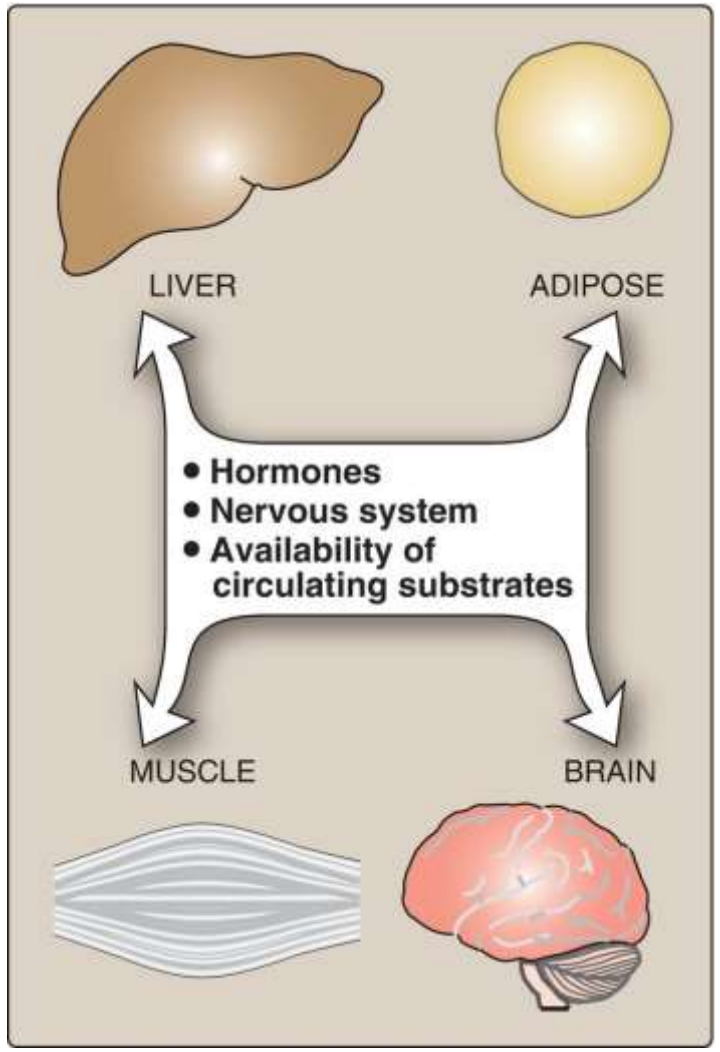
Integration of Metabolism

Dr. Nabil Bashir

Each tissue has a specialized metabolic function

- Four **major organs** play a dominant role in fuel metabolism.
- The integration of energy metabolism is controlled primarily by **hormones**.
- Communication between tissues is mediated by:
  - The nervous system
  - The availability of circulating substrates
  - The levels of plasma hormones
- Two main metabolic states: **feed/fast cycle**
- Three main classes of nutrients
  - Three main circulating substrates?

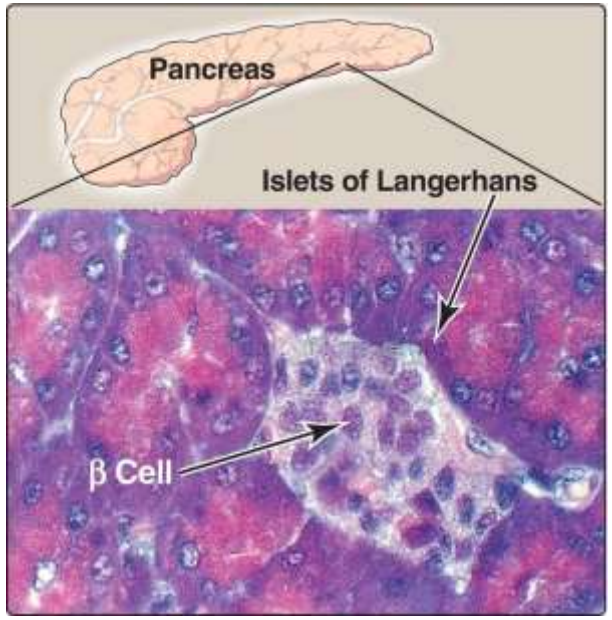


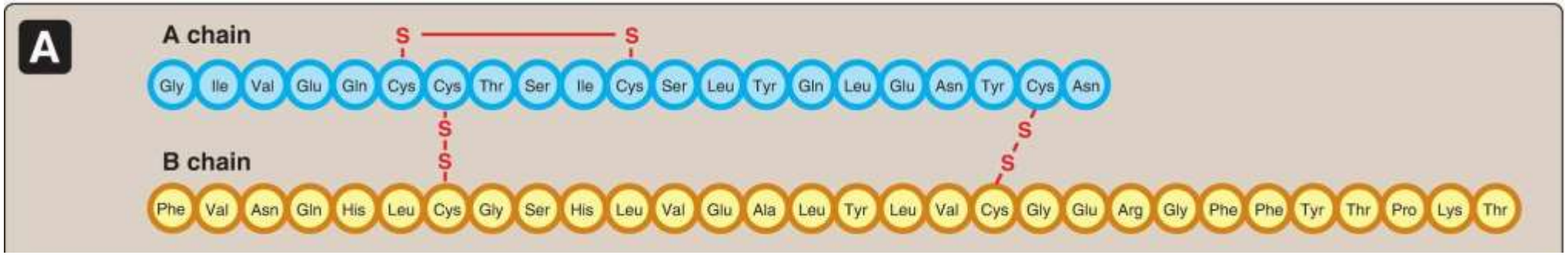
CONCEPTS OF INTEGRATED METABOLISM

- The major tissues of the body **work together** in order to maintain a constant supply of oxidizable fuels.
- The liver of a **well-fed** person is **glycogenic, glycolytic, lipogenic, and cholestrologenic.**
- The liver of the **fasting** person is **glycogenolytic, gluconeogenic, ketogenic, and proteolytic**
- The strategy of metabolism is to **store** fuel when food is **available** and to **mobilize** these stores when **necessary.**

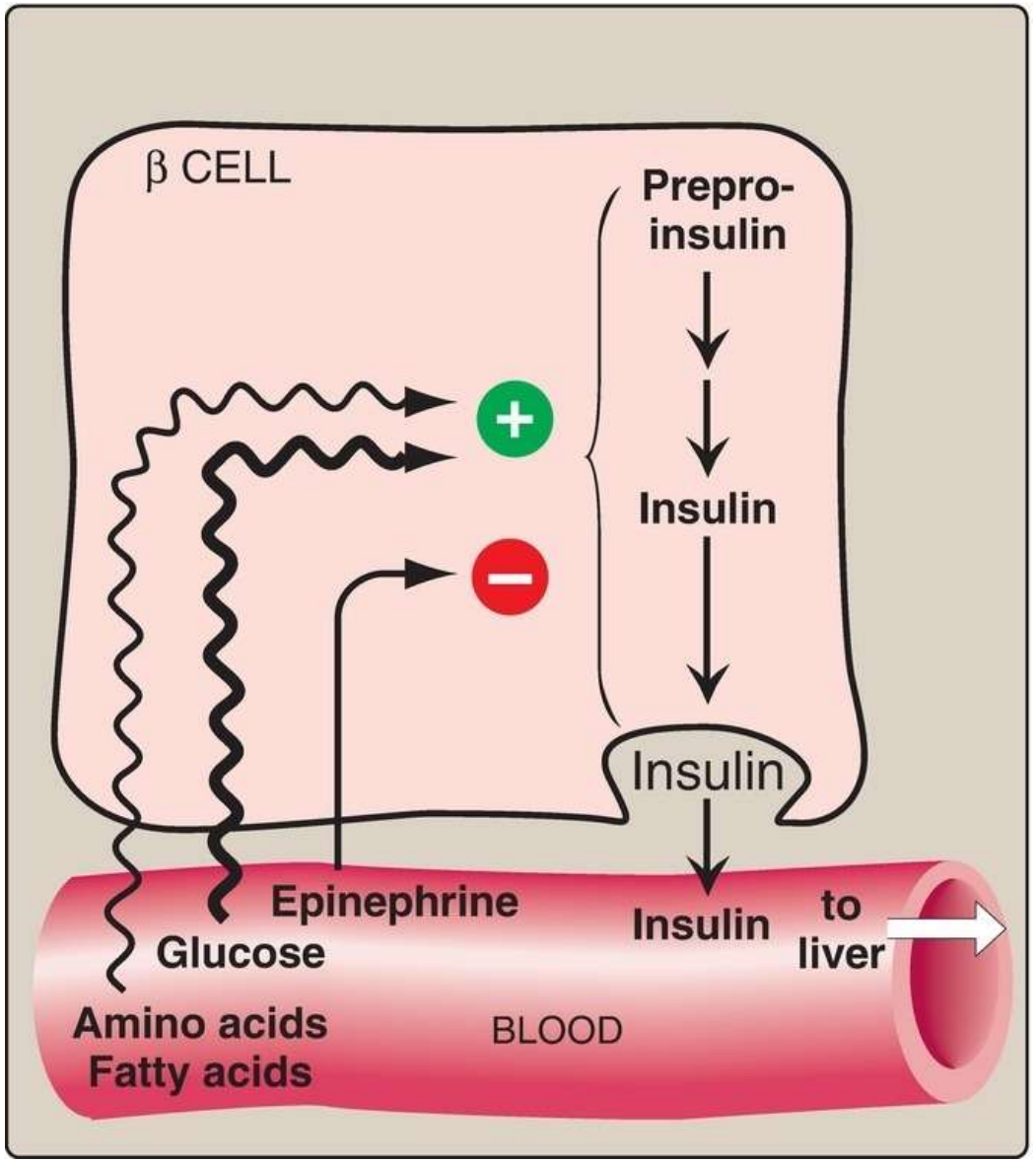
Insulin is a peptide hormone

- Insulin is a peptide hormone produced by the β cells of the islets of Langerhans
- Insulin is the most important hormone coordinating the use of fuels by tissues.
- Insulin has anabolic metabolic effects

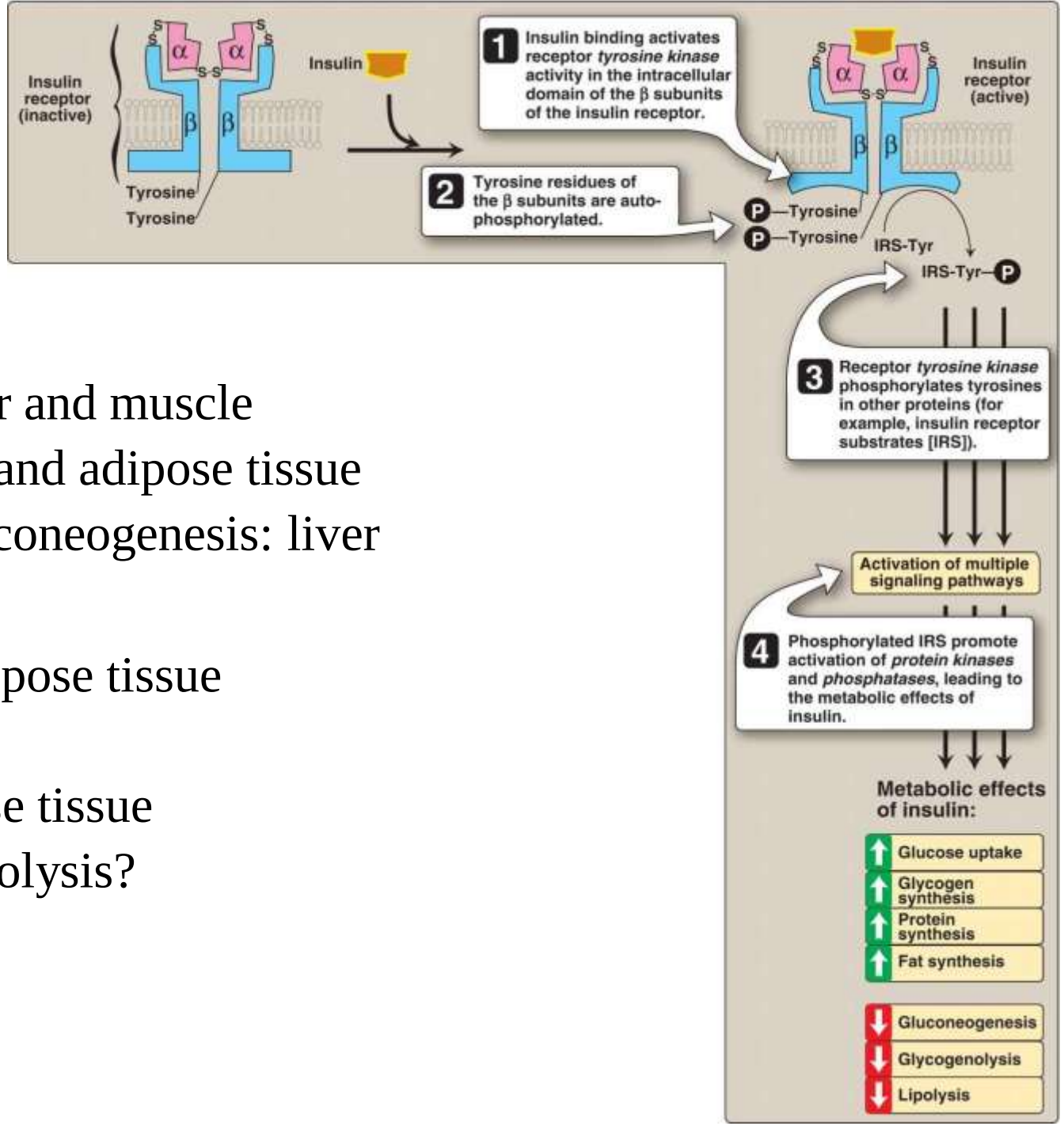




The secretion of insulin is regulated by bloodborne fuels and hormones

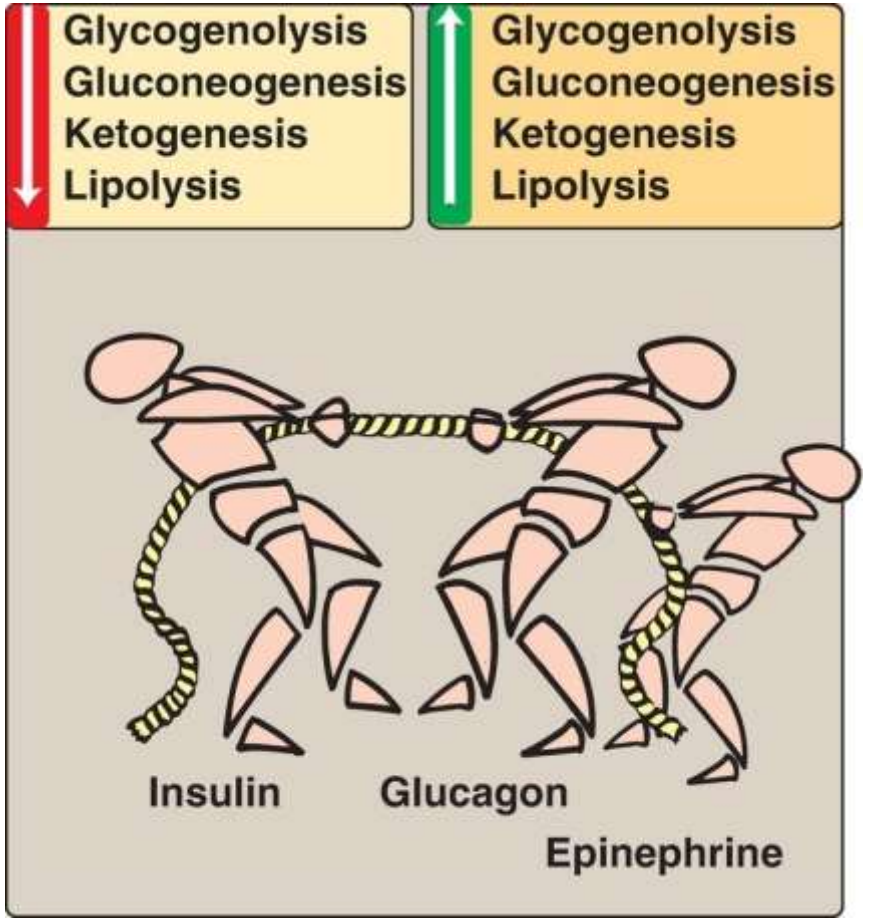


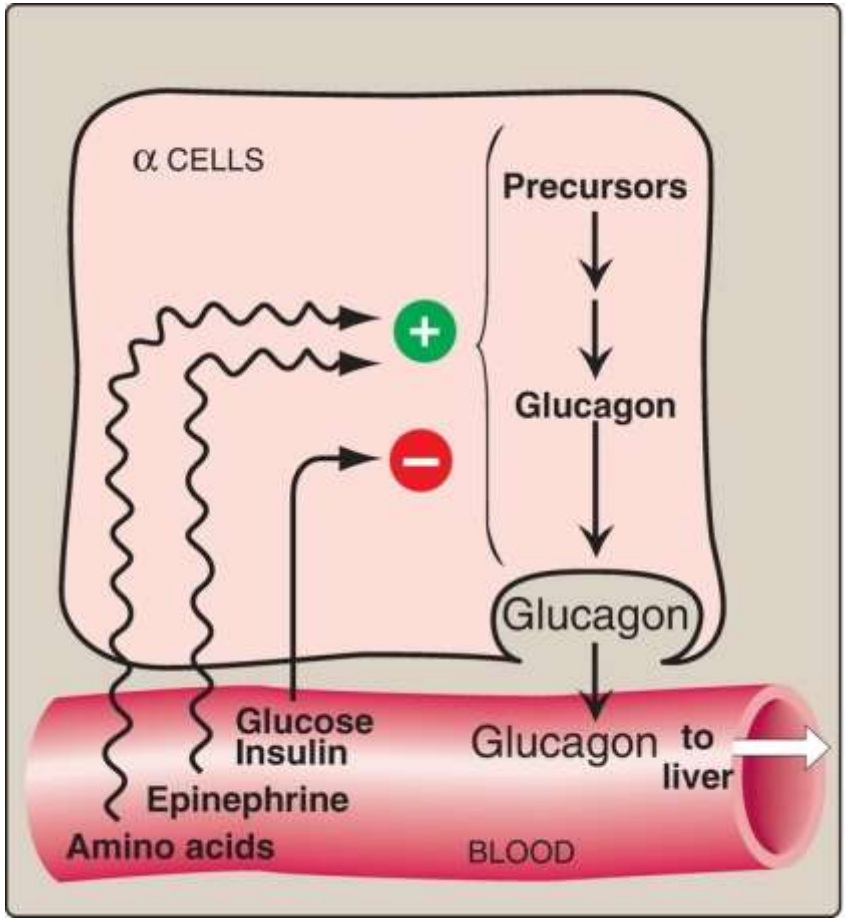
Insulin has an anabolic metabolic effect



- Carbohydrates:
  - Increases glycogen synthesis: liver and muscle
  - Increases glucose uptake: muscle and adipose tissue
  - Decreases glycogenolysis and gluconeogenesis: liver
- Lipids:
  - Decreases TAG degradation in adipose tissue
    - Hormone-sensitive lipases
  - Increases TAG synthesis in adipose tissue
    - Glycerol-3-phosphate via glycolysis?
- Protein: protein synthesis

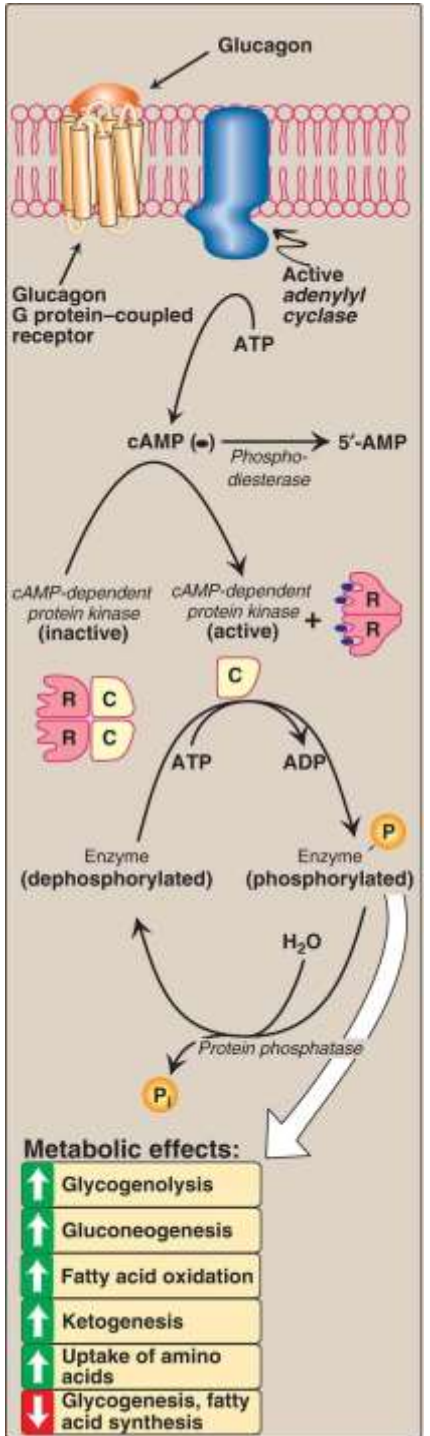
Glucagon, epinephrine, norepinephrine, cortisol, and growth hormone are counterregulatory hormones.





Glucagon has a catabolic metabolic effect

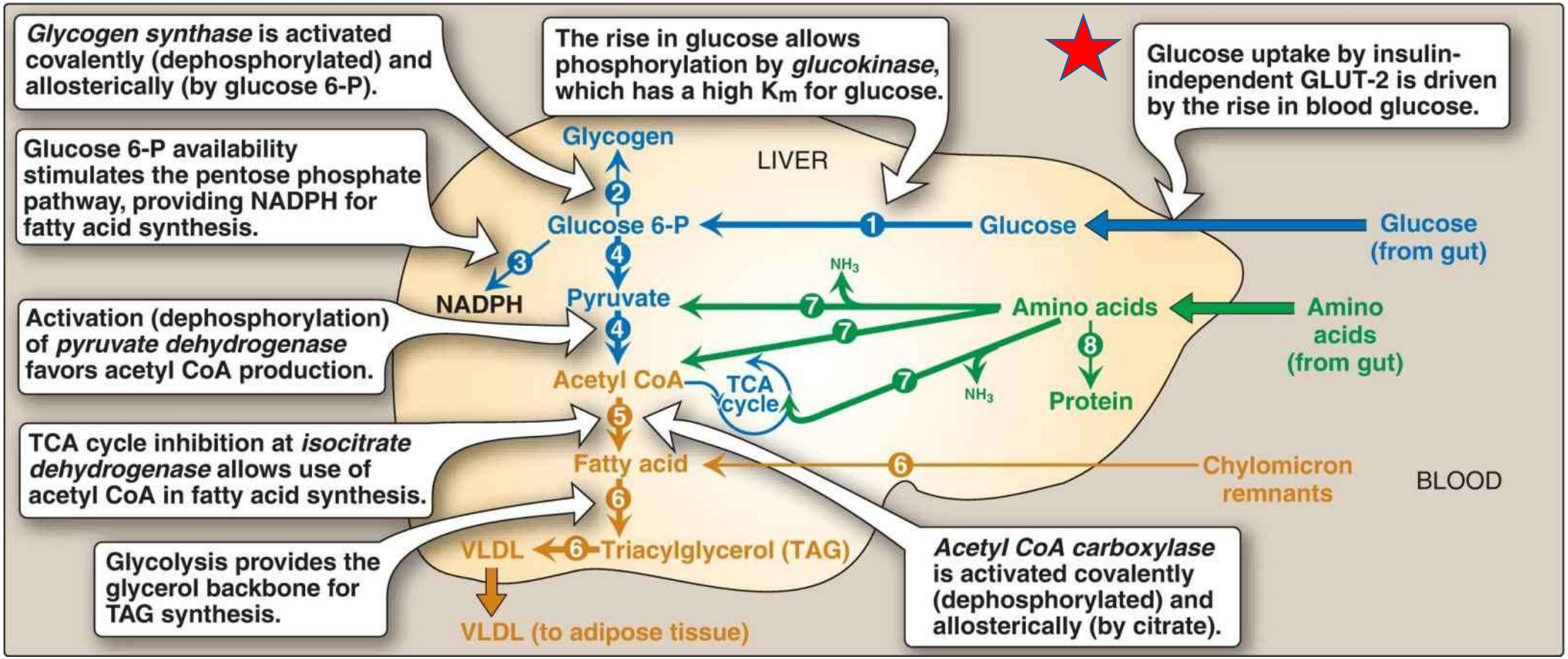
- Carbohydrates:
  - Breakdown liver glycogen
  - Increases hepatic gluconeogenesis
- Lipid:
  - Inhibition of FA synthesis through phosphorylation and subsequent inactivation of *ACC* by *adenosine monophosphate* (*AMP*)– *activated protein kinase.*
  - The free FA released –via catecholamine on lipolysis -are taken up by the liver and oxidized to acetyl CoA, which is used in ketone body synthesis.
- Protein: increases AAs uptake-gluconeogenesis



Well fed-absorptive state (0-4 hr)
High ratio of insulin/glucagon ; hyperglycemia, Hyperlipemia, Hyperaminoacidemia

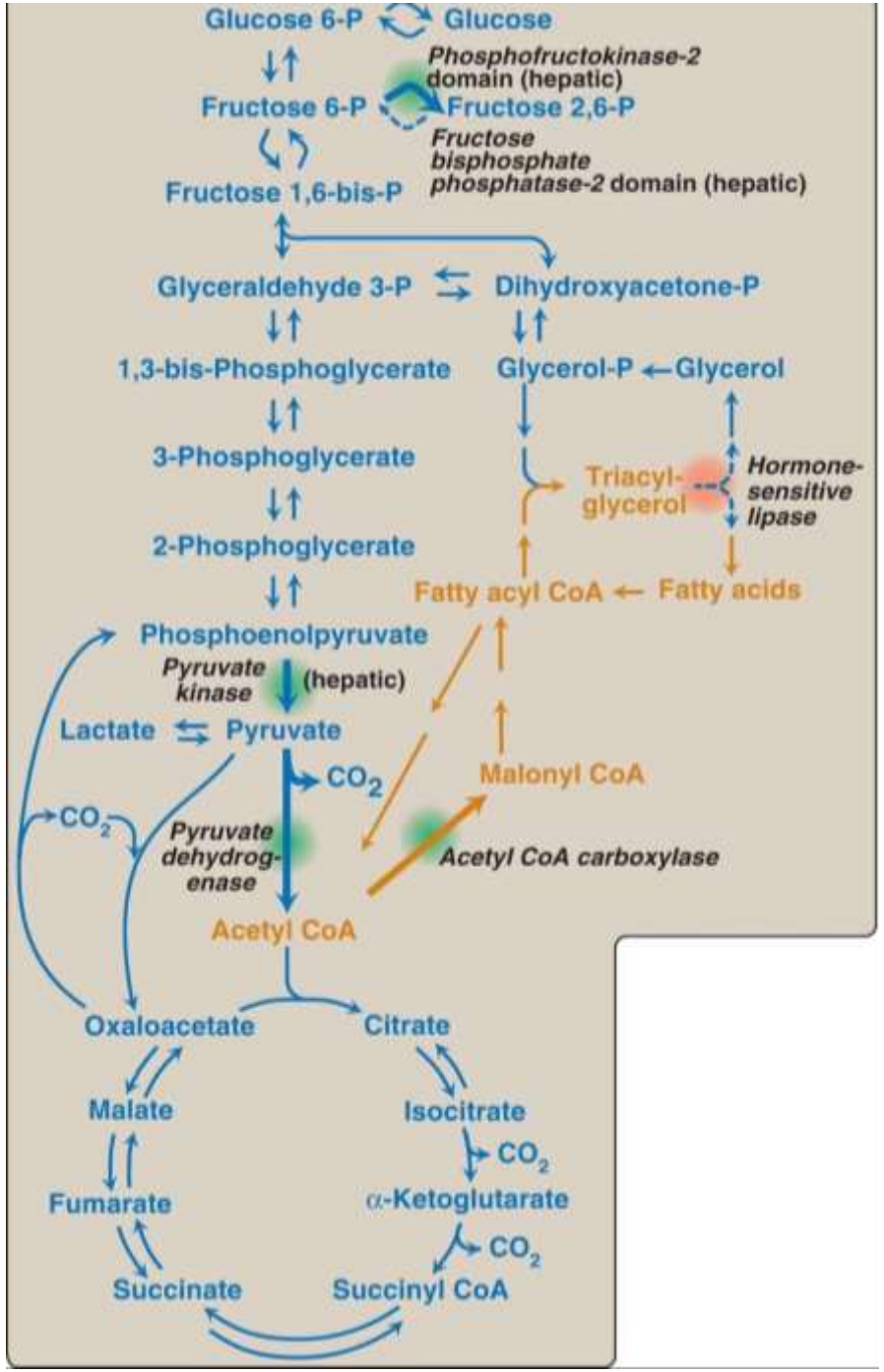
Liver processes and distribute nutrients

The liver smooths out potentially broad fluctuations in the availability of nutrients for the peripheral tissues



Liver has increased glycolysis in the absorptive state

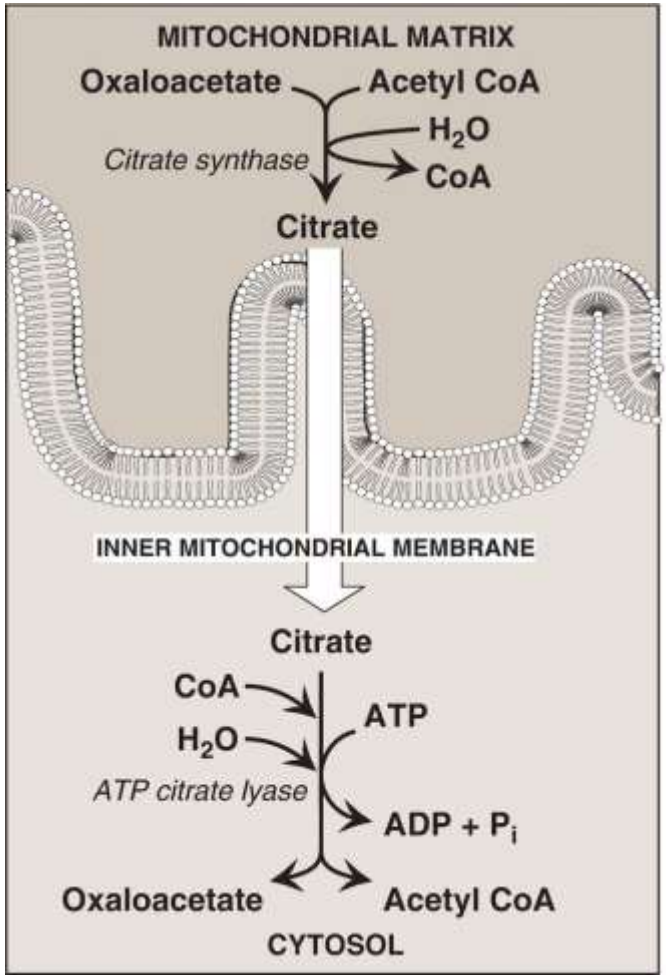
- High insulin/glucagon inducs the conversion of glucose to pyruvate
  - *Glucokinase* , ***PFK-1*** , *pyruvate kinase and Pyruvate dehydrogenase*
  - Covalent and allosteric regulation

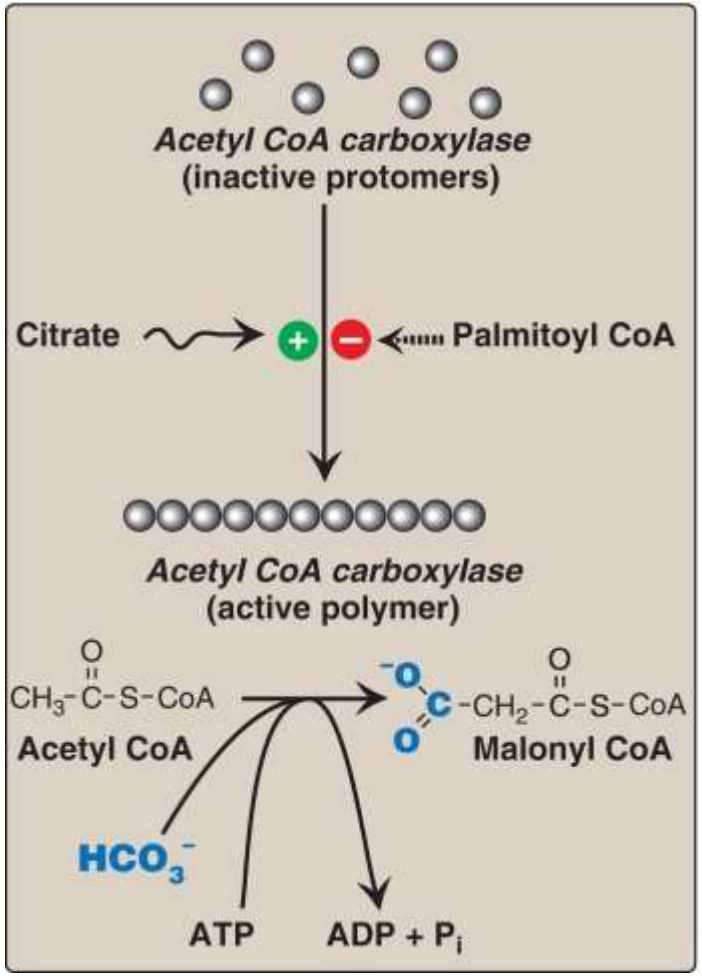


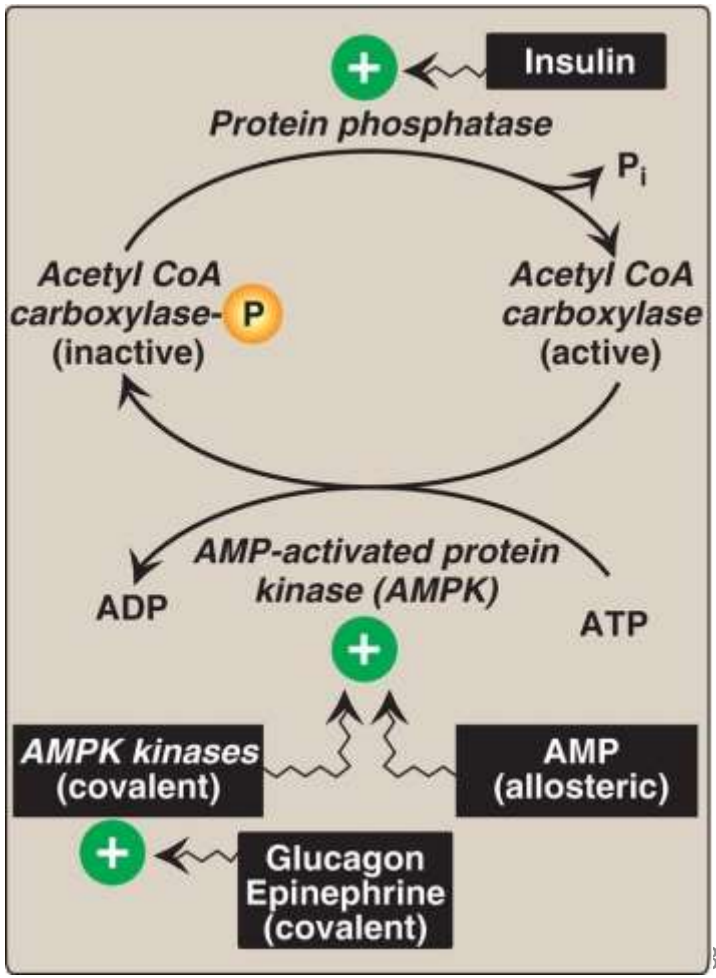
The liver decreases glucose production in the fed state

- The liver inhibits gluconeogenesis and glycogenolysis
- Gluconeogenesis
  - Low levels of **acetyl CoA** deactivate ***Pyruvate carboxylase* (*PC)*** - acetyl CoA is used in FA synthesis
  - High insulin/glucagon ratio deactivate ***fructose 1,6-bisphosphatase***
- Glycogenolysis:
  - *Glycogen phosphorylase* and *phosphorylase kinase* are inhibited by dephosphorylation

Liver increased fatty acid and TAG synthesis in the absorptive state

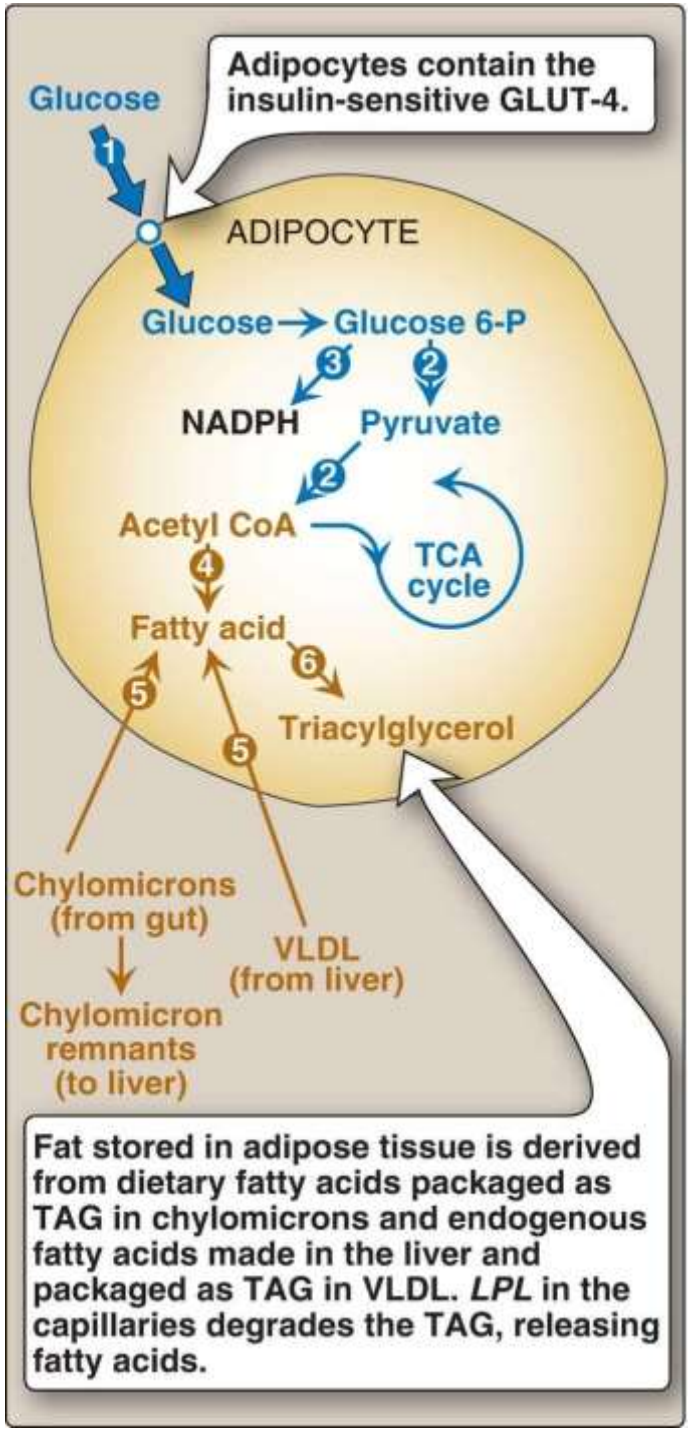






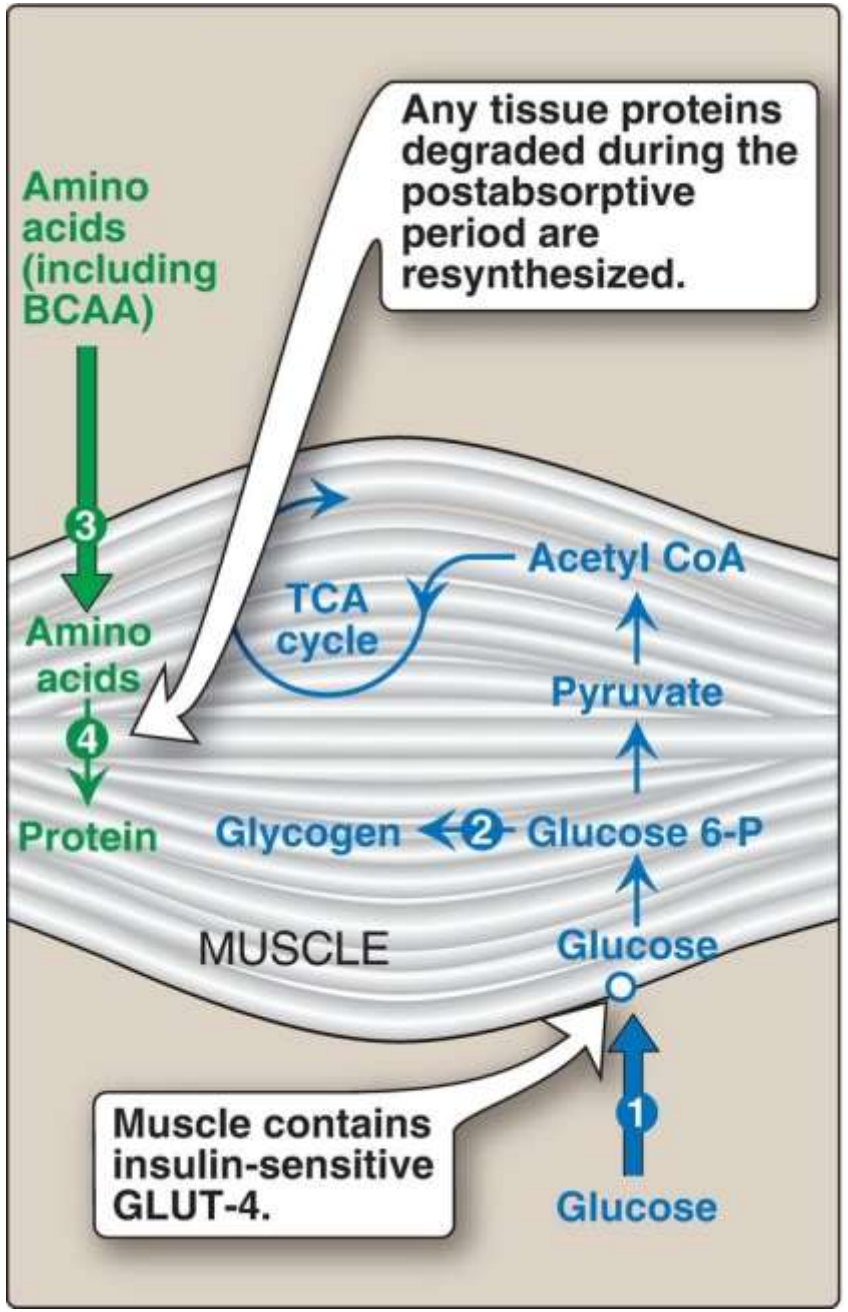
Adipose tissue is second only to the liver in its ability to distribute fuel molecules

- Adipose in the absorptive state has:
  - Increased glucose uptake- insulin sensitive
  - **Increased glycolysis to provide glycerol 3- phosphate for** TAG synthesis
    - Adipose tissue lacks glycerol kinase
  - Increased pentose phosphate pathway activity that provides NADPH for FA synthesis-minor
  - Increased lipoprotein lipase (LPL) by insulin: LPL frees FA from VLDL and chylomicrons for TAG synthesis



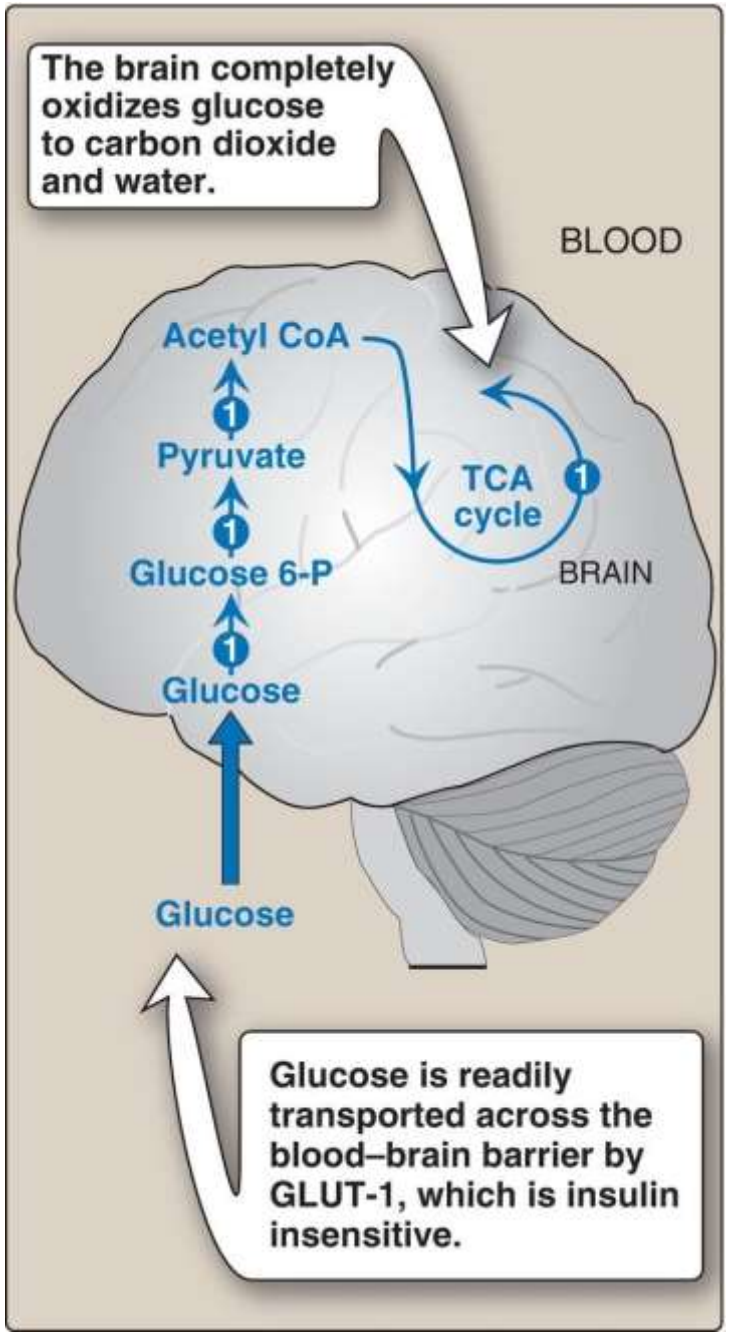
In the fed state: Muscle takes up glucose for energy and glycogen synthesis and amino acids for energy and protein synthesis

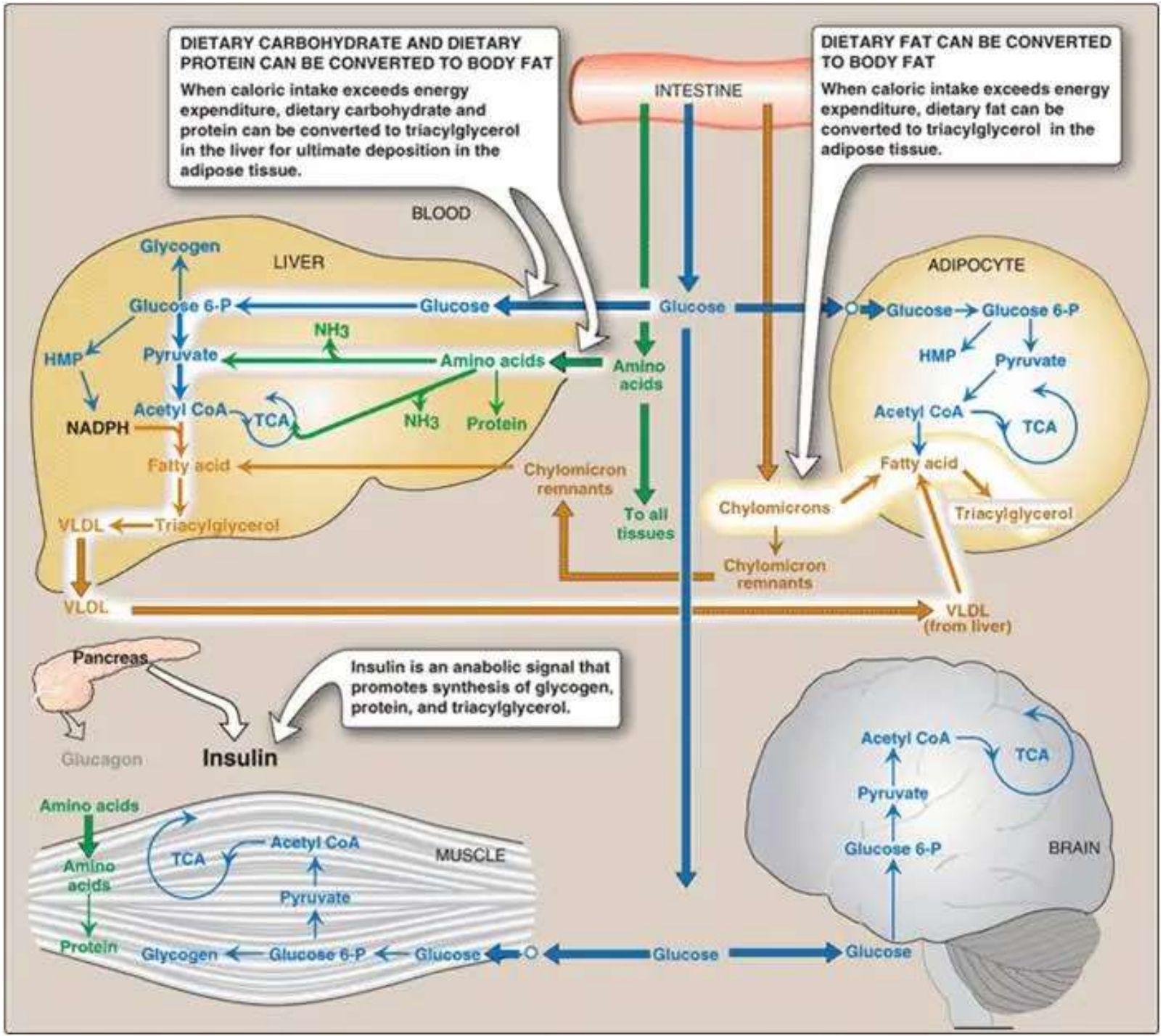
- Increased glucose uptake
- Increased Glucose phosphorylation to glucose 6-phosphate by hexokinase
- High insulin/glucagon ratio and glucose 6-phosphate increase glycogenesis
- FA are released from chylomicrons and VLDL by the action of *LPL-minor*
- Note: there is no covalent regulation of *PFK-2* in skeletal muscle. There is no glucagon receptor
- Increased AA (branched) uptake and protein synthesis.



The brain exclusively uses glucose as a fuel in the fed state

- The brain contains no significant stores of glycogen and TAG




DIETARY CARBOHYDRATE AND DIETARY PROTEIN CAN BE CONVERTED TO BODY FAT
When caloric intake exceeds energy expenditure, dietary carbohydrate and protein can be converted to triacylglycerol in the liver for ultimate deposition in the adipose tissue.
DIETARY FAT CAN BE CONVERTED TO BODY FAT
When caloric intake exceeds energy expenditure, dietary fat can be converted to triacylglycerol in the adipose tissue.
INTESTINE
BLOOD
LIVER
Glycogen
Glucose 6-P
Glucose
HMP
Pyruvate
NH3
Amino acids
Acetyl CoA
TCA
NADPH
Protein
Fatty acid
Chylomicron remnants
VLDL
Triacylglycerol
To all tissues
Glucose
ADIPOCYTE
Glucose
Glucose 6-P
HMP
Pyruvate
Acetyl CoA
TCA
Fatty acid
Triacylglycerol
Chylomicrons
Chylomicron remnants
VLDL
VLDL (from liver)
Pancreas
Glucagon
Insulin
Insulin is an anabolic signal that promotes synthesis of glycogen, protein, and triacylglycerol.
Amino acids
Amino acids
TCA
Acetyl CoA
Pyruvate
MUSCLE
Protein
Glycogen
Glucose 6-P
Glucose
Glucose
Glucose
Acetyl CoA
TCA
Pyruvate
Glucose 6-P
BRAIN

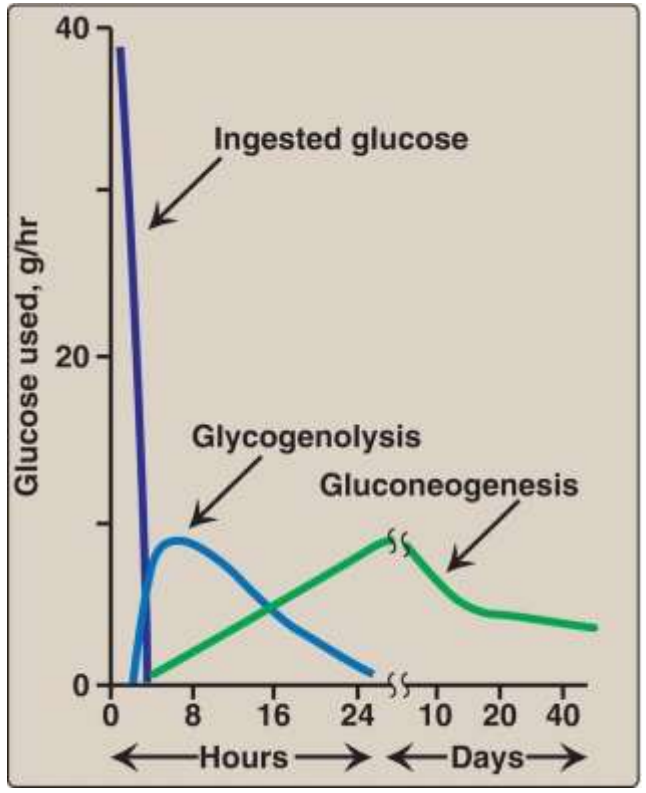
The fasted state & starvation

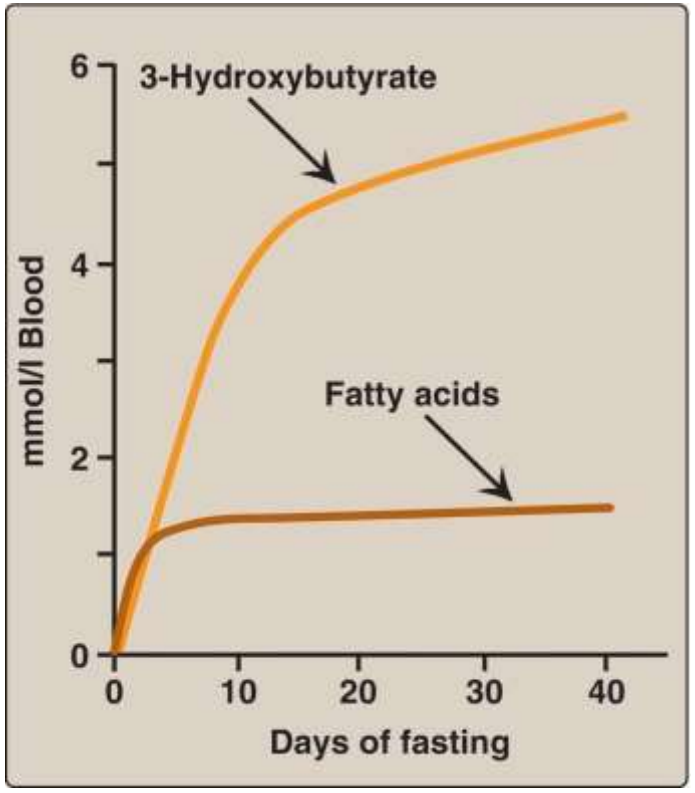
Fasted state induces a catabolic metabolic state

- In the absence of food, plasma levels of glucose, amino acids, and TAG fall, triggering a decline in insulin secretion and an increase in glucagon, epinephrine, and cortisol secretion.
- Low insulin/counterregulatory hormone induces a catabolic metabolic state.
  - Degradation of TAG, glycogen, and protein
- Substrates are exchanged among the liver, adipose tissue, skeletal muscle, and brain
  - Sustain energy metabolism in the brain, red blood cells, and other glucose-requiring tissues
    - Pyruvate, alanine, and glycerol are needed for gluconeogenesis
  - Mobilize FA from TAG in WAT for the synthesis and release of ketone bodies by the liver to supply energy to other tissues and spare body protein

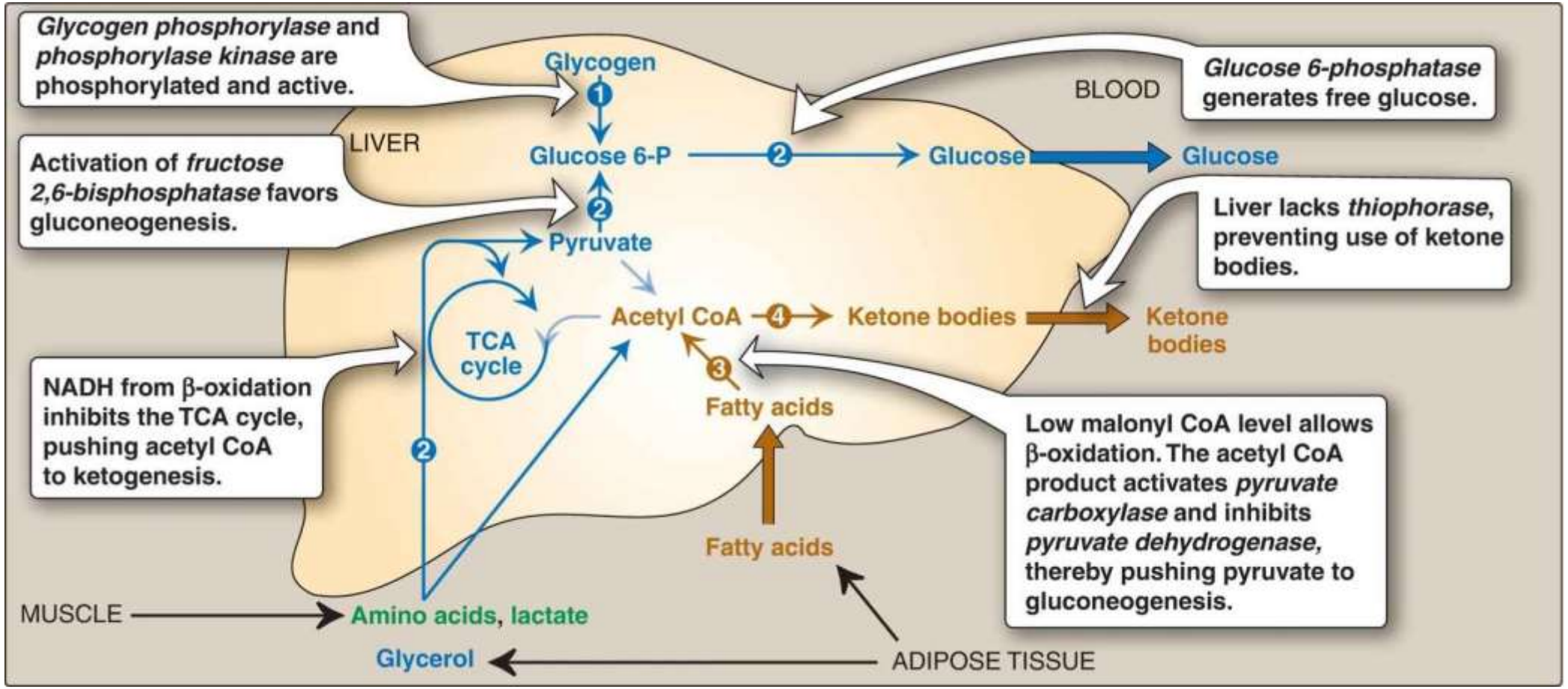
The liver maintains the blood glucose levels during the fasting state

- Liver produces glucose via glycogenolysis and gluconeogenesis for glucose-requiring tissues.
  - **Increased glycogenolysis- short term:**
    - *PKA* -mediated phosphorylation (and activation) of *glycogen phosphorylase kinase* that phosphorylates (and activates) *glycogen phosphorylase*
    - **exhausted by 24h**
  - **Increased gluconeogenesis-short and long-term**
    - The carbon skeletons for gluconeogenesis are derived primarily from glucogenic amino acids and lactate from muscle and glycerol from adipose tissue
    - *fructose 1,6-bisphosphatase by* fructose 2,6-bisphosphate ?
    - PEPCK by glucagon?
  - **Increased fatty acid oxidation**
- The liver synthesizes and distributes ketone bodies for use by other tissues.-preserve essential body proteins
  - Concentration of acetyl CoA from FA oxidation exceeds the oxidative capacity of the TCA cycle



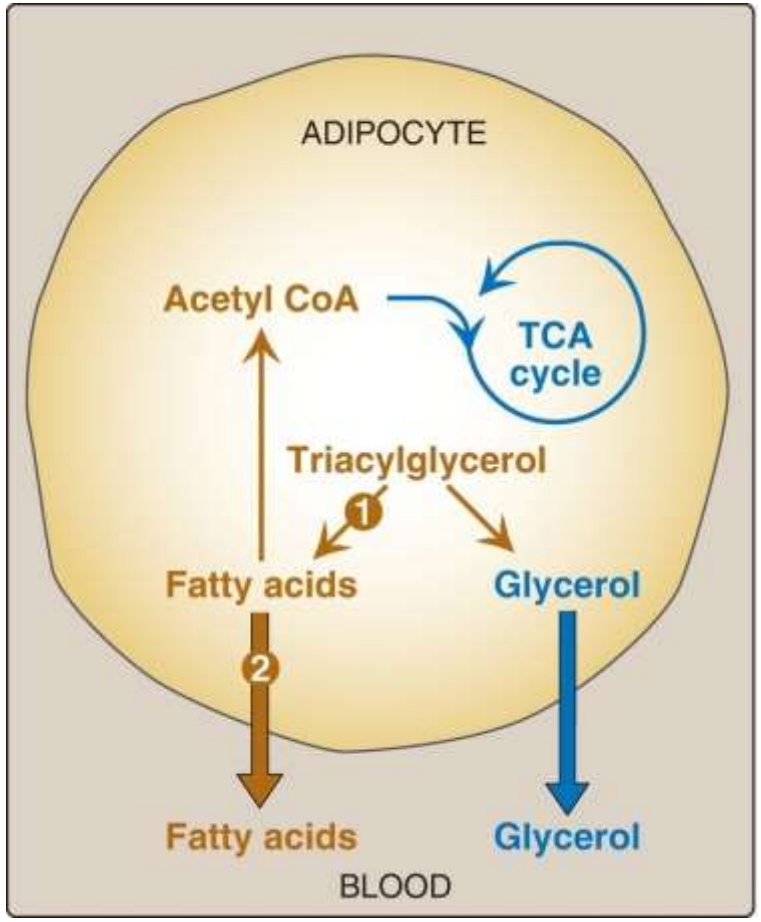


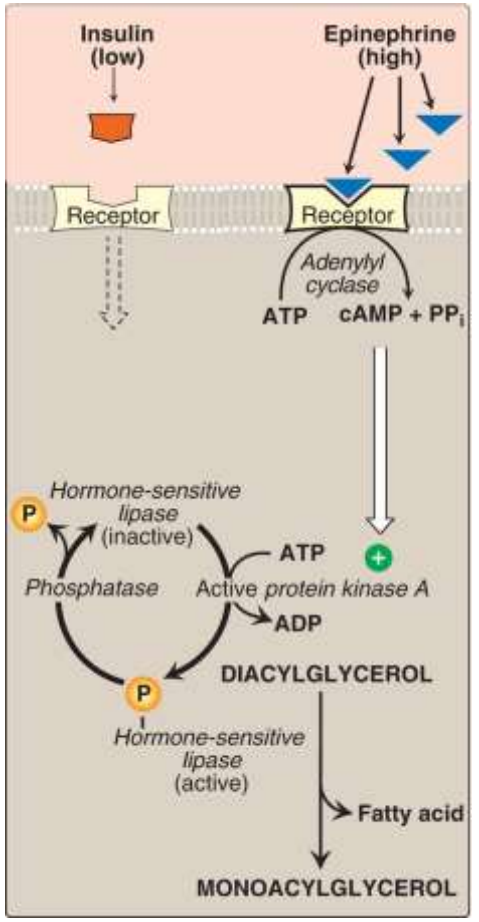
In the fasting state: Liver produces glucose via glycogenolysis and gluconeogenesis for glucose-requiring tissues



Adipose tissue has increased TAG degradation in the fasting state

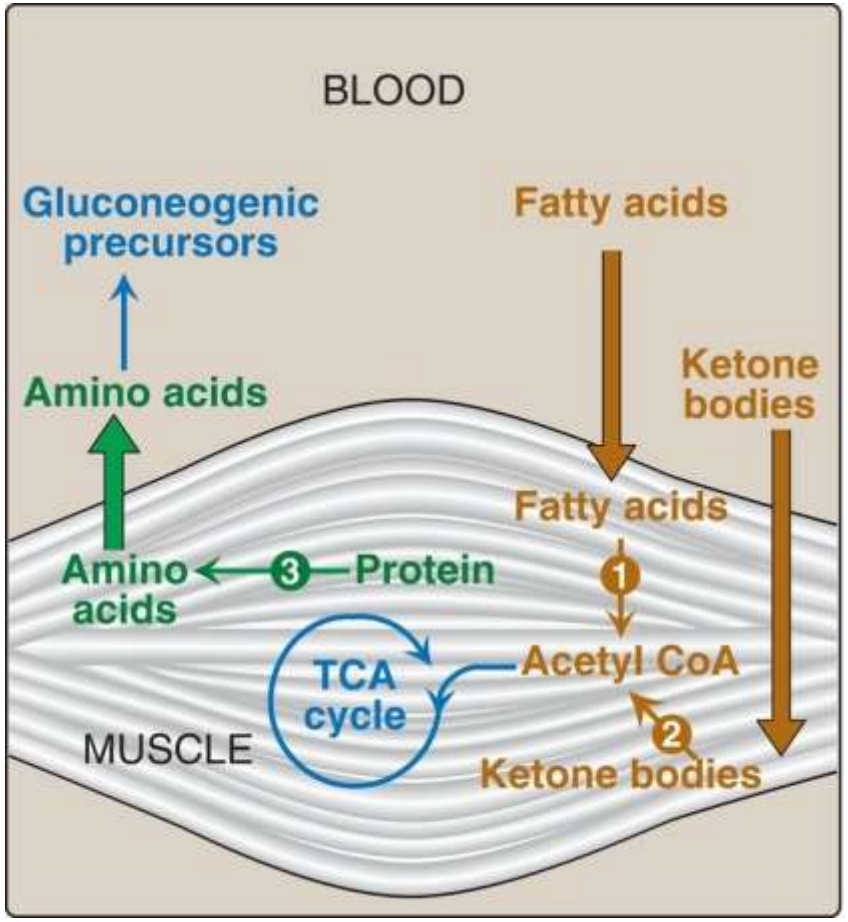
- Low plasm glucose level decreases TAG synthesis
- Catecholamines norepinephrine and epinephrine induce HSL by PKA
- Hydrolysis of TAG releases fatty acid
- Low LPL activity decreases fatty acid uptake



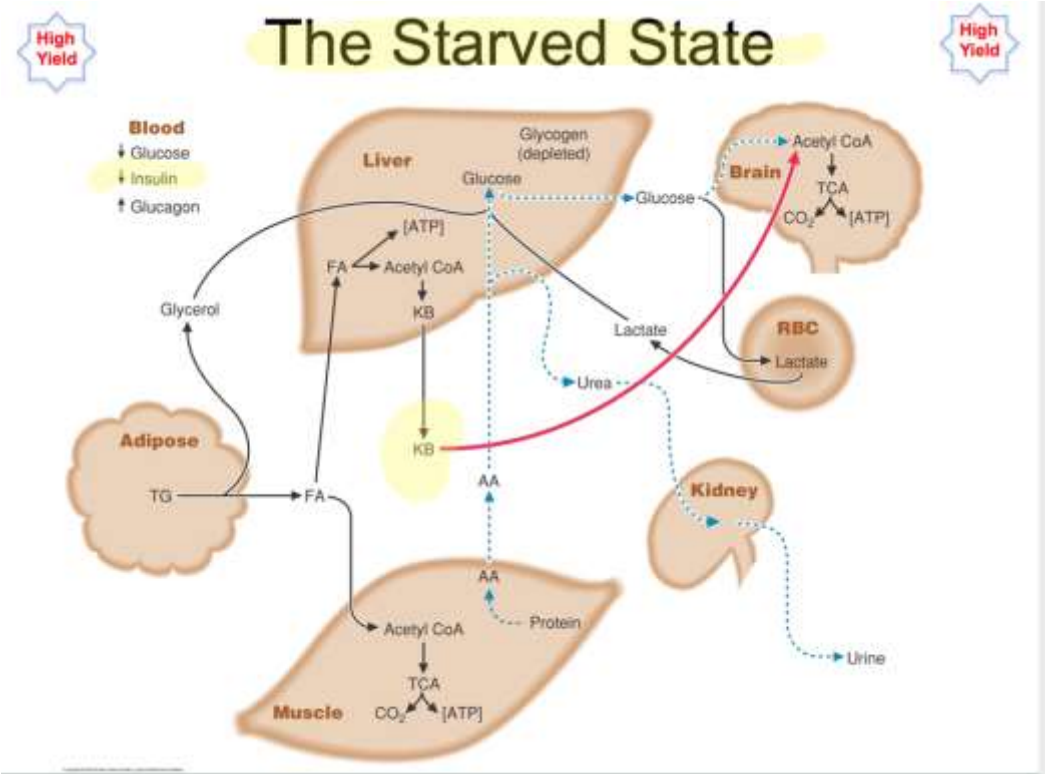


Resting muscle switches from glucose to FA for fuel source in fasting state

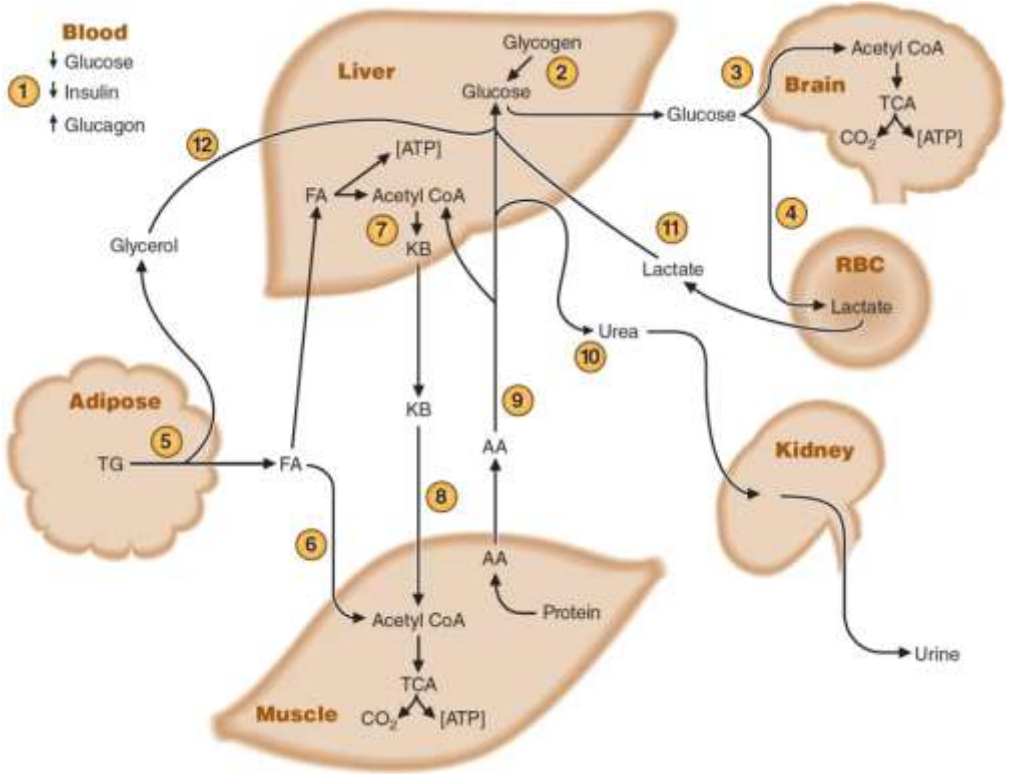
- Muscle uses FA from adipose tissue and ketone bodies from the liver as fuels
- Protein degradation for liver gluconeogenesis during the first days of fasting
  - This declines by the 2nd week of fasting as the brain uses ketone bodies as fuel.
- In prolonged fasting, muscle decreases its use of ketone bodies (thus sparing them for the brain) and oxidizes FA almost exclusively



STARVATION

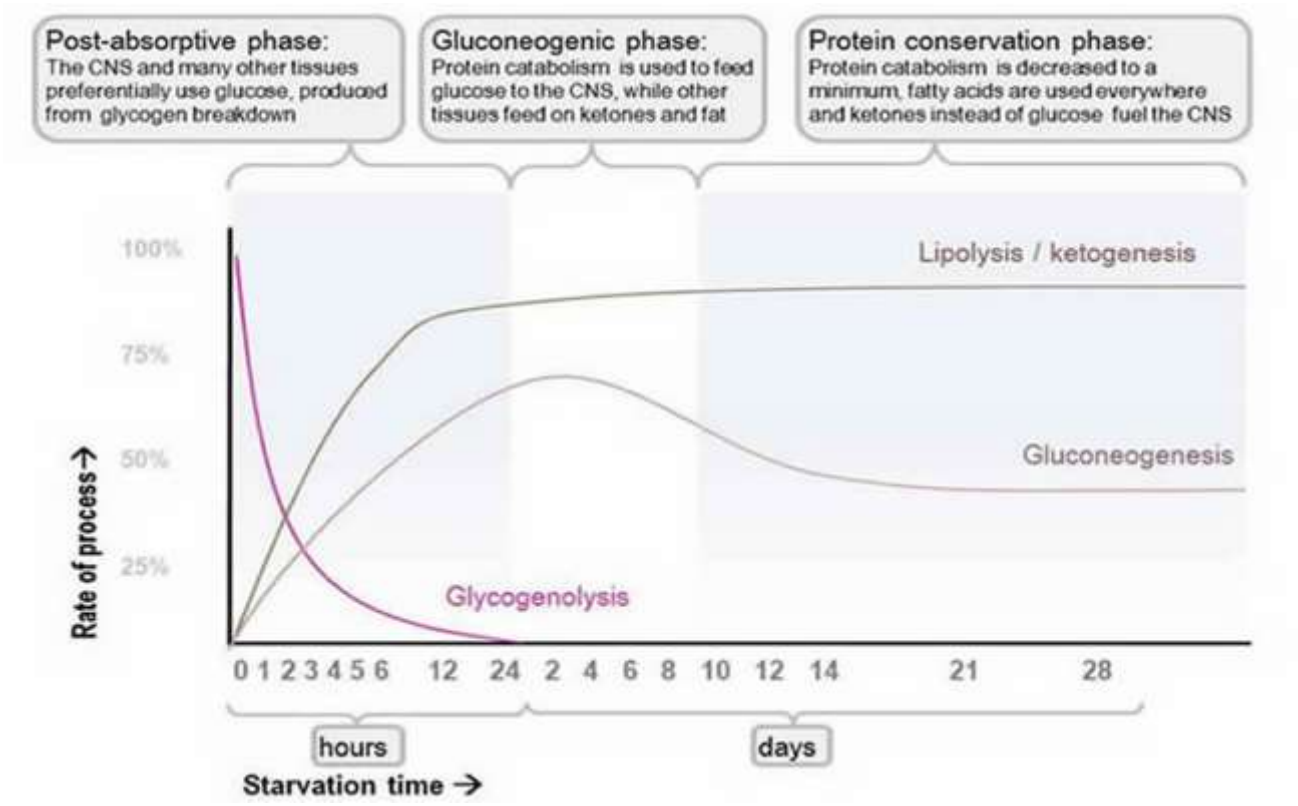


FASTING



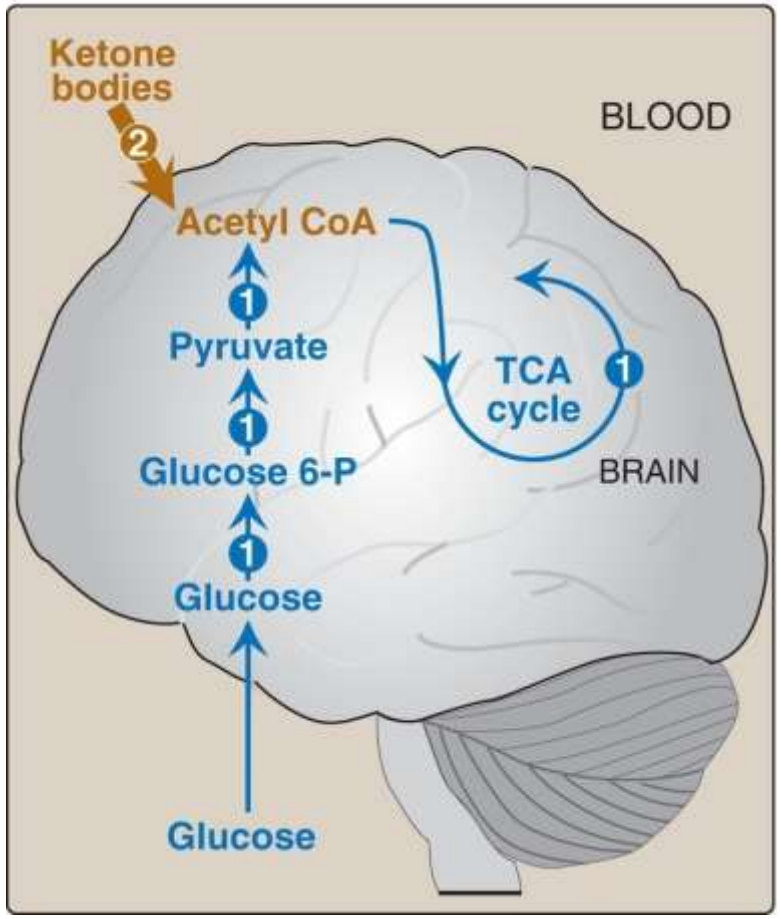
Prolonged starvation

- After 24 days of starvation, the steady state rates of carbohydrates, lipid, and amino acid metabolism appear to be established
- ➢ About 30% of energy requirement of the brain is met by glucose
- ➢ 50% by β-hydroxybutyrate
- ➢ 5% by acetoacetate
- ➢ 15% by amino acids
- Prolonged starvation ends with death or refeeding



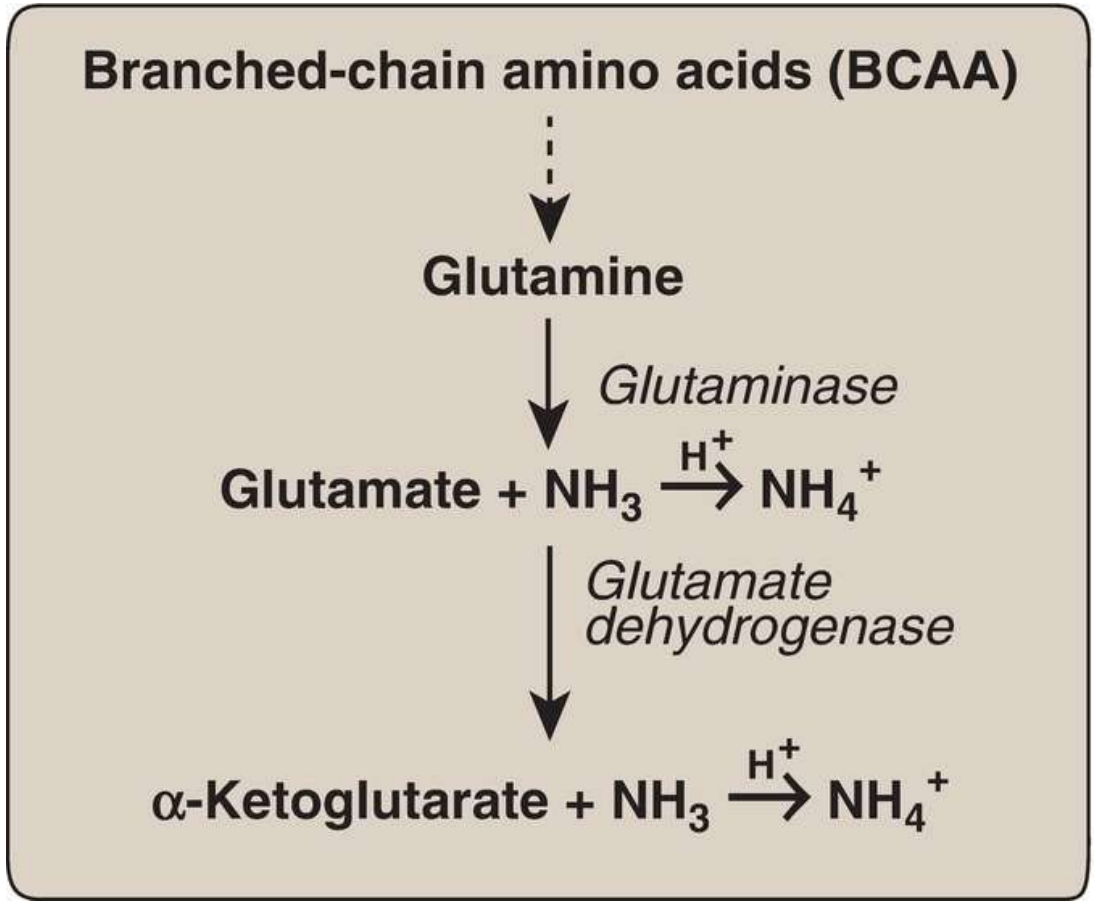
The brain uses ketone bodies during prolonged fasting

- During the first few days of fasting, the brain uses glucose as fuel.
  - Blood glucose is maintained by hepatic gluconeogenesis from glucogenic precursors, such as amino acids from proteolysis and glycerol from lipolysis
- After prolonged fasting (2-3 weeks), the brain uses ketone bodies as a fuel
- This spares glucose and muscle proteins



50% of gluconeogenesis occurs in the kidney in late fasting

- The kidney expresses *glucose 6-phosphatase*
- Ketoacidosis and AA catabolism.



Referenses

- Lippincott’s Illustrated Reviews, 7e: Chapters 23 and 24