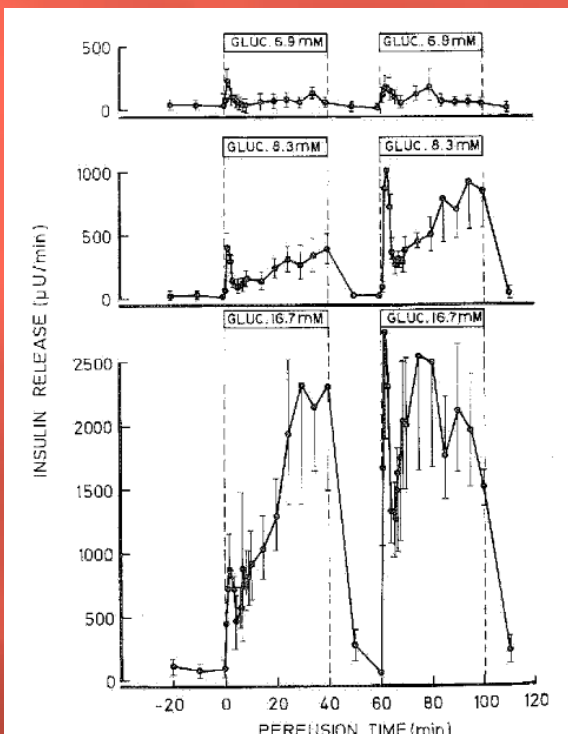
Different dynamics of insulin secretion in the perfused pancreas of mouse and rat

Ove Berglund

Acta endocrinologica 1980, 93: 54–60

Time-dependent Potentiation

- Stimulus-Rest-Stimulus



0013-7227/87/1213-1017$02.00/0
Endocrinology
Vol. 121, No. 3
Printed in U.S.A.

Biphasic Insulin Release as the Expression of Combined Inhibitory and Potentiating Effects of Glucose*

RAFAEL NESHER AND EROL CERASI

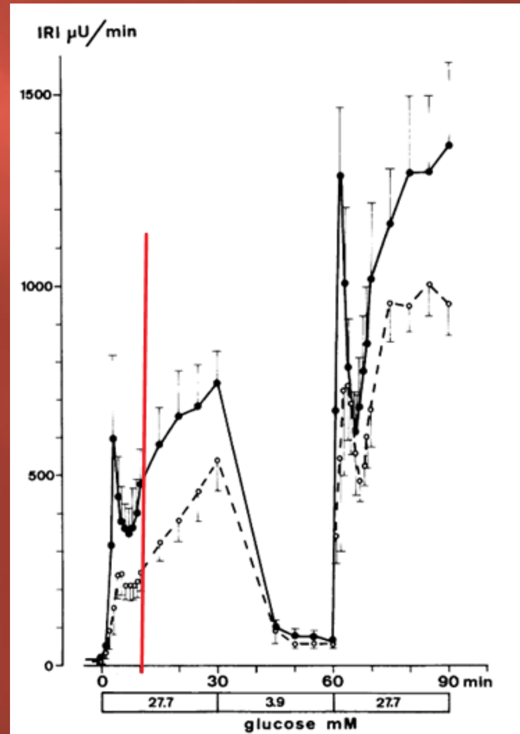


FIGURE 1 Effect of two 30-min pulses of 27.7 mM glucose on insulin secretion in perfused pancreas in fasted (○ - - - ○) or fed (● —— ●) animals. Mean±SEM of 10 and 5 experiments, respectively.

Fed-vs-Fasted

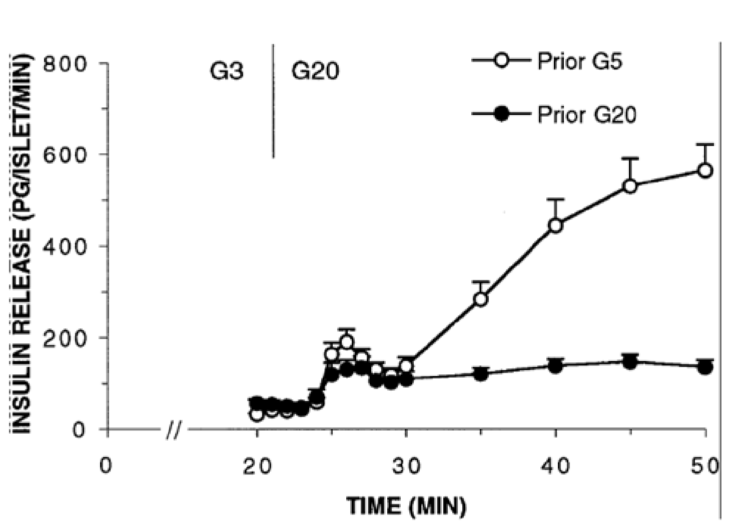
VALDEMAR GRILL, ULF ADAMSON, and EROL CERASI, *Department of Endocrinology, Karolinska Hospital, S-104 01 Stockholm 60, Sweden*

J. Clin. Invest. © The American Society for Clinical Investigation, Inc., 0021-9738/78/0401-1034

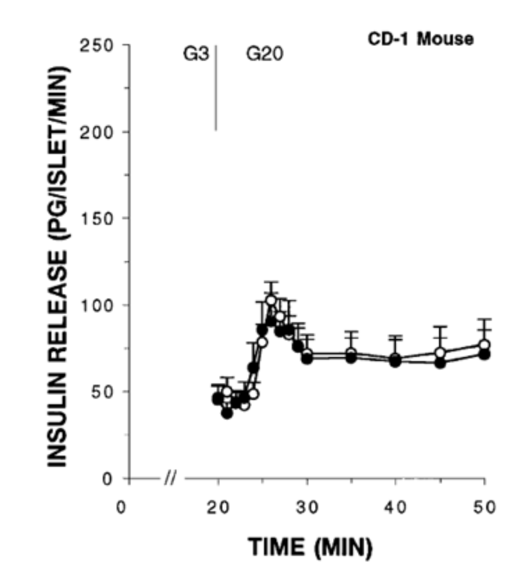
Desensitization

- Prior long-term stimulation

Rat



Mouse



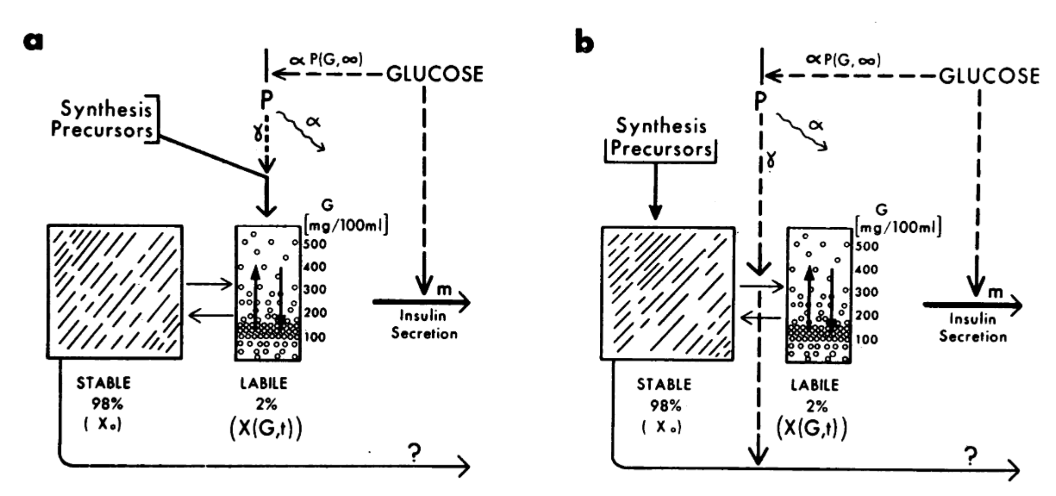
Walter S. Zawalich, Marc Bonnet-Eymard and Kathleen C. Zawalich
Am J Physiol Endocrinol Metab 275:917-924, 1998.

Mathematical Models

- Grodsky, 1972

$$dP(G,t)/dt = \propto (P[G,\infty] - P[G,t])$$

$$P(G,\infty) = G^{K_p}/(C_p + G^{K_p})$$

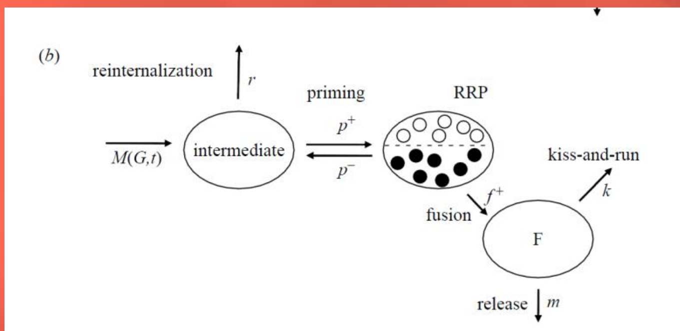


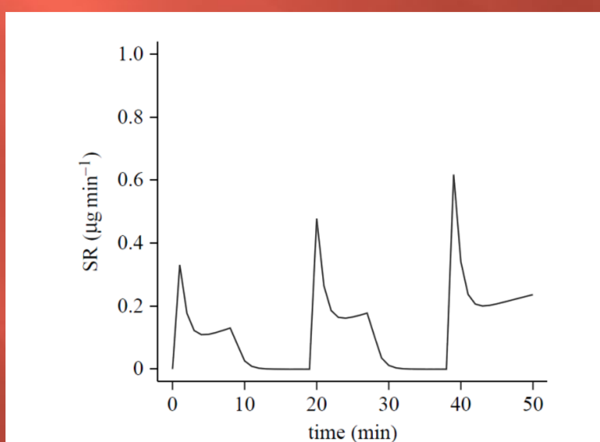
Equations

$dX(G,t)/dt$	$K_1(G,t)\,X_s\,(G,t) - (K_2 + m)\,X\,(G,t)$
$K_1(G,t)$	$K_0 + \gamma\,P(G,t)/X_s(G,0)$
$X(G,0)$	$\int_0^G Z(\theta,0)\,d\theta = X_{max}\,G^K/(C + G^K)$
$X_s(G,0)$	$X_{s\,max}\,G^K/(C + G^K)$
$dX_s(G,t)/dt$	$K_2X(G,t) - K_1(G,t)X_s(G,t)$
$S(G,t)$	$mX(G,t)$

Mathematical Models

- Pedersen *etal.*, 2008





$$\mathrm{d}M(G,t)/\mathrm{d}t = (M(G,t) - M_\infty(G))/\tau,$$

$$M_\infty(G) = cG^{nM}/((K_{mM})^{nM} + G^{nM}) + M_0,$$

$$\mathrm{d}I(t)/\mathrm{d}t = M(G,t) - rI(t) - p^+ I(t) + p^- \int_0^\infty h(g,t)\mathrm{d}g,$$

$$\mathrm{d}h(g,t)/\mathrm{d}t = p^+ I(t)\phi(g)| - p^- h(g,t) - f^+ h(g,t)\theta(G-g).$$

$$\mathrm{d}F(t)/\mathrm{d}t = f^+ \int_0^G h(g,t)\mathrm{d}g - kF(t) - mF(t),$$

$$SR(t) = mF(t),$$

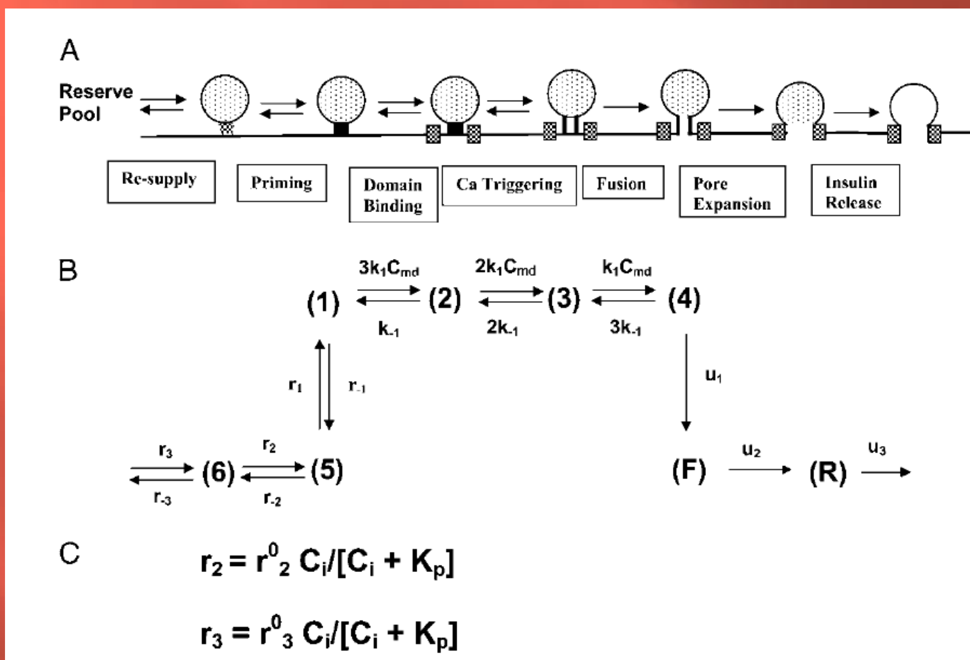
A subcellular model of glucose-stimulated pancreatic insulin secretion

Morten Gram Pedersen, Alberto Corradin, Gianna M Toffolo and Claudio Cobelli

Phil. Trans. R. Soc. A 2008 **366**, 3525-3543
doi: 10.1098/rsta.2008.0120

Mathematical Models

- Chen *etal., 2008*



$$
\begin{aligned}
dN_1/dt &= -[3k_1C_{md}(t) + r_{-1}]N_1 + k_{-1}N_2 + r_1N_5 \\
dN_2/dt &= 3k_1C_{md}(t)N_1 - [2k_1C_{md}(t) + k_{-1}]N_2 + 2k_{-1}N_3 \\
dN_3/dt &= 2k_1C_{md}N_2 - [k_1C_{md}(t) + 2k_{-1}]N_3 + 3k_{-1}N_4 \\
dN_4/dt &= k_1C_{md}(t)N_3 - [3k_{-1} + u_1]N_4 \\
dN_5/dt &= r_{-1}N_1 - [r_1 + r_{-2}]N_5 + r_2N_6 \\
dN_6/dt &= r_3 + r_{-2}N_5 - [r_{-3} + r_2]N_6 \\
dN_F/dt &= u_1N_4 - u_2N_F \\
dN_R/dt &= u_2N_F - u_3N_R,
\end{aligned}
$$

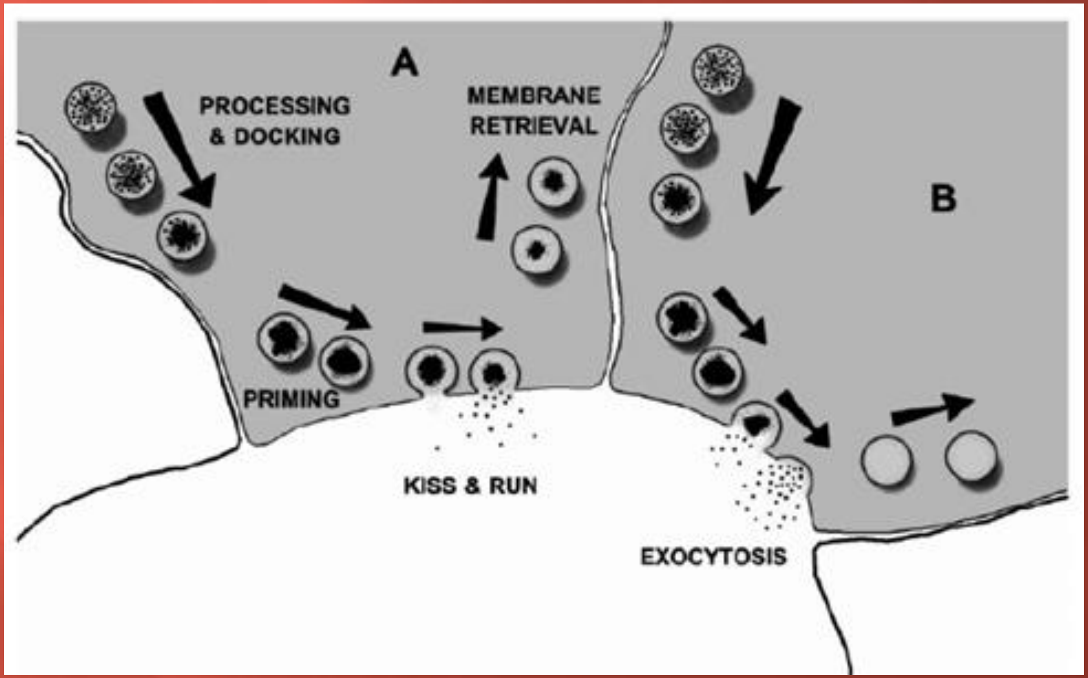
2226 Biophysical Journal Volume 95 September 2008 2226–2241

Identifying the Targets of the Amplifying Pathway for Insulin Secretion in Pancreatic β-Cells by Kinetic Modeling of Granule Exocytosis

Yi-der Chen,* Shaokun Wang,† and Arthur Sherman*

My Model's Inspiration

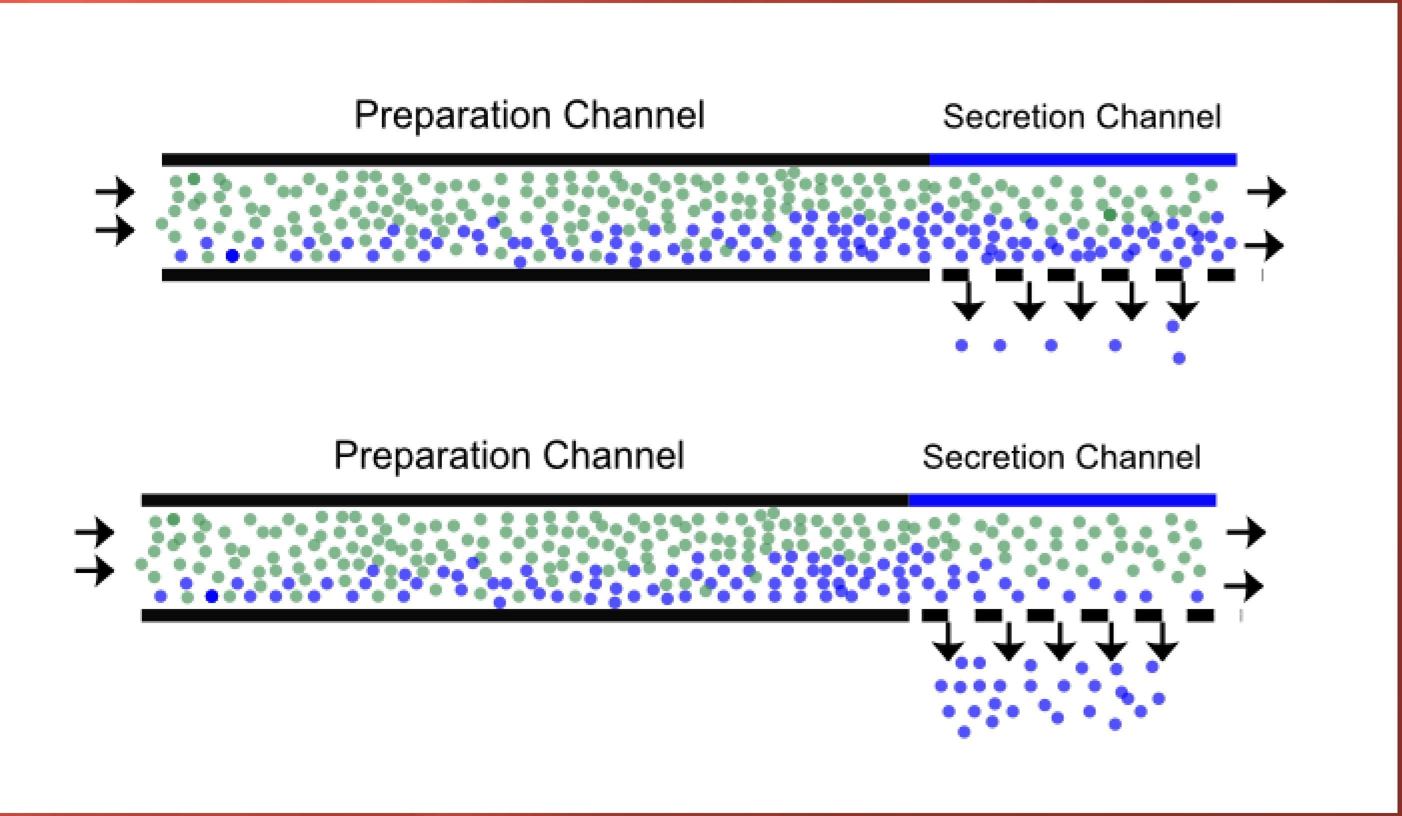
- Cobelli *etal.*, 2007



Claudio Cobelli, Gianna Maria Toffolo, Chiara Dalla Man, Marco Campioni, Paolo Denti, Andrea Caumo, Peter Butler and Robert Rizza
Am J Physiol Endocrinol Metab 293:E1-E15, 2007. First published 6 March 2007;
doi:10.1152/ajpendo.00421.2006

Channel Model

- Insulin Granules



Mathematics of Channel Model

- Convection-Reaction Equations.

$$\frac{\partial I_s}{\partial t} + U\frac{\partial I_s}{\partial x} = -Q.$$

Linear densities

$$\frac{\partial I_p}{\partial t} + U\frac{\partial I_p}{\partial x} = (I_0 - I_p)R.$$

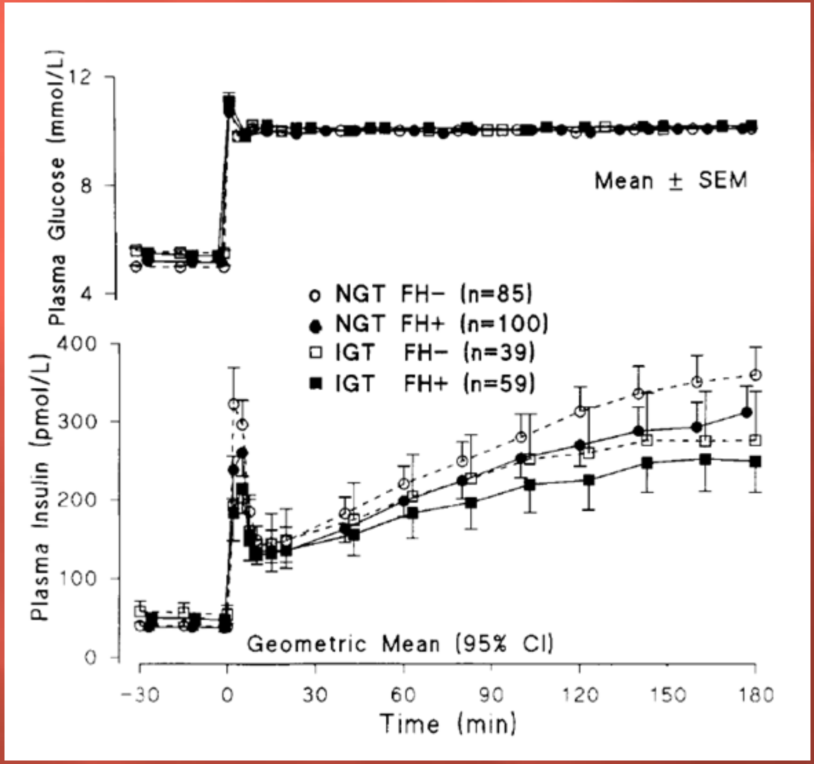
$$\mathrm{ISR}_\beta = \int_0^L Q\left(I_s(x,t), G(t)\right)\, dx$$

Total secretion rate.

$$\frac{dI_B}{dt} = -\delta I_B + \sum_\beta ISR_\beta$$

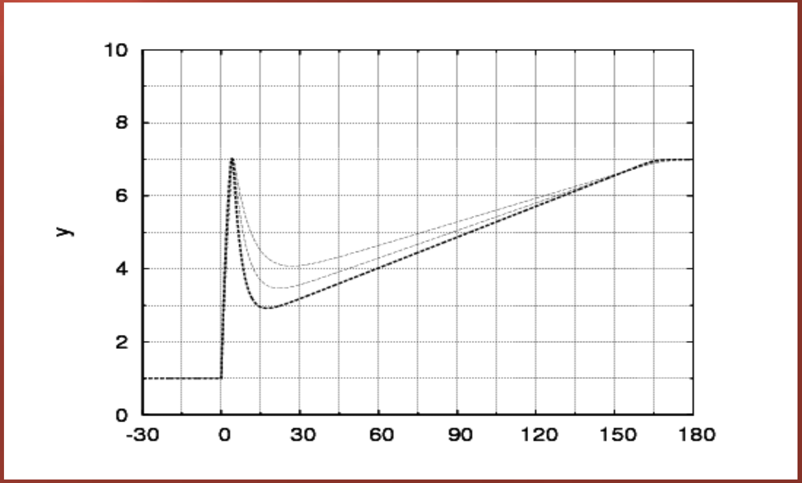
Compare to Experiments

- Potentiation



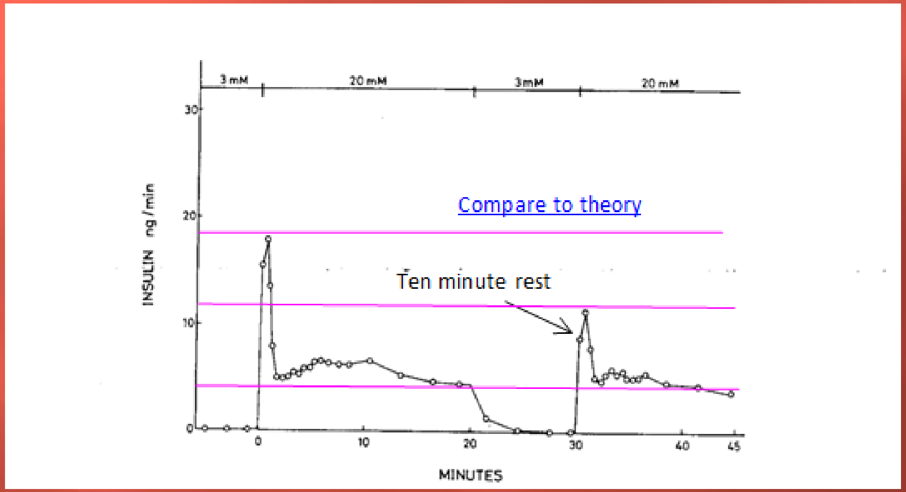
q_{low} to q_{high}

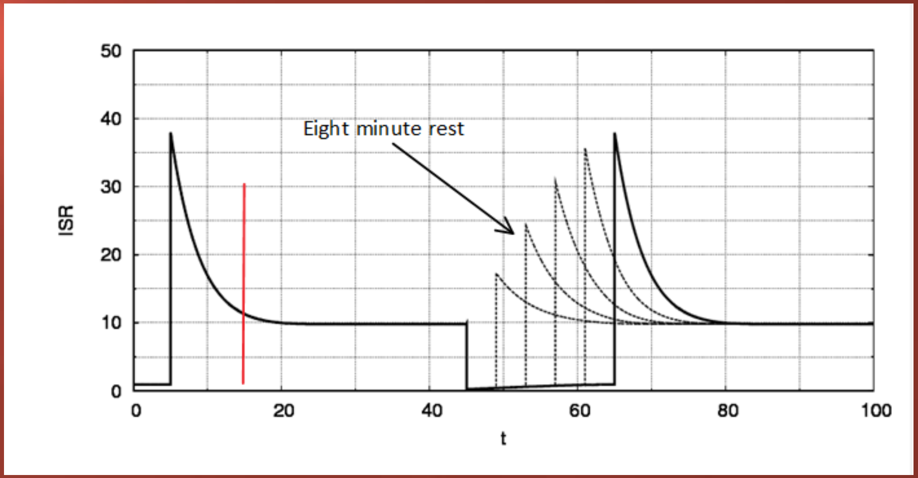
r_{low} to r_{high}



Compare to Experiments

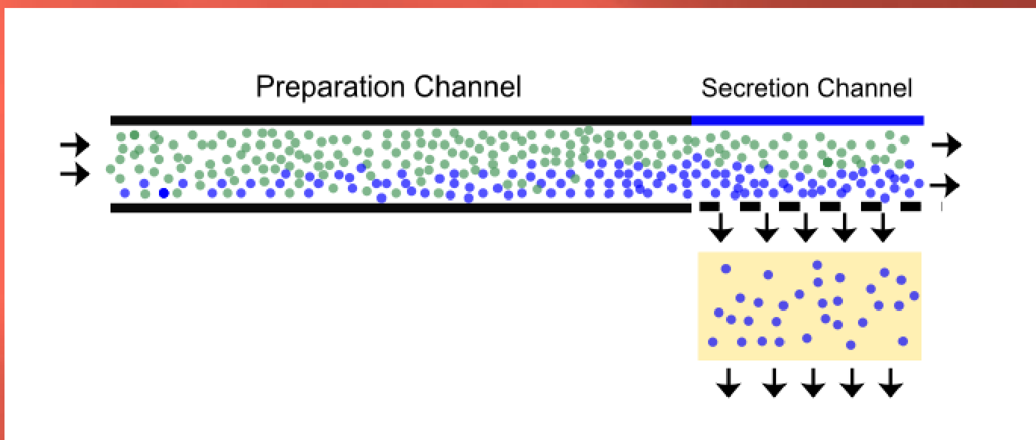
- Time-dependent Inhibition
- Can be extended for potentiation cases.





Modifications

- Quick Release Pool

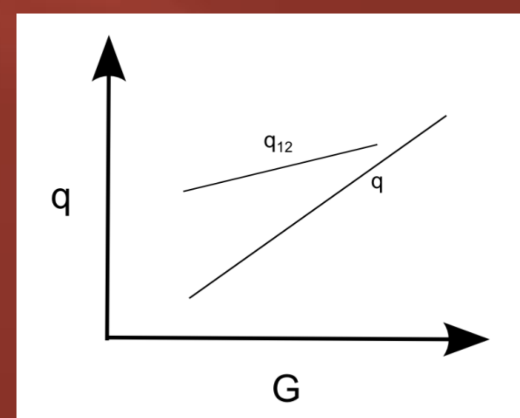


$$\frac{dI_Q}{dt} = -qI_Q + \int_0^L q_{12}\,dx$$

$$I_Q^0 = \frac{1}{q_{low}}\int_0^L q_{12_{low}}\,dx$$

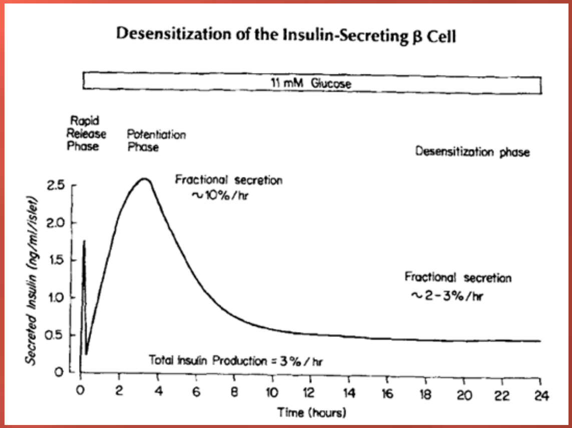
$$ISR = \begin{cases} q_{low} I_Q^0 & t<0 \\ q_{high} I_Q^0 e^{-q_{high} t} + \dots & t>0 \end{cases}$$

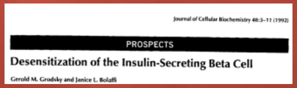
- Immediate response for q
- Delay due to diffusion for q_{12}
- Assisted diffusion
- Changes in U?



Desensitization

- Closed loop
- Slow replacement
- Loop empties
- Secretion rate declines

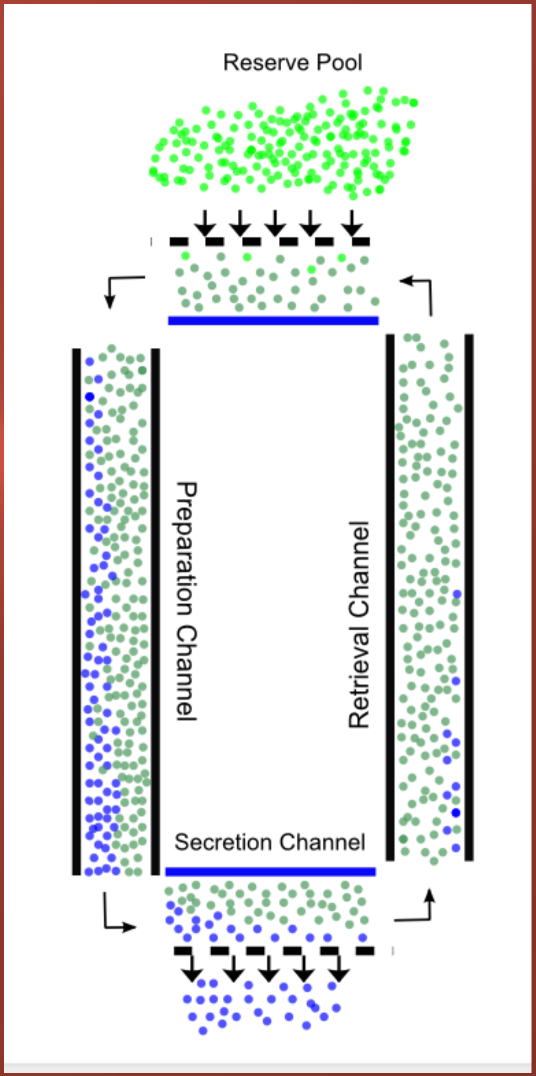



Journal of Cellular Biochemistry 48:3–11 (1992)

PROSPECTS

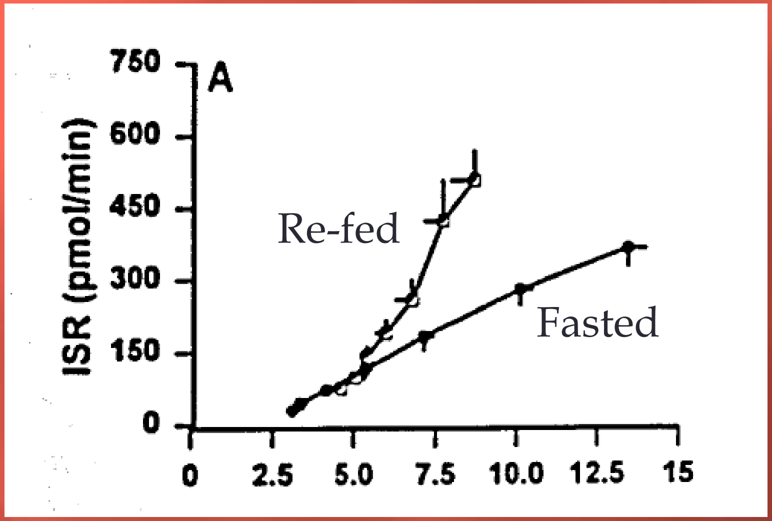
Desensitization of the Insulin-Secreting Beta Cell

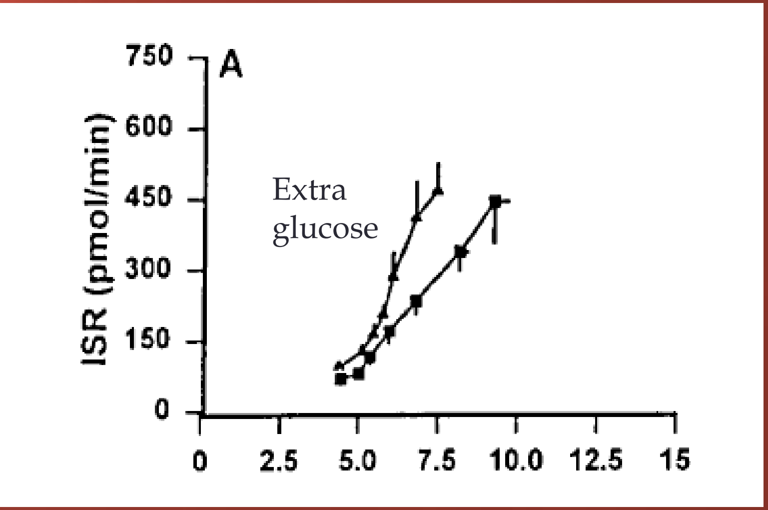
Gerold M. Grodsky and Janice L. Bolaffi



Fed *vs.* Fasted

- Increased release from reserve pool
- Increased neogenesis



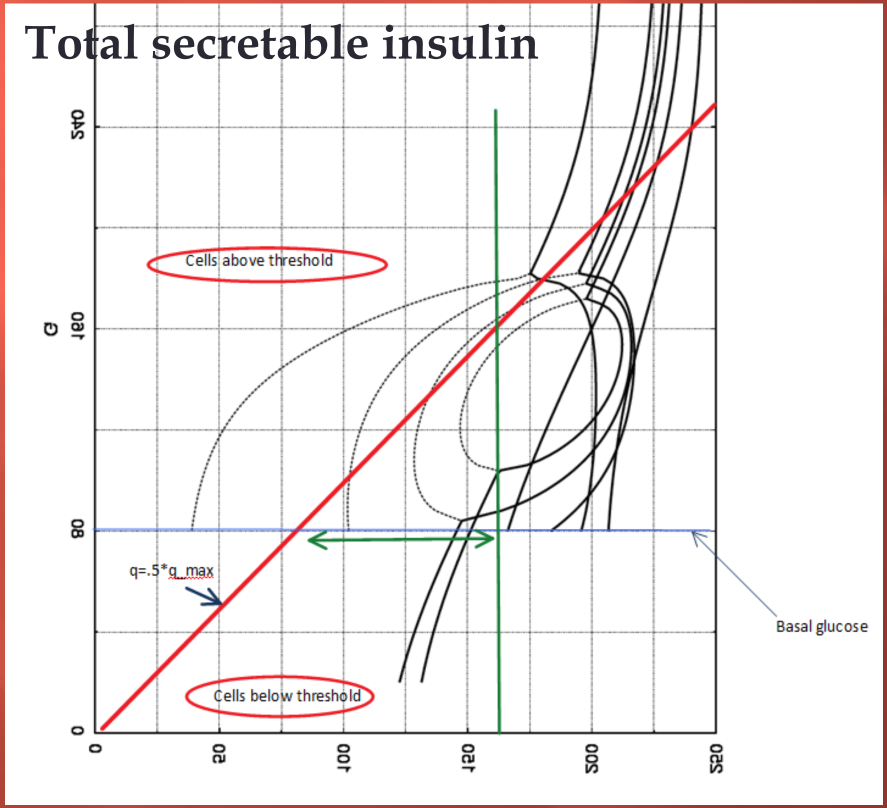


Journal Title: American journal of physiology. Endocrinology and metabolism.

Volume: 268 **Issue:**
Month/Year: 1995 **Pages:** E21-E27

Secretion Threshold depends on Insulin Content

- Highly Nonlinear Problem.



Conclusion

- Simple concept provides proper structure.
- Many cases to examine.