Casual Friday Series

Endocrine Expertise: IR and AI Mechanics in Diabetes

A Biogenetix Clinical Presentation

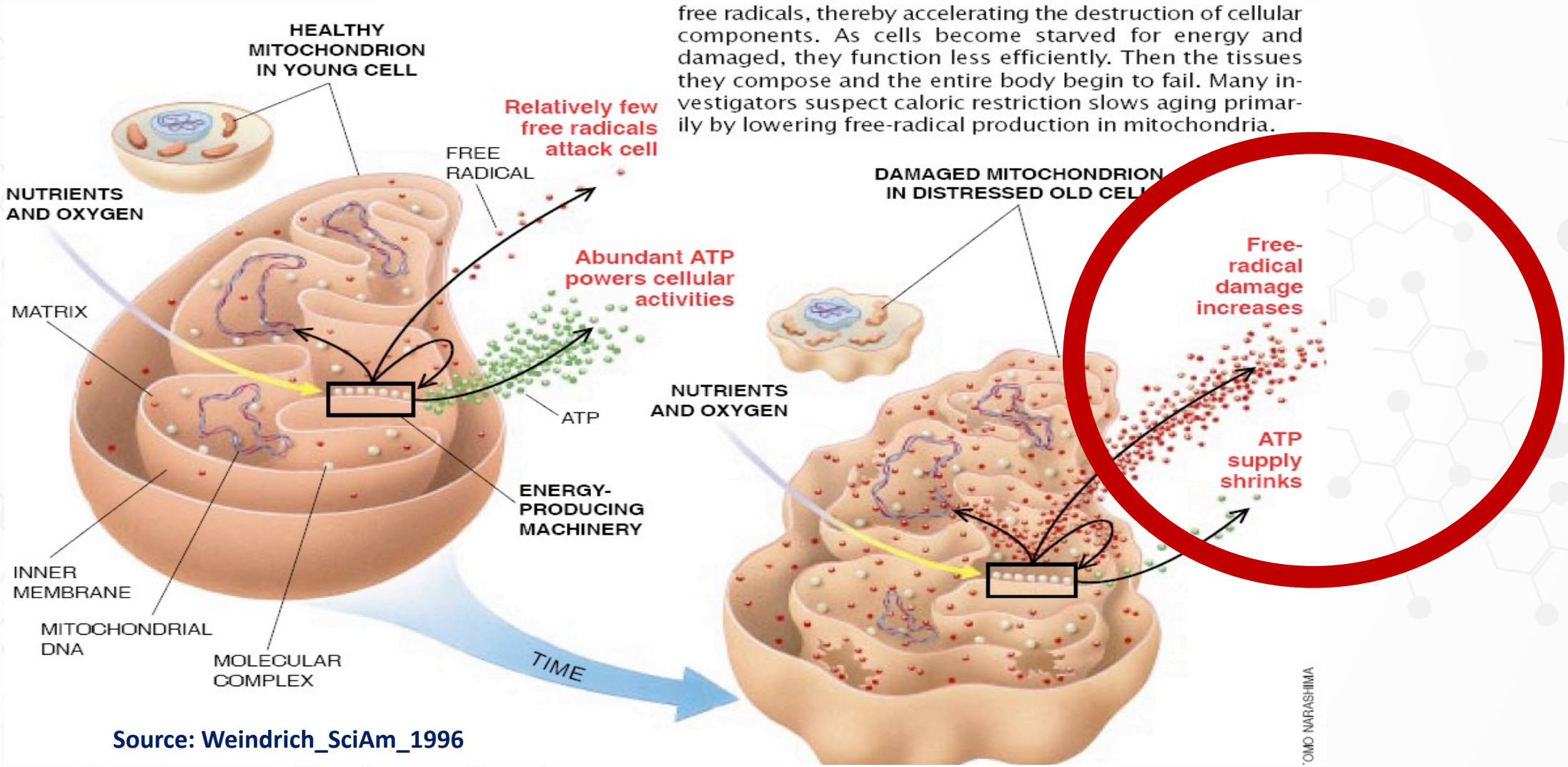
BIOGENETIX.COM

Disclaimer

- *Information in this presentation is not intended, in itself, to diagnose, treat, reverse, cure, or prevent any disease. While this presentation is based on medical literature, findings, and text, The following statements have not been evaluated by the FDA.*
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*

Lifestyle + Genetics = Chronic Health IMPROVEMENT

Mitochondria Deteriorate with Stress



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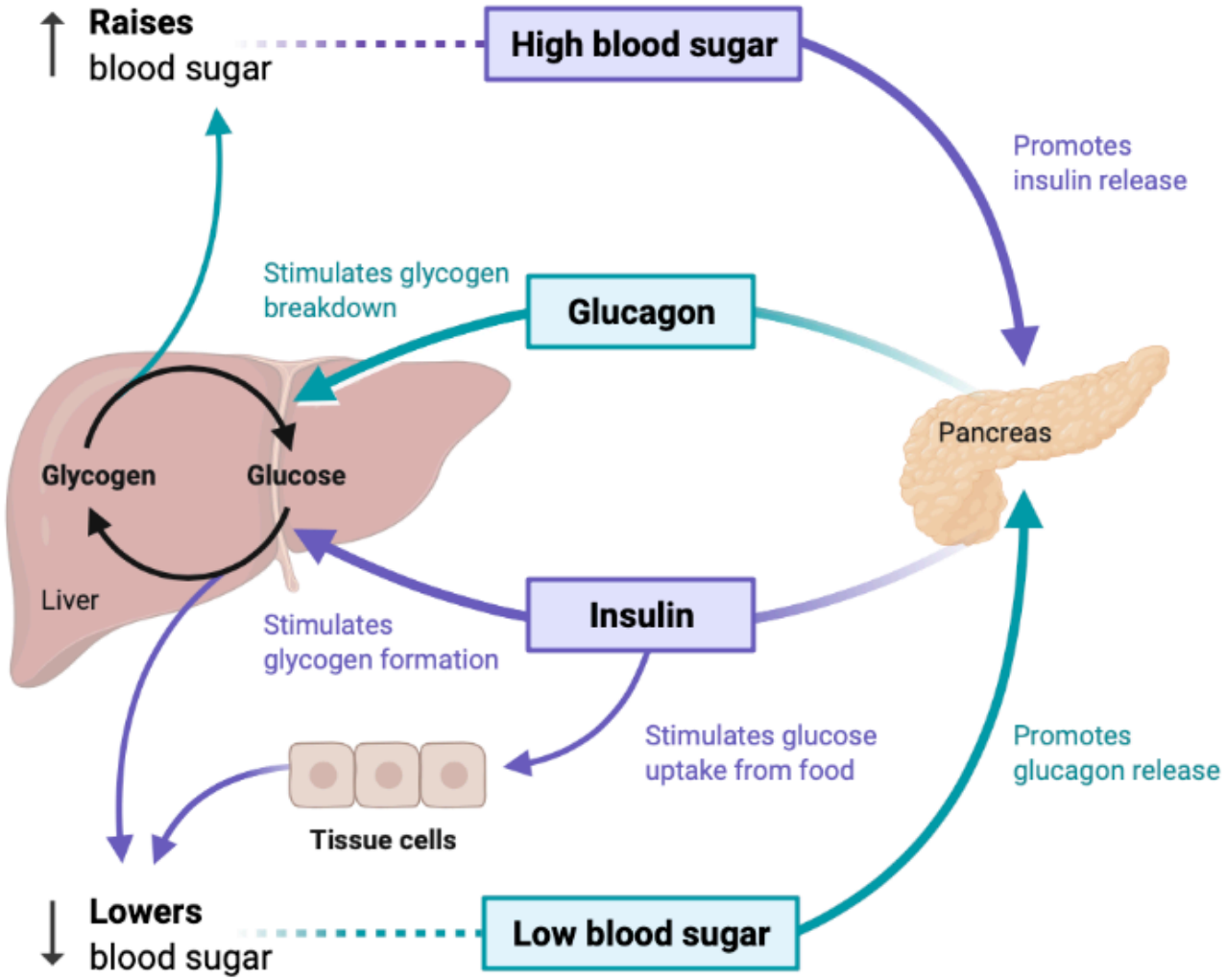

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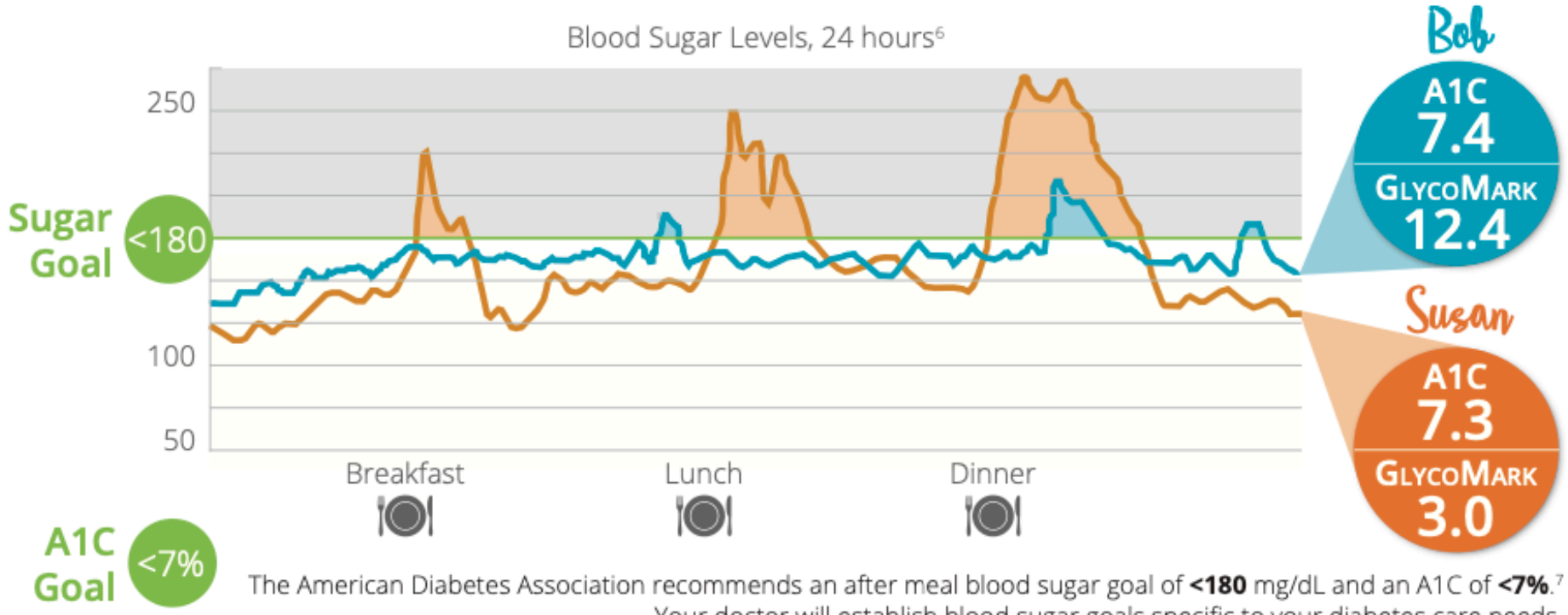
GlycoMark®

https://glycomark.com

Why is knowing GlycoMark Important? **Bob**† and **Susan**† have a similar "good" A1C, but **Susan** is experiencing harmful blood sugar swings that put her health at risk. **Susan**'s recent high blood sugar swings are not detected with A1C, but are detected by GlycoMark (<10).*



The American Diabetes Association recommends an after meal blood sugar goal of **<180** mg/dL and an A1C of **<7%**.[7]
Your doctor will establish blood sugar goals specific to your diabetes care needs.

Physiol Rev. 2018 Oct 1; 98(4): 2133–2223.
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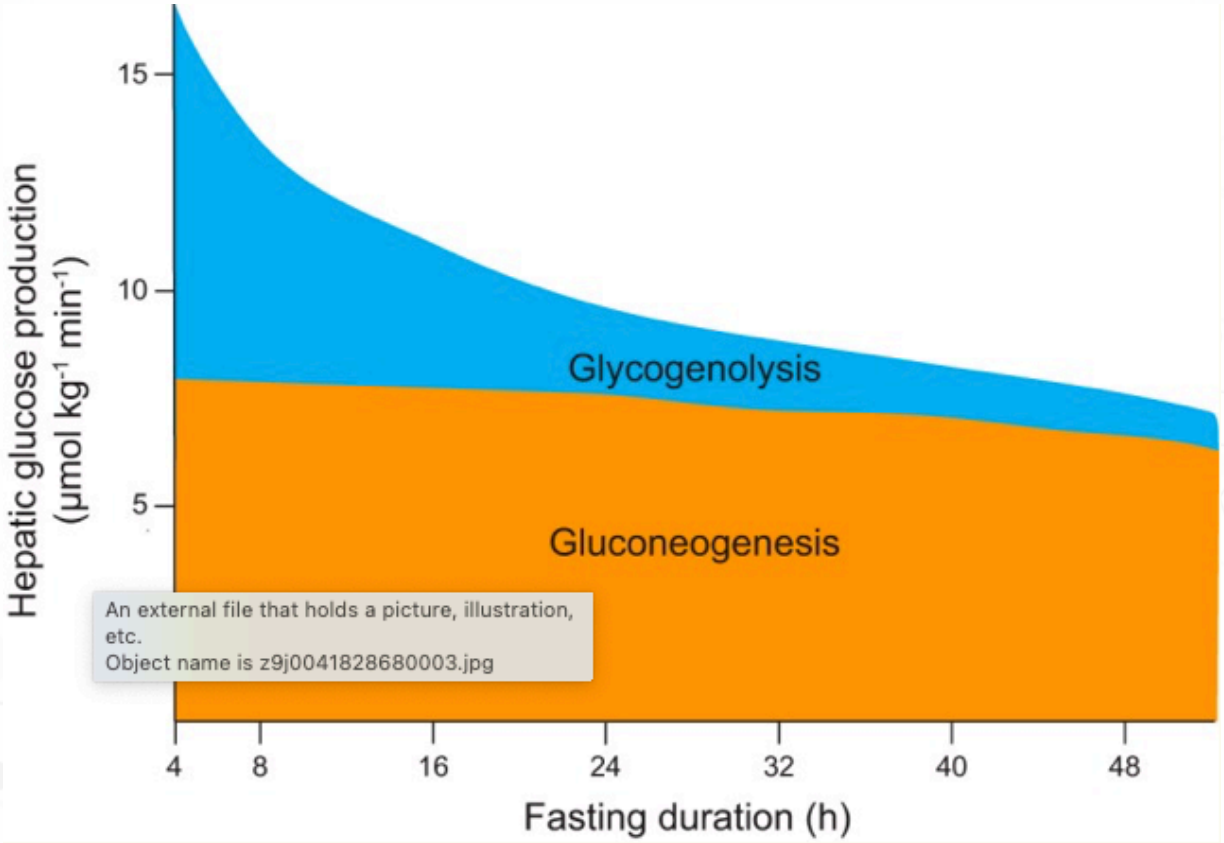
PMCID: PMC6170977
PMID: 30067154

Mechanisms of Insulin Action and Insulin Resistance

Max C. Petersen and Gerald I. Shulman

Several lipid moieties, including diacylglycerol (DAG), ceramides, and acylcarnitines, have been implicated in the pathogenesis of liver and skeletal muscle insulin resistance (127, 561, 724). The mechanistic pathways elucidated, with varying levels of experimental support, largely run parallel to one another such that the involvement of one mediator does not preclude the involvement of another. The putative mediators, pathways, and networks involved in lipid-induced liver and muscle insulin resistance are discussed in section V.

Finally, increasing recognition of the integrated nature of metabolic physiology has sparked investigation of mechanisms of insulin resistance that involve crosstalk between insulin-responsive tissues. Inflammatory signaling has emerged as a key paracrine/endocrine driver of insulin resistance; for example, activated adipose tissue macrophages have been strongly linked to metabolic dysfunction (331, 446, 594). The mechanisms by which inflammation promotes insulin resistance are under intense investigation. Additionally, the last two decades have yielded the identification of dozens of endogenous circulating bioactive peptide hormones with putative effects on insulin sensitivity and have also revealed that circulating branched-chain amino acids may be a predictive biomarker of insulin resistance (577). Rather than providing a catalog entry for each of these circulating factors, section VII focuses on those with established mechanistic links to cellular mechanisms of insulin action and resistance: retinol binding protein-4 (RBP4), adiponectin, fetuin-A, and fibroblast growth factor 21 (FGF21).



Sources of hepatic glucose production during fasting in humans. During the early postprandial period (not shown), the liver performs net glucose uptake as ingested glucose is stored as liver glycogen. Gluconeogenic flux continues but is diverted into glycogen storage. After this period, gluconeogenic flux contributes to hepatic glucose production and continues at a relatively constant rate for ~48 h, eventually decreasing due to declining substrate availability. Net hepatic glycogenolysis, in contrast, initially contributes about half of hepatic glucose production, but its rate decreases exponentially in concordance with hepatic glycogen content. Hepatic glycogenolysis still contributes appreciably to hepatic glucose production after 24 h of fasting, but is nearly depleted by 48 h. Because plasma glucose concentrations reflect rates of hepatic glucose production during a fast, the plasma glucose concentration is a systemic signal of hepatic glycogen content during fasting. [Data from Rothman et al. (704).]

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Insulin also has direct hepatocellular effects on lipid metabolism. Most prominent among these effects is transcriptional upregulation of several genes of de novo lipogenesis (DNL), though increased triglyceride-rich lipoprotein clearance and decreased very-low-density lipoprotein (VLDL) export have also been reported (457). The overall effect is to promote lipid storage in the hepatocyte and decrease the availability of fatty acids for oxidation by other tissues. Indeed, plasma triglyceride concentrations decrease precipitously within 15 min of insulin infusion, although in the setting of a mixed meal, absorbed triglycerides will negate this effect.

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Mechanisms of Insulin Action and Insulin Resistance

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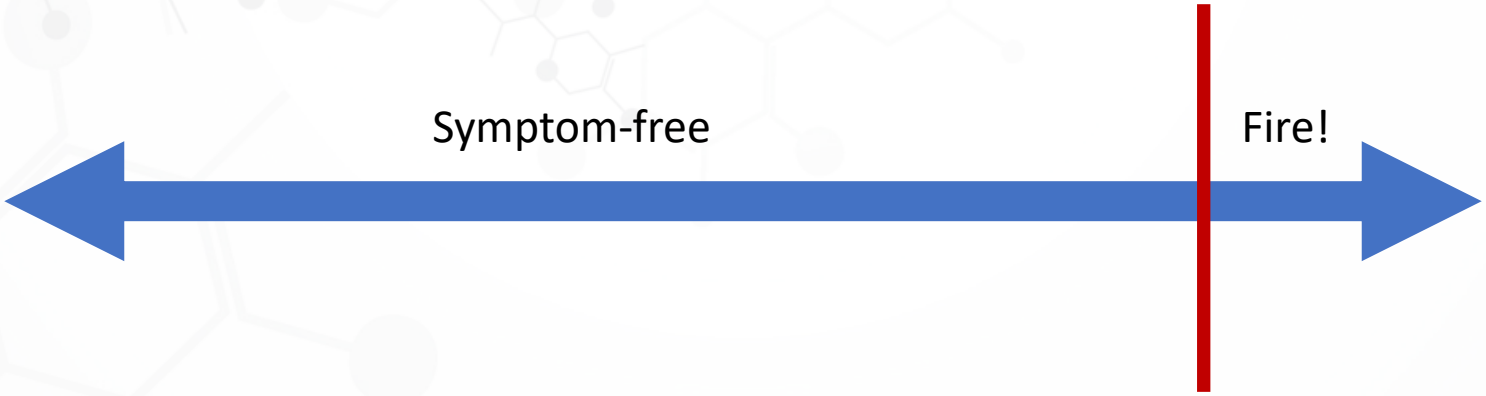
and are consequently less well understood than direct, cell-autonomous effects of insulin. An example of indirect insulin action is the effect of insulin suppression of WAT lipolysis to decrease hepatic acetyl-CoA content, in turn allosterically decreasing pyruvate carboxylase activity. This mechanism, together with suppression of glycerol turnover, enables insulin suppression of WAT lipolysis to suppress hepatic gluconeogenesis (684, 903). Insulin suppression of glucagon secretion through paracrine signaling in the pancreatic islet and insulin action in the central nervous system (CNS) represent other important pathways of indirect insulin action. These physiological processes will be examined in section III.

Question: How do we take this information and turn the diabetes world on its head?



Intra-islet insulin suppresses glucagon release via GABA-$GABA_A$ receptor system

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Excessive secretion of glucagon is a major contributor to the development of diabetic hyperglycemia. Secretion of glucagon is regulated by various nutrients, with glucose being a primary determinant of the rate of α cell glucagon secretion. The intra-islet action of insulin is essential to exert the effect of glucose on the α cells since, in the absence of insulin, glucose is not able to suppress glucagon release in vivo. However, the precise mechanism by which insulin suppresses glucagon secretion from α cells is unknown. In this study, we show that insulin induces activation of $GABA_A$ receptors in the α cells by receptor translocation via an Akt kinase-dependent pathway. This leads to membrane hyperpolarization in the α cells and, ultimately, suppression of glucagon secretion. We propose that defects in this pathway(s) contribute to diabetic hyperglycemia.

Scenario #1

GlycoMark(R)(1,5 AG)	14.3		ug/mL	

GlycoMark(TM) is intended for use with managing glycemic control in diabetic patients. A low result corresponds to high glucose peaks.
1, 5-AG blood levels can be affected by clinical conditions or medications. Please refer to the directory of services or labcorp website test menu for detailed list of limitations.
Reference Range:
Adults Males: 10.7 - 32.0
Glycemic control goal for diabetic patients: >10

Hemoglobin A1c

Hemoglobin A1c	**6.5**	**High**	%	4.8-5.6

Please Note:
Prediabetes: 5.7 - 6.4
Diabetes: >6.4
Glycemic control for adults with diabetes: <7.0

Testosterone, Serum	395		ng/dL	264-916

Adult male reference interval is based on a population of healthy nonobese males (BMI <30) between 19 and 39 years old.
Travison, et.al. JCEM 2017,102;1161-1173. PMID: 28324103.

TSH	**6.230**	**High**	uIU/mL	0.450-4.500

Scenario #2

GlycoMark(R)(1,5 AG)	**<1.0**	**Low**	ug/mL

GlycoMark(TM) is intended for use with managing glycemic control in diabetic patients. A low result corresponds to high glucose peaks.
1, 5-AG blood levels can be affected by clinical conditions or medications. Please refer to the directory of services or labcorp website test menu for detailed list of limitations.
Reference Range:
Adults Females: 6.8 - 29.3
Glycemic control goal for diabetic patients: >10

Hgb A1c with eAG Estimation

Hemoglobin A1c	**9.3**	**High**	%	4.8-5.6

Please Note:
Prediabetes: 5.7 - 6.4
Diabetes: >6.4
Glycemic control for adults with diabetes: <7.0

Estim. Avg Glu (eAG)	220	mg/dL

Scenario #3

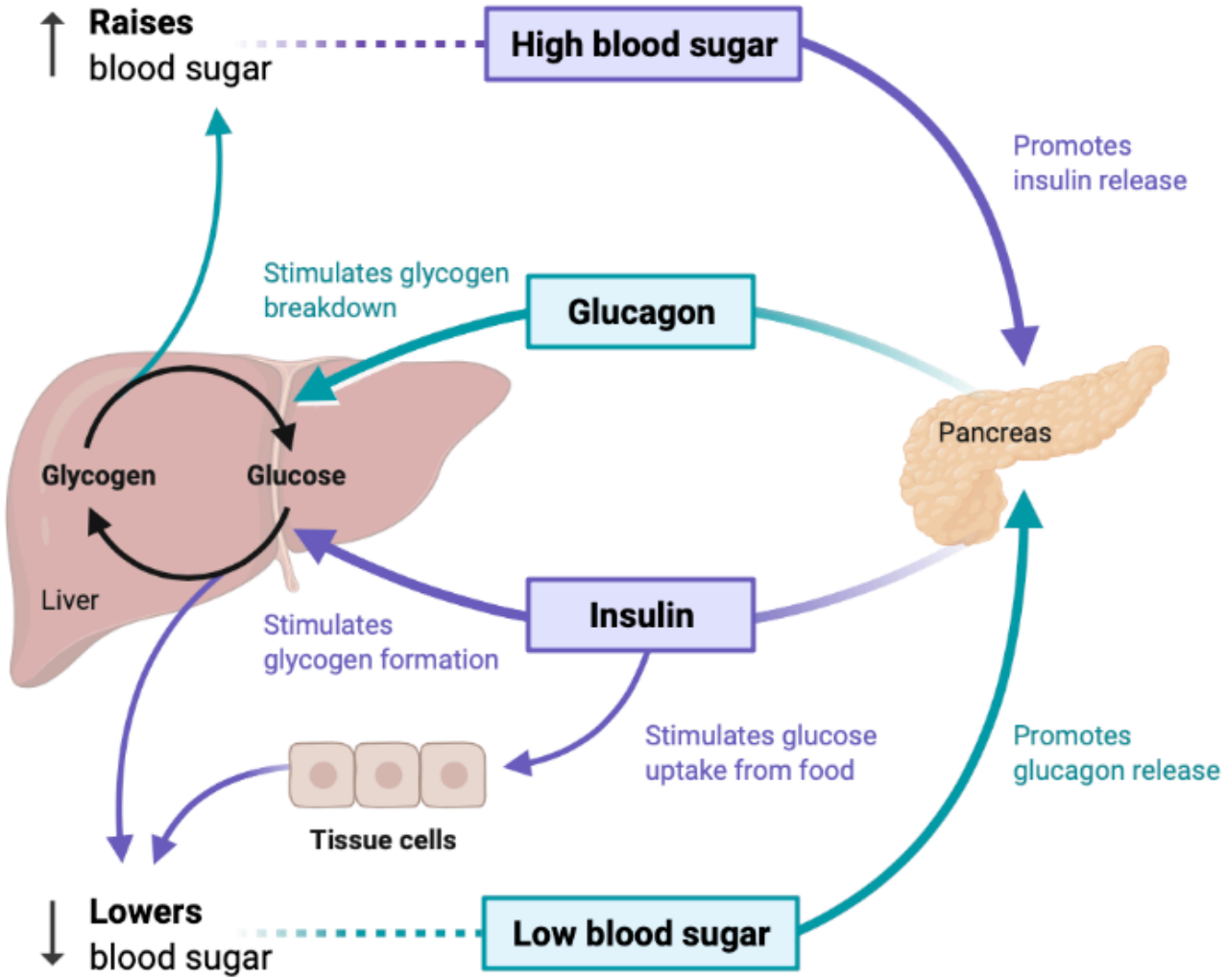
GlycoMark(R)(1,5 AG)	**3.0**	**Low**	ug/mL

GlycoMark(TM) is intended for use with managing glycemic control in diabetic patients. A low result corresponds to high glucose peaks.
1, 5-AG blood levels can be affected by clinical conditions or medications. Please refer to the directory of services or labcorp website test menu for detailed list of limitations.
Reference Range:
Adults Females: 6.8 - 29.3
Glycemic control goal for diabetic patients: >10

Hemoglobin A1c

Hemoglobin A1c	5.0	%	4.8-5.6

Please Note:



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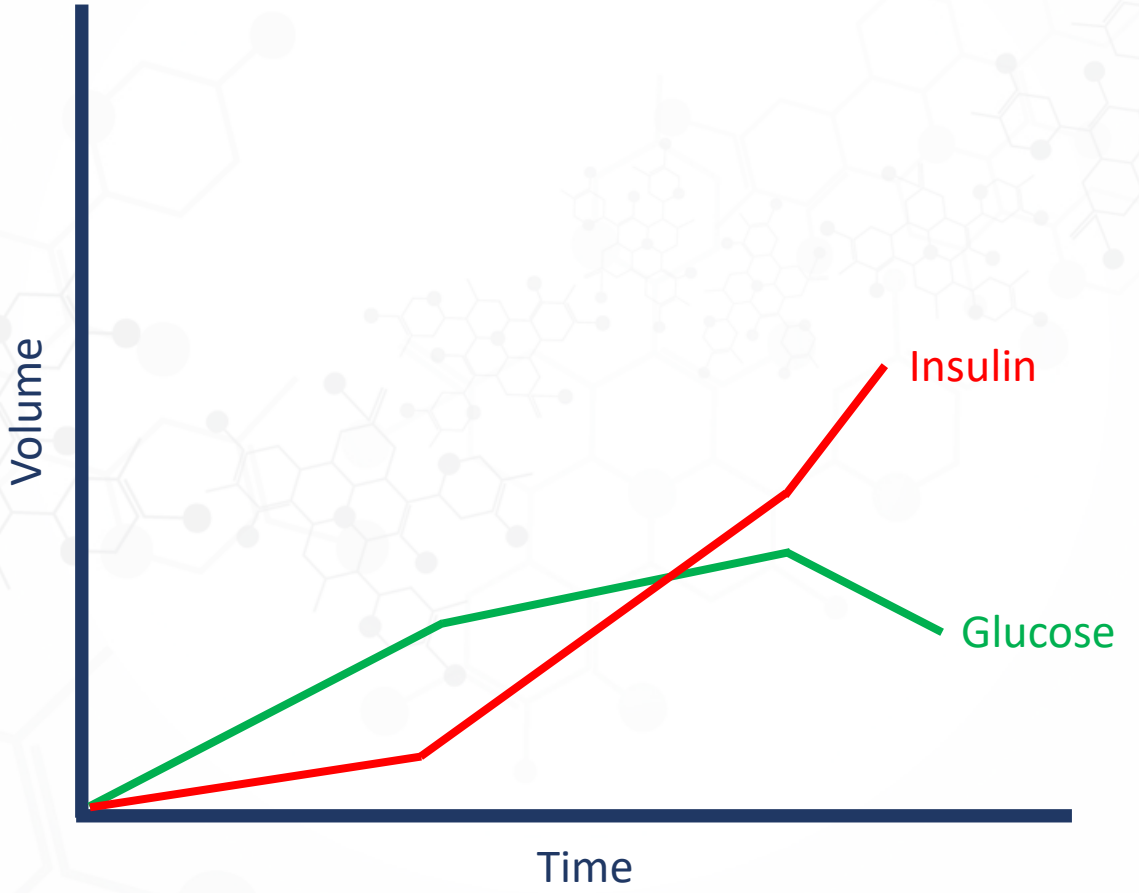
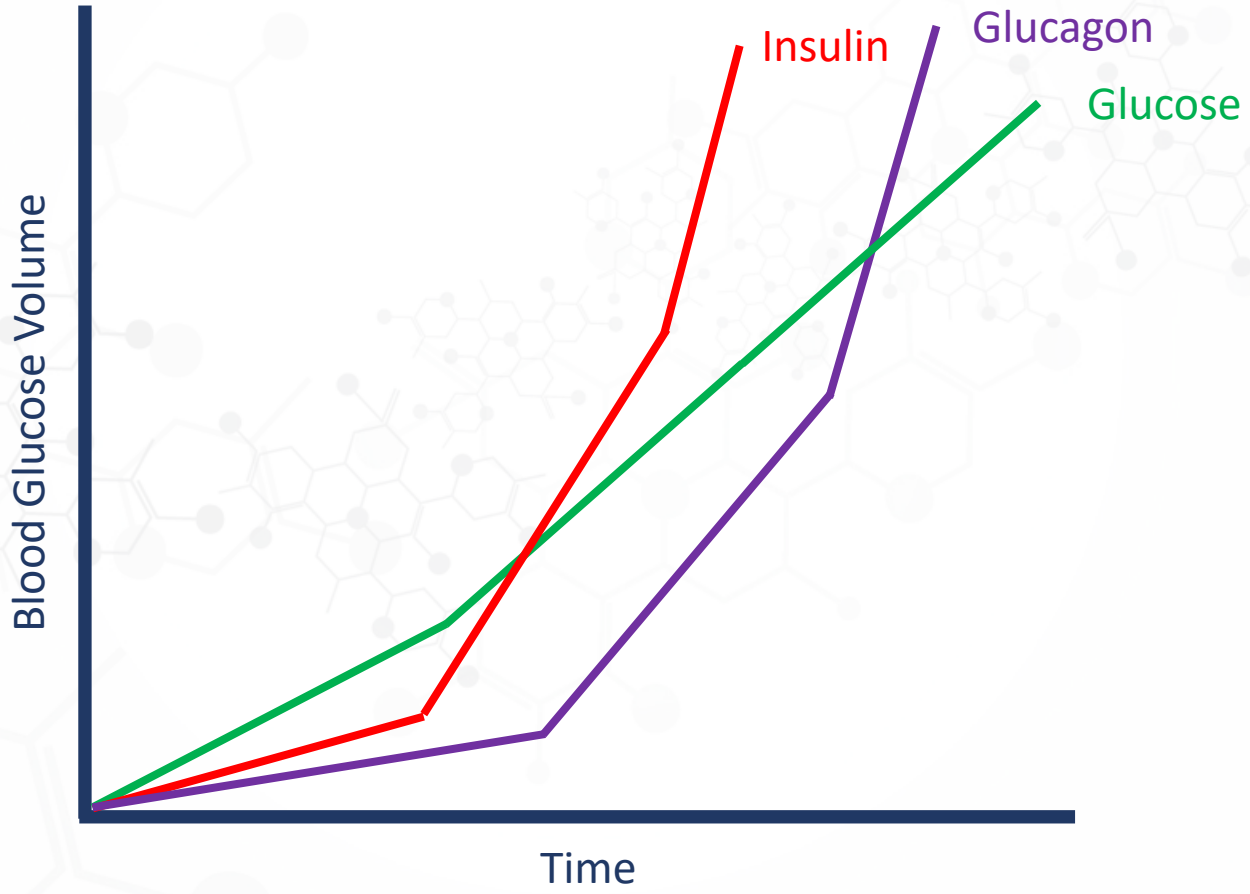
Optimal Relationship



And Insulin Resistant Relationship



> Diabetes. 2007 Feb;56(2):320-7. doi: 10.2337/db06-0712.

Glucose-dependent regulation of gamma-aminobutyric acid (GABA A) receptor expression in mouse pancreatic islet alpha-cells

Sara

The mechanism(s) by which glucose regulates glucagon secretion both acutely and in the longer term remain unclear. Added to isolated mouse islets in the presence of 0.5 mmol/l glucose, gamma-aminobutyric acid (GABA) inhibited glucagon release to a similar extent (46%) as 10 mmol/l glucose (55%), and the selective GABA(A) receptor (GABA(A)R) antagonist SR95531 substantially reversed the inhibition of glucagon release by high glucose. GABA(A)R alpha4, beta3, and gamma2 subunit mRNAs were detected in mouse islets and clonal alphaTC1-9 cells, and immunocytochemistry confirmed the presence of GABA(A)Rs at the plasma membrane of primary alpha-cells. Glucose dose-dependently increased GABA(A)R expression in both islets and alphaTC1-9 cells such that mRNA levels at 16 mmol/l glucose were approximately 3.0-fold (alpha4), 2.0-fold (beta3), or 1.5-fold (gamma2) higher than at basal glucose concentrations (2.5 or 1.0 mmol/l, respectively). These effects were mimicked by depolarizing concentrations of K(+) and reversed by the L-type Ca(2+) channel blocker nimodipine. We conclude that 1) release of GABA from neighboring beta-cells contributes substantially to the acute inhibition of glucagon secretion from mouse islets by glucose and 2) that changes in GABA(A)R expression, mediated by changes in intracellular free Ca(2+) concentration, may modulate this response in the long term.

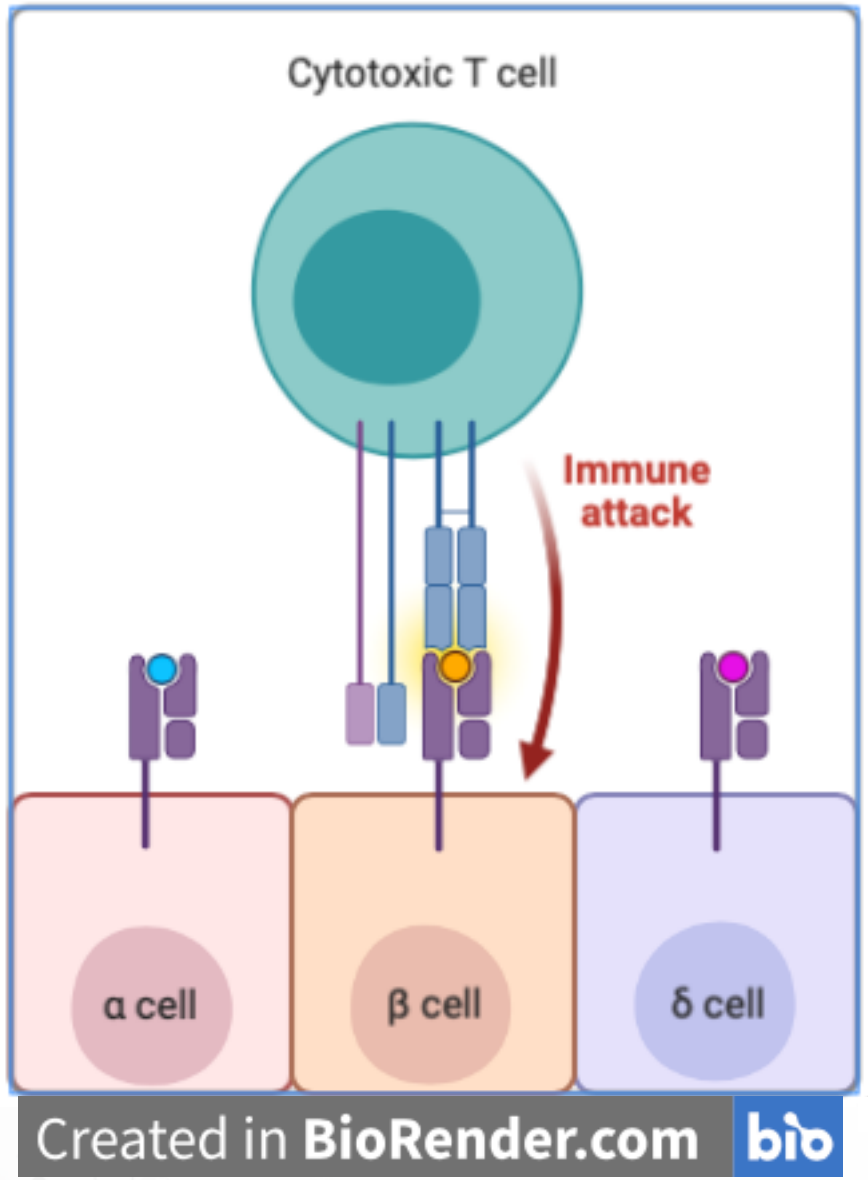
Commentary

GABAergic System in β-Cells: From Autoimmunity Target to Regeneration Tool

Paolo Fiorina

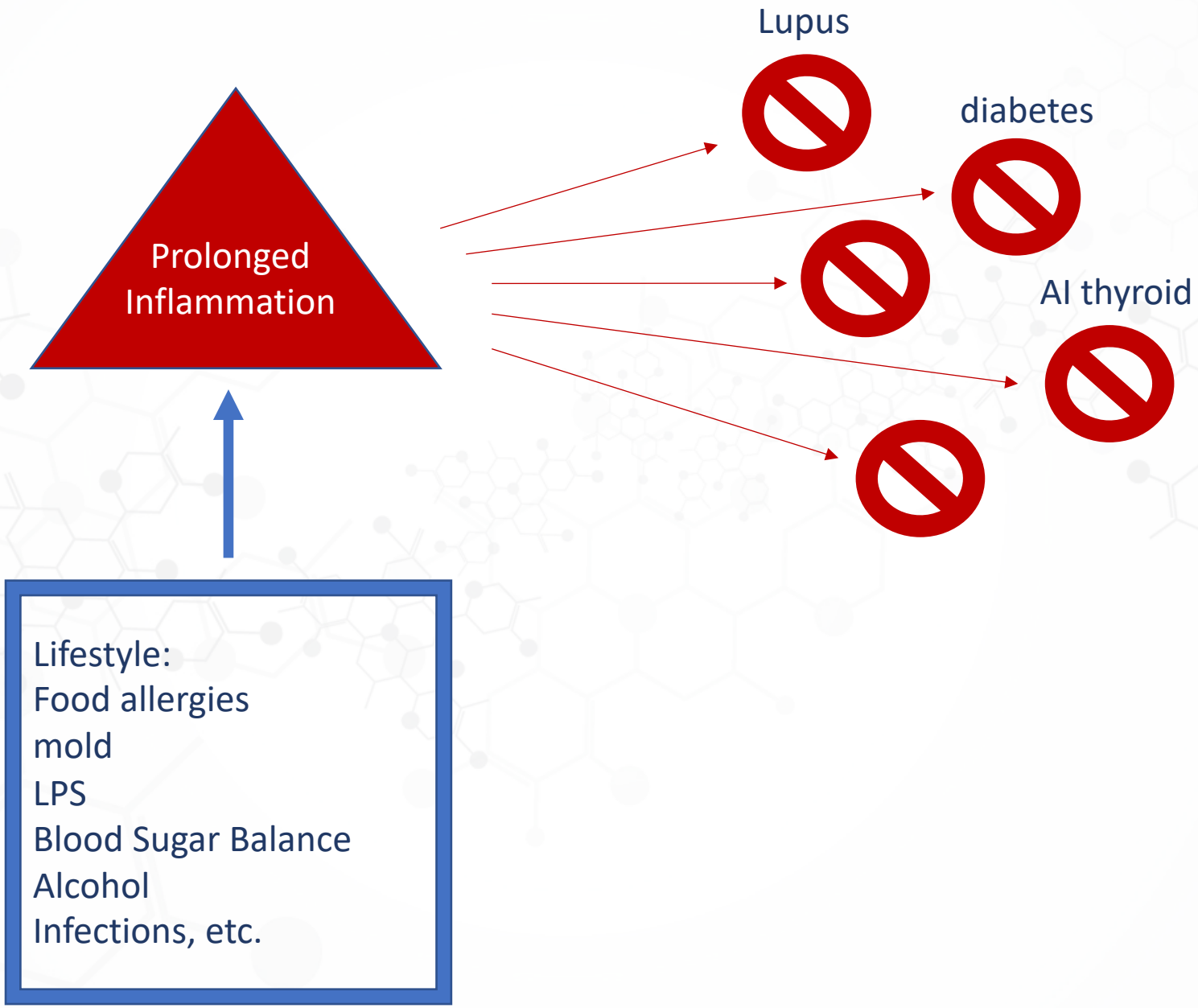
The important message and strength of Tian et al. (15) is its description of how GABA protects murine and, more important, human β-cells from inflammation and apoptosis and how it induces β-cell proliferation.

knowledge may change the view of how β-cells modulate their own fate and how they potentially modulate inflammation. The release of stored GABA by β-cells may protect β-cells themselves and potentially reduce inflammation. The investigators showed that activation of $GABA_A$ or $GABA_B$ receptors inhibited STZ-induced murine and human β-cell apoptosis (15).

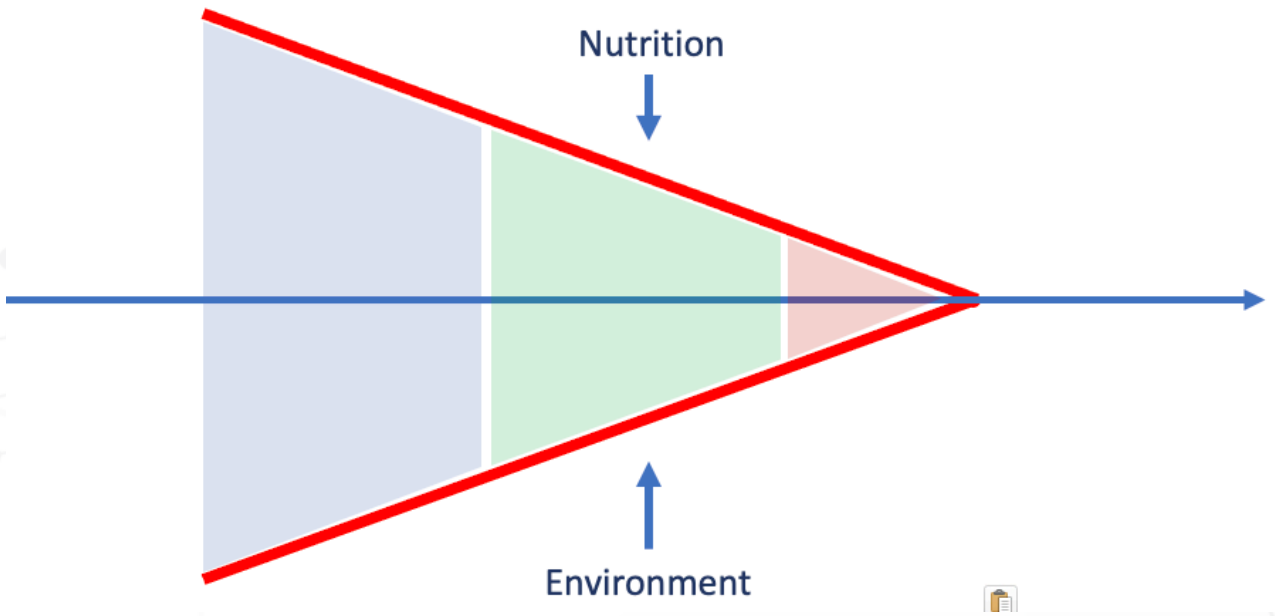


Type 1/1.5 Diabetes:

- GAD-65 Ab
- Glutamate --------> GABA
- GABA excretion by Beta cells holds key to immune defense.
- “if you have GAD-65 Ab, it’s only a matter of time…”


Lupus
diabetes
AI thyroid
Prolonged Inflammation
Lifestyle:
Food allergies
mold
LPS
Blood Sugar Balance
Alcohol
Infections, etc.

BioG-Max Gaba



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