Metabolism

فريق طوفان الأقصى

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Integration of Metabolism

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NOTE: what is meant by this topic? In all past lectures we took about "Metabolism", now we'll talk about combination of these metabolic pathways in different tissues and how these tissues coordinate with each other under different conditions -fasting and well fed state-, to maintain the levels of glucose in the body

NOTE: Take a breath, relax, and let's start. This lecture, Insha'Allah, will be the easiest, as it is simply about connecting the pathways we have already covered, demonstrating their great harmony and their remarkable interdependence

" إِنَّا كُلَّ شَيْءٍ خَلَقْنَاهُ بِقَدرٍ "

Each tissue has a specialized metabolic function

NOTE: this regulated by hormones such as insulin ,glucagon, epinephrine

NOTE: availability of fatty acids in adipose tissue will be useful for energy production in other tissues such as muscle. Also, when liver synthesize glucose and release it to Brain –or any other tissue- it's also an example for coordination.

Four **major organs** play a dominant role in fuel metabolism.

The integration of energy metabolism is controlled primarily by **hormones**.

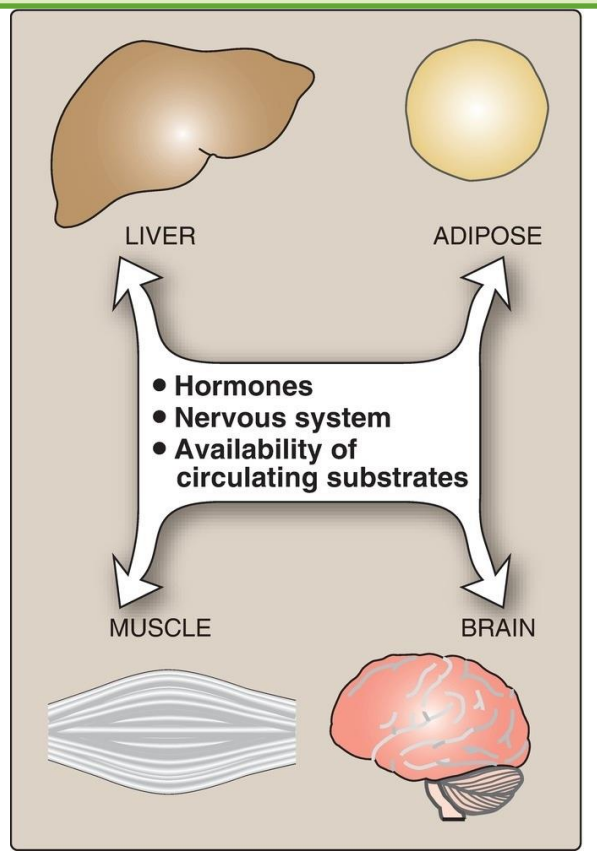
Communication between tissues is mediated by:

- 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.

- **NOTE:** those oxidizable fuels are amino acids, glucose, fatty acids, and Ketone bodies (as they cross BBB)

The liver of a **well-fed** person is **glycogenic, glycolytic, lipogenic, and cholestrologenic.**

- **NOTE:** glycogenic: synthesis of glycogen
  glycolytic :degradation of glucose (**Warning: it's not the same as " glycogenolysis"**
- Lipogenic: synthesis of TAG , cholestrologenic: synthesis of cholesterol

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.**

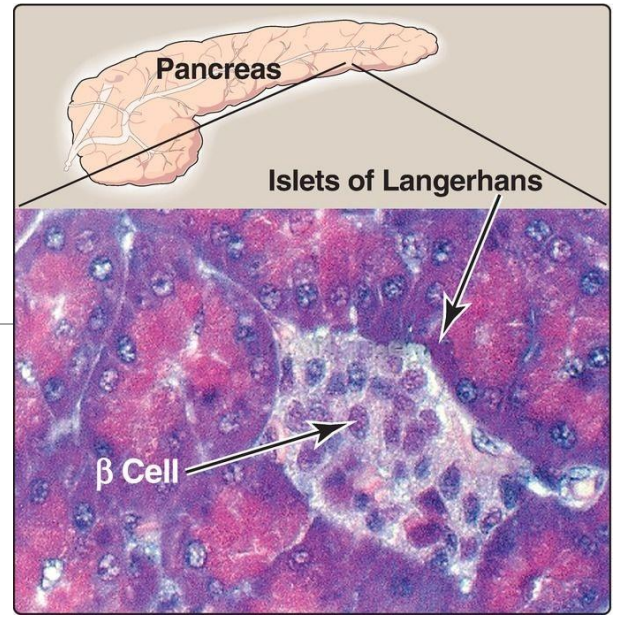
- **NOTE:** store fuel: such as TAG, Glycogen, proteins
  * mobilize = degrade

- **NOTE: let's explain the previous sentence " The liver of the fasting person is glycogenolytic, gluconeogenic, ketogenic, and proteolytic "**
- **Glycogenolysis: This is the process where the liver breaks down glycogen**
- **Gluconeogenesis: When glycogen stores are depleted, the liver starts producing glucose from non-carbohydrate sources**
- **Ketogenic: As fasting continues and the body's glucose and glycogen stores diminish, the liver begins to produce ketone bodies from fatty acids. Ketone bodies serve as an alternative energy source, particularly for the brain, when glucose is scarce**
- **Proteolytic: Proteins from muscle and other tissues are broken down into amino acids, Some of these amino acids are then used by the liver for gluconeogenesis.**

- **NOTE: remember the enzyme "glycogen synthase" when it's phosphorylated = inactive. While glycogen phosphorylase= active when phosphorylated. which make sense because we don't have synthesis and degradation at the same time ,**

Insulin is a peptide hormone

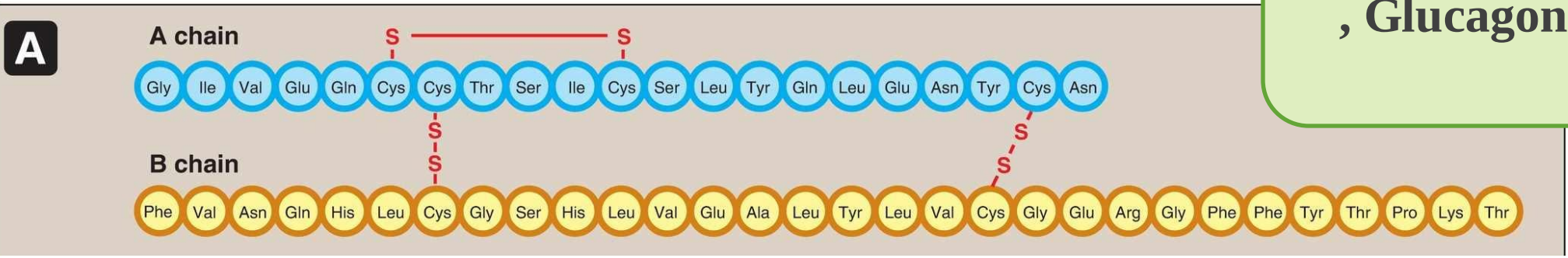
β (beta) cells in the pancreas produce insulin initially as 'proinsulin.' Proinsulin is then processed, and during this process, C-peptide is cleaved off. This results in the formation of mature 'insulin'.



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



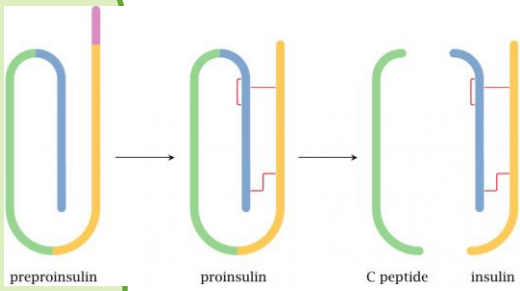
NOTE: Insulin has anabolic metabolic effects , Glucagon has catabolic ones

- NOTE: when insulin is high it stops glycogenolysis by inhibiting glycogen phosphorylase .. Also we stop gluconeogenesis by inhibit " PEPCK " and pyruvate carboxylase and glu-6 phosphatase and fru 1,6 bisphosphatase.
- insulin also inhibits hormone sensitive lipase (in adipose tissue)

- Additional information: let's talk a little bit about insulin synthesis in pancreas but keep in mind that this Additional information is not required.
- We can use C-peptide test to differentiate between DM-1 and DM-2 ..How?

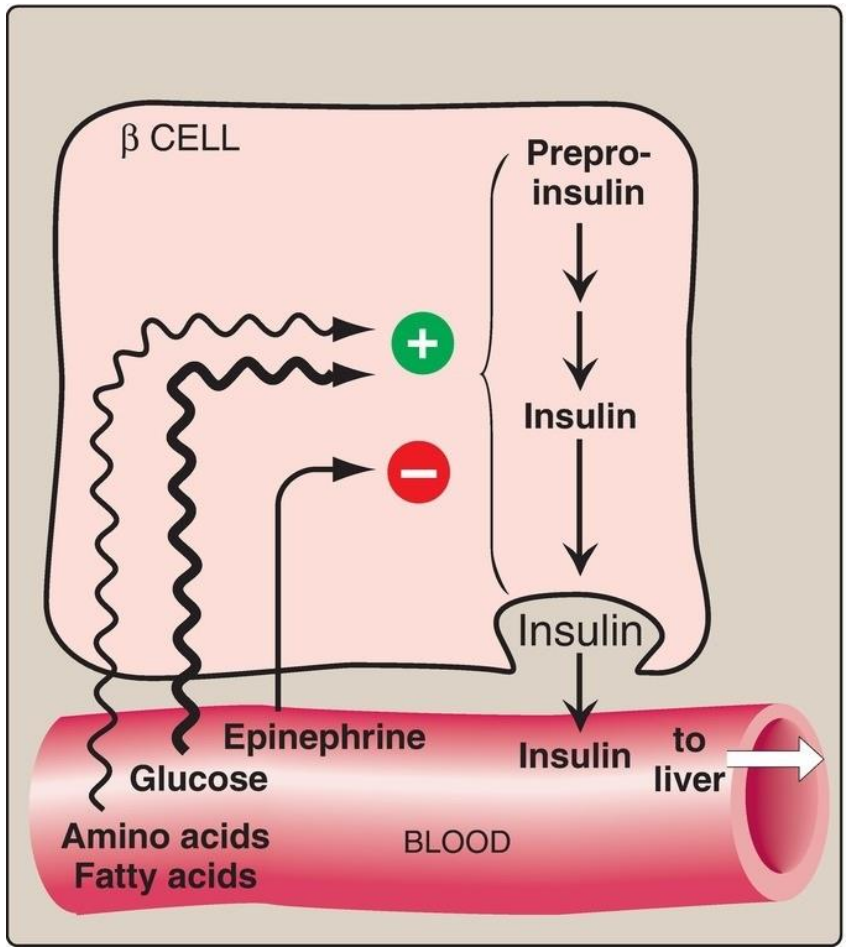
In Type 1 Diabetes (DM1), the pancreas produces little to no insulin due to the autoimmune destruction of insulin-producing beta cells. Therefore, C-peptide levels are typically very low.

In Type 2 Diabetes (DM2), the pancreas usually secretes insulin normally, especially in the early stages of the disease. Thus, C-peptide levels are often normal or even elevated, reflecting the body's insulin production.



باختصار كل انسولين بطلع معه سي ببتايد صح ..بالسكري النوع الأول اصلا الانسولين بالدم قليل لانه البنكريا س ما بفرزه ف أكيد" سي ببتايد " قليل كمان ، على عكس النوع الثاني يلي كليهما مرتفعين بكونواوبهاي الطريقة بنعرف المريض عنده اي نوع سكري

The secretion of insulin is regulated by bloodborne fuels and hormones



- **NOTE:** let's remember the regulation of some metabolic enzymes because the Dr revised them in the lec:(**they are just for a quick revision)**
- glycolysis : glucokinase, pyruvate kinase, PFK-1 and PFK-2
- TCA cycle:isocitrate dehydrogenase,alpha ketoglutarate dehydrogenase
  pyruvate dehydrogenase: regulated by insulin , glucagon , allosteric regulators
- Fatty acid synthase:which involves regulation of fatty acid synthesis and acetyl coa carboxylase.
- Beta oxidation: The CAT-1 enzyme: is a key regulatory point

Insulin has an anabolic metabolic effect

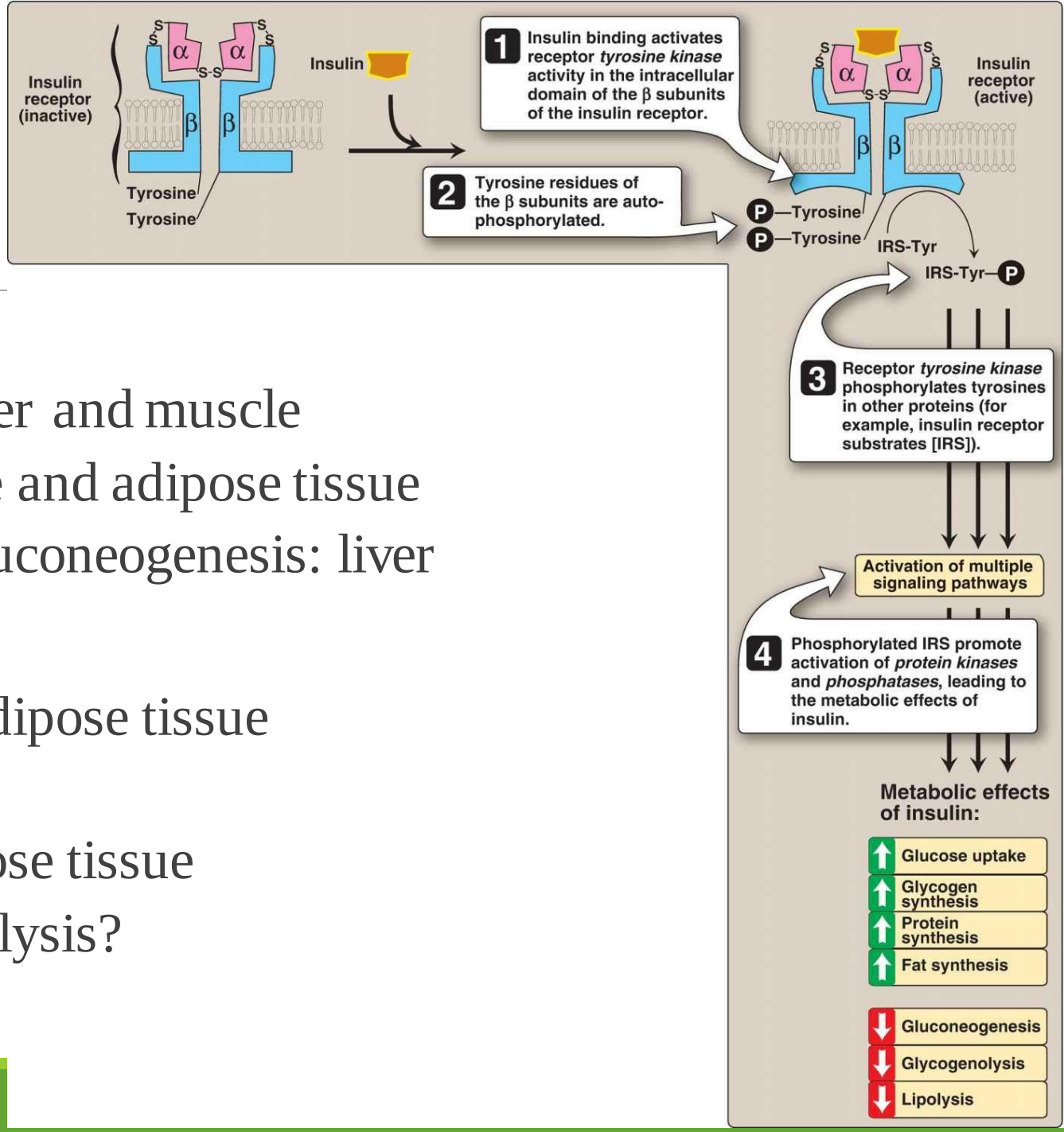
Carbohydrates:

- Increases glycogen synthesis: liver and muscle
- Increases glucose uptake: muscle and adipose tissue
- Decreases glycogenolysis and gluconeogenesis: liver

Lipids:

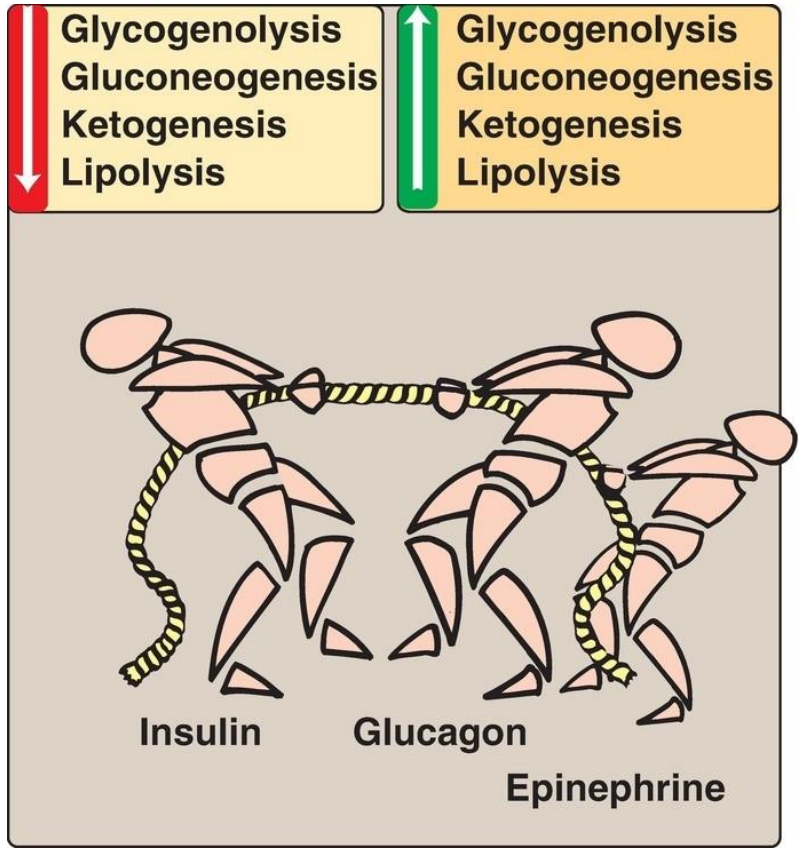
- Decreases TAG degradation in adipose tissue
  - Hormone-sensitive lipases
- Increases TAG synthesis in adipose tissue
  - Glycerol-3-phosphate via glycolysis?

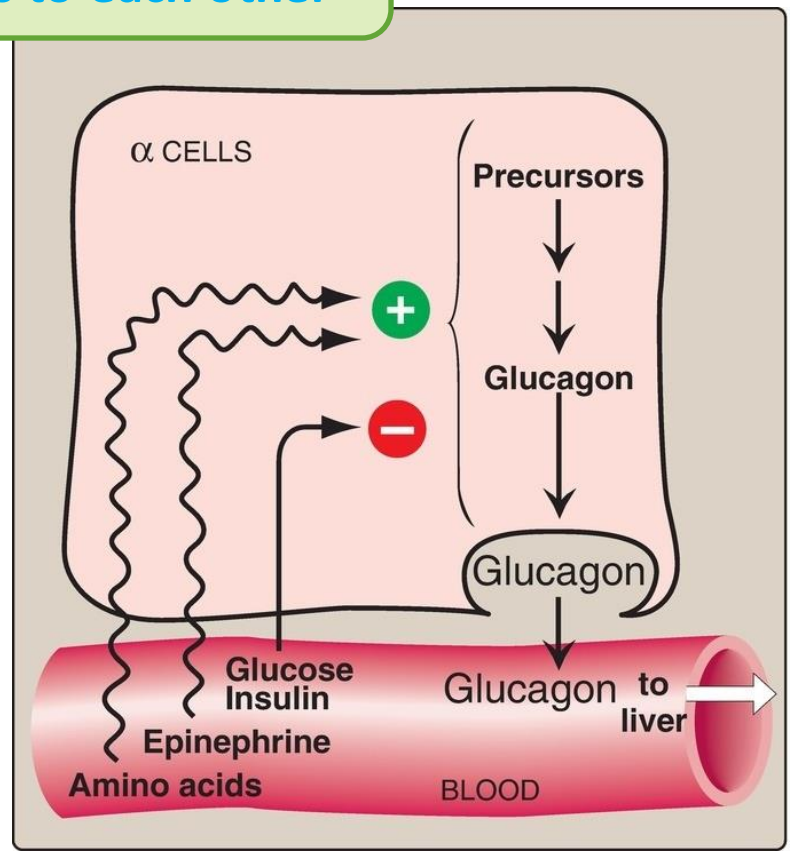
Protein: protein synthesis



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

NOTE: **Again, they have opposite effects to each other**





Glucagon has a catabolic metabolic effect

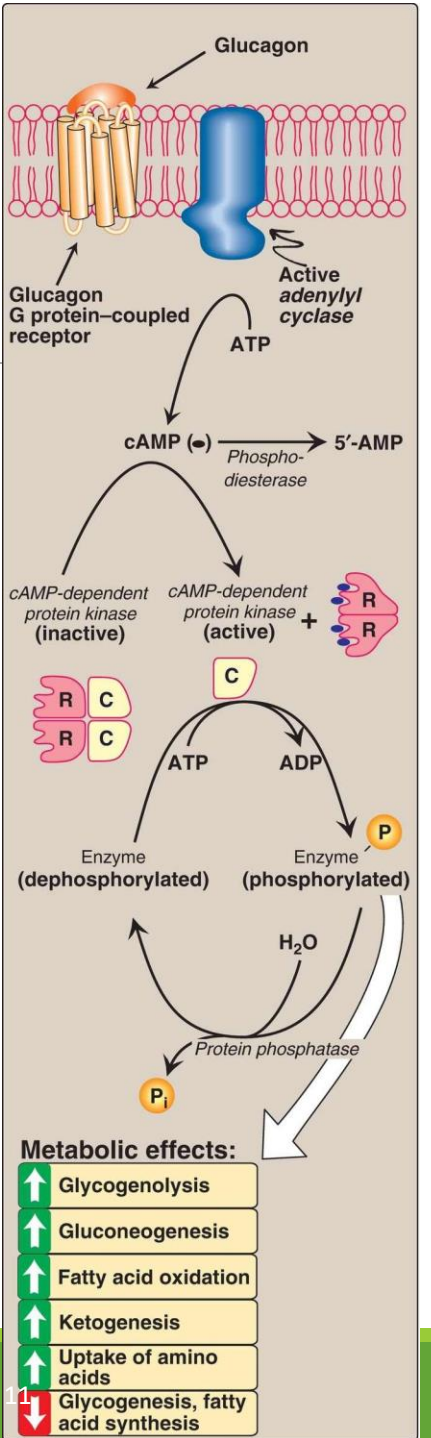
Carbohydrates:

- 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

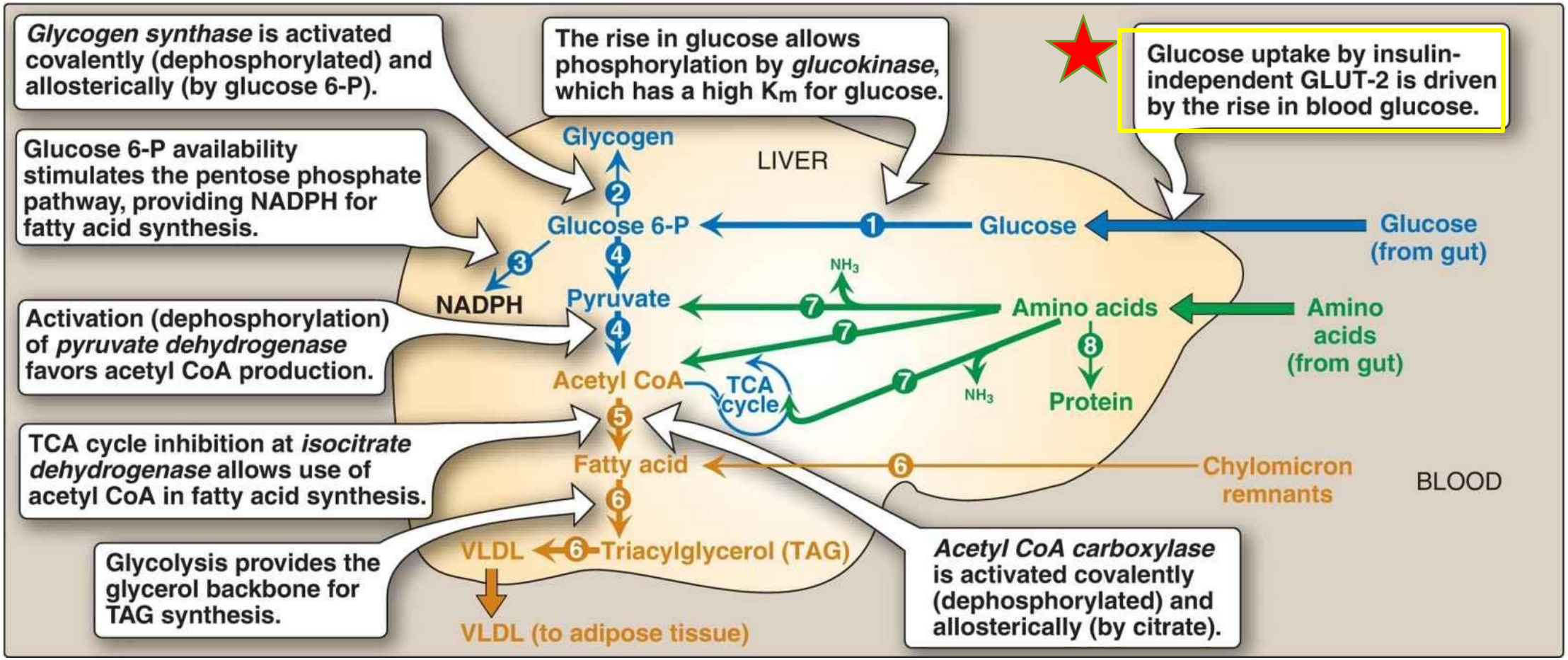


Well fed-absorptive state (0-4 hr)
High ratio of insulin/glucagon ; hyperglycemia, Hyperlipemia, Hyperaminoacidemia

- **NOTE:** **we will talk about the metabolism picture in fed state for carbs, lipids, proteins in each of these tissues: Brain, muscle, Liver and adipose tissue. And How these tissues coordinate in fed state.**

Liver processes and distribute nutrients

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



- **The complement in this slide**: when we have a rich meal, there will be hyperglycemia, hyperlipidemia, Hyperaminoacidemia. During the absorptive period (0-4 hours), the liver takes up carbohydrates, lipids, and most amino acids, leading to a normalization of these levels in the blood.
- Because of insulin/ glucagon ratio is high, glucose uptake in liver, using GLUT2.
- Glucose will be phosphorylated to Glucose 6 phosphate by glucokinase.

  * In anabolic metabolism, the strategy of metabolism is to store of sources of energy.
- Glucose 6 phosphate **mainly** enters **glycogen synthesis**, & some will be oxidized to PPP(Pentose Phosphate Pathway) to provide NADPH for F.A. synthesis.

  *this is a type of coordination between carbohydrates & lipid metabolism in liver in well fed state.
- Another pathway, G6P ----> pyruvate (Glycolysis) by activation of pyruvate kinase & PFK1.
- Pyruvate ---> Acetyl CoA by pyruvate dehydrogenase.
- Some Acetyl CoA ----> Krebs cycle (for energy)
- Rest Acetyl CoA ----> FA synthesis by Acetyl-CoA Carboxylase "ACC" (most regulated) & FA synthase are activated allosterically by citrate.

Induced by Insulin

- **The complement in this slide:**
- Chylomicrons remnant also gives free F.A to the liver from diet by lipoprotein lipase, TAGs --- hydrolyzes ----------> Free F.A + glycerol.
- DHAP is an intermediate in both gluconeogenesis and glycolysis. In gluconeogenesis, DHAP can be used to produce glucose, which may subsequently be stored as glycogen.

- more **amino acids** are present than the liver can use in the synthesis of proteins especially the enzymes used for metabolic purposes not storage
- **AA -------> Acetyl CoA by ketogenic Amino Acids.**
- **AA -------> Pyruvate by Glucogenic Amino Acids.**
- AA ----> Krebs cycle intermediates.

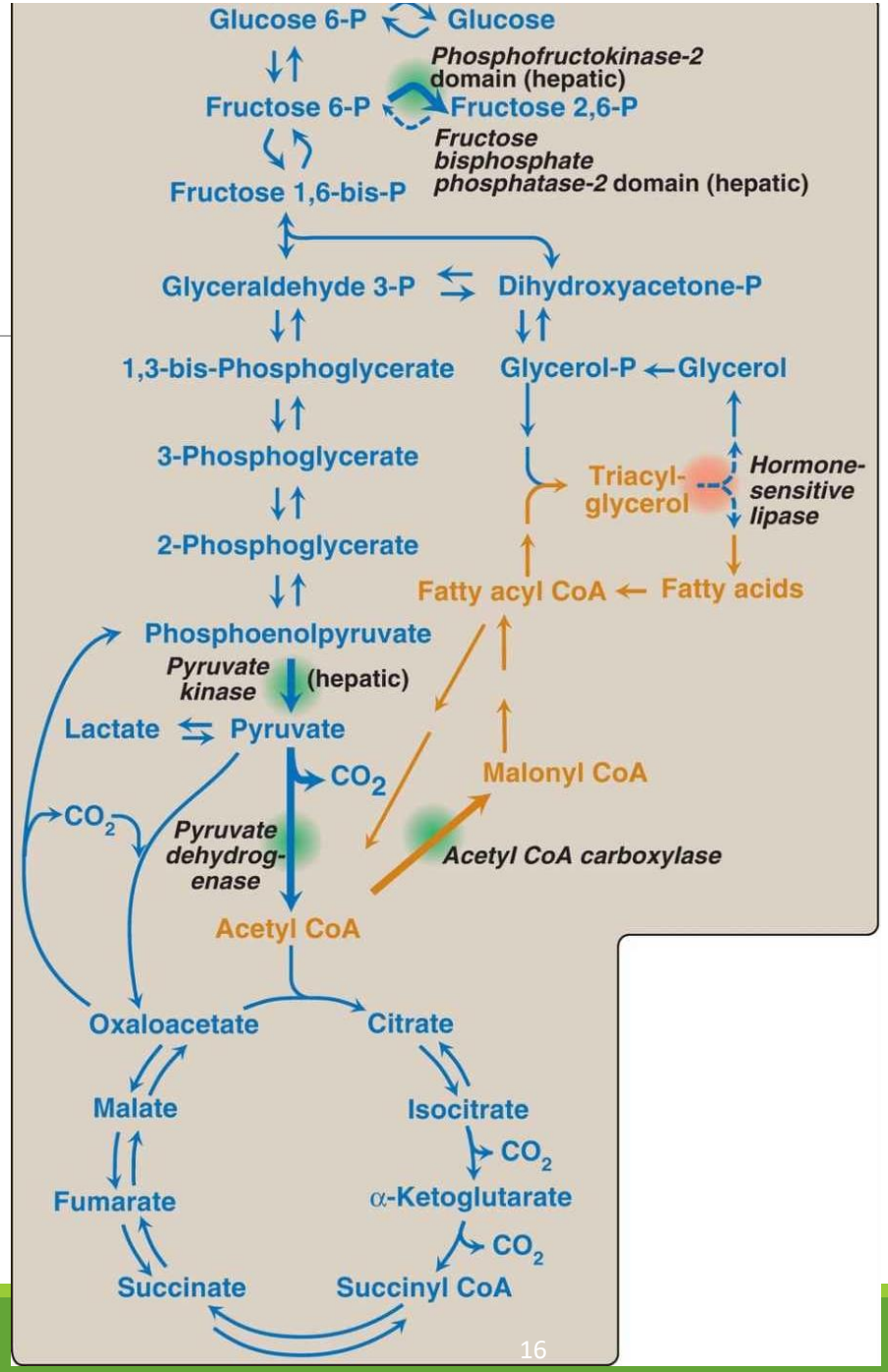
Liver has increased glycolysis in the absorptive state

High insulin/glucagon inducs the conversion of glucose to pyruvate

- *Glucokinase* , ***PFK-1*** , *pyruvate kinase and Pyruvate dehydrogenase*
- Covalent and allosteric regulation

- **NOTE:**
- **الدكتور ما رح يسأل عن regulation بس اعرفوا الenzymes.**
- **We need to know who is active & not in the well fed state.**

وين ذانك يا جحا 😳



The liver decreases glucose production in the fed state

The liver inhibits gluconeogenesis and glycogenolysis

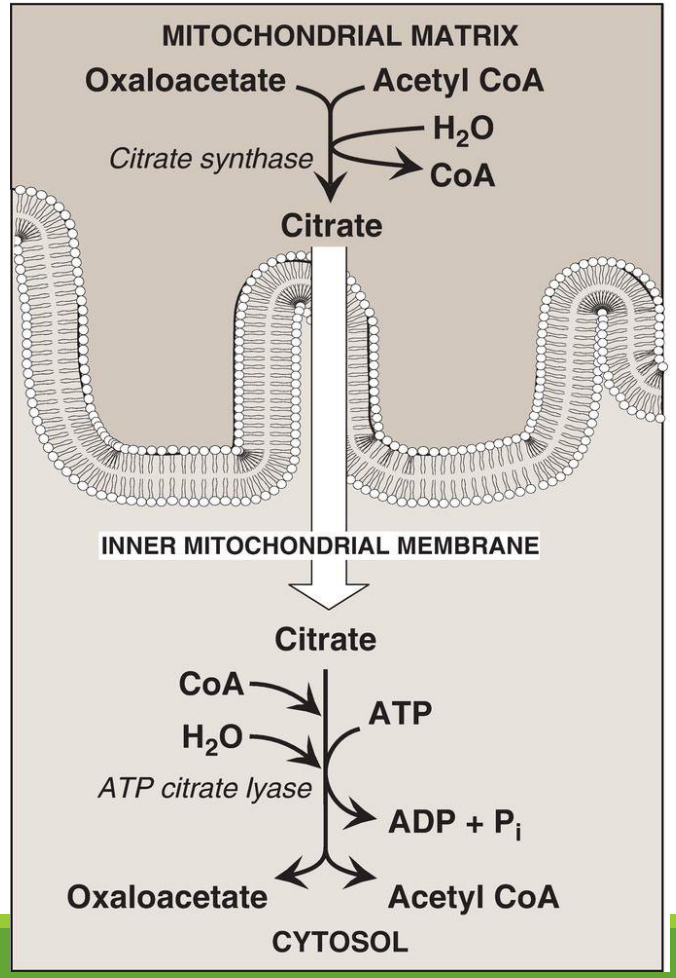
Gluconeogenesis

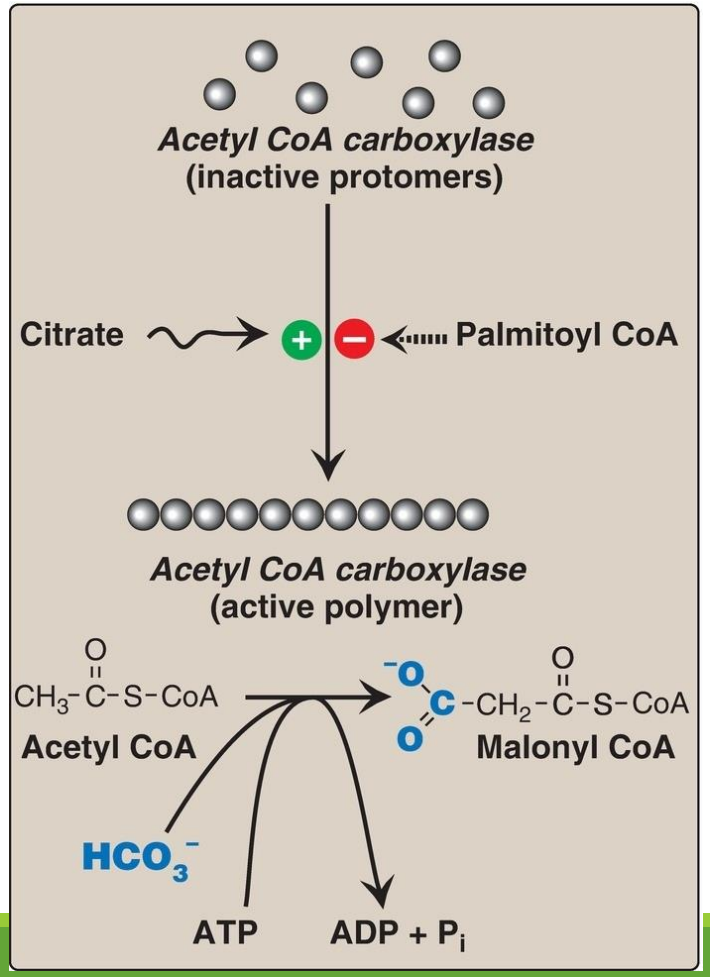
- Low levels of **acetyl CoA** deactivate ***Pyruvate carboxylase* (*PC)*** - acetyl CoA is used in FA synthesis
- High insulin/glucagon ratio deactivate ***fructose 1,6-bisphosphatase***

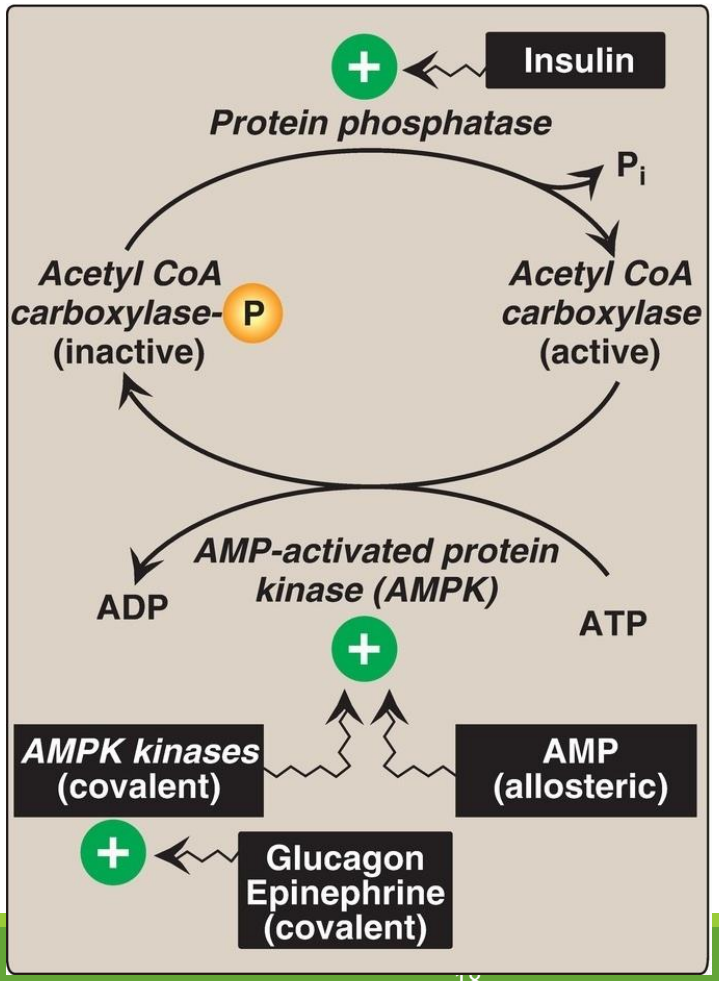
Glycogenolysis:

- *Glycogen phosphorylase* and *phosphorylase kinase* are inhibited by dephosphorylation

Liver increased fatty acid and TAG synthesis in the absorptive state



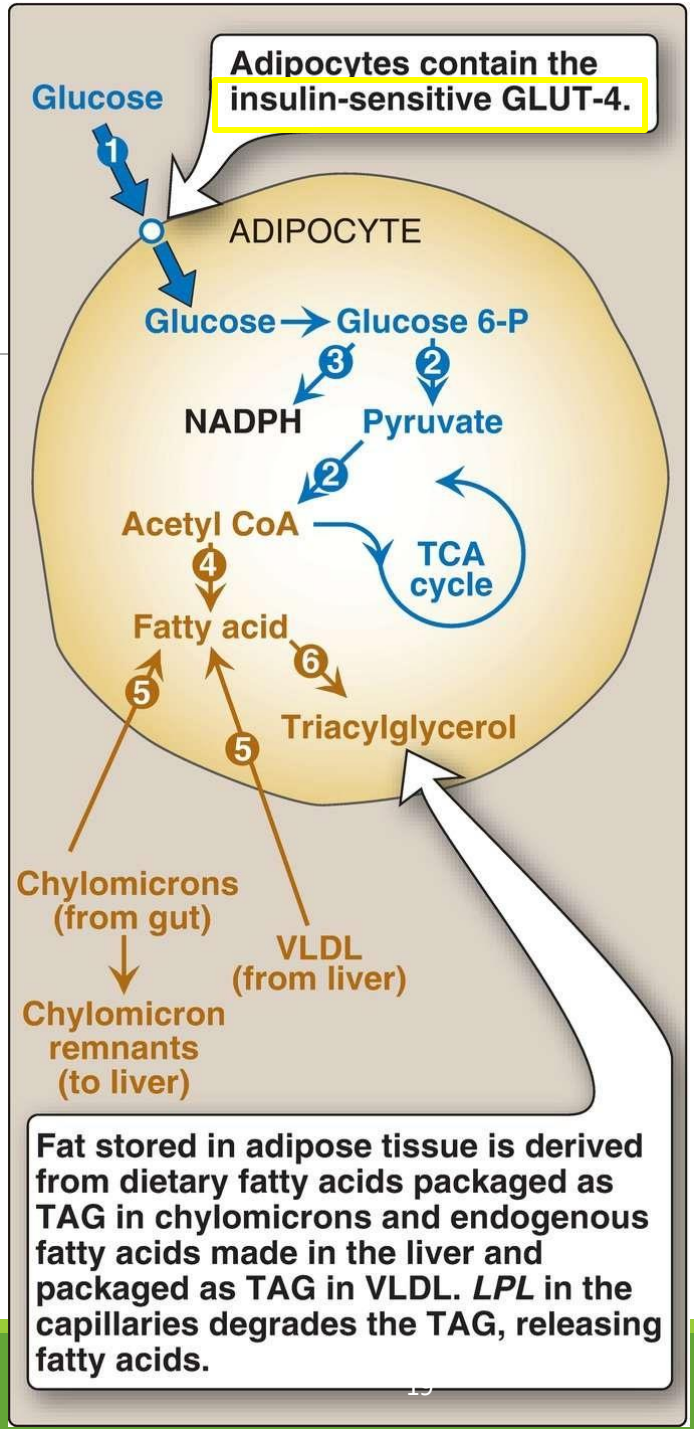




Adipose tissue is second only to the liver in its ability to distribute fuel molecules

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



NOTE: Know the type of GLUTs

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

Increased glucose uptake.

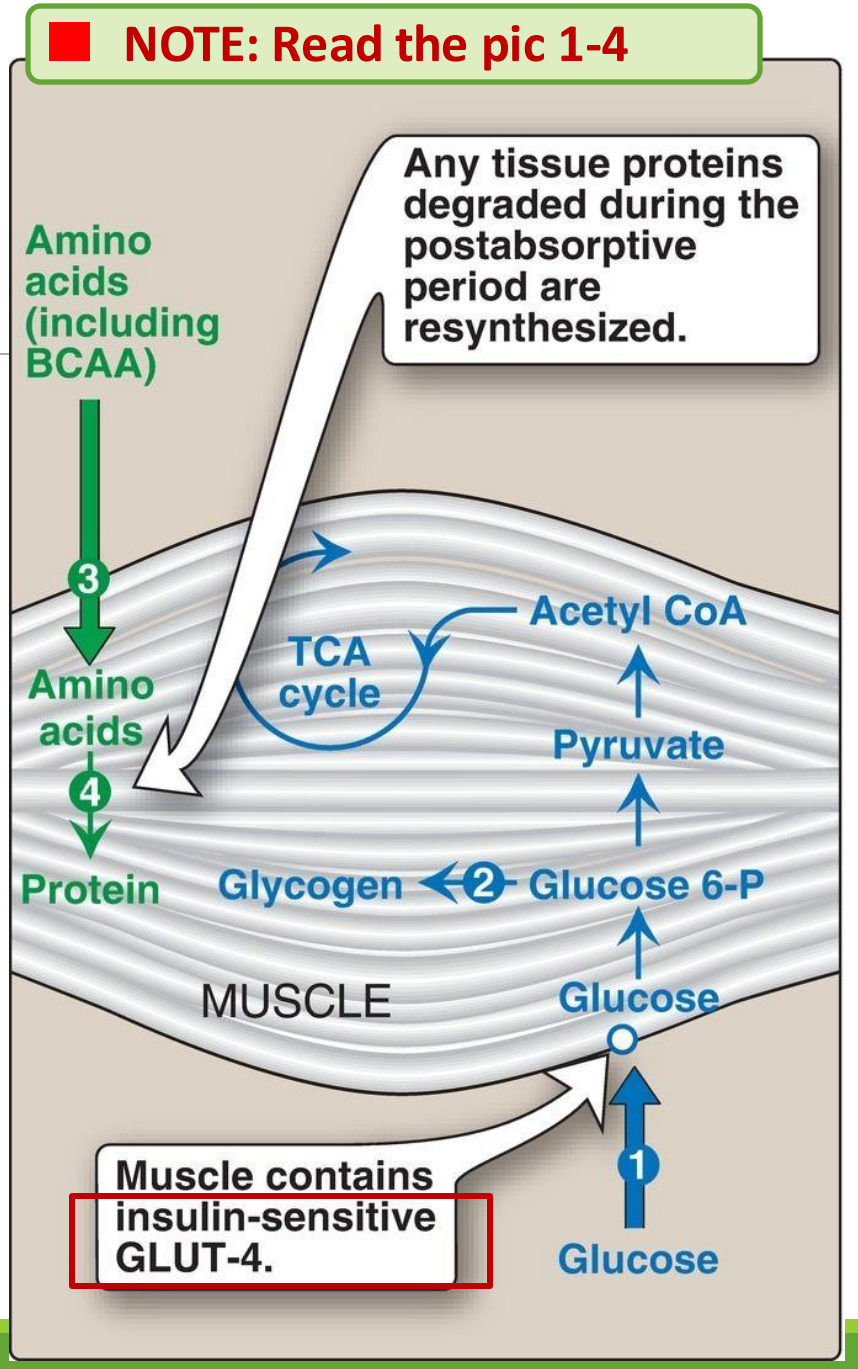
Increased Glucose phosphorylation to glucose 6-phosphate by hexokinase.

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.

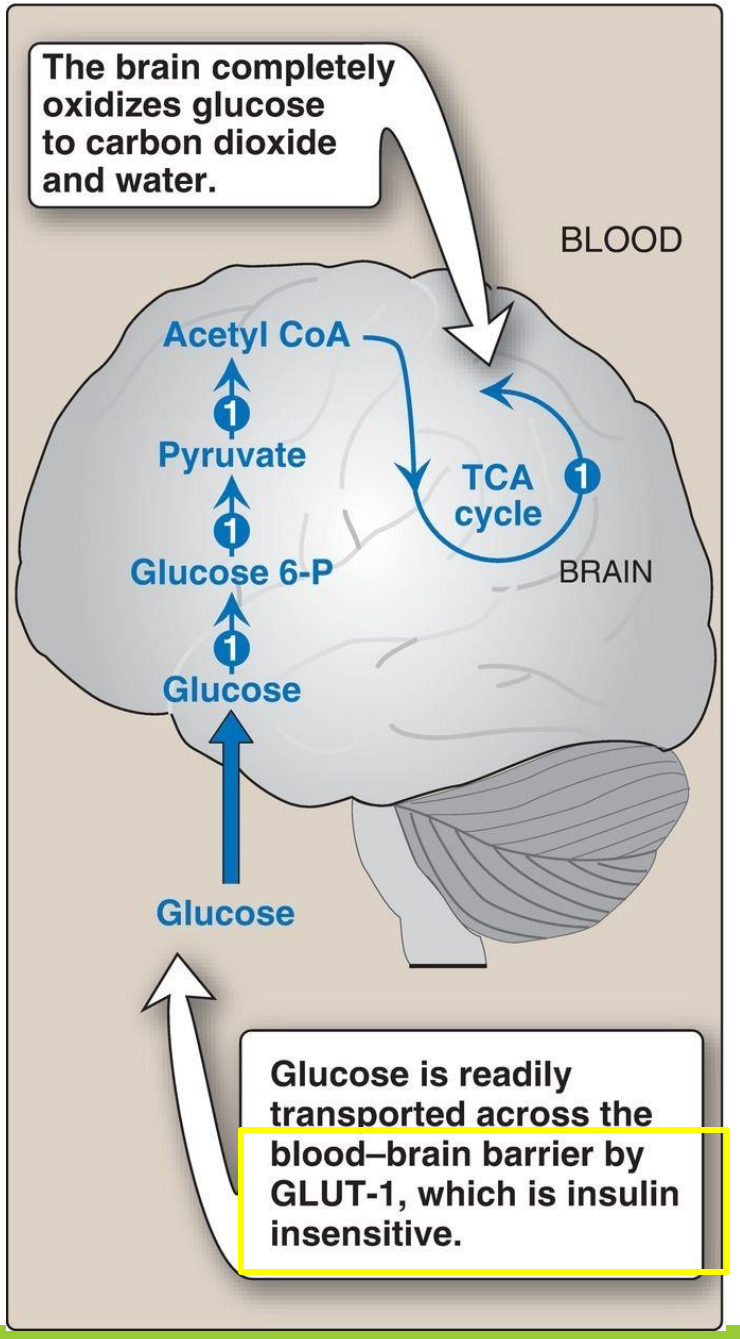
Increased AA (branched) uptake and protein synthesis.

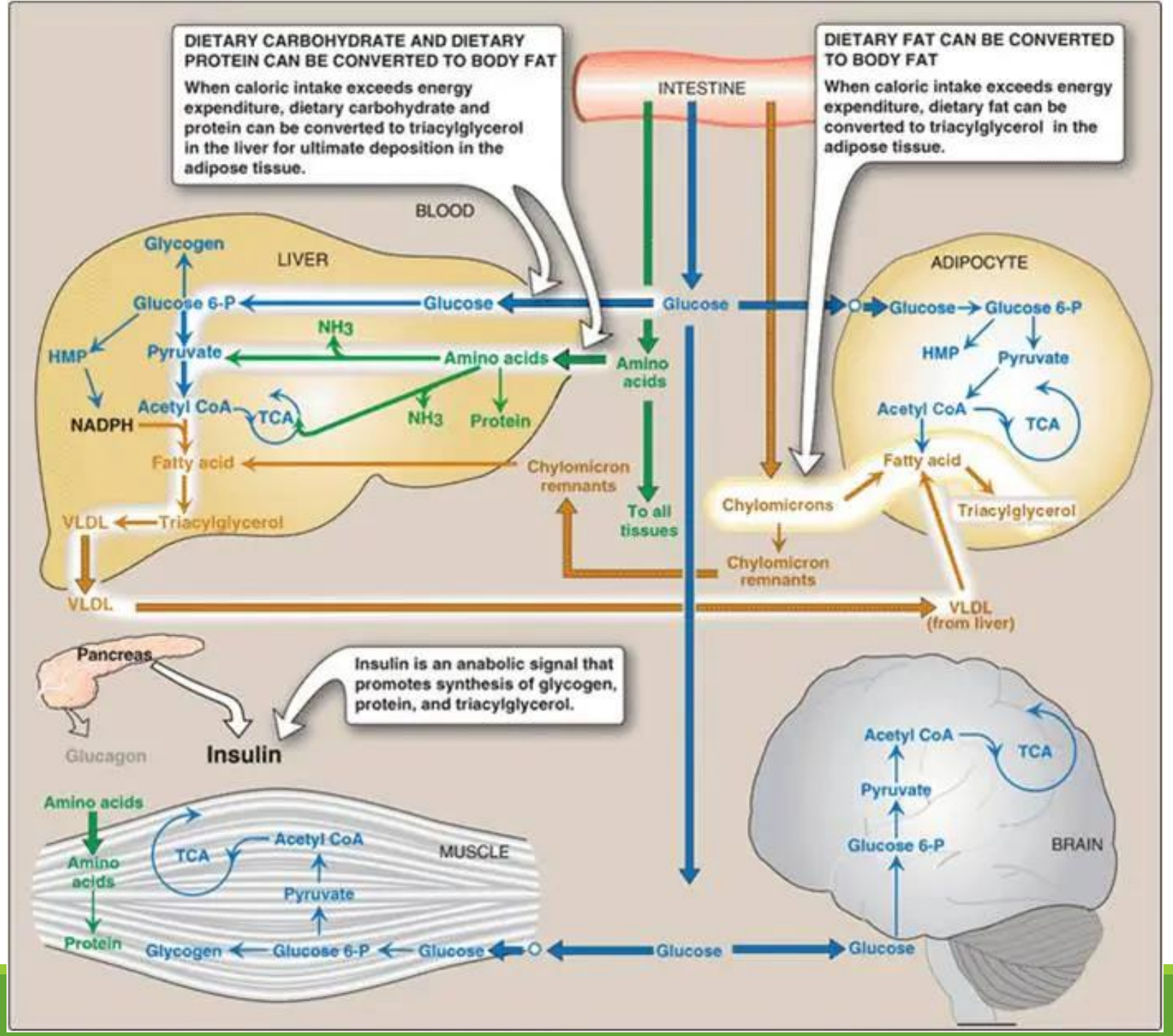


The brain exclusively uses glucose as a fuel in the fed state

- The brain contains no significant stores of glycogen and TAG

NOTE: Brain depends entirely on glucose, but in starvation it will change some pathways, and switch to consume Ketone bodies.




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
ADIPOCYTE
Chylomicrons
Chylomicron remnants
VLDL (from liver)
Pancreas
Glucagon
Insulin
Insulin is an anabolic signal that promotes synthesis of glycogen, protein, and triacylglycerol.
Amino acids
MUSCLE
BRAIN

The fasted state & starvation

- **NOTE:** Fasted state induces secretion of glucagon and inhibits secretion of insluin, so we have high glucagon/insulin ratio (in other words, low insulin/glucagon ratio). Metabolism during fasted state is mainly catabolic. Why? To sustain energy for every cell in the body. Main metabolic pathways are going to be: glycogenolysis, gluconeogenesis, and fatty acid oxidation.

Fasted state induces a catabolic metabolic state

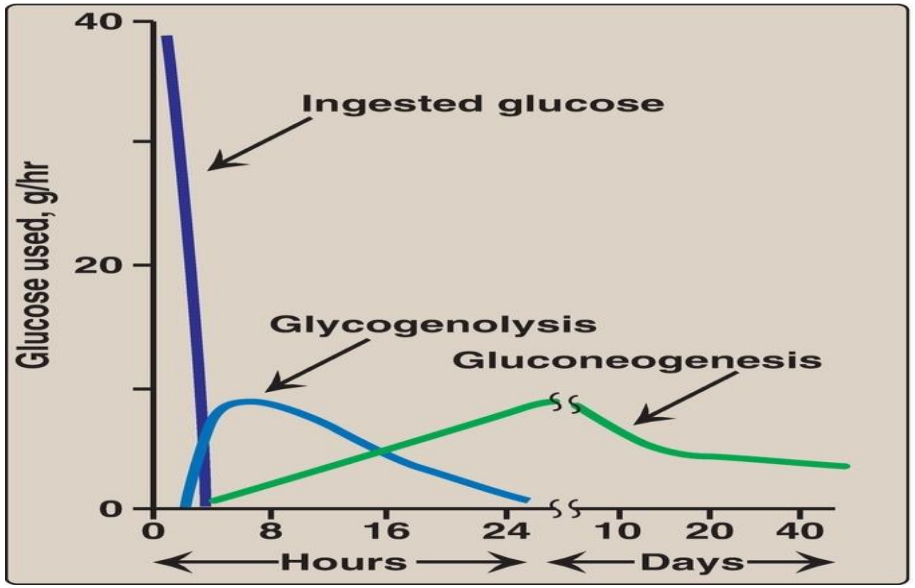
In the absence of food, plasma levels of glucose, amino acids, and TAG fall, triggering a decline in insulin secretion and an increase in glucagon, epinephrine, and cortisol secretion.

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

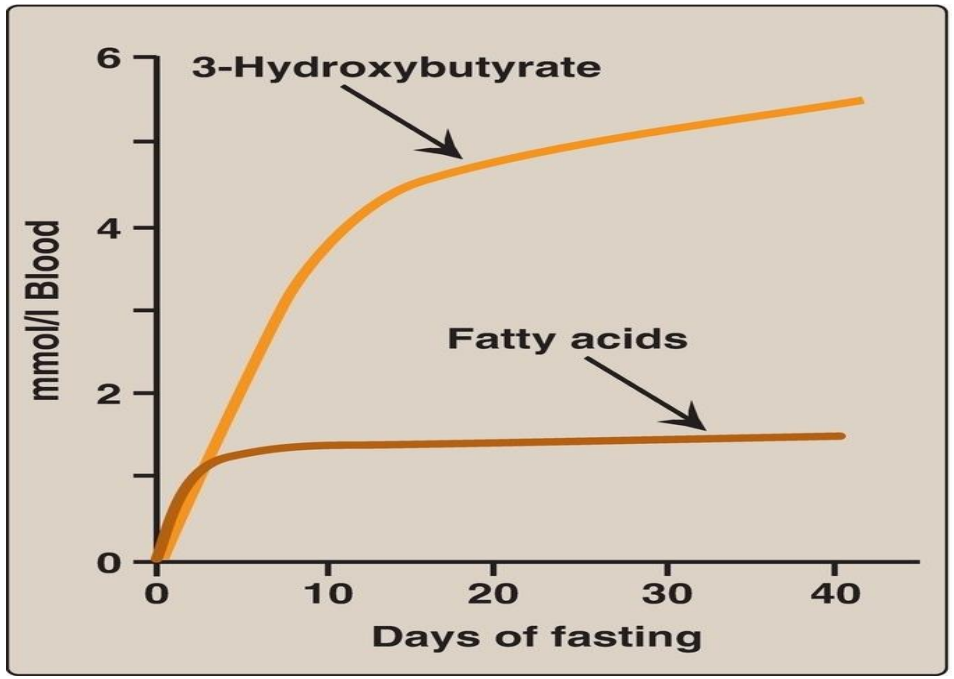


- **The complement in this slide: 1)** The X-axis represents time while the Y-axis represents amount of glucose used by the body. This graph is to show you at what point in the fasted state each metabolic pathway is active.

- **The complement in this slide: 2)** In 0-4 hours **(well-fed state, uptake of glucose increases)**, glucose is going to be digested and its concentration will decrease.

- **The complement in this slide: 3)** After digestion and absorption of glucose(after the 0-4 hours), if the body continues fasting, **glycogen will start to be degraded.** Remember, **high glucagon/insulin ratio**, activation of G-protein coupled receptors, adenylate cyclase, cAMP, protein kinase A, **phosphorylation** of glycogen phosphorylase kinase, **phosphorylation** of glycogen phosphorylase. The glycogen stores will be depleted in approximately **10 hours**.

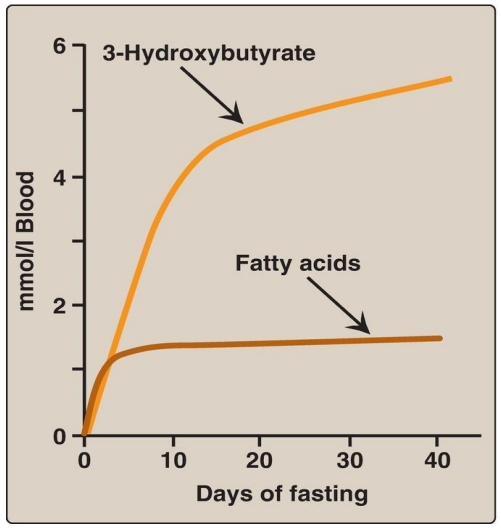
- **The complement in this slide: 4)** At the same time, there is a gradual increase in **gluconeogenesis**, and it reaches its peak of activity in the first **three** days of fasting.

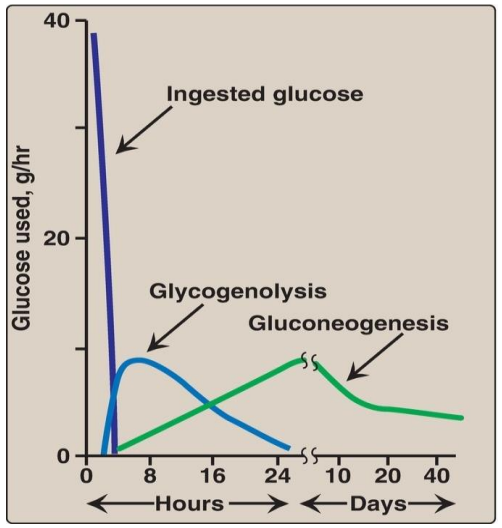


- **The complement in this slide: 5) Then, gluconeogenesis rate will decrease, and this is very important, because the substates of this pathway are mainly amino acids, so if the body continues to synthesize glucose during fasting, proteins in the body (muscles) are going to be degraded, and that is incompatible with life.**

- **The complement in this slide: 6) At the same time gluconeogenesis decreases, degradation of triacylglycerols from adipose tissue (Lipolysis) increases. Degradation products are glycerol and free fatty acids which will be distributed to the liver and muscles where beta-oxidation takes place. The liver will also synthesize ketone bodies, which are going to be utilized by the brain since there is no glucose, and other peripheral tissues.**

The liver maintains the blood glucose levels during the fasting state





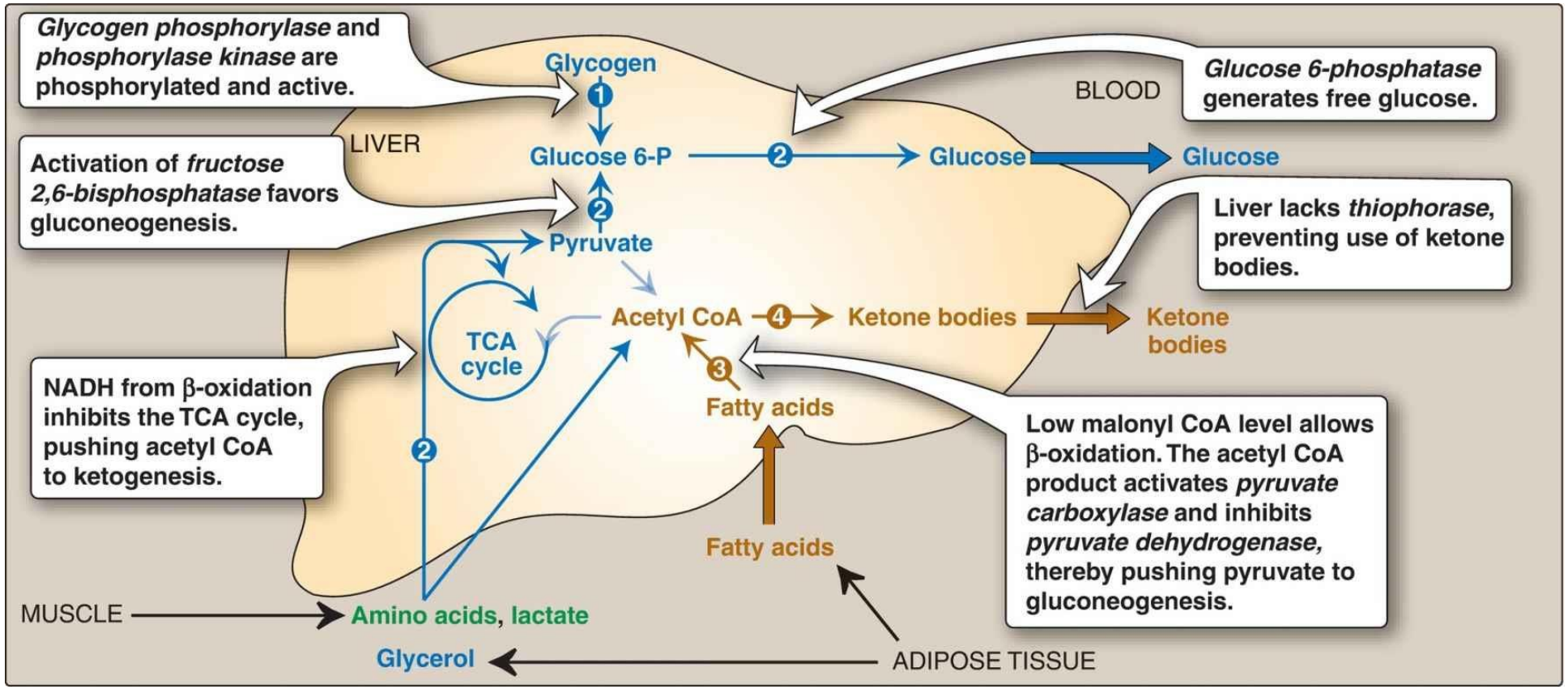
Liver produces glucose via glycogenolysis and gluconeogenesis for glucose-requiring tissues.

- **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



NOTE: Note that unlike the well-fed state, there is no entry of glucose, amino acids or fatty acids because there is no intake of food. Also, this clearly represents one of the strategies of metabolism, which is storing excess food to use it when required.

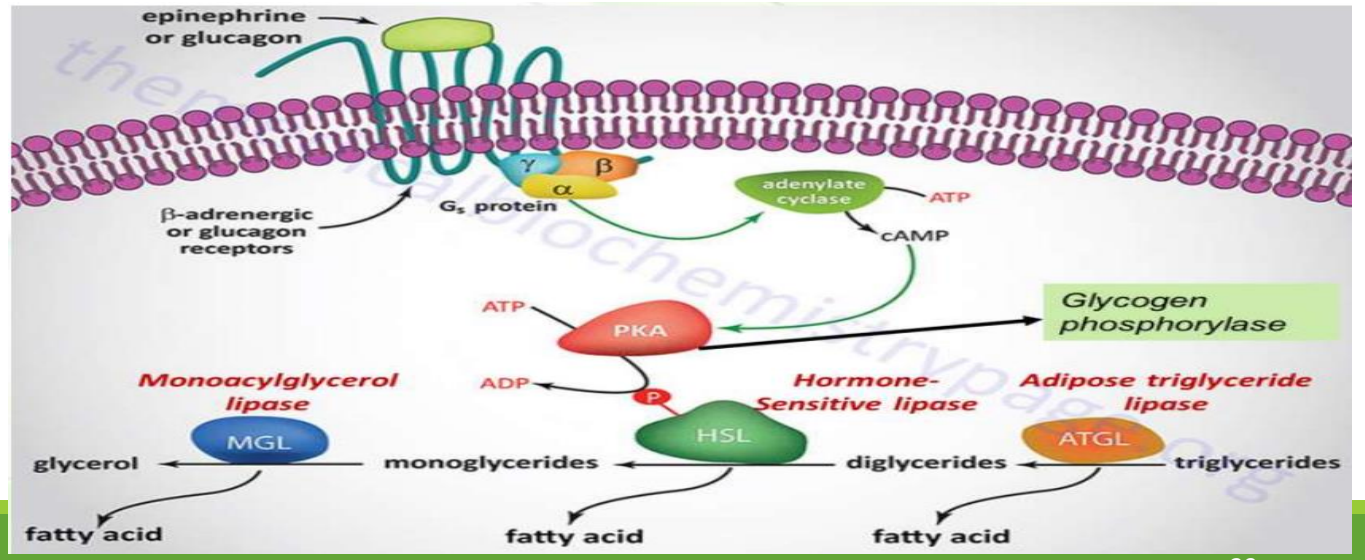
NOTE: Focus on every detail in the picture.

- **The complement in this slide:** Remember that the liver has the enzyme **glucose-6-phosphatase**, which is not present in muscles, this enzyme will convert glucose-6-phosphate to glucose. Glucose will be transported out to peripheral tissues such as the brain and RBCs.

- **The complement in this slide:** Lipolysis will also take place, where TAGs will be degraded from adipose tissue by the enzyme **hormone-sensitive lipase** (different from lipoprotein lipases) producing fatty acids and glycerol. **Fatty acids** will enter the liver, beta oxidation will occur and result in acetyl CoA which will be used for the **synthesis of ketone bodies**. In prolonged starvation, these ketone bodies will be used by the brain. **Glycerol** will be phosphorylated by **glycerol kinase** and then be used for **gluconeogenesis**.

- **The complement in this slide:** Some amino acids will also provide acetyl CoA, some will be converted to pyruvate. Pyruvate dehydrogenase is **inactive** in the fasted state, so pyruvate will be used for **gluconeogenesis**, not for acetyl CoA production and this makes sense, as there is enough acetyl CoA from fatty acids oxidation.

- **Attachment:** Remember this from Degradation of Fatty Acids lecrure:



Adipose tissue has increased TAG degradation in the fasting state

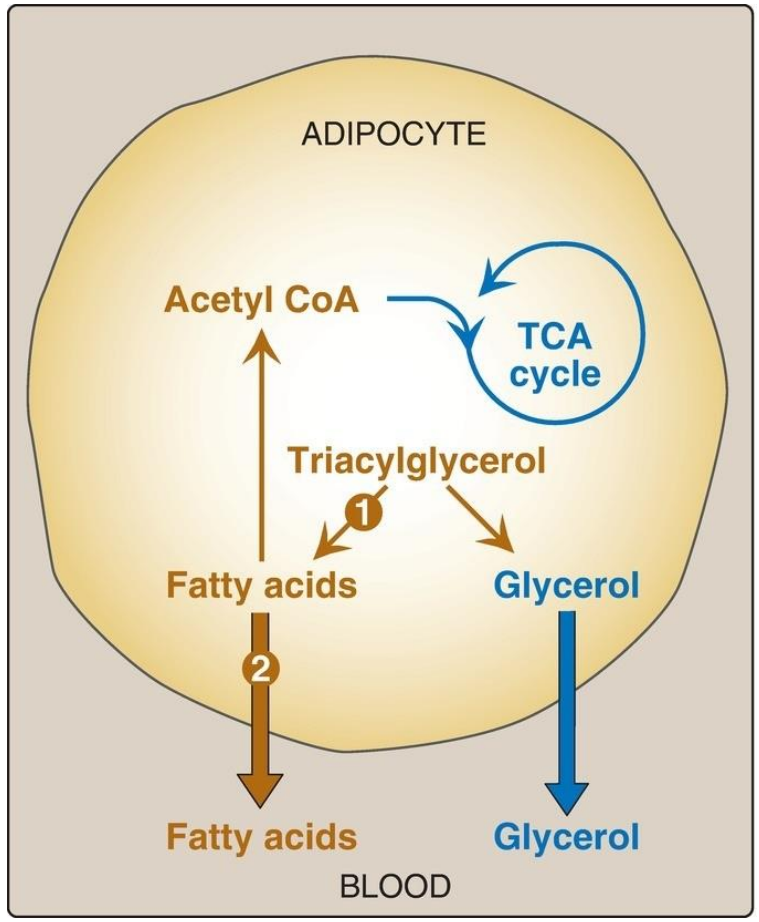
Low plasma glucose level decreases TAG synthesis

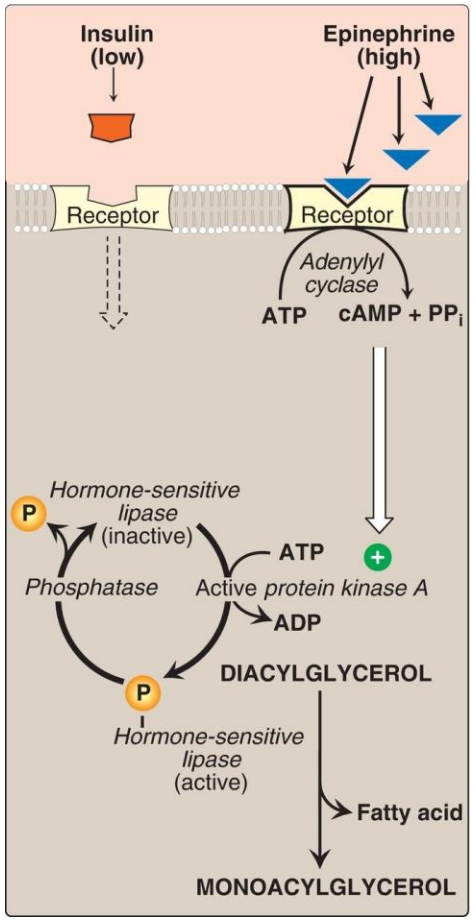
Catecholamines norepinephrine and epinephrine induce HSL by PKA

Hydrolysis of TAG releases fatty acid

Low LPL activity decreases fatty acid uptake

NOTE: **Note the coordination and the transfer of substances between organs as needed.**





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

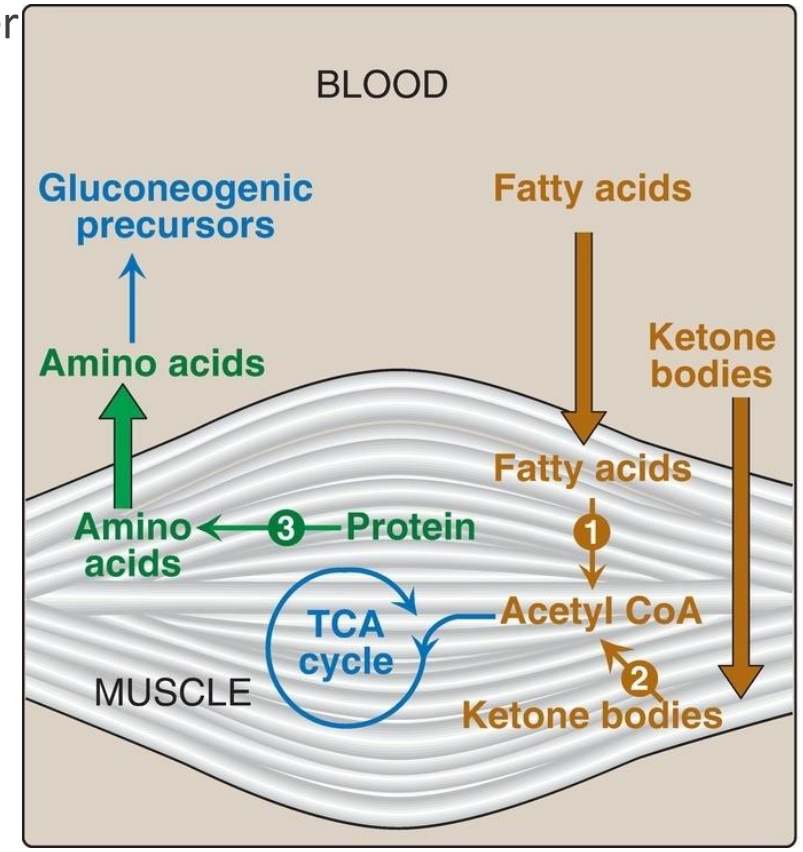
Muscle uses FA from adipose tissue and ketone bodies from the liver as fuels

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.

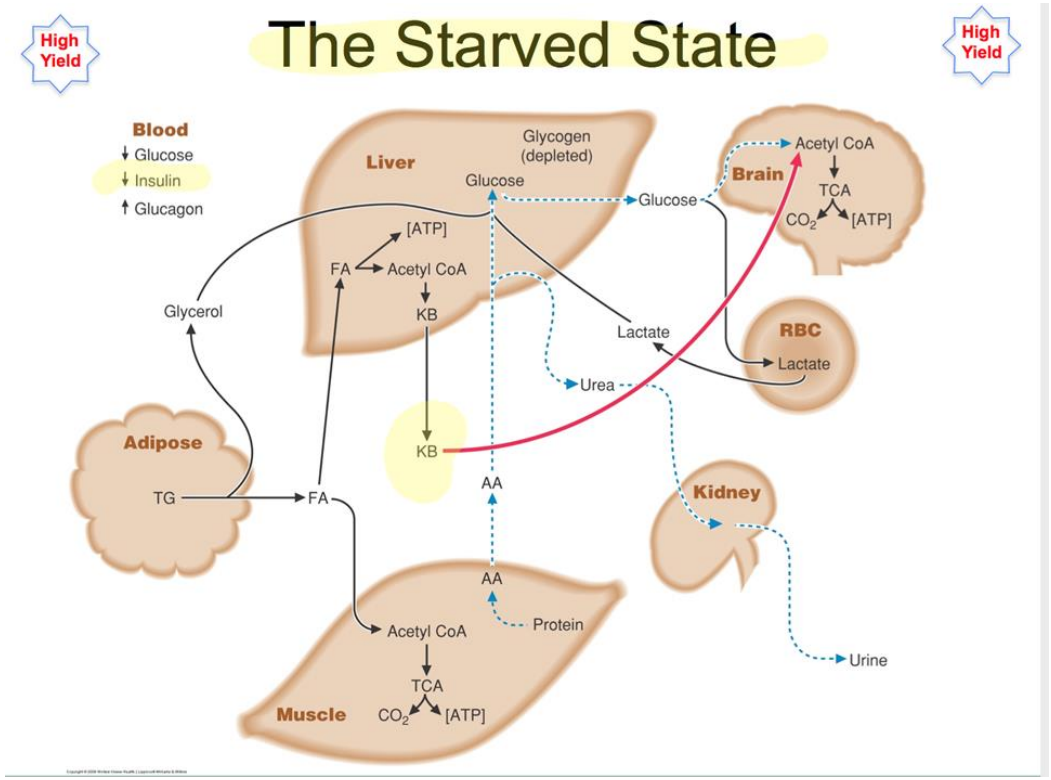
In prolonged fasting, muscle decreases its use of ketone bodies (thus sparing them for the brain) and oxidizes FA almost exclusively

NOTE: **Acetyl CoA will enter TCA cycle for some energy. Proteins will be degraded to amino acids which will leave to the liver for gluconeogenesis. Note that there is no glycolysis and gluconeogenesis. Its main source of energy is acetyl CoA from fatty acid oxidation.**

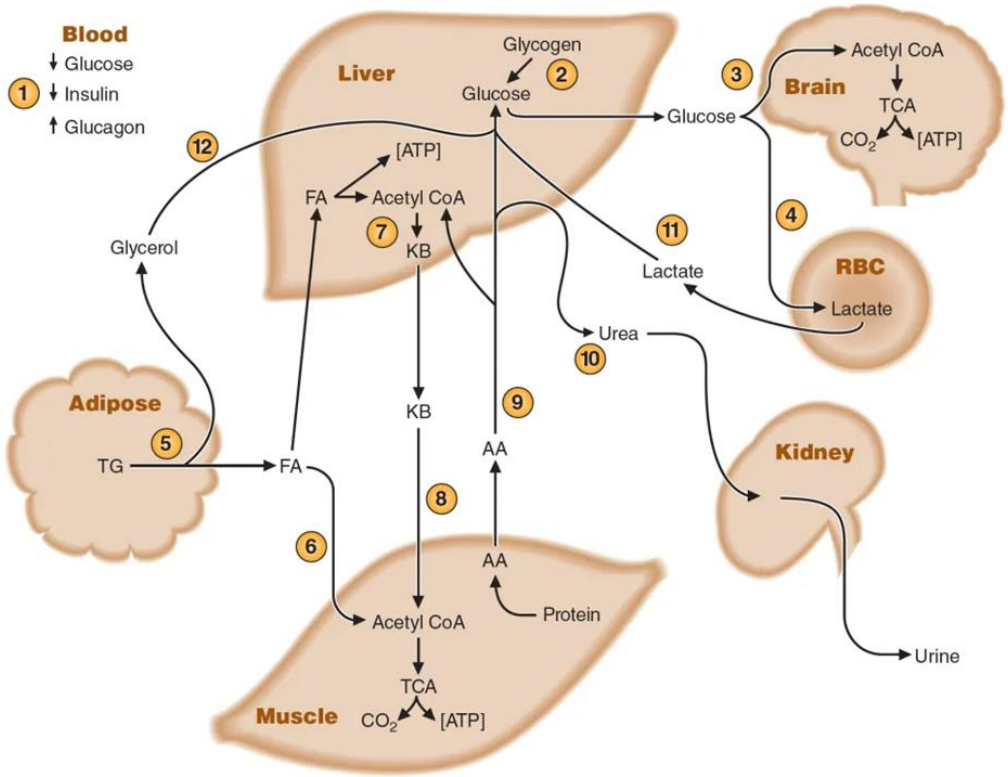


NOTE: This is a comparison between starvation and fasting states. They are nearly the same except for ketone bodies, in starvation they are sent to the brain, unlike fasting where they are sent to the muscles.

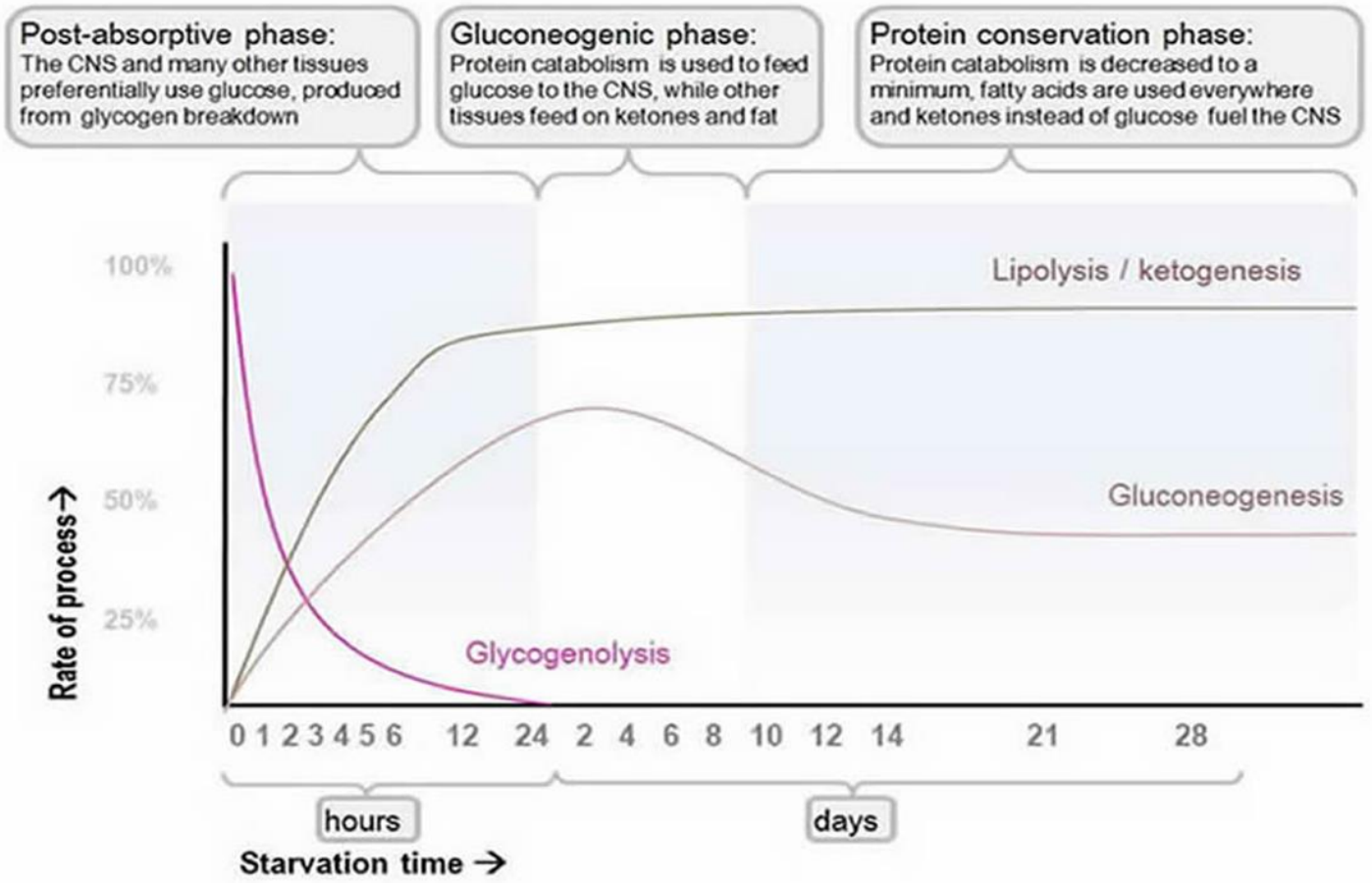
STARVATION



FASTING



Prolonged starvation



- After 24 days of starvation, the steady state rates of carbohydrates, lipid, and amino acid metabolism appear to be established

Ø About 30% of energy requirement of the brain is met by glucose

Ø 50% by β-hydroxybutyrate

Ø 5% by acetoacetate

Ø 15% by amino acids

- Prolonged starvation ends with death or refeeding

NOTE: The doctor focused on amount of substances utilized by the brain for energy .

NOTE: One could survive starvation for about three weeks. Obese people could last longer as they have more lipid stores.

The brain uses ketone bodies during prolonged fasting

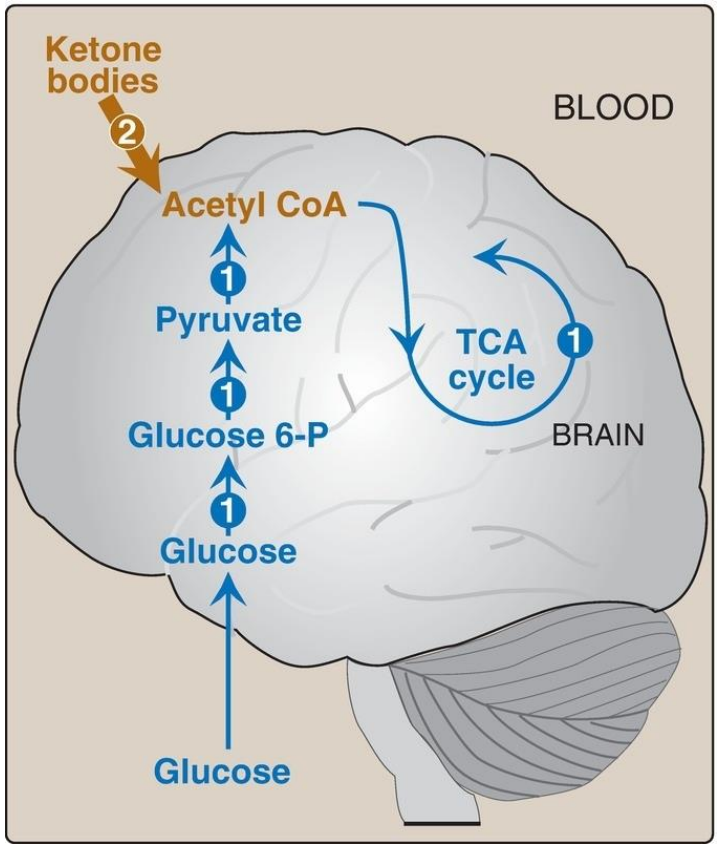
During the first few days of fasting, the brain uses glucose as fuel.

- 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

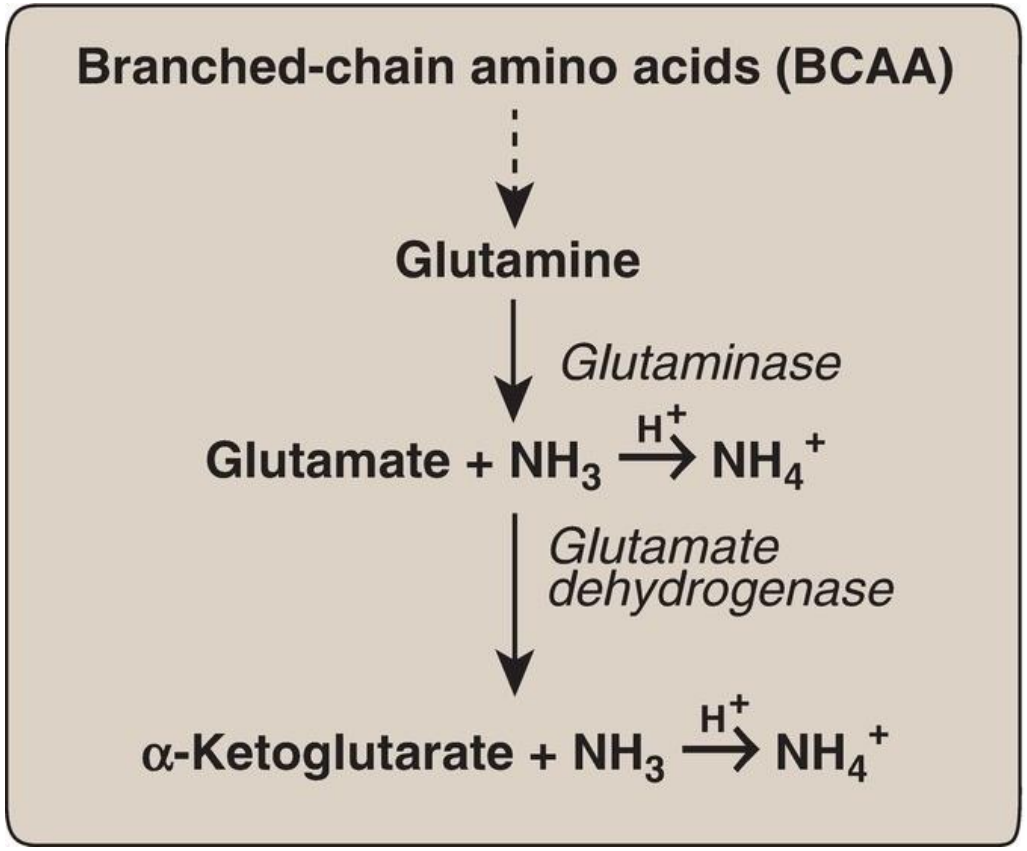
NOTE: **The main ketone used is 3-hydroxybutyrate.**



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