Integration of Metabolism

Integration, regulation and perturbation of metabolism

Learning Objectives

Describe tissue & cellular metabolic response to feeding, fasting and starvation

Ref.; Markes Medical Biochemistry

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The fuels used by tissues

1- Glucose
2- Lactic acid
3- Fatty acids
4- Ketone bodies
5- Glycerol
6- Carbon skeleton of AA

Different organs/tissues or same organs at different states (well fed /fasting states) have different needs for fuel metabolism.

Preferred fuel for brain: Glucose. In extreme situations it can use *ketone bodies.*
Preferred fuel for Heart: FA (70 %)

Anerobic tissues (No Mit, or poor blood supply) use glucose: e.g. RBCs, Retina, Adrenal Medulla, Lens

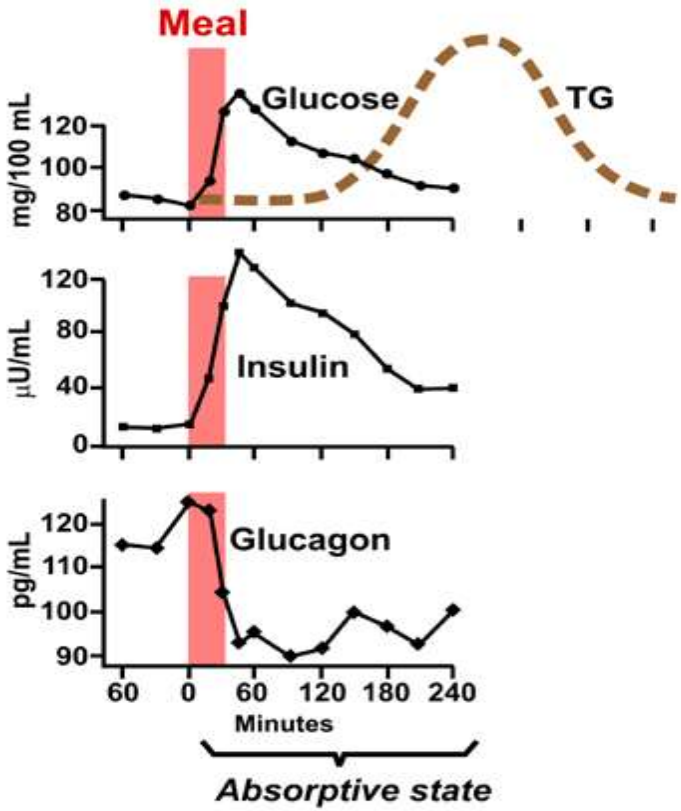
Inter-conversion of food stuffs

- Glucose → acetyl CoA → FA mainly in the liver (Lipogenesis)
- FAs cant not give glucose (conversion of pyruvate into active acetate is irreversible).
- Glycerol of TAG ⇢ Glucose (gluconeogenesis)
- Lactate from RBCs and skeletal muscles can give glucose (gluconeogenesis) (Cori cycle)
- Carbon skeleton of ketogenic AAs ⇢ acetyl CoA ⇢ ketone bodies (ketogenesis)
- Carbon skeleton of glucogenic AAs ⇢ Glucose (gluconeogenesis)
- Non –essential AAs could be formed from intermediates of glycolysis and kreb's cycle (transamination)

Metabolism in well –fed state (WFS)

Absorptive state: 2-4 hrs after a normal meal.

- Circulating dietary glucose, amino acids and chylomicrons (TAG)
- High *insulin/glucagons* ratio promotes anabolic period of glycogen, TAG and protein synthesis.
- Almost all tissues use *glucose* as fuel during this period.



Changes in blood levels of glucose, insulin, and glucagon after ingestion of a carbohydrate-rich meal.

Fuel Stores: occurs during feeding state in presence of insulin

Glycogen – smallest and used up to < 1 day.

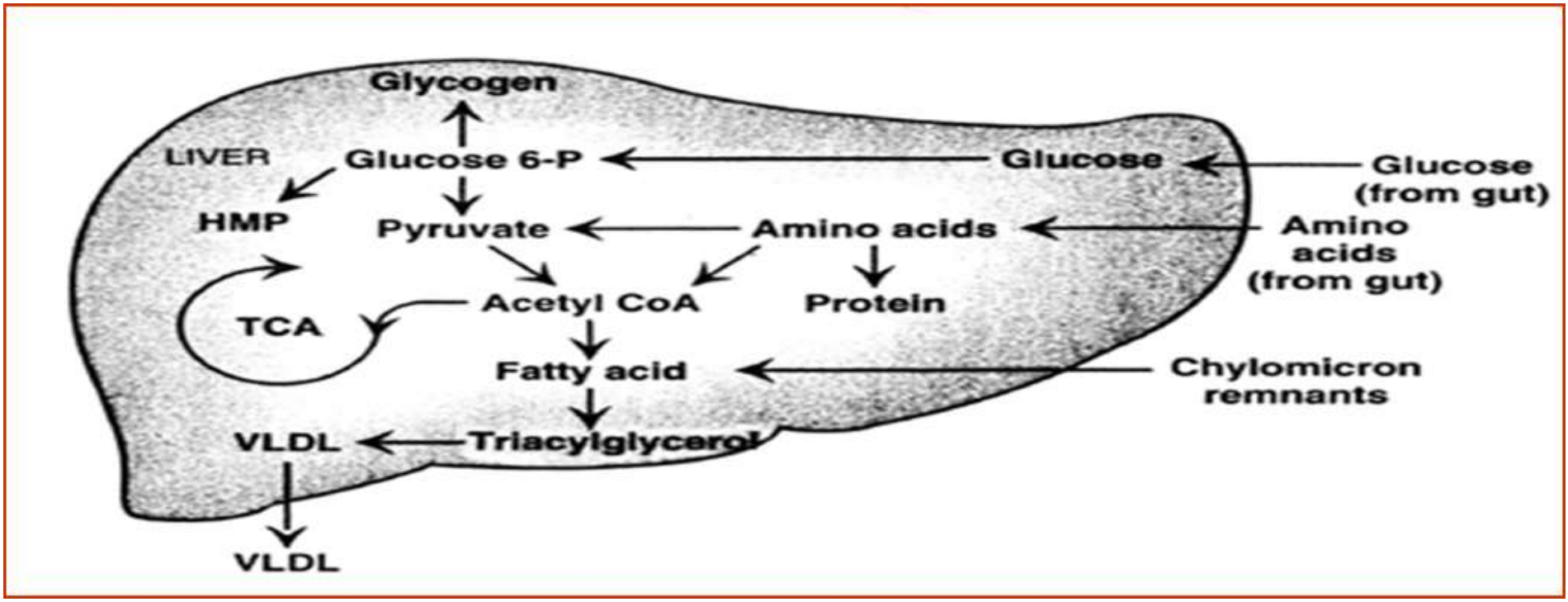
TAG stores largest (three months without any food intake)

Protein is used to produce glucose by gluconeogenesis

liver In well –fed state (WFS)

Carbohydrates:

- **Glucose rapidly transported into liver**: And phosphorylated by **glucokinase** to glucose-6- P.
- **Increase glycolysis**
- **Acetyl CoA** (produced from pyruvate by pyruvate dehydrogenase, PDH) enters TCA cycle for energy production and used for **FA synthesis**.
- Increase activity of HMP shunt to produce **NADPH** that is necessary for FA synthesis
- Increase glycogen synthesis.



Fats:

- Increased FA synthesis (lipogenesis)
- Increase**TAG** synthesis (HSL is inhibited) ----- exported from liver as VLDL (TAG carrier)

Amino acids:

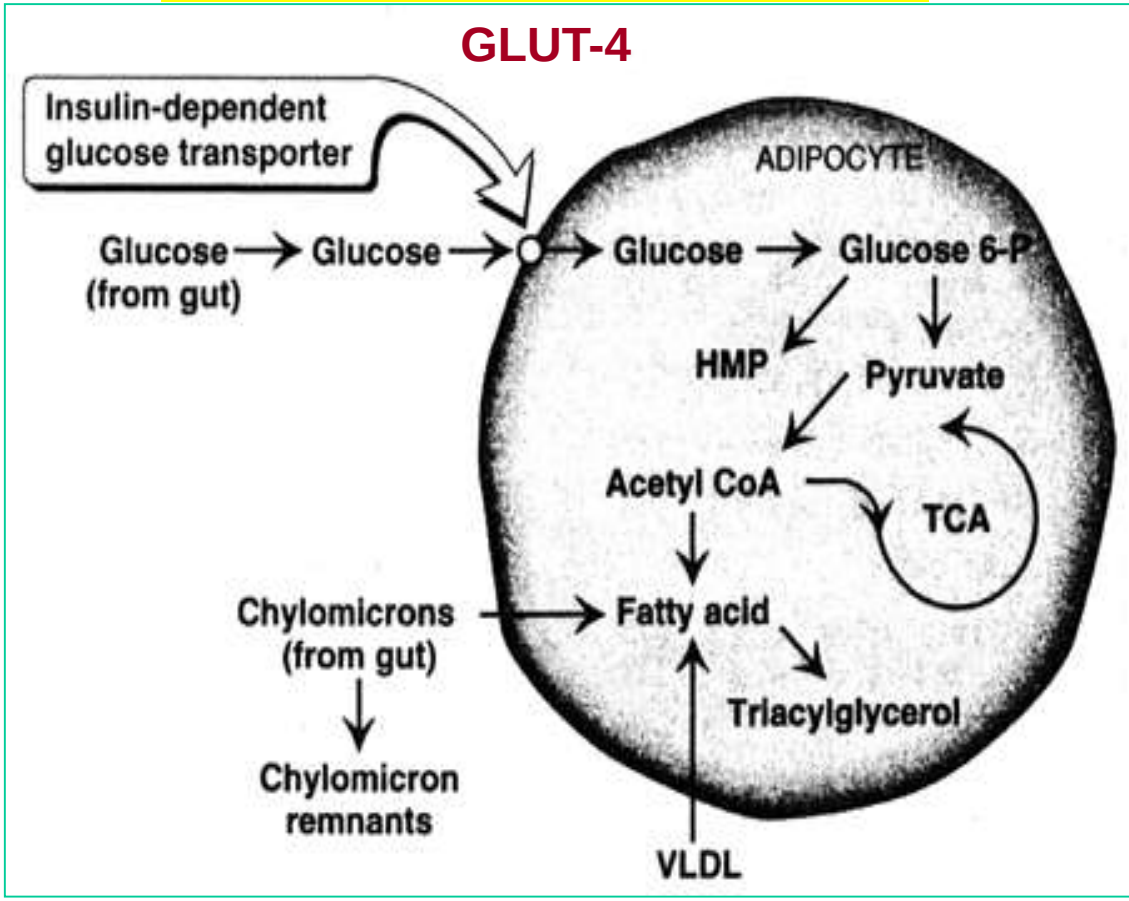
- Increase protein synthesis and exported to other tissues.
- Excess AAs are **deaminated**, *carbon skeletons u*sed for *energy production* or *fatty acid synthesis*).

Adipose tissue

In well –fed state (WFS)

Carbohydrates:

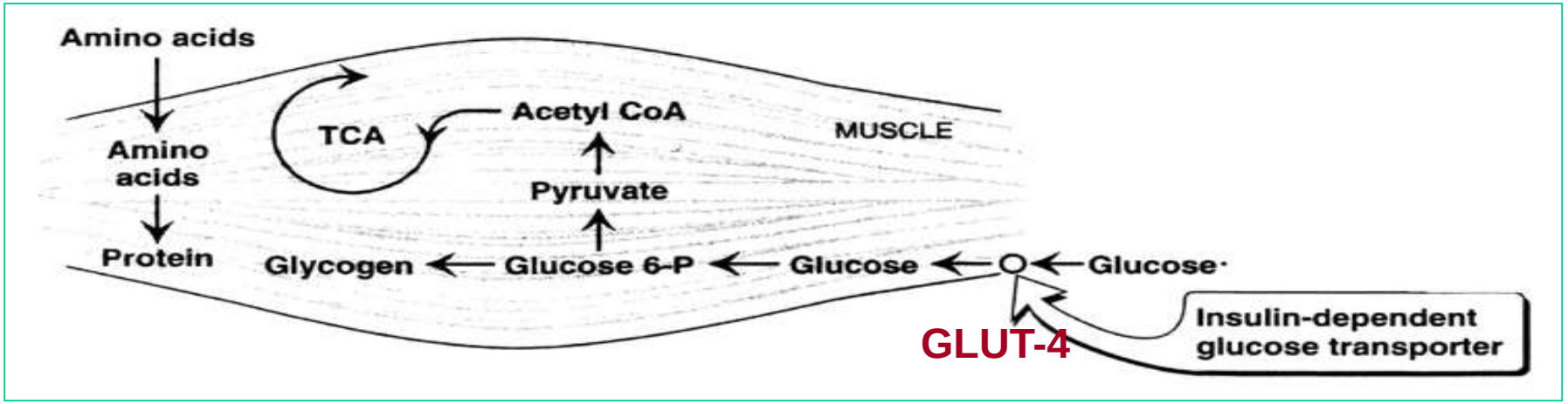
- Increased insulin promotes **glucose uptake**
- Increased glycolysis yields ***glycerol-3 phosphate*** for TAG synthesis
- Increased HMP activity produces **NADPH** for FA synthesis.
- ***It lacks Glycerol kinase***



Fats:

- FA synthesis is increased, but in humans **FA come mostly from chylomicrons (major) and VLDL (minor)**
- Increased TAG synthesis and Decreased TAG degradation

Skeletal muscle **In well –fed state (WFS)**



Carbohydrates: Increase insulin promotes **glucose uptake** (by **GLUT-4**)

- increase **glycolysis and glucose oxidation and glycogenesis**.
- Inhabit glycogenolysis

Fats: FAs from chylomicrons and VLDL are used for energy

Amino acids: increase amino acids → Increased protein synthesis.

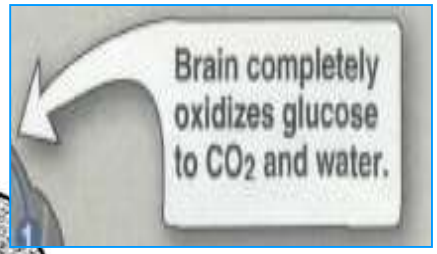
BCAAs (**Val, Ile, Leu**) used for protein synthesis and energy (muscle is the principal metabolizer) branched chain amino acids (**BCAAs**)

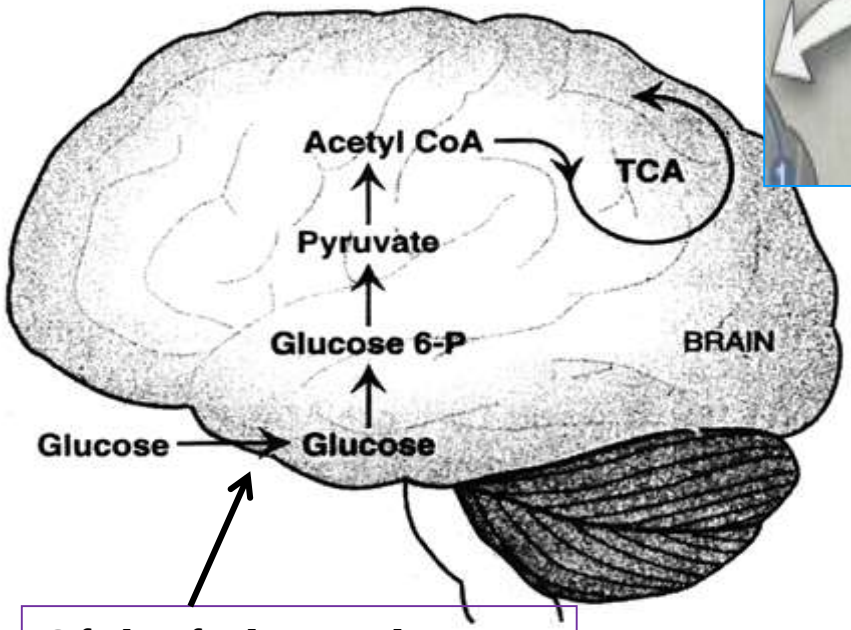
brain

In well –fed state (WFS)

No fuel storage in brain

No fuel output from brain





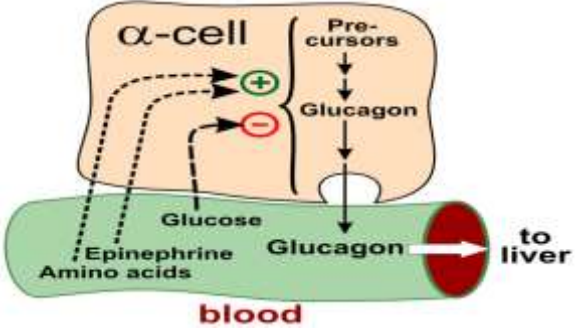
Of the fuels circulating in the blood can penetrate the blood-brain barrier

- It uses about 120 g glucose/day
- Brain consumes 20% of total O2 consumption
- Depends on blood glucose for energy
- FAs (carried on Alb.) **do not pass** efficiently through blood brain barrier (**No beta – oxidation of FA occur**)

A glucose consumer organ

Brain depends entirely of the blood glucose. Lower level of glucose (less than 40 mg/dL) causes brain dysfunction (a significant deterioration in attention) **and coma.**

Starvation



- **Fasting**-decline in blood glucose results in decreased insulin and increased glucagon.
- In this ***catabolic state***, glycogen, TAG and proteins are **degraded.**
- Priorities are to supply glucose to brain (& other glucose – requiring tissues) and metabolize FA and ketone bodies as **fuels** in other tissues.

Table 36.1. Fuel Utilization by Various Tissues during Starvation (Fasting)

Tissue	Glucose	Fatty Acids	Ketone Bodies
Nervous system	++	–	++
Skeletal muscle	–	++	++
Heart muscle	–	++	++
Liver	–	++	–
Intestinal epithelial cells	–	–	++
Kidney	–	+	+

Prolonged Starvation

First priority -> provide sufficient glucose to brain and other tissues that are dependent on it

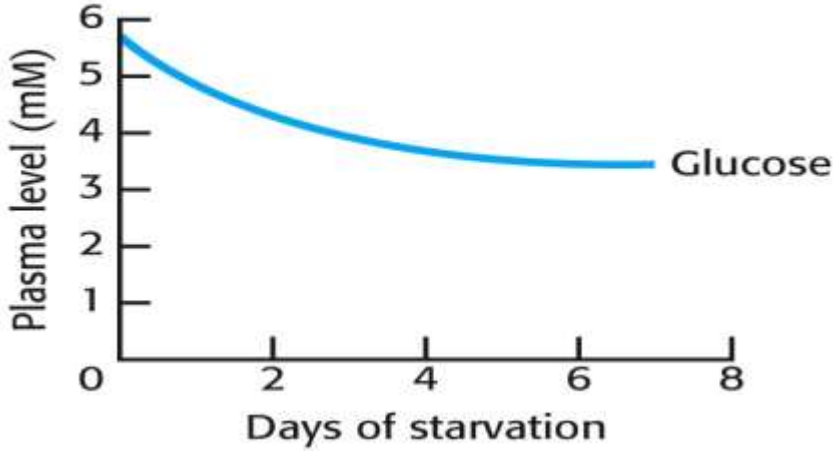
Second priority -> preserve protein -> shift from utilization of glucose to utilization of fatty acids + ketone bodies

-> mobilization of TAG in adipose tissues + gluconeogenesis by liver -> muscle shift from glucose to fatty acids as fuel

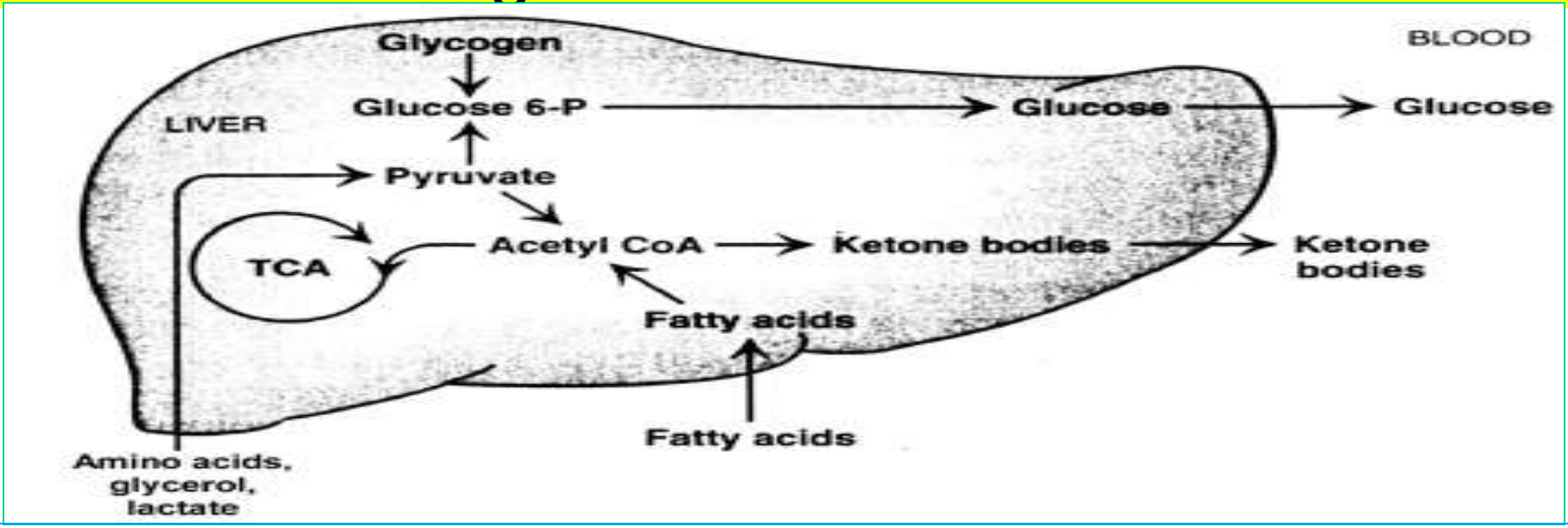
After 3 days of starvation -> liver forms large amounts of ketone bodies (**shortage of oxaloacetate**) -> released into blood -> brain and heart start to use ketone bodies as fuel

After several weeks of starvation -> ketone bodies major fuel of brain

After depletion of TAG stores -> proteins degradation accelerates -> death due to loss of heart, liver, and kidney function



Liver in fasting state



<u>Liver produces</u> a lot of KBs from FAs oxidation as a message to other tissues to stop using glucose.

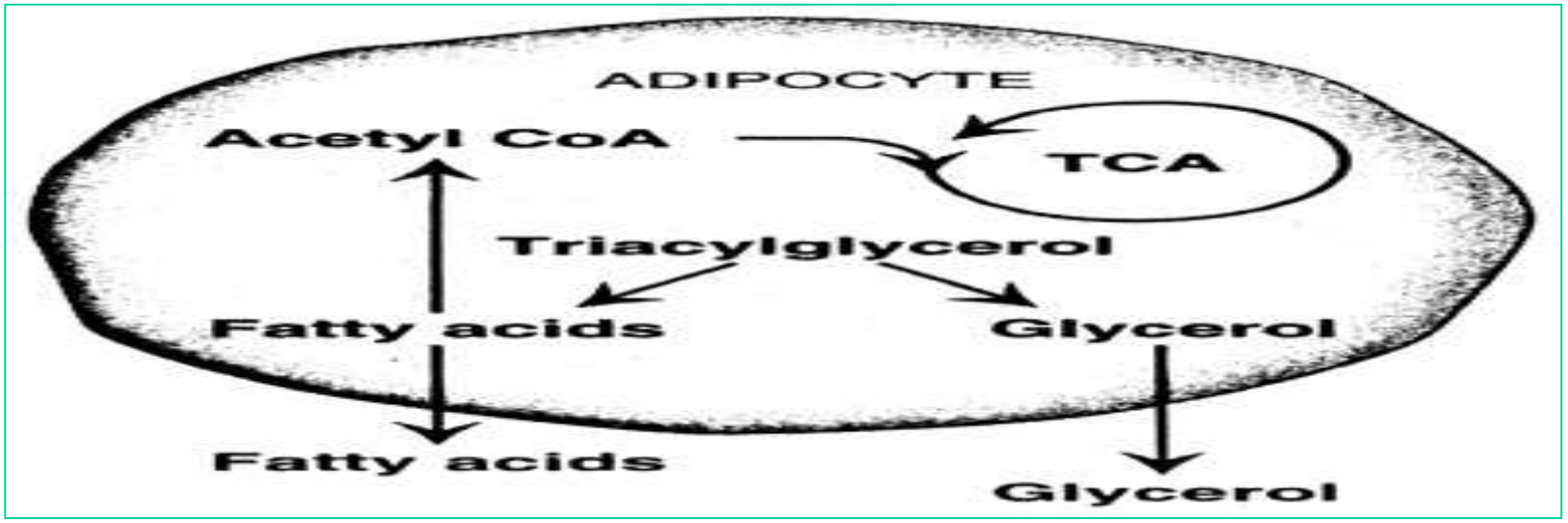
- **Glyogenolysis:** for glucose export (depleted in about 18-24 hrs
- **Gluconeogenesis:** ----- synthesis of glucose from amino acids, glycerol and lactate
- **FA oxidation** (FA comes from adipose tissue) & (**ketogenesis**) for export ketone bodies to extrahepatic tissues.

Metabolic role of ketone bodies during starvation

1. Source of energy for most of tissues [except anaerobic tissues [needs Kreb's cycle and RC].
2. Inhibit muscle proteolysis [proteolysis of > 50% is incompatible with life].
3. Spare glucose utilization for brain and glucose depending tissues.

Drawbacks: **Metabolic ketoacidosis.**

Adipose tissue in fasting

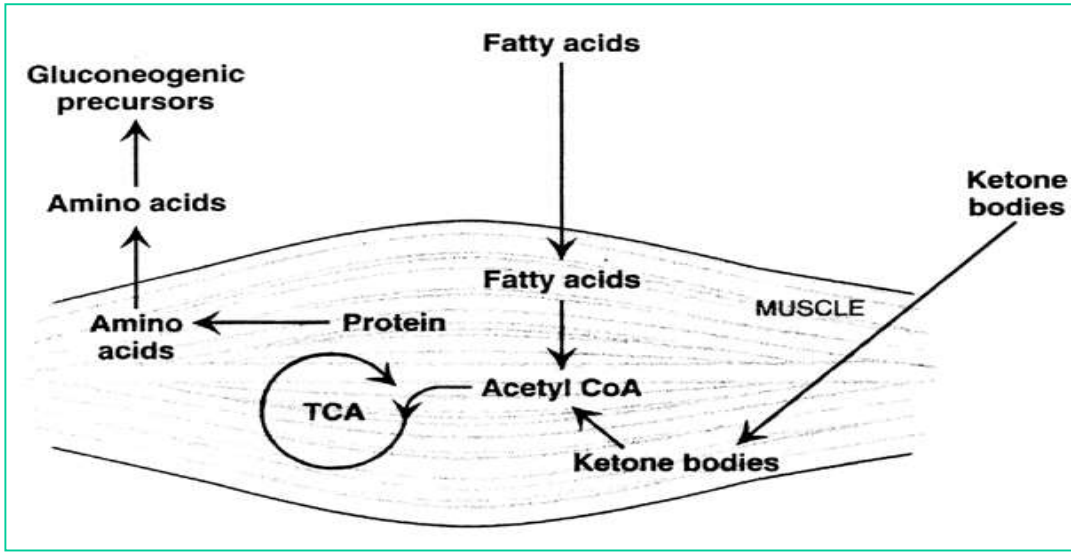


- **Glucose doesn't enter <u>because insulin is required</u>**
- **TAG** degradation occurs
- Adipose tissue uses FAs as energy source
- FA are released, circulate bound to serum *albumin*, and are used for energy in various tissues
- **Glycerol** goes to liver for *gluconeogenesis*

Skeletal muscle in fasting —

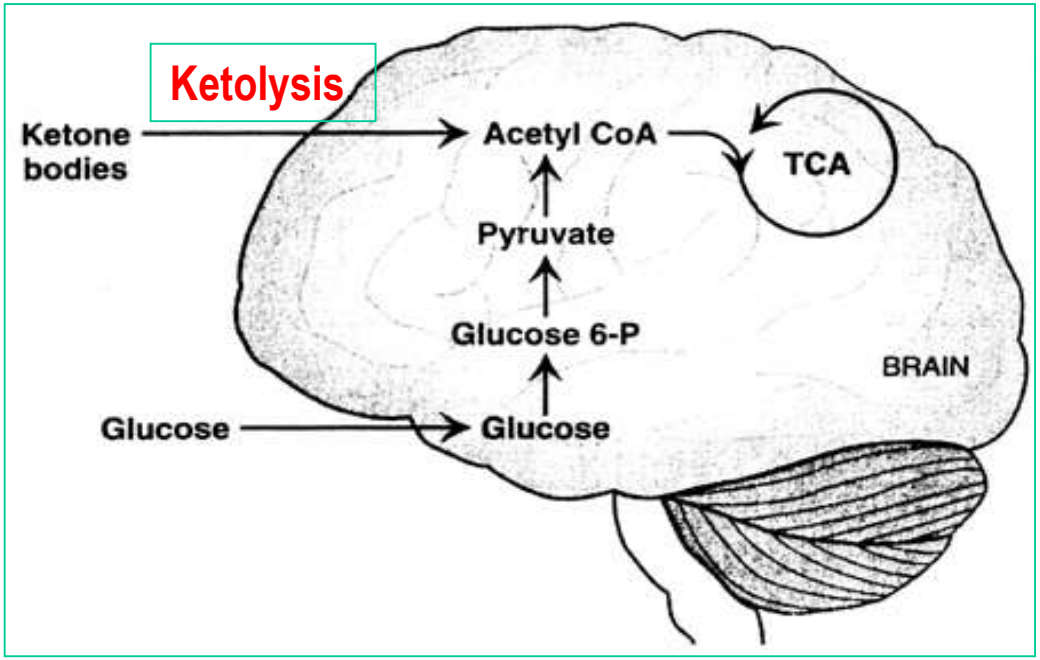
Skeletal muscle normally makes up about one half of the body's mass

- It cannot dephosphorylate Glucose-6-P (***Absence of G-6-phosphatase***)
- It *lacks receptors for* ***glucagon***.



- Decreased glucose entry (GLUT-4, insulin dependent)
- FAs and KBs are **used as fuels**.
- Protein degradation to supply gluconeogenesis in the liver (alanine, glutamine are most abundant in export)
- **BCAAs** (Val, Ile, Leu) used for energy (muscle is the principal metabolizer) after conversion them into alpha keto acids and NH3 which removed as glutamine and alanine from skeletal muscle.

Brain in fasting —



Uses glucose

After 2-3 weeks of fasting , it adapts to use KBs (70% of energy) and glucose.

Long chain of FA do not pass through blood-brain barrier

A person's survival time under starvation condition is mainly determined by the size of the TAG depot.
What happens after depletion of the TAG stores?. *The only source of fuel that remains is* ***proteins****. Protein degradation accelerates and death inevitably results from a loss of heart, liver or kidney function.*

- **Death from starvation occurs as a result of:**
- Metabolic acidosis and dehydration
- Pneumonia (muscle weakness, decreased Antibodies formation)
- Shock (depletion of blood volume)
- Protein degradation and loss of heart, kidney and liver functions