Casual Friday Series

Functional Blood Chemistry Series pt. IV: Glucose

A Biogenetix Clinical Presentation

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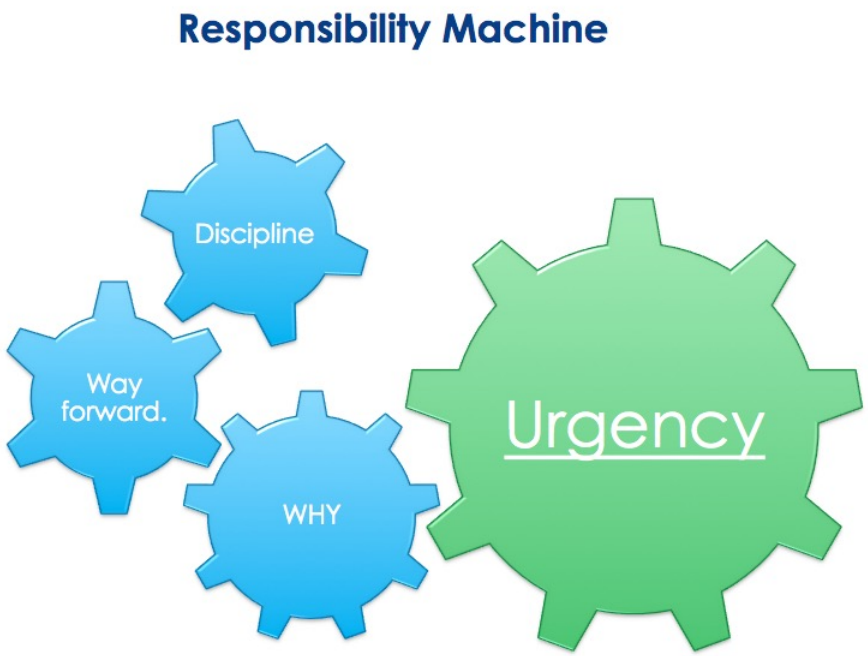
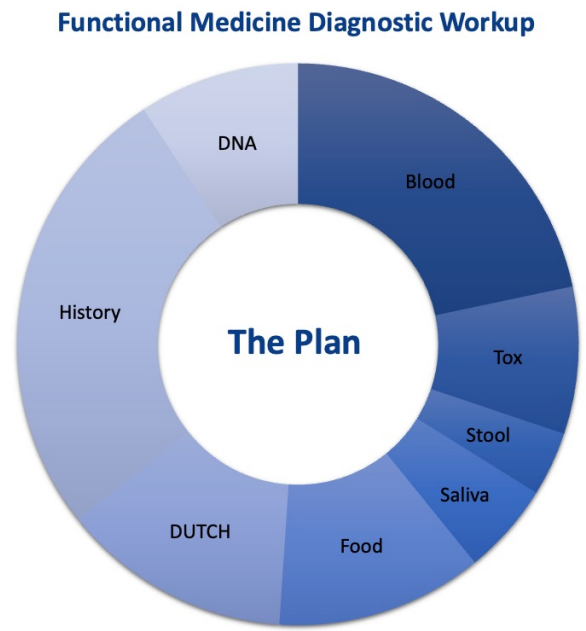
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*

Applied FM





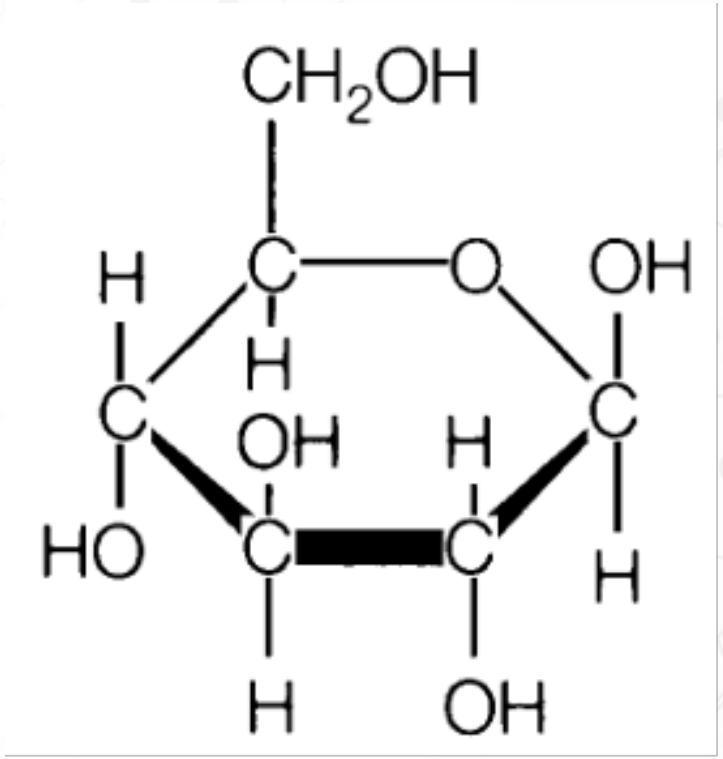
Progress.

Glucose

Primary substrate for ATP production within cells

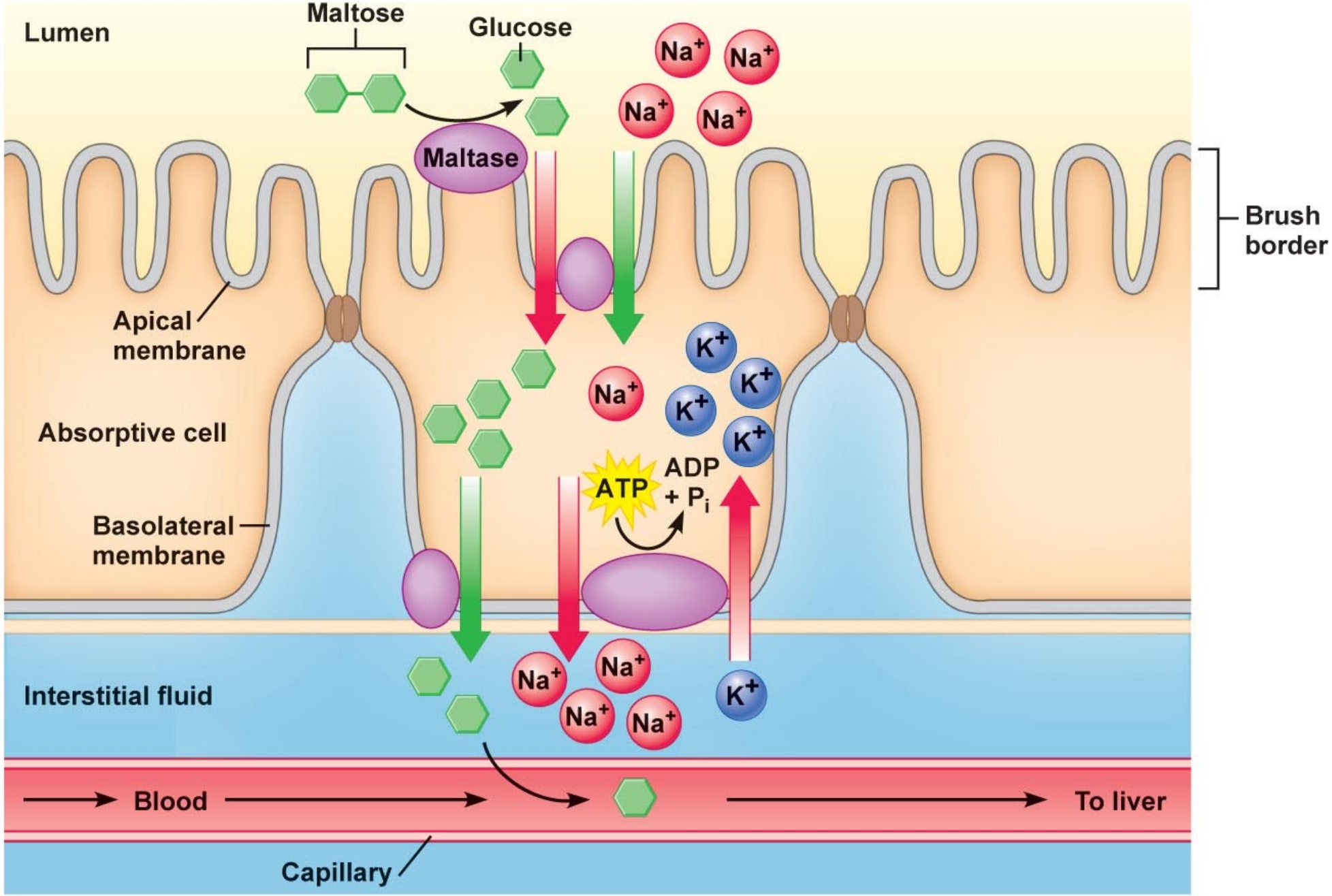
- Glycolysis, CAC, ETC/OP
- Other substrates can be used, eg fatty acids, amino acids

Also used for glycolipids & glycoproteins



Digestion and Absorption

- Consumed as polysaccharides (Eg starch), oligosaccharides (eg stacchyose), disaccharides (eg sucrose, lactose), or monosaccharides (eg glucose, fructose)
- Glycosidic bonds broken down by alpha-amylase (salivary, pancreatic)
- Brush border enzymes (maltase, sucrase, lactase) break down dipeptides
- Absorbed across brush border of enterocytes via Na dependent co-transport
- Leaves enterocytes into hepatic portal circulation to the liver



Biochemically speaking

Insulin stimulates:

-Lipogenesis (fatty acid synthesis)

    -Triacylglycerol synthesis

-Cholesterol synthesis

-Glycogen synthesis

-Glycolysis

Glucagon stimulates:

- Lipolysis
- Gluconeogenesis
- Glycogenolysis

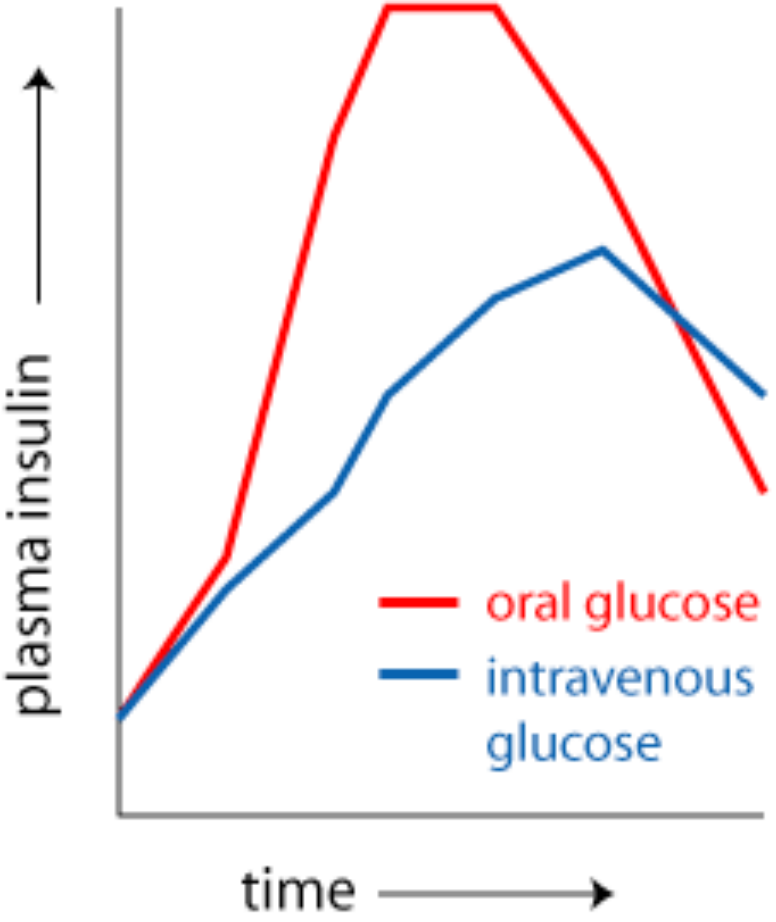
Serum glucose – where does it come from?

1. Food intake
2. Glycogenolysis (breakdown of glycogen)
3. Gluconeogenesis

Incretins – Gut Hormones

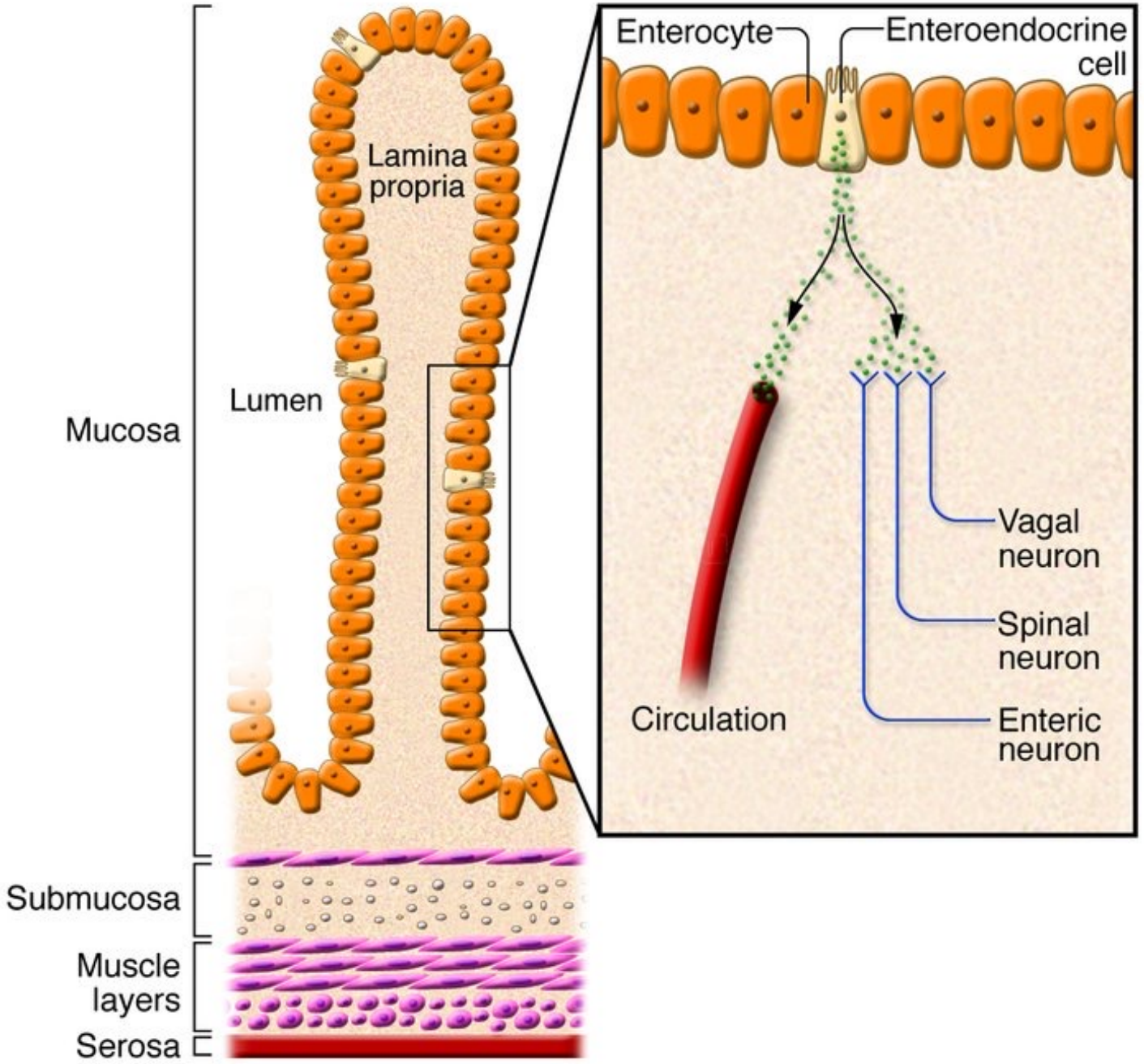
When glucose is present in the small intestine, regulatory hormones are released to stimulate insulin production *before* glucose enters the blood stream

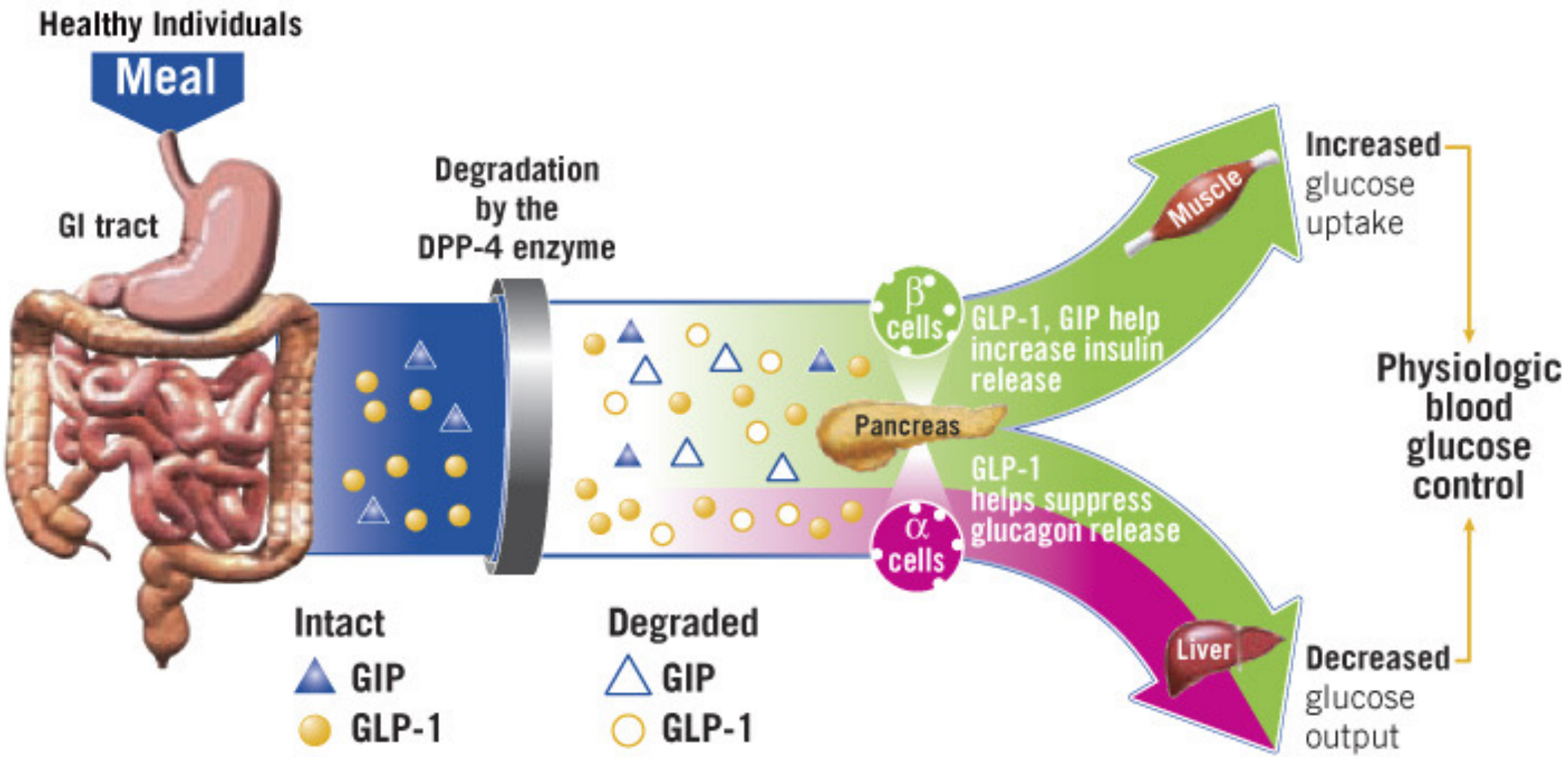
Concept was developed when it was observed that oral glucose increased insulin levels more than intravenous glucose



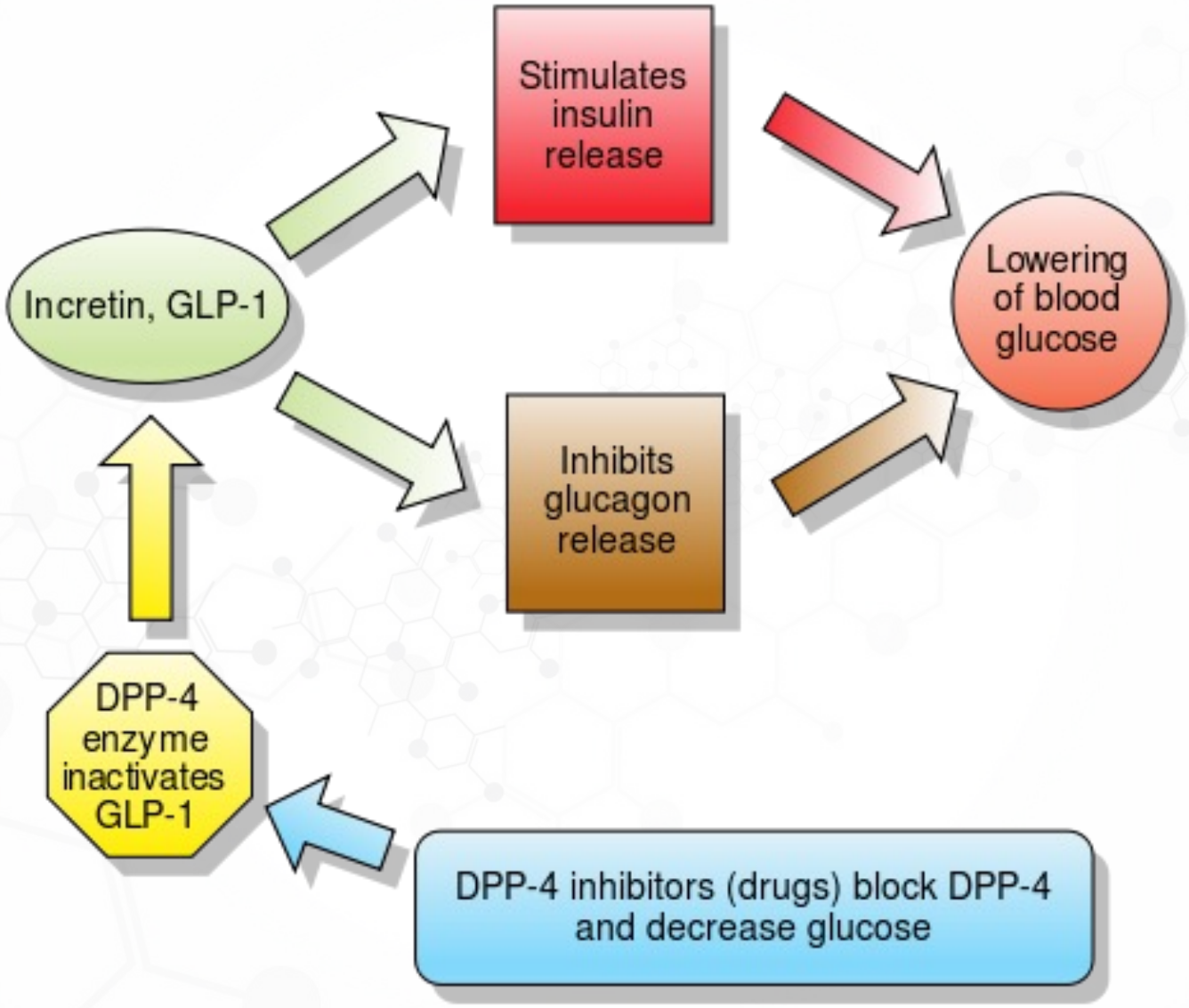
Incretins

- Glucose-Dependent Insulinotropic Peptide (GIP)
  - Previously gastric inhibitory peptide
- Glucagon-Like Peptide-1 (GLP-1)
  - Agonists include Trulicity, Ozempic, Victoza
- Produced by enteroendocrine cells in the small intestine (duodenum)
- Both stimulate insulin secretion and decrease gastric motility
  - Delays stomach emptying
- GLP-1 also inhibits glucagon, reduces food intake, and may increase number and mass of beta cells of the pancreas
- Dipeptidyl Peptidase-4 (DPP-IV) breaks down GIP and GLP-1
  - Inhibitors include Januvia, Tradjenta, Onglyza


Enterocyte
Enteroendocrine cell
Lamina propria
Lumen
Mucosa
Vagal neuron
Spinal neuron
Enteric neuron
Circulation
Submucosa
Muscle layers
Serosa



This illustration is an artistic rendition and is not necessarily representative of clinical effects.


Stimulates insulin release
Incretin, GLP-1
Lowering of blood glucose
Inhibits glucagon release
DPP-4 enzyme inactivates GLP-1
DPP-4 inhibitors (drugs) block DPP-4 and decrease glucose

Digestion and Absorption

When glucose enters circulation, pancreatic beta cells synthesize and release insulin.

First phase insulin response – *preformed* insulin stored within the beta cells is released.

- Limits post-prandial glucose elevation
- Suppresses hepatic glucose production (gluconeogenesis)
- Begins within 2 minutes of nutrient ingestion, continues for 10-15 minutes

Second phase insulin response – insulin synthesis and release continues until serum glucose levels are normalized; longer process due to need to synthesize new insulin.

First Phase Insulin Response

Diminished first phase insulin response considered to be one of the earlier predictive markers of metabolic syndrome and Type II Diabetes

- Occurs well before significant changes in absolute glucose concentrations
- May even occur prior to insulin resistance

Thought to indicate early beta cell dysfunction.

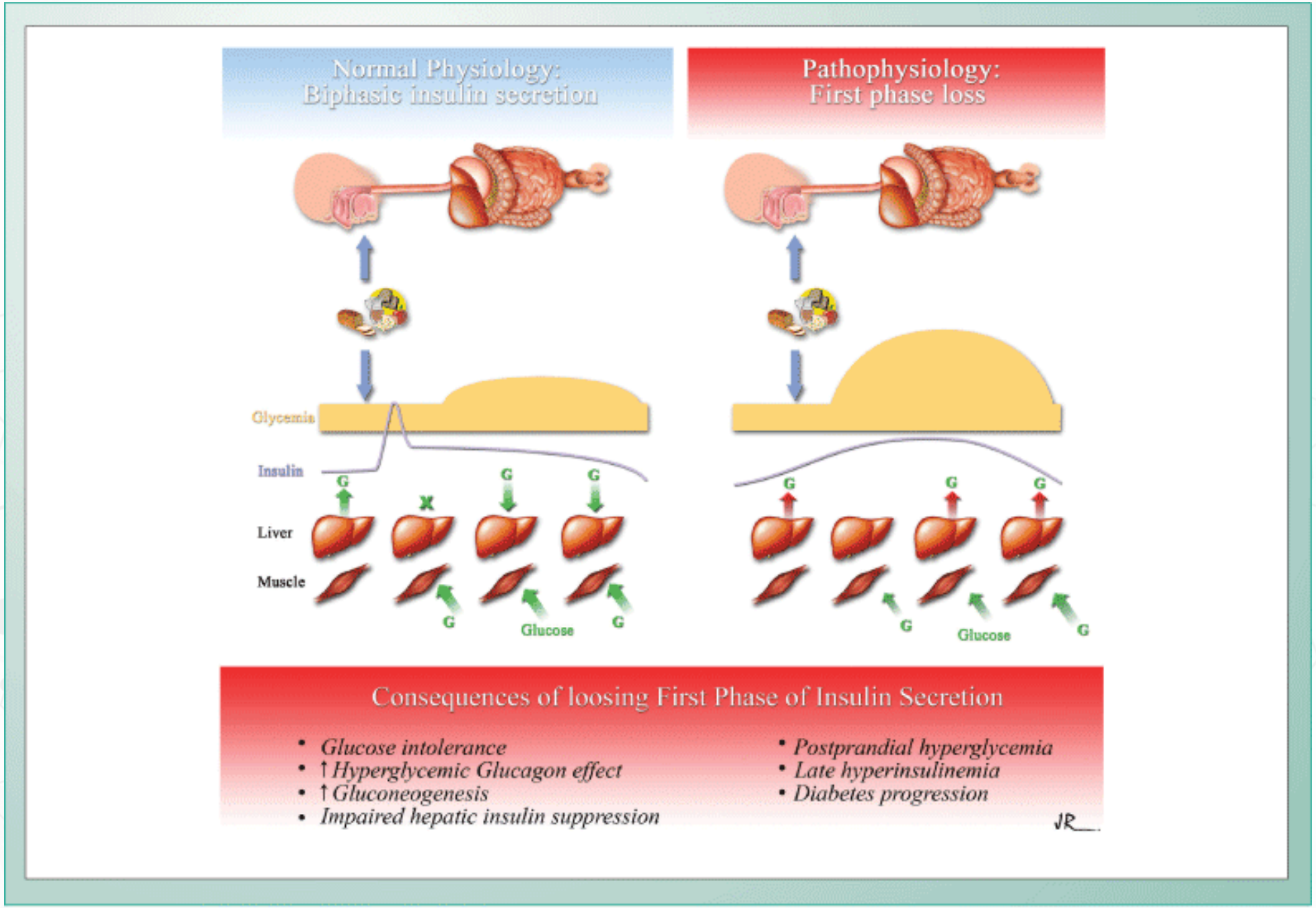
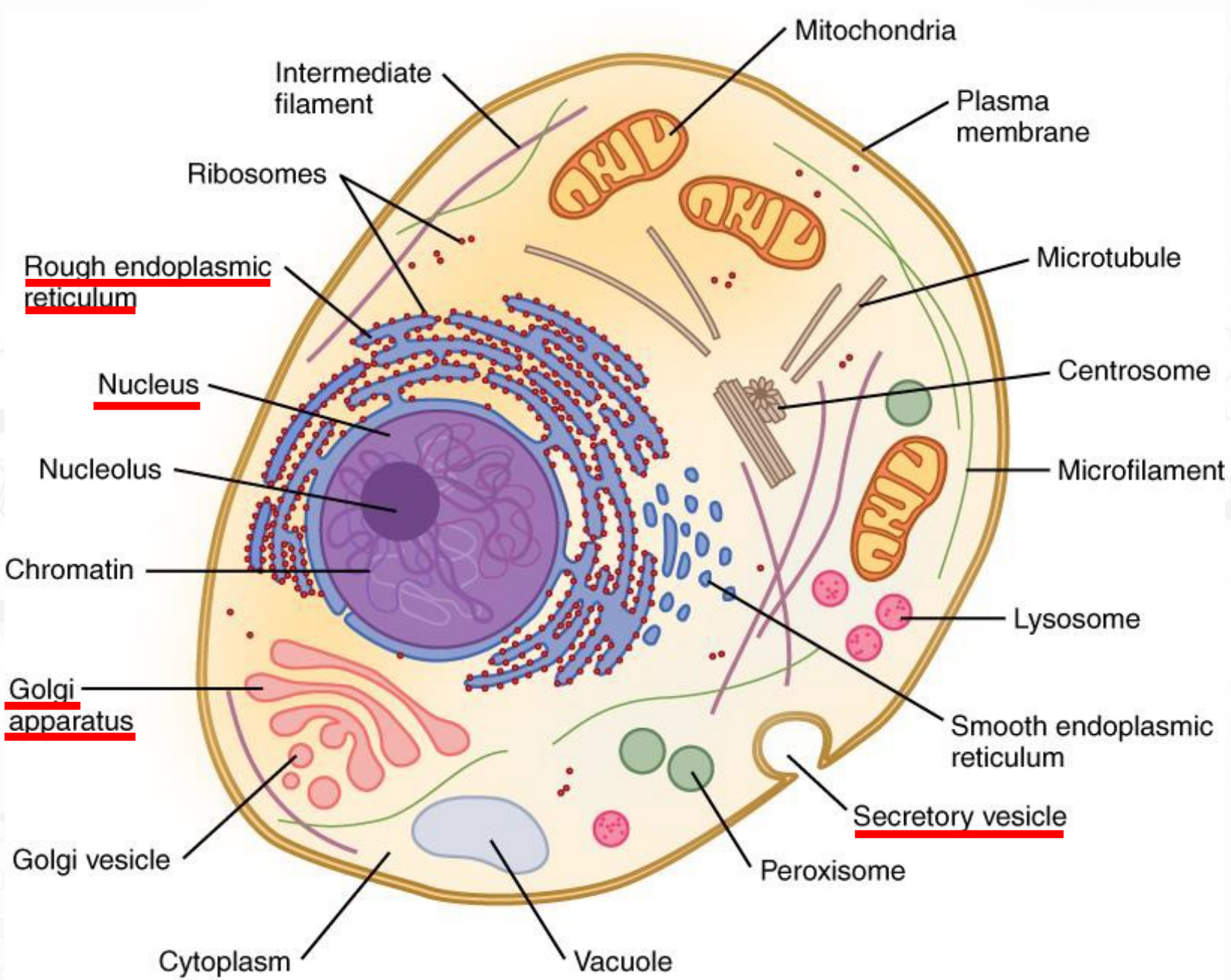


Fig. 1 *- Effects of first phase failure: Sustained hepatic glucose output, reduced peripheral glucose uptake, resulting in postprandial hyperglycemic.*

Brief Review



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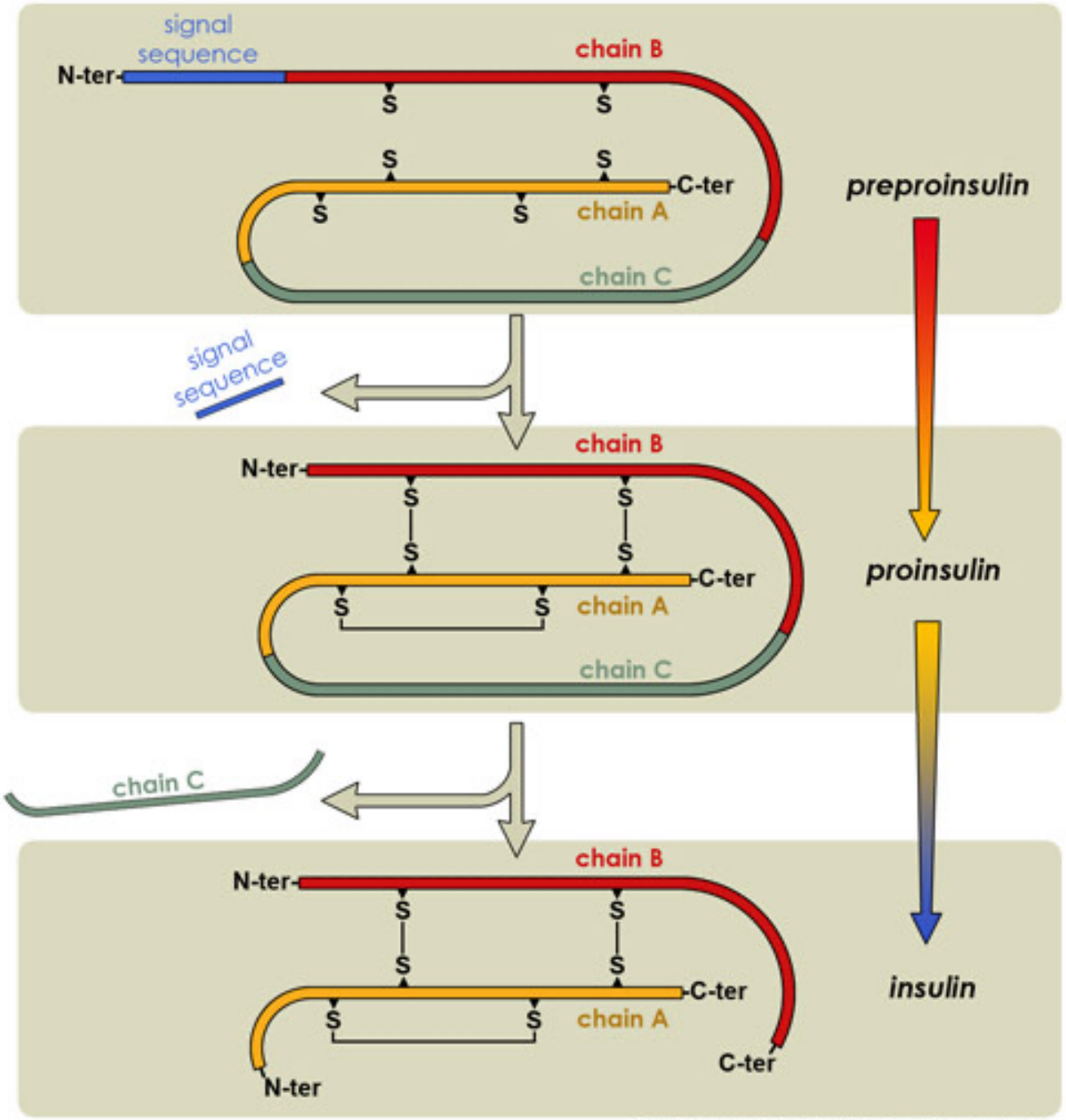
Insulin Synthesis

51 amino acid anabolic peptide hormone.

Occurs within the beta cells of the pancreatic islets.

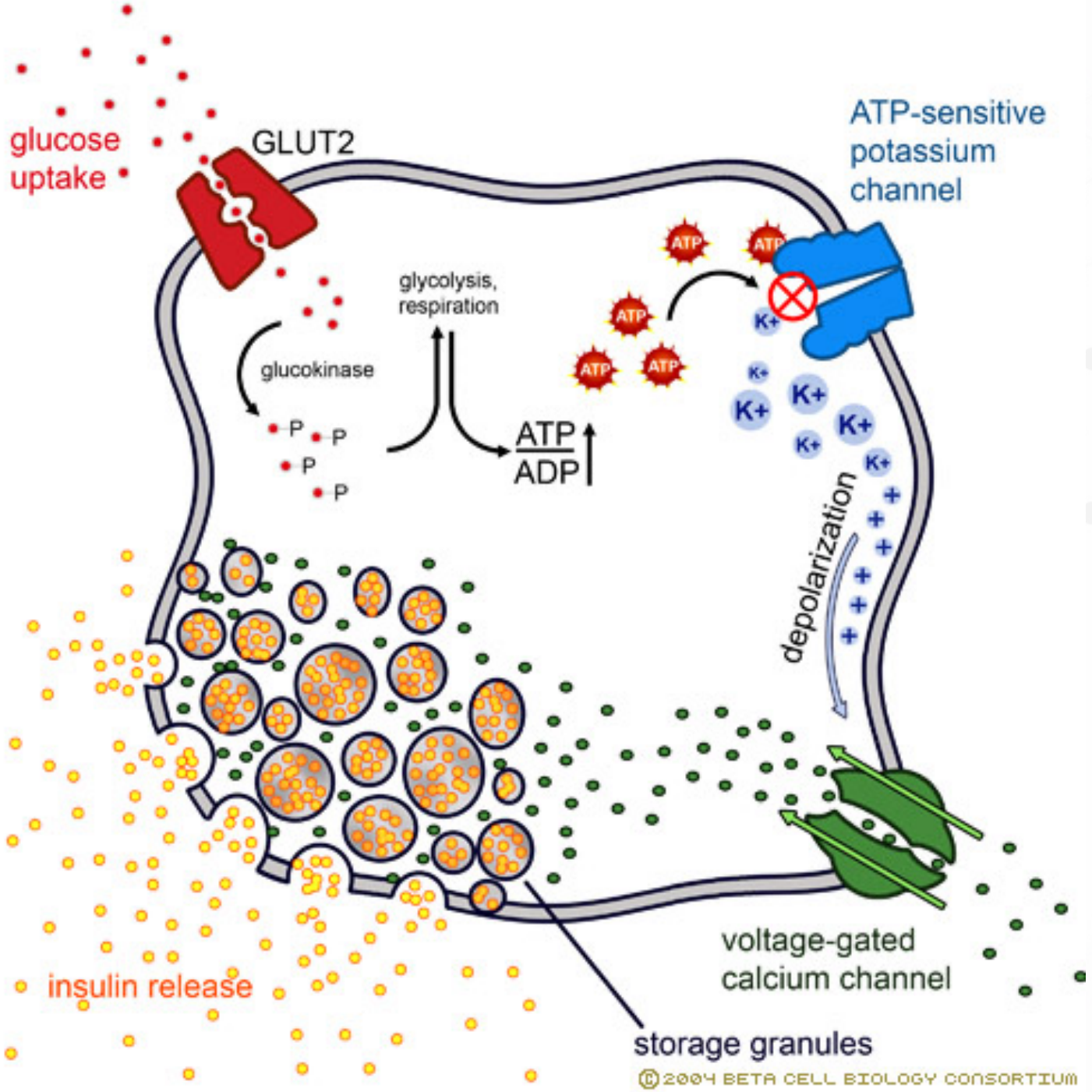
1. mRNA transcript creates a single chain precursor called preproinsulin
2. Preproinsulin enters the endoplasmic reticulum. Proteolytic enzymes cleave *signal peptide* to form proinsulin.
3. Proinsulin contains three domains
    1. Carboxy-terminal A chain
    2. Amino-terminal B chain
    3. Connecting peptide – C chain
4. Within the ER, endopeptidases cleave the C peptide, which is packaged and stored in the golgi apparatus and secretory vesicles until stimulated



Insulin Release

1. GLUT-2 transporters bring glucose into beta cells of the pancreas
2. This leads to an increase in ATP production (glycolysis, CAC, ETC)
3. Increased ATP stimulates the KATP Channel to block potassium ions, causing depolarization of the cell membrane*
4. The depolarizing cell membrane allows Ca2+ to enter via voltage-gated calcium channels, causing exocytosis of insulin-containing secretory vesicles

*Hypokalemia (low potassium) has been shown to decrease insulin production from the pancreas.


glucose uptake
GLUT2
ATP-sensitive potassium channel
glycolysis, respiration
glucokinase
ATP
ADP
depolarization
voltage-gated calcium channel
insulin release
storage granules
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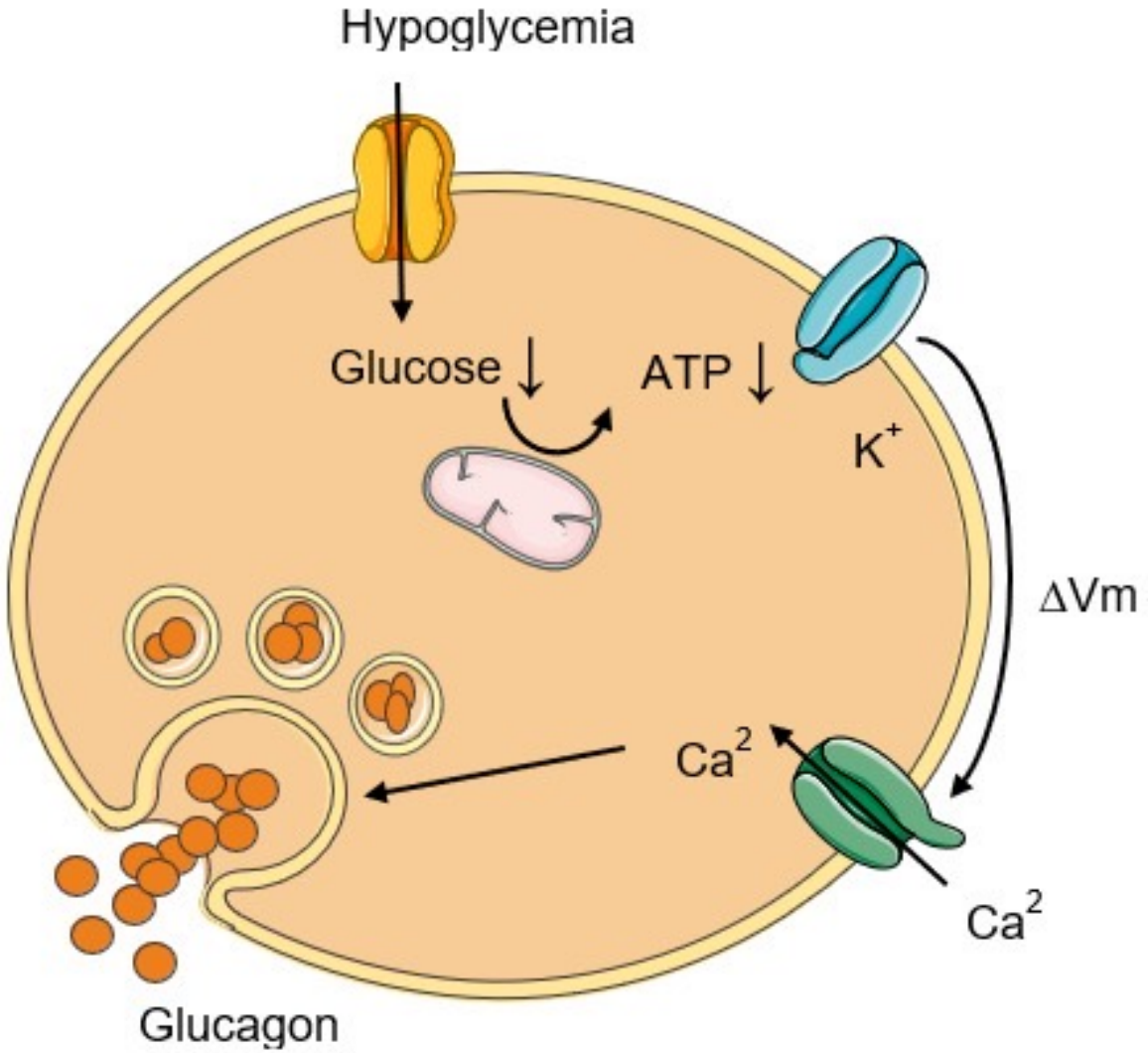
Insulin Actions

- Suppresses pancreatic glucagon
- Pancreatic insulin first goes to the liver via the hepatic portal system
- In the liver, insulin stimulates glycogen storage, cellular respiratory pathways and depending on the level of glucose, fatty acid and triacyglycerol synthesis

Glucagon

29 amino acid polypeptide hormone produced by alpha cells of pancreas

1. Low ATP within alpha cells stimulates Adenylate cyclase, increasing cAMP.
2. cAMP stimulates Protein Kinase A, K+ channels closes (efflux stops), triggers membrane action potential.
3. Ca++ channels open, stimulating exocytosis of glucagon



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Glucagon

Conversely, if ATP is elevated (due to glucose, free fatty acids, ketone bodies), the process is reversed, Calcium channels remain closed, and glucagon is not released.

Glucagon

Stimulators of glucagon:

-Hypoglycemia

-Amino acids

  -Also stimulate insulin which, during a non-carbohydrate meal could result in hypoglycemia, thus glucagon is released to compensate

-Epinephrine (beta adrenergic receptors)

Inhibitors of glucagon:

-Hyperglycemia

-Ketones, fatty acids (likely to help regulate ketogenesis)

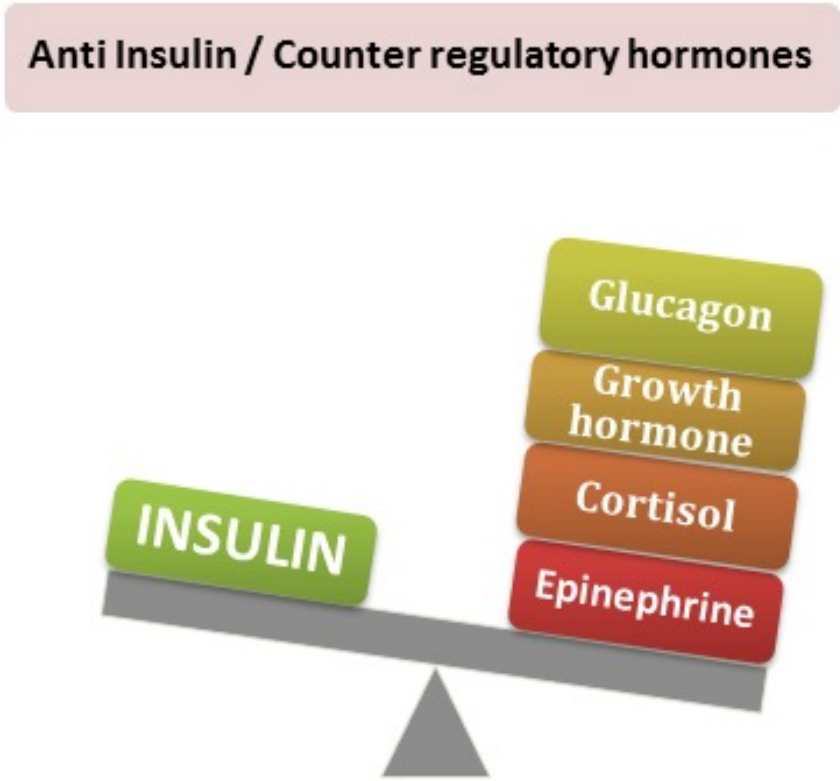
  -If glucagon was elevated, it would increase glucose and inhibit ketogenesis

Glucagon Action

Increases:

- Glycogenolysis – increases glycogen phosphorylase, decreases glycogen synthase
- Gluconeogenesis – increases hepatic uptake of amino acids, which can be used by the liver to make glucose
- Lipolysis – liberating free fatty acids and thus ketogenesis (long term starvation)

Other glucose regulatory hormones



Lab Testing – Glucose related markers

- Fasting glucose
- Fasting insulin
- Hemoglobin A1C
- C-Peptide (Insulin)
- Glycomark

Fasting Glucose

Traditional Reference range:

65-100 mg/dL

Optimal Reference Range:

82 - 88 mg/dL

85-99 mg/dL

Shin et al. Cardiovascular Diabetology 2011, 10:30
http://www.cardiab.com/content/10/1/30

CARDIO VASCULAR DIABETOLOGY

ORIGINAL INVESTIGATION Open Access

Increased arterial stiffness in healthy subjects with high-normal glucose levels and in subjects with pre-diabetes

Jin Young Shin[1], Hye Ree Lee[1] and Duk Chul Lee[2*]

Abstract

Background: Increased fasting plasma glucose (FPG), which includes impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and diabetes, is a risk factor for arterial stiffness. While IFG is widely accepted as a cardiovascular risk factor, recent studies have argued that subjects with high-normal glucose level were

FPG has an independent, positive association with arterial stiffness in non-diabetic subjects after correcting for confounding variables, including age, sex, BMI, blood pressure, resting heart rate, hs-CRP, lipid profile, and behavioral habits.

An increase in FPG, even within the normal range, was associated with aggravated arterial stiffness.

FPG level for the prevention of cardiovascular risk is a topic of active research [5-7]. While IFG is widely accepted as a cardiovascular risk factor, recent studies have demonstrated that subjects with high-normal

[11,12]. Brachial-ankle PWV (ba-PWV) is a suitable measure for screening for vascular dysfunction and the development of atherosclerosis in a preventive setting [13,14]. We assessed whether the FPG level is associated with arterial stiffness by measuring ba-PWV in non-diabetic healthy subjects with no history of cardiovascular disease, hypertension, or dyslipidemia.

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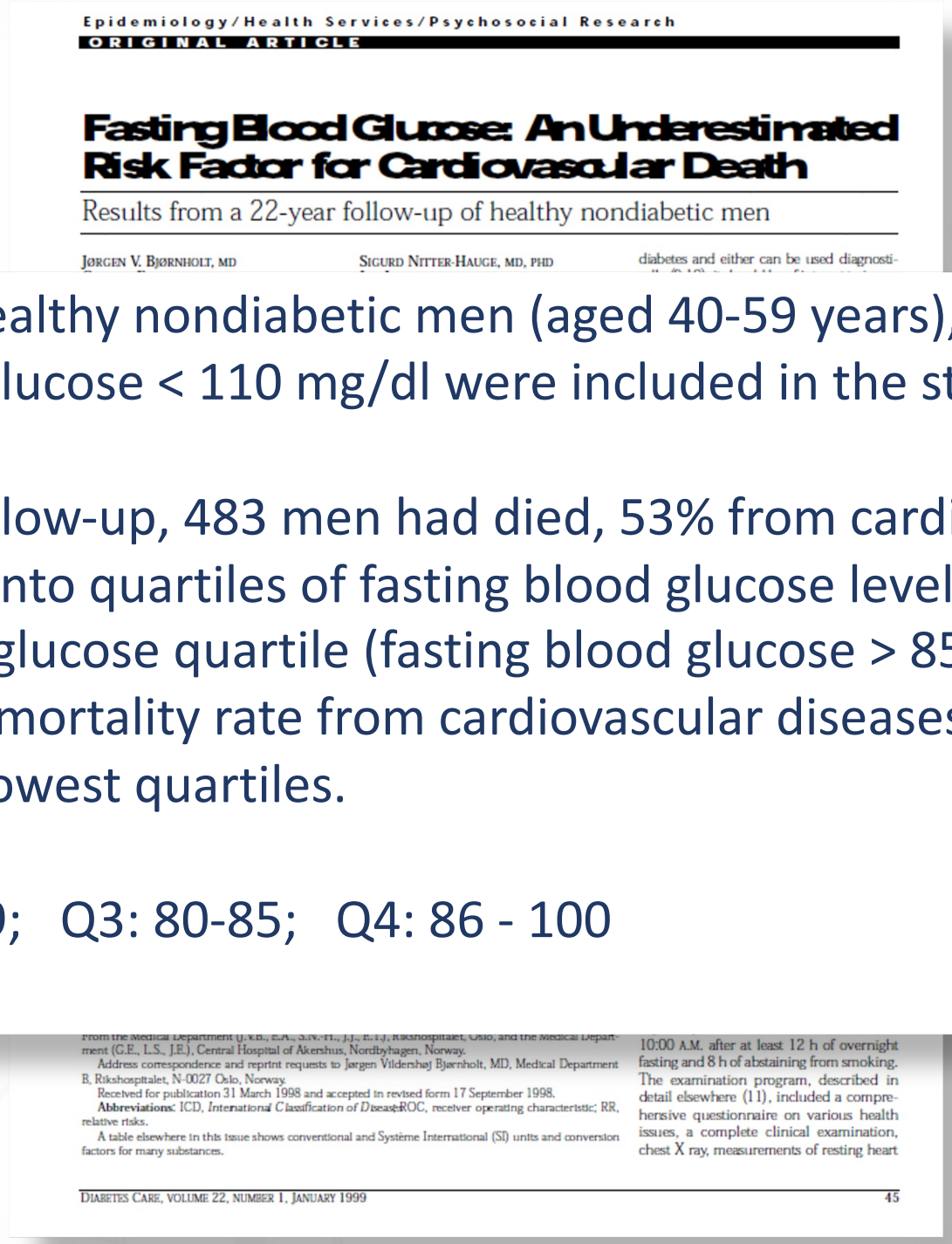
Epidemiology/Health Services/Psychosocial Research

ORIGINAL ARTICLE

Fasting Blood Glucose: An Underestimated Risk Factor for Cardiovascular Death

Results from a 22-year follow-up of healthy nondiabetic men

JØRGEN V. BJØRNHOLT, MD SIGURD NITTER-HAUGE, MD, PHD

diabetes and either can be used diagnosti-

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Received for publication 31 March 1998 and accepted in revised form 17 September 1998.

Abbreviations: ICD, *International Classification of Diseases*; ROC, receiver operating characteristic; RR, relative risks.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

10:00 A.M. after at least 12 h of overnight fasting and 8 h of abstaining from smoking. The examination program, described in detail elsewhere (11), included a comprehensive questionnaire on various health issues, a complete clinical examination, chest X ray, measurements of resting heart

DIABETES CARE, VOLUME 22, NUMBER 1, JANUARY 1999 45

1,998 apparently healthy nondiabetic men (aged 40-59 years), a total of 1,973 with fasting blood glucose < 110 mg/dl were included in the study

After 22 years of follow-up, 483 men had died, 53% from cardiovascular diseases. After dividing men into quartiles of fasting blood glucose level, it was found that men in the highest glucose quartile (fasting blood glucose > 85 mg/dl) had a significantly higher mortality rate from cardiovascular diseases compared with those in the three lowest quartiles.

Q1: <73; Q2: 74-79; Q3: 80-85; Q4: 86 - 100

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE

Normal Fasting Plasma Glucose and Risk of Type 2 Diabetes Diagnosis

Gregory A. Nichols, PhD, Teresa A. Hillier, MD, MS, Jonathan B. Brown, PhD, MPP
Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon.

ABSTRACT

PURPOSE: The study compares the risk of incident diabetes associated with fasting plasma glucose levels in the normal range, controlling for other risk factors.

METHODS: We identified 46,578 members of Kaiser Permanente Northwest who had fasting plasma glucose levels less than 100 mg/dL between January 1, 1997, and December 31, 2000, and who did not previously have diabetes or impaired fasting glucose. After assigning subjects to 1 of 4 categories (<85,

46,578 members of Kaiser Permanente Northwest who had fasting plasma glucose levels less than 100 mg/dL.

Assigned subjects to 1 of 4 categories (<85, 85-89, 90-94, or 95-99 mg/dL)

We followed them until they developed diabetes, died, or left the health plan, or until April 30, 2007.

betes development.[4]

The reduction of the impaired fasting glucose cut-point generated international controversy, in part because the re-

of other risk factors (family history of diabetes, smoking, hypertension, physical activity levels, triglycerides, and the ratio of total to high-density lipoprotein cholesterol) found that fasting plasma glucose levels significantly increased diabetes risk among young men (aged 26-45 years) with fasting plasma glucose levels less than 100 mg/dL.[7] We recently reported that fasting plasma glucose independently increased diabetes risk among a community-based sample

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doi:10.1016/j.amjmed.2008.02.026

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE

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Compared with those with fasting plasma glucose levels less than 85 mg/dL, subjects with glucose levels of 95 to 99 mg/dL were 233% more likely to develop diabetes. Subjects in the 90 to 94 mg/dL group were 49% more likely to progress to diabetes.

Each milligram per deciliter of fasting plasma glucose increased diabetes risk by 6%.

betes development.[4]

The reduction of the impaired fasting glucose cut-point generated international controversy, in part because the re-

More recently, an Israeli study that adjusted for a number of other risk factors (family history of diabetes, smoking, hypertension, physical activity levels, triglycerides, and the ratio of total to high-density lipoprotein cholesterol) found that fasting plasma glucose levels significantly increased diabetes risk among young men (aged 26-45 years) with fasting plasma glucose levels less than 100 mg/dL.[7] We recently reported that fasting plasma glucose independently increased diabetes risk among a community-based sample

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0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2008.02.026

ORIGINAL ARTICLE

Impaired Fasting Glucose: How Low Should It Go?

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OBJECTIVE — Impaired fasting glucose (IFG) has been recently introduced as a stage of abnormal carbohydrate metabolism, but the evidence on which its glucose limits (fasting plasma glucose [FPG] 6.1–6.9 mmol/l) are based is not strong. The aim of this study was to determine if 6.1 mmol/l represents a clear cutoff in terms of the risk of future diabetes and in terms of elevated cardiovascular risk factor levels, and to examine the use of other lower limits of IFG.

RESEARCH DESIGN AND METHODS — A population-based survey of the island of

The risk of developing hypertension at follow-up was greater for those people with baseline FPG > or =6.1 mmol/l (110 ng/dL). The risk of developing diabetes at follow-up increased with increasing baseline FPG, but there was little evidence of a threshold near 110 ng/dL.

A number of studies over the last few years have shown that levels of fasting glucose below the diagnostic threshold for diabetes (7.0 mmol/l) may not be normal, in that they are associated with an increased risk of both macrovascular disease and future diabetes. The Paris Prospective Study reported that the risk of developing diabetes over 3 years was greater among middle-aged men with a fasting plasma glucose (FPG) >6.1 mmol/l than it was for those with a lower FPG (1). Within the same cohort, it has also been reported that coronary heart disease mortality is elevated among people with FPG 5.8–6.9 mmol/l (2). Evidence from such studies has led to the introduction of impaired fasting glucose (IFG) by the American Diabetes Association (ADA) (3), as a stage in the natural history of disordered glucose metabolism, analogous to (although clearly different from) impaired glucose tolerance (IGT). This category has been supported by the World Health Organization (WHO) in a recent consultation document (4). Both the ADA and WHO have adopted the same criteria for IFG, an FPG ≥6.1 mmol/l and <7.0 mmol/l, although studies now show that the individuals identified by these limits are mostly different from those identified as having IGT (5,6).

In the few studies that have investigated nondiabetic FPG levels, only broad categories of FPG have been assessed, so that it

diabetes and hypertension.

In a population-based survey in Mauritius in 1987, we determined glucose tolerance status by oral glucose tolerance test (OGTT), and investigated cardiovascular risk factors. Diabetes, almost universally type 2, was found in 11.9% of adults aged 25–74 years (7). A follow-up survey was performed in 1992, measuring the same parameters. This allowed us to assess the associations between a range of FPG values and parameters related to diabetes, both cross-sectionally and prospectively.

RESEARCH DESIGN AND METHODS

— Mauritius is an Indian Ocean island nation ~800 km east of Madagascar. The population consists of ~70% Asian Indians, 2% Chinese, and 28% "general population" who are predominantly people of African ancestry (Creoles) with varying amounts of European, Malagasy, and Indian admixture. A population-based sur-

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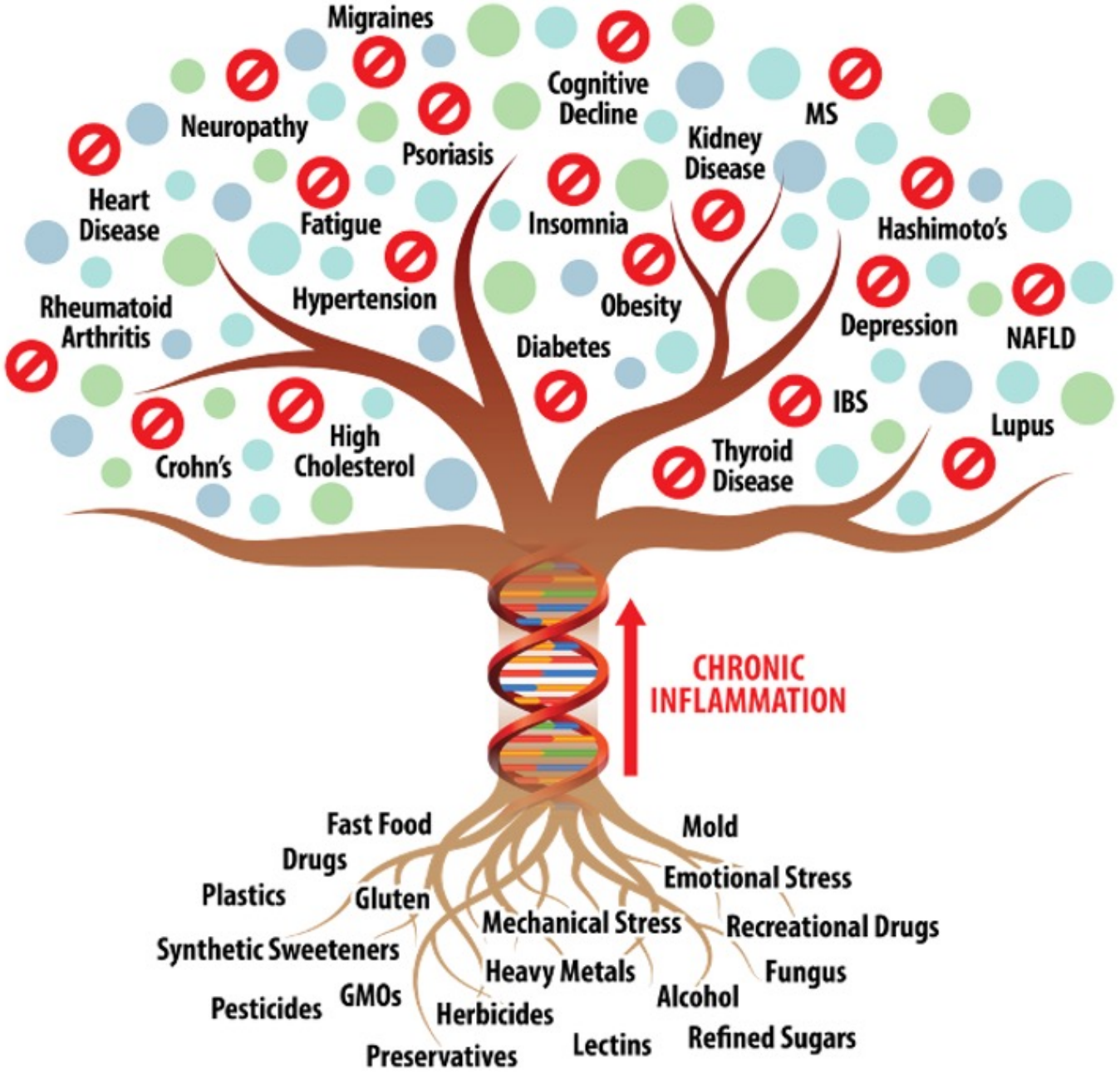
Abbreviations: 2-h PG, 2-h plasma glucose; ADA, American Diabetes Association; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; PPV, positive predictive value; ROC, receiver operator characteristic; WHO, World Health Organization; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Glucose – Elevated

Cause	Reason	Additional Inquiry
Insulin resistance (increased glucagon)	Dysfunctional insulin signaling (eg receptors) causing glucose to remain elevated in the blood.	Fatigue after meals, sweets cravings even after carbohydrate ingestion; evaluate c-peptide, hemoglobin A1C
Pancreatic dysfunction	Poor insulin production	Evaluate c-peptide.
Hyperthyroidism	Shorter half-life of insulin, increased intestinal glucose absorption, increased FFA and thus hepatic gluconeogenesis, excess lactate leading to increased hepatic gluconeogenesis (Cori cycle), increase in GH, glucagon and catecholamines all promote hyperglycemia	Evaluate thyroid markers.
Hyperadrenal function	Increased cortisol and/or catecholamine increase glucose levels	Consider evaluating cortisol levels.


Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Herbicides
Alcohol
Preservatives
Lectins
Refined Sugars

The Wedge Protocol