

Pancreatic Function and Glucoregulation

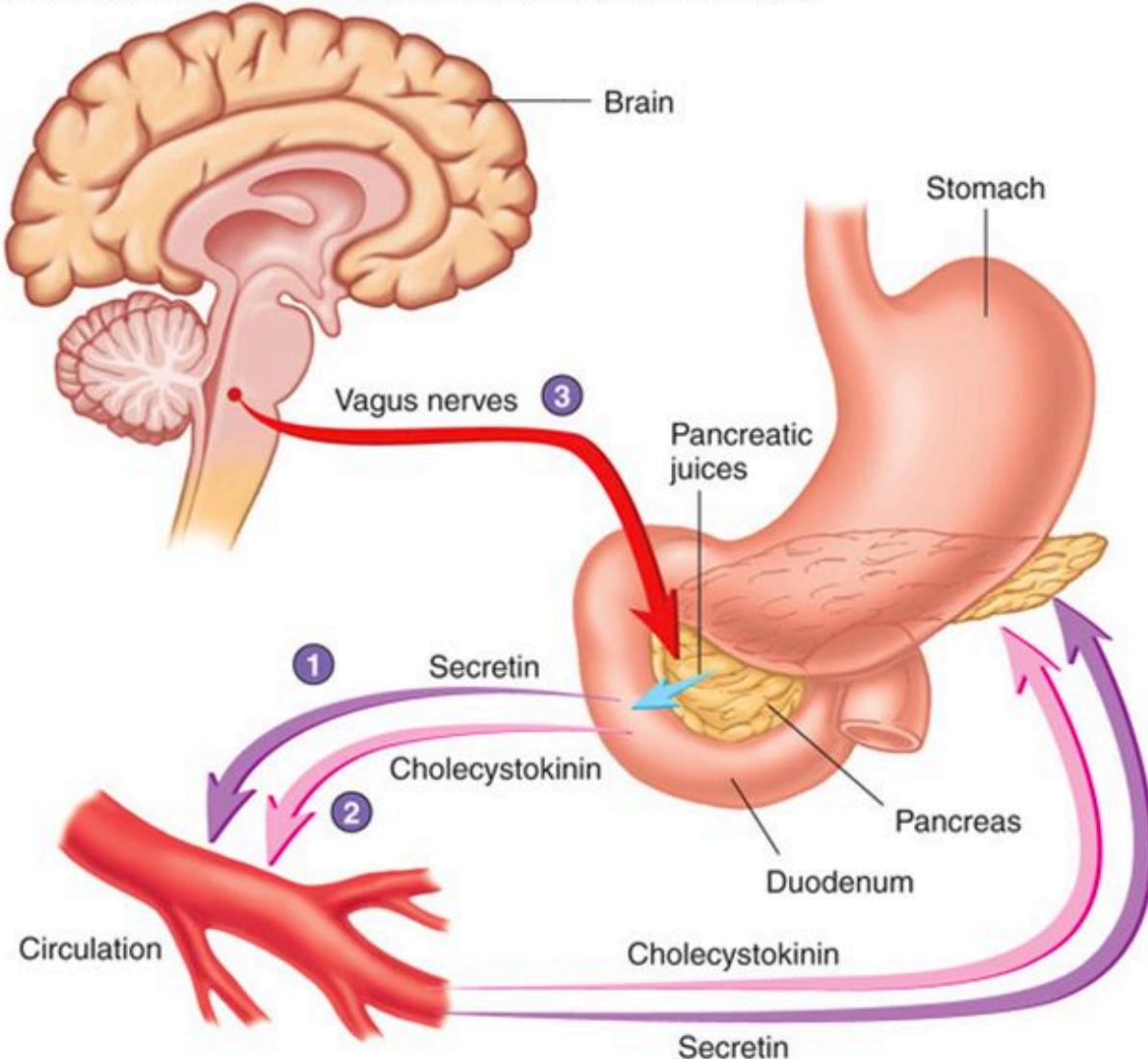
Learning Objectives

- Name the cell types of the Islets of Langerhans and name the hormones secreted by them.
- Describe the main targets and functions of glucagon.
- List the major factors that stimulate or inhibit glucagon and insulin.
- Describe the important physiological roles of insulin.
- List the major actions of insulin in muscle, adipose tissue, and liver.
- Explain briefly the mechanism of glucose uptake into the muscle.
- Name the tissues in which insulin facilitates glucose uptake and those in which insulin does not facilitate glucose uptake.
- List the major factors that stimulate or inhibit insulin secretion.
- Draw an oral glucose tolerance test (oGTT) (glucose, insulin, and glucagon levels) and describe what is occurring and why. Explain how the two hormones act to promote glucose homeostasis in the plasma.
- State which nutrient storages are preferably used for short-term regulation of energy metabolism if no nutrients are available from the GI tract.
- Discuss the hormones involved, fuel storage capacity, fuel storage consumption, and glucose (or fatty acid) levels during 1) the postprandial period, 2) the post-absorptive period, 3) fasting.
- List the insulin-counteracting hormones and their roles in glucose homeostasis. Discuss the hormones involved in minute-to-minute regulation and long-term regulation of glucose homeostasis.

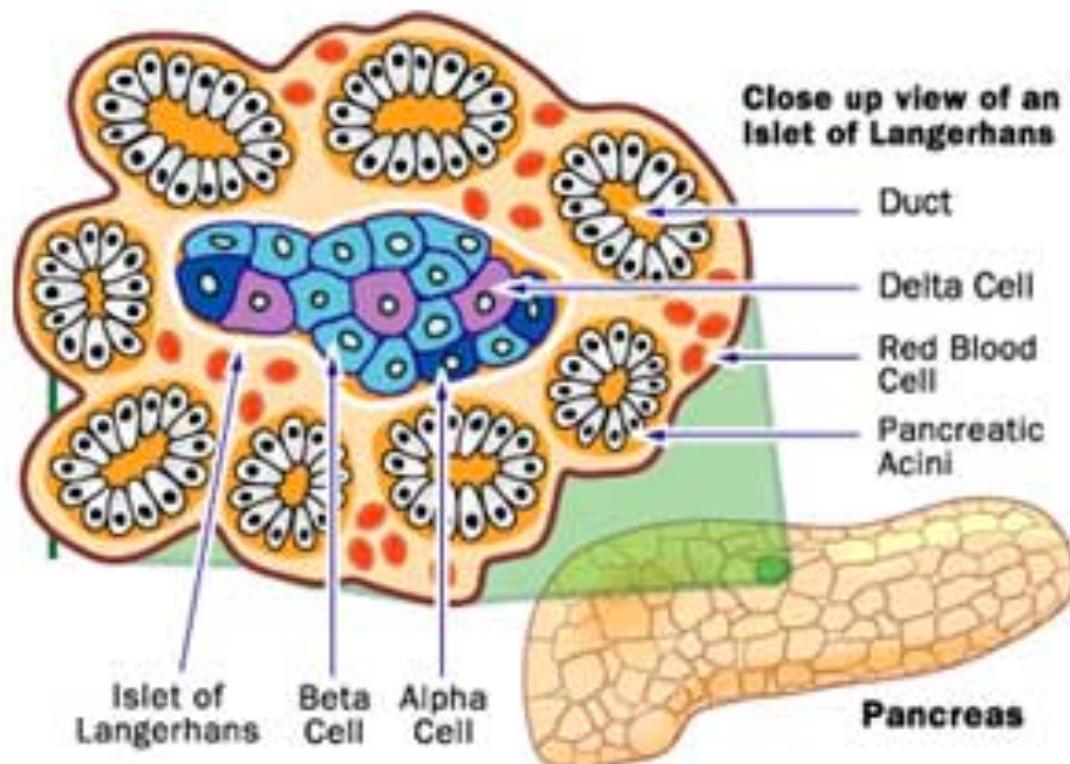
Control of Pancreatic Secretion

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1. Secretin (purple arrows) released from the duodenum stimulates the pancreas to release a watery secretion rich in HCO_3^- .
2. Cholecystokinin (pink arrows) released from the duodenum causes the pancreas to release a secretion rich in digestive enzymes.
3. Parasympathetic stimulation from the vagus nerve (red arrow) causes the pancreas to release a secretion rich in digestive enzymes.



Pancreatic Anatomy



Close up view of an Islet of Langerhans

Duct

Delta Cell

Red Blood Cell

Pancreatic Acini

Islet of
Langerhans

Beta
Cell

Alpha
Cell

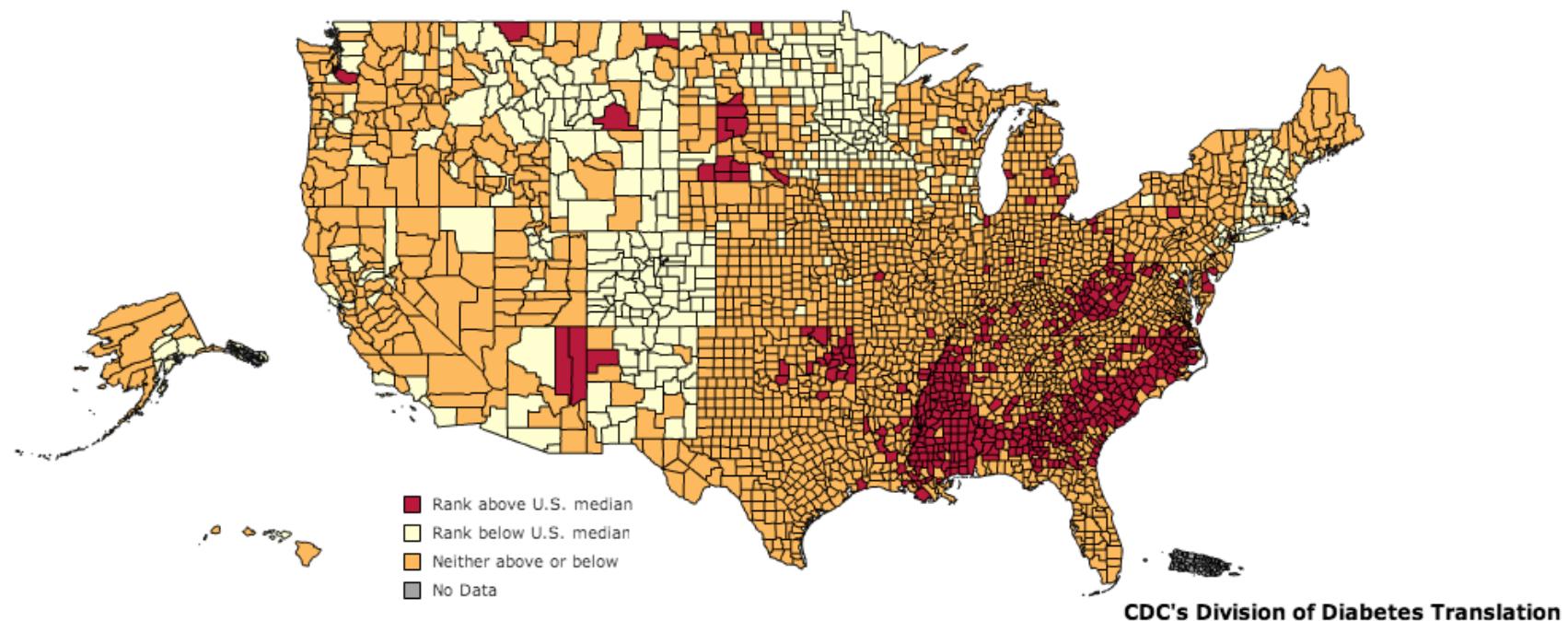
Pancreas

Cell	Hormone
Beta Cells	Insulin
Alpha Cells	Glucagon
Delta Cells	Somatostatin
Ductal Cells	Exocrine

Diabetes Mellitus

- One of the first described diseases (1500 BC)
- Named diabetes by Appolonius of Memphis (Egypt)
 - Diabetes (to pass through)
 - Mellitus (from honey)

Diabetes in the United States



Complications of Diabetes

- Retinopathy
 - Leading cause of blindness in 20-75 year olds
- Nephropathy
 - 30% to 40% of all diabetics are symptomatic
- Neuropathy
 - risk of amputation >25 times greater than that of people without diabetes.
- Cardiovascular
 - Heart Attack/Stroke Risk 2-4X with diabetes

The Discovery of Insulin



The Discovery of Insulin

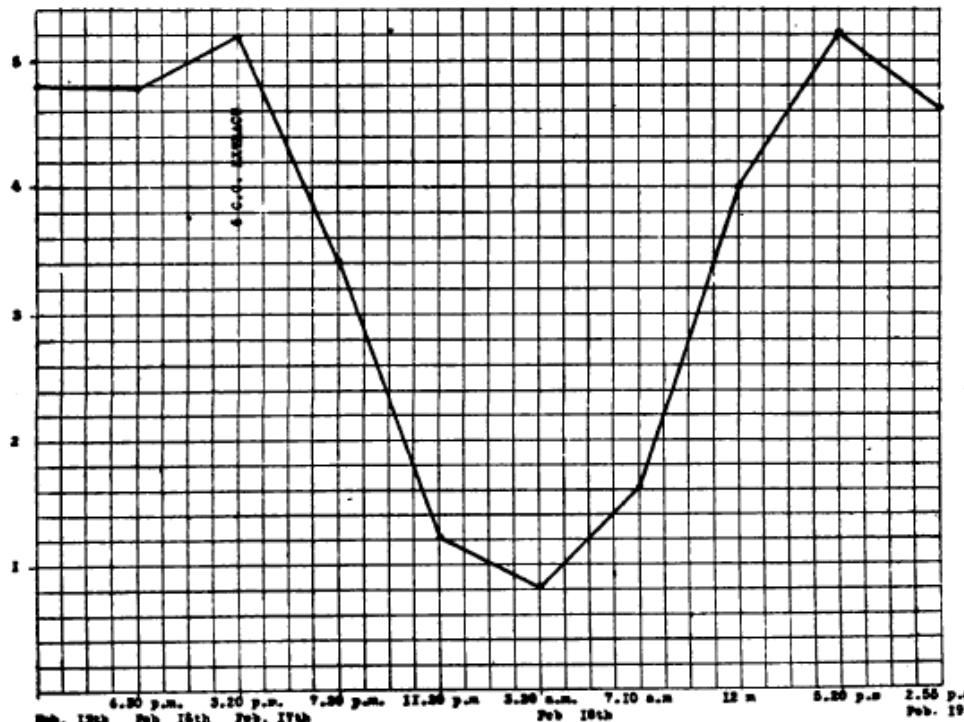


CHART III.—Effect of one injection of extract on Blood
Sugar (mgs. per c.c.e=tenth per cent)

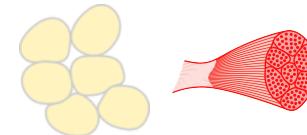
Regulation of Blood Glucose Levels

- Gluconeogenesis
- Disposal
 - Glucose Uptake
 - Glucose Storage
 - Glucose Utilization

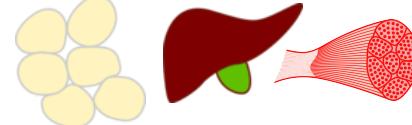
Glucose Production



Glucose Uptake

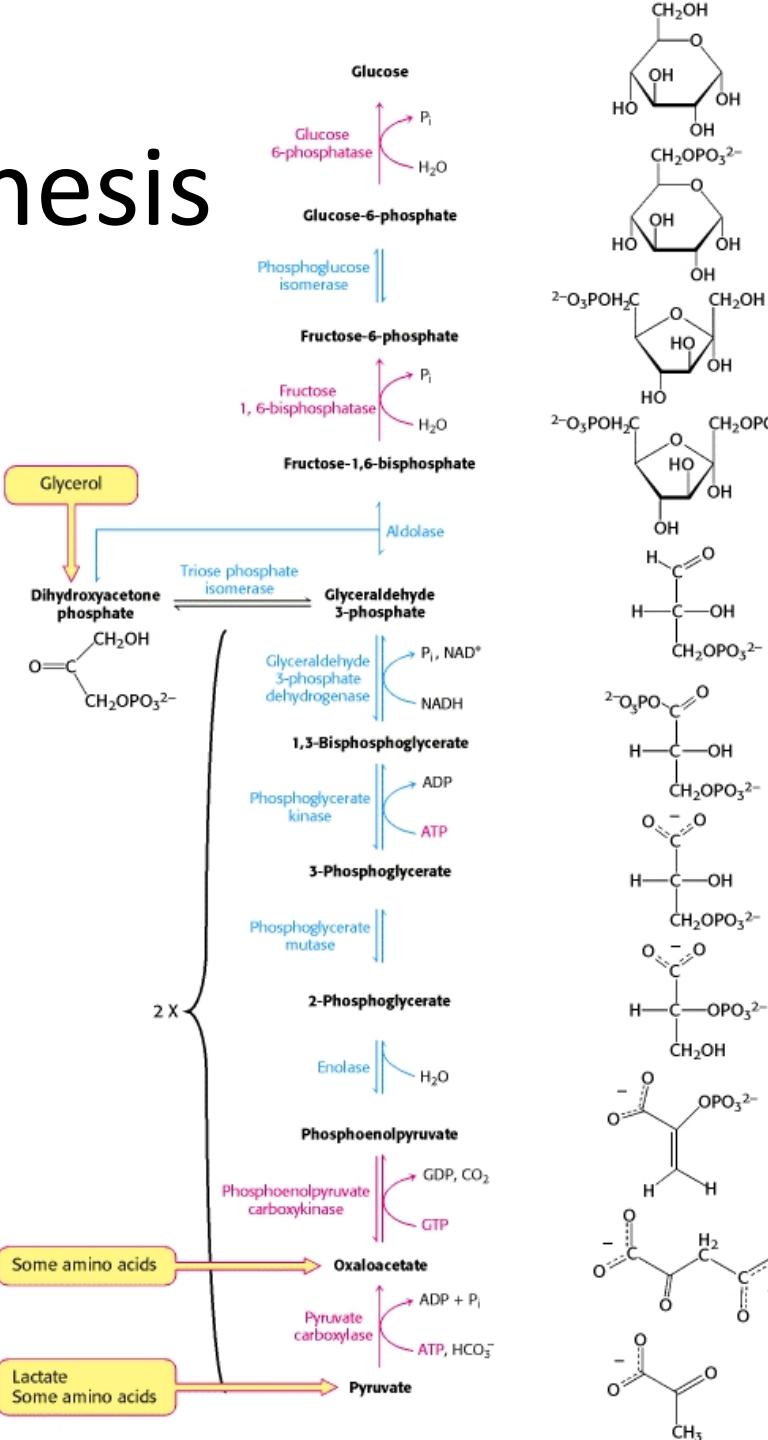


Glucose Storage
and Utilization



Gluconeogenesis

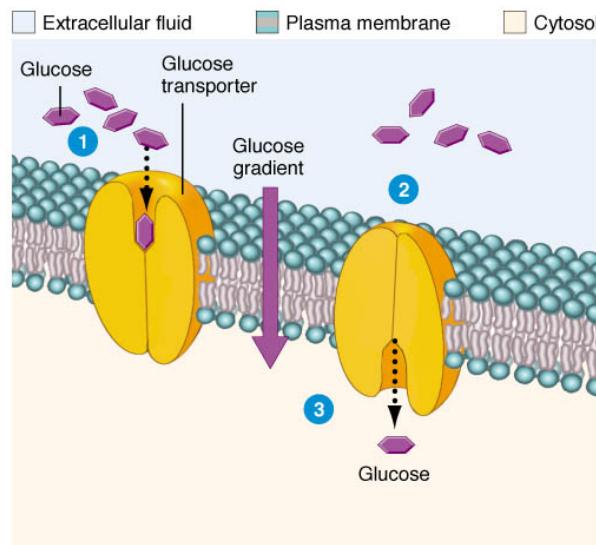
- Uses amino acids and fatty acids to generate glucose
- Key enzymes are PEPCK, FBPase and G6Pase



Glucose Uptake

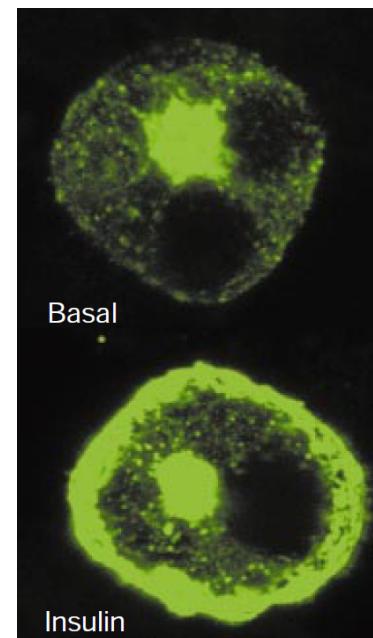
Passive Glucose Uptake

- Brain
- Liver
- Kidneys



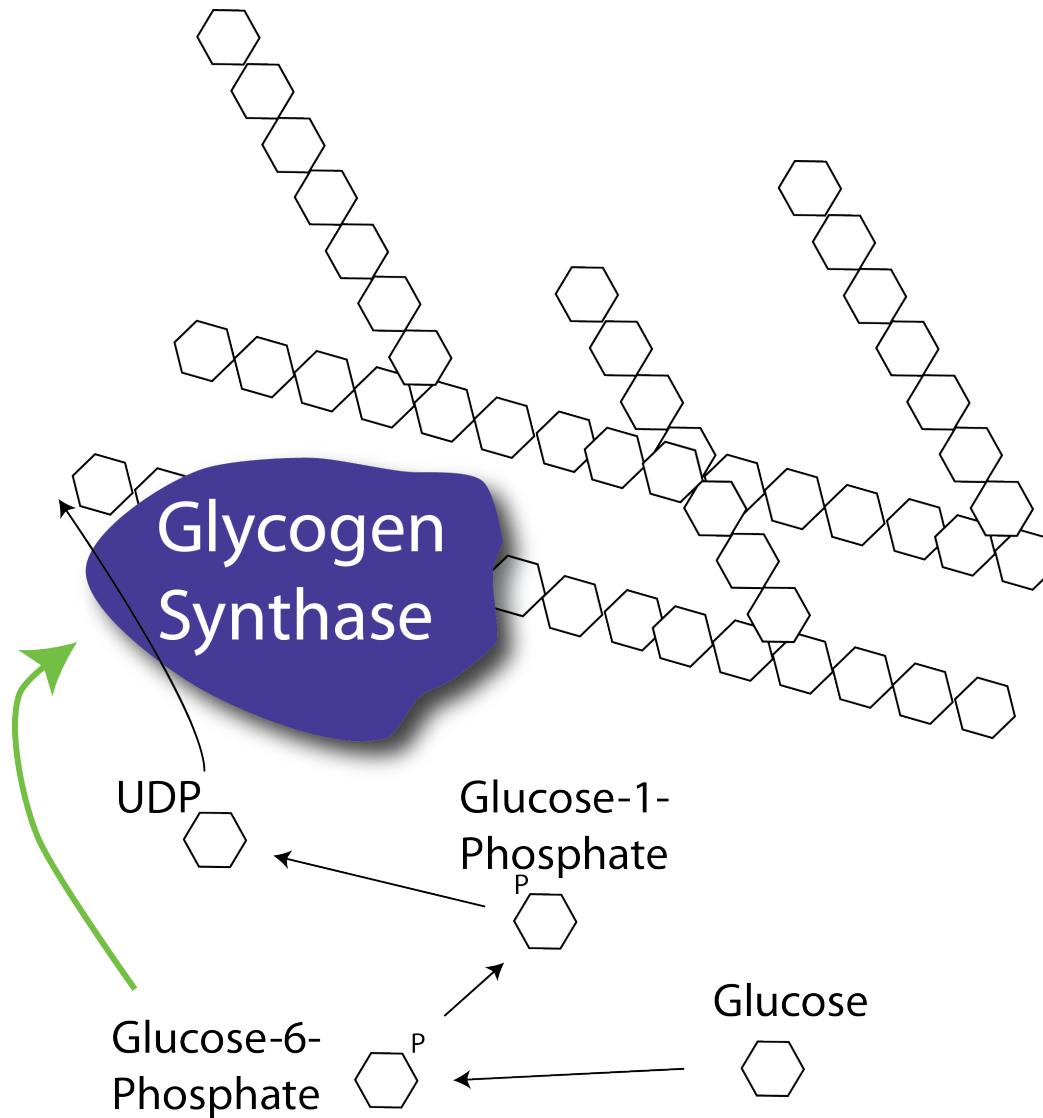
Stimulated Glucose Uptake

- Fat
- Muscle

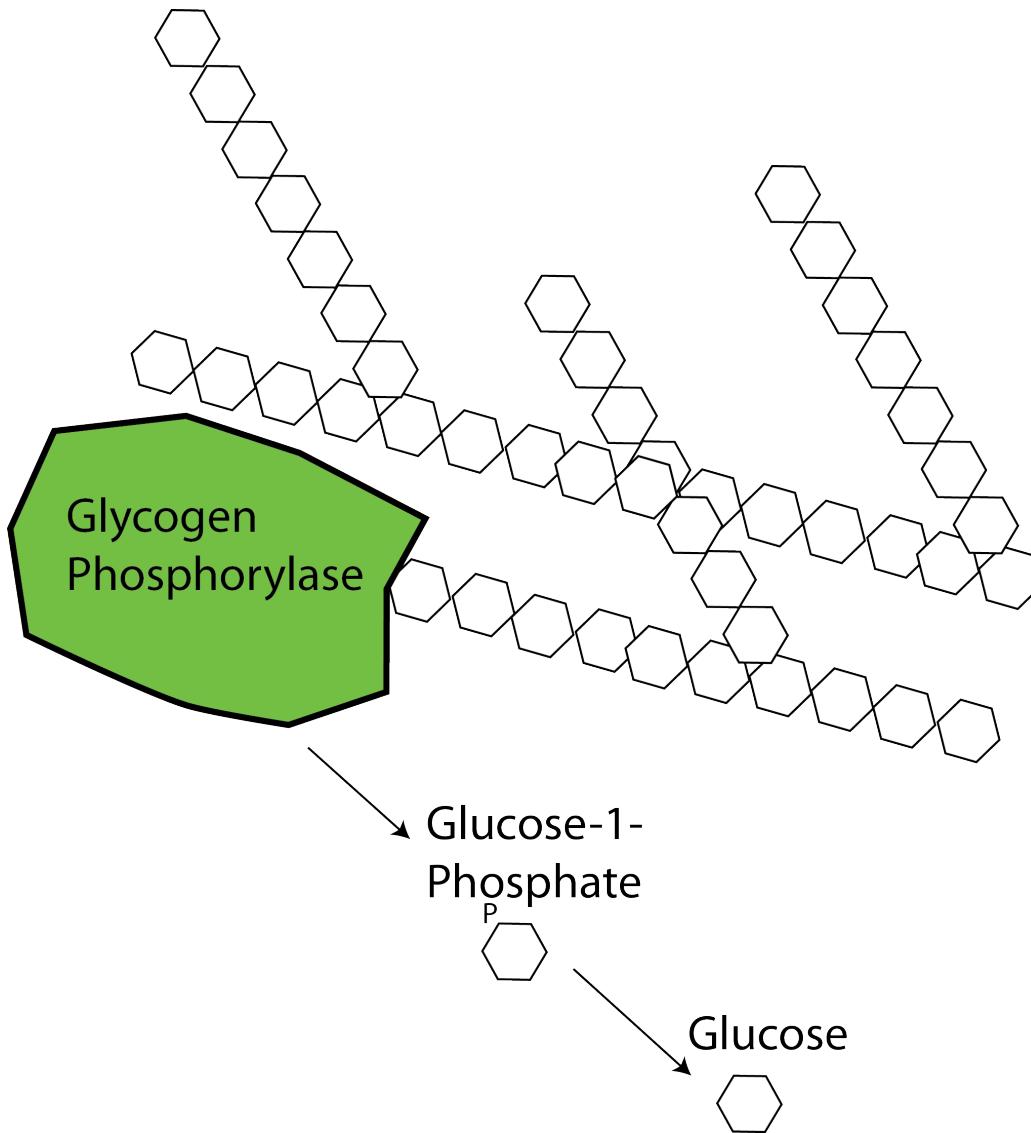


GLUT4-eGFP
From Saltiel and Kahn
(2001) Nature
414:799-806

Glycogenesis



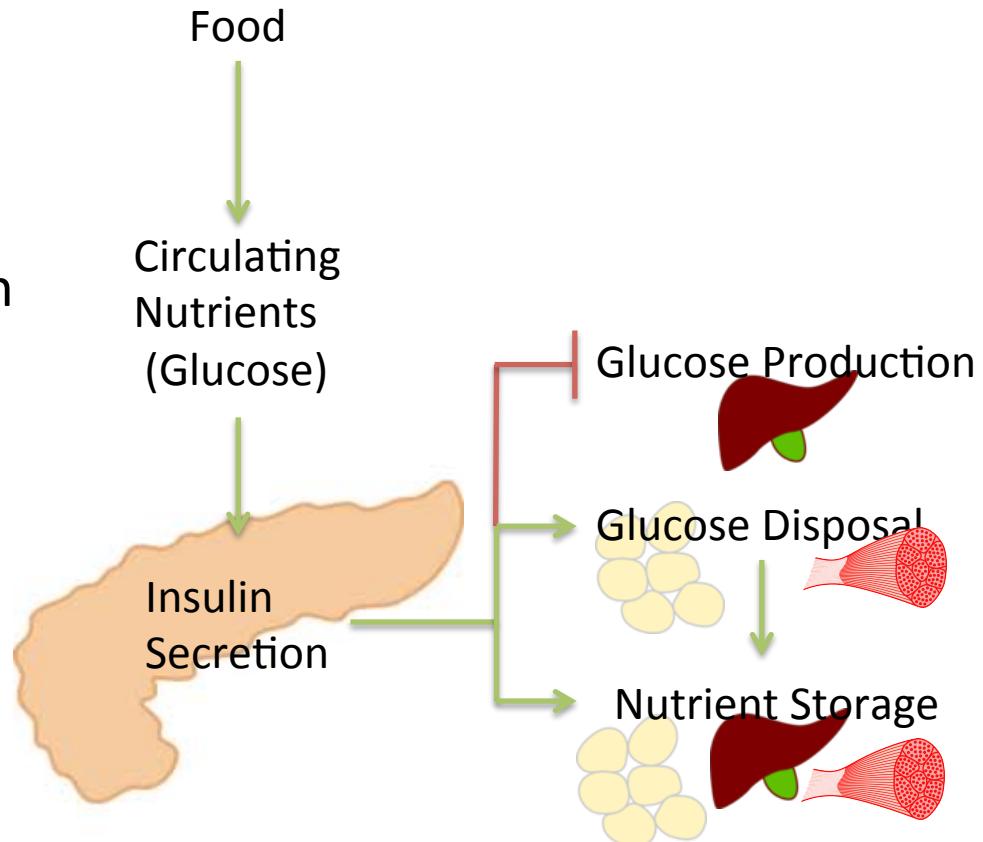
Glycogenolysis



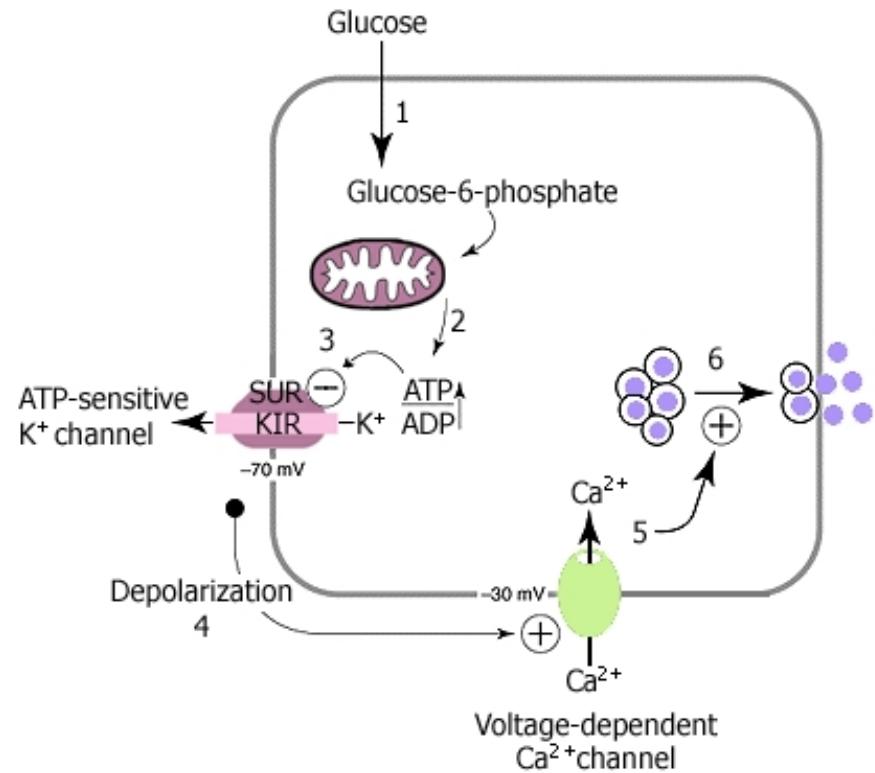
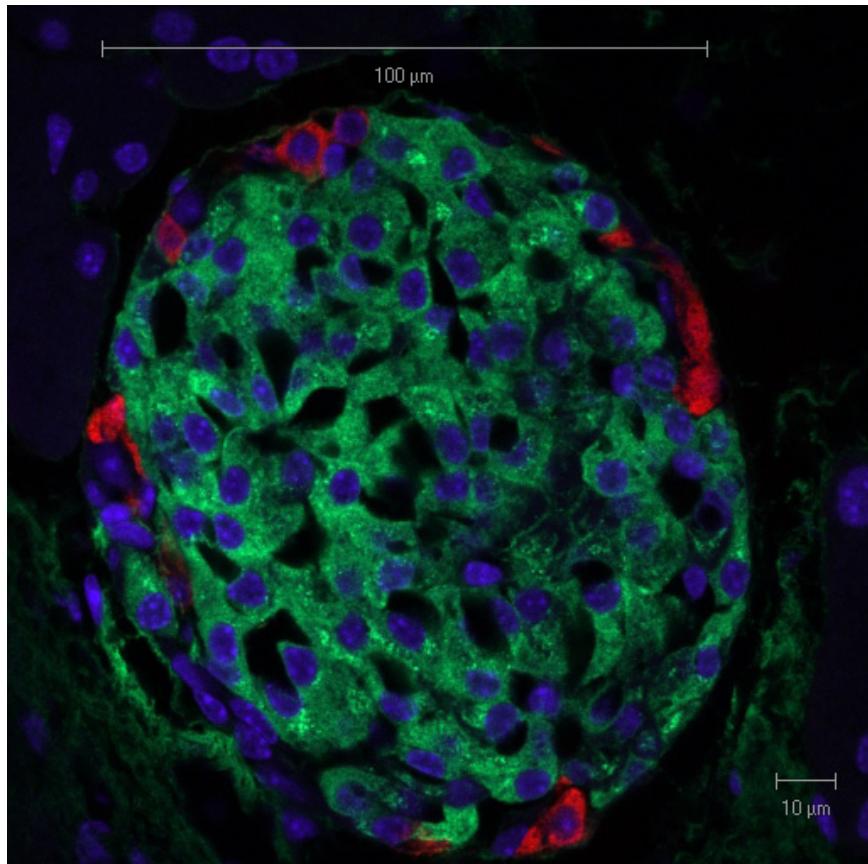
MECHANISMS TO REDUCE BLOOD GLUCOSE

Functions of Insulin

1. Promotes the uptake of glucose from the blood into muscle and adipose tissue.
2. Enhances the synthesis of glycogen and triglycerides in liver, adipose and muscle.
3. Insulin inhibits gluconeogenesis, or the production of glucose from non-glucose precursors such as amino acids and lipids.
4. Promote glucose breakdown and prevent lipid breakdown



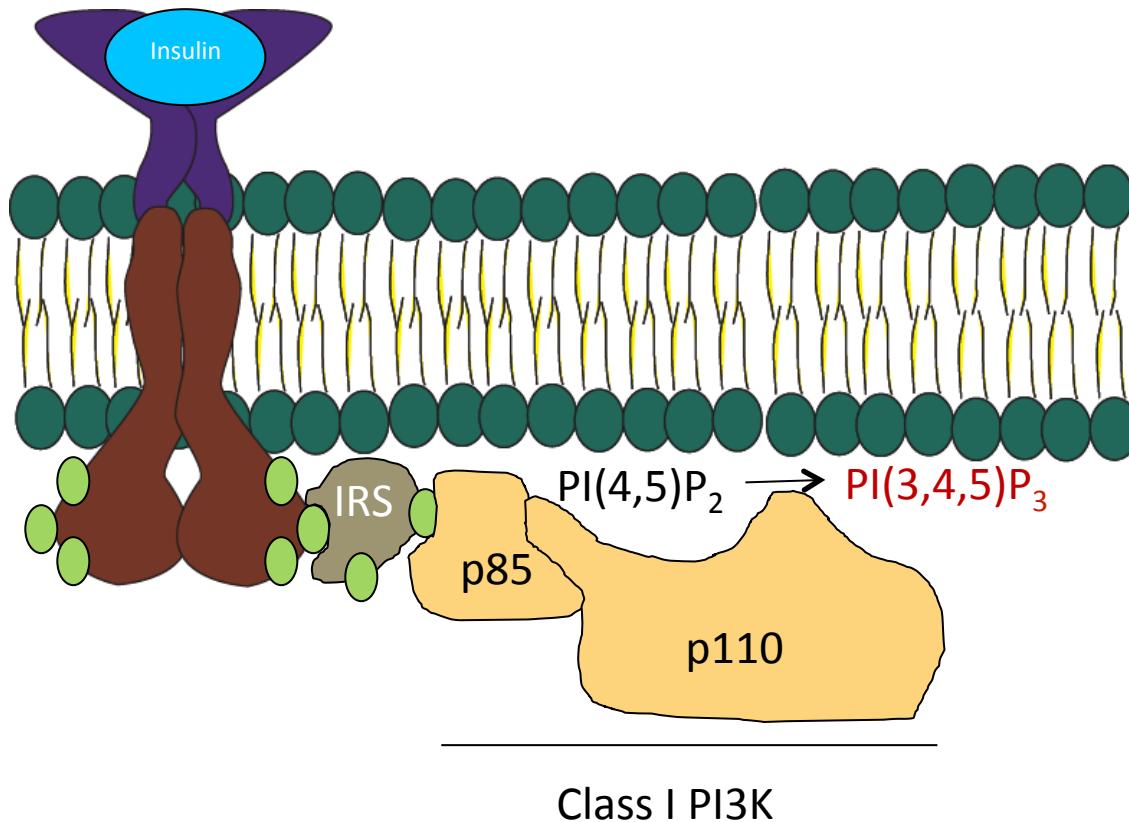
Insulin Secretion



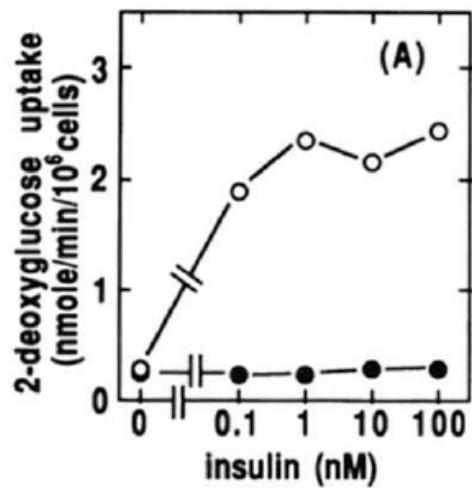
Suckale and Solimena (2008) Frontiers in bioscience 13:7156-71

Pancreatic Islet with **Glucagon** and **Insulin** Staining
From Solilema Lab (http://en.wikipedia.org/wiki/Islets_of_Langerhans)

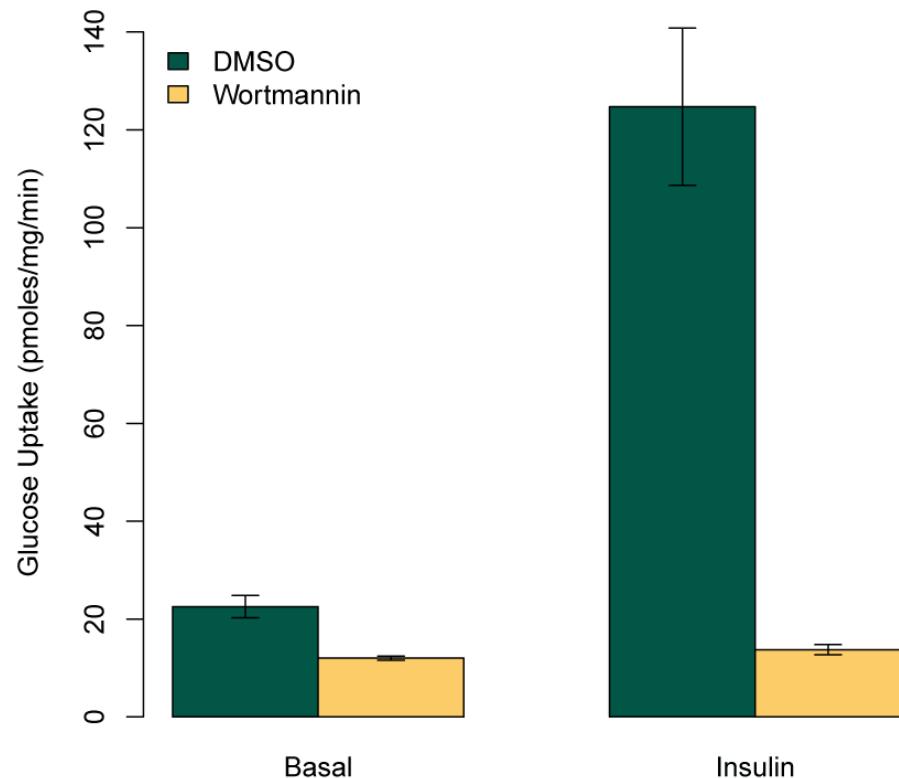
Insulin Signaling – PI3K Signaling



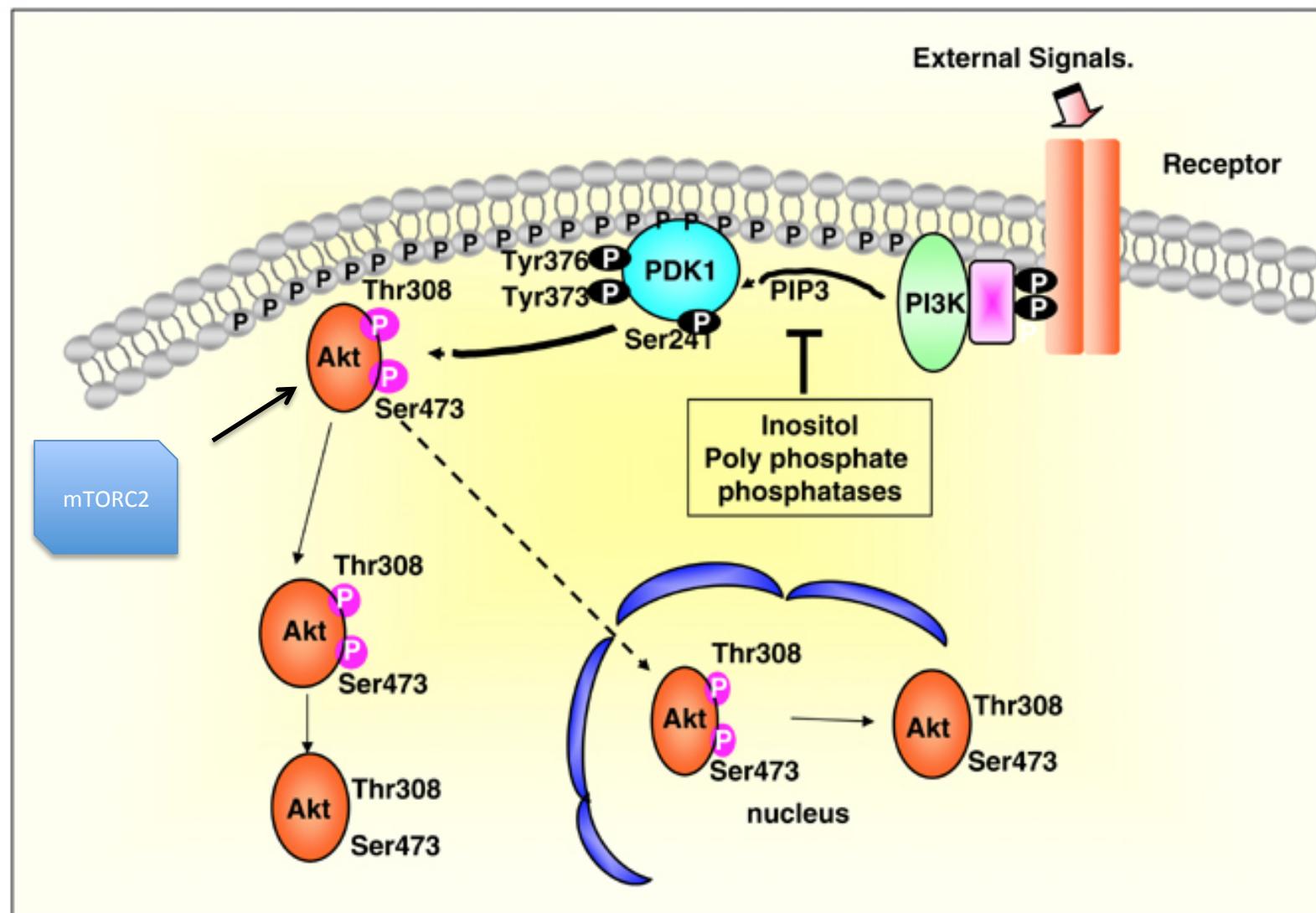
Key Role of PI3K in Insulin Signaling



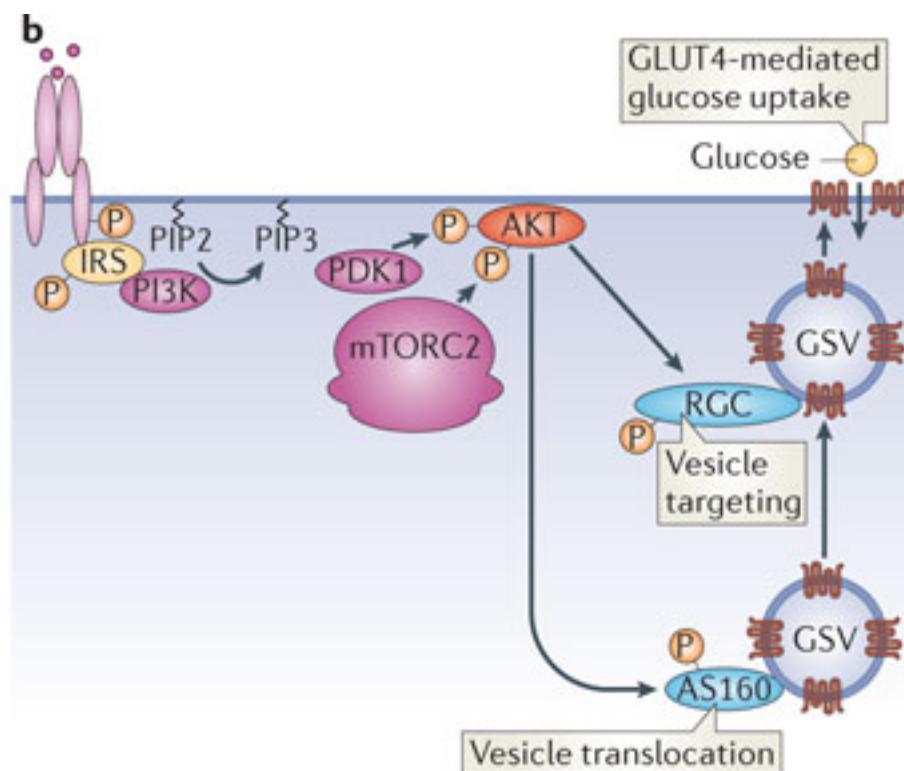
Kanai *et al* (1993) Biochem Biophys.
Res. Comm. 195:762:768



Akt Activation by the PI3K Pathway



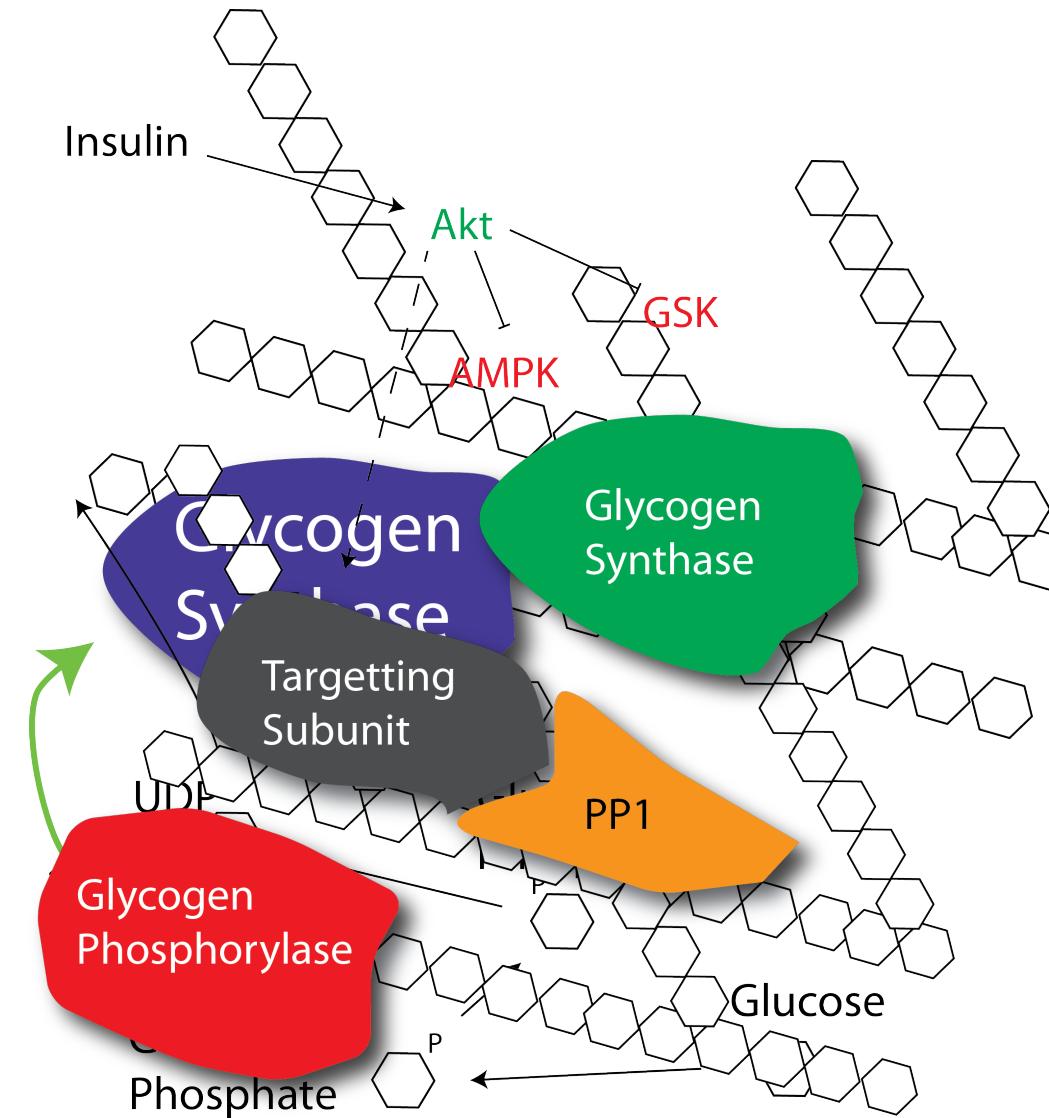
Insulin Stimulated GLUT4 Translocation



Nature Reviews | Molecular Cell Biology

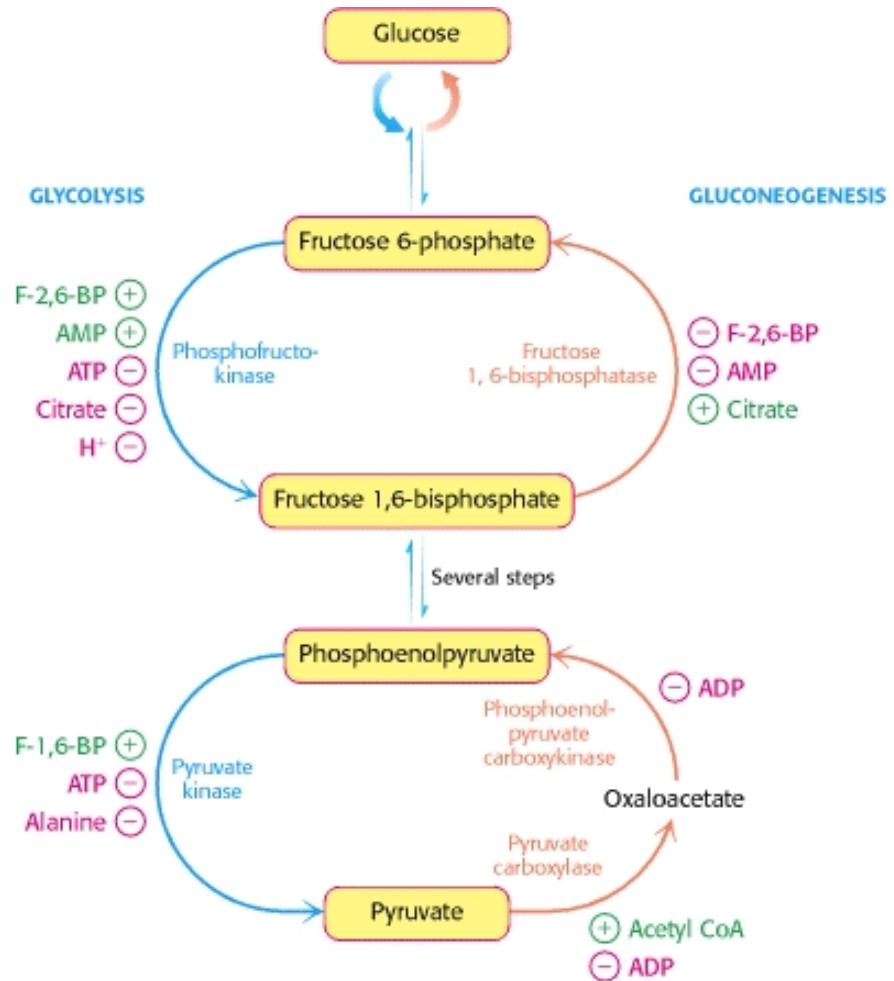
How does insulin promote glycogenesis?

- Allosteric activation
- Protein dephosphorylation

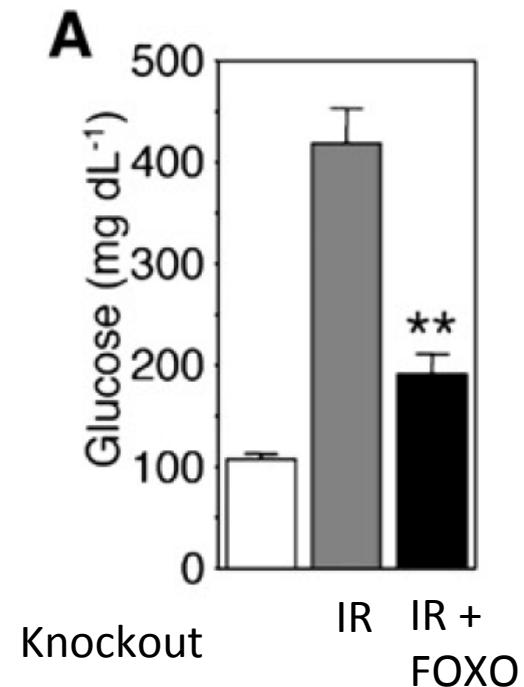
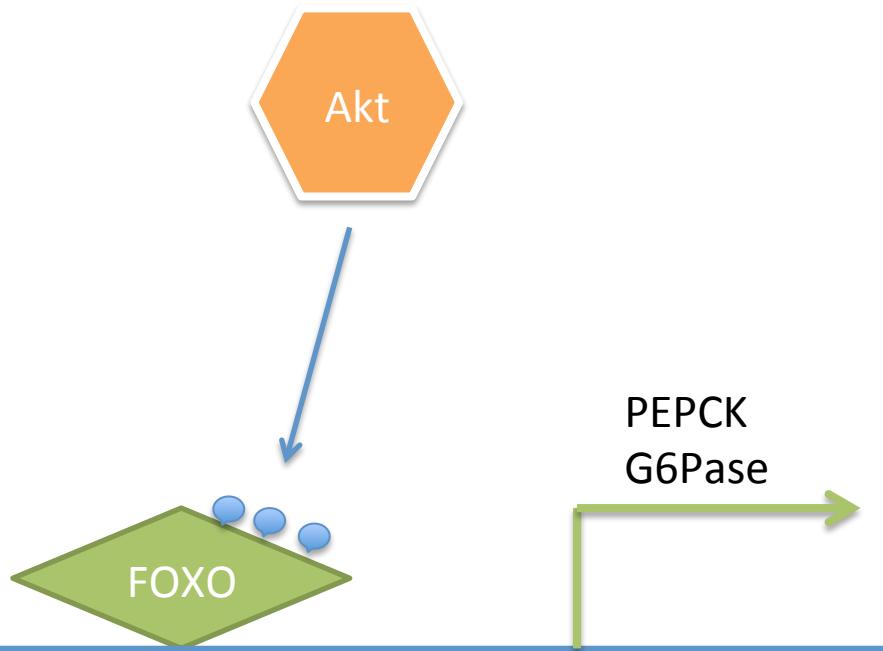


How does insulin reduce gluconeogenesis

- FBPase is negatively regulated by F-2,6-BP
- PEPCK and G6Pase are inhibited by insulin
 - Allosterically
 - Protein phosphorylation
 - Transcriptionally repressed



Transcriptional Regulation of Gluconeogenesis

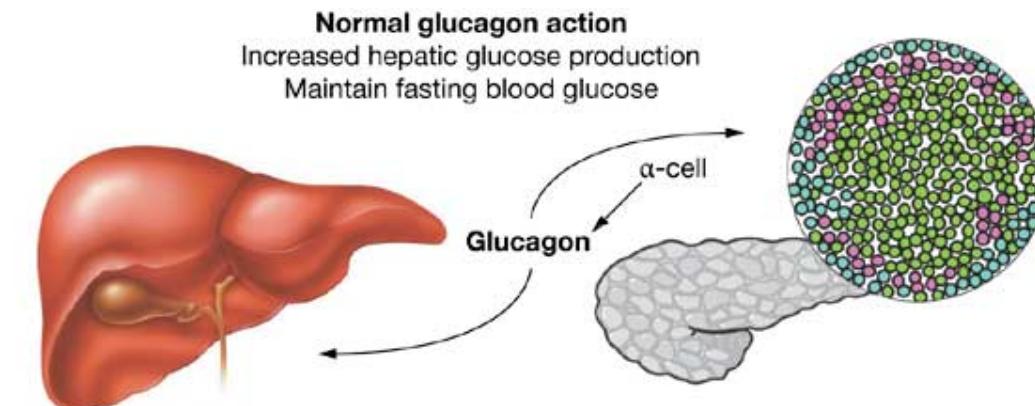


Matsumoto *et al.* (2007) Cell
Metab. 6:208-16

MECHANISMS TO INCREASE BLOOD GLUCOSE

Glucagon Secretion

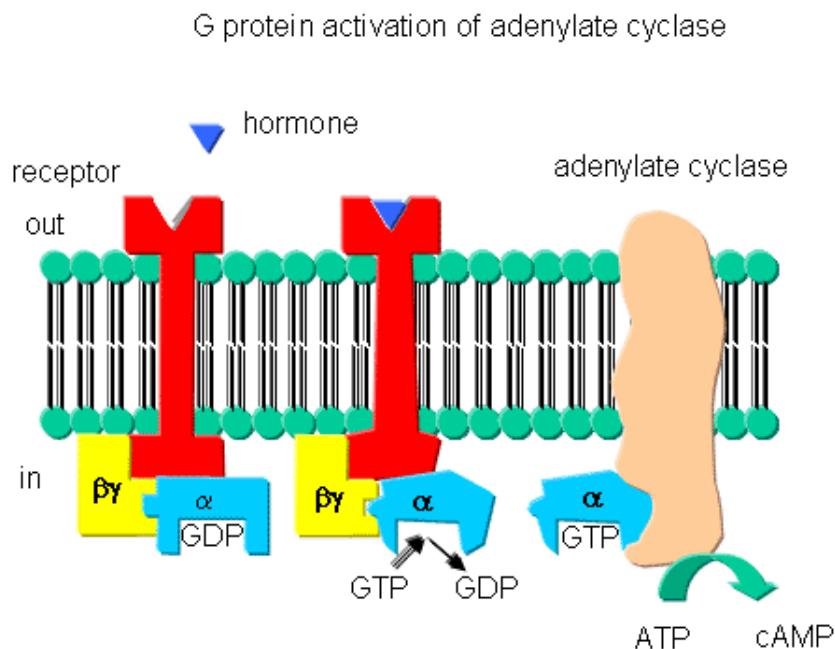
- Secreted from alpha cells of the pancreas
- Released by low blood sugar levels
- Acts on the liver not the muscle or fat tissues



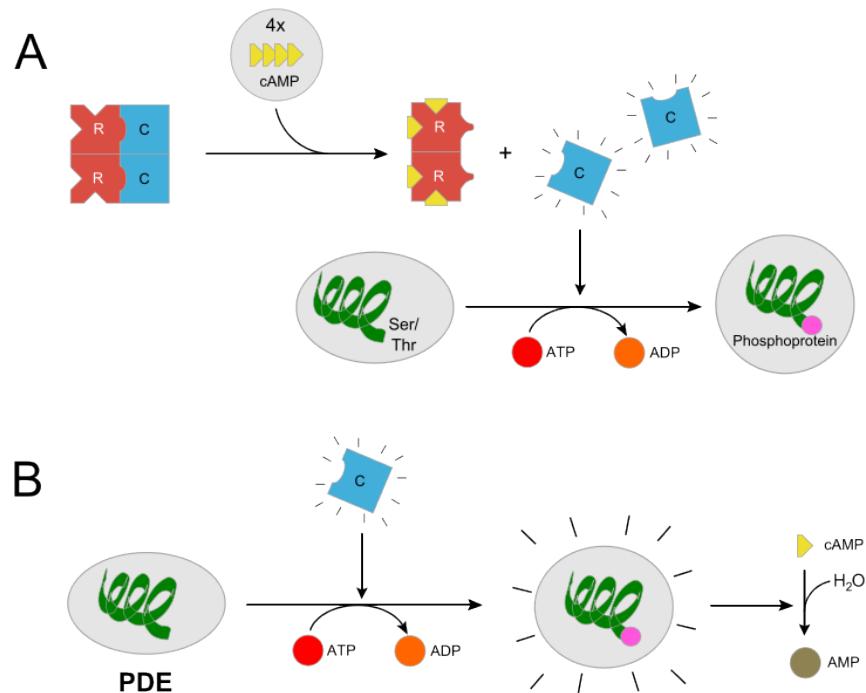
Reduced or absent glucagon action
Reduced hepatic glucose production
Fasting hypoglycemia
Islet α -cell hyperplasia
Pancreatic GLP-1 production
Hyperglucagonemia

Drucker (2013): Nat Rev Endo 1:22-31

Glucagon Signaling

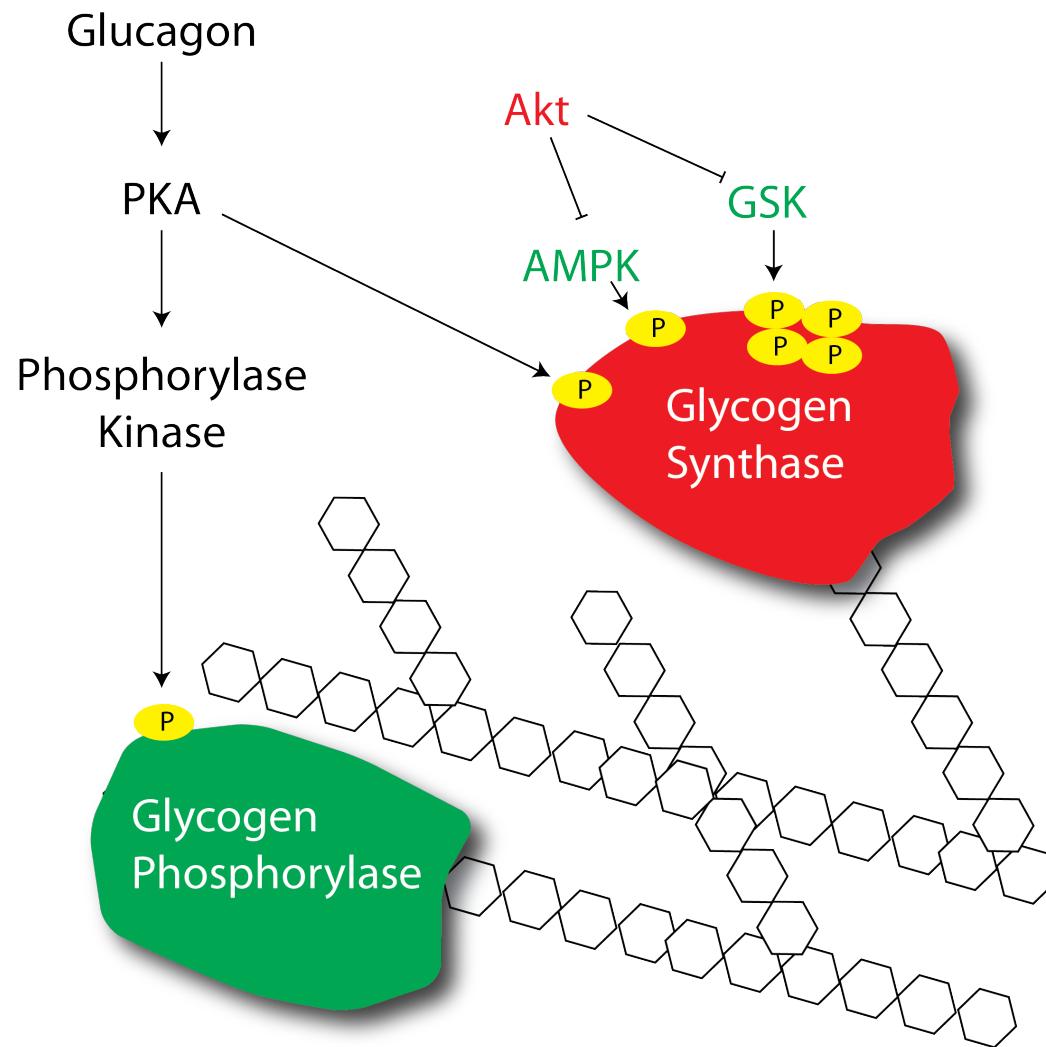


From http://biowiki.ucdavis.edu/Biochemistry/Signal_Transduction/Signal_Transduction_at_Cell_Membranes%3A_Protein_Kinases_and_Phosphotases

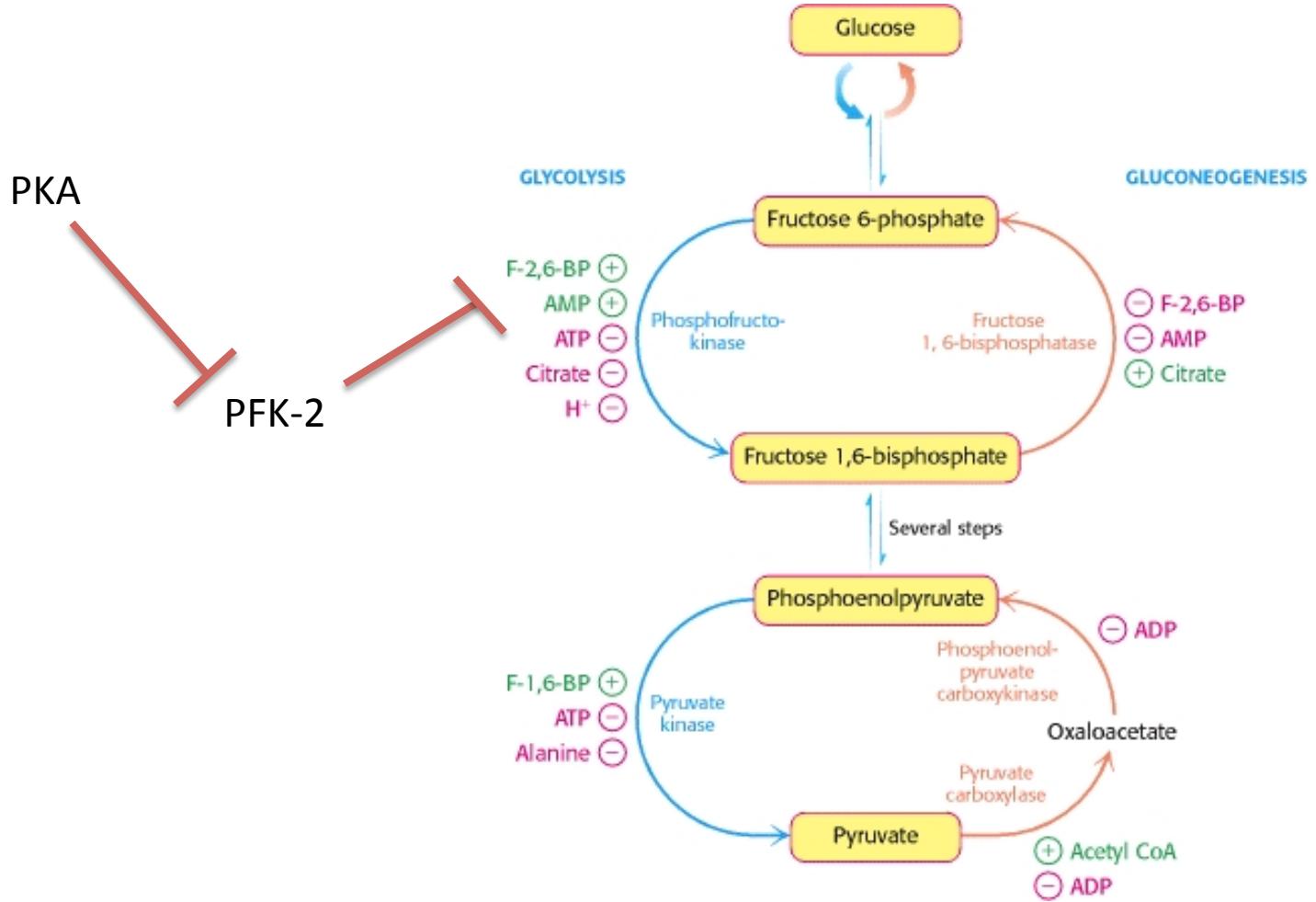


From http://en.wikipedia.org/wiki/Protein_kinase_A

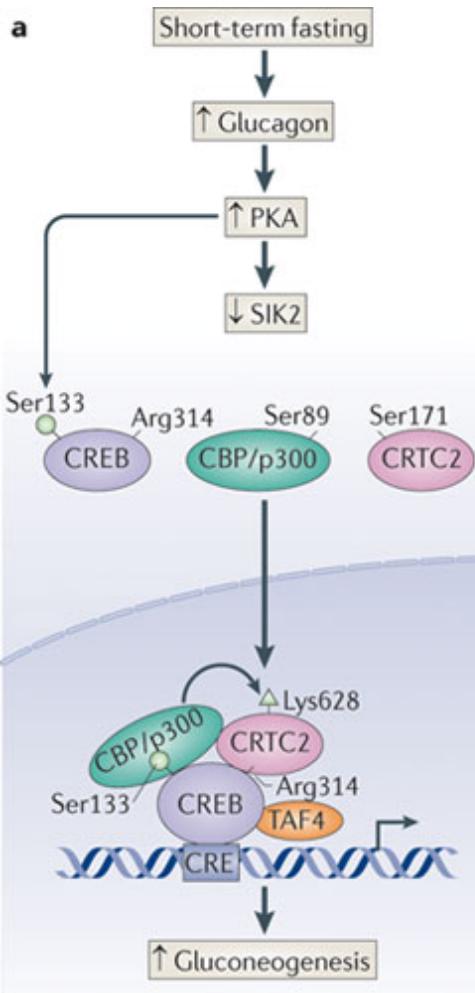
How does glucagon regulate glycogenolysis?



How does glucagon promote gluconeogenesis?



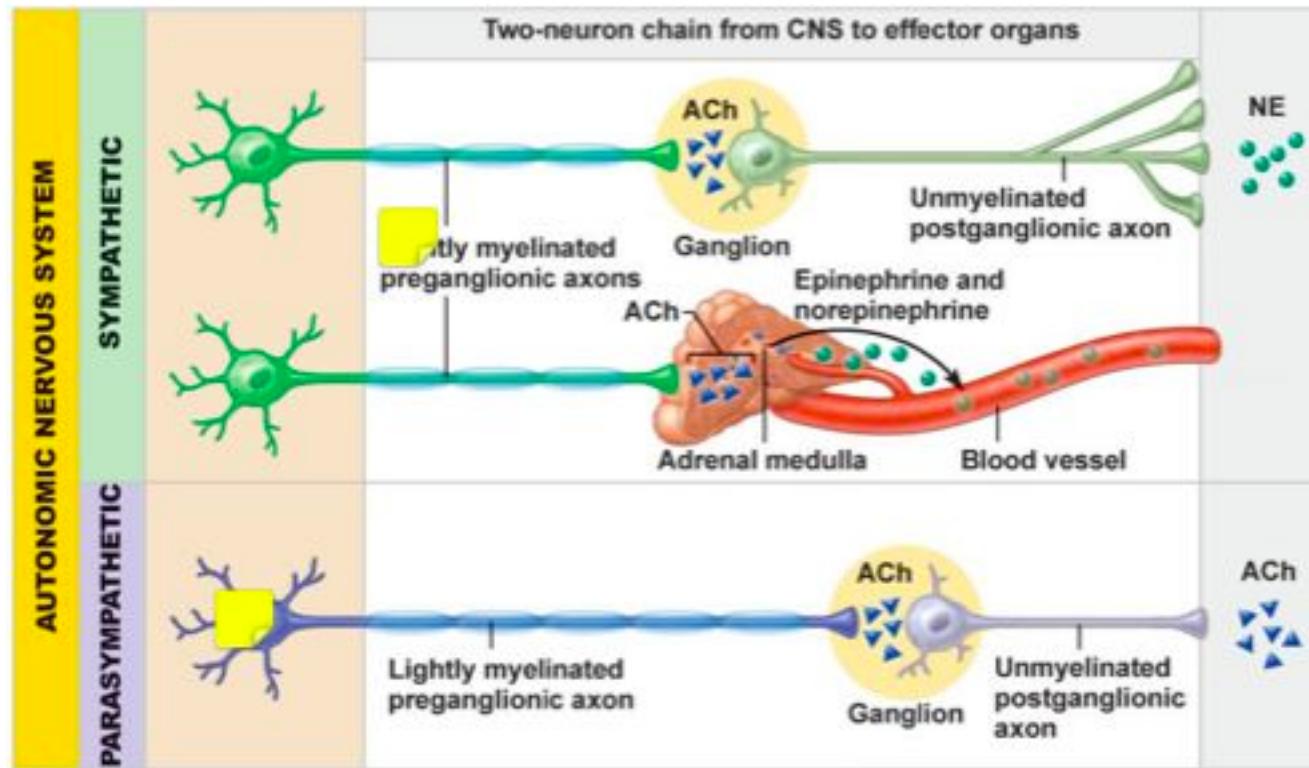
Transcriptional Regulation of Gluconeogenesis



More G6Pase, FBPase and PEPCK

Altajeros and Montminy (2008)
Nat. Rev. MCB. 3:141-151

Nervous Control of Pancreatic Function



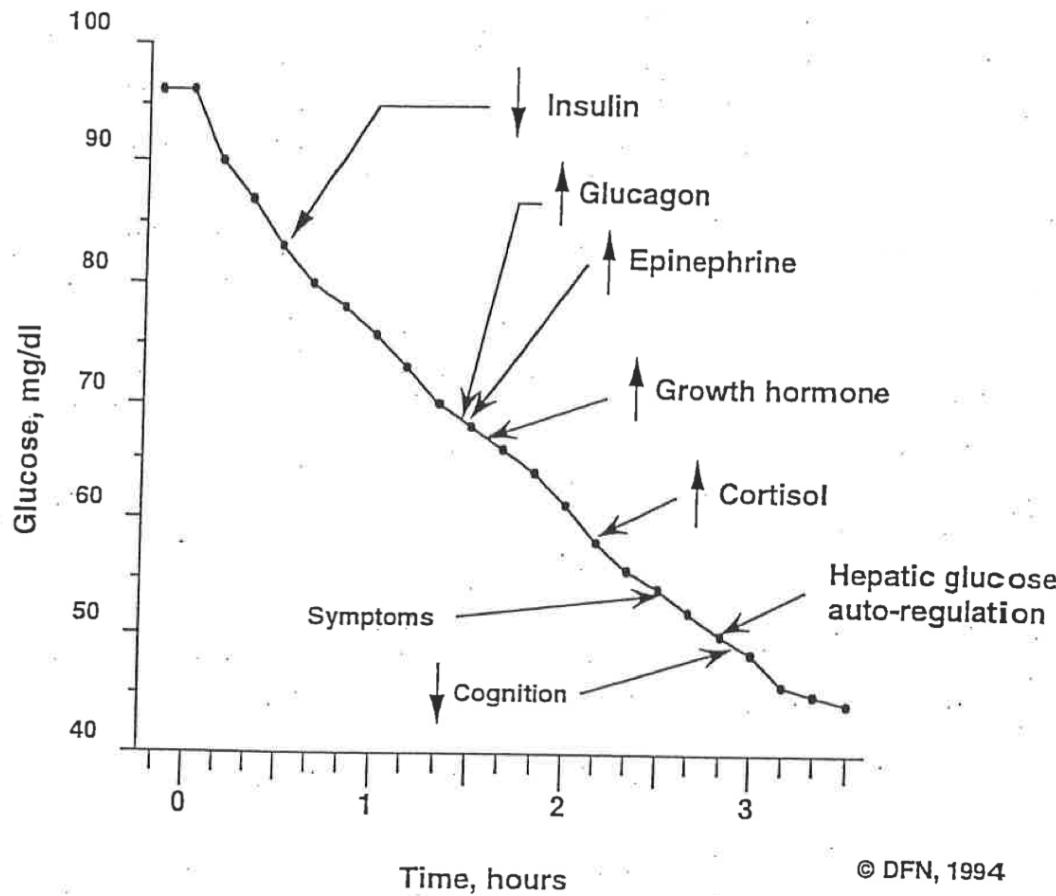
More Glucagon
Less Insulin

More Insulin
Less Glucagon

Glucose and Hormones After a Meal

- First glucose goes up (due to the food)
- Then insulin increases (in response to glucose)
- This causes glucose levels to drop
- At the same time glucagon levels will decrease as glucose levels are high, then increase as normoglycemia is maintained

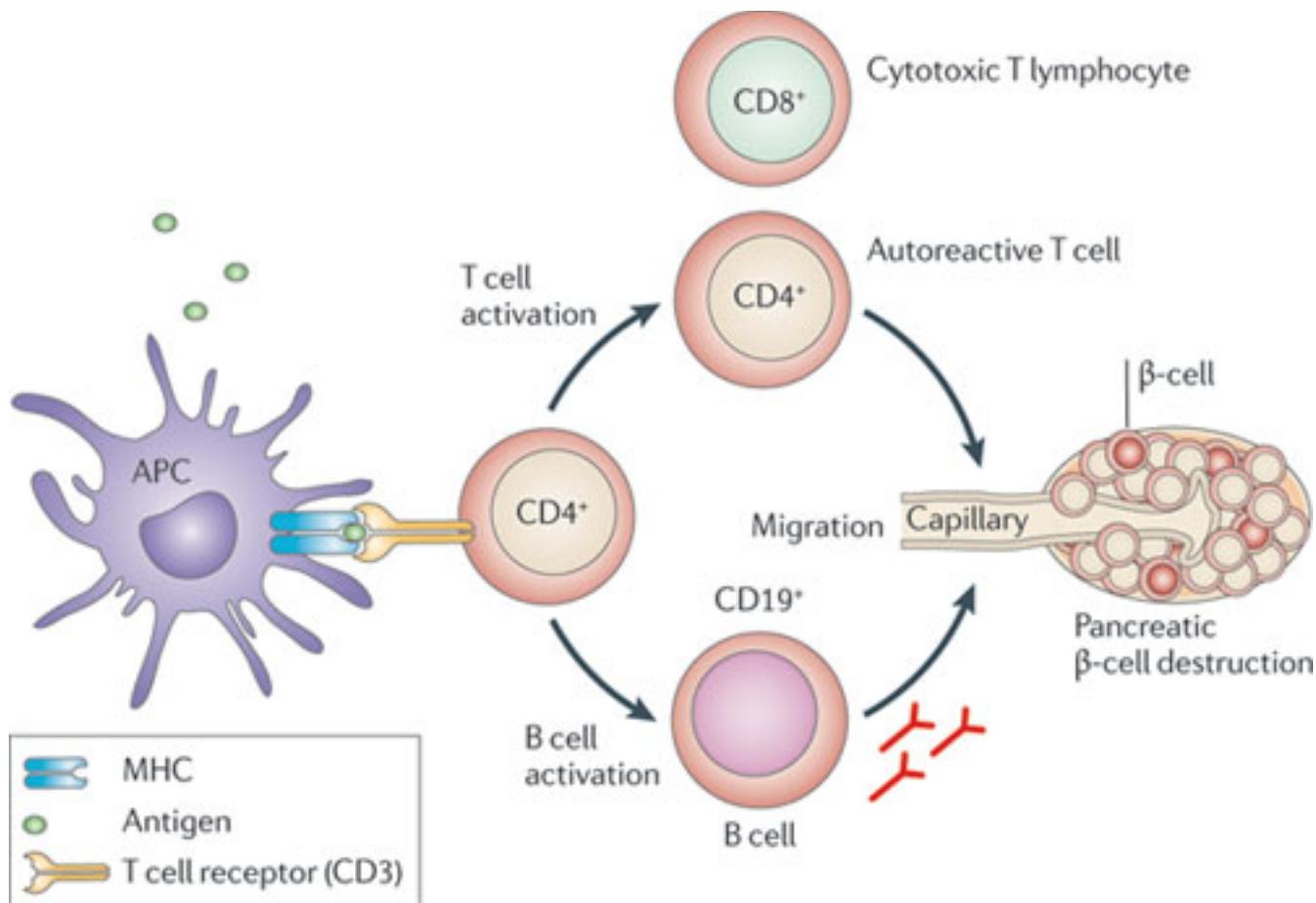
Long Term Glucoregulation



Adapted from: P.E. Cryer, et al., in
Am. J. Physiol. 264: E149, 1993 and
J. Clin. Endo. Metab. 76: 462, 1993.

PATHOPHYSIOLOGY OF GLUCOSE CONTROL

Type I Diabetes Results from a Loss of Beta Cells

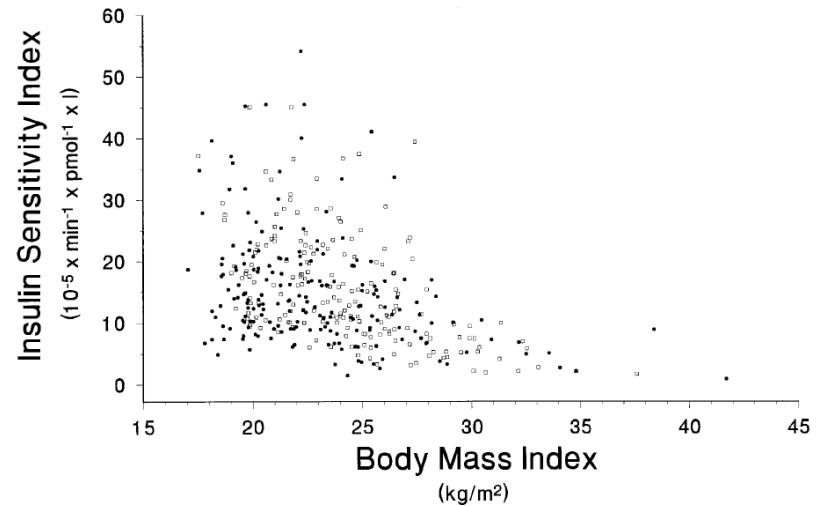


Type II Diabetes

1. Excessive nutrient storage
2. Tissues Become Insulin Resistant
3. Pancreas Compensates by Secreting More Insulin to Normalize Glucose
4. Tissues Become More Insulin Resistant
5. Eventually Pancreas Fails to Compensate
6. Hyperglycemia

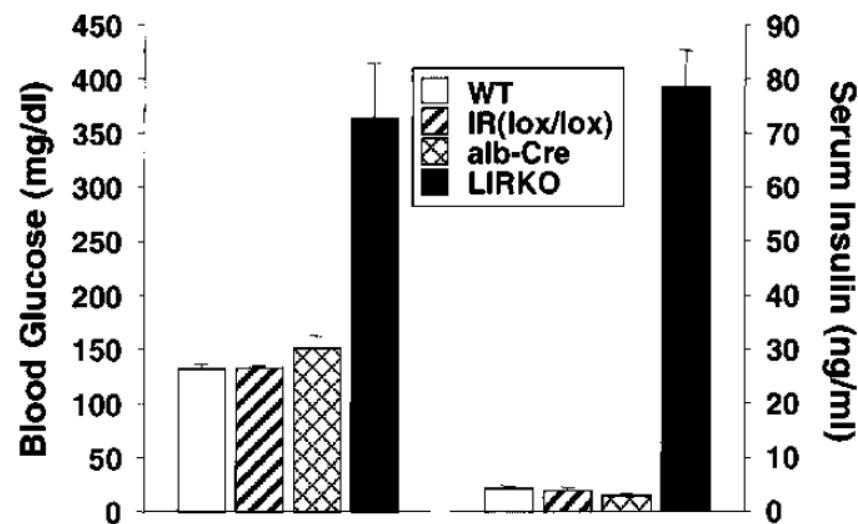
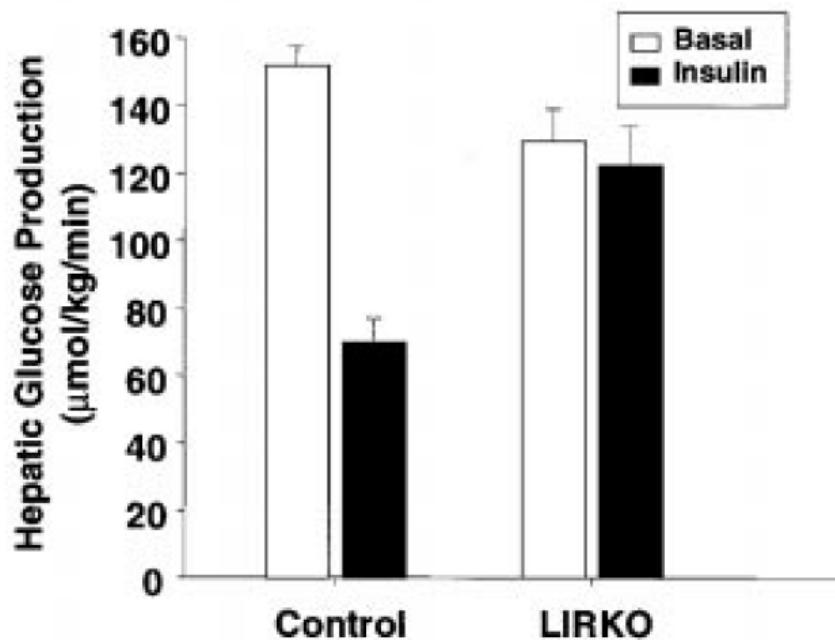
Why Is There Insulin Resistance

- Negative feedback loops are common in most endocrine organs
- A mechanism to avoid excessive nutrient storage
- The “Thrifty Genotype” Hypothesis



Clausen et al. 1996 J. Clin. Invest. 98:1195–1209

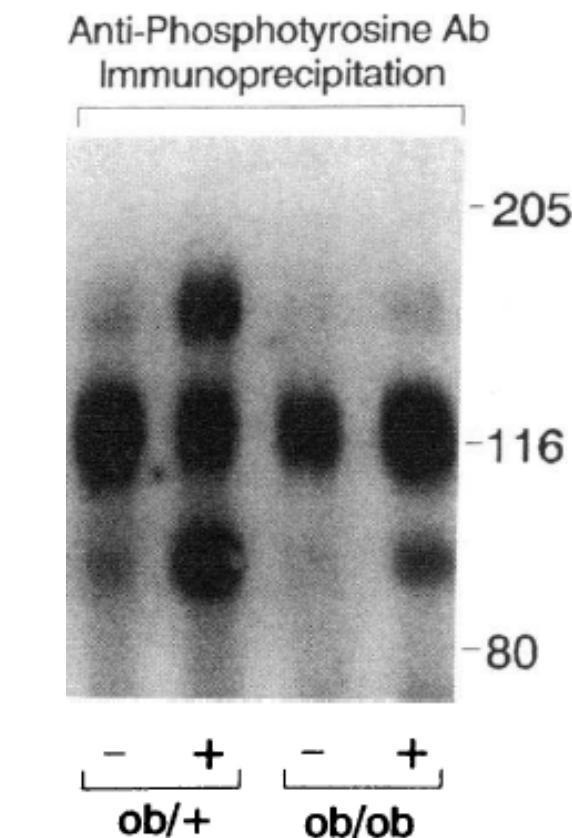
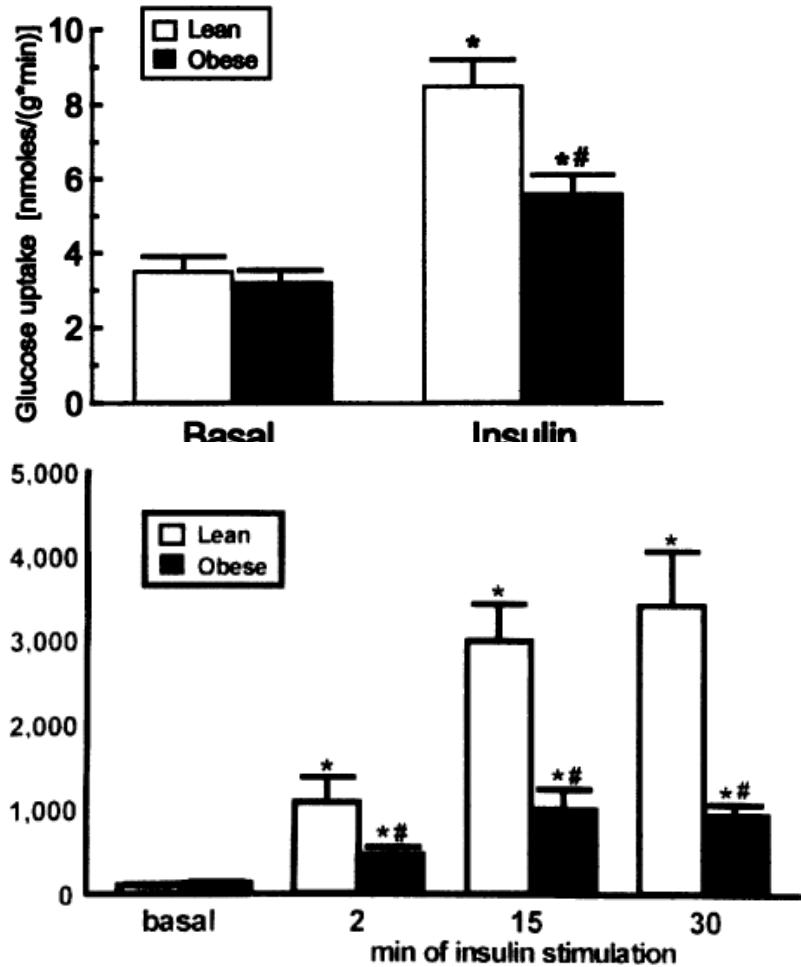
Liver Insulin Receptor Knockout



Mechanisms of Insulin Resistance

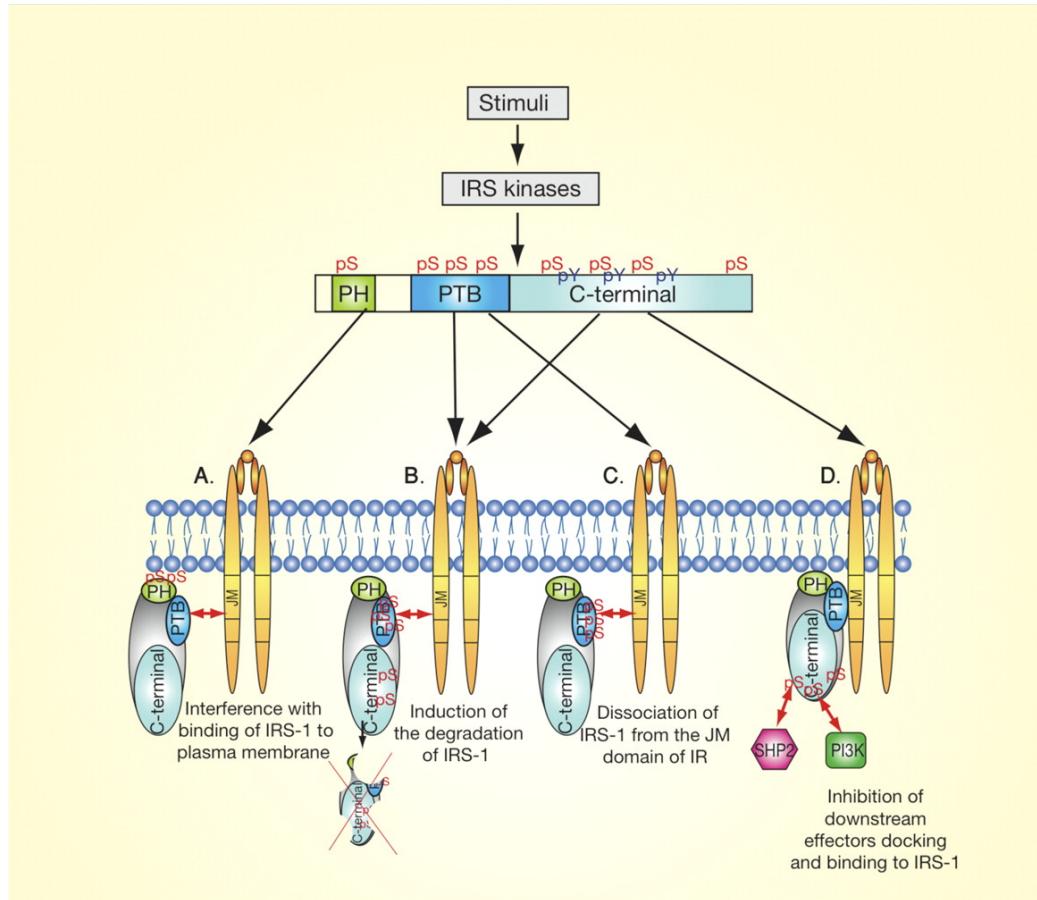
1. Overnutrition induced insulin resistance
2. Lipid mediated insulin resistance
3. Inflammation associated insulin resistance

Molecular Mechanisms of Insulin Resistance



Saad *et al.* (1992)
J. Clin. Invest. 90:1839–1849

IRS Serine Phosphorylation



Boura-Halfon and Zick (2009) Am. J.
Endo. Metab. 296:E581-E591

Learning Objectives

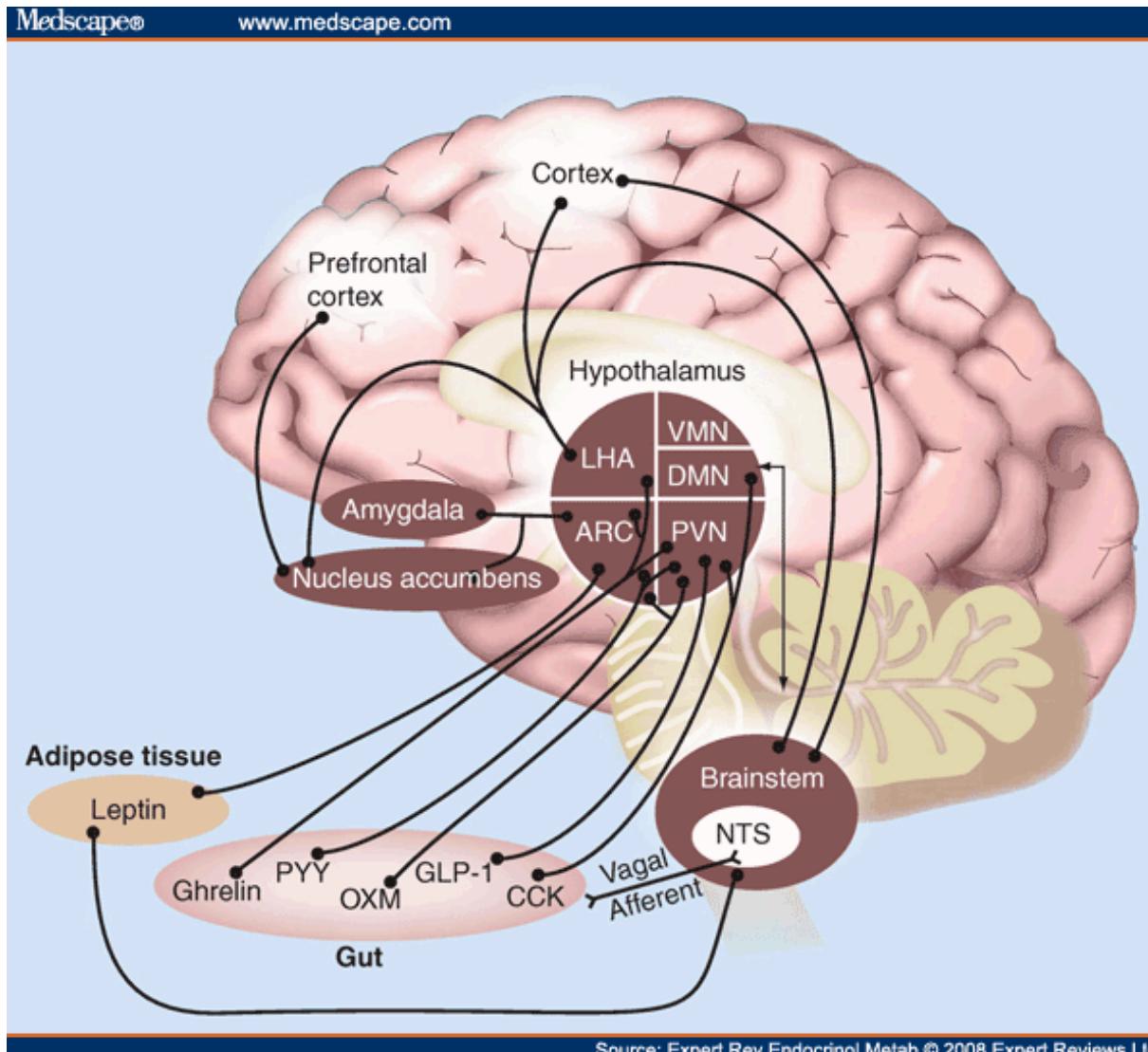
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REGULATION OF APPETITE

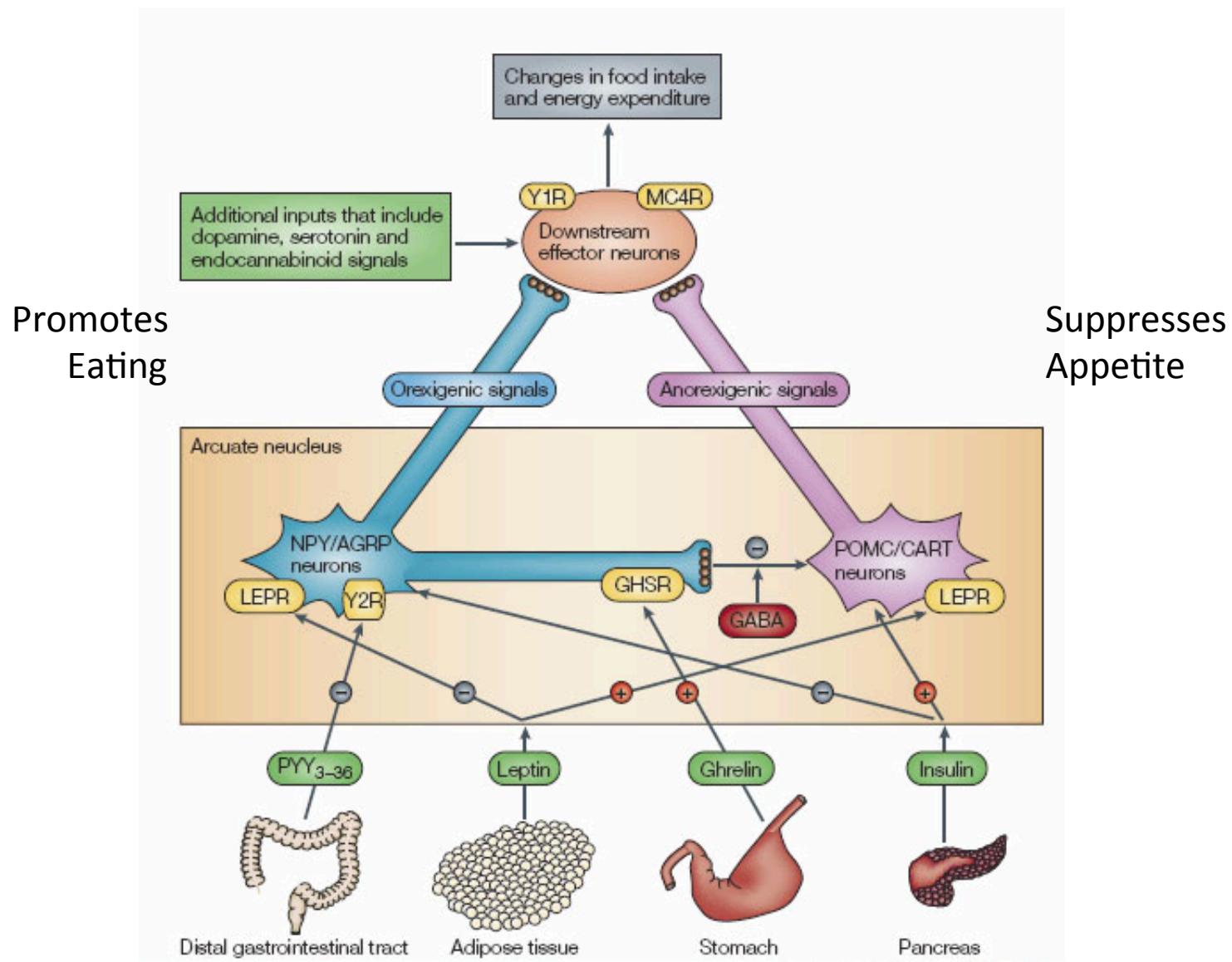
Learning Objectives

- Describe the appetite-regulating hormones secreted from the gut, how they are regulated and under what conditions they are released.
- Describe the AgRP/POMC circuit and its relationship to both circulating factors and neuropeptides.
- Understand the relationship between adipose mass and appetite regulation, including how adipokines are regulated and what role they play.
- List the effects of insulin on appetite and what the neurological targets of insulin are.
- Describe the role of the blood-brain barrier in the regulation of appetite and how it is altered in obesity.
- Describe how hypothalamic feeding circuits integrate with other pleasure and reward circuits in the brain.
- Explain how neuroendocrine obesity differs from idiopathic obesity and how they might be treated in different ways.

The Central Role of The Hypothalamus

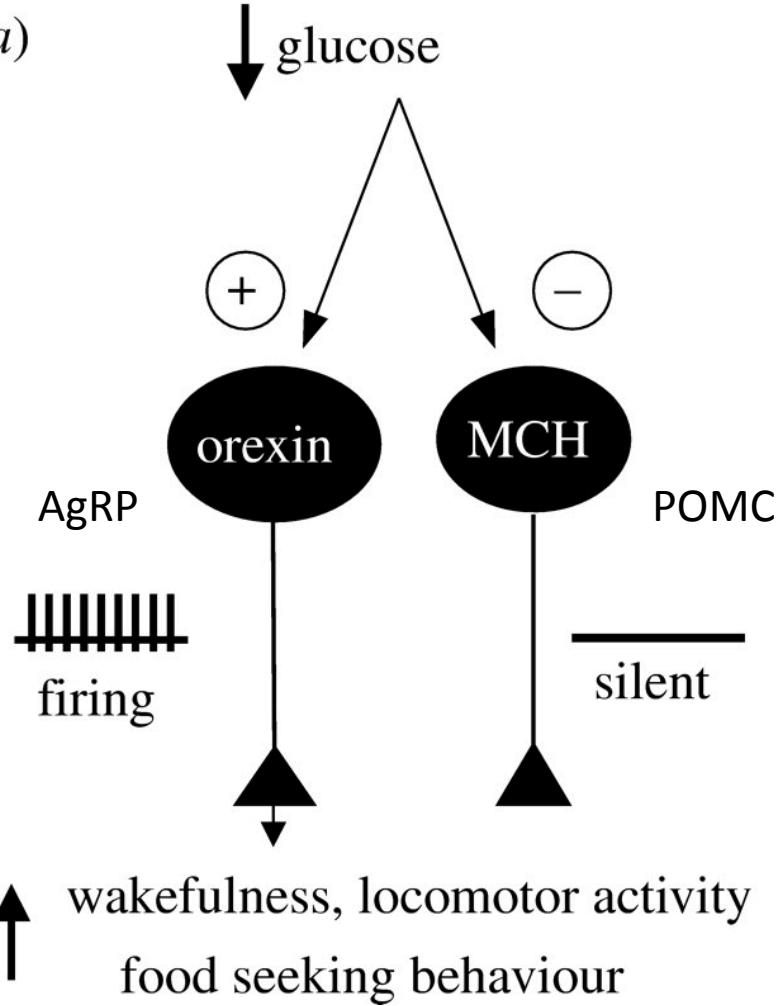


The POMC/AgRP Circuit

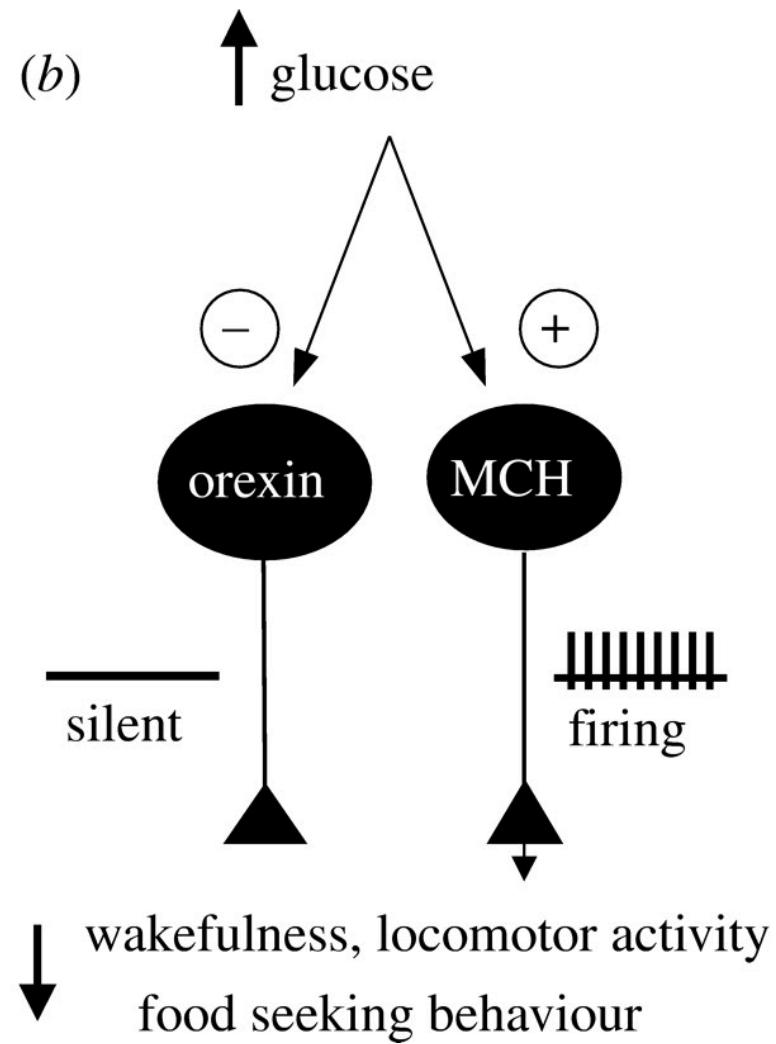


Glucose Sensing Neurons

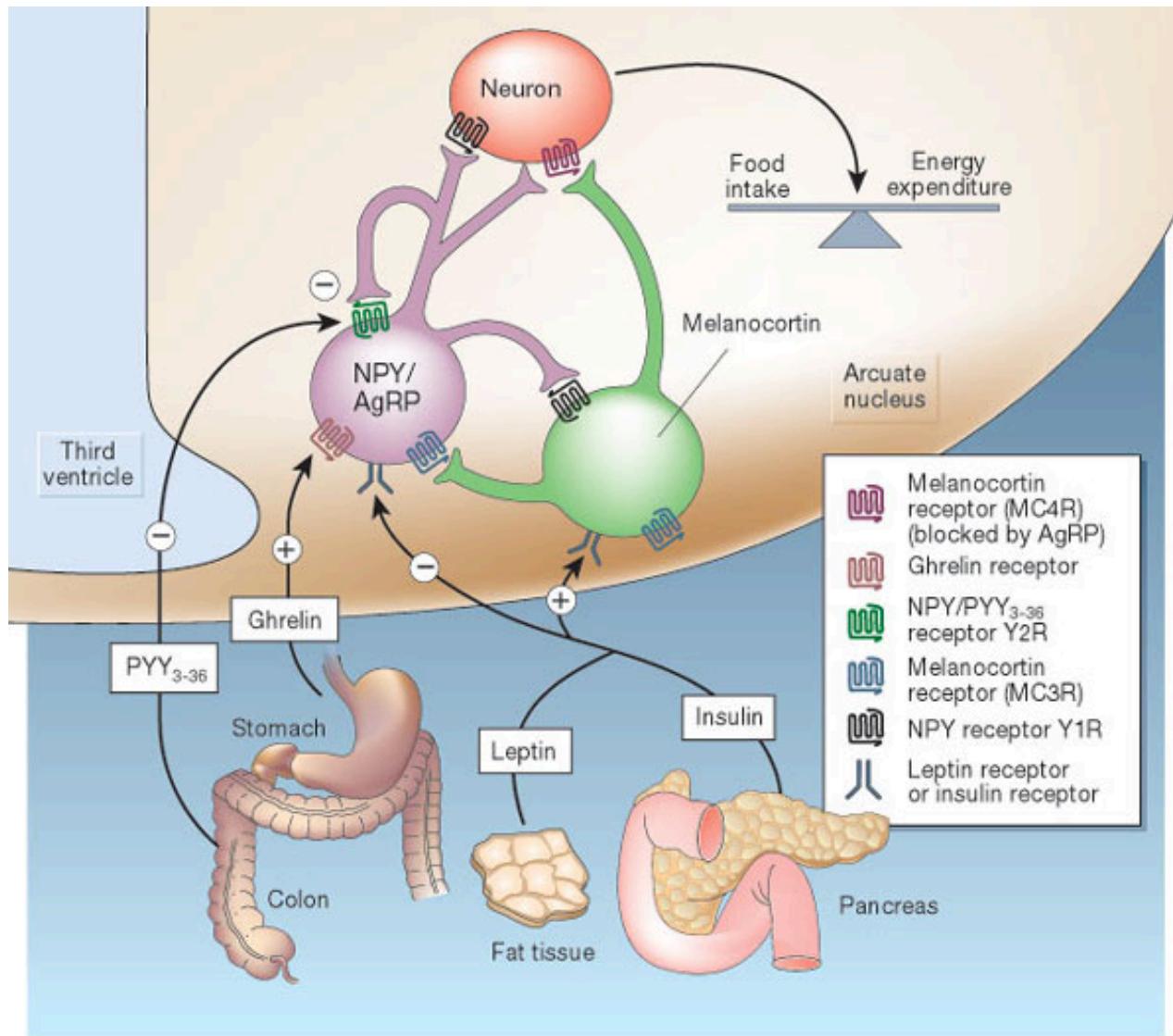
(a)



(b)



Hormonal Control of Appetite



Insulin Regulation of Appetite

- Acts on both AgRP and POMC Neurons
- Enhances excitability of POMC but inhibits AgRP Neurons -> **Decreases appetite**
- Requires transport across blood-brain barrier
- What would insulin resistance in the brain do to appetite?

Leptin and the Ob/Ob Mouse

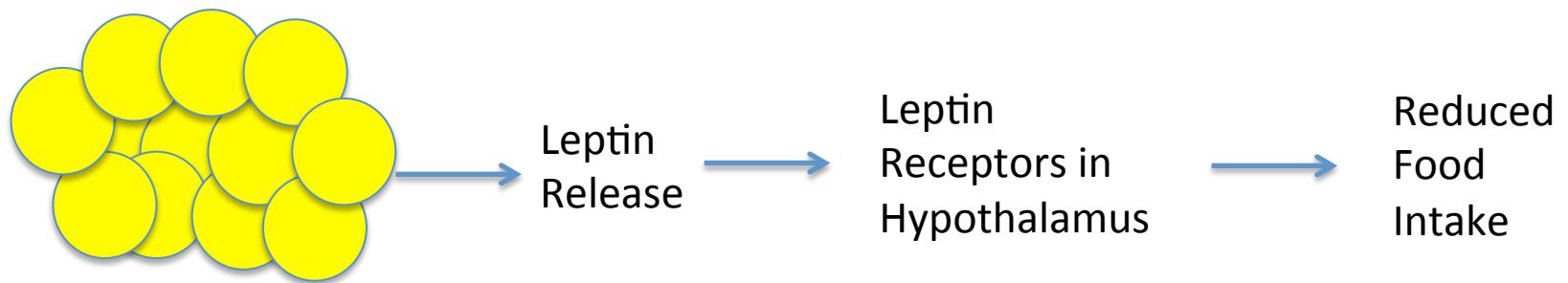


ob/ob mouse



db/db mouse

The Leptin/Leptin Receptor Genes

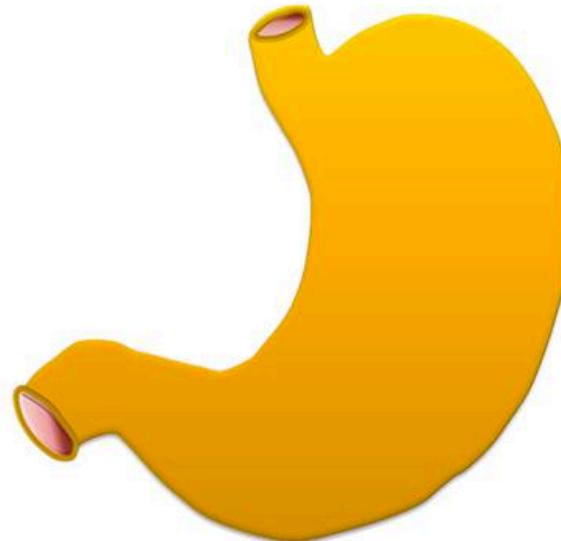


Leptin Summary

What chemical type?	Protein	
Where is it made?	Adipocytes	
What causes its release?	Fat Expansion	
What are its receptors?	LepR (JAK/STAT)	
What tissues does it affect?	Brain Adipose, Liver, Muscle	Activates POMC, Inhibits AgRP -> Reduced Food Uptake Fat Oxidation
How does it get turned off?	Receptor desensitization, reduced BBB transport	

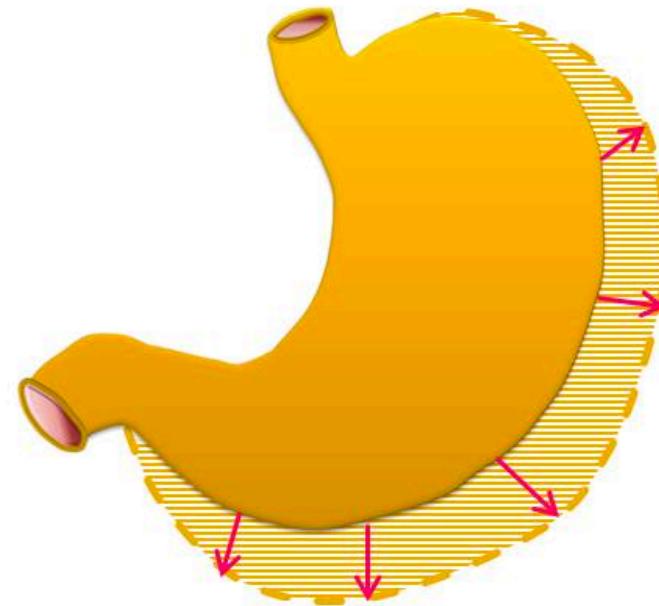
Ghrelin, the Hunger Hormone

Stomach Empty



↑ Ghrelin = ↑ Appetite

Stomach Full

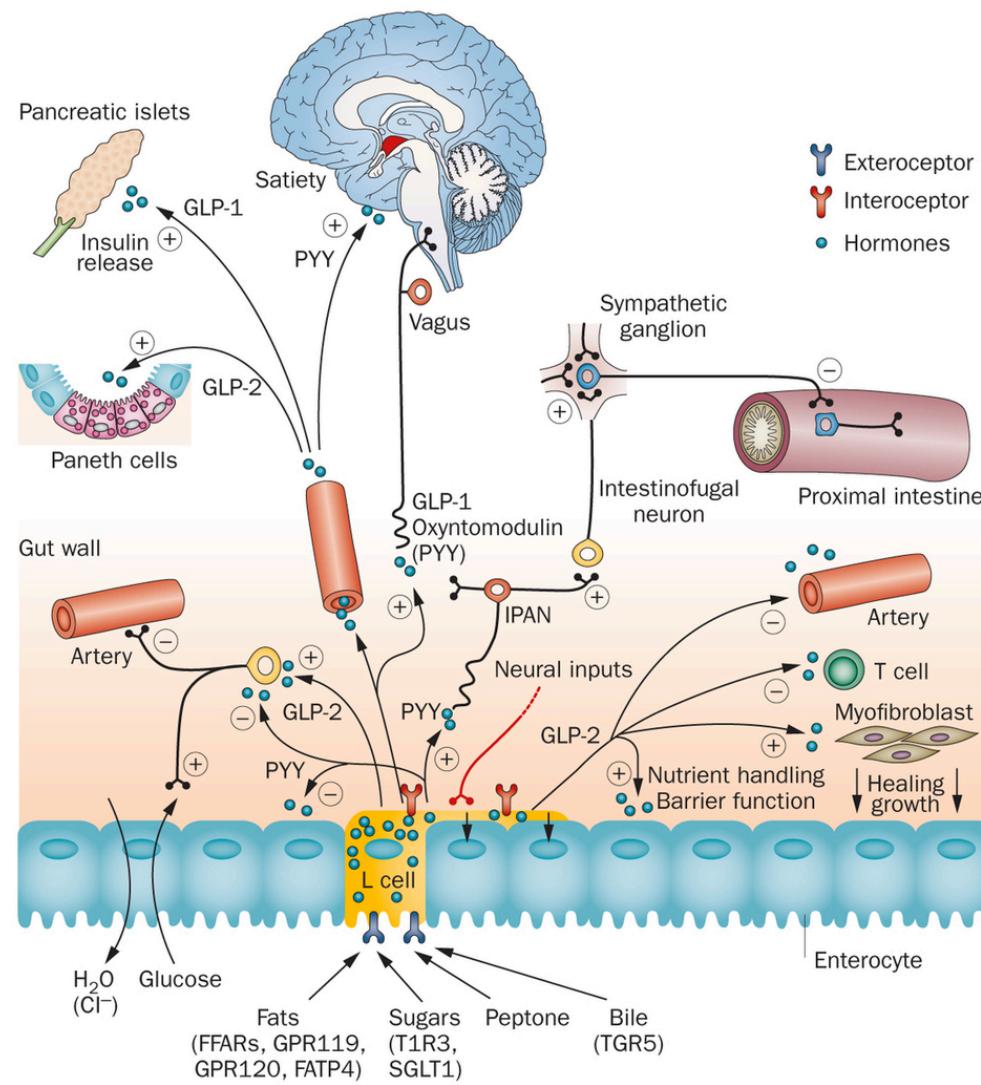


↓ Ghrelin = ↓ Appetite

Ghrelin Summary

Where is it made?	Protein	
What causes its release?	Less Stomach Stretch	
What are its receptors?	GHSR (Gq-GPCR)	AgRP Neurons
What tissues does it affect?	Brain	Inhibits AgRP-> Increased Food Intake
How does it get turned off?	Receptor desensitization, reduced BBB transport, food intake -> stomach stretch	

PYY



PYY Summary

Where is it made?	PYY	
What causes its release?	Nutrients in Colon	
What are its receptors?	Y1R	AgRP/POMC Neurons
What tissues does it affect?	Brain	Increased Food Intake
	GI Tract	Smooth Muscle Contraction (GI Motility)
How does it get turned off?	Receptor desensitization, food moves out of GI	

Obesity and the BBB

- Leptin, Ghrelin and Insulin transport is reduced.
- PYY and Adrenaline permeability is not reduced

Monogenic Forms of Obesity

Gene	Function	Incidence
<i>LEP</i>	Leptin -> Reduces Appetite	Rare
<i>LEPR</i>	Leptin Receptor	2-5% of obese individuals
<i>POMC</i>	MSH/ACTH	Rare
<i>MC4R</i>	MSH Receptor	2-5% of obese individuals
<i>BDNF</i>	Downstream of MC4R	Rare
<i>NTRK2</i>	BDNF Receptor	Rare

How could a leptin deficient patient be treated that might be different from how a idiopathically obese patient is treated?

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