EAT TO LIVE: THE ROLE OF THE PANCREAS

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THE ROLE OF THE PANCREAS

- Exocrine pancreas
- Endocrine pancreas

THE ROLE OF THE PANCREAS

- EXOCRINE PANCREAS
  - **Digestive enzymes**
  - **Sodium bicarbonate**

EAT TO LIVE: THE ROLE OF THE PANCREAS

- Digestive enzymes
  - Trypsin, chymotrypsin and carboxypeptidase
  - Pancreatic amylase
  - Pancreatic lipase, cholesterol esterase, phospholipase
  - Nucleases including RNase and DNase
- Bicarbonate ions

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- Regulation of exocrine pancreatic secretion

- **1. Acetylcholine**
- **2. Cholecystokinin (CCK)**
- **3. Secretin**

THE PANCREAS

- *Clinical correlation*
  - *Acute pancreatitis*
  - *Exocrine pancreatic insufficiency*
  - *Endocrine pancreatic insufficiency*

THE ROLE OF THE PANCREAS

- ENDOCRINE PANCREAS

  - **Insulin**
  - **Glucagon**
  - **Somatostatin**
  - **Pancreatic polypeptide**

EAT TO LIVE: THE ROLE OF THE PANCREAS

- Insulin
  - Hypoglycemic hormone
  - Beta cells
  - Two chain polypeptide
  - Receptor interactions
  - Intracellular interactions
  - Transporters
  - *Clinical correlation*

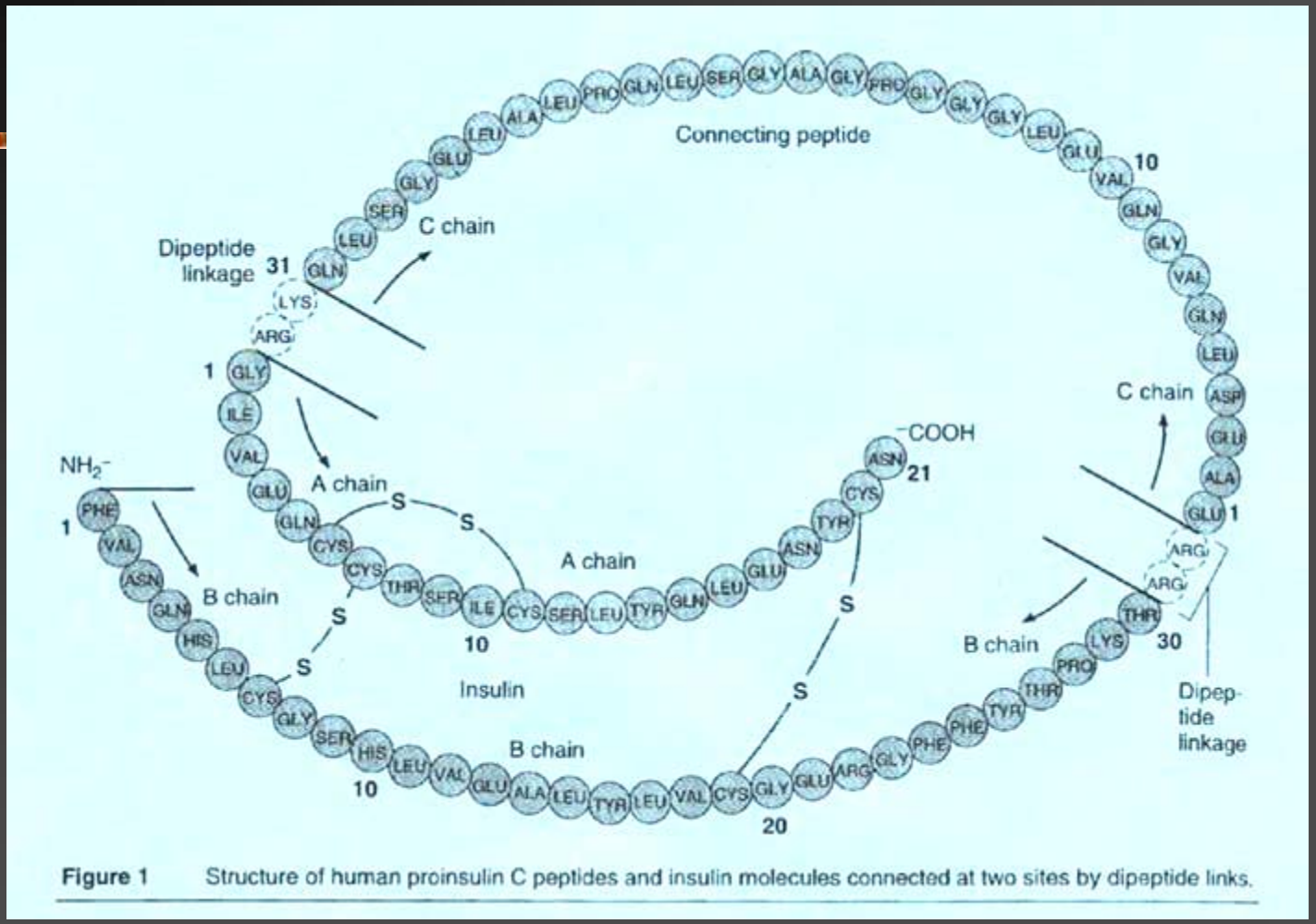
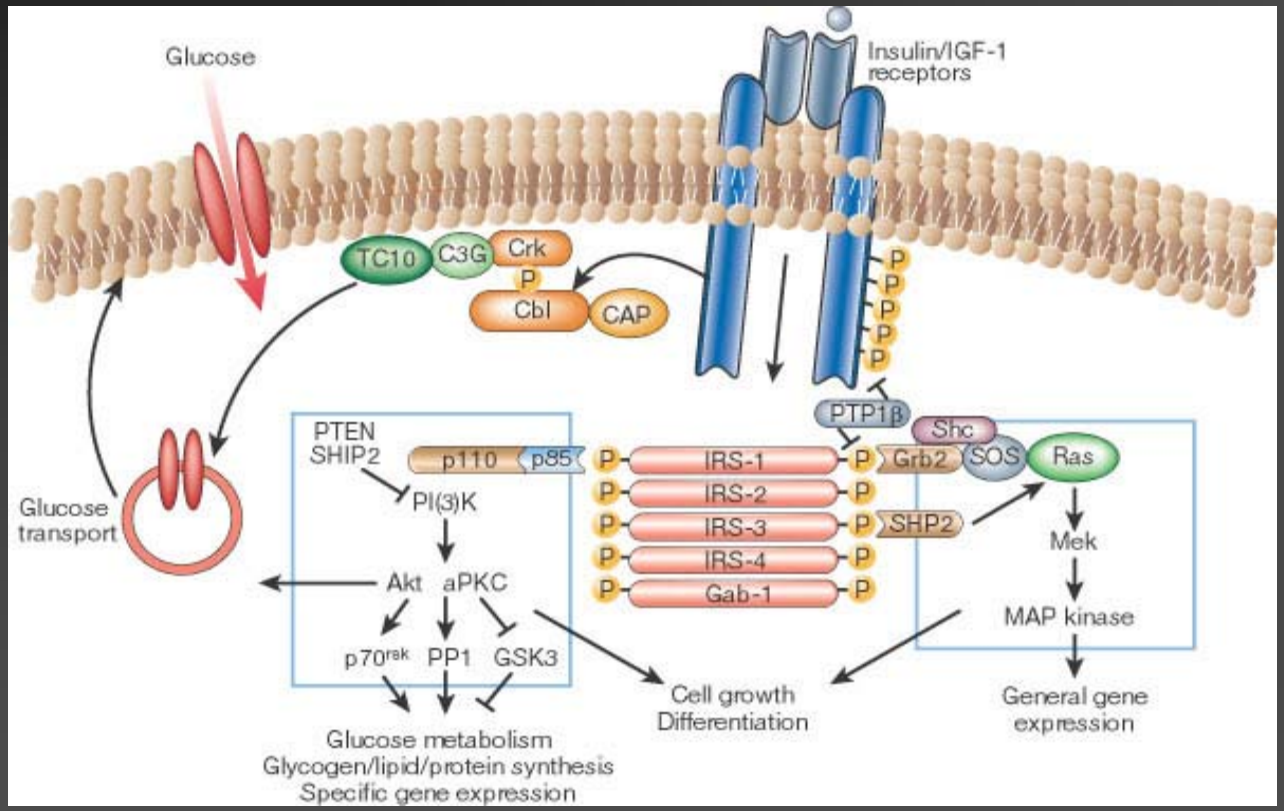


Figure 1 Structure of human proinsulin C peptides and insulin molecules connected at two sites by dipeptide links.

INSULIN MECHANISM OF ACTION

- Insulin binds to its transmembrane receptor.
- β subunits of the receptor become phosphorylated; receptor has intrinsic tyrosine kinase activity.
- Intracellular proteins are activated/inactivated—IRS-1, IRS-2 and seven PI-3-kinases; GLUT-4, transferrin, LDL-R, IGF-2-R move to the cell surface.
- Cell membrane permeability increases: glucose, K^+, amino acids, PO_4

INSULIN Signaling



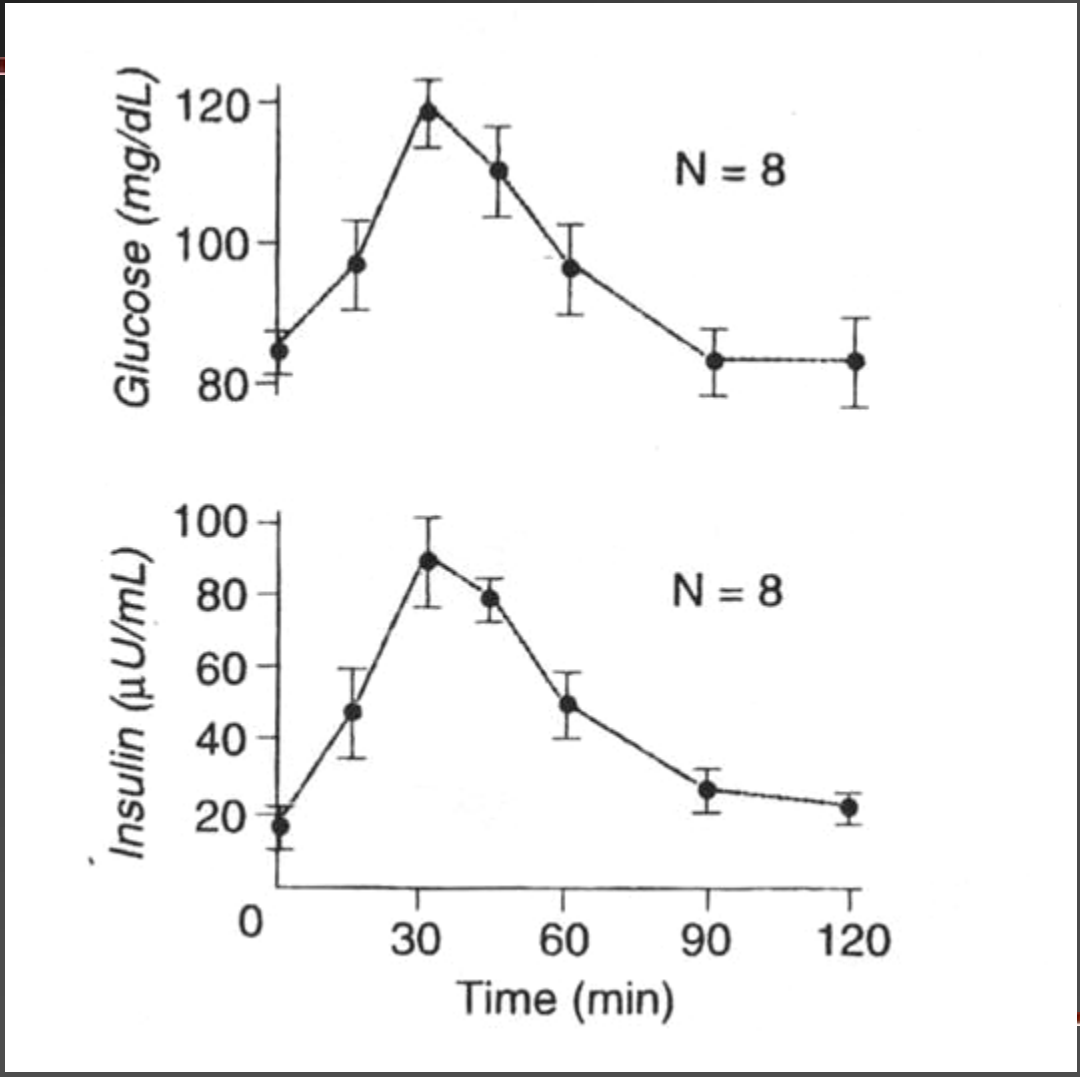
INSULIN MECHANISM OF ACTION

- Delayed effects include gene activation or deactivation, upregulation or downregulation of mRNA and protein synthesis.
- *Insulin receptor interactions are altered in insulin resistance syndromes and Type 2 diabetes mellitus.*
- *Insulin-receptor binding is also altered by obesity, high carbohydrate diet, fasting or exercise.*

INSULIN

- Insulin Release
  - In a 24 hour period, 50% of the insulin secreted is basal and 50% is stimulated.
  - The main stimulator is glucose.
  - Amino acids also stimulate insulin release, especially lysine, arginine and leucine. This effect is augmented by glucose.

CONTROL OF INSULIN SECRETION



CONTROL OF INSULIN SECRETION

Glucose interacts with the GLUT2 transporter on the pancreatic beta cell.

Glucose $\xrightarrow[RLS]{hexokinase}$ G-6-P

Increased metabolism of glucose $\xrightarrow{*}$ ATP $\rightarrow$ blockade of ATP-dependent K channels $\rightarrow$ membrane depolarization $\rightarrow \uparrow$ cytosolic Ca++ $\rightarrow \uparrow$ insulin secretion.

- * $\uparrow$NADH with oxidation of glyceraldehyde-3-P
- $\uparrow$Pyruvate $\rightarrow$ TCA cycle $\rightarrow$ respiratory chain

CONTROL OF INSULIN SECRETION

Insulin secretion is also increased by intestinal polypeptide hormones

GLP-1 (glucagon like peptide) [exendin-4]

Glucose-dependent insulinotropic peptide (GIP)

Cholecystokinin

And by pancreatic glucagon.

Insulin secretion is decreased by pancreatic somatostatin.

CONTROL OF INSULIN SECRETION

Insulin secretion is also increased by

- growth hormone (acromegaly)
- glucocorticoids (Cushings')
- prolactin (lactation)
- placental lactogen (pregnancy)
- sex steroids

THE ROLE OF INSULIN

Summary of feedback mechanism for regulation of insulin secretion

↑ blood glucose

↓

↑ insulin

↓

↑ transport of glucose into cells, ↓ gluconeogenesis, ↓ glycogenolysis

↓

↓ blood glucose

↓

↓ insulin

THE ROLE OF INSULIN

- Metabolic Effects of Insulin
  - main effect is to promote storage of nutrients
  - paracrine effects
  - carbohydrate metabolism
  - lipid metabolism
  - protein metabolism and growth

THE ROLE OF INSULIN

- The main effect of insulin is to promote storage of nutrients.

THE ROLE OF INSULIN

- Paracrine effects
  - decreases glucagon secretion

THE ROLE OF INSULIN

- Carbohydrate metabolism
  - increases uptake of glucose
  - promotes glycogen storage
    - Stimulates glucokinase
  - inhibits gluconeogenesis
  - inhibits hepatic glycogenolysis
    - Inactivates liver phophorylase

SOURCES OF GLUCOSE

- Glucose is derived from 3 sources
  1. Intestinal absorption of dietary carbohydrates
  2. Glycogen breakdown in liver and to a lesser degree in the kidney. Only liver and kidney have glucose-6-phosphatase. Liver stores 25-138 grams of glycogen, a 3 to 8 hour supply.
  3. Gluconeogenesis, the formation of glucose from precursors including lactate and pyruvate, amino acids (especially alanine and glutamine), and to a lesser degree, from glycerol

FASTING STATES

- Short fast
  - utilize free glucose (15-20%)
  - break down glycogen (75%)
- Overnight fast
  - glycogen breakdown (75%)
  - gluconeogenesis (25%)
- Prolonged fast
  - Only 10 grams or less of liver glycogen remains.
  - Gluconeogenesis becomes sole source of glucose; muscle protein is degraded for amino acids.
  - Lipolysis generates ketones for additional fuel.

THE ROLE OF INSULIN

- Lipid Metabolism
  - Insulin promotes fatty acid synthesis
    - stimulates formation of α-glycerol phosphate
    - α-glycerol phosphate + FA CoA = TG
    - TG are incorporated into VLDL and transported to adipose tissues for storage.
  - Insulin inhibits hormone-sensitive lipase, thus decreasing fat utilization.

THE ROLE OF INSULIN

- Protein Metabolism and Growth
  - increases transport of amino acids
  - increases mRNA translation and new proteins, a direct effect on ribosomes
  - increases transcription of selected genes, especially enzymes for nutrient storage
  - inhibits protein catabolism
  - acts synergistically with growth hormone

THE ROLE OF THE PANCREAS

- Lack of insulin
  - Occurs between meals, and in diabetes.
  - Transport of glucose and amino acids decreases, leading to hyperglycemia.
  - Hormone sensitive lipase is activated, causing TG hydrolysis and FFA release.
  - ↑ FFA conversion in liver → PL and cholesterol → lipoproteinemia, FFA breakdown leads to ketosis and acidosis.

What causes insulin resistance?

- Decreases in receptor concentration and kinase activity,
- changes in concentration and phosphorylation of IRS-1 and -2,
- decreases in PI3-kinase activity,
- decreases in glucose transporter translocation,
- changes in the activity of intracellular enzymes.

THE ROLE OF THE PANCREAS

Other pancreatic hormones

- Somatostatin
  - 14 amino acid paracrine factor
  - Potent inhibitor of glucagon release
  - Stimili: glucose, arginine, GI hormones
- Pancreatic polypeptide
  - 36 amino acids, secreted in response to food
- Glucagon

THE COUNTER REGULATORY HORMONES

- Early response
  - glucagon
  - epinephrine
- Delayed response
  - cortisol
  - growth hormone

THE COUNTER REGULATORY HORMONES

- Glucagon
  - Acts to increase blood glucose
  - Secreted by alpha cells of the pancreas
  - Chemical structure
    - 29 amino acids derived from 160 aa proglucagon precursor
    - GLP-1, the most potent known insulin secretagogue, is made in the intestine by alternative processing of the same precursor
  - Intracellular actions

THE ROLE OF GLUCAGON

- Metabolic Effects of Glucagon
  - increases hepatic glycogenolysis *
  - increases gluconeogenesis
  - increases amino acid transport
  - increases fatty acid metabolism (ketogenesis)

GLUCAGON SECRETION

- Stimulation of glucagon secretion
  - blood glucose < 70 mg/dL
  - high levels of circulating amino acids especially arginine and alanine
  - s and ps nerve stimulation
  - catecholamines
  - CCK, gastrin and GIP
  - glucocorticoids

Response to Decreasing Glucose Concentrations

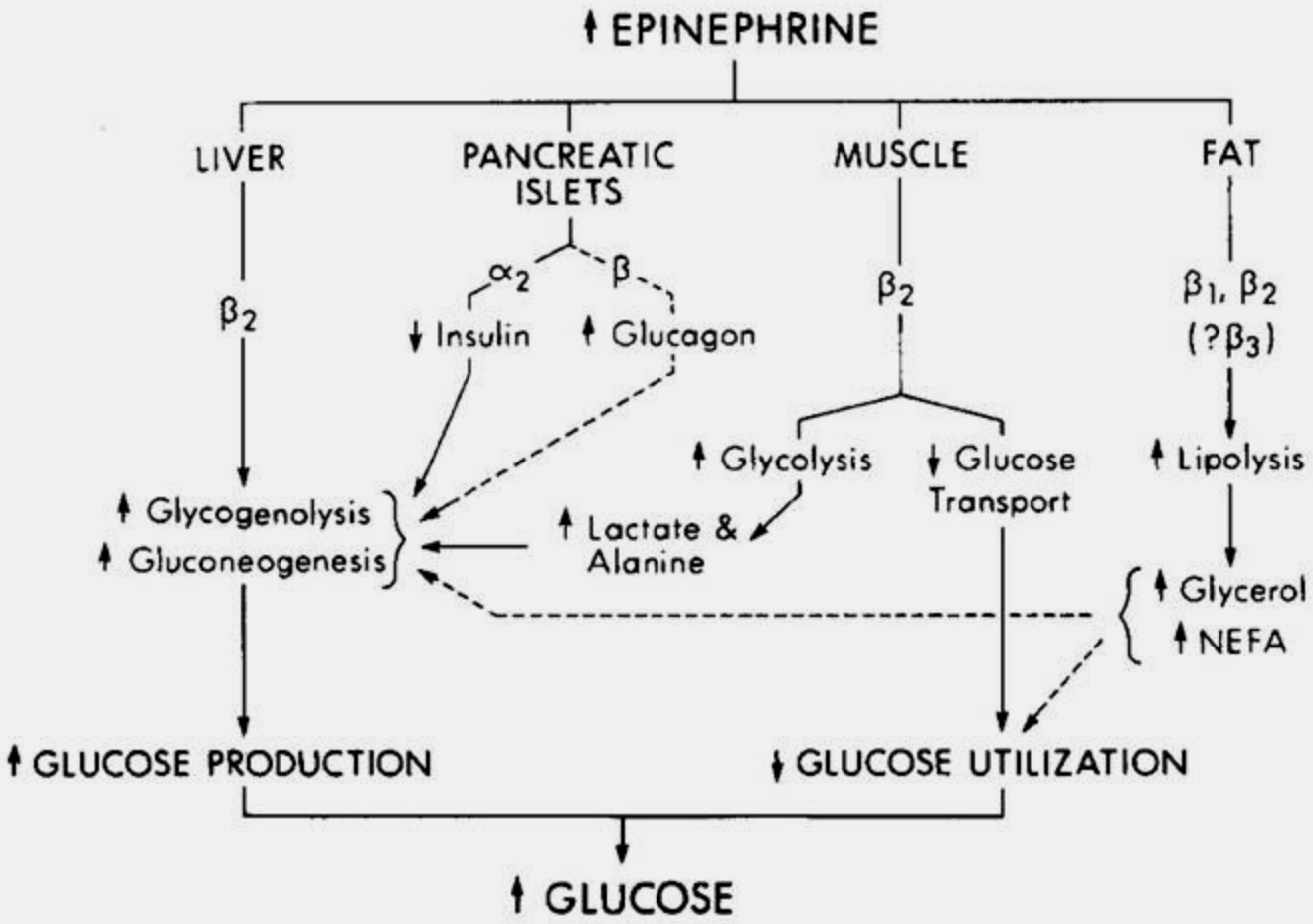
Response	Glycemic Threshold	Physiological Effects	Role in Counterreg.
↓ insulin	80-85 mg/dL	↑ R_a (↓ R_d)	Primary First defense
↑ glucagon	65-70	↑ R_a	Primary 2nd defense
↑epinephrine	65-70	↑ R_a ↓ R_d	Critical 3rd defense
↑ cortisol, ↑ GH	65-70	↑ R_a ↓ R_d	Not critical
↑ Food ingestion	50-55	↑ Exogenous glucose	< 50, Cognitive change halts

Ra-rate of glucose appearance; Rd-rate of glucose disappearance

ROLE OF EPINEPHRINE

- Epinephrine is the second early response hyperglycemic hormone.
- This effect is mediated through the hypothalamus in response to low blood glucose (VMN and others).
- Stimulation of sympathetic neurons causes release of epinephrine from adrenal medulla .
- Epinephrine causes glycogen breakdown, gluconeogenesis, and glucose release from the liver.
- It also stimulates glycolysis in muscle, lipolysis in adipose tissue, decreases insulin secretion and increases glucagon secretion.

Hyperglycemic Effect of Epinephrine



ROLE OF CORTISOL AND GH

- These are long term hyperglycemic hormones; activation takes hours to days.
- Cortisol and GH act to decrease glucose utilization in most cells of the body.
- Effects on these hormones are mediated through the CNS.

CORTISOL

- Cortisol is a steroid hormone.
- It is synthesized in the adrenal cortex.
- Synthesis is regulated via the
  - hypothalamus (CRF) and
  - anterior pituitary (ACTH).
- *Clinical correlation: Cushing's Disease*

GROWTH HORMONE

- GH is a single chain polypeptide hormone.
- Source is the anterior pituitary somatotrophs.
- It is regulated by the hypothalamus.
  - GHRH has a stimulatory effect.
  - somatostatin (GHIF) has an inhibitory effect.
- *Clinical correlation: Gigantism and acromegaly cause insulin resistance.*
  - Glucose intolerance—50%
  - Hyperinsulinemia—70%

Liver and Kidney

- Major source of net endogenous glucose production by gluconeogenesis and glycogenolysis when glucose is low, and of glycogen synthesis when glucose is high.
- Can oxidize glucose for energy and convert it to fat which can be incorporated into VLDL for transport.

Muscle

- Can convert glucose to glycogen.
- Can convert glucose to pyruvate through glycolysis which can be further metabolized to lactate or transaminated to alanine or channeled into the TCA cycle.
- In the fasting state, can utilize FA for fuel and mobilize amino acids by proteolysis for transport to the liver for gluconeogenesis.
- Can break down glycogen, but cannot liberate free glucose into the circulation.

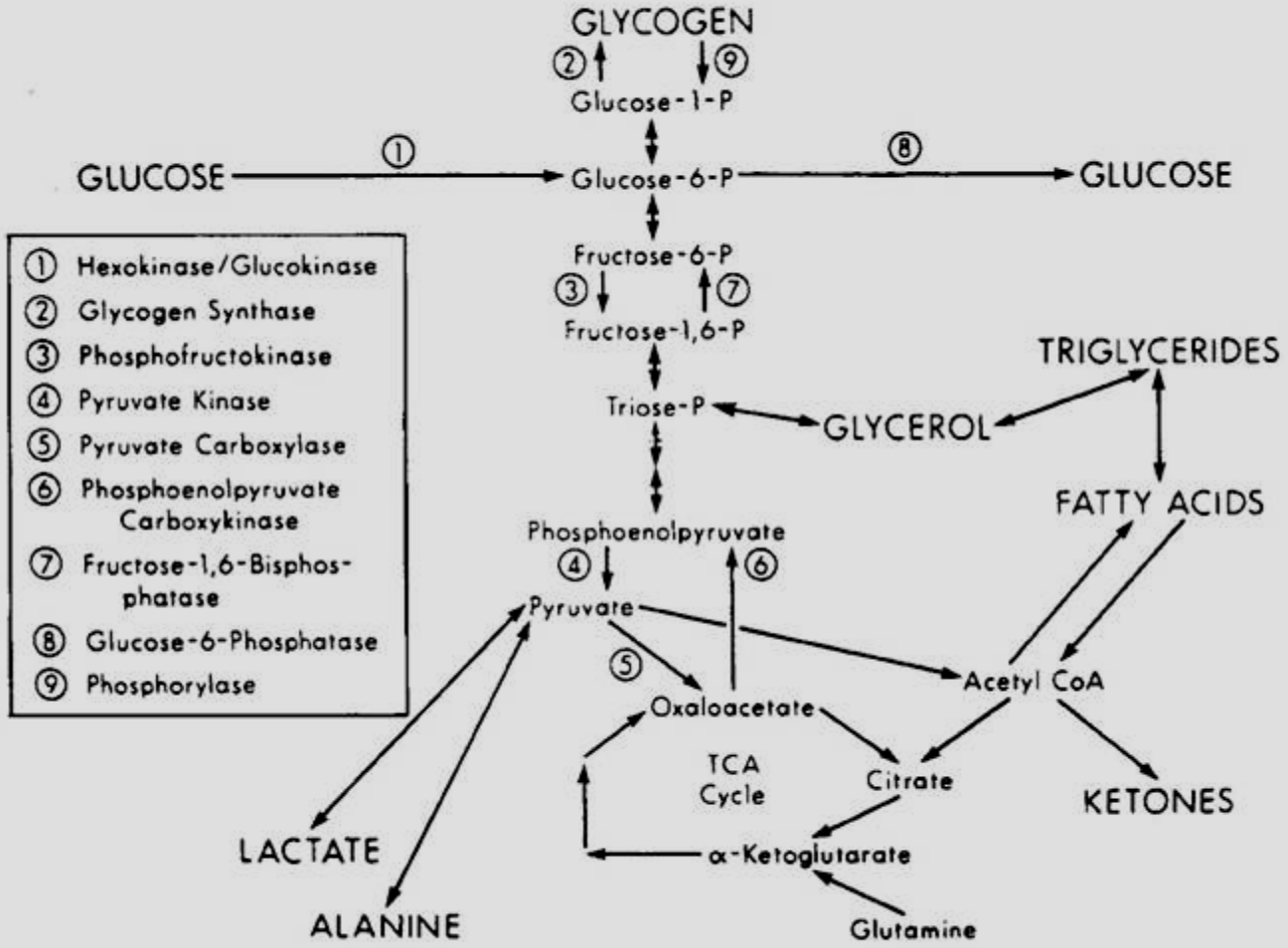
Adipose Tissue (AKA fat)

- Can store glucose by conversion to fatty acids and combine these with VLDL to make triglycerides.
- In the fasting state can use fatty acids for fuel by beta oxidation.

Brain

- Converts glucose to CO_2 and H_2O.
- Can use ketones during starvation.
- Is not capable of gluconeogenesis.
- Has no glycogen stores.

Glucose Metabolism



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- Why is glucose regulation so important?
- What are the CNS manifestations of hypoglycemia?
- What states alter the threshold for these manifestations?

EAT TO LIVE: THE ROLE OF THE PANCREAS

- *Clinical correlation*
  - *Case study*
  - *Insulin therapy during surgery*
  - *What hypoglycemic drug should be avoided during the perioperative period?*

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