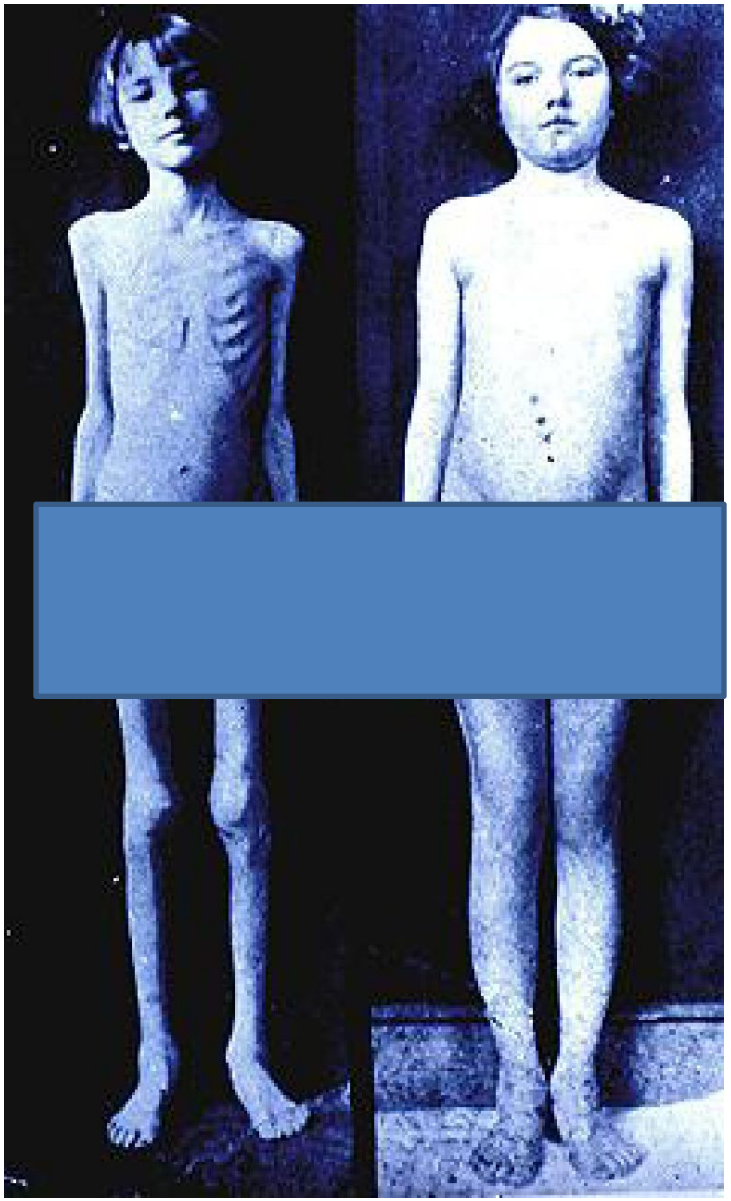
Endocrine Pancreas and Diabetes

Before and After

One of the first patients to ever receive insulin therapy



Best, Banting and the first dog successfully treated with insulin.

Fred Banting and Charles Best
University of Toronto

- 1921 worked on purifying insulin from extracts of dog pancreas and connected insulin to pancreatic islets
- 1922 first injection in a person
- 1923 commercial insulin manufactured and distributed
- 1923 Nobel Prize to Banting and McLeod

Insulin

First peptide drug

First protein sequenced

First protein structure solved

First hormone measured in blood (RIA)

First hormone gene cloned (at UCSF)

First recombinant and first biotech drug

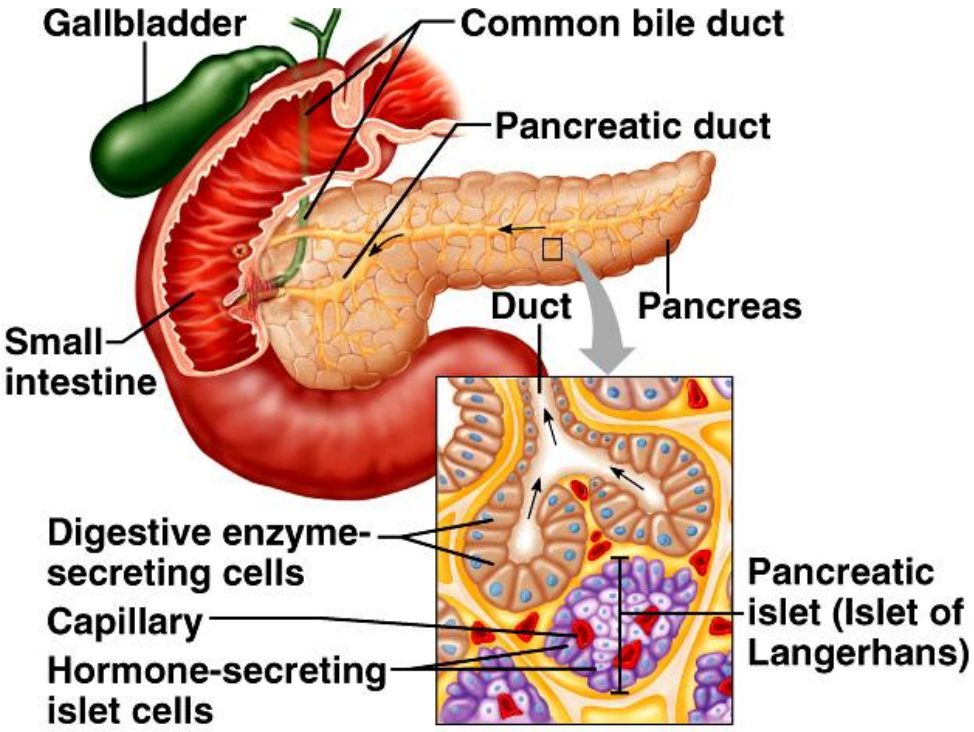
Basis of 4 Nobel Prizes

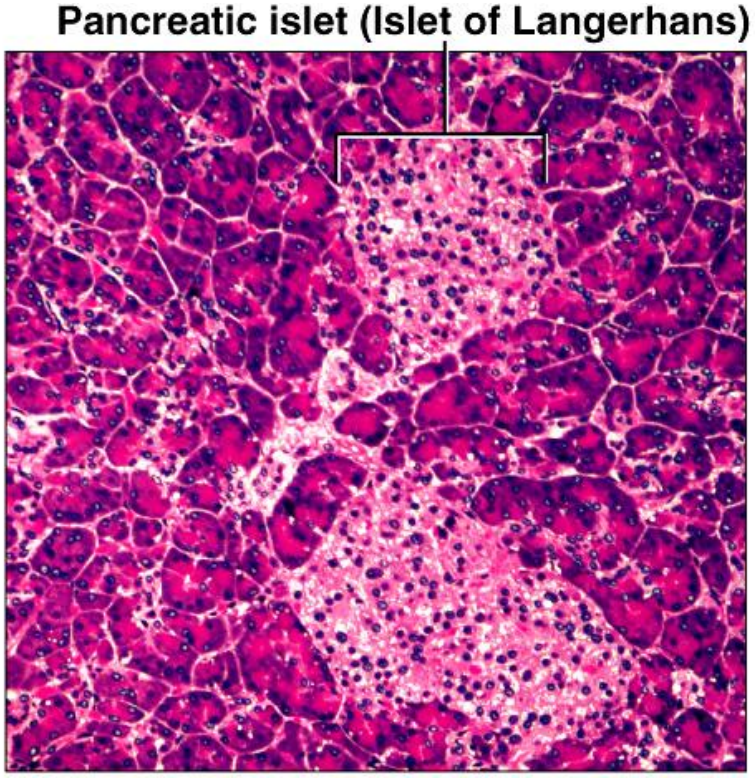
Overview of the Content

- Anatomy and Physiology of the Pancreas
  - Anatomy of Pancreas
    - Be able to identify the different functions of the endocrine and exocrine portions of the pancreas
    - Know the different types of cells in the Islets of Langerhans and what their functional roles plays in the physiology of the pancreases
  - Physiology of Insulin
    - Know the synthesis, release and actions on insulin on the body
  - Physiology of Glucagon
    - Understand the mechanism of action of Glucagon on a cellular and gross scale
  - Physiology of other Regulators of Blood Glucose
    - Be able to list some other hormones affecting blood glucose
- Diabetes Mellitus
  - Compare and Contrast Type I vs Type II DM
    - Age of Onset
    - Basic Pathology differences
    - Risk Factors
  - Be able to identify some treatments for Type I vs Type II DM.

ANATOMY OF THE PANCREAS

Endocrine Pancreas and Diabetes

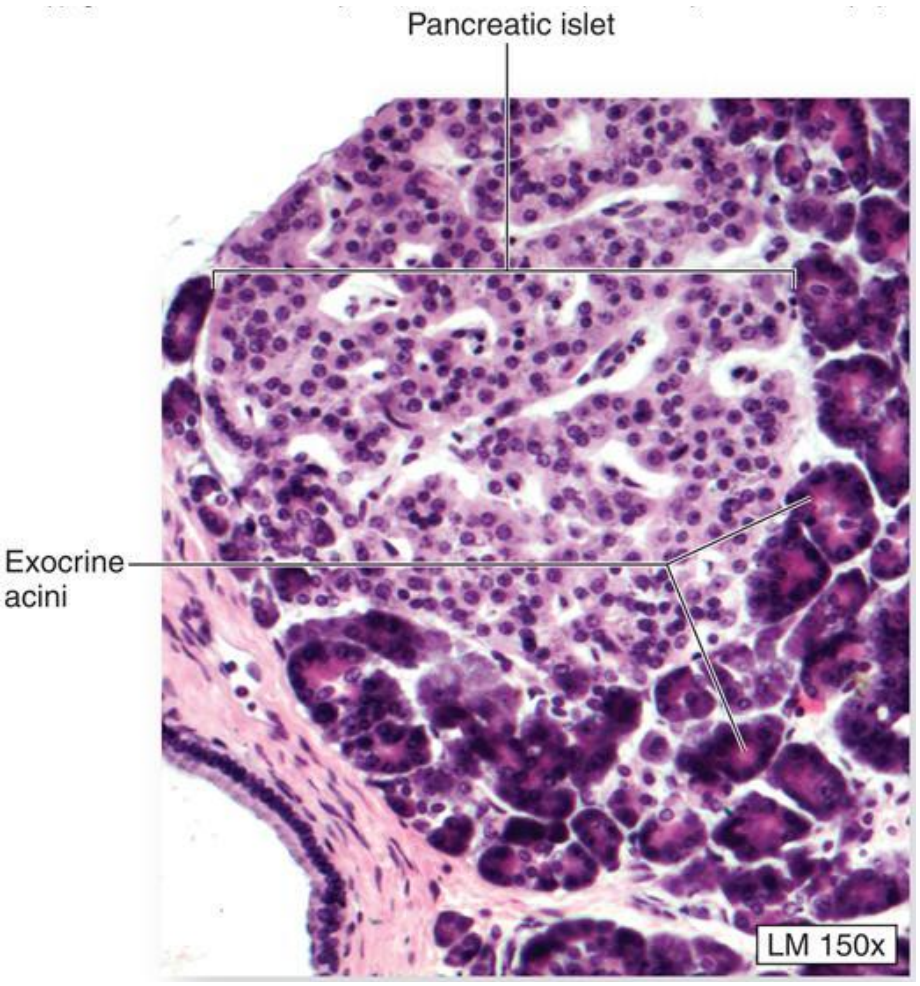


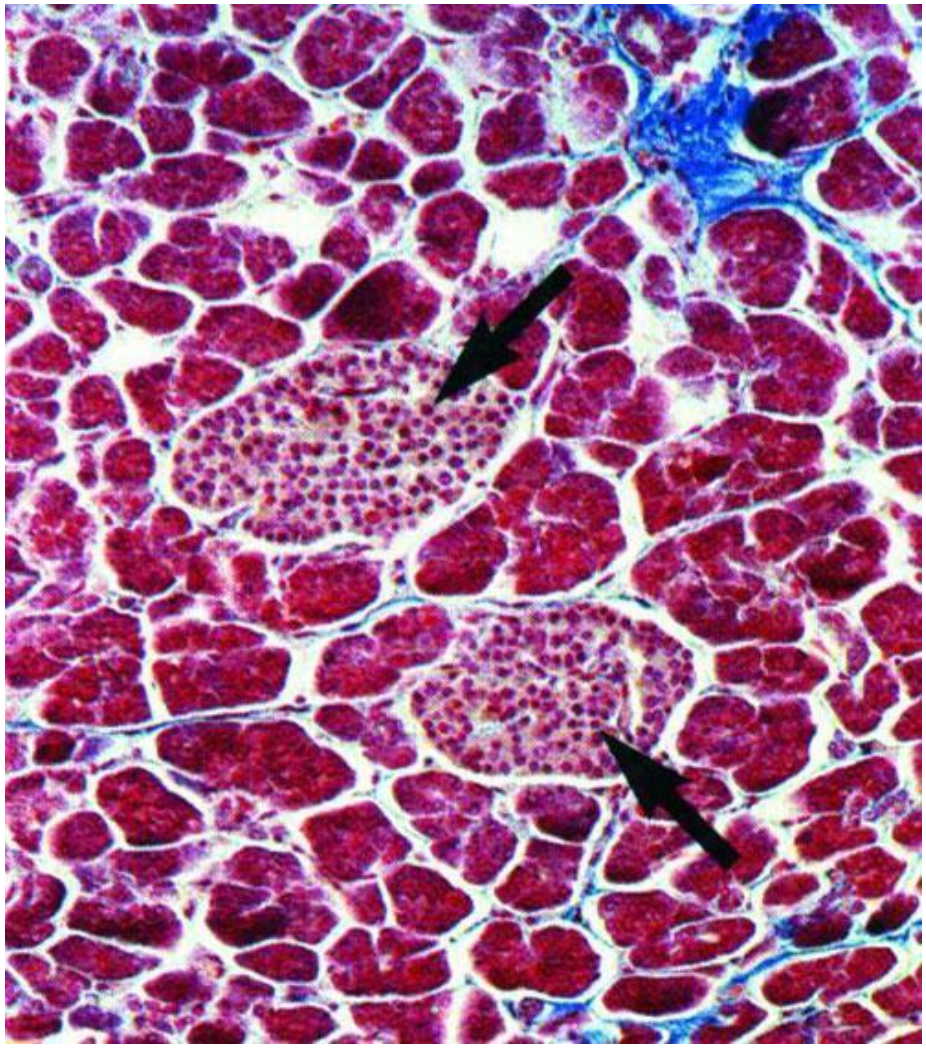


Pancreas – 2 types of glands:

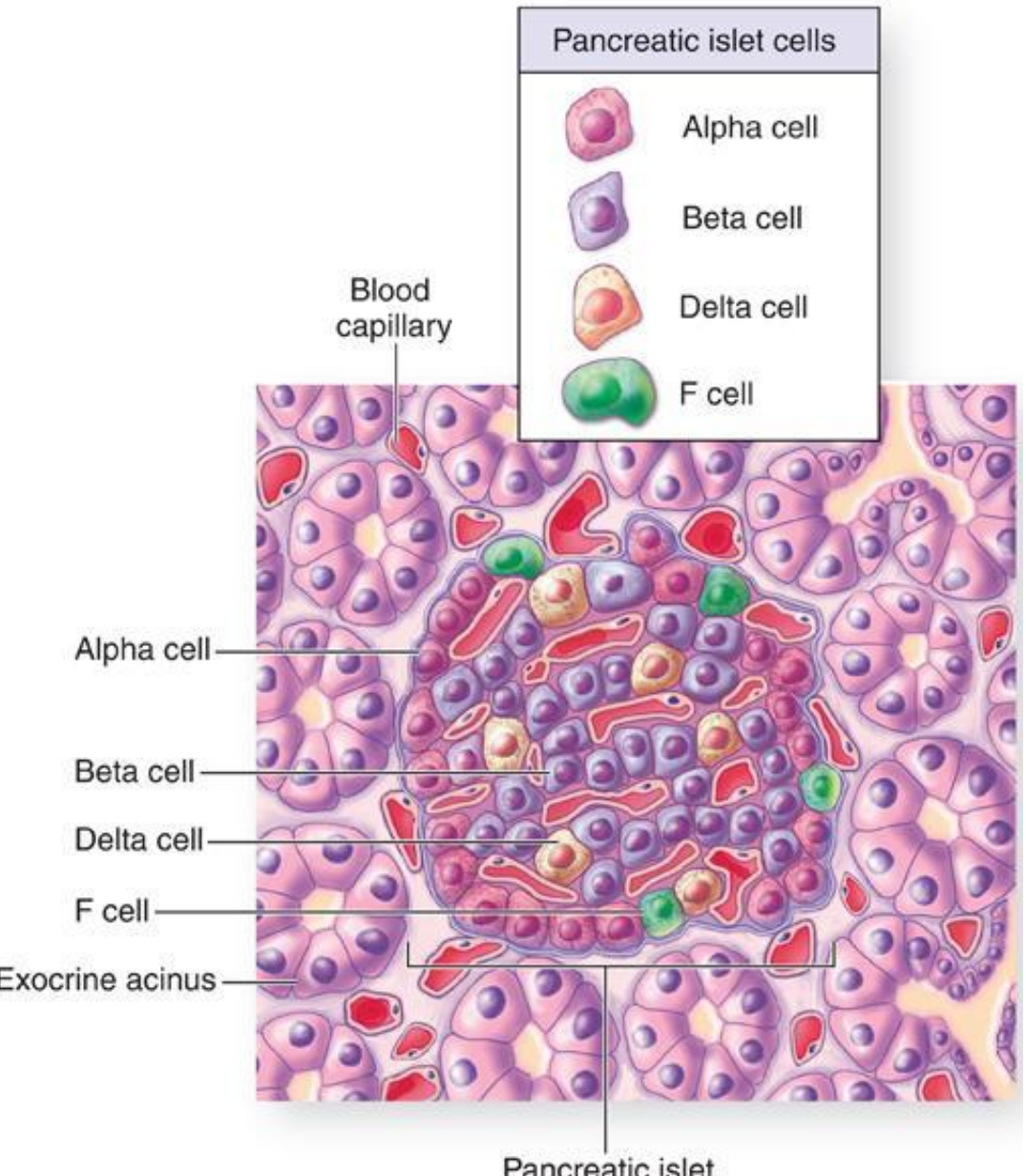
1) exocrine glands – secrete digestive enzymes and HCO_{3-}
2) endocrine glands – Islets of Langerhans

Islets of Langerhan (Pancreatic Islets)





Pancreas Histology



Products of Pancreatic Islet Cells

α- Glucagon

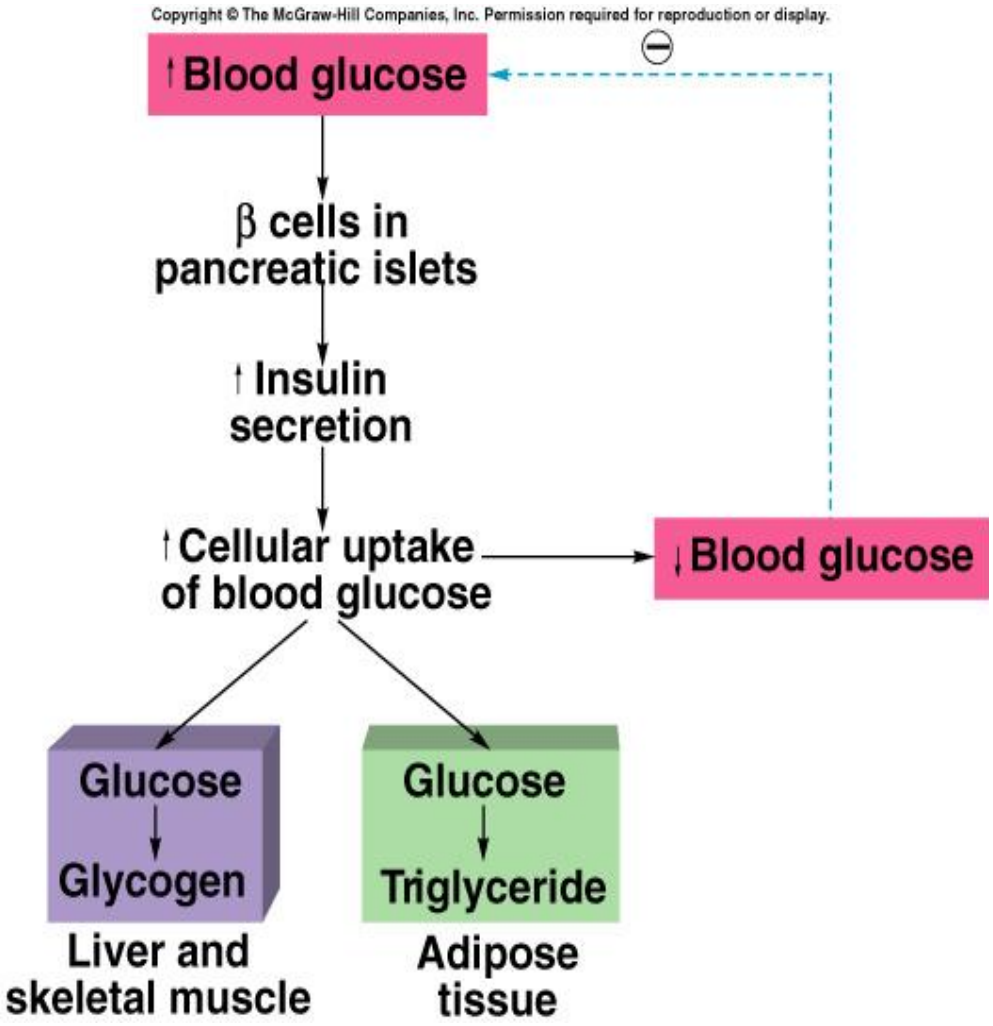
β- Insulin, Proinsulin

δ- Somatostatin

F- Pancreatic Polypeptides

Pancreatic Islets (Islets of Langerhans)

- Alpha cells secrete glucagon.
  - Stimulus is decrease in blood [glucose].
  - Stimulates glycogenolysis and lipolysis.
  - Stimulates conversion of fatty acids to ketones.
- Beta cells secrete insulin.
  - Stimulus is increase in blood [glucose].
  - Promotes entry of glucose into cells.
  - Converts glucose to glycogen and fat.
  - Aids entry of amino acids into cells.



The pancreas contains exocrine and endocrine cells.

The exocrine pancreas secretes pancreatic juice consisting of

a. digestive enzymes: secreted by the aciner cells
b. an aqueous alkaline fluid: secreted by the duct cells . The alkaline fluid has sodium bicarbonate.
c. Pancreatic exocrine secretion is regulated by secretin and CCK hormones that secreted by the small intestine.
d. Secretin stimulates the secretion of sodium bicarbonate from the pancreas.
e. CCK stimulates (regulates) the secretion of pancreas digestive enzymes.

Endocrine cells are isolated islands called islets of Langerhans.

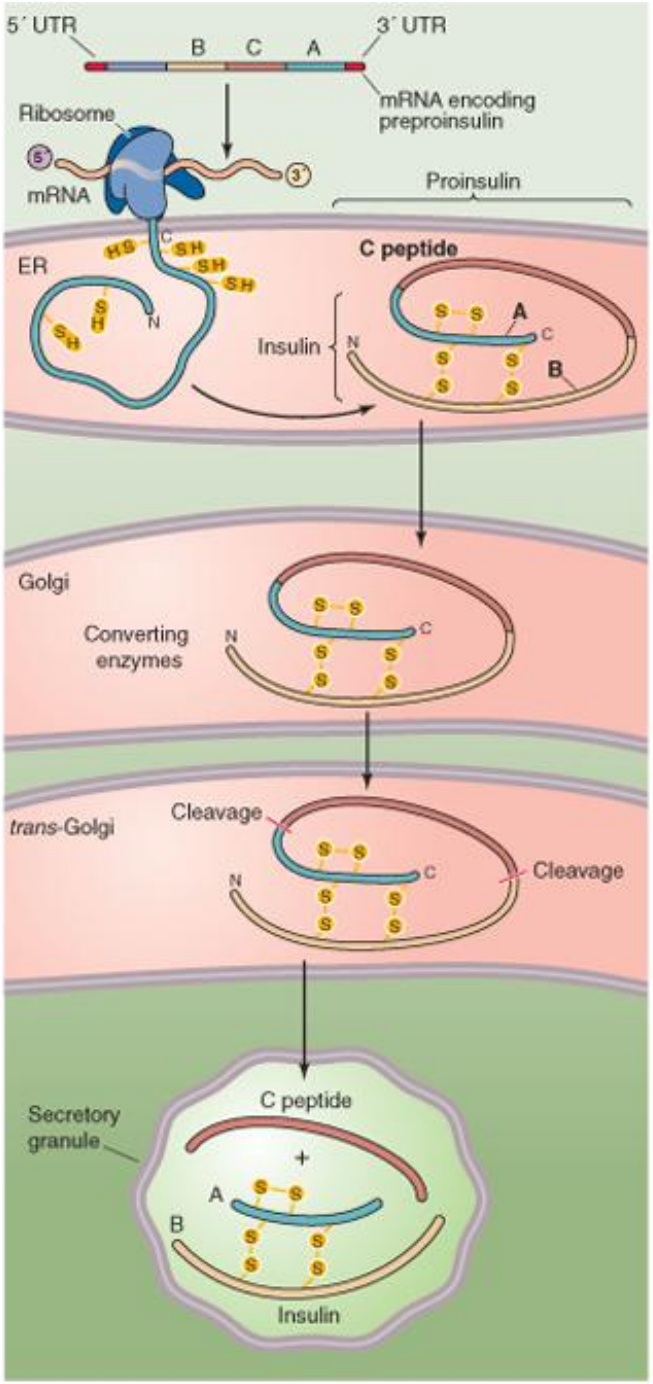
- secrete hormones (insulin and glucagon) into blood.

PHYSIOLOGY OF INSULIN

Roles of Insulin

- Acts on tissues (especially liver, skeletal muscle, adipose) to increase uptake of glucose and amino acids.
- - without insulin, most tissues do not take in glucose and amino acids well (except brain).
- Increases glycogen production (glucose storage) in the liver and muscle.
- Stimulates lipid synthesis from free fatty acids and triglycerides in adipose tissue.
- Also stimulates potassium uptake by cells (role in potassium homeostasis).

Synthesis and processing of insulin



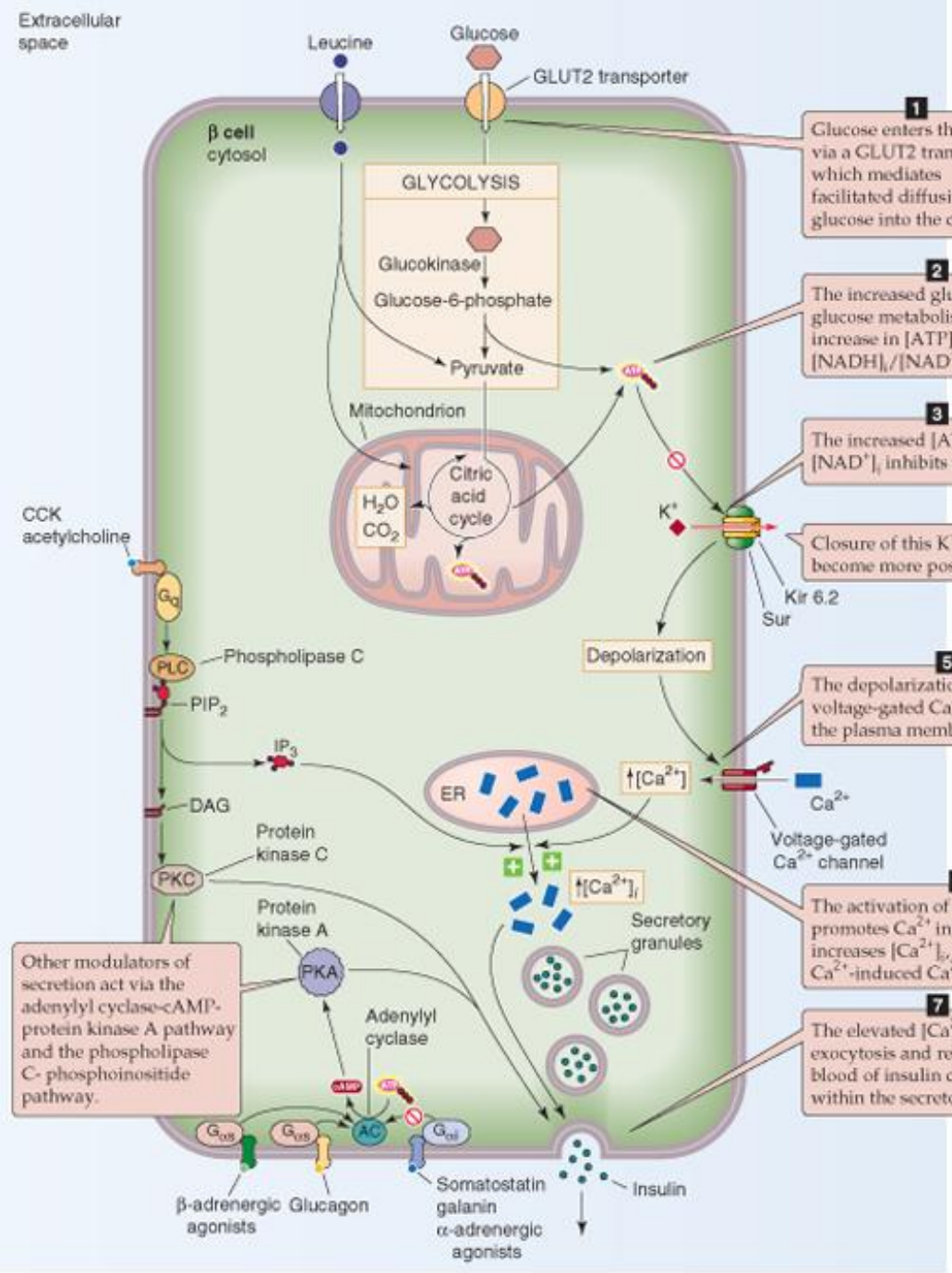
Preproinsulin: mRNA encodes a leader sequence and peptide domains A, B, C

Proinsulin: encodes peptide domains A, B, C

Golgi packages proinsulin: Proteases cleave proinsulin molecule and excise C peptide

Secretory granule: Packages insulin, Peptide C and proinsulin for release

Insulin secretion in pancreatic β cells

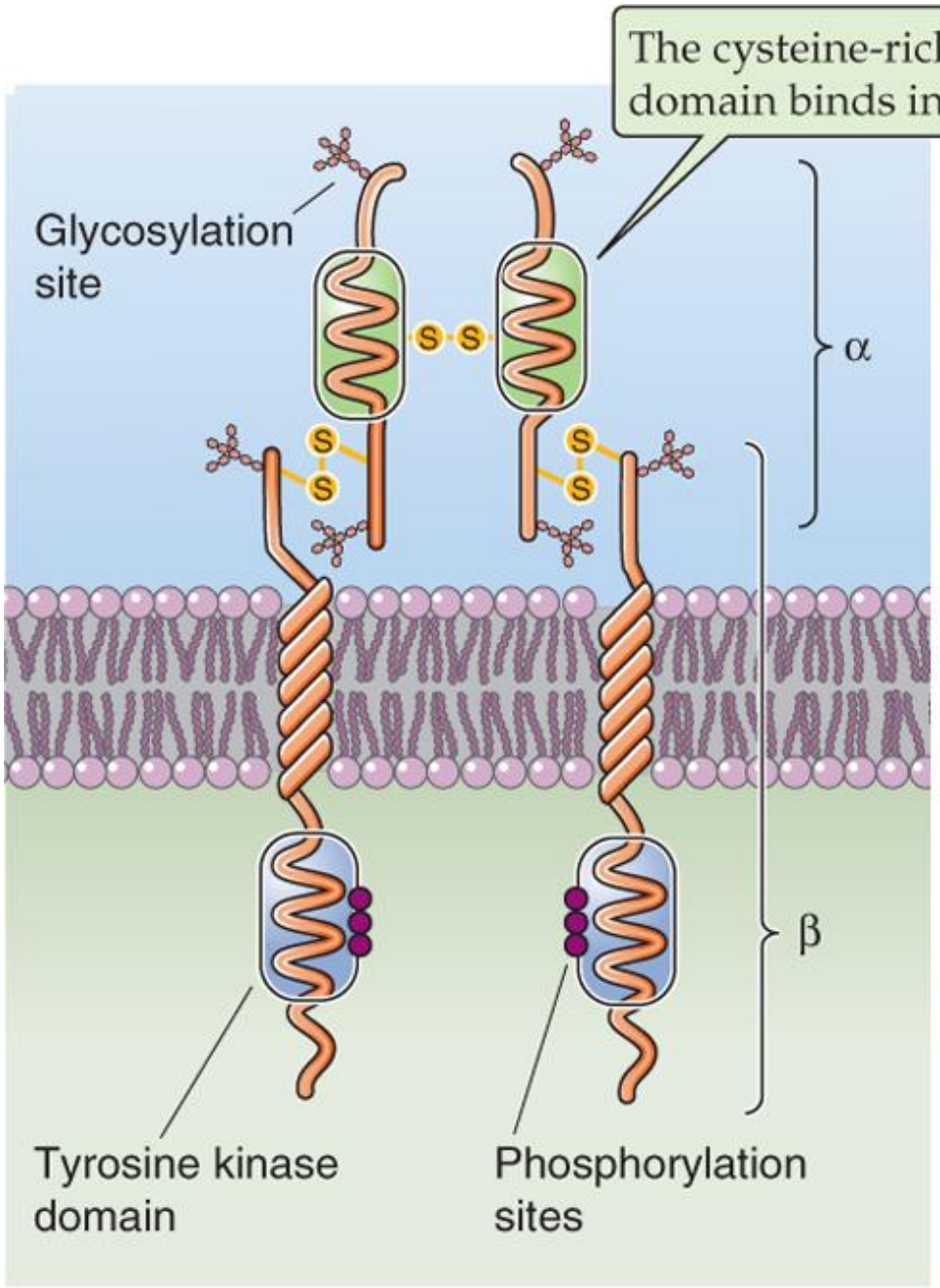


Neural and Hormonal Factors Modulate Insulin Secretion

Islets are richly innervated by both sympathetic and parasympathetic divisions

Parasympathetic: vagus nerve releases Ach increase insulin release

Sympathetic: β-adrenergic – stimulate islet insulin secretion
α-adrenergic –inhibits insulin secretion (Norepi and synthethic α agonists supress its release)



Boron & Boulpaep: Medical Physiology, 2nd Edition.

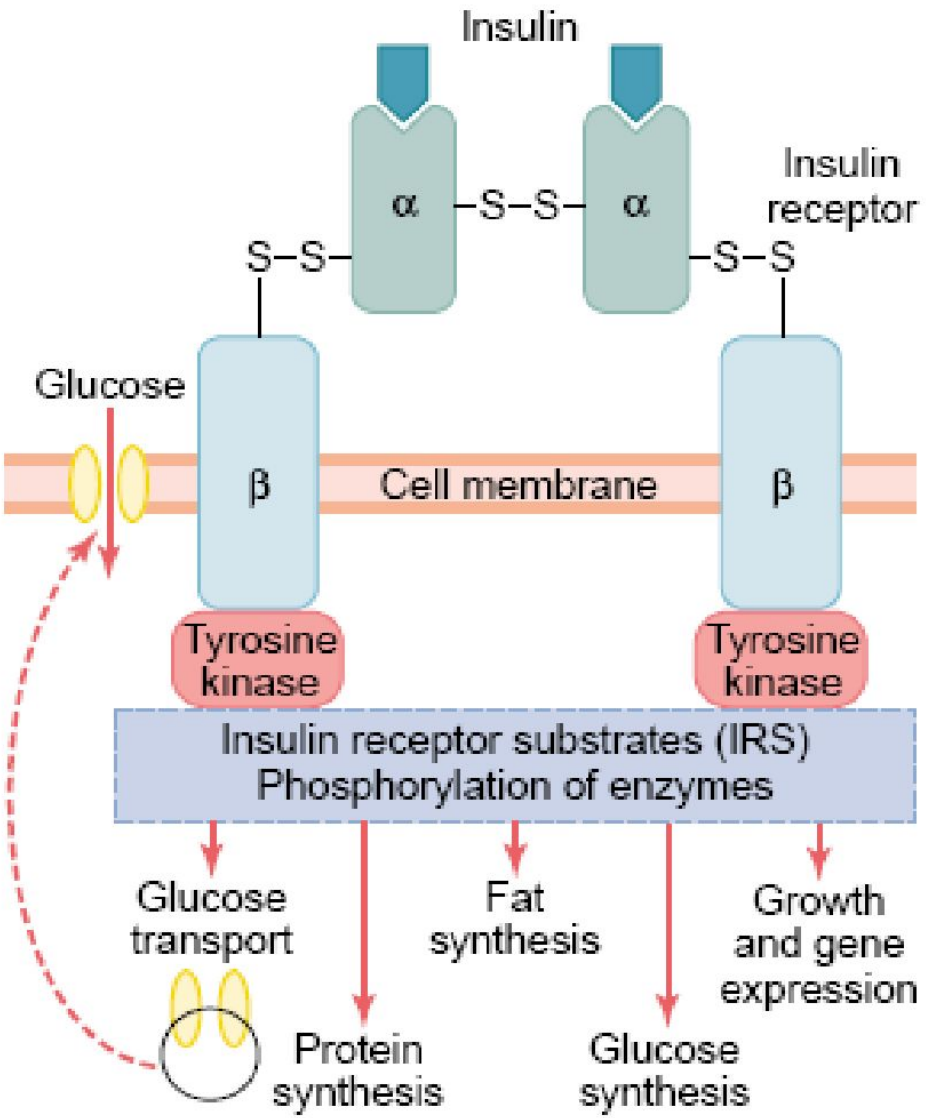
Insulin Receptor:
Receptor Tyrosine Kinase

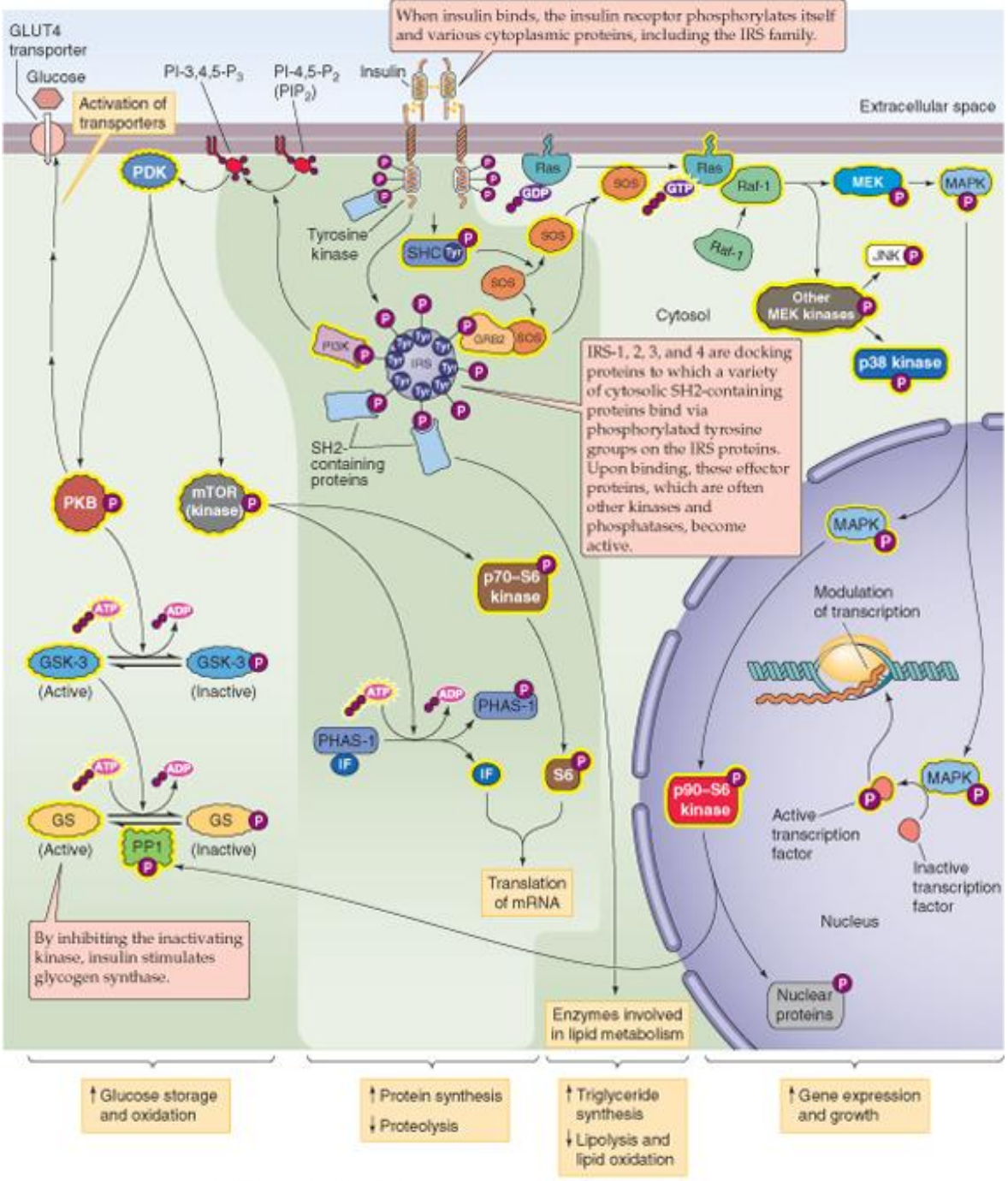
Heterotetramer consisting of two extracellular α chains and two membrane spanning β chains.

Insulin binding results in autophosphorylation

The Insulin Receptor

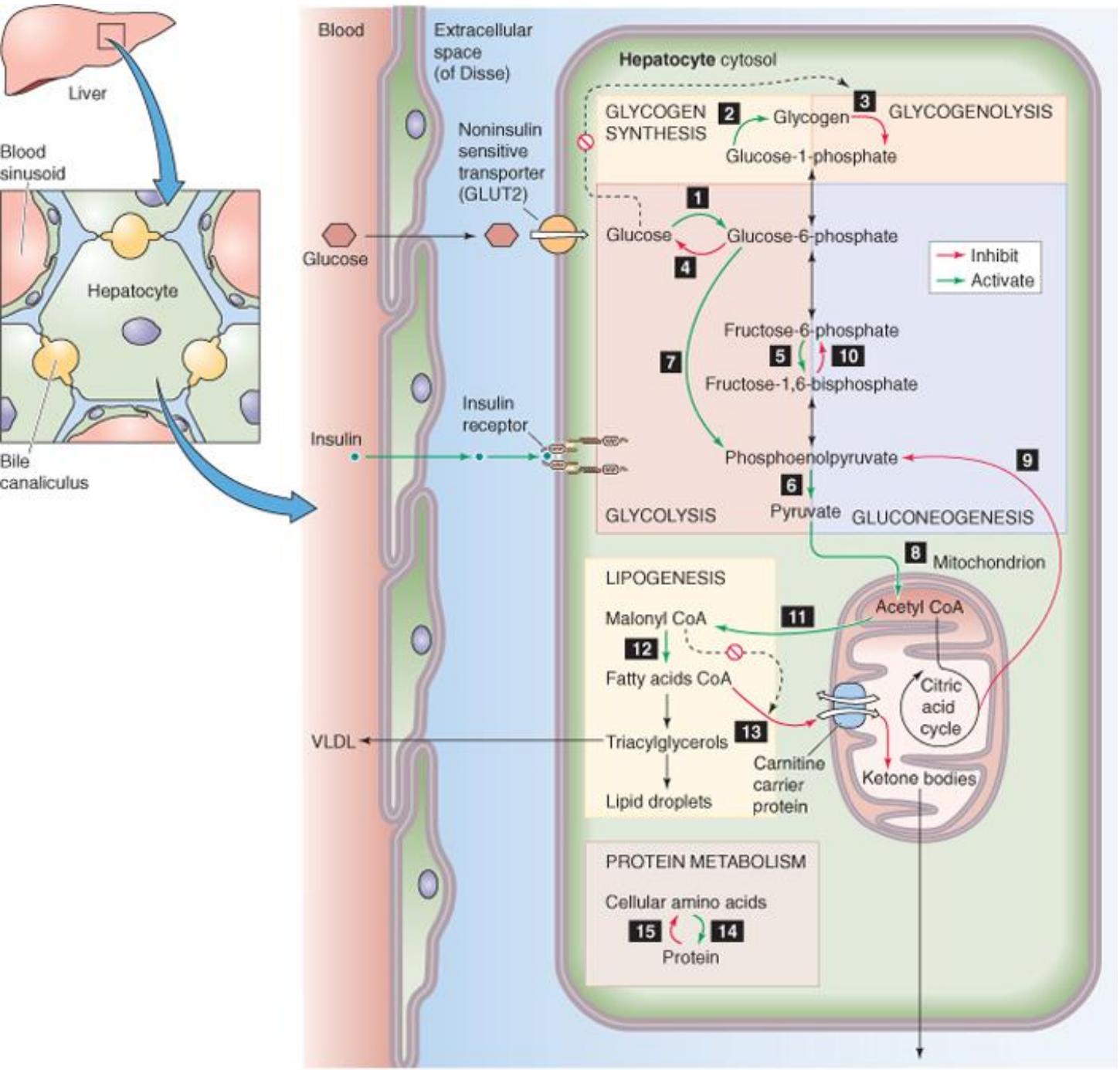
- Membrane glycoproteins composed of 2 subunits
- Tyrosine kinase activity
- Sequence of events:
  - Insulin binds alpha subunit
  - Beta activates itself via autophosphorylation





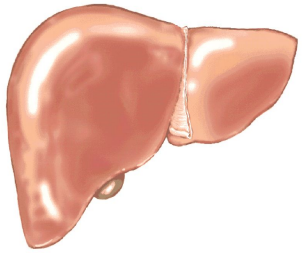
Insulin Action on Cells: Dominates in Fed State Metabolism

- ↑ glucose uptake in most cells
  (not active muscle)
- ↑ glucose use and storage
- ↑ protein synthesis
- ↑ fat synthesis



Metabolic Effects of Insulin

- Energy storage
  - **Liver**
    - Promotes anabolism:
      - glycogen synthesis and storage
      - Inhibits glycogen breakdown
      - Promotes glycolysis
      - Inhibits gluconeogenesis
      - Increases protein, triglyceride and VLDL formation



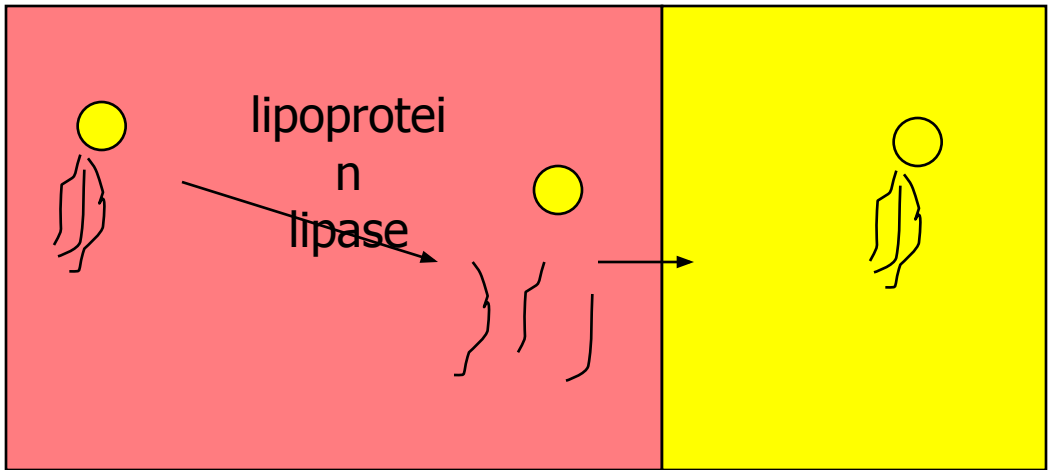
    - Inhibits catabolism
      - Decrease hepatic glycogenolysis, ketogenesis and gluconeogenesis

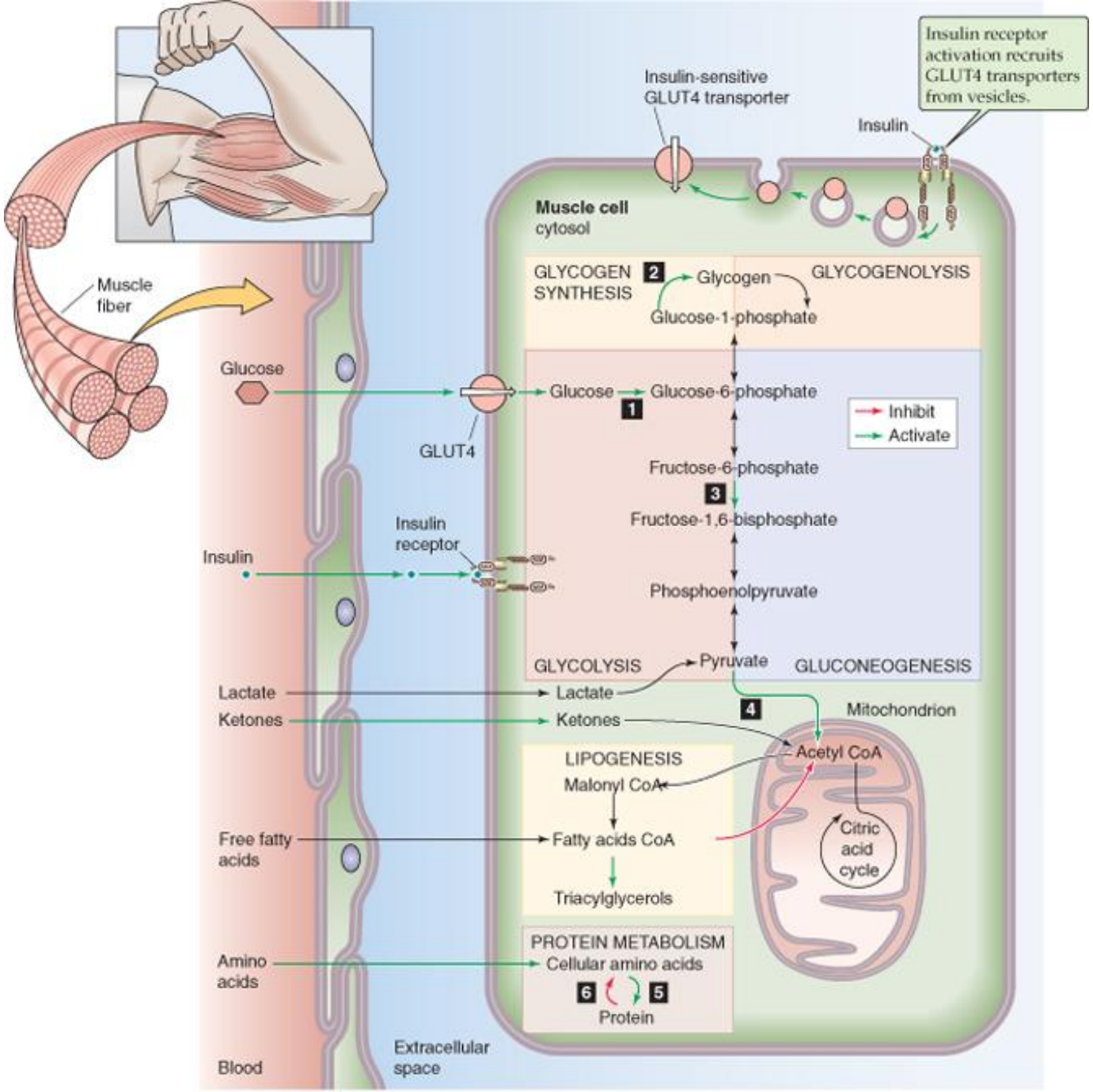
Actions of Insulin on the Liver

- Stimulates glucose uptake
- Stimulates glycogenesis
- Stimulates glycolysis
- Stimulates HMP shunt activity
- Inhibits glycogenolysis
- Inhibits gluconeogenesis
- Stimulates lipogenesis
- Inhibits lipolysis
- Stimulates cholesterol synthesis
- Increases VLD lipoprotein
- Increases potassium and phosphate uptake
- Inhibit Urea cycle activity

Specific Targets of Insulin Action: Lipids

- Activation of acetyl CoA carboxylase. Stimulates production of free fatty acids from acetyl CoA.
- Activation of lipoprotein lipase (increases breakdown of triacylglycerol in the circulation). Fatty acids are then taken up by adipocytes, and triacylglycerol is made and stored in the cell.



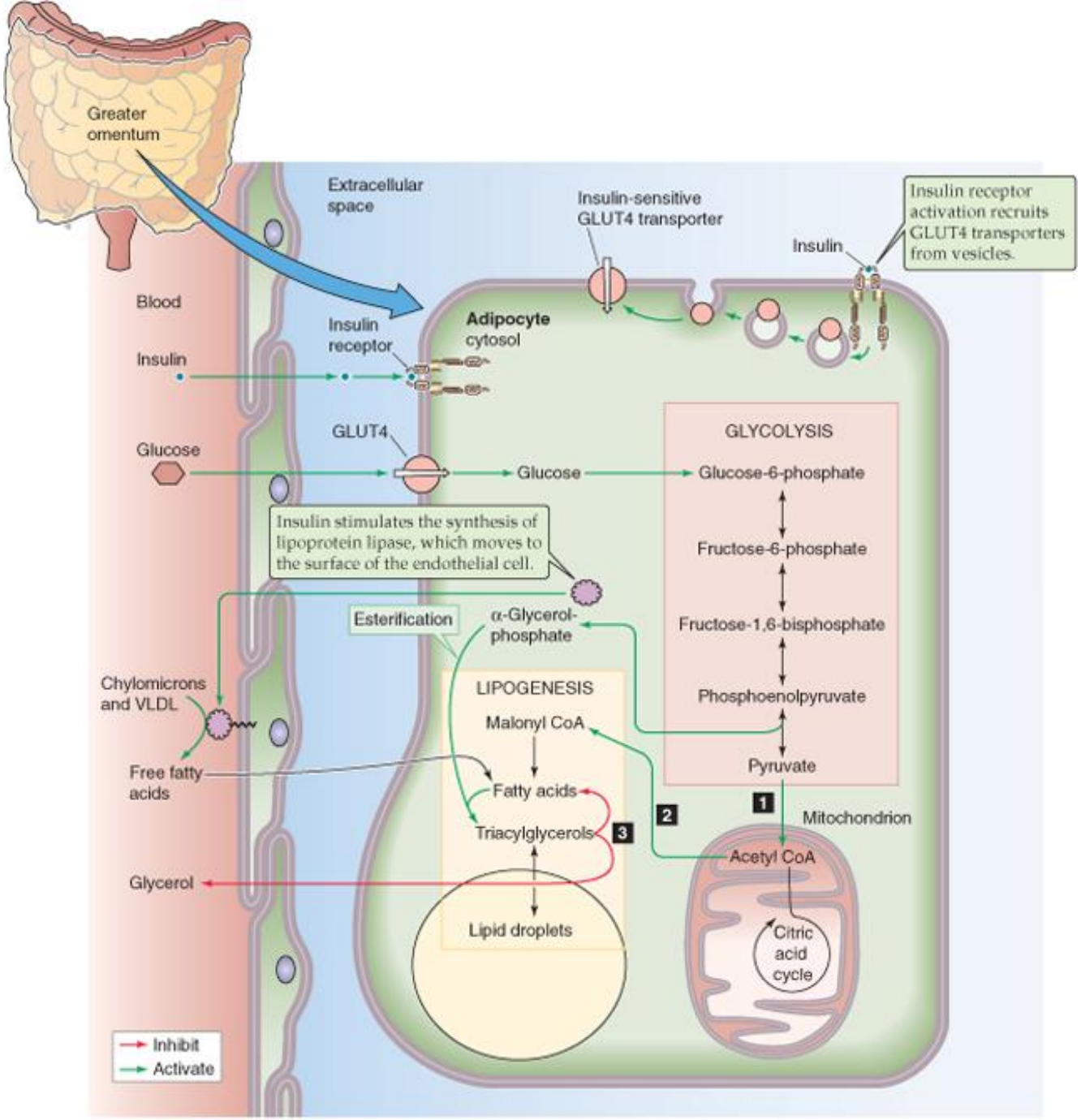


Metabolic Effects of Insulin

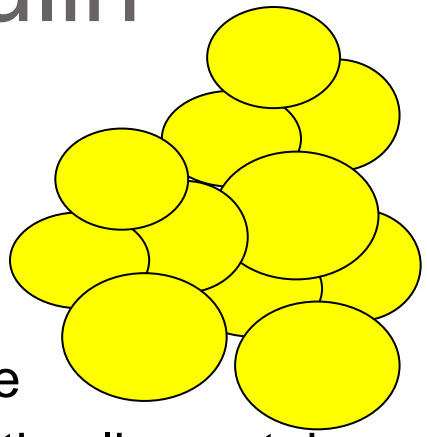
- Muscle
  - Promotes protein synthesis
    - Increased amino acid transport
    - Stimulating ribosomal protein synthesis
  - Promotes glycogen synthesis
    - Enhanced by increased glucose transport i
    - Enhanced activity of glycogen synthase
    - Inhibiting activity of glycogen phosphorylas
  - Increased glucose transport into muscle cells

Actions of Insulin on Muscle

- Stimulates glucose uptake
- Stimulates glycogenesis
- Stimulates glycolysis
- Inhibits glycogenolysis
- Inhibits FFA uptake and oxidation
- Stimulates proteogenesis
- Inhibits proteolysis
- Stimulates uptake of potassium, phosphate and magnesium
- Increases blood flow



Metabolic Effects of Insulin



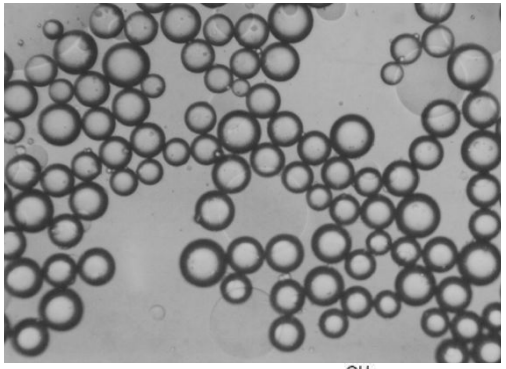
- Adipose tissue
  - Promotes triglyceride storage
    - Increased production of lipoprotein lipase
      - Hydrolysis of triglycerides from circulating lipoproteins
    - Increasing glucose transport into fat cells
      - Increased cellular levels of alpha-glycerol phosphate – esterification of fatty acids to triglycerides
    - Inhibition of intracellular lipolysis (lipase)

Action of Insulin on Adipose Tissue

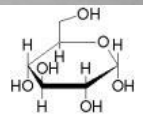
- Stimulates glucose uptake by increasing GLUT-4 availability
- Stimulates glycolysis
- Stimulates lipogenesis
- Inhibits lipolysis and ketogenesis

Insulin Stimulates Cellular Glucose Uptake

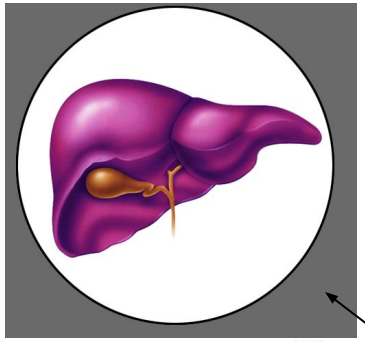
Adipocytes



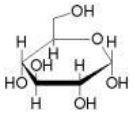
Insulin



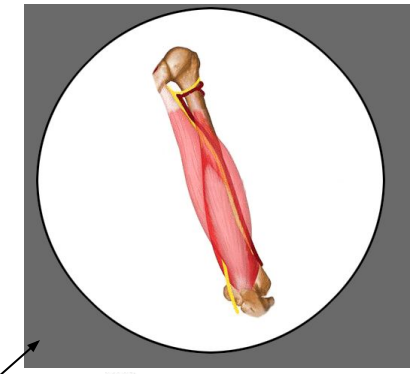
Liver

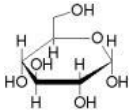


Insulin

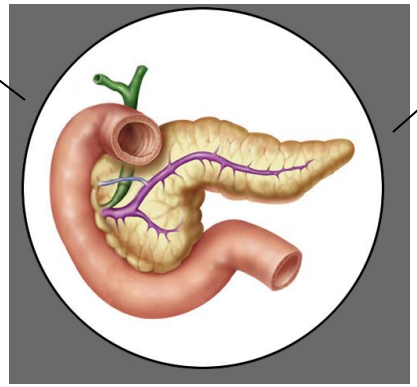


Skeletal Muscle





Insulin



Intestine & Pancreas

Other Factors Regulating Insulin Release

- Amino acids stimulate insulin release (increased uptake into cells, increased protein synthesis).
- Keto acids stimulate insulin release (increased glucose uptake to prevent lipid and protein utilization).
- Insulin release is inhibited by stress-induced increase in adrenal epinephrine

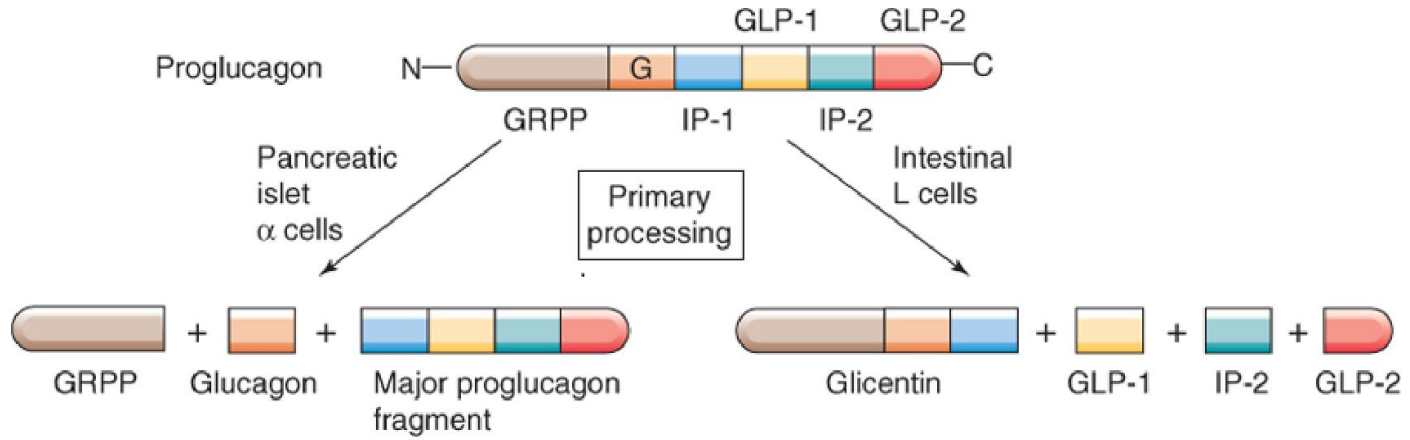
  - epinephrine binds to alpha adrenergic receptors on beta cells

    - maintains blood glucose levels
- Glucagon stimulates insulin secretion (glucagon has opposite actions).

PHYSIOLOGY OF GLUCAGON

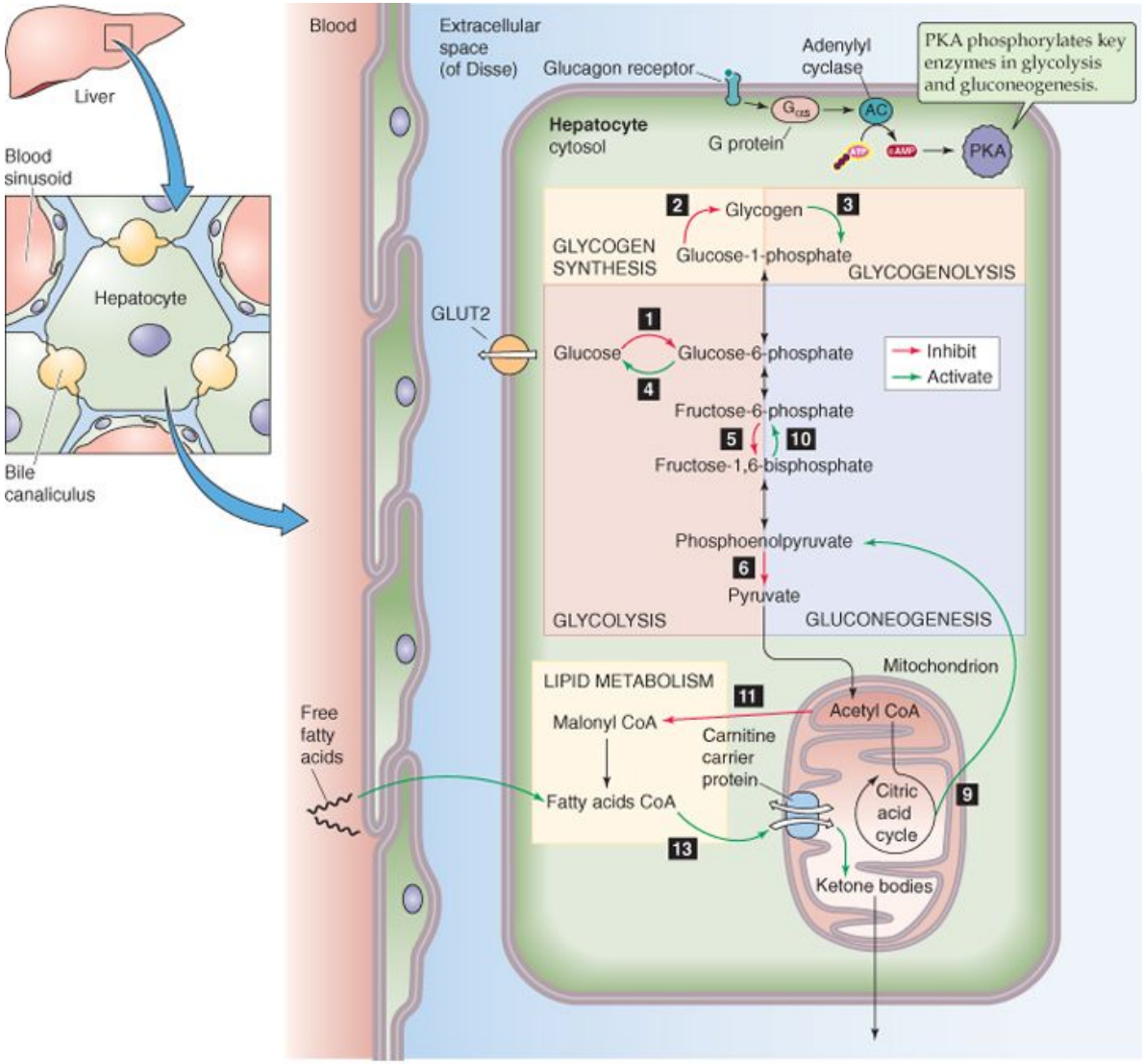
Structure and Actions of Glucagon

- Peptide hormone, 29 amino acids
- Acts on the liver to cause breakdown of glycogen (glycogenolysis), releasing glucose into the bloodstream.
- Inhibits glycolysis
- Increases production of glucose from amino acids (gluconeogenesis).
- Also increases lipolysis, to free fatty acids for metabolism.
- Result: maintenance of blood glucose levels during fasting.



Mechanism of Action of Glucagon

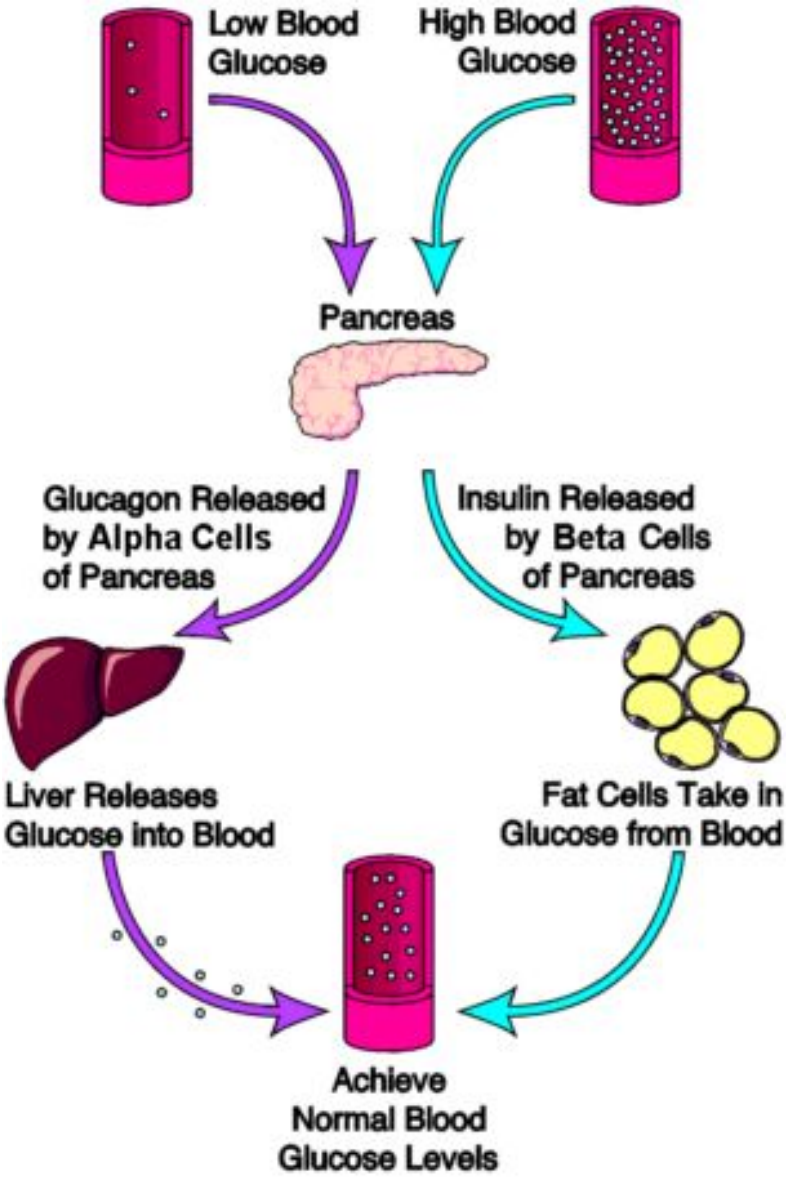
- Main target tissues: liver, muscle, and adipose tissue
- Binds to a $G\alpha_s$-coupled receptor, resulting in increased cyclic AMP and increased PKA activity.
- Also activates IP3 pathway (increasing Ca^{++})



Glucagon

- Counter-regulatory hormone
- Increases blood glucose concentration, i.e. hyperglycemic
- Effects:
  - Breakdown of liver glycogen (glycogenolysis)
    - Via activation of adenlyl cyclase
    - Using an amplification mechanism (i.e. each product is greater than the one before)
    - Can cause blood glucose to double within a few minutes
  - Increase gluconeogenesis in the liver
    - Increased uptake of amino acids which are then used to make glucose

Glucagon and Insulin



Effects on Glucagon Secretion

Stimuli for Glucagon Secretion

↓ Blood glucose
↑ Serum amino acids (arginine, alanine)
Sympathetic nervous system stimulation
Stress
Exercise

Inhibitors of Glucagon Secretion

Somatostatin
Insulin
↑ Blood glucose

Glucagon

- Supra-physiological levels
  - Activation of adipose cell lipase
  - Inhibits storage of triglycerides in the liver
  - Increased blood levels of fatty acids
  - Enhances heart strength
  - Increases blood flow to kidneys
  - Enhances bile secretion
  - Inhibits gastric acid secretion

Regulation of Glucagon Secretion

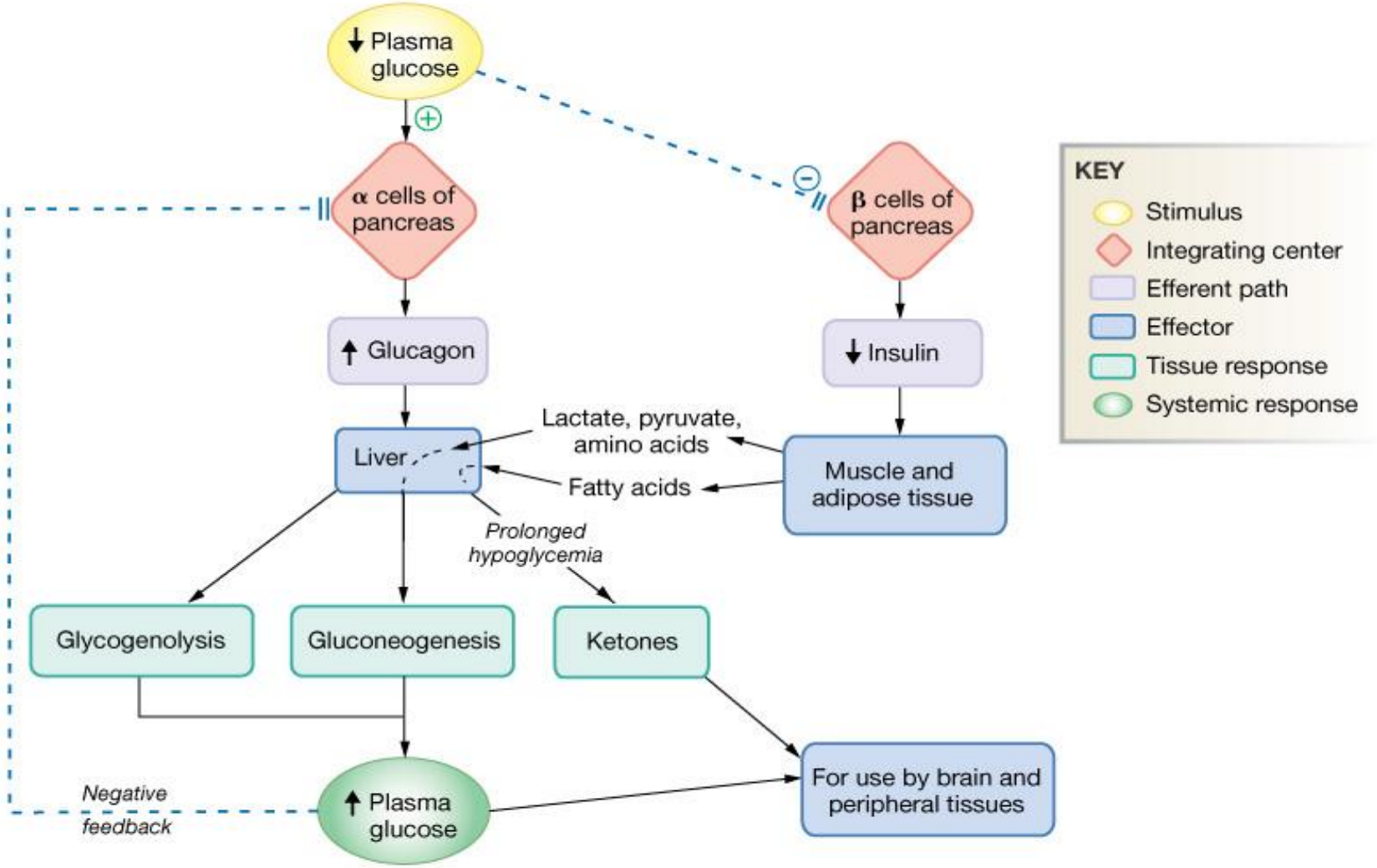
- Blood glucose – most potent regulator

- Increased amino acids in the circulation
  - Especially arginine and alanine
  - Used to make glucose
- Catecholamines
- Gastrointestinal hormones (cholecystokinin, gastrin, GIP)
- Glucocorticoids
- Sympathetic and parasympathetic stimulation
- Exercise
  - Can increase glucagon 4-5 fold
  - Due to increased amino acids?
  - Beta-adrenergic stimulation of the islets of Langerhans?

Actions of Glucagon on the Liver

- Stimulates glycogenolysis
- Stimulates gluconeogenesis
- Inhibits glycolysis
- Stimulates lipolysis and ketogenesis

Glucagon Action on Cells: Dominates in Fasting State Metabolism



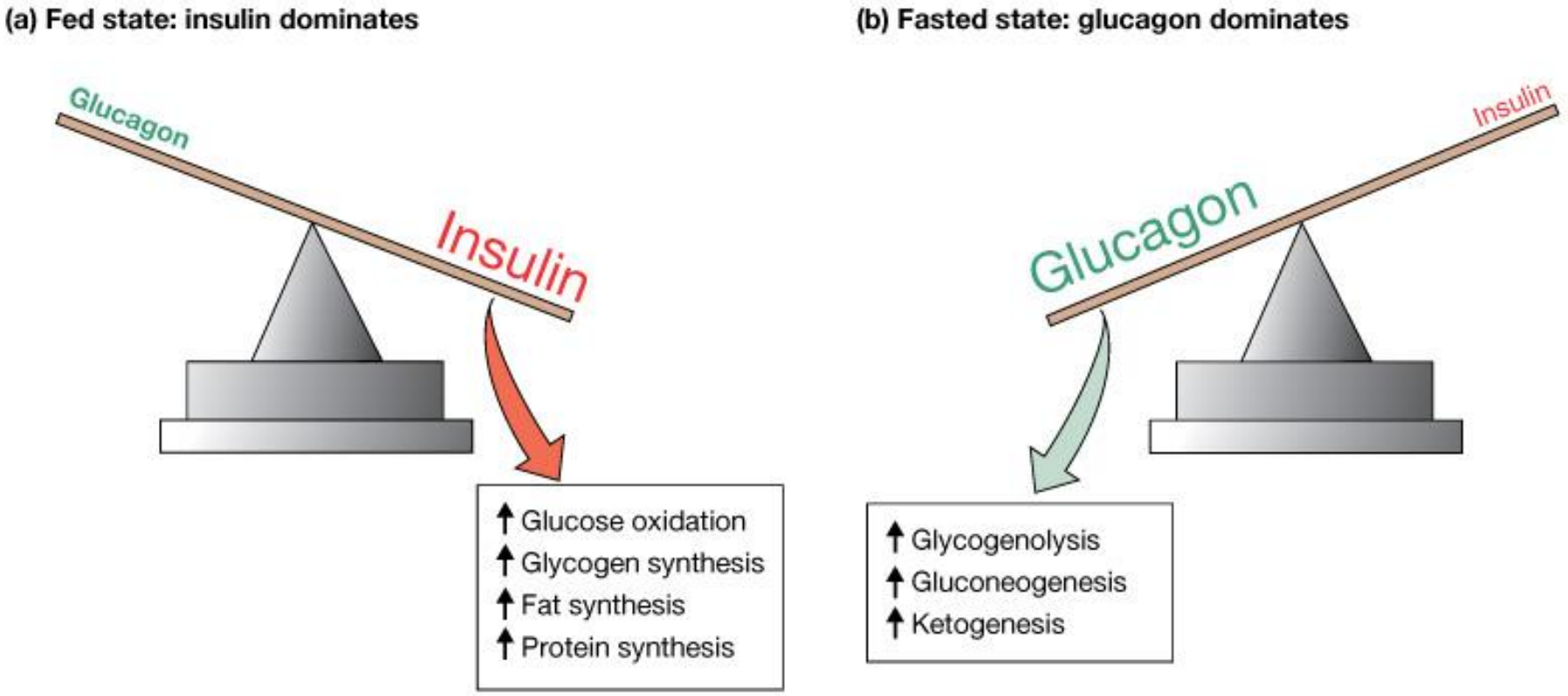
Targets of Glucagon Action

- Activates a phosphorylase, which cleaves off a glucose 1-phosphate molecule off of glycogen.
- Inactivates glycogen synthase by phosphorylation (less glycogen synthesis).
- Increases phosphoenolpyruvate carboxykinase, stimulating gluconeogenesis
- Activates lipases, breaking down triglycerides.
- Inhibits acetyl CoA carboxylase, decreasing free fatty acid formation from acetyl CoA
- Result: more production of glucose and substrates for metabolism

Regulation of Glucagon Release

- Increased blood glucose levels inhibit glucagon release.
- Amino acids stimulate glucagon release (high protein, low carbohydrate meal).
- Stress: epinephrine acts on beta-adrenergic receptors on alpha cells, increasing glucagon release (increases availability of glucose for energy).
- Insulin inhibits glucagon secretion.

Pancreatic Hormones, Insulin & Glucagon Regulate Metabolism

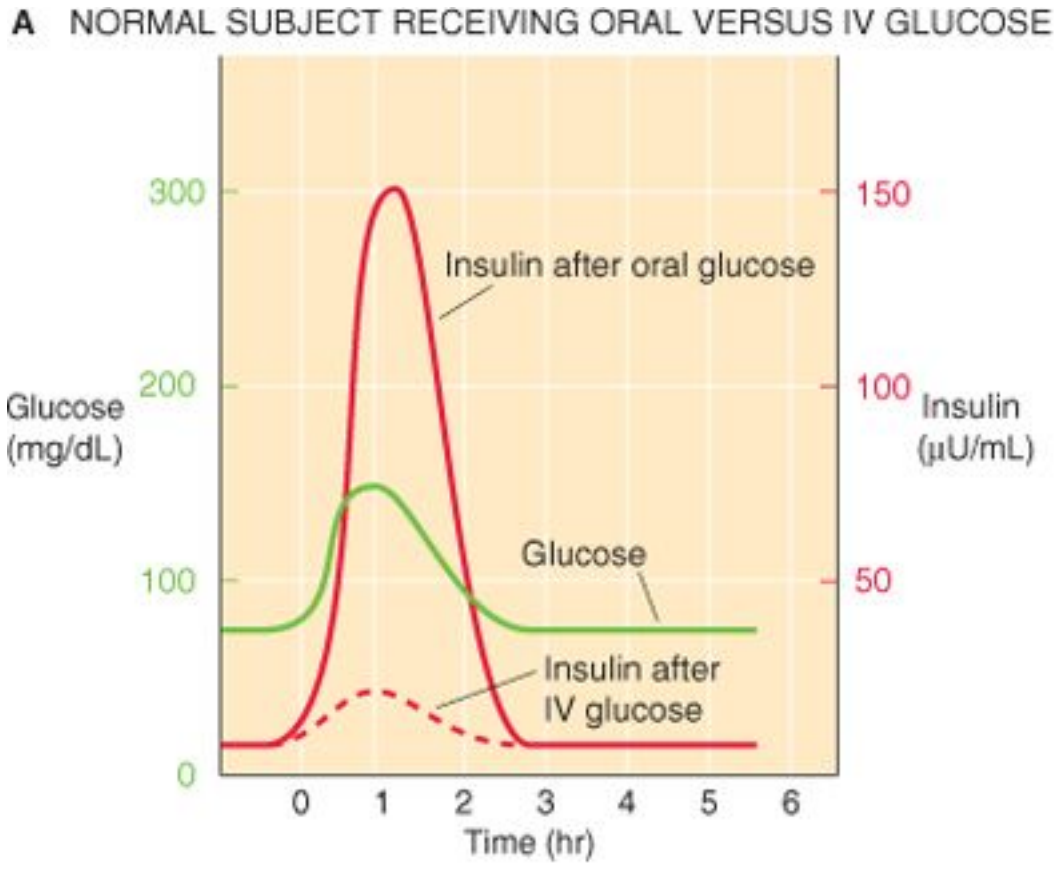


Metabolism is controlled by insulin and glucagon

FURTHER CONTROL OF GLUCOSE HOMEOSTATIS

Other Factors Regulating Glucose Homeostasis

- Glucocorticoids (cortisol): stimulate gluconeogenesis and lipolysis, and increase breakdown of proteins.
- Epinephrine/norepinephrine: stimulates glycogenolysis and lipolysis.
- Growth hormone: stimulates glycogenolysis and lipolysis.
- Note that these factors would complement the effects of glucagon, increasing blood glucose levels.


A NORMAL SUBJECT RECEIVING ORAL VERSUS IV GLUCOSE
300
200
100
0
Glucose
(mg/dL)
150
100
50
Insulin
(μU/mL)
Insulin after oral glucose
Glucose
Insulin after
IV glucose
0
1
2
3
4
5
6
Time (hr)

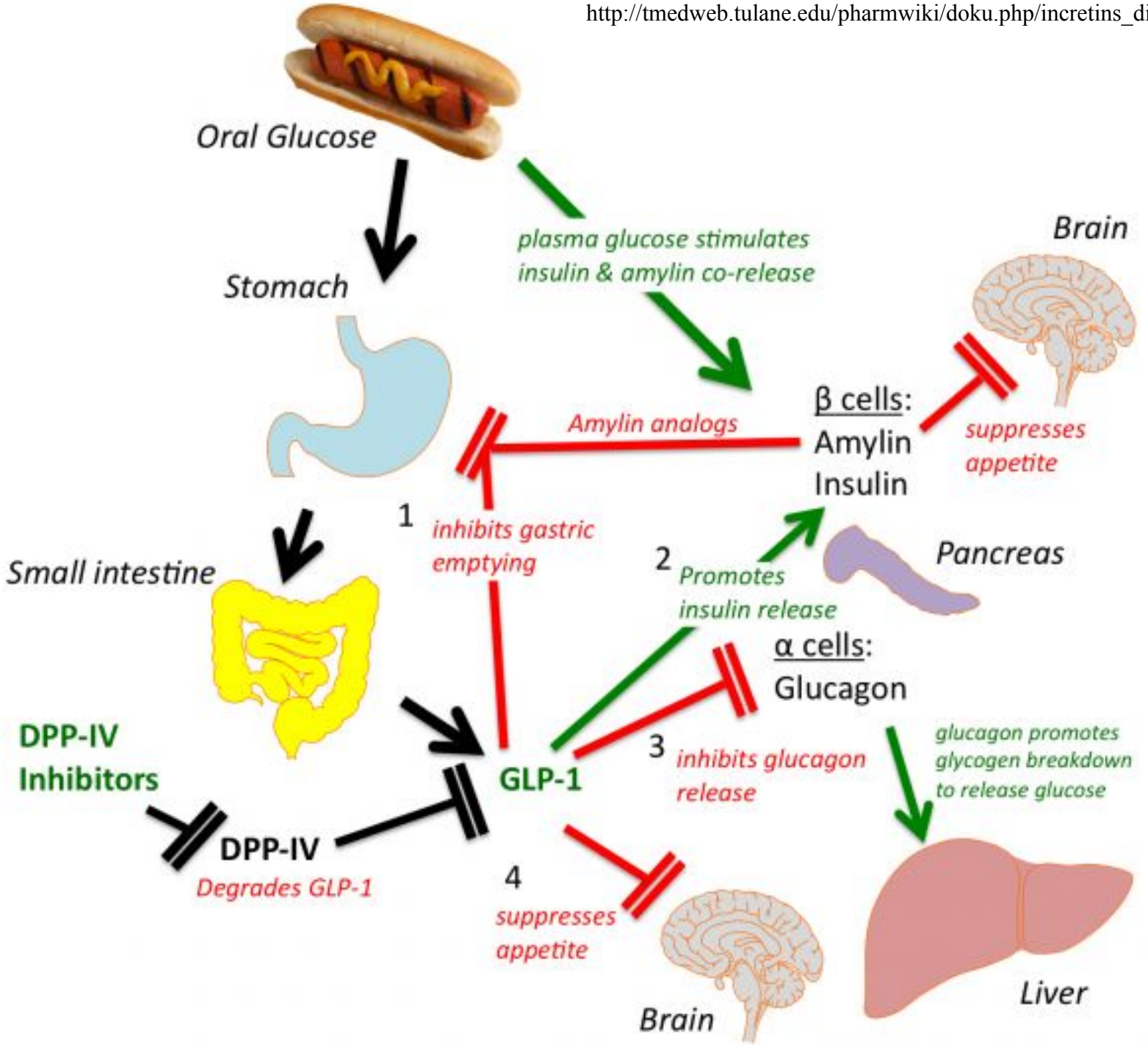
Incretins

Peptides released from the gut tissue in response to a meal that augment insulin secretion

3 Peptides:

1) CCK
2) glucagon-like-intestinal peptide 1 (GLP-1)
3) gastric inhibitory peptide (GIP)
4) Dipetidyl peptidase-4 (DPP-4 or DPP-IV)

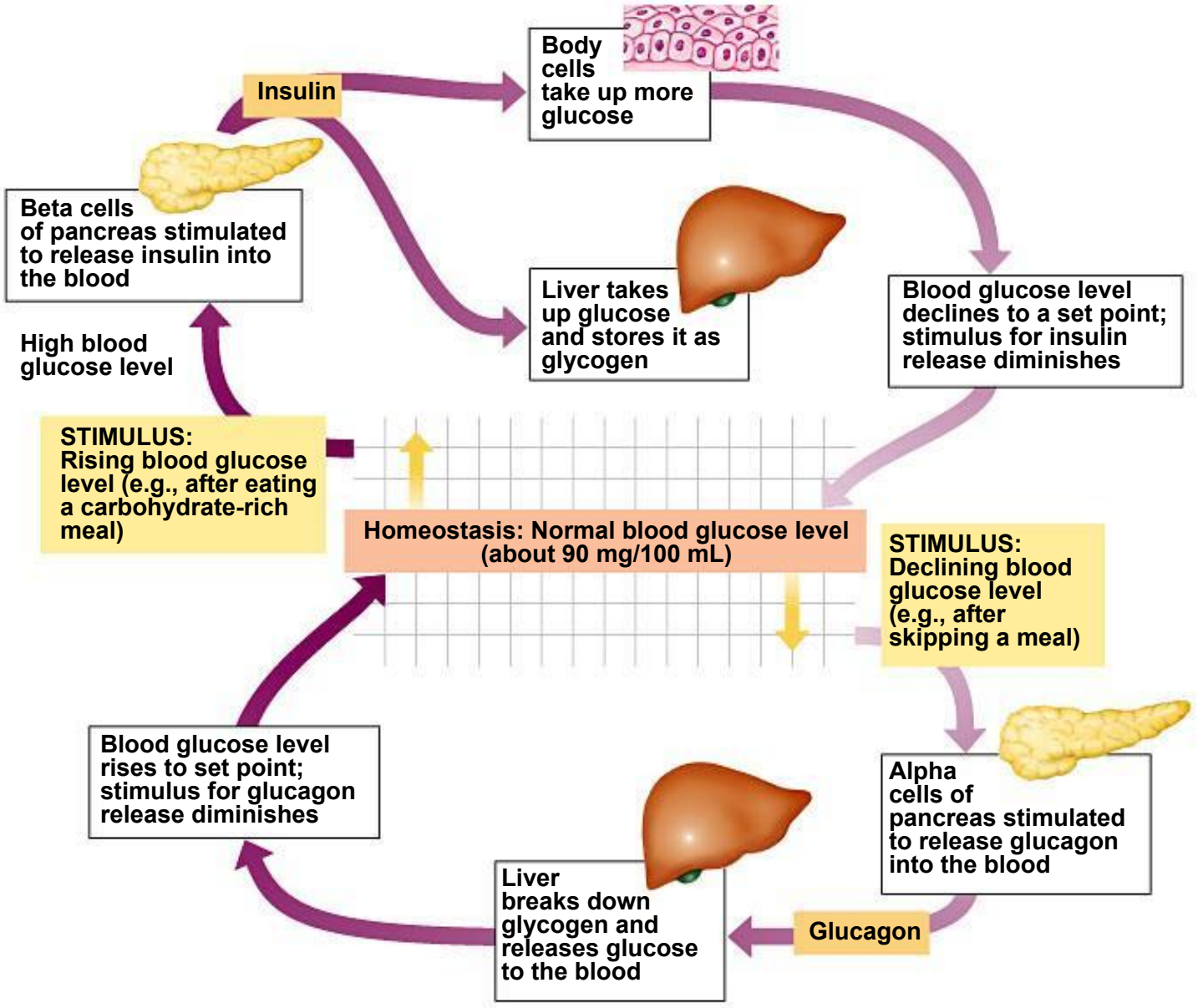
http://tmedweb.tulane.edu/pharmwiki/doku.php/incretins_diabetes



Regulation of Insulin and Glucagon

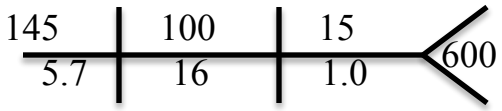
- Parasympathetic nervous system:
  - Stimulates insulin secretion.
- Sympathetic nervous system:
  - Stimulates glucagon secretion.
- GIP:
  - Stimulates insulin secretion.
- GLP-1:
  - Stimulates insulin secretion.
- CCK:
  - Stimulates insulin secretion.

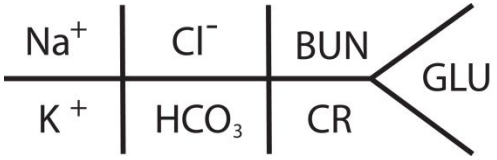
Glucose homeostasis



Case Vignette

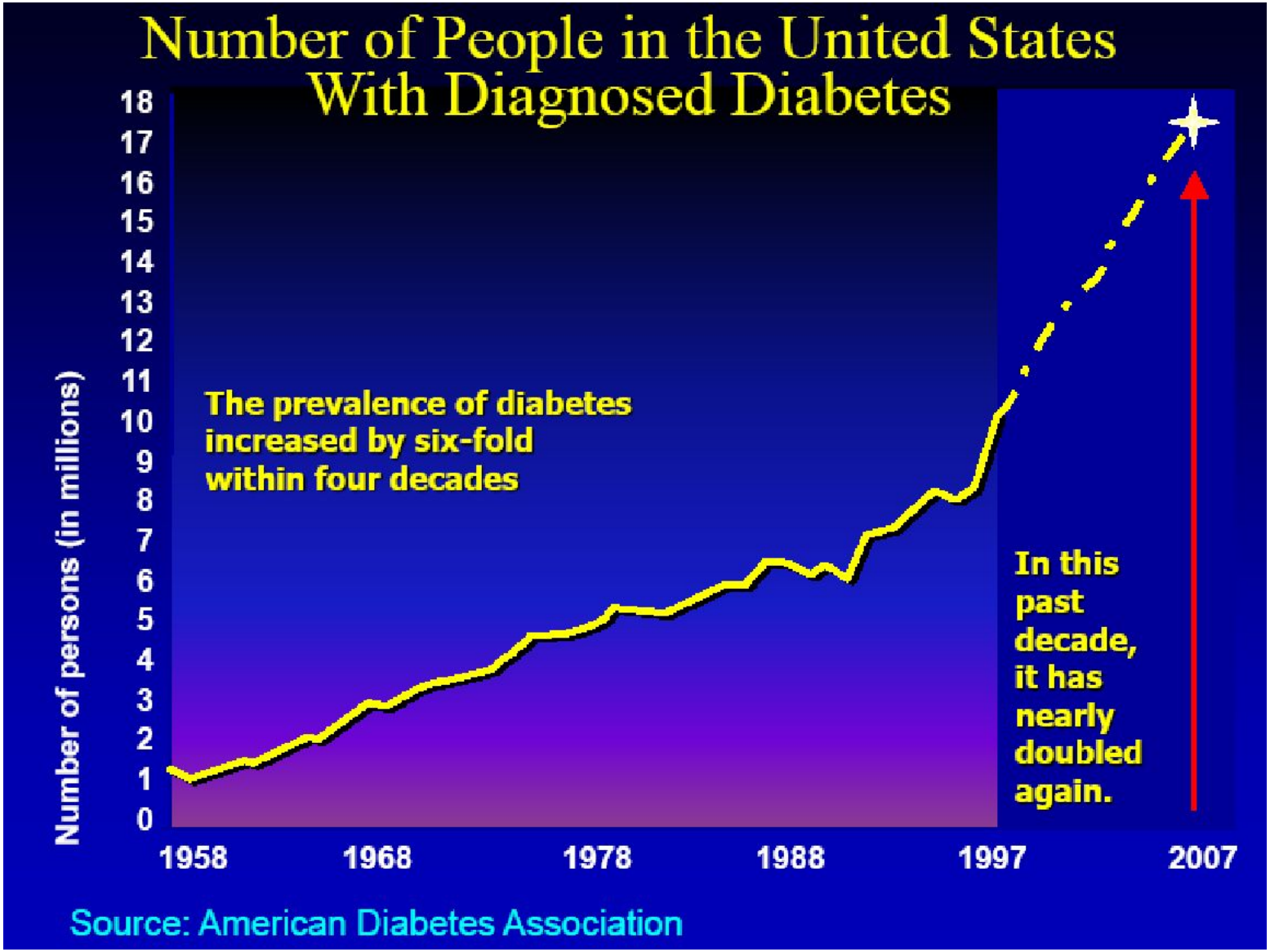
- 21 year old female presents unconscious to the ED. The boyfriend tells you that they were at a party last night and that she had 7-8 drinks last night at a party. When they got home both were still intoxicated but they both fell asleep together. When he awoke she was highly lethargic and would not wake up and he called 911 immediately.
- According to the boyfriend she has no previous medical history, she is on Prilosec (omeprazole) and Birth control.
- VS: HR: 135 RR: 35 BP: 100/50 Temp: 37.6 C
- PE: **General:** This is an unresponsive female that otherwise looks well fed. She does not appear obese. **Skin:** Appears dehydrated around the mouth and increased skin turgor. Skin appears pale lacking color. **Heart:** She has a regular rhythm of heart but tachycardiac. No murmurs, rubs or thrills are observed on auscultation/palpation. **Lung:** Patient is tachypneic with deep inspirations. Indicative of Kussmals breathing . Breath sounds are heard throughout and no rales, rhonchi or wheezing appreciated.
- Labs: EKG an abnormality in conduction (decreased QT interval with increased PR interval). CBC came back with all values in the normal ranges. Electrolytes:



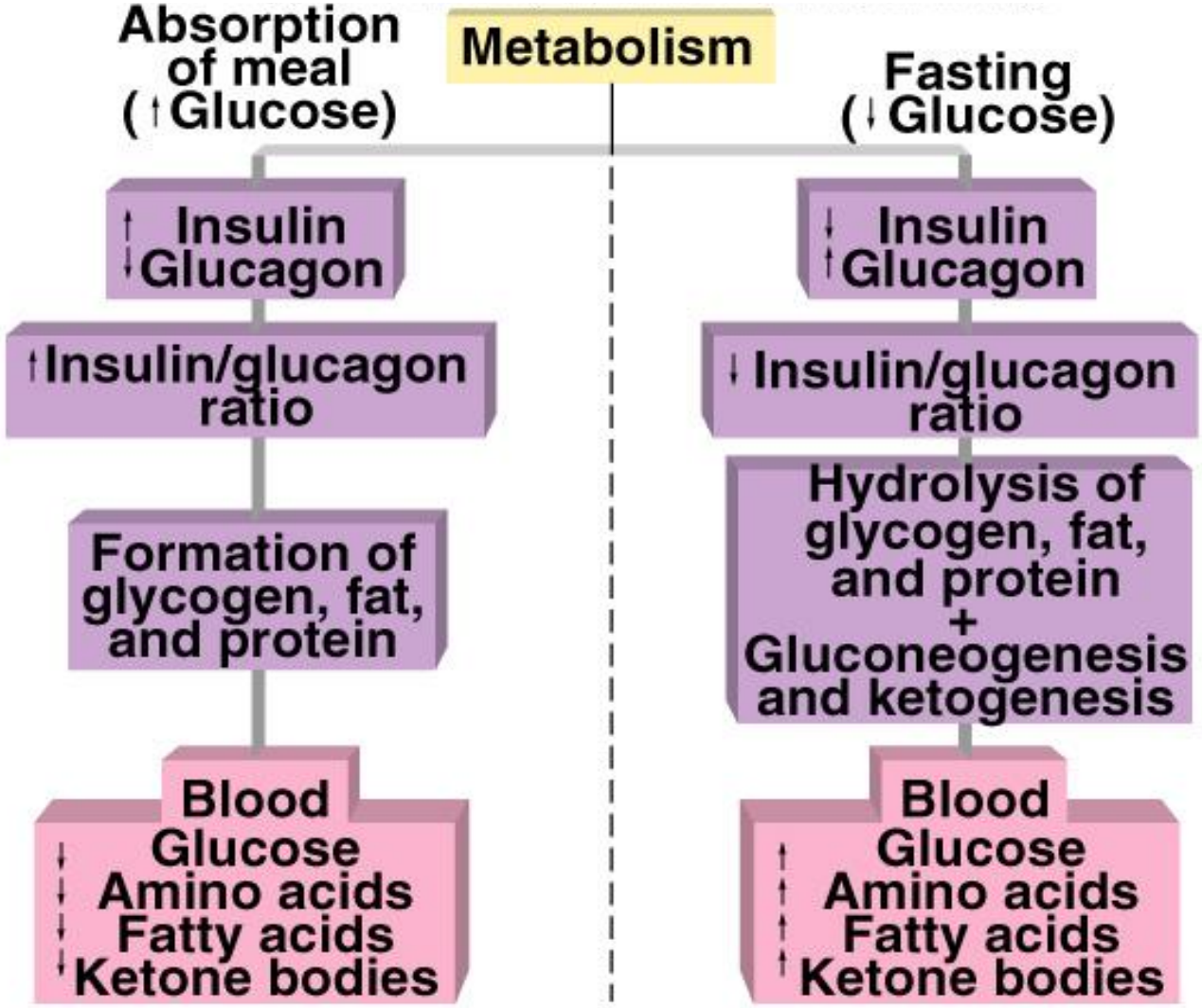


Comparison of Type I and Type II Diabetes Mellitus

Feature	Type I	Type 2
Usual age at onset	Under 20 years	Over 40 years
Development of symptoms	Rapid	Slow
Percentage of diabetic population	About 10%	About 90%
Development of ketoacidosis	Common	Rare
Association with obesity	Rare	Common
Beta cells of islets (at onset of disease)	Destroyed	Not destroyed
Insulin secretion	Decreased	Normal or increased
Autoantibodies to islet cells	Present	Absent
Associated with particular MHC antigens*	Yes	Unclear
Treatment	Insulin injections	Diet and exercise; oral stimulators of insulin sensitivity


Number of People in the United States With Diagnosed Diabetes
Number of persons (in millions)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
1958
1968
1978
1988
1997
2007
The prevalence of diabetes increased by six-fold within four decades
In this past decade, it has nearly doubled again.
Source: American Diabetes Association

Effect of Feeding and Fasting on Metabolism



Diabetes Mellitus

- Chronic high blood [glucose].
- 2 forms of diabetes mellitus:
  - Type I: insulin dependent diabetes (IDDM).
  - Type II: non-insulin dependent diabetes (NIDDM).

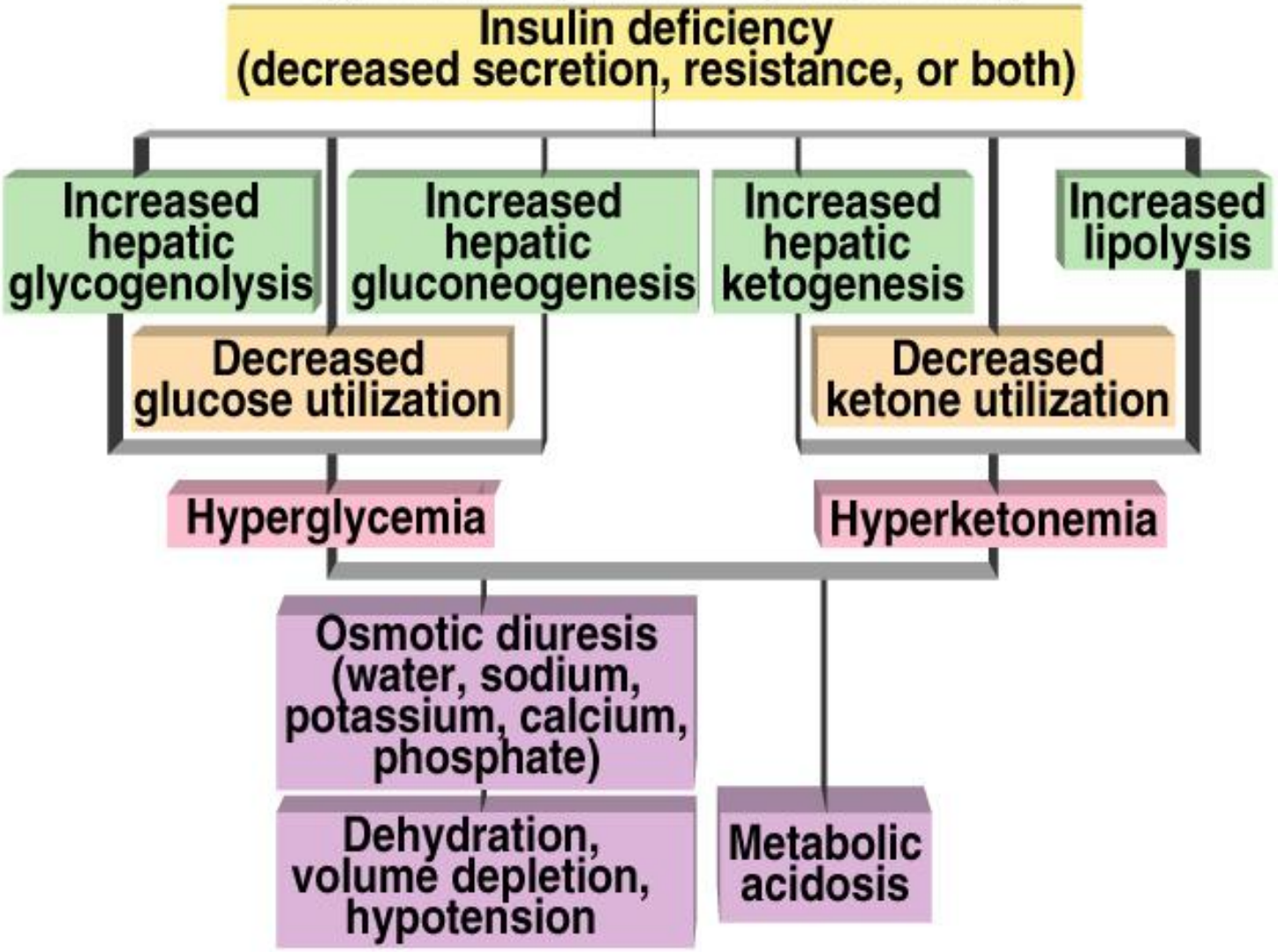
Type I Diabetes (10% of cases)

- Develops suddenly, usually before age 15
- Caused by inadequate production of insulin because T cell-mediated autoimmune response destroys beta cells
- Controlled by insulin injections

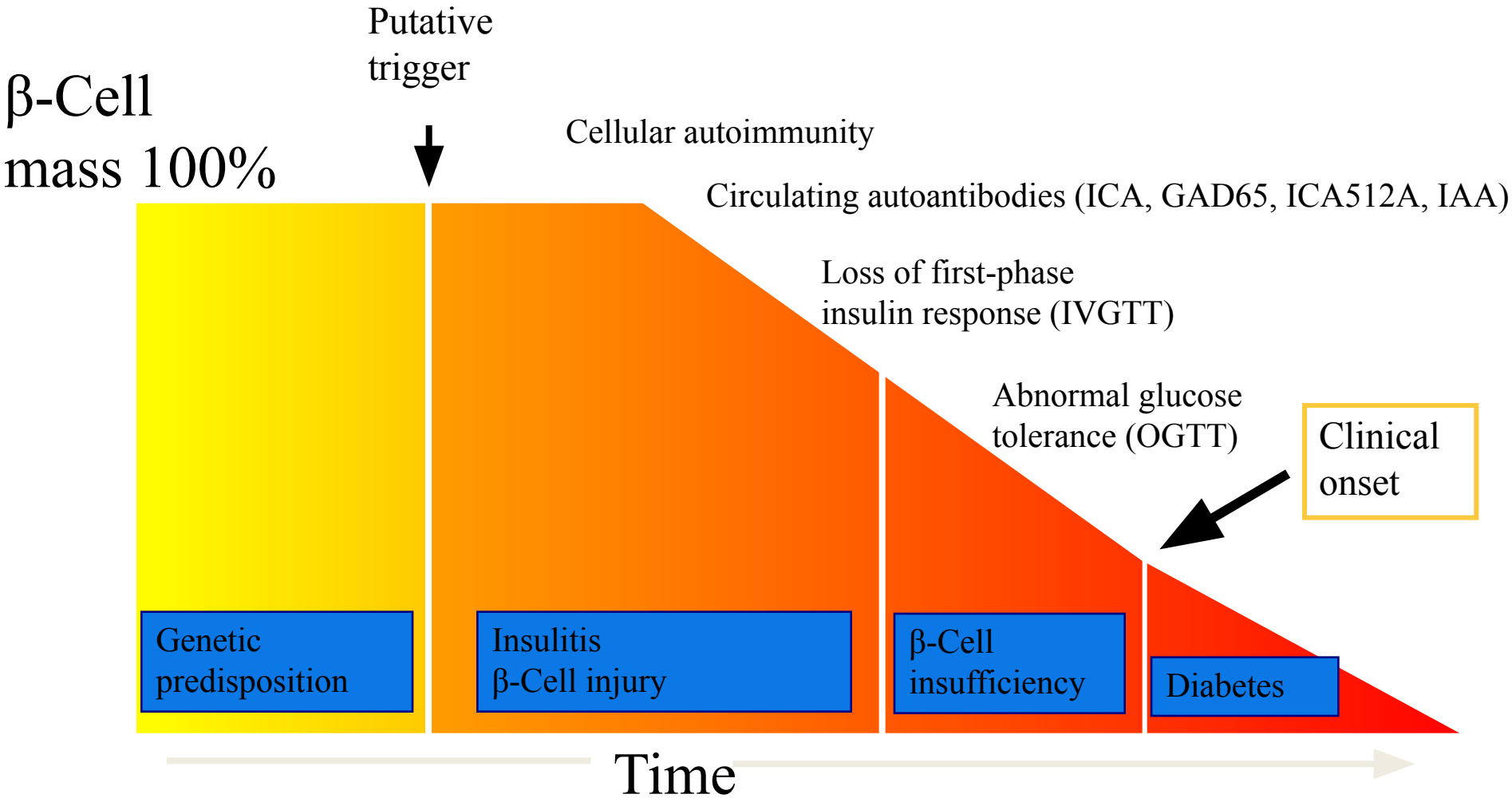
Type I Diabetes Mellitus

- b cells of the islets of Langerhans are destroyed by autoimmune attack which may be provoked by environmental agent.
  - Killer T cells target glutamate decarboxylase in the b cells.
- Glucose cannot enter the adipose cells.
  - Rate of fat synthesis lags behind the rate of lipolysis.
    - Fatty acids converted to ketone bodies, producing ketoacidosis.
- Increased blood [glucagon].
  - Stimulates glycogenolysis in liver.

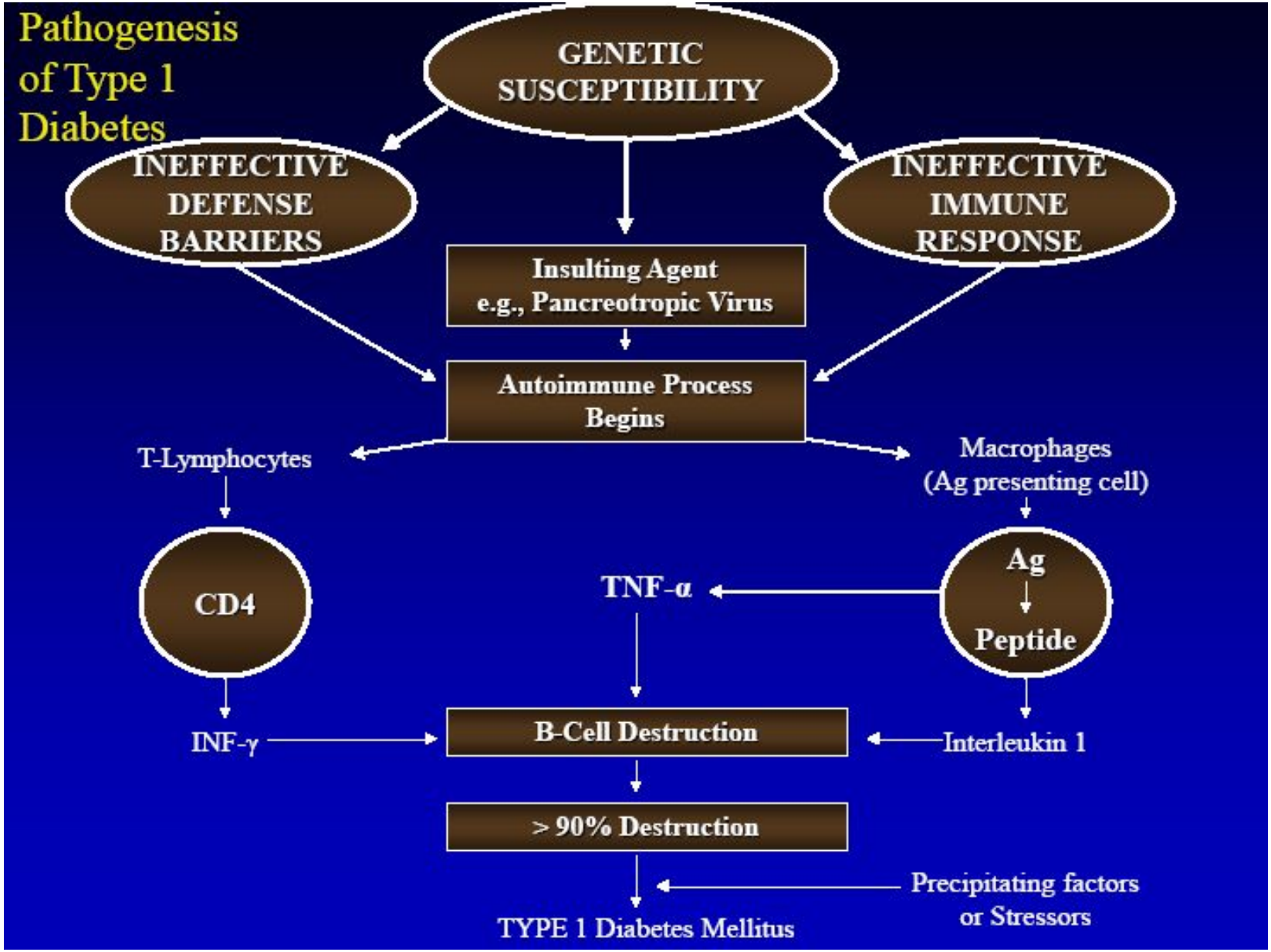
Consequences of Uncorrected Deficiency in Type I Diabetes Mellitus



Natural History of "Pre"–Type 1 Diabetes



Eisenbarth GS. *N Engl J Med*. 1986;314:1360-1368

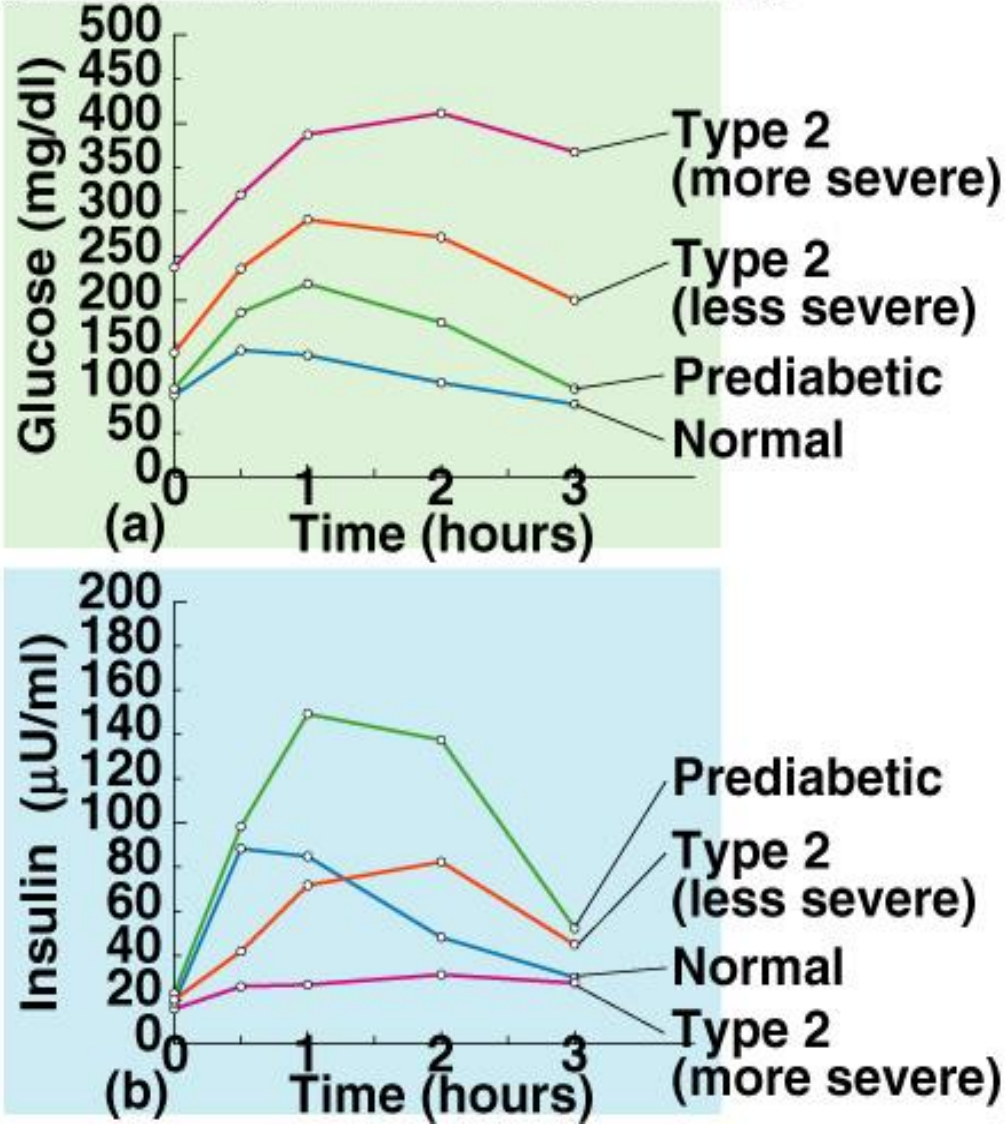

Pathogenesis of Type 1 Diabetes
GENETIC SUSCEPTIBILITY
INEFFECTIVE DEFENSE BARRIERS
INEFFECTIVE IMMUNE RESPONSE
Insulting Agent e.g., Pancreotropic Virus
Autoimmune Process Begins
T-Lymphocytes
Macrophages (Ag presenting cell)
CD4
TNF-α
Ag
Peptide
INF-γ
B-Cell Destruction
Interleukin 1
> 90% Destruction
Precipitating factors or Stressors
TYPE 1 Diabetes Mellitus

Type II diabetes (90% of cases)

- Usually occurs after age 40 and in obese individuals
- Insulin levels are normal or elevated but there is either a decrease in number of insulin receptors or the cells cannot take it up.
- Controlled by dietary changes and regular exercise

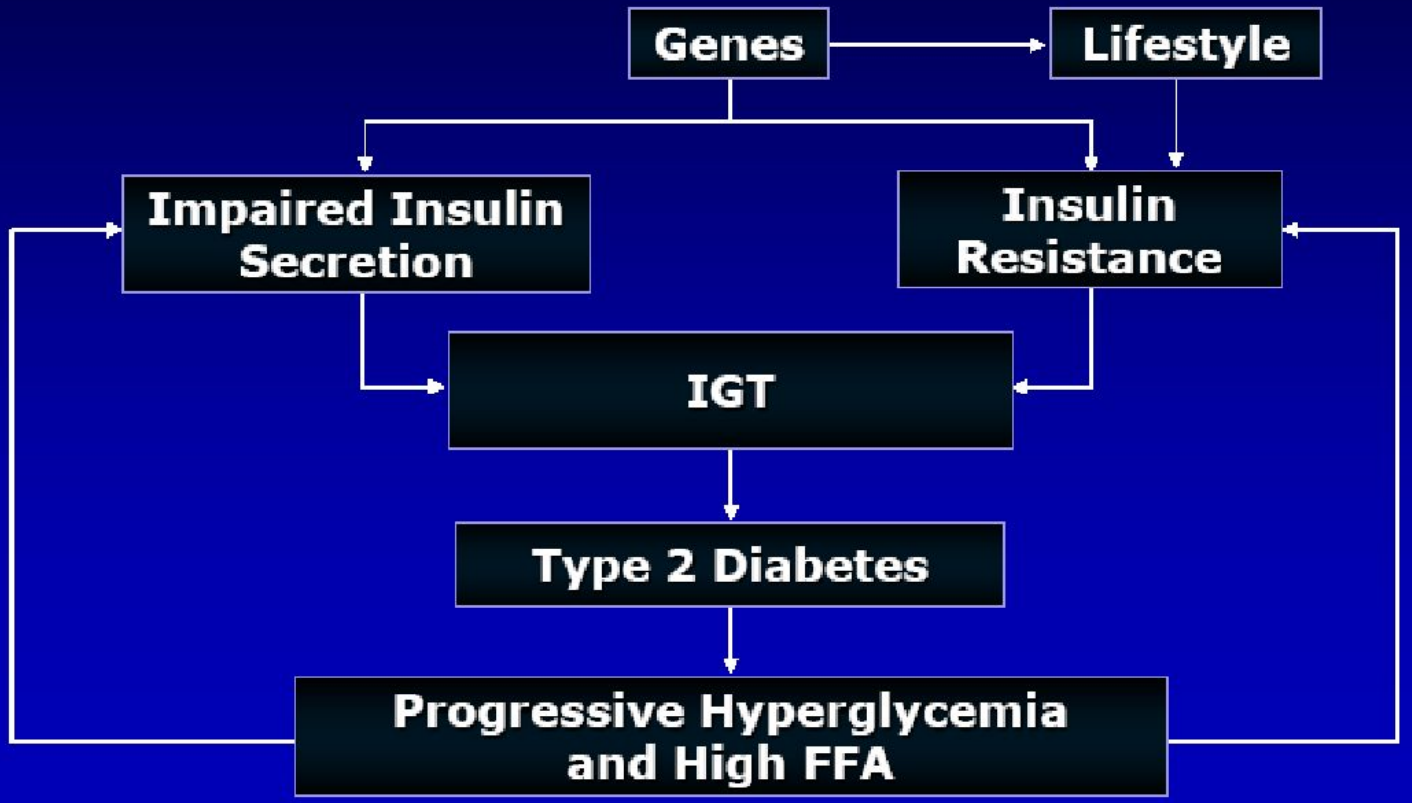
Type II Diabetes Mellitus

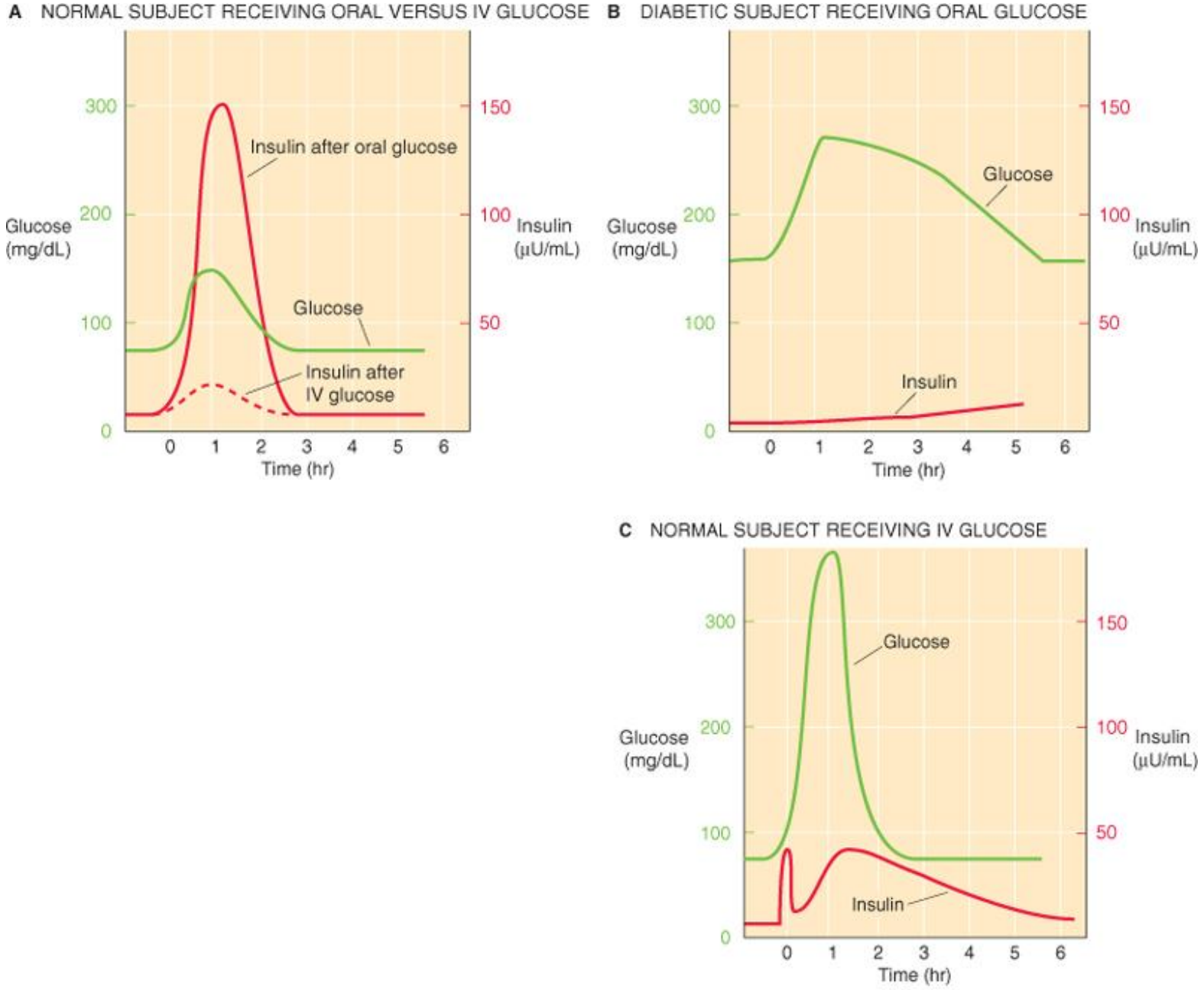
- Slow to develop.
- Genetic factors are significant.
- Occurs most often in people who are overweight.
- Decreased sensitivity to insulin or an insulin resistance.
  - Obesity.
- Do not usually develop ketoacidosis.
- May have high blood [insulin] or normal [insulin].

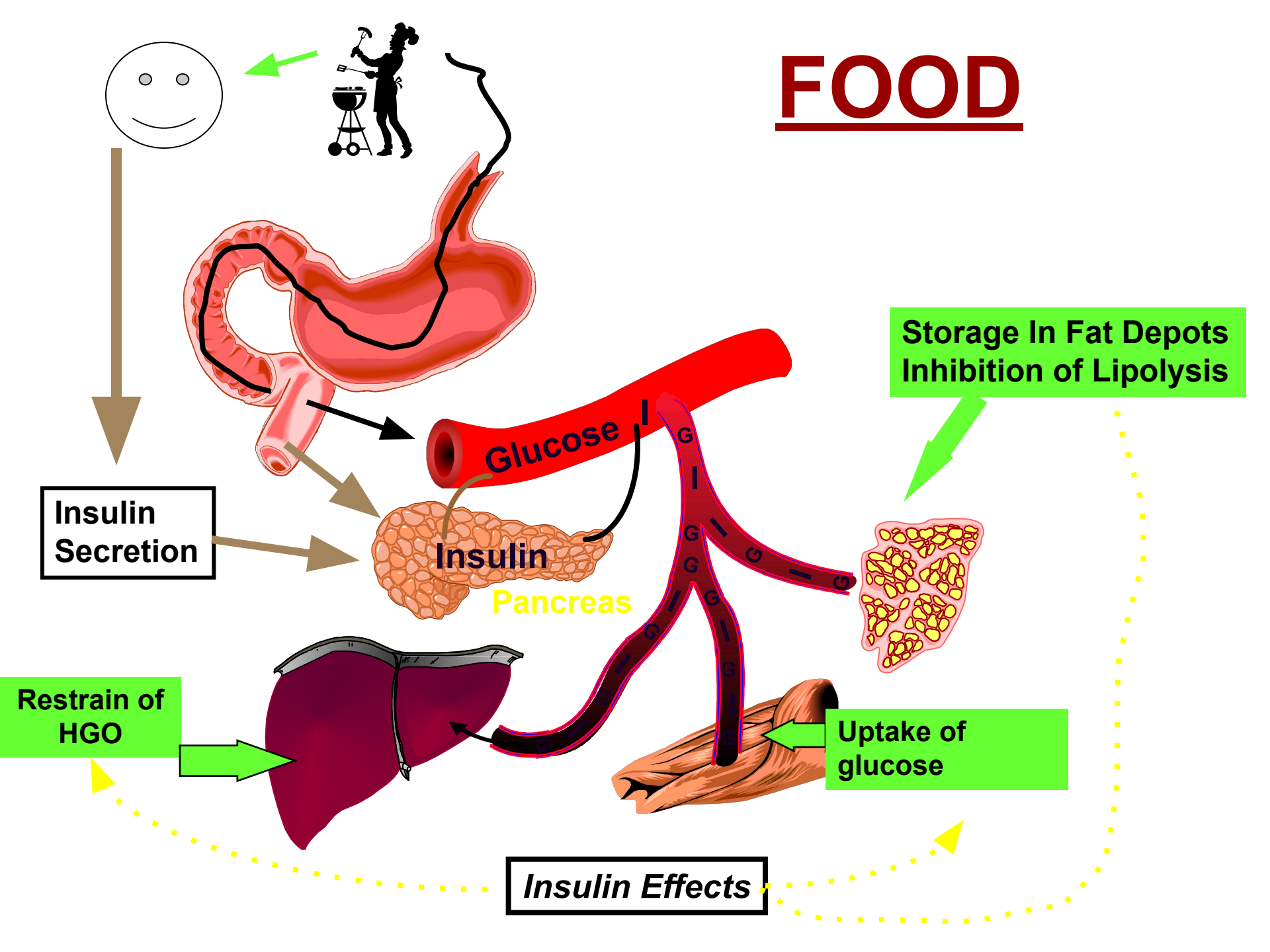


Pathogenesis of Type 2 Diabetes

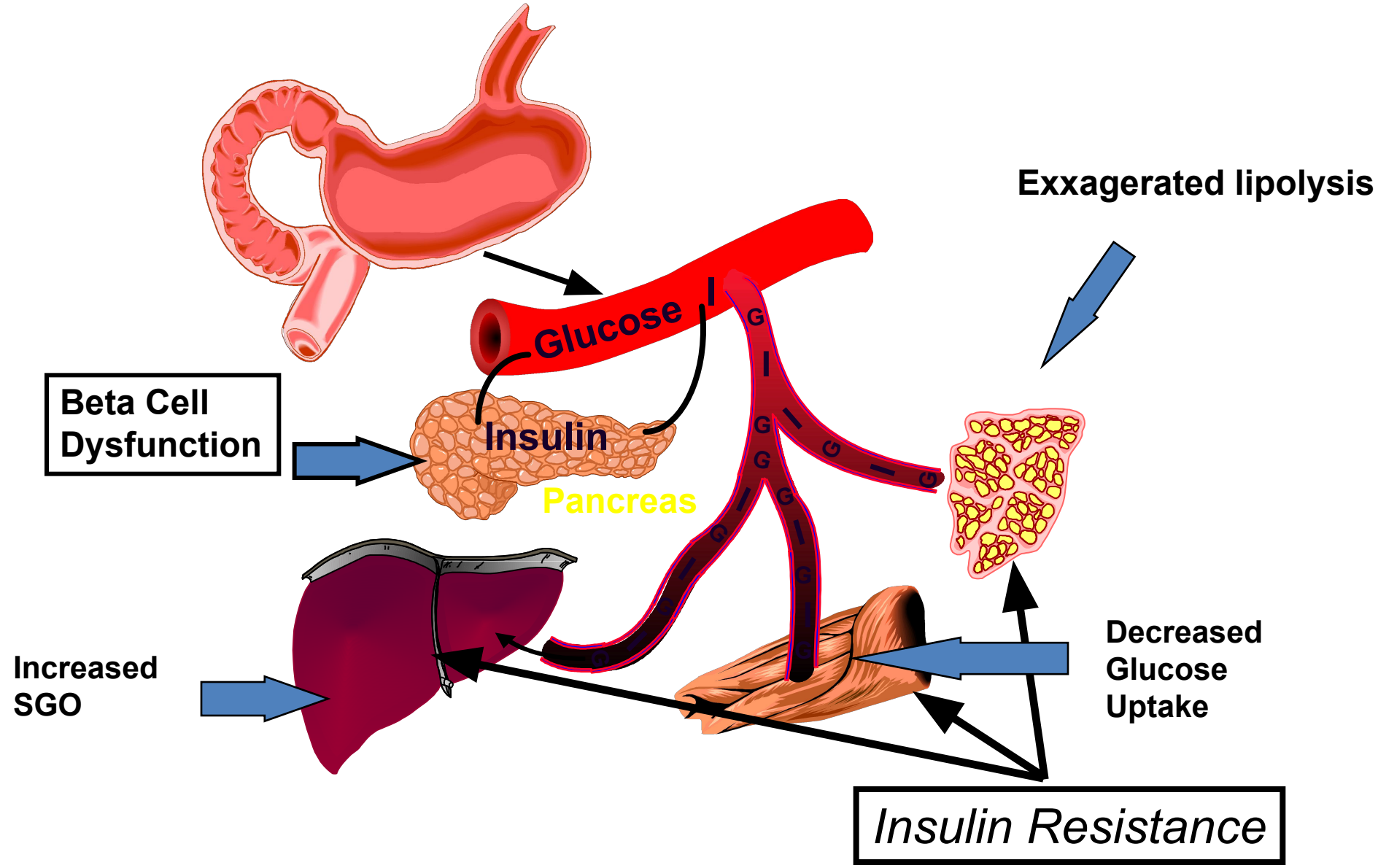
Impaired Insulin Secretion and Insulin Resistance






FOOD
Storage In Fat Depots
Inhibition of Lipolysis
Insulin
Secretion
Glucose
Insulin
Pancreas
Restrain of
HGO
Uptake of
glucose
Insulin Effects

Type 2 diabetes: pathophysiology



Treatment in Diabetes

- Change in lifestyle:
  - Increase exercise:
    - Increases the amount of membrane GLUT-4 carriers in the skeletal muscle cells.
  - Weight reduction.
  - Increased fiber in diet.
  - Reduce saturated fat.

Treatment of DM

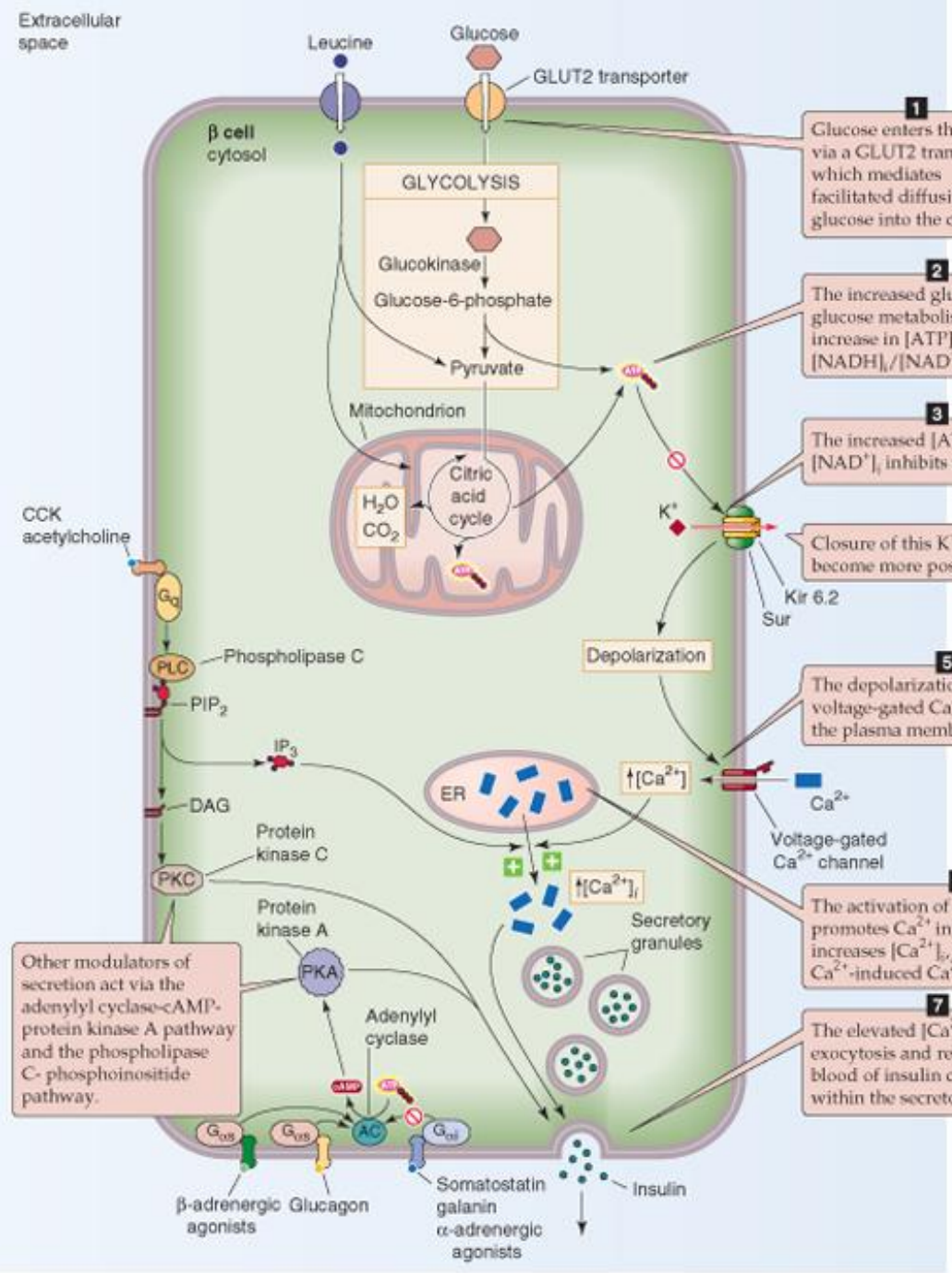
Hypoglycemics

- Insulin
- Sulfonylurea
- Glycosurics
  - Conaglifozin (Invokana)

Nonhypoglycemics

- Biguanides
  - Metformin
- Thiazolidinediones (TZDs)
- Incretin Drugs
  - GLP-1
  - DPP-4 Inhibitors

Insulin secretion in pancreatic β cells



AACE/ACE Diabetes Algorithm *For Glycemic Control*

A1C Goal ≤ 6.5%*

LIFESTYLE MODIFICATION

A1C 6.5 – 7.5%**

Monotherapy

MET †	DPP4 [1]	GLP-1	TZD [2]	AGI [3]

2 - 3 Mos.***

Dual Therapy

MET	+	GLP-1 or DPP4 [1]
		TZD [2]
		Glinide or SU [5]
TZD	+	GLP-1 or DPP4 [1]
MET	+	Colesevelam
		AGI [3]

2 - 3 Mos.***

Triple Therapy

MET + GLP-1 or DPP4 [1]	+	TZD [2]
		Glinide or SU [4,7]

2 - 3 Mos.***

INSULIN ± Other Agent(s) [6]

A1C 7.6 – 9.0%

Dual Therapy [8]

MET	+	GLP-1 or DPP4 [1] or TZD [2]
		SU or Glinide [4,5]

2 - 3 Mos.***

Triple Therapy [9]

MET	+	GLP-1 or DPP4 [1]	+ TZD [2]
		GLP-1 or DPP4 [1]	+ SU [7]
		TZD [2]	

2 - 3 Mos.***

INSULIN ± Other Agent(s) [6]

A1C > 9.0%

Drug Naive / *Under Treatment*

Symptoms / *No Symptoms*

INSULIN ± Other Agent(s) [6]

MET	+	GLP-1 or DPP4 [1]	± SU [7]
		TZD [2]	
		GLP-1 or DPP4 [1]	± TZD [2]

INSULIN ± Other Agent(s) [6]

AACE/ACE Algorithm for Glycemic Control Committee

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Etie S. Moghissi, MD, FACP, FACE
Stanley S. Schwartz, MD, FACE

* May not be appropriate for all patients

** For patients with diabetes and A1C < 6.5%, pharmacologic Rx may be considered

*** If A1C goal not achieved safely

† Preferred initial agent

1 DPP4 if ↑PPG and ↑FPG or GLP-1 if ↑↑PPG

2 TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)

3 AGI if ↑PPG

4 Glinide if ↑PPG or SU if ↑FPG

5 Low-dose secretagogue recommended

6 a) Discontinue insulin secretagogue with multidose insulin
b) Can use pramlintide with prandial insulin

7 Decrease secretagogue by 50% when added to GLP-1 or DPP-4

8 If A1C <8.5%, combination Rx with agents that cause hypoglycemia should be used with caution

9 If A1C >8.5%, in patients on Dual Therapy, insulin should be considered

Available at www.aace.com/pub

Glycemic Control Algorithm

LIFESTYLE MODIFICATION
(Including Medically Assisted Weight Loss)

ENTRY A1c < 7.5%

MONOTHERAPY*
- Metformin
- GLP-1 RA
- DPP4-i
- AG-i
- SGLT-2 **
- TZD
- SU/GLN

If A1c > 6.5% in 3 months add second drug (Dual Therapy)

ENTRY A1c ≥ 7.5%

DUAL THERAPY*

MET or other first-line agent +
- GLP-1 RA
- DPP4-i
- TZD
- ** SGLT-2
- Basal insulin
- Colesevelam
- Bromocriptine QR
- AG-i
- SU/GLN

If not at goal in 3 months proceed to triple therapy

TRIPLE THERAPY*

MET or other first-line agent + 2ND LINE AGENT +
- GLP-1 RA
- TZD
- ** SGLT-2
- Basal insulin
- DPP4-i
- Colesevelam
- Bromocriptine QR
- AG-i
- SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

ENTRY A1c > 9.0%

NO SYMPTOMS	SYMPTOMS
DUAL THERAPY OR TRIPLE THERAPY	INSULIN ± OTHER AGENTS

ADD OR INTENSIFY INSULIN

* Order of medications listed are a suggested hierarchy of usage

** Based upon phase 3 clinical trials data

LEGEND

✓ = Few adverse events or possible benefits

⚠ = Use with caution

PROGRESSION OF DISEASE

Profiles of Antidiabetic Medications

	MET	DPP-4i	GLP-1 RA	TZD	AGI	COLSVL	BCR-QR	SU / GLN	INSULIN	SGLT-2	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Moderate to Severe	Neutral	Neutral
WEIGHT	Slight Loss	Neutral	Loss	Gain	Neutral	Neutral	Neutral	Gain	Gain	Loss	Loss
RENAL/ GU	Contra-indicated Stage 3B,4,5	Dose Adjustment May be Necessary (Except Linagliptin)	Exenatide Contra-indicated CrCl < 30	May Worsen Fluid Retention	Neutral	Neutral	Neutral	More Hypo Risk	More Hypo Risk & Fluid Retention	Infections	Neutral
GI Sx	Moderate	Neutral	Moderate	Neutral	Moderate	Mild	Moderate	Neutral	Neutral	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
CVD	Benefit			Neutral			Safe	?			
BONE	Neutral	Neutral	Neutral	Moderate Bone Loss	Neutral	Neutral	Neutral	Neutral	Neutral	? Bone Loss	Neutral

Few adverse events or possible benefits — Use with caution — Likelihood of adverse effects

Prevention of obesity