As you take your seats

- Get out your clickers
- Set them to channel 22

Endocrine Pancreas: Histology and Physiology

Dave Bridges, PhD
dbridge9@uthsc.edu

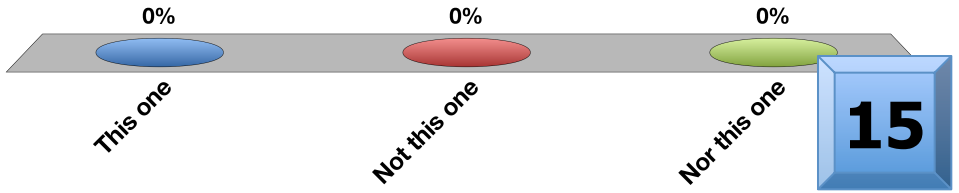
Select “A”

A. This one

B. Not this one

C. Nor this one

Response Counter



What hormone is secreted from the pancreatic alpha cell

A. Insulin
B. Glucagon
C. Somatostatin
D. None of the above

Which tissue exhibits insulin stimulated glucose uptake

A. Brain
B. Liver
C. Adipose
D. Heart
E. All of the above

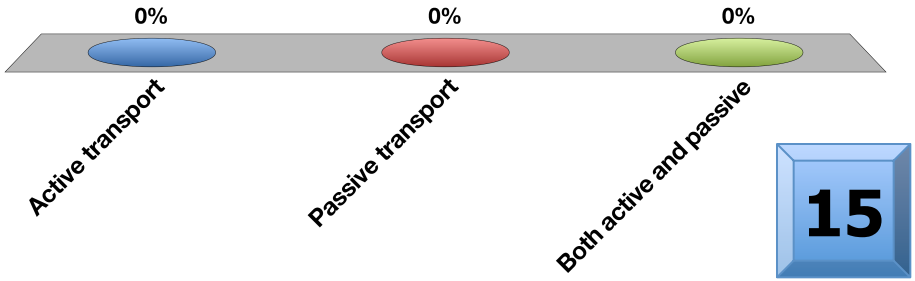
What is the main target tissue for glucagon?

A. Brain
B. Liver
C. Adipose
D. Heart
E. All of the above

Insulin Stimulated Glucose Uptake is

A. Active transport
B. Passive transport
C. Both active and passive

Response Counter



What order are these metabolites used

A. Glycogen, glucose then fat
B. Glucose, glycogen then fat
C. Fat then glycogen then glucose
D. Fat then glucose then glycogen

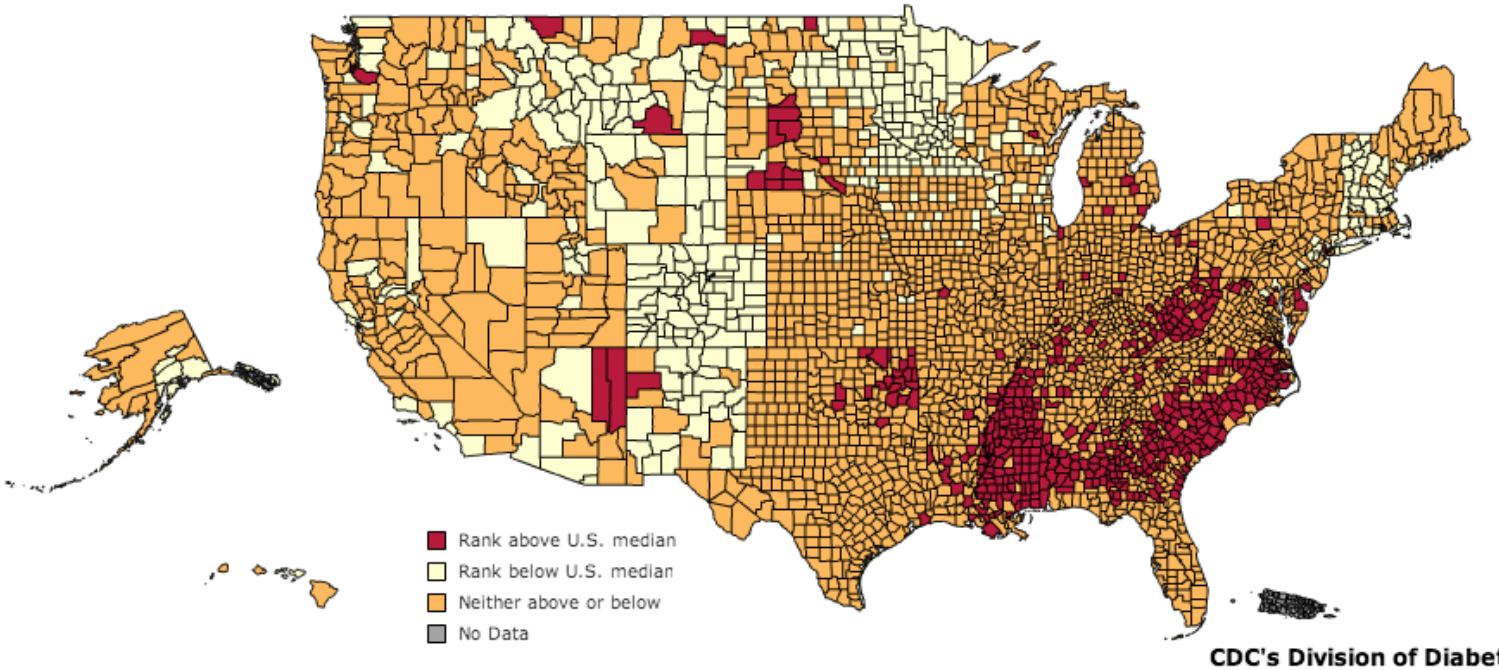
Learning Objectives

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

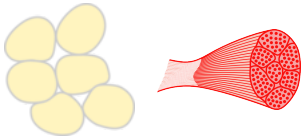
GLUCOSE REGULATION

Regulation of Blood Glucose Levels

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

Glucose Production

Glucose Uptake



Glucose Storage
and Utilization

Consuming carbohydrates

Gluconeogenesis

Glycogenolysis

MAKING MORE GLUCOSE

Gluconeogenesis

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

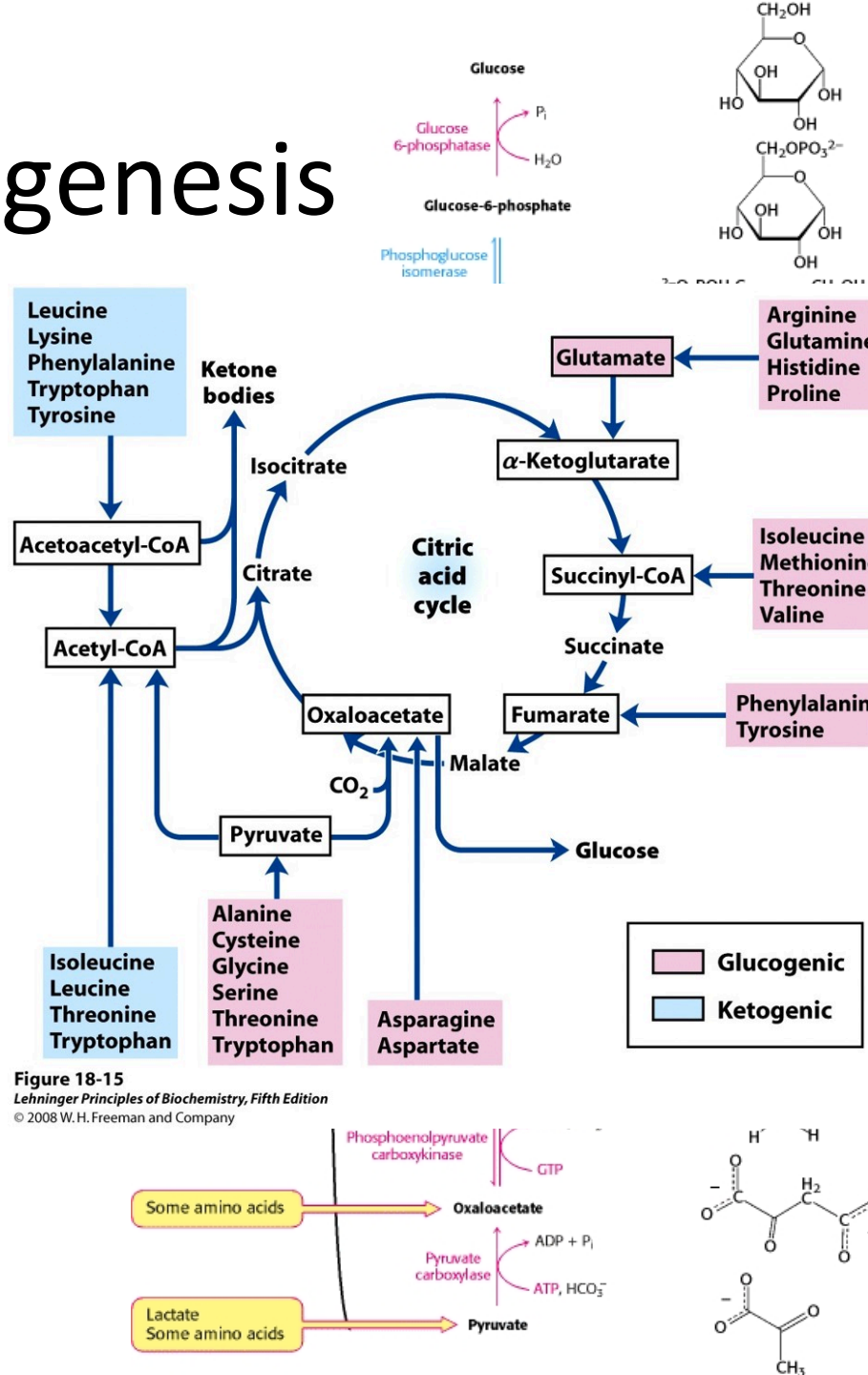
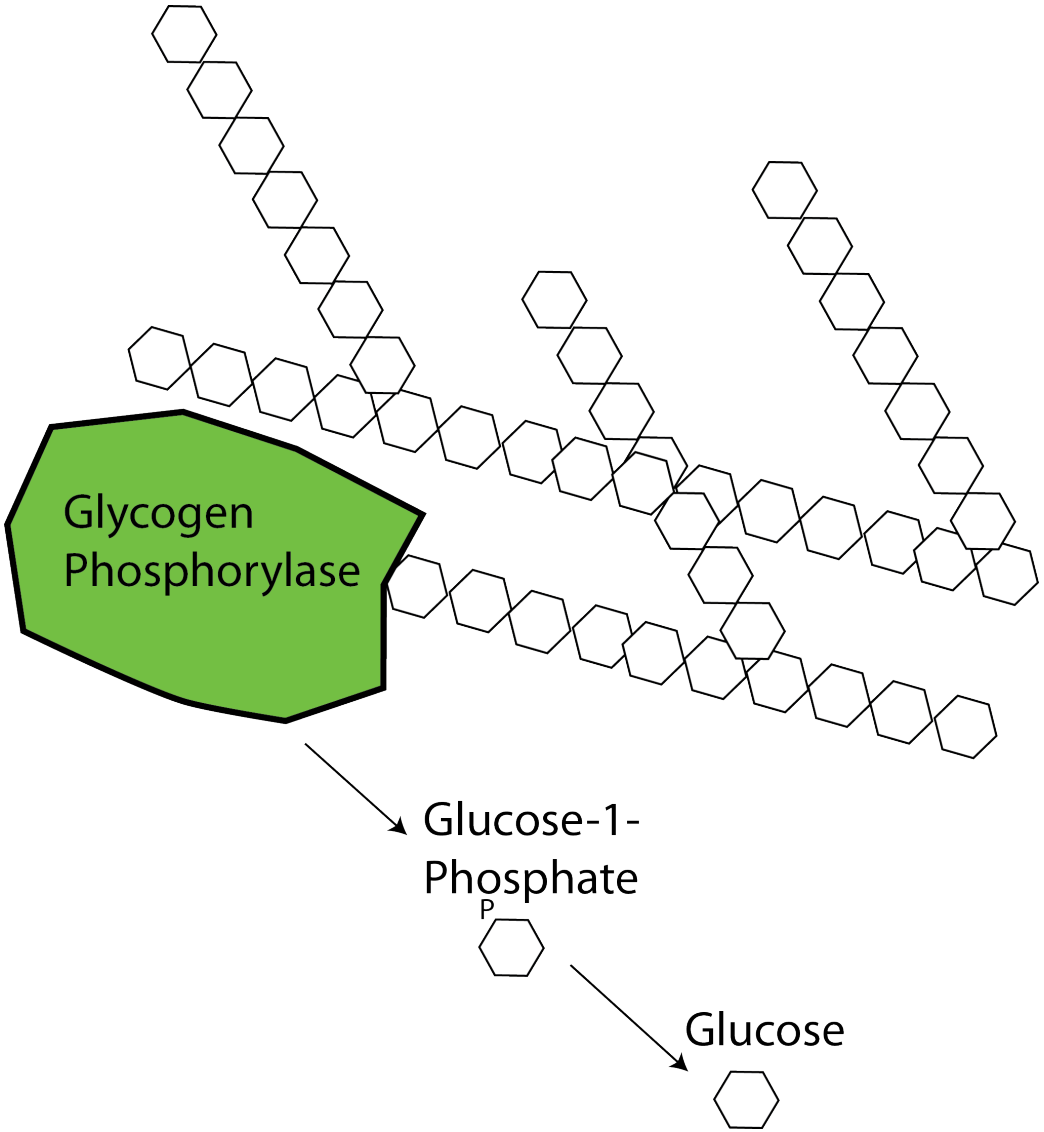


Figure 18-15
Lehninger Principles of Biochemistry, Fifth Edition

Glycogenolysis



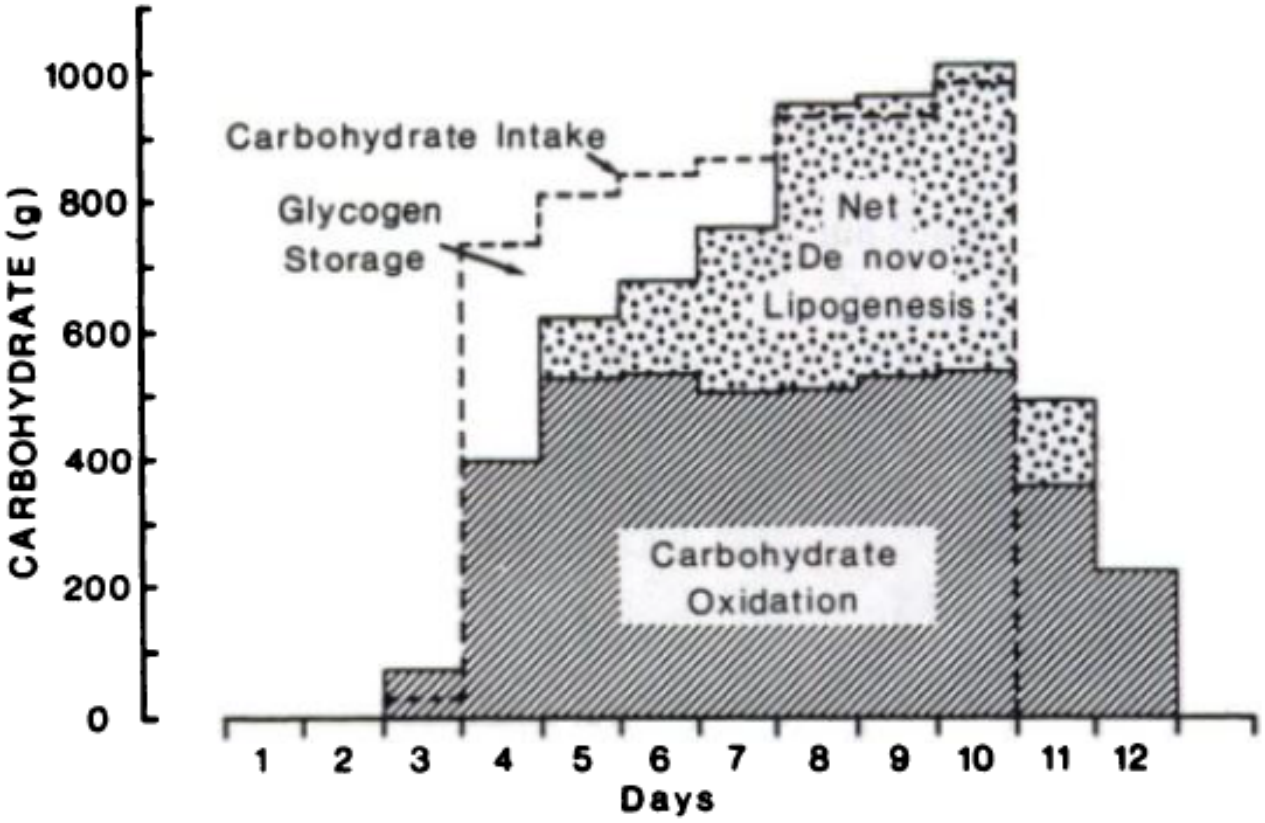
Glucose Oxidation

Glucose uptake

Glycogen and Lipid Synthesis

REMOVING BLOOD GLUCOSE

Responses to Overfeeding

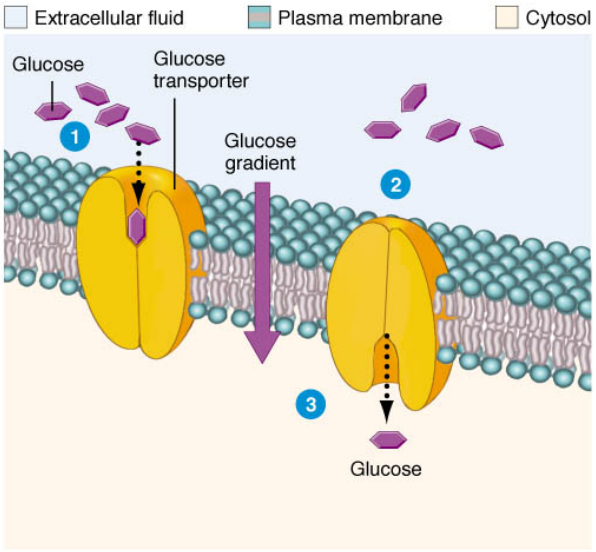


K. J. Acheson, Y. Schutz, T. Bessard, K. Anantharaman, J. P. Flatt, E. Jequier, Glycoprotein storage capacity and de novo lipogenesis during massive carbohydrate overfeeding in man **Am. J. Clin. Nutr.** 48, 240–247 (1988).

Glucose Uptake

Non-Stimulated Glucose Uptake

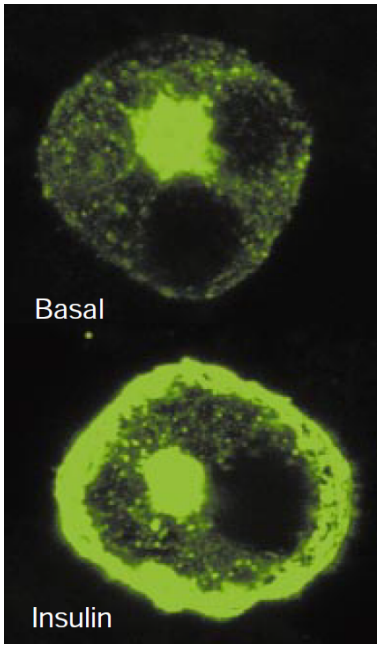
- Brain
- Liver
- Kidneys



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

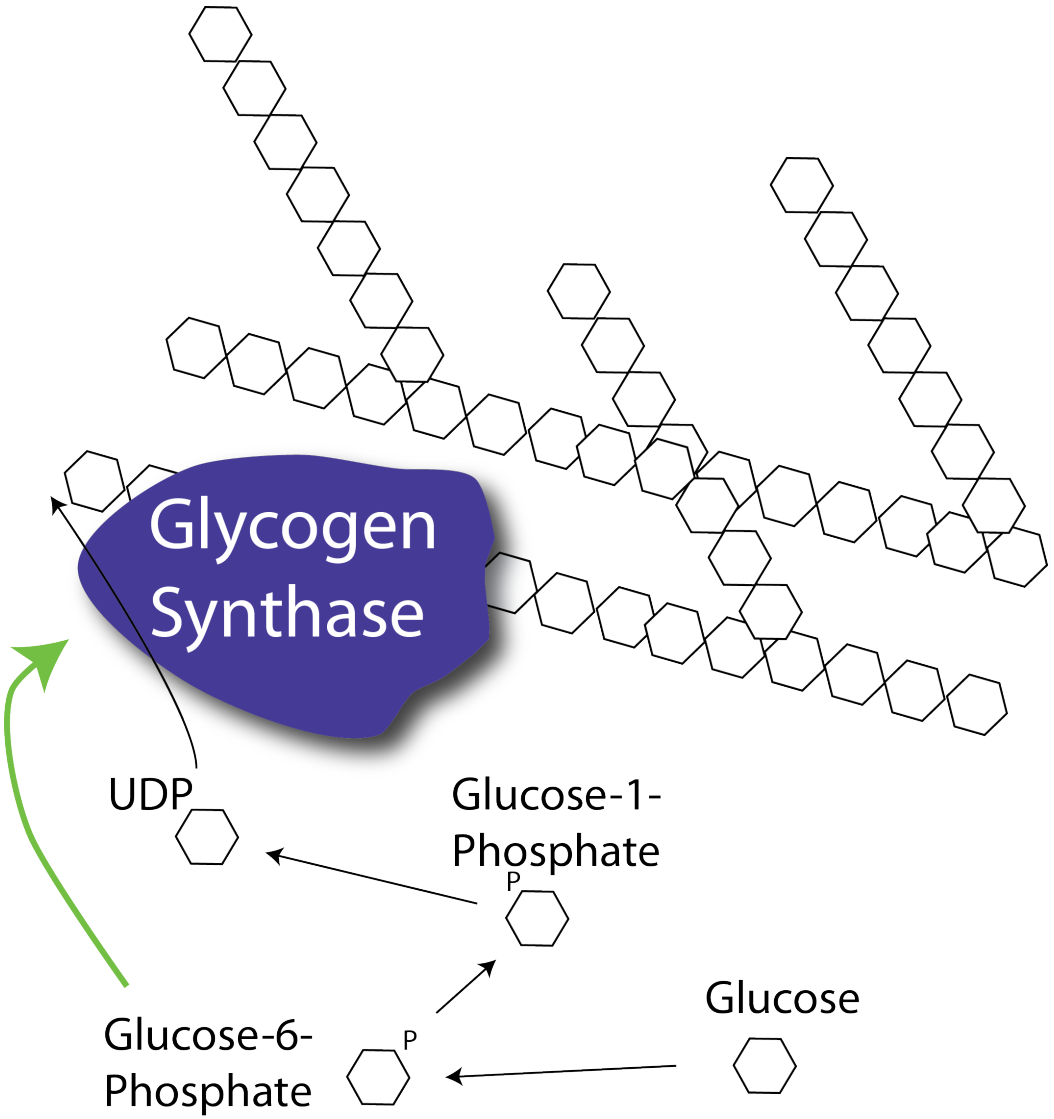
Stimulated Glucose Uptake

- Fat
- Muscle



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

Glycogenesis



Order of Fuel Utilization/Storage

Energy Production (Fasting)

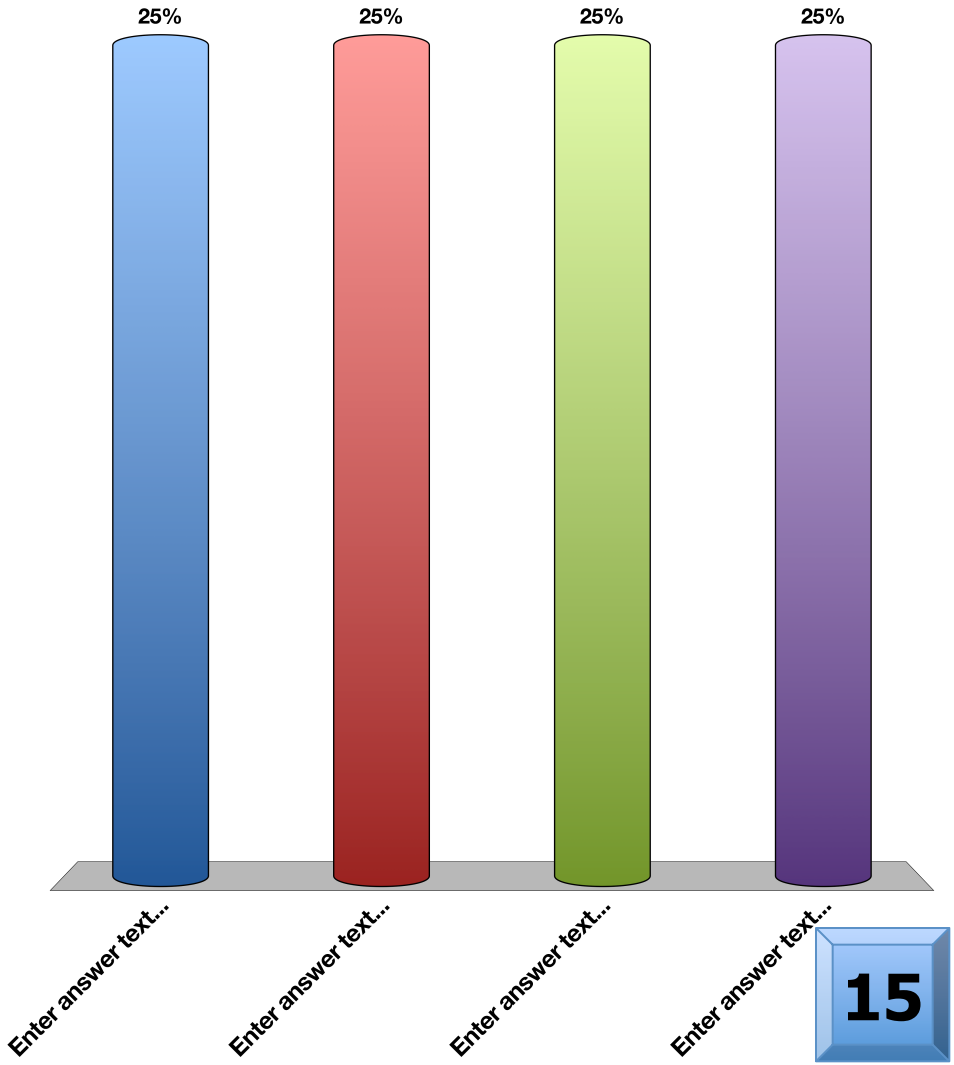
- Creatine phosphate
- Glycolysis
- Glycoge
- Gluconeogenesis
- Fat Oxidation

Fuel Storage (Fed)

- Glucose uptake/oxidation
- Glycogenesis
- Lipogenesis

What would happen if you are unable to store glucose only in adipose

A. Obese, hyperglycemic
B. Obese, hypoglycemic
C. Lean, hyperglycemic
D. Lean, hypoglycemic



Response Counter

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MECHANISMS TO REDUCE BLOOD GLUCOSE

The Discovery of Insulin

The Discovery of Insulin

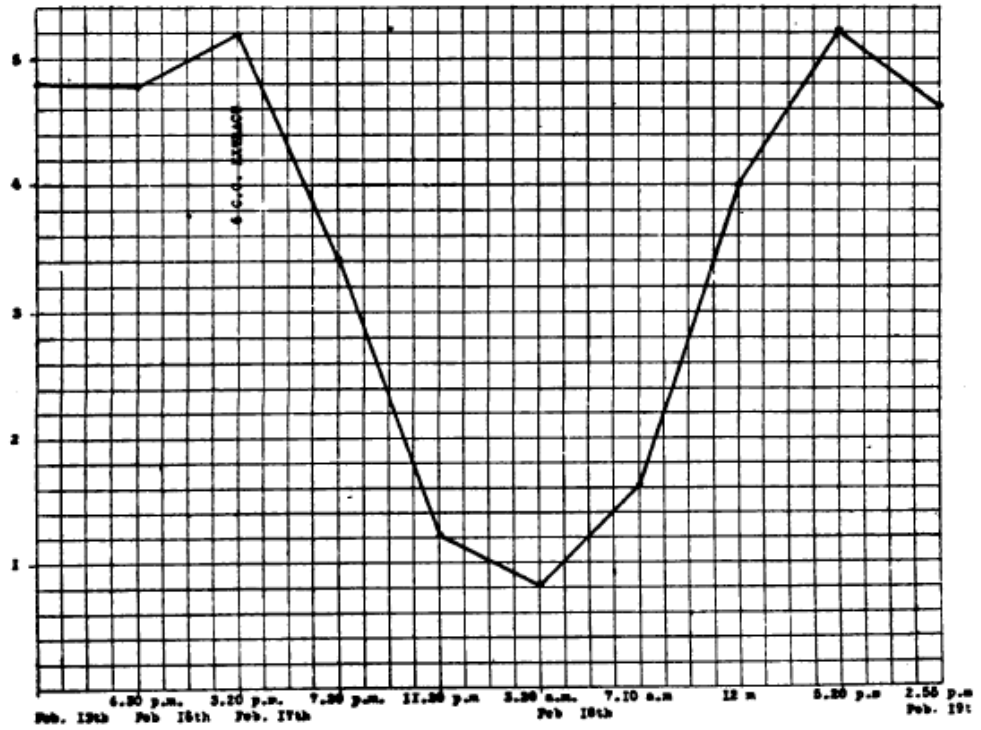


CHART III.—*Effect of one injection of extract on Blood Sugar (mgs. per c.c.e=tenth per cent)*

Banting *et al*. 1922

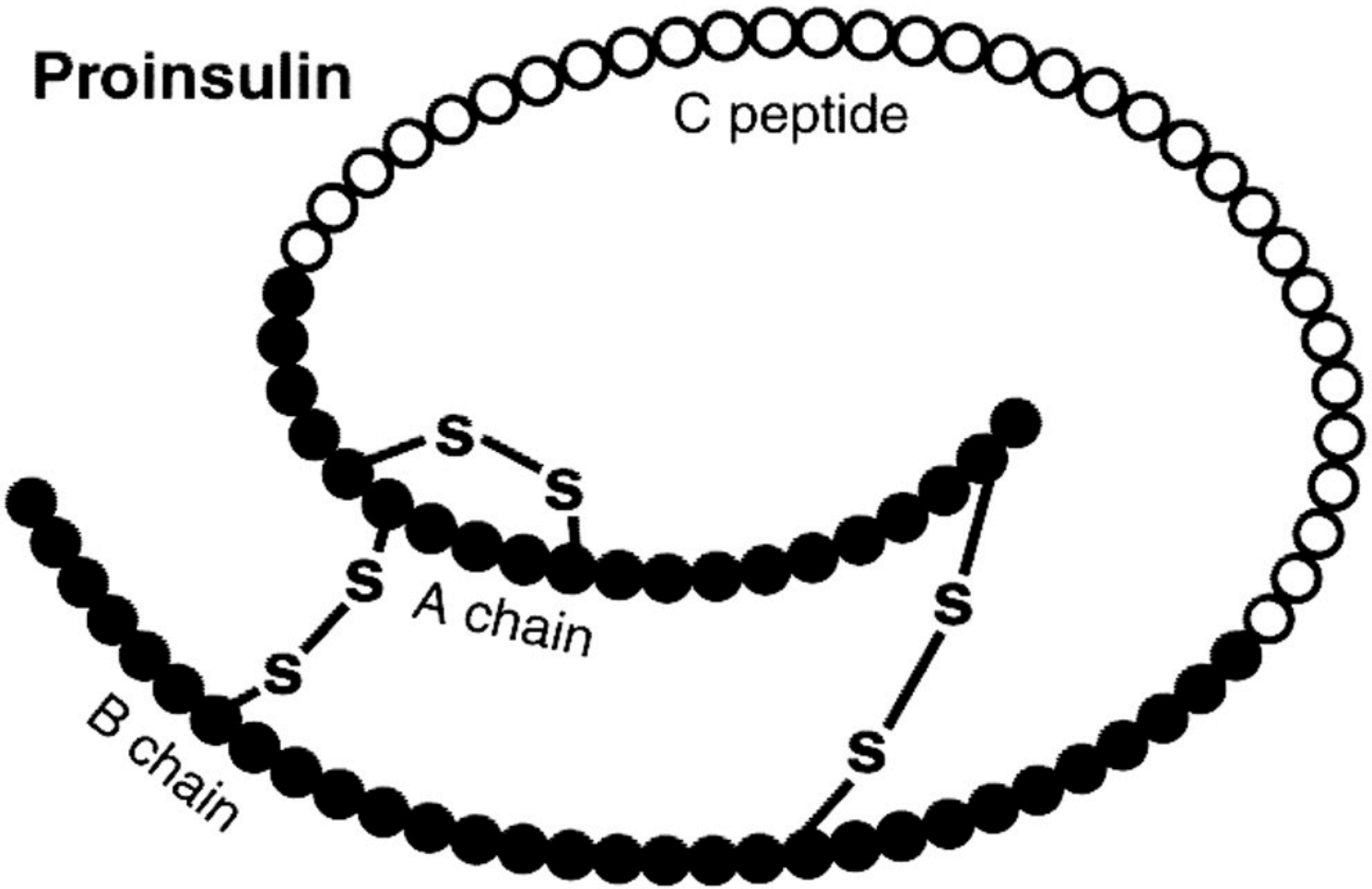
Which of these should insulin block?

A. Glucose oxidation
B. Gluconeogenesis
C. Glucose uptake
D. Glycogenesis

Think and discuss

- A patient has no insulin response in the liver, what should be the effects on
  - Blood glucose
  - Lipid storage
  - Insulin levels
  - Obesity

Insulin Structure



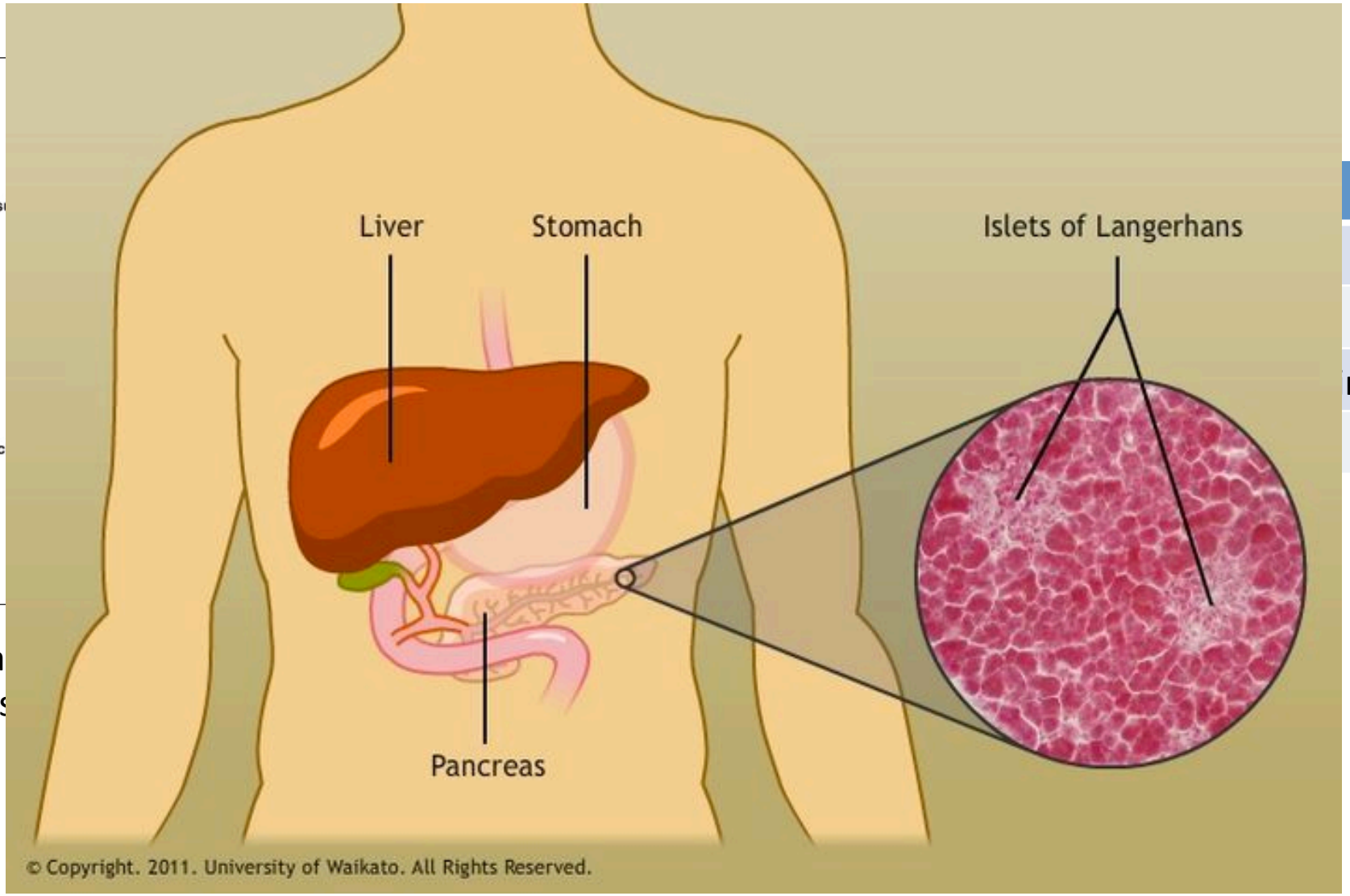
If you want to know insulin production in someone who is also taking injected insulin what would you measure?

A. insulin
B. C-peptide ✓
C. Glucagon
D. Glucose

Response Counter

15

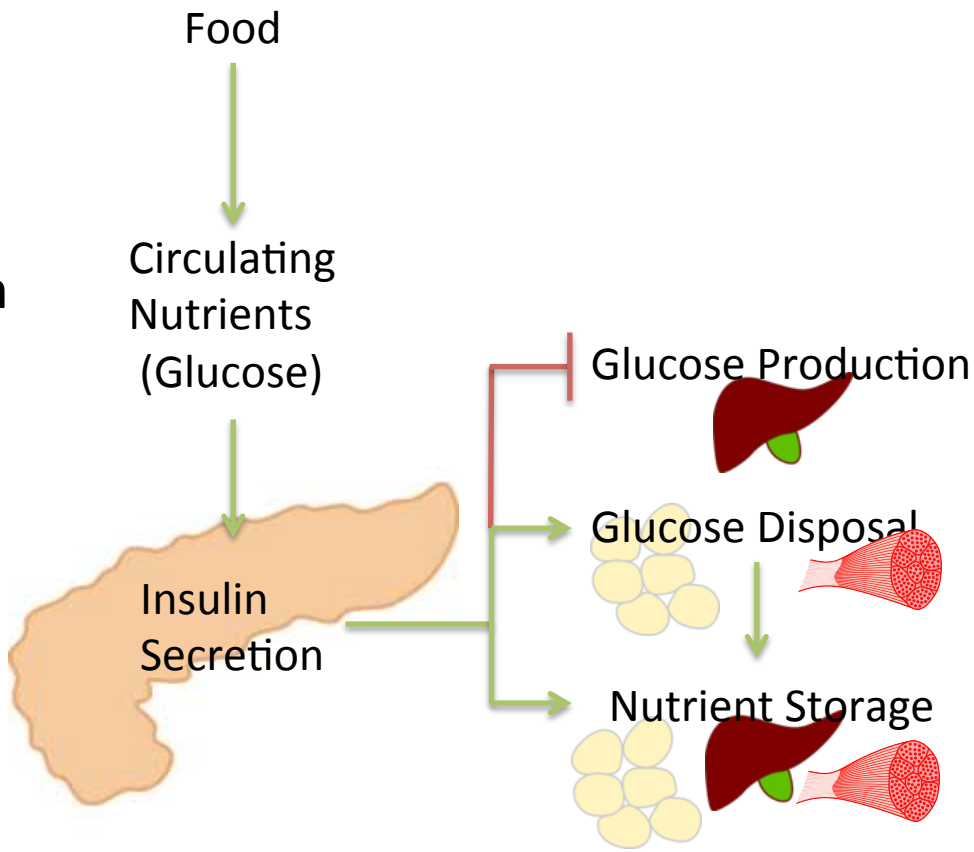
Pancreatic Anatomy



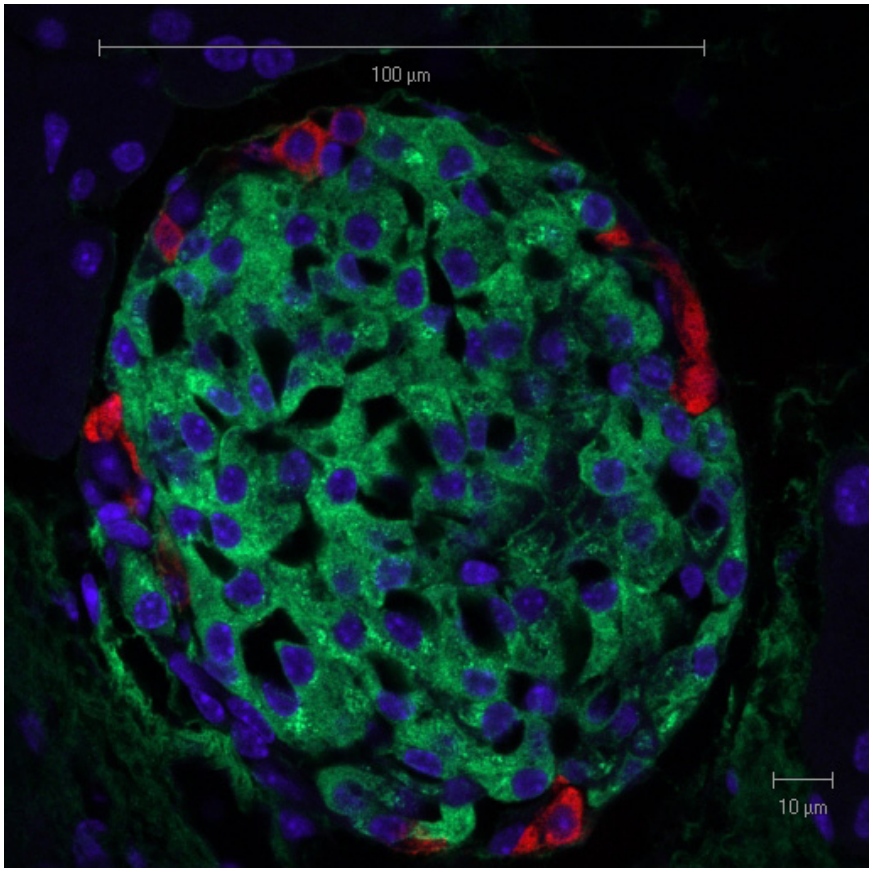
S. Efra
Trends

Functions of Insulin

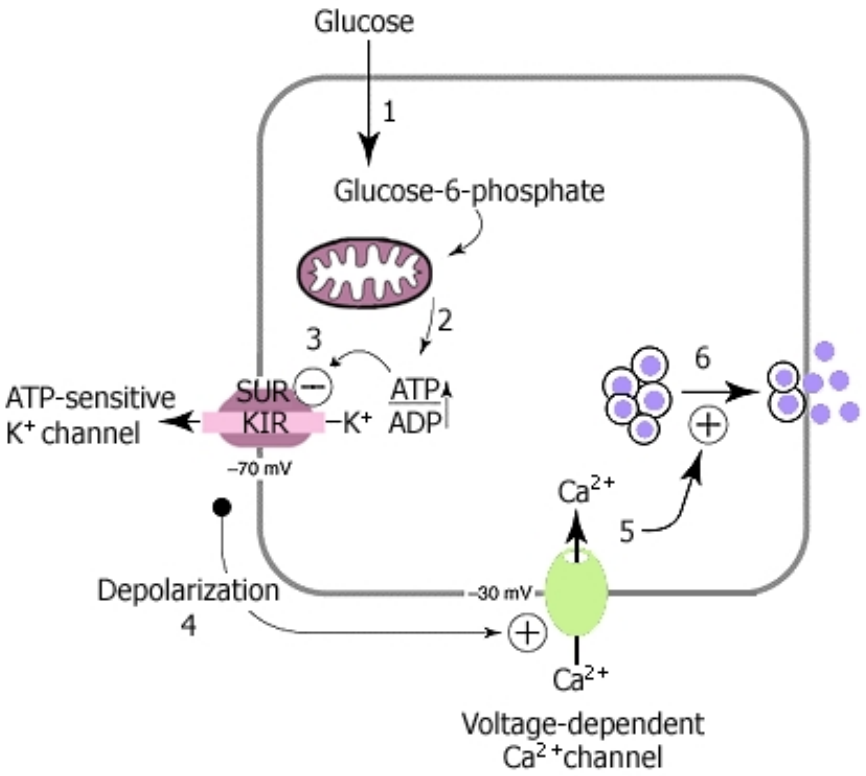
1. Promotes the uptake of glucose from the blood into muscle and adipose tissue.
2. Enhances the synthesis of glycogen and triglycerides in liver, adipose and muscle.
3. Insulin inhibits gluconeogenesis, or the production of glucose from non-glucose precursors such as amino acids and lipids.
4. Promote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



Insulin Secretion

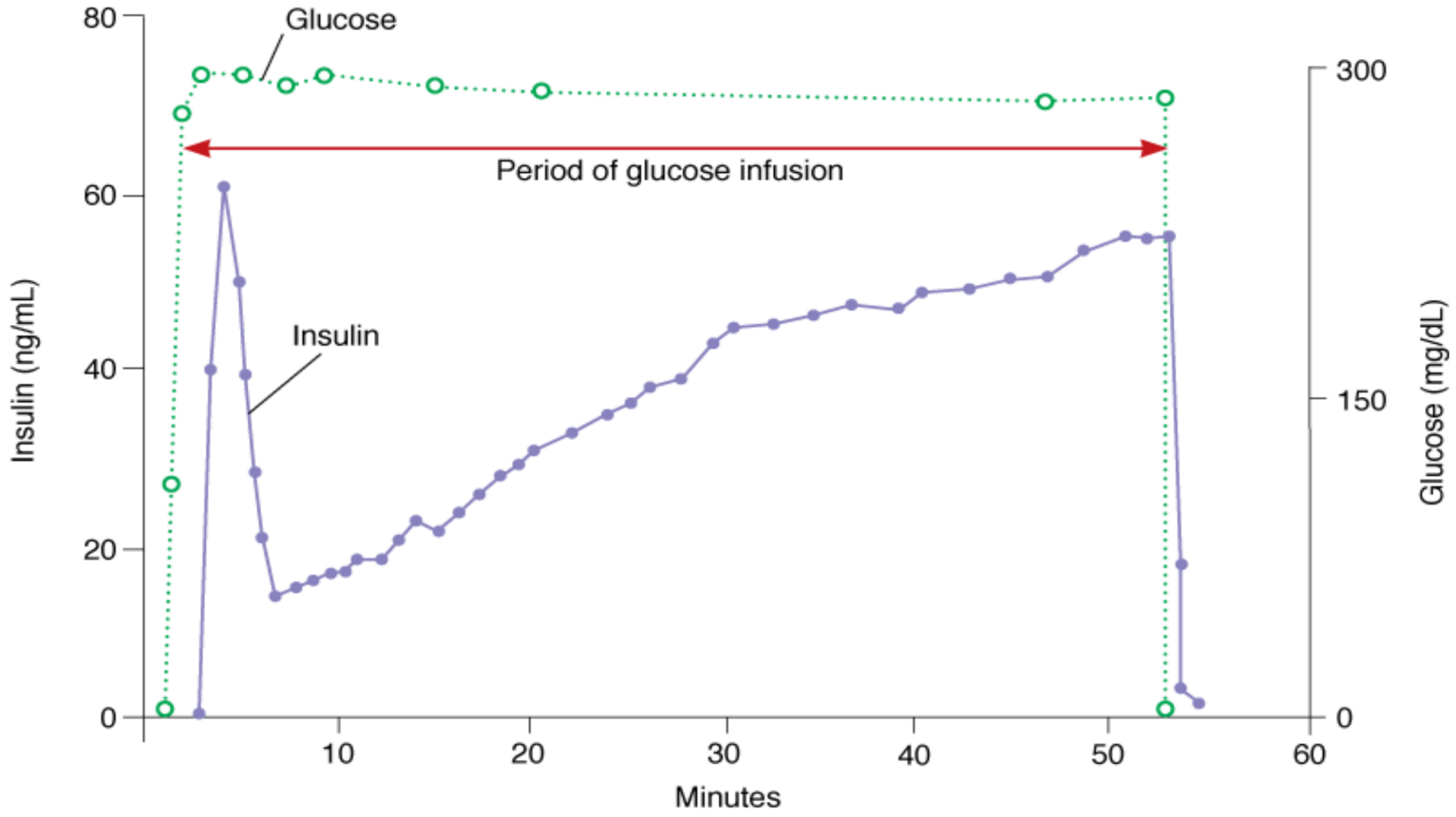


Pancreatic Islet with Glucagon and Insulin Staining From Solilema Lab (http://en.wikipedia.org/wiki/Islets_of_Langerhans)



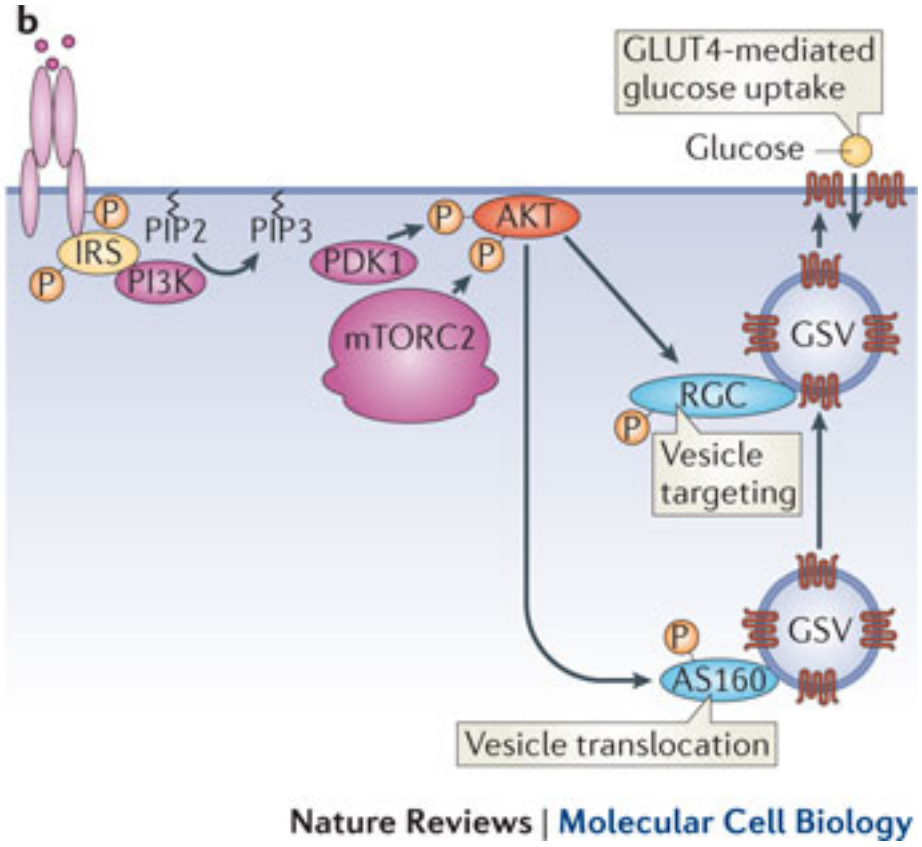
Suckale and Solimena (2008) Frontiers in bioscience 13:7156-71

Biphasic Insulin Secretion



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

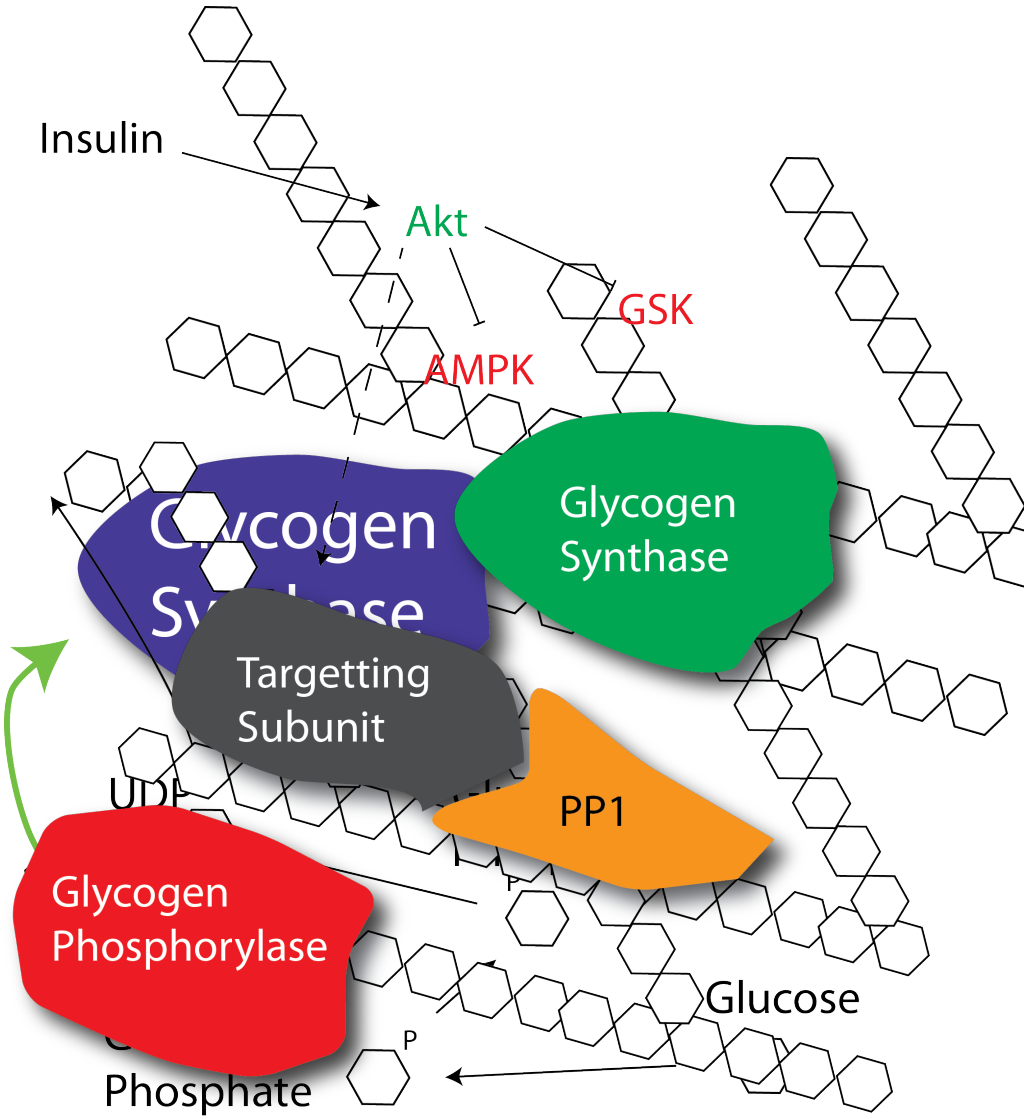
Insulin Stimulated GLUT4 Translocation



Leto and Saltiel Nat. Rev. MCB (2012)

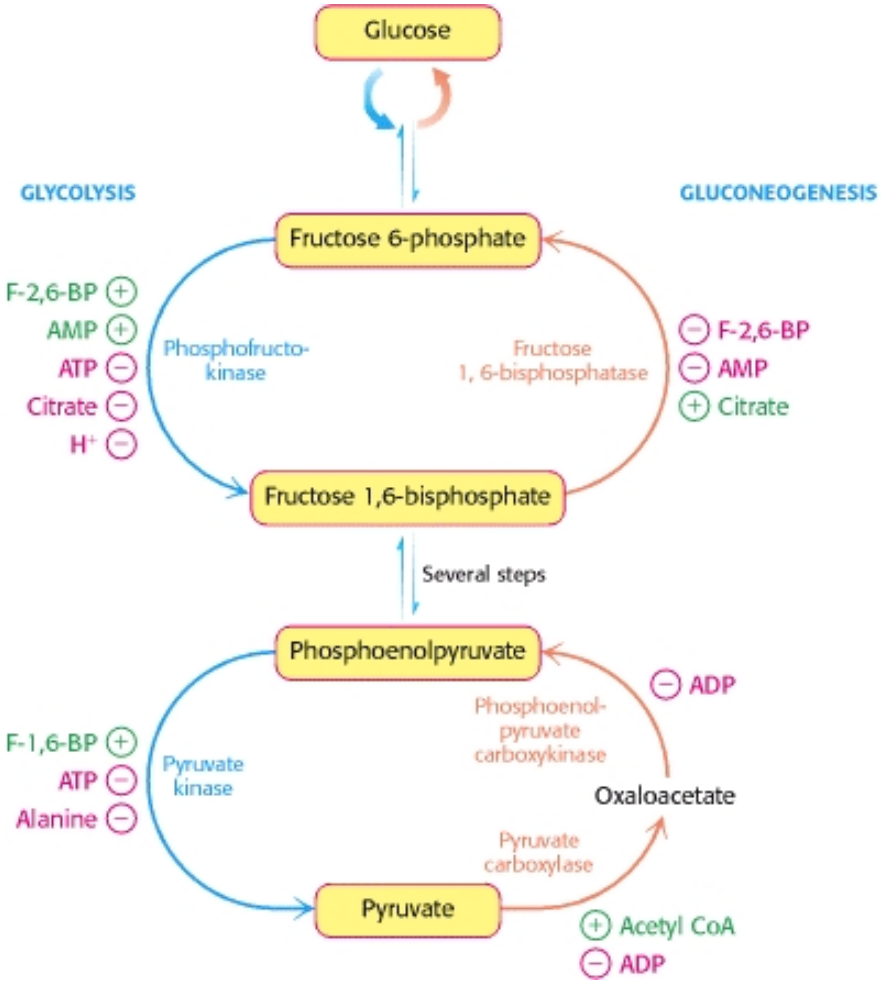
How does insulin promote glycogenesis?

- Allosteric activation
- Protein dephosphorylation

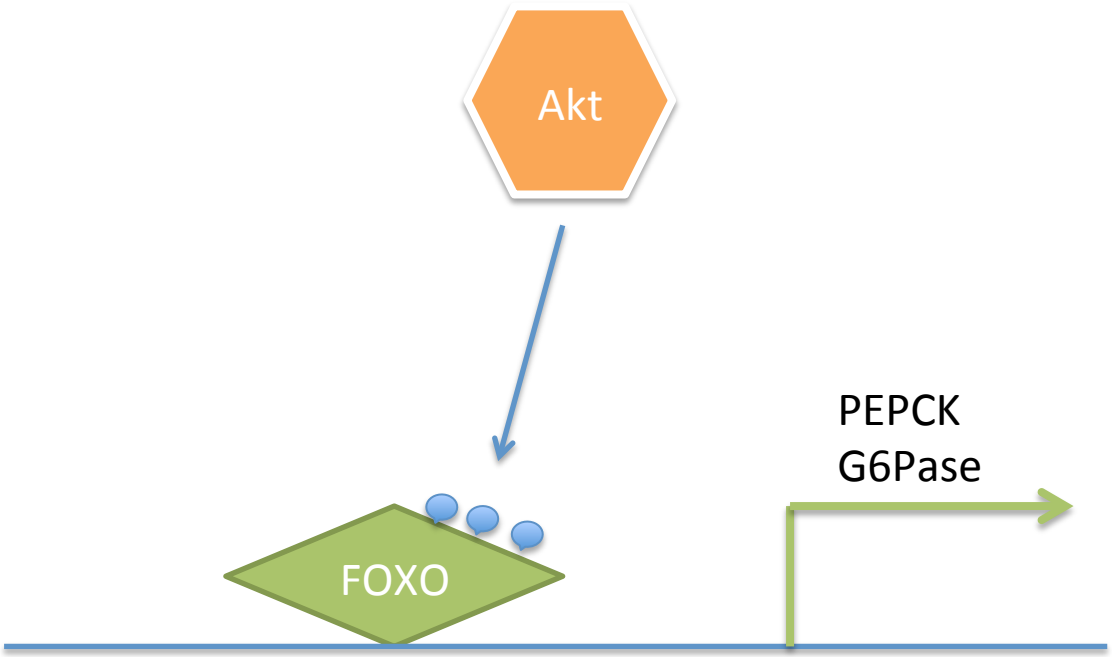


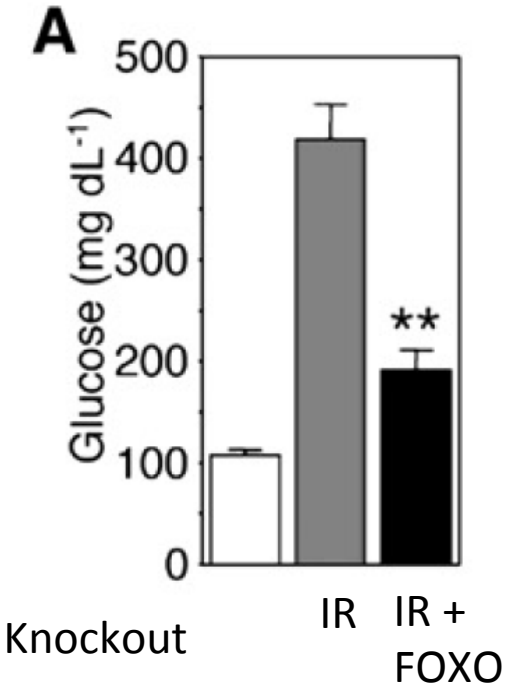
How does insulin reduce gluconeogenesis

- 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

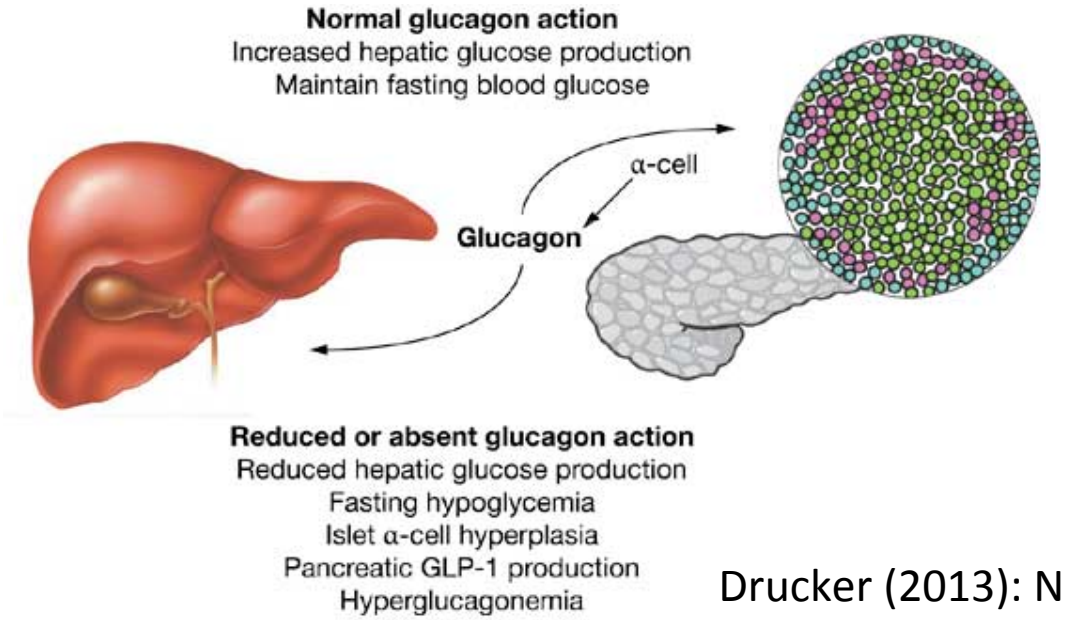
Talk amongst yourselves

- Why would gluconeonesis be under transcriptional control, wheras glycogenesis is primarily under post-translational control
- Hint: think about the speed of post-translational vs transcriptional responses

MECHANISMS TO INCREASE BLOOD GLUCOSE

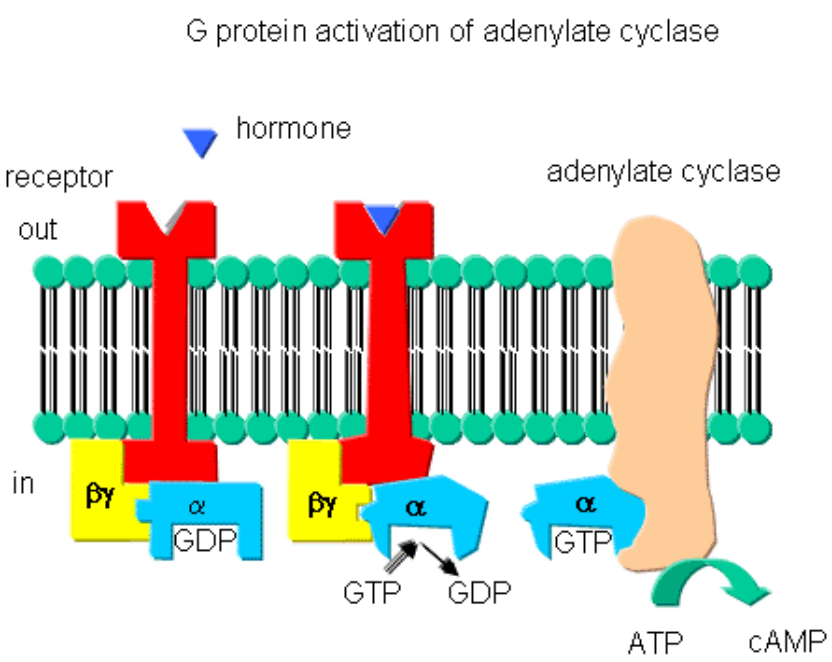
Glucagon Secretion

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

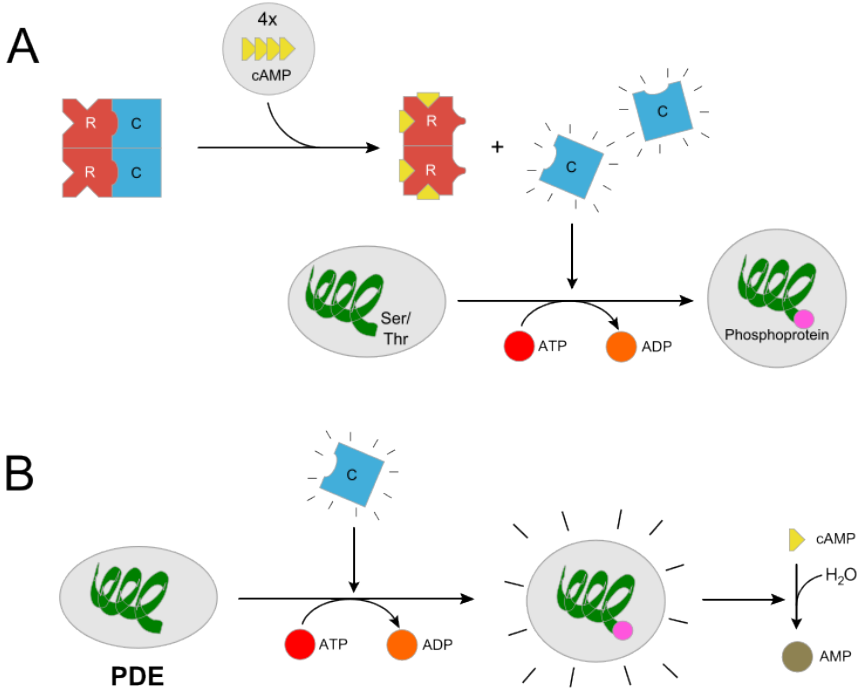


Drucker (2013): Nat Rev Endo 1:22-31

Glucagon Signaling

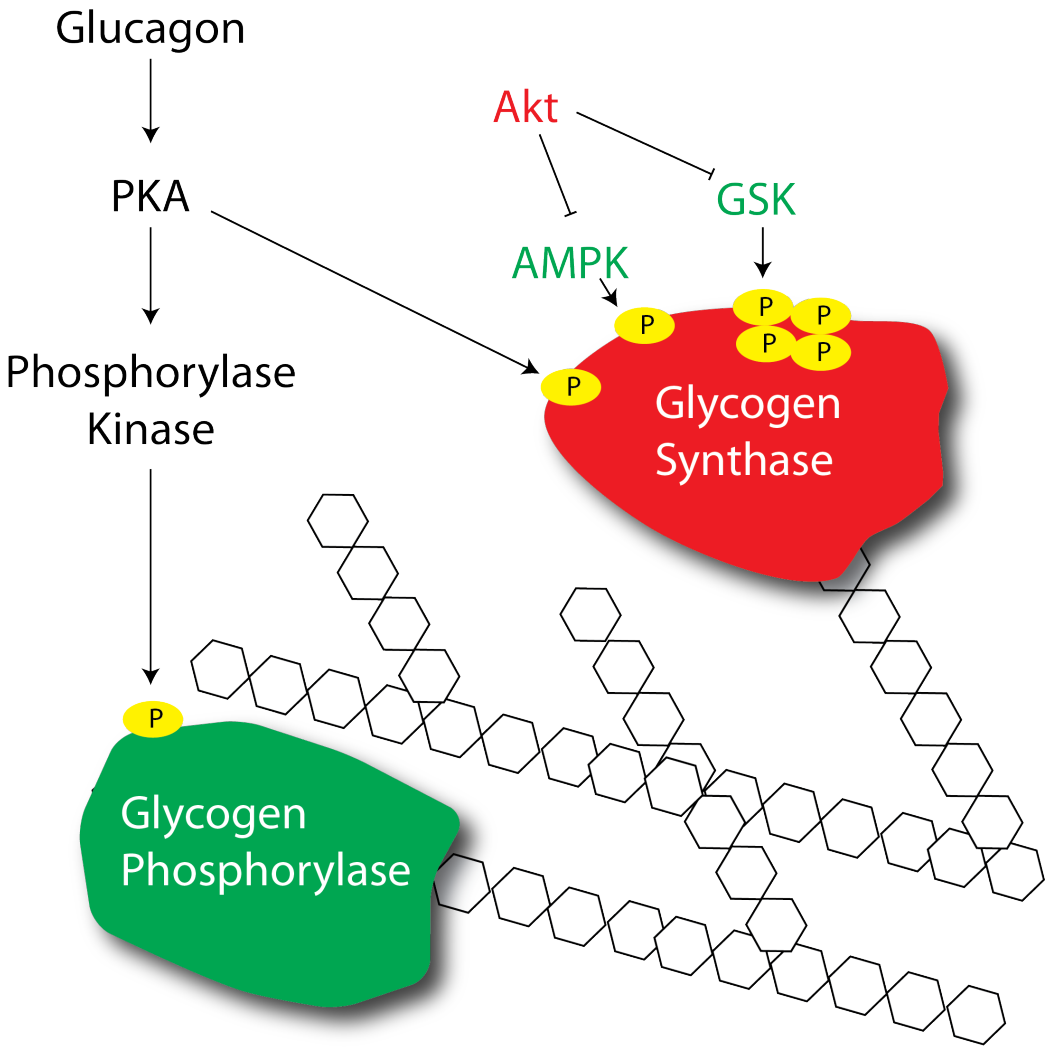


From http://biowiki.ucdavis.edu/Biochemistry/Signal_Transduction/Signal_Transduction_at_Cell_Membranes%3A_Protein_Kinases_and_Phosphotases

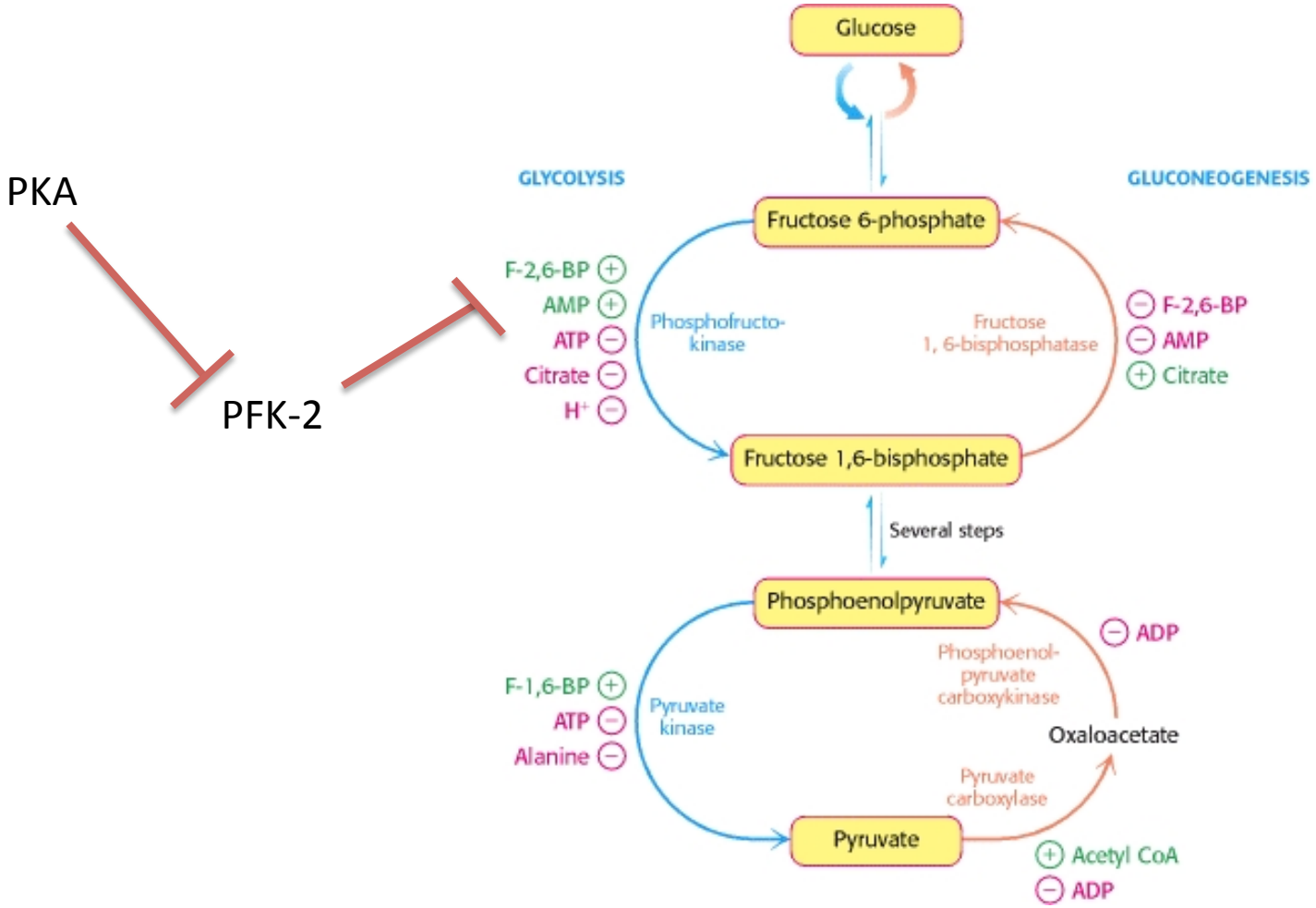


From http://en.wikipedia.org/wiki/Protein_kinase_A

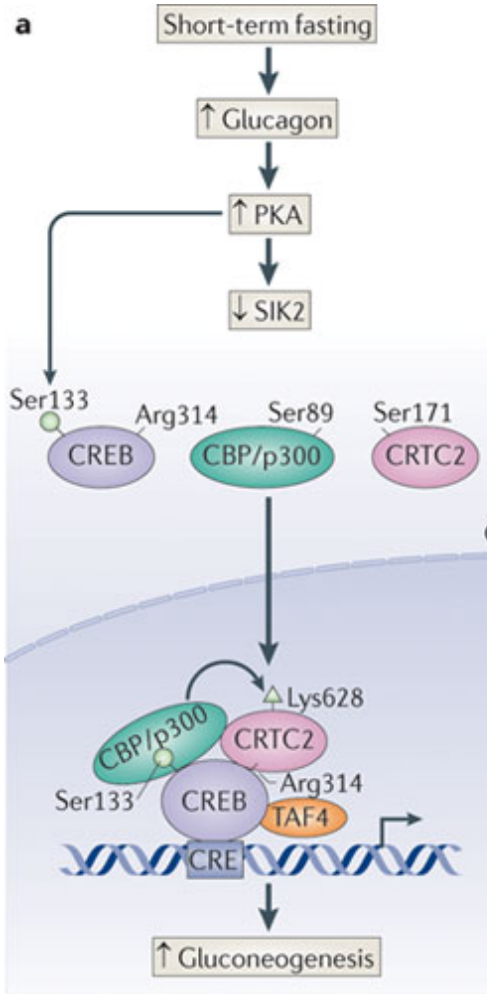
How does glucagon regulate glycogenolysis?



How does glucagon promote gluconeogenesis?



Transcriptional Regulation of Gluconeogenesis



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

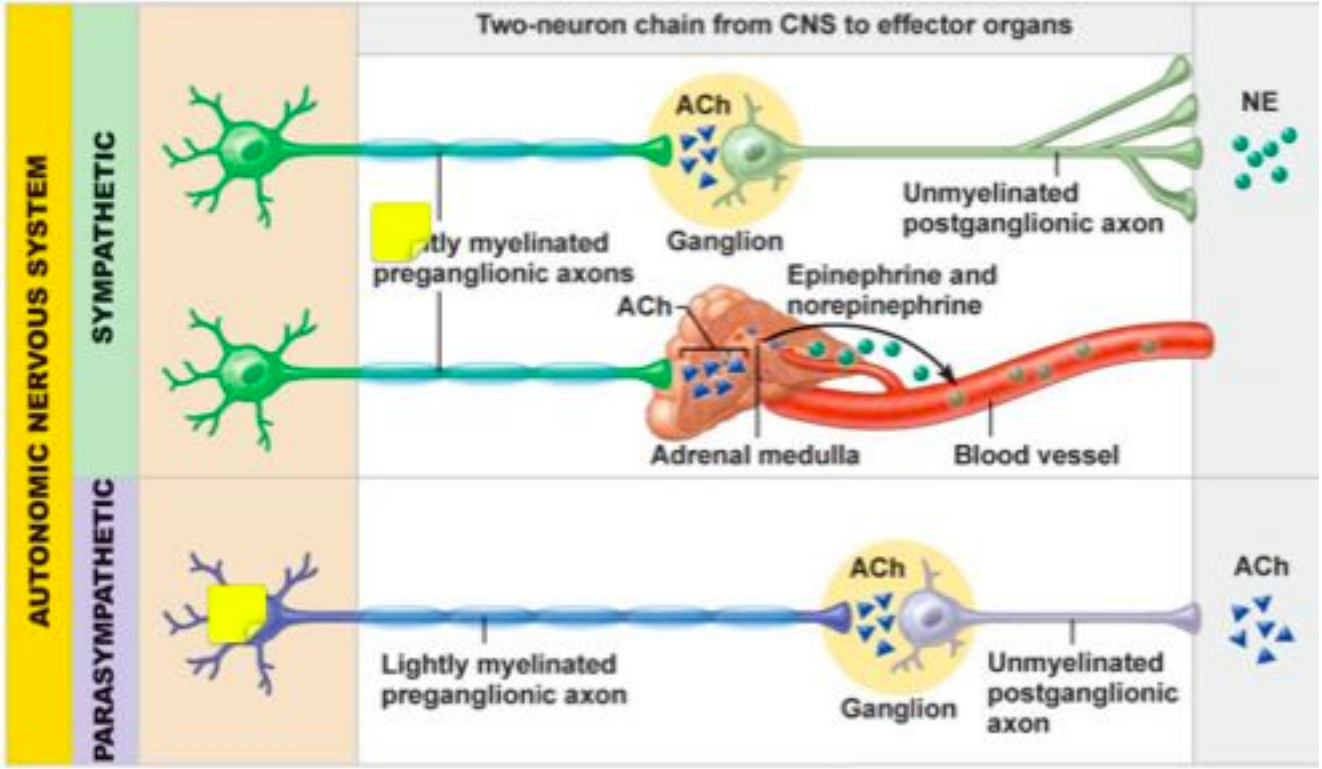
- Blocks gluconeogenesis
- Blocks glycogenolysis
- Promotes glycogenesis
- Enhances glucose uptake
- Promotes lipid storage

Glucagon

- Promotes gluconeogenesis
- Promotes glycolysis
- Blocks glycogenesis

SECONDARY REGULATION OF GLUCOSE METABOLISM

Nervous Control of Pancreatic Function



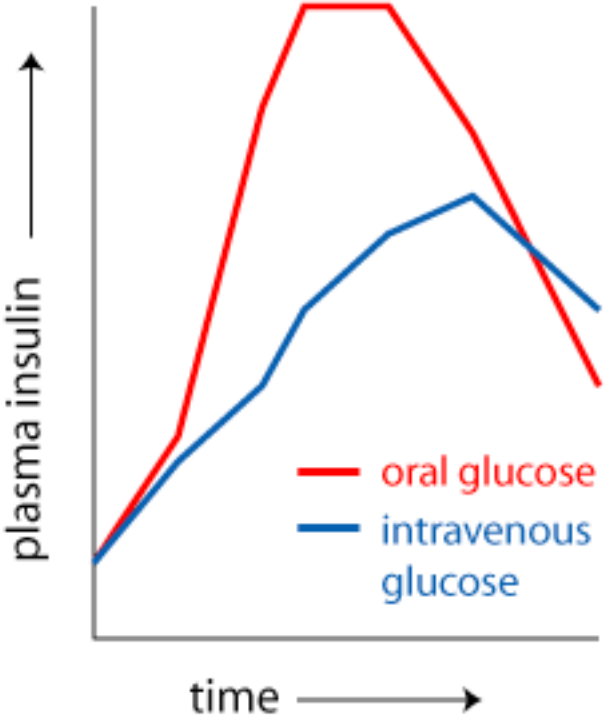
More Glucagon
Less Insulin

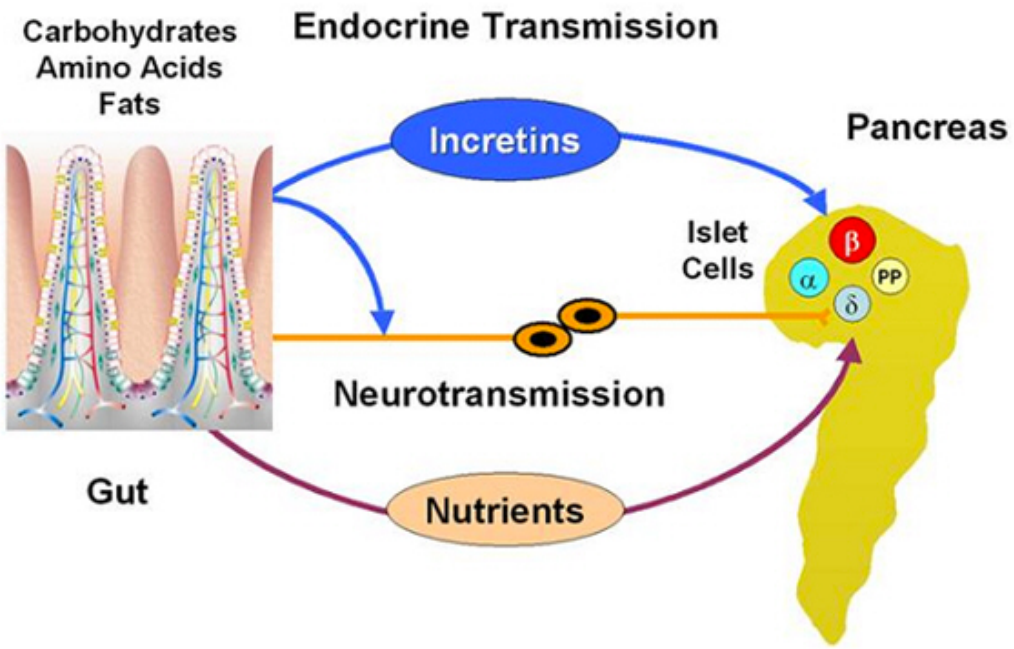
More Insulin
Less Glucagon

A tumor secretes adrenaline constantly, what are the effects

A. More insulin
B. Less insulin
C. No effect on insulin

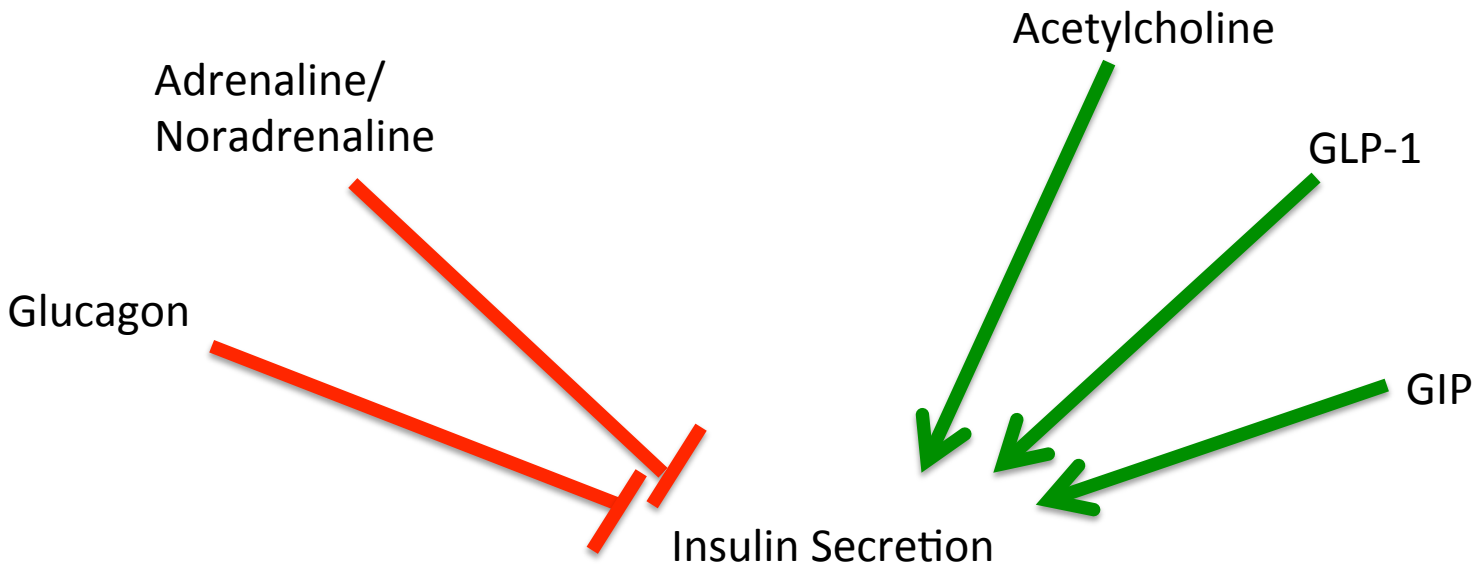
Incretins and Secondary Control of Insulin Secretion





GLP1/GIP1 both released from gut

Endocrine Control of Insulin Secretion



DPP-4 Degrades GLP-1 and GIP, What would it do to insulin and blood glucose?

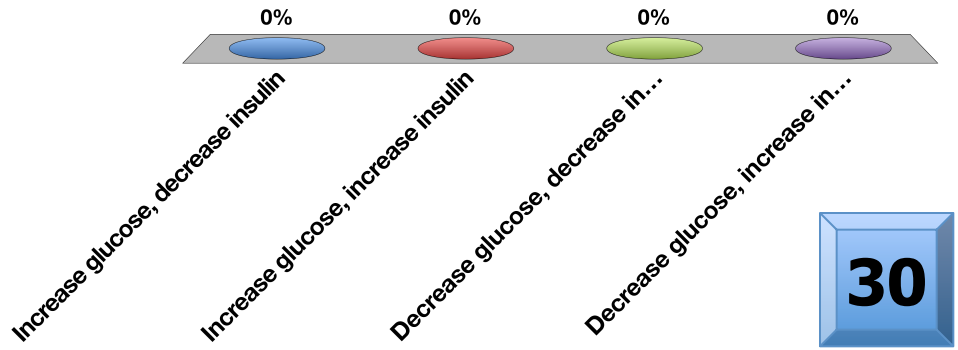
A. Increase glucose, decrease insulin

B. Increase glucose, increase insulin

C. Decrease glucose, decrease insulin

D. Decrease glucose, increase insulin

Response Counter



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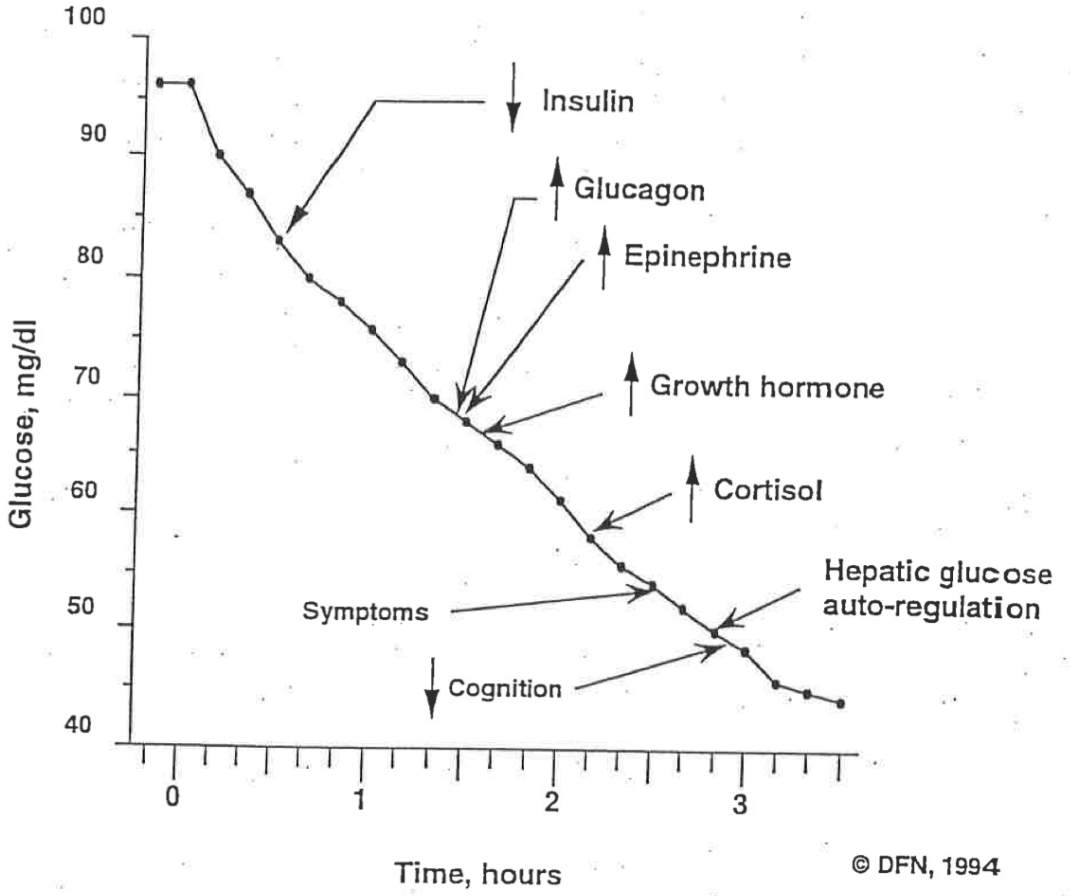
Long Term Glucoregulation



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

Oral glucose tolerance test

- Draw what happens to glucose after a meal over time
- Sketch out changes in glucagon, insulin and GLP-1
- Sketch out a new one, for someone who is a type I diabetic (show insulin and GLP-1)
- Sketch out a new one, for someone who is a type II diabetic (show insulin, glucagon and GLP-1)

Learning Objectives

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2. Describe the main targets and functions of glucagon.
3. List the major factors that stimulate or inhibit glucagon and insulin.
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7. Name the tissues in which insulin facilitates glucose uptake and those in which insulin does not facilitate glucose uptake.
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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.