Endocrine Pancreas: Histology and Physiology

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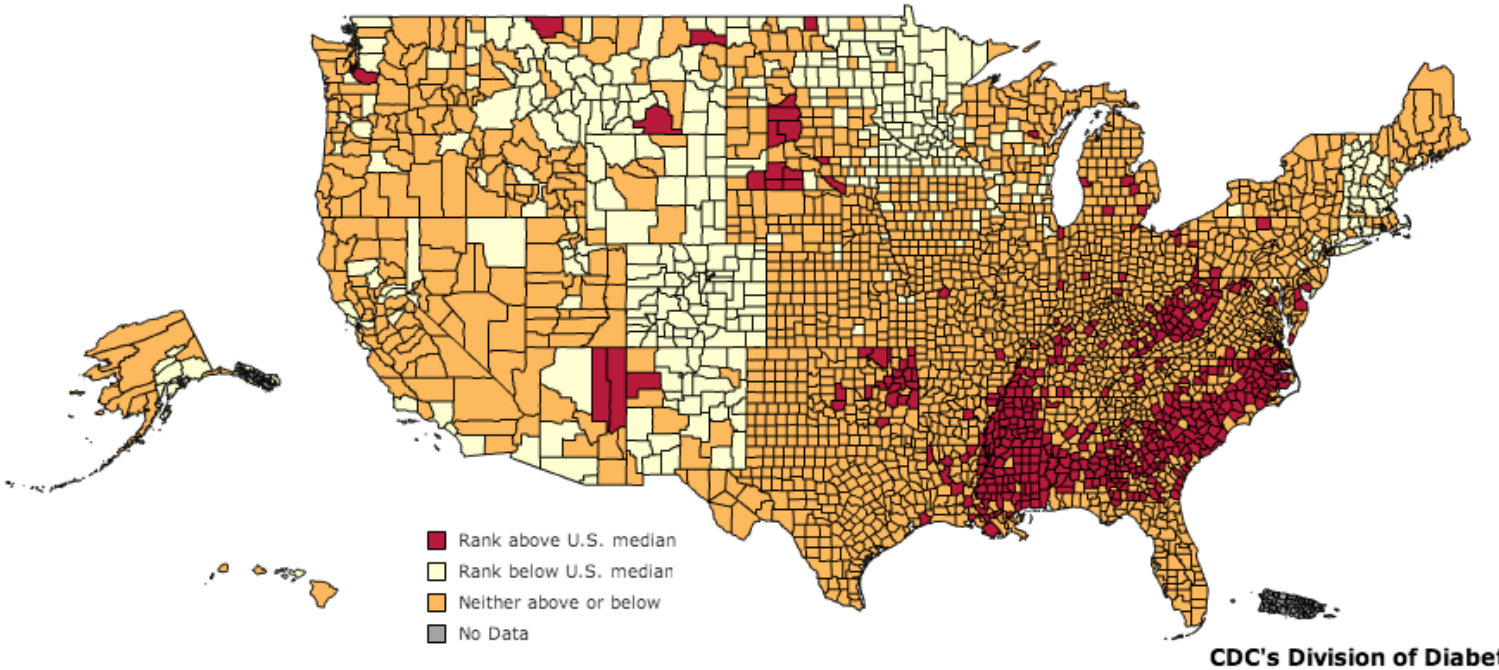
Learning Objectives

1. Name the cell types of the Islets of Langerhans and name the hormones secreted by them.
2. Describe the main targets and functions of glucagon.
3. List the major factors that stimulate or inhibit glucagon and insulin.
4. Describe the important physiological roles of insulin.
5. List the major actions of insulin in muscle, adipose tissue, and liver.
6. Explain briefly the mechanism of glucose uptake into the muscle.
7. Name the tissues in which insulin facilitates glucose uptake and those in which insulin does not facilitate glucose uptake.
8. List the major factors that stimulate or inhibit insulin secretion.
9. Draw an oral glucose tolerance test (oGTT) (glucose, insulin, and glucagon levels) and and describe what is occurring and why. Explain how the two hormones act to promote glucose homeostasis in the plasma.
10. State which nutrient storages are preferably used for short-term regulation of energy metabolism if no nutrients are available from the GI tract.
11. 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.
12. 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.

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



CDC, 2010

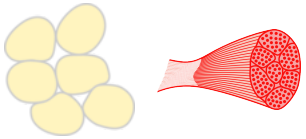
GLUCOSE REGULATION

Regulation of Blood Glucose Levels

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

Glucose Production

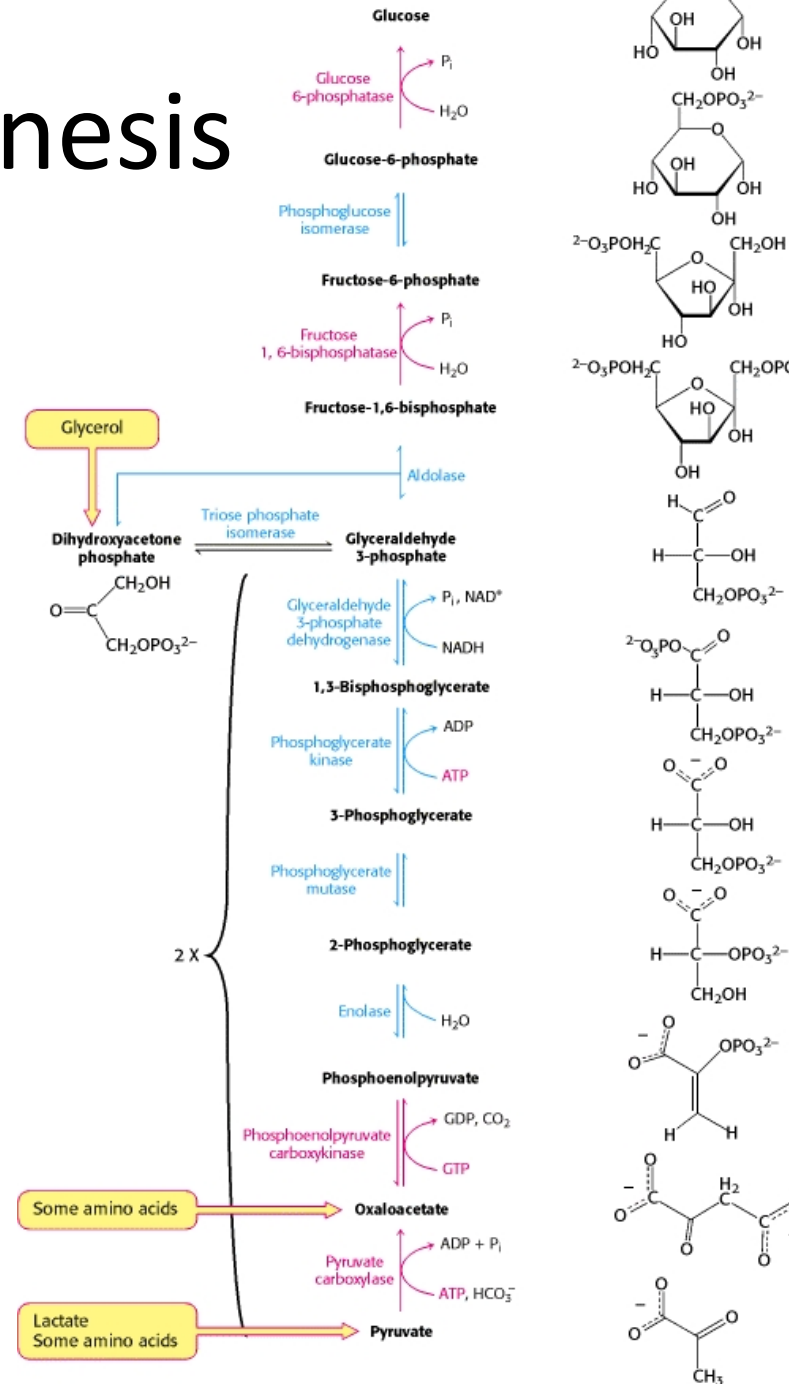
Glucose Uptake



Glucose Storage
and Utilization

Gluconeogenesis

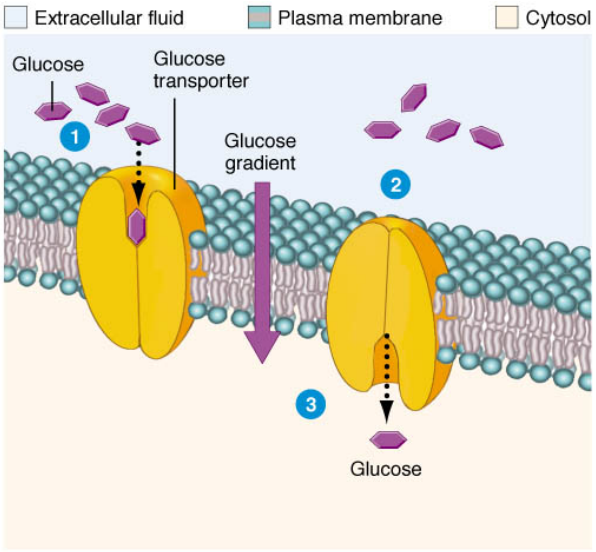
- Primarily occurs in the liver
- Uses amino acids and fatty acids to generate glucose



Glucose Uptake

Passive Glucose Uptake

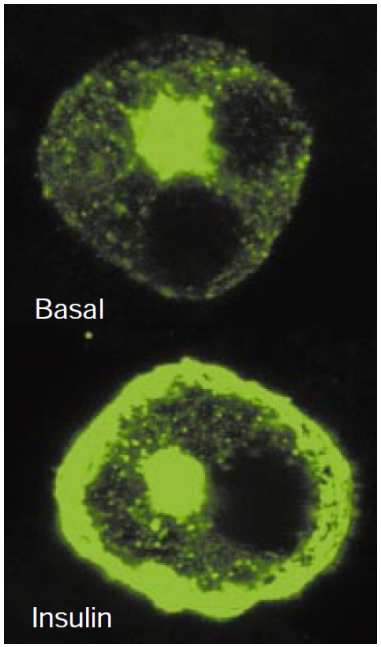
- Brain
- Liver
- Kidneys



From http://classroom.sdmesa.edu/eschmid/Chapter3-Zoo145.htm

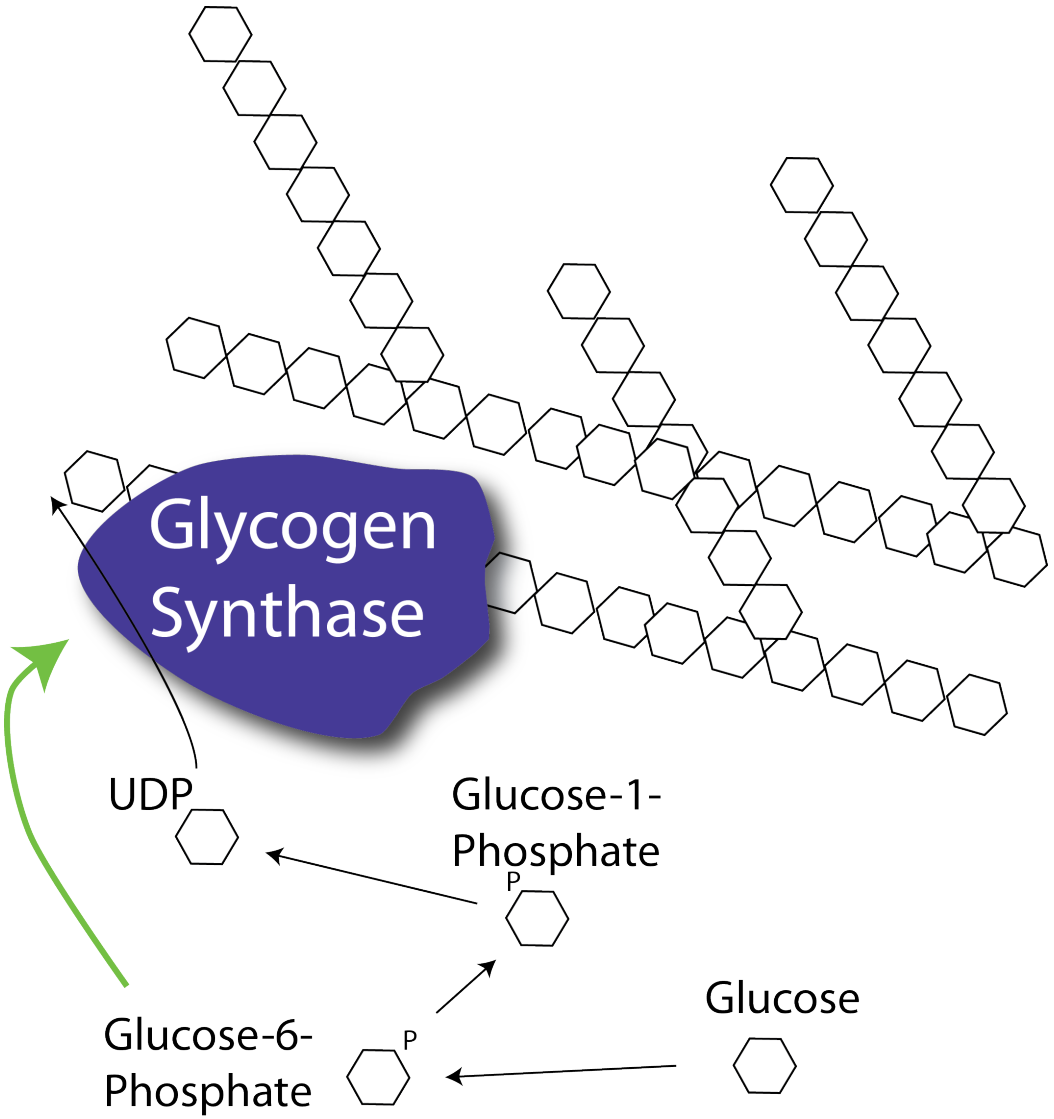
Stimulated Glucose Uptake

- Fat
- Muscle

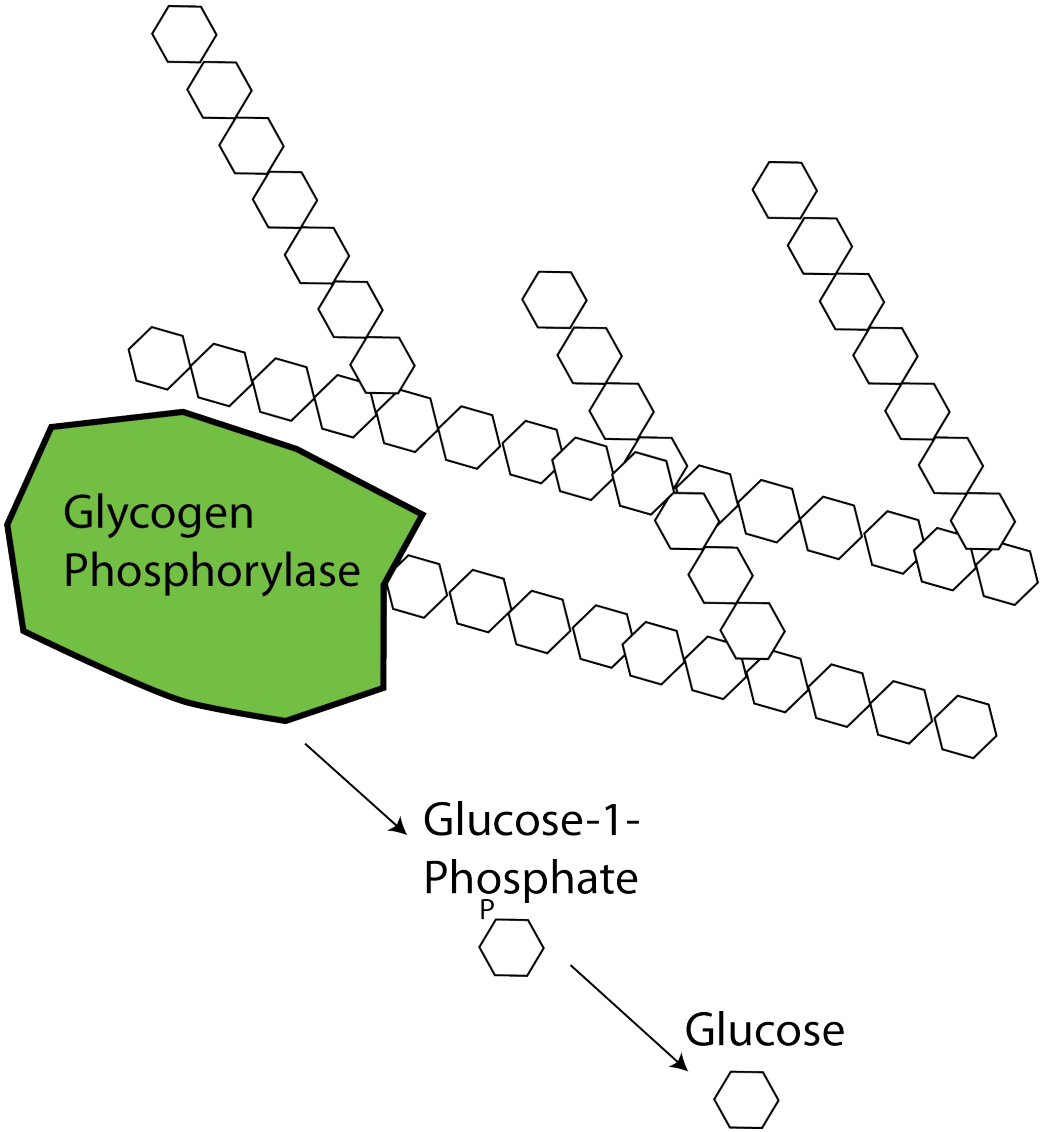


GLUT4-eGFP
From Saltiel and Kahn (2001) Nature 414:799-806

Glycogenesis



Glycogenolysis



Order of Fuel Utilization/Storage

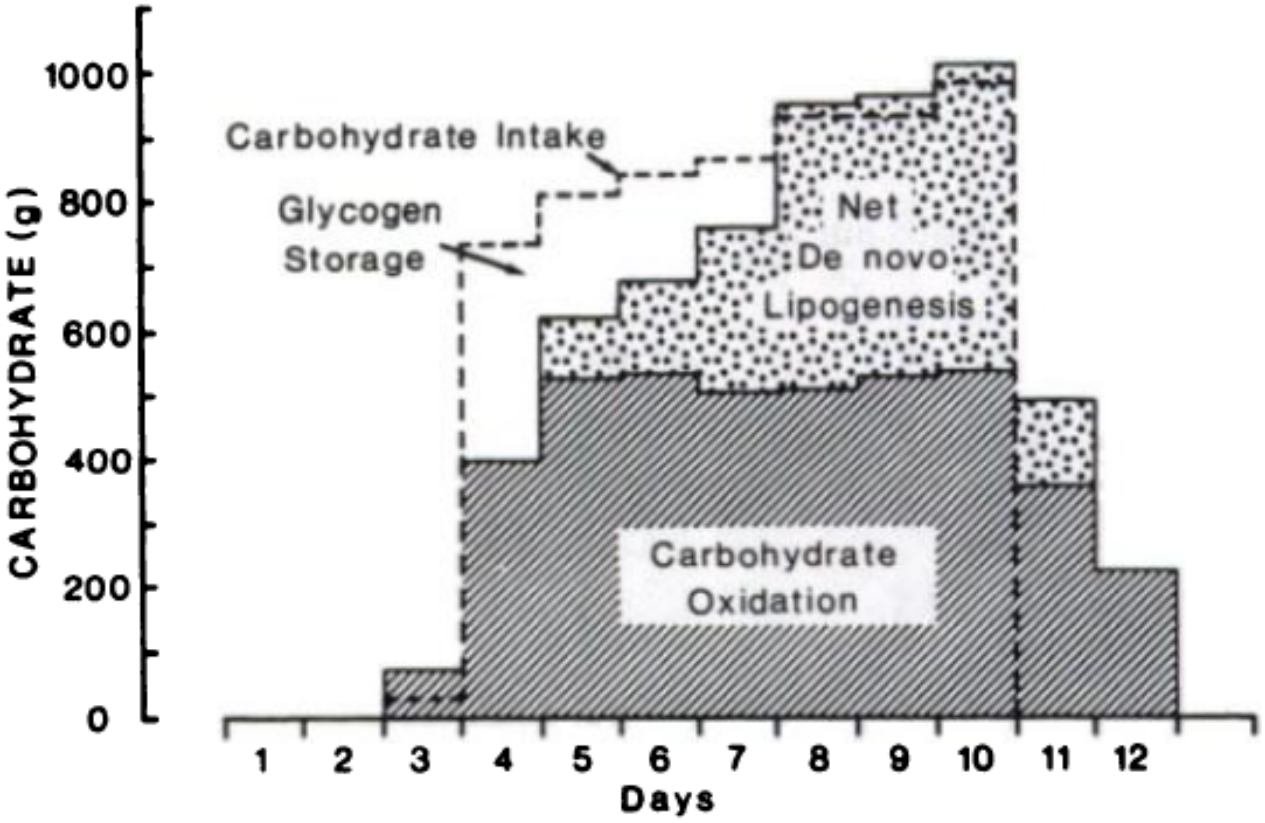
Energy Production (Fasting)

- Creatine phosphate
- Glycolysis
- Glycogenesis
- Gluconeogenesis
- Fat Oxidation

Fuel Storage (Fed)

- Glucose uptake/oxidation
- Glycogenesis
- Lipogenesis

Responses to Overfeeding



K. J. Acheson, Y. Schutz, T. Bessard, K. Anantharaman, J. P. Flatt, E. Jequier, Glycoprotein storage capacity and de novo lipogenesis during massive carbohydrate overfeeding in man **Am. J. Clin. Nutr.** 48, 240–247 (1988).

MECHANISMS TO REDUCE BLOOD GLUCOSE

The Discovery of Insulin

The Discovery of Insulin

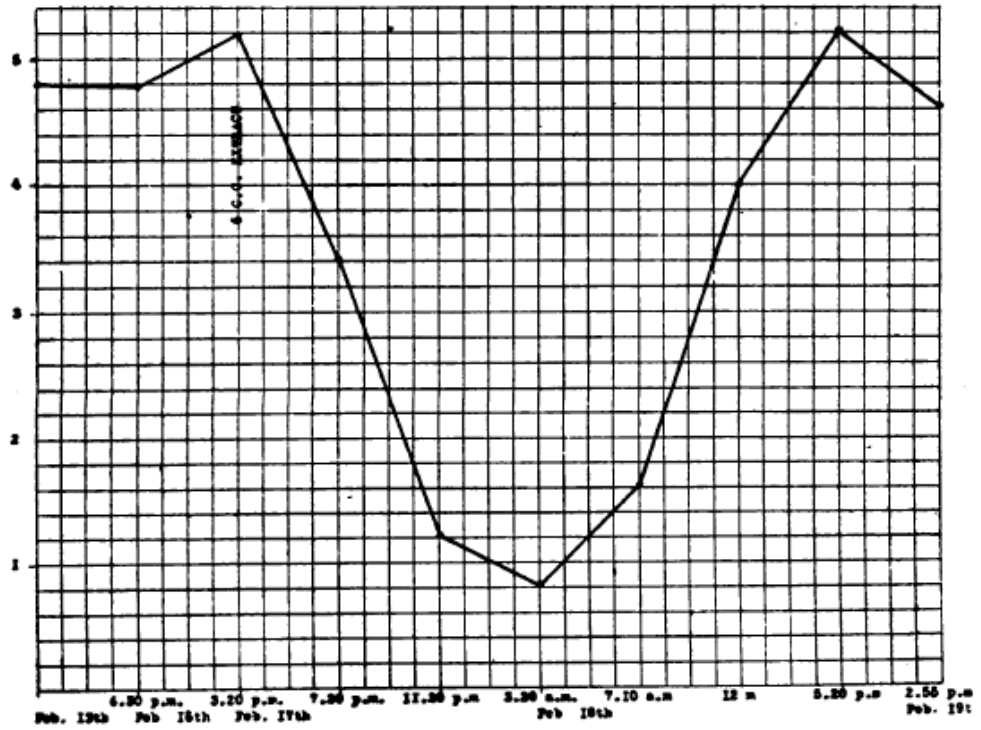
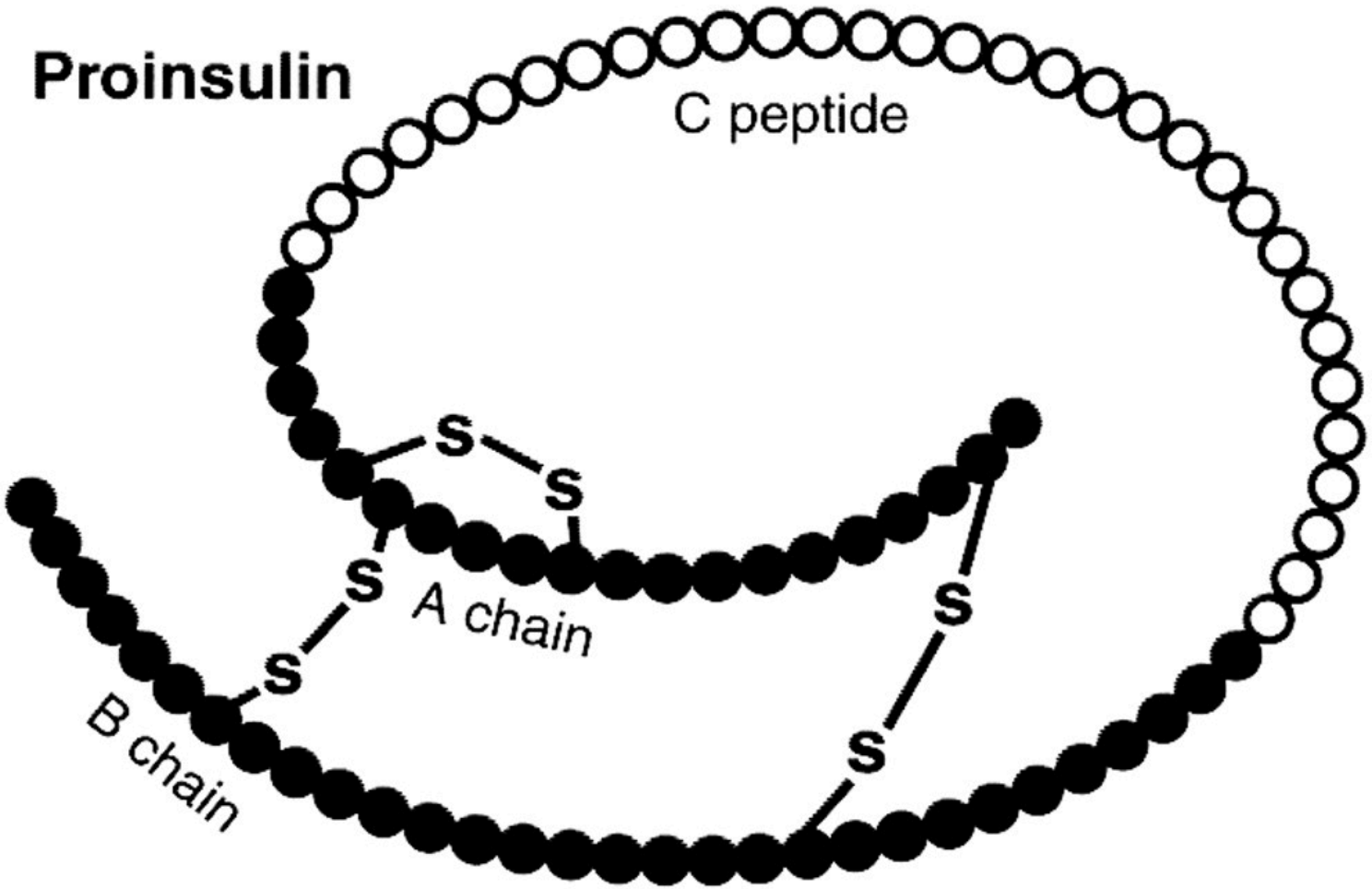


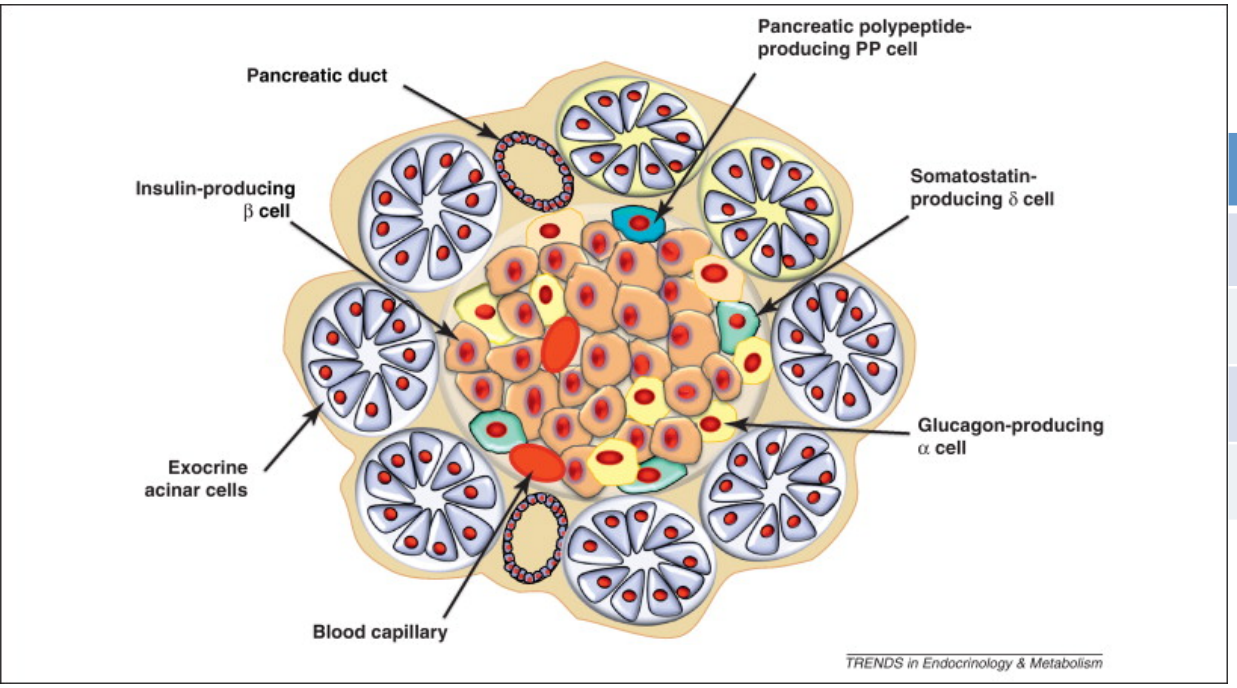
CHART III.—*Effect of one injection of extract on Blood Sugar (mgs. per c.c.e=tenth per cent)*

Banting *et al*. 1922

Insulin Structure



Pancreatic Anatomy

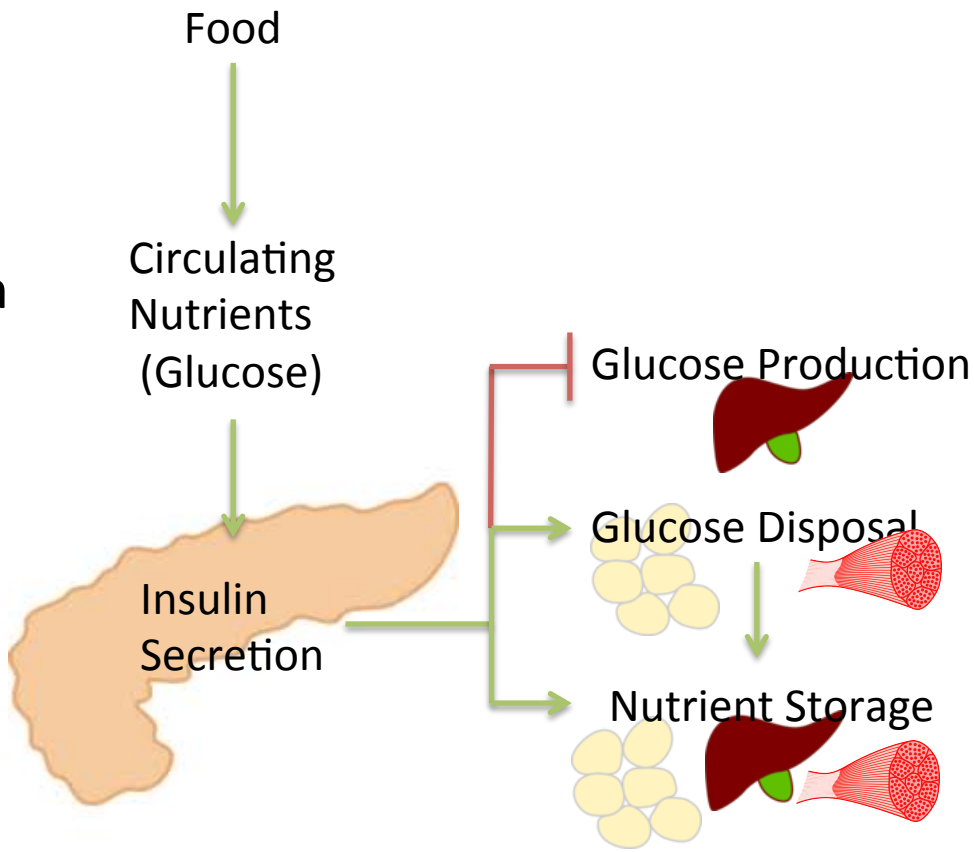


Cell	Hormone
Beta Cells	Insulin
Alpha Cells	Glucagon
Delta Cells	Somatostatin
Ductal Cells	Exocrine

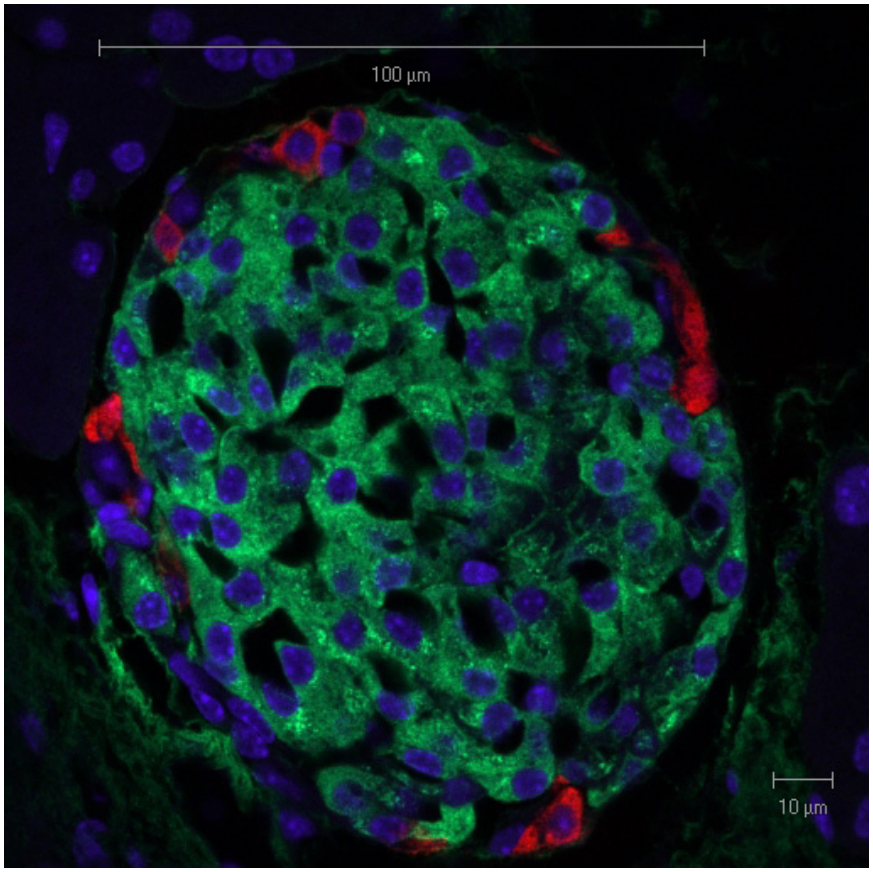
S. Efrat, H. A. Russ, Making β cells from adult tissues, Trends Endocrinol. Metab. 23, 278–285 (2012).

Functions of Insulin

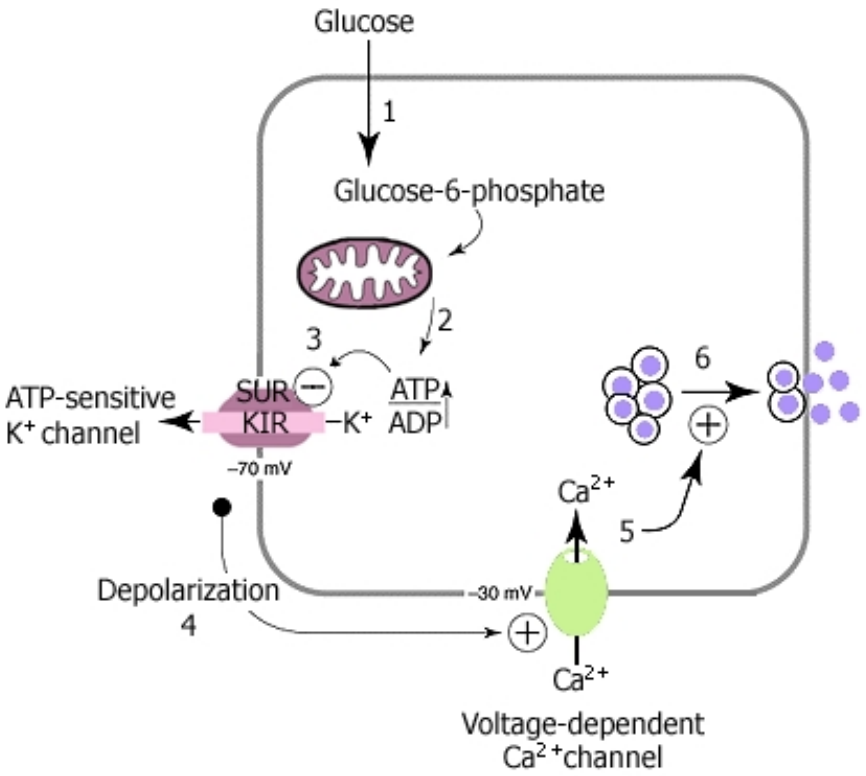
1. Promotes the uptake of glucose from the blood into muscle and adipose tissue.
2. Enhances the synthesis of glycogen and triglycerides in liver, adipose and muscle.
3. Insulin inhibits gluconeogenesis, or the production of glucose from non-glucose precursors such as amino acids and lipids.
4. Promote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



Insulin Secretion

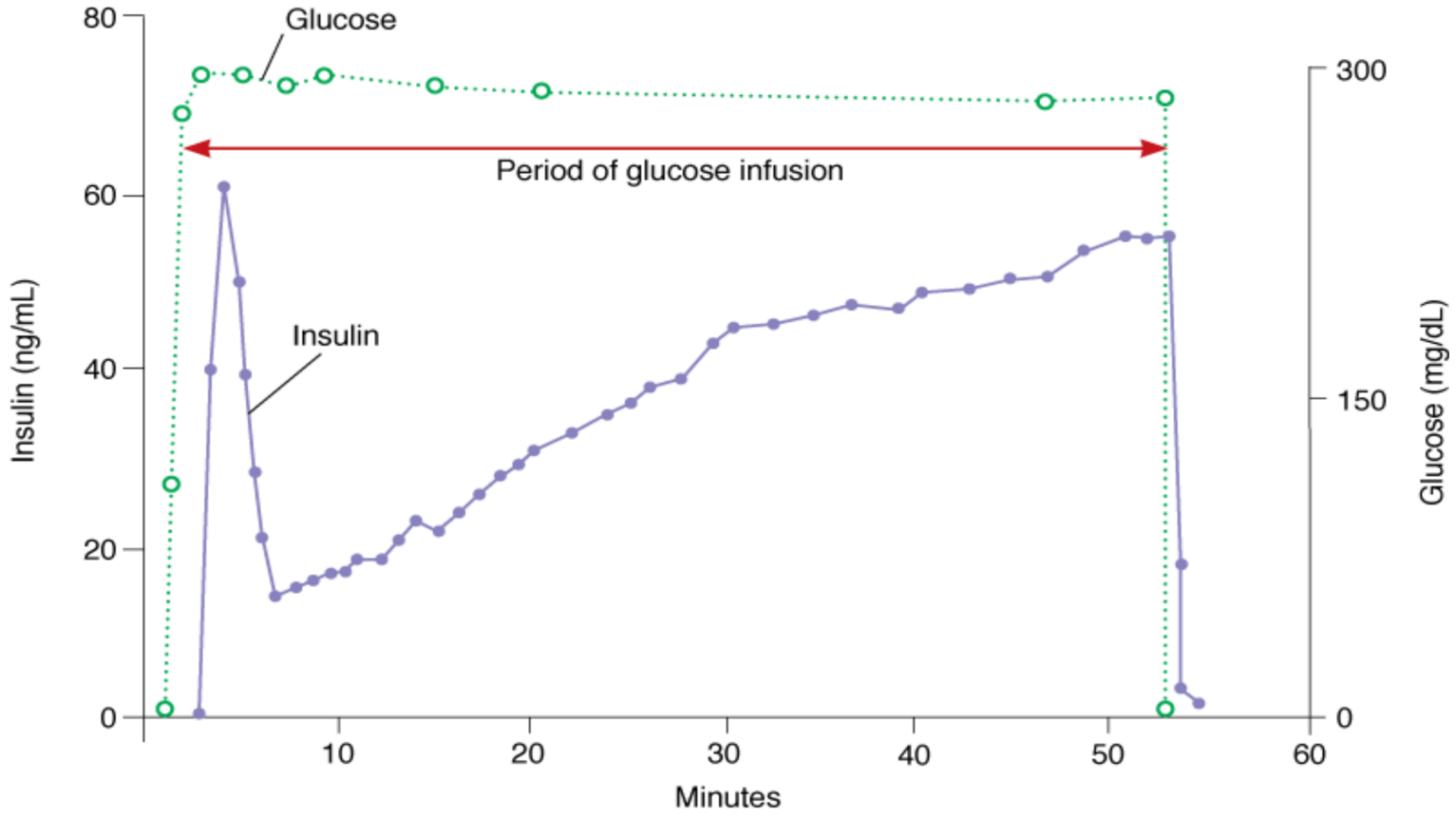


Pancreatic Islet with Glucagon and Insulin Staining From Solilema Lab (http://en.wikipedia.org/wiki/Islets_of_Langerhans)



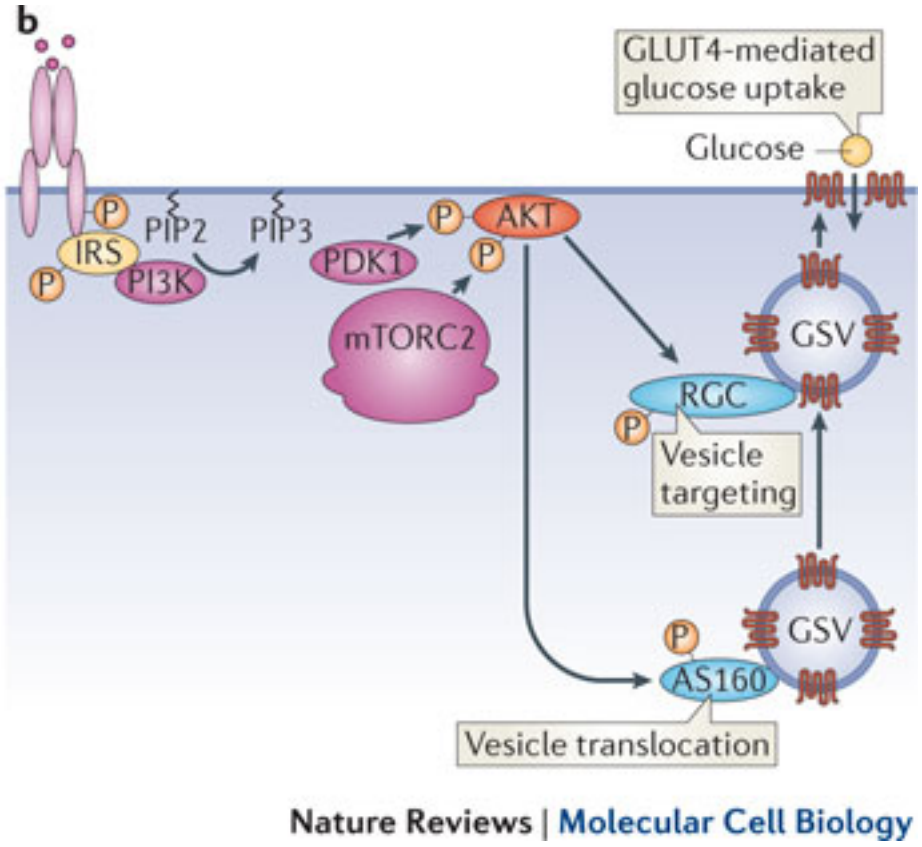
Suckale and Solimena (2008) Frontiers in bioscience 13:7156-71

Biphasic Insulin Secretion



Source: Gardner DG, Shoback D: *Greenspan's Basic & Clinical Endocrinology, 9th Edition:* www.accessmedicine.com

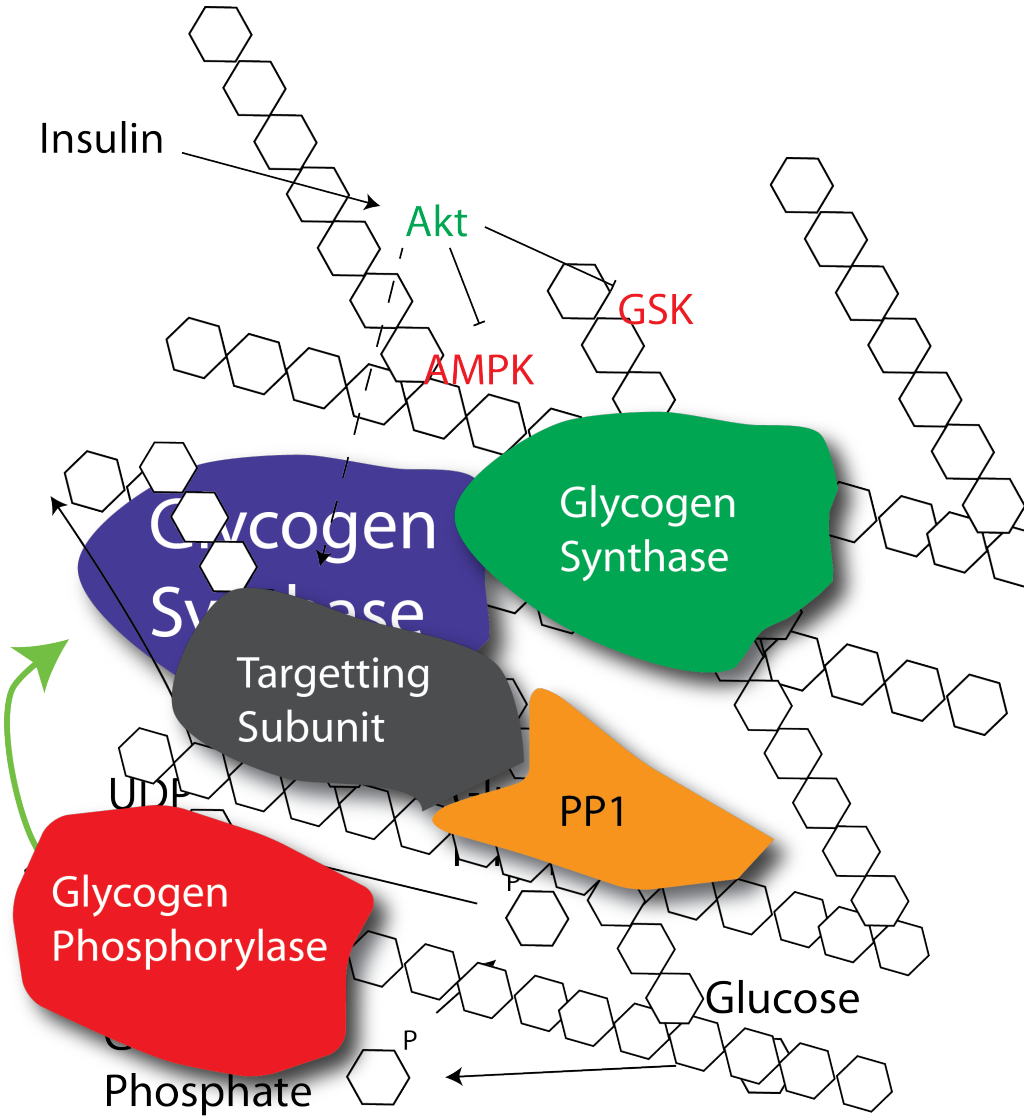
Insulin Stimulated GLUT4 Translocation



Leto and Saltiel Nat. Rev. MCB (2012)

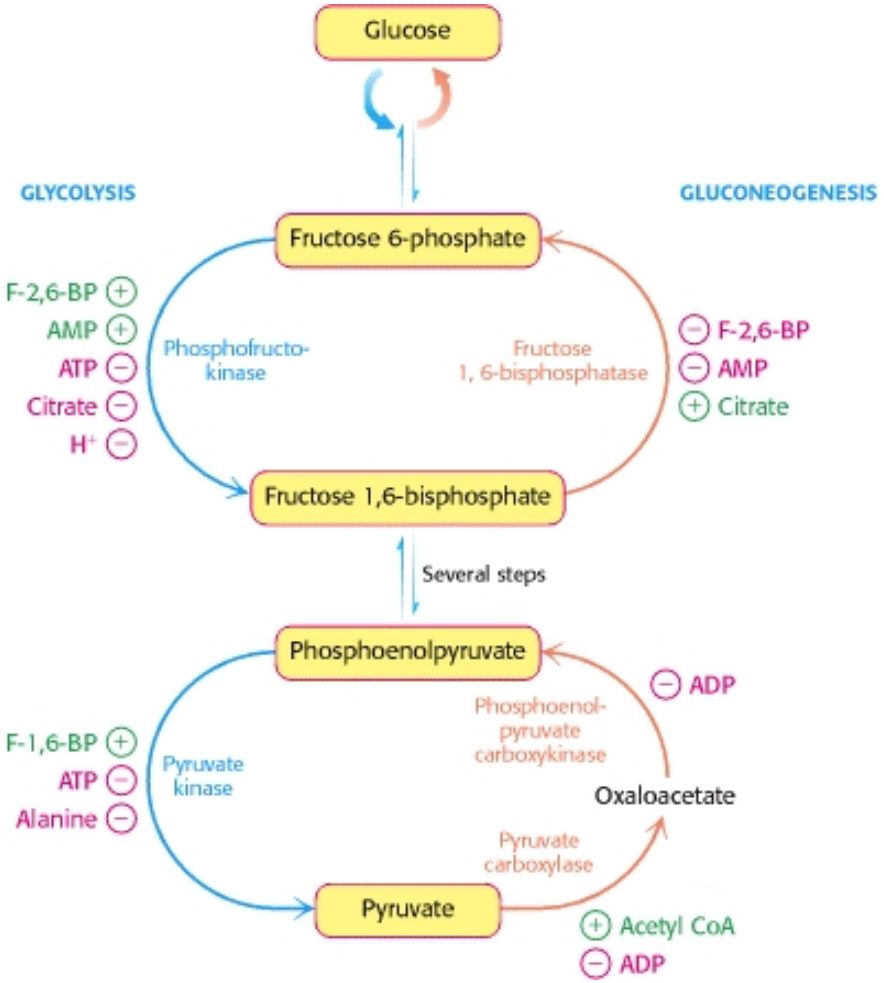
How does insulin promote glycogenesis?

- Allosteric activation
- Protein dephosphorylation

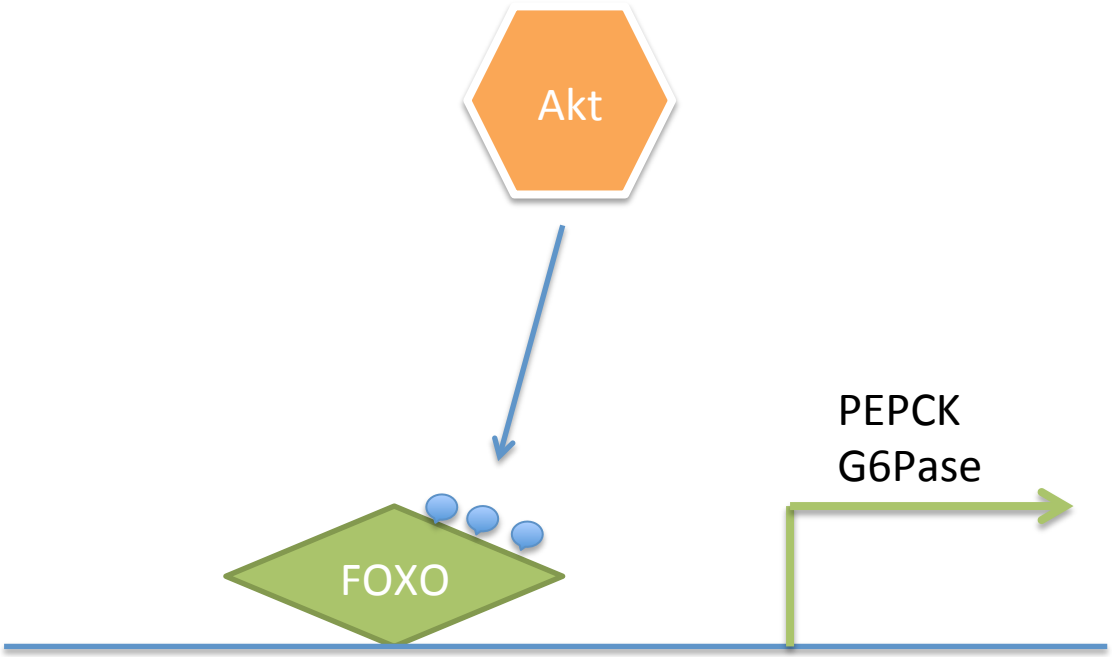


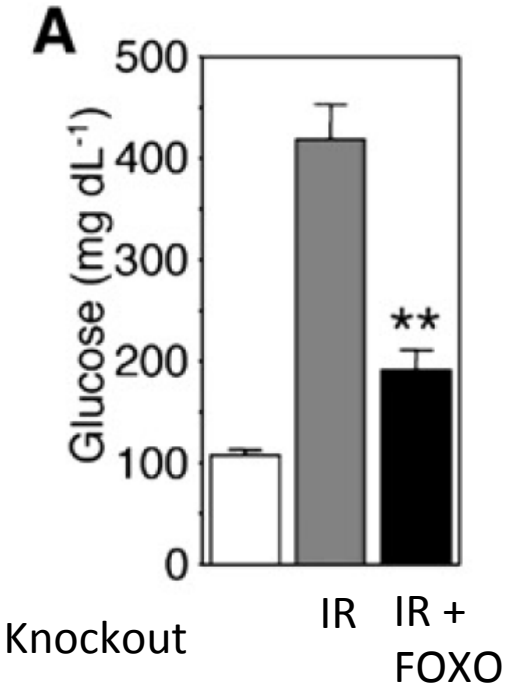
How does insulin reduce gluconeogenesis

- 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



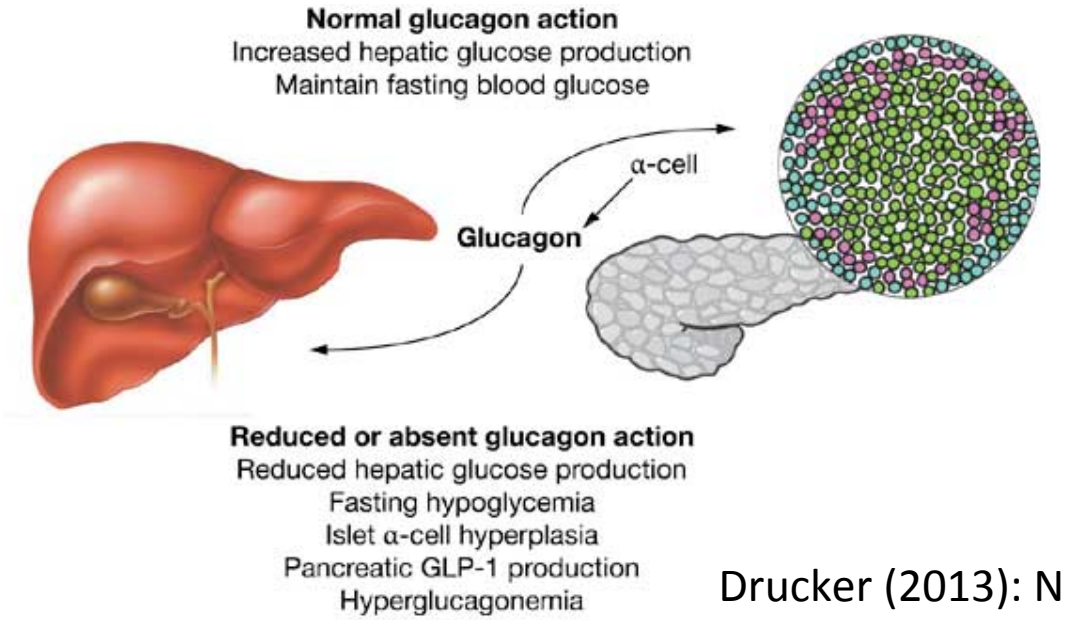


Matsumoto *et al.* (2007) Cell Metab. 6:208-16

MECHANISMS TO INCREASE BLOOD GLUCOSE

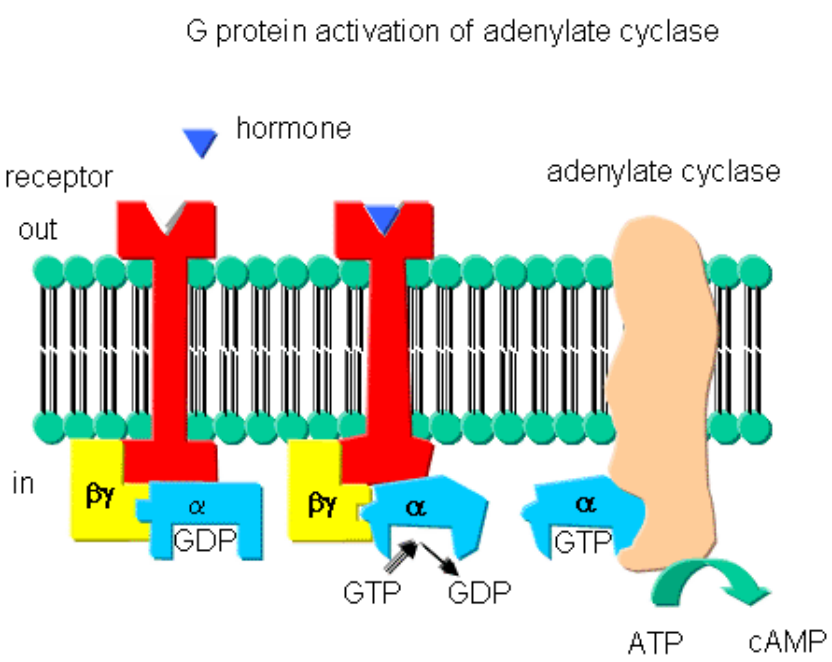
Glucagon Secretion

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

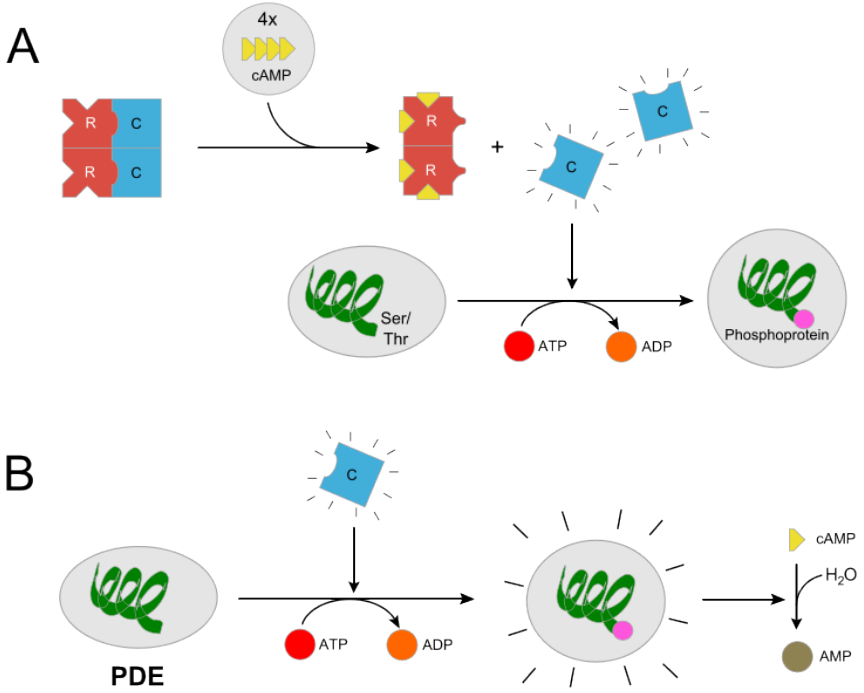


Drucker (2013): Nat Rev Endo 1:22-31

Glucagon Signaling

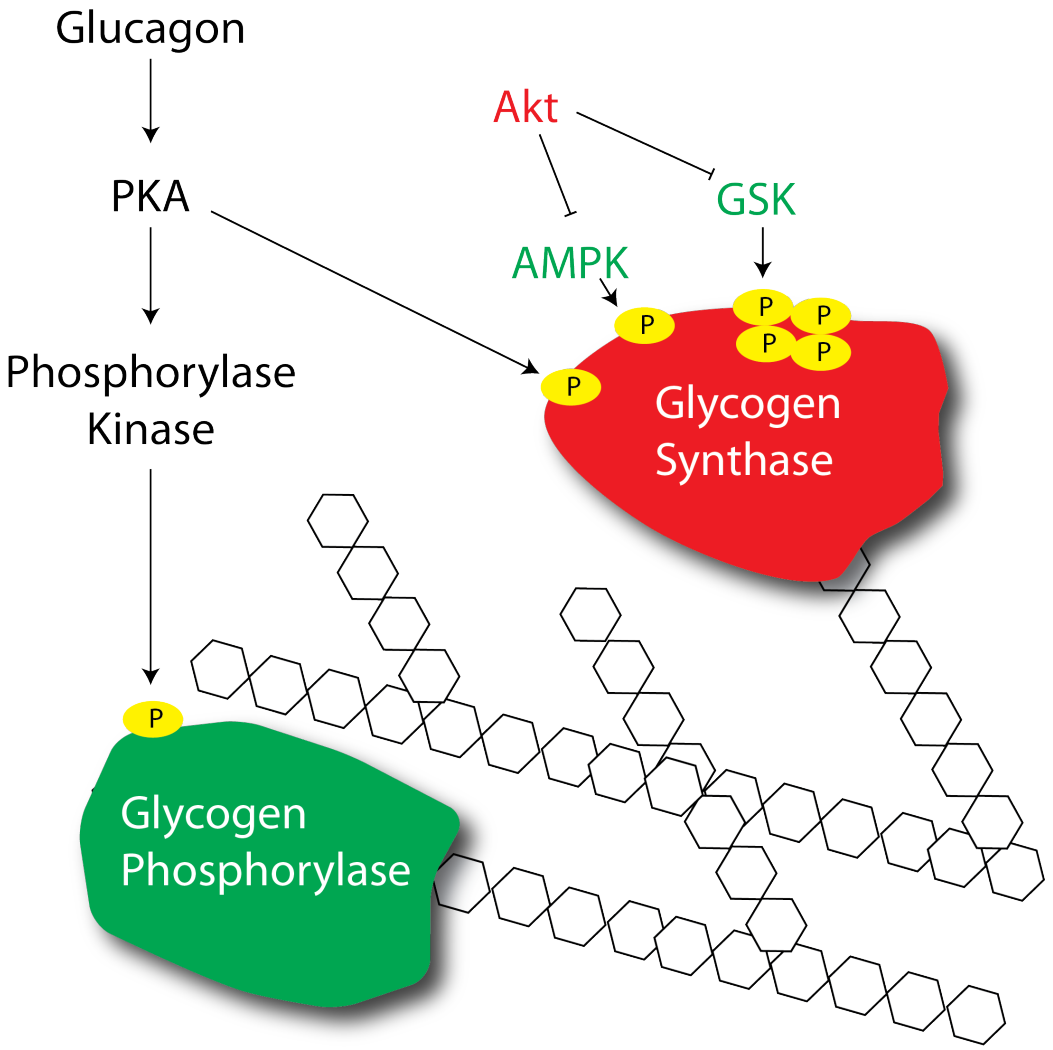


From http://biowiki.ucdavis.edu/Biochemistry/Signal_Transduction/Signal_Transduction_at_Cell_Membranes%3A_Protein_Kinases_and_Phosphotases

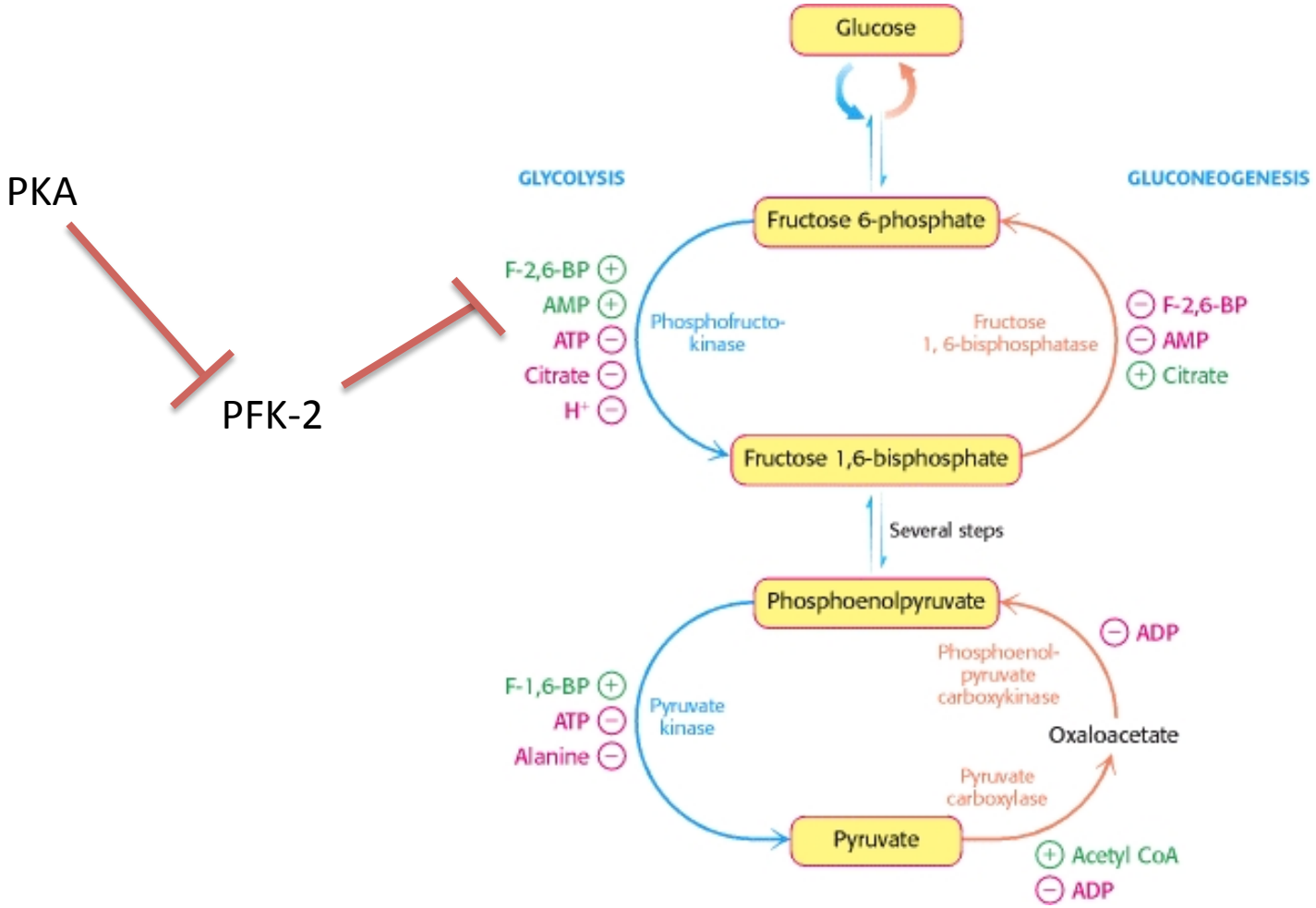


From http://en.wikipedia.org/wiki/Protein_kinase_A

How does glucagon regulate glycogenolysis?



How does glucagon promote gluconeogenesis?



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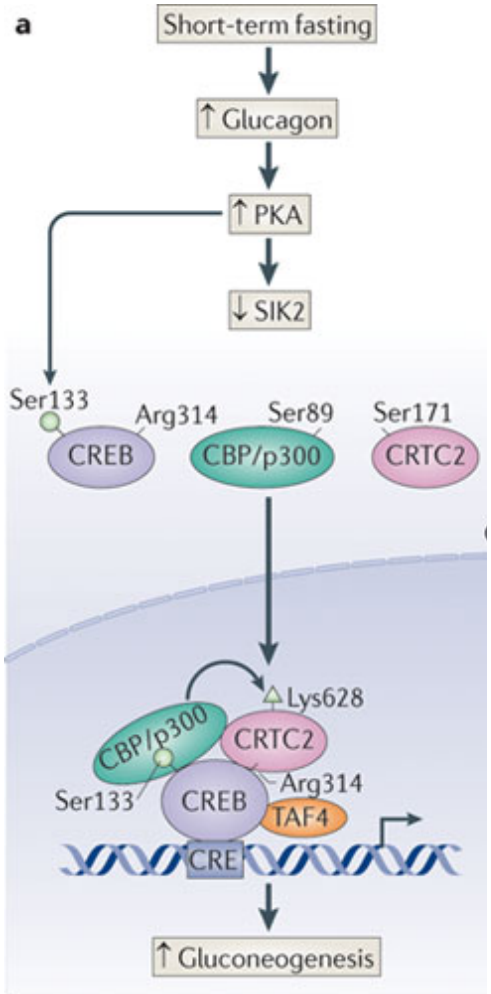


More G6Pase, FBPase and PEPCK

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

Glucagon and Insulin Clearance

- Half lives in blood:
  - Insulin: about 5 minutes
  - Glucagon: about 5-10 minutes

  - Insulin degradation:
    - About 80 % in liver and kidney
    - Rest in other tissues (target tissues and non-target tissues)
    - Insulinase (insulin protease)
      - may act when insulin-insulin receptor is internalized
      - possible site of drugs to prolong insulin life and make limited supply last longer

  - Glucagon degradation:
    - Most occurs in the liver; perhipheral concentrations of Gg are low

Summary of Insulin and Glucagon

Insulin

- Blocks gluconeogenesis
- Blocks glycogenolysis
- Promotes glycogenesis
- Enhances glucose uptake
- Promotes lipid storage

Glucagon

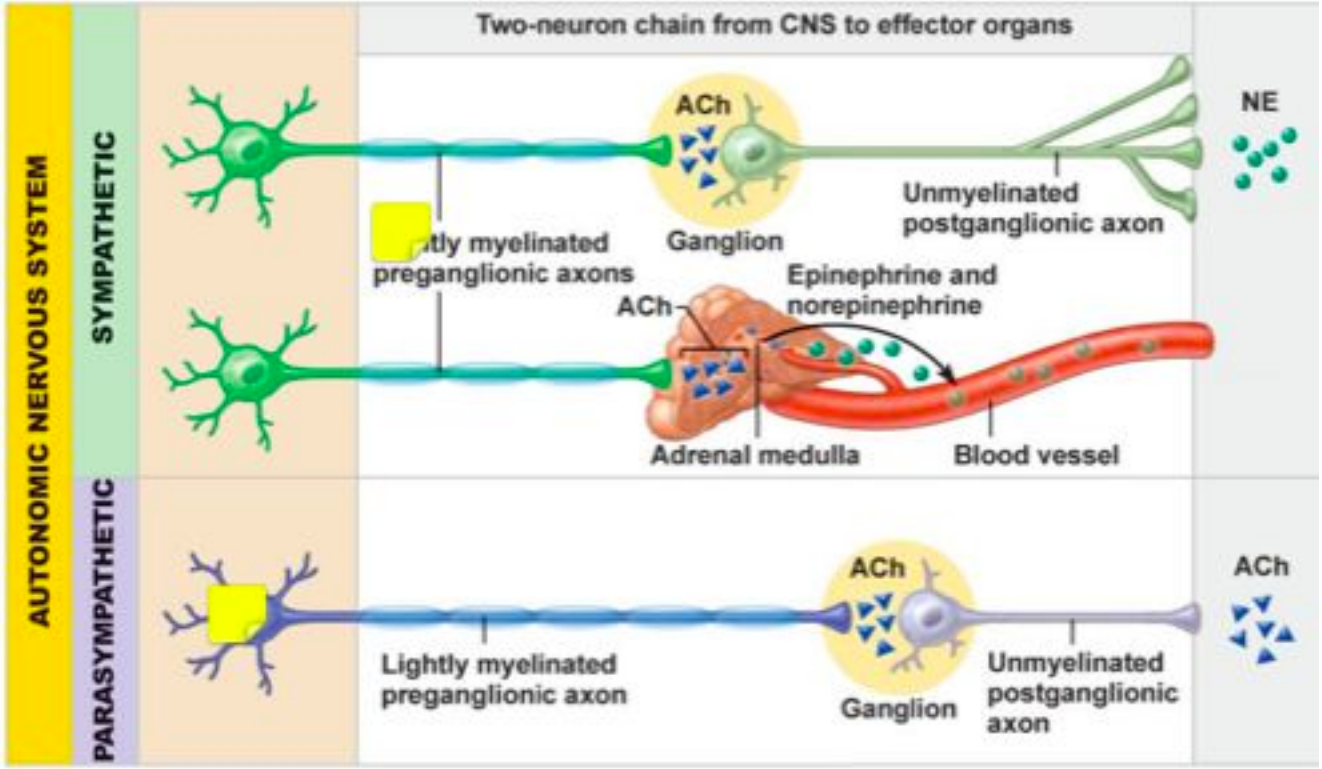
- Promotes gluconeogenesis
- Promotes glycolysis
- Blocks glycogenesis

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

SECONDARY REGULATION OF GLUCOSE METABOLISM

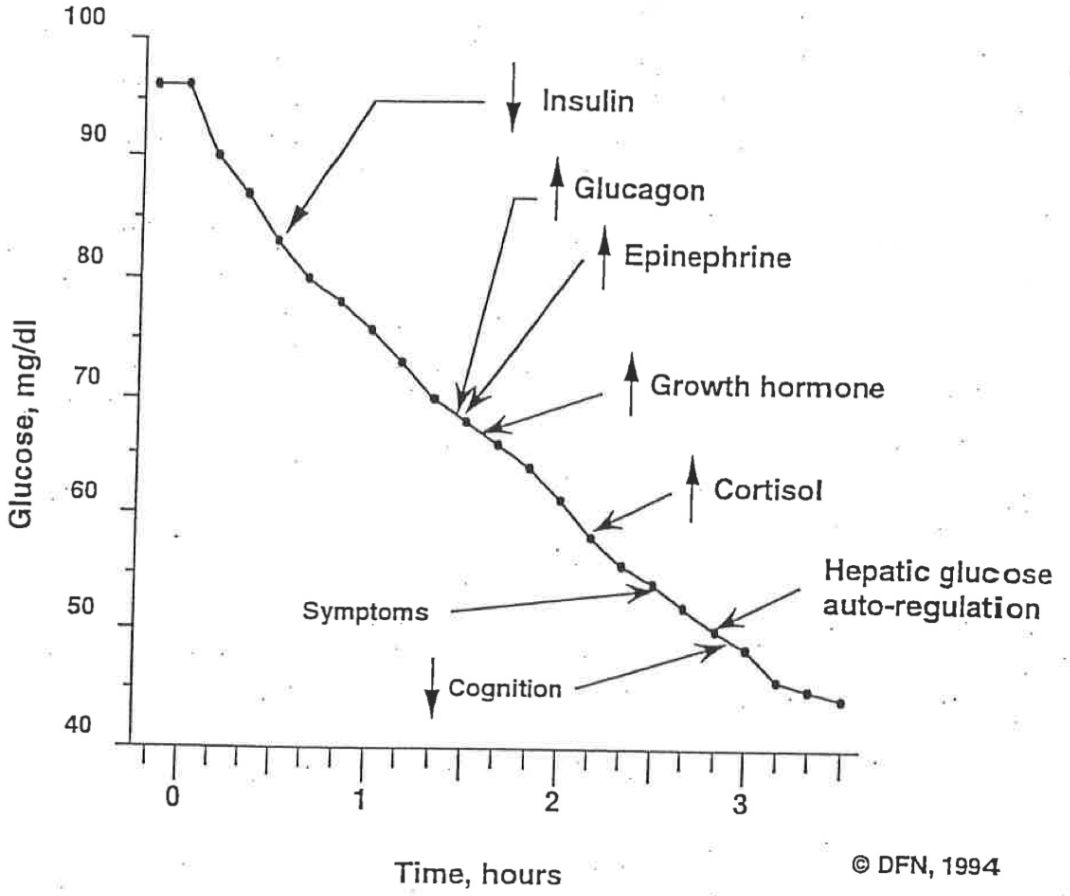
Nervous Control of Pancreatic Function



More Glucagon
Less Insulin

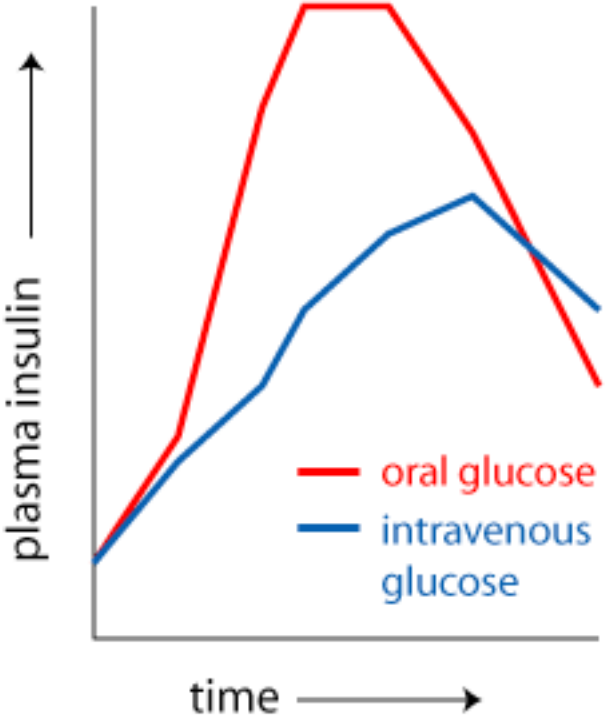
More Insulin
Less Glucagon

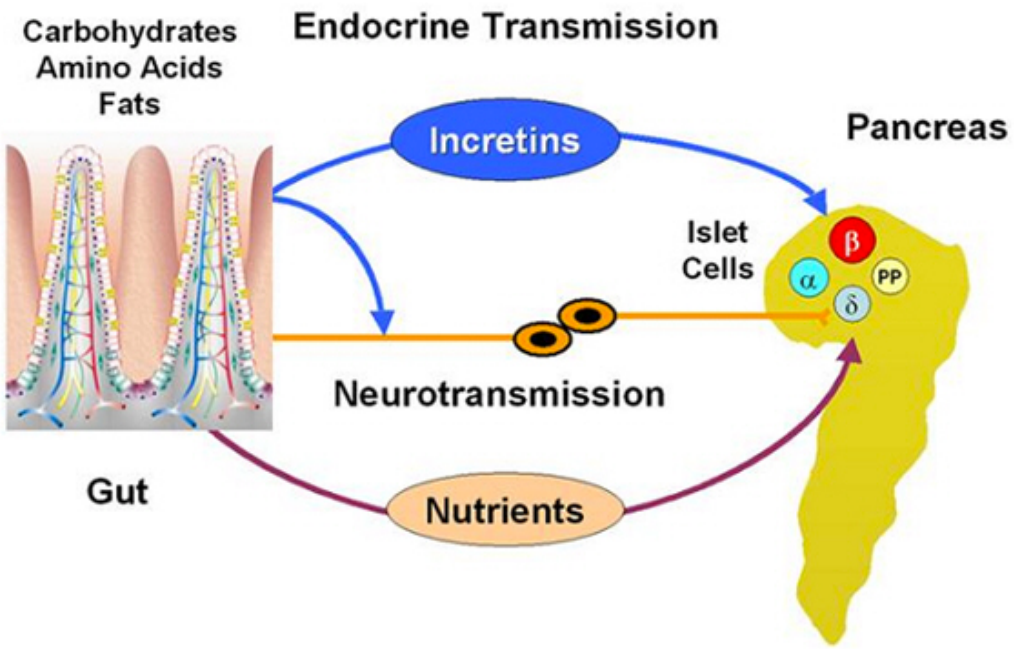
Long Term Glucoregulation



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

Incretins and Secondary Control of Insulin Secretion





GLP1/GIP1 both released from gut

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