Types of Metabolic Pathways

Anas Althebyan

What is Metabolism

Thousands of chemical reactions are taking place inside a cell in an organized, well-coordinated, and purposeful manner; all these reactions are collectively called **Metabolism**.

Purpose of Metabolism

- Obtaining Chemical Energy.
- Converting Food materials into the building block precursors, such as Amino Acids.

What is Metabolism

Metabolic Pathways are regulated at different levels, and these are:

- Allosteric Regulation.
- Hormonal Regulation.
- Regulation at the DNA level (synthesis of enzymes).

Types of Metabolic Pathways

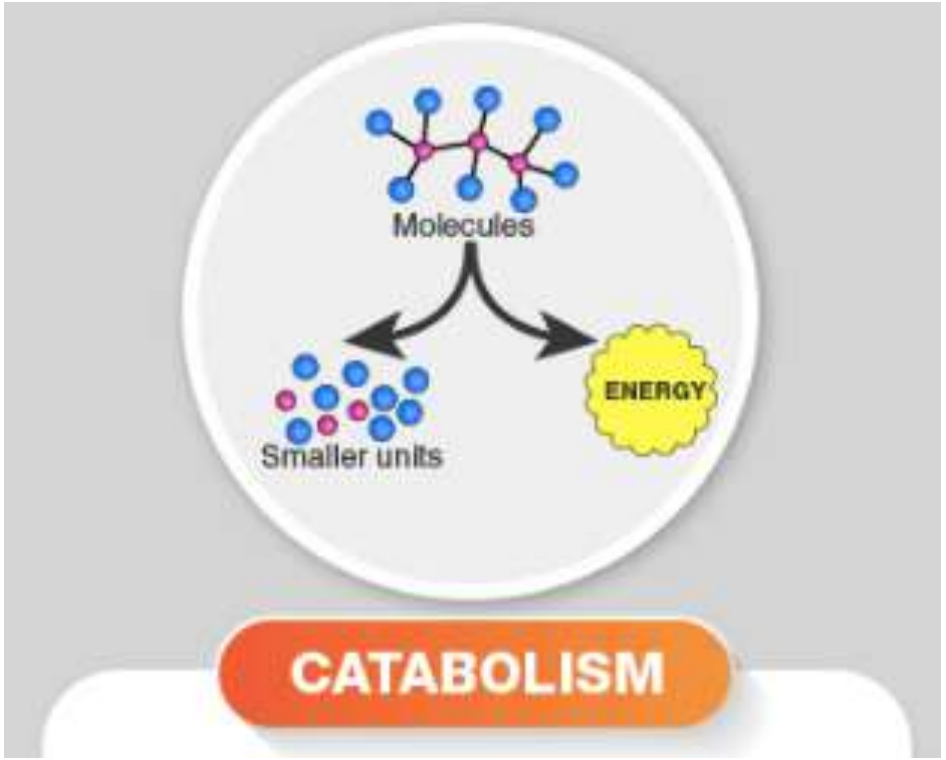
Metabolic Pathways are divided into 3 main categories, which are:

- Catabolic Pathways
- Anabolic Pathways
- Amphibolic Pathways

Catabolic Pathways

Catabolic or **Degradation** pathways, where energy-rich complex macromolecules are degraded into smaller molecules. The energy released during this process is trapped as chemical energy, usually as ATP.

Examples of Catabolic pathways include glycolysis, the citric acid cycle and gluconeogenesis.

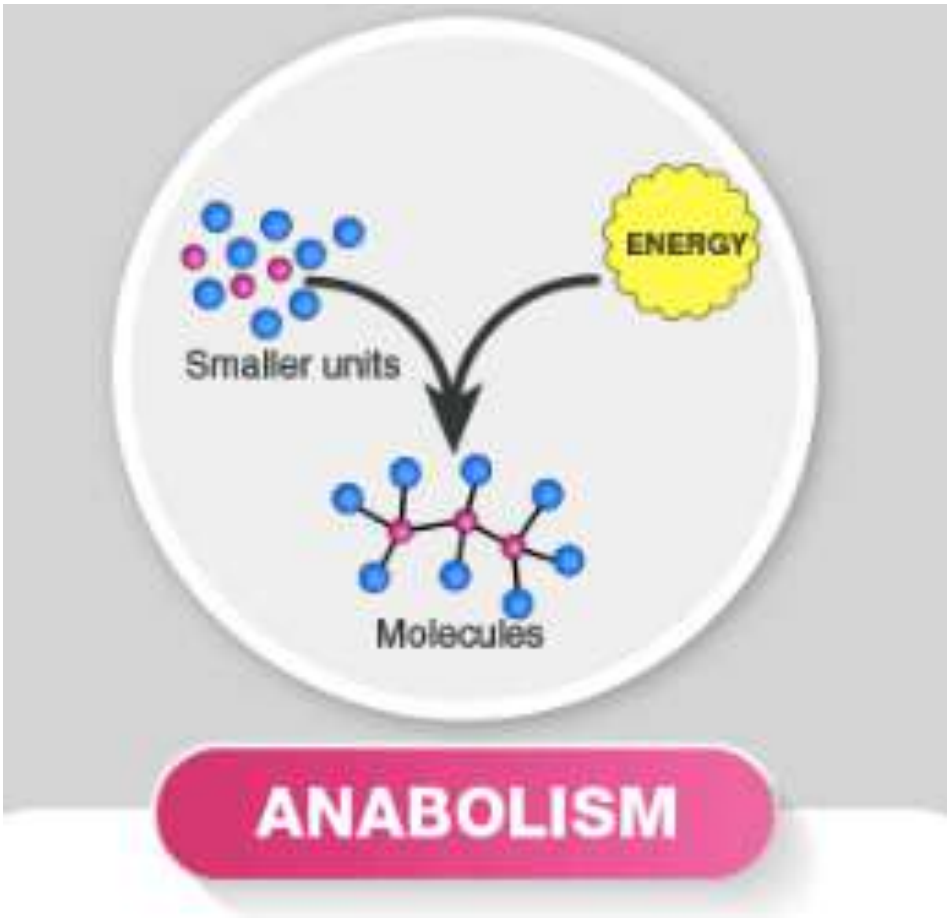


Catabolic pathways produce energy.

Anabolic Pathways

Anabolic or **Biosynthesis** pathways. The cells synthesize complex molecules from simple precursors. This needs energy.

Building **Glucose** from carbon dioxide is one example. Other examples include the synthesis of **Proteins** from amino acids, or of **DNA strands** from nucleotides.



Anabolic pathways require Energy

Amphibolic Pathways

Amphibolic pathways are seen at the **crossroads** of metabolism, where both anabolic and catabolic pathways are linked.

- A great example of Amphibolic pathways is the Cellular Respiration
- Respiration is the result of both making and breaking. When energy is required, proteins are broken down to form **acetyl-CoA** and further processes of respiration occur. This is the **catabolism** part. When the body requires fatty acids or proteins, the same **acetyl-CoA** is utilized, and fatty acids are manufactured. And this is the **Anabolism** part.

Stages of Metabolism

The degradation of foodstuffs occurs in three stages. Which are:

- *Primary* Metabolism
- *Secondary* (intermediary) Metabolism
- *Tertiary* Metabolism (Celluler Respiration)

Primary Metabolism

- Here is where digestion takes place.
- Converting Macromolecules into smaller units. For example, Proteins are digested into Amino Acids

Secondary Metabolism

- Absorption occurs in this stage.
- Glycolysis starts in this stage.
- The products from Primary Metabolism are catabolized into smaller components and ultimately **oxidized** to CO2.
- The **reducing equivalents** are generated in this step (Mainly in the Mitochondria), which are NADH & FADH2, they are generated by Substrate level phosphorylation.

Tertiary Metabolism

- NADH & FADH2 enter the ETC (Electron Transport Chain), where energy is released in the form of ATP.
- Tertiary Metabolism is also called Cellular Respiration, as the final electron acceptor is O2.

The rate of Metabolism affects weight gain. Fact or Myth?

The rate of Metabolism affects weight gain. Fact or Myth?

- It is true that Metabolism affects weight gain & loss, People might have fast, slow, or average metabolism, regardless of their body size and composition.
- It is mainly determined by genes, age and gender.
- However, in most cases, metabolism has a minor effect, so we can't entirely blame a sluggish metabolism for weight gain and the greatest factors as we age are often poor diet and inactivity."

Macromolecules that undergo Metabolism

- ***Carbohydrates***. They are catabolized into glucose, glucose then enters the **glycolysis** pathway, is converted to **acetyl CoA**, and is oxidized in the **citric acid cycle**.
- ***Lipids***. They are catabolized into **Glycerol** and **Fatty Acids**, Fatty Acids mainly enter the **β-oxidation** pathway, While the energy from Glycerol is utilized mainly through **Gluconeogenesis**.
- ***Amino Acids***. The main purpose of them is the synthesis of Proteins. However, most of the amino acids are eventually **trans-aminated** depending on the body's needs. This will provide some energy. But energy production is not the main purpose of amino acid metabolism.

The connection between different pathways

- All of the catabolic pathways for carbohydrates, proteins, and lipids eventually connect into **glycolysis** and the **citric acid cycle** pathways.
- Substances enter from other pathways, and intermediates leave for other pathways. These pathways are **not closed systems**. Many of the substrates, intermediates, and products in a particular pathway are reactants in other pathways.
- The breakdown and synthesis of carbohydrates, proteins, and lipids connect with the pathways of **glucose catabolism**. The simple sugars are catabolized during **glycolysis**. The fatty acids from lipids connect with glucose catabolism through **acetyl CoA**. The amino acids from proteins connect with glucose catabolism through **pyruvate, acetyl CoA, and components of the citric acid cycle**.

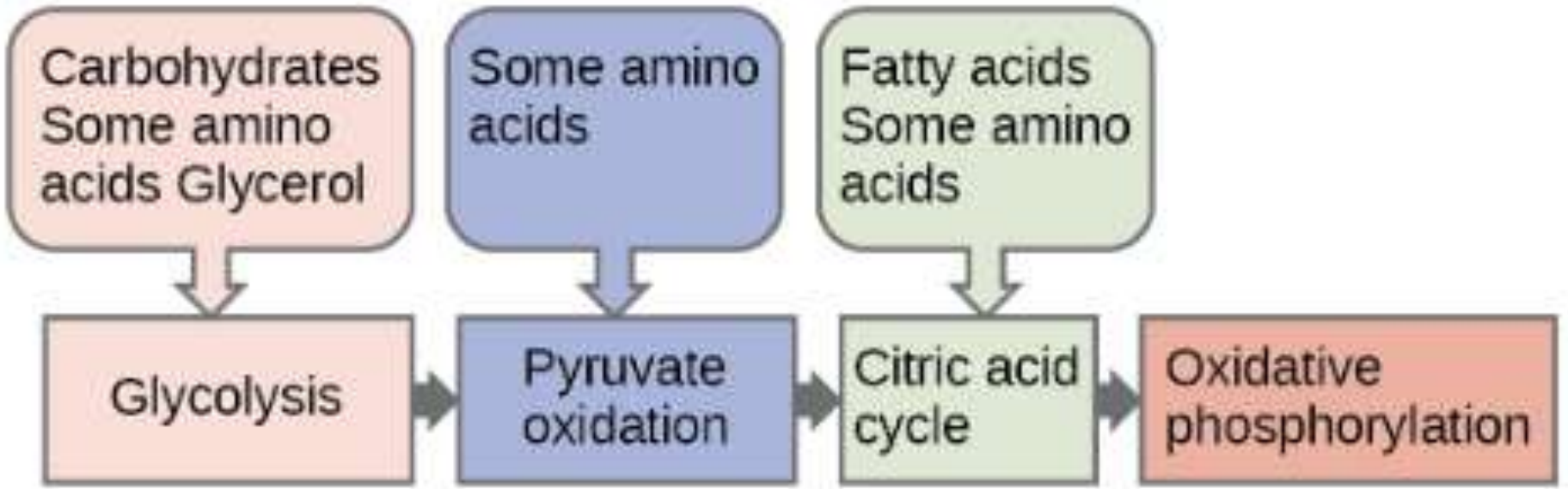
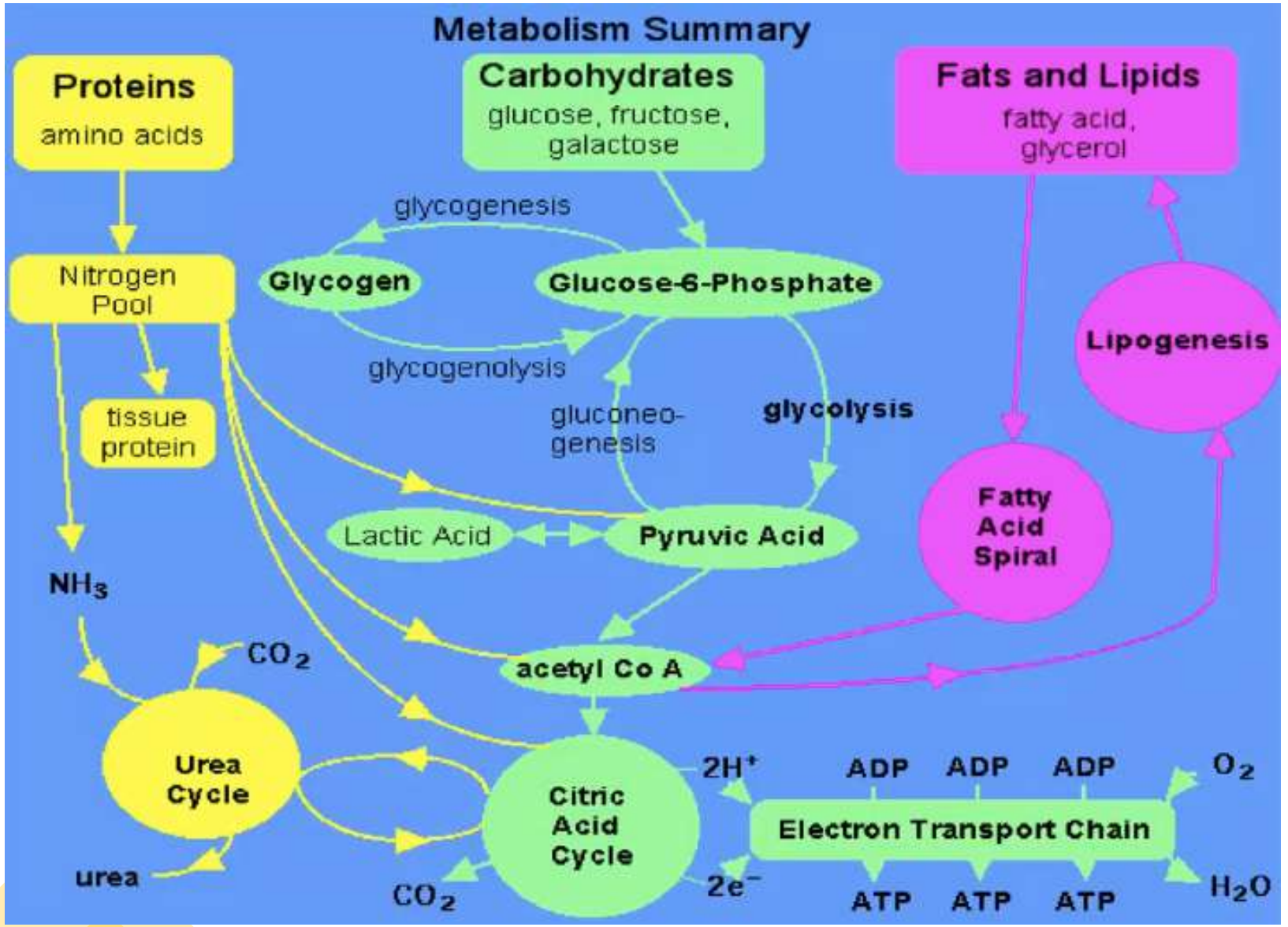
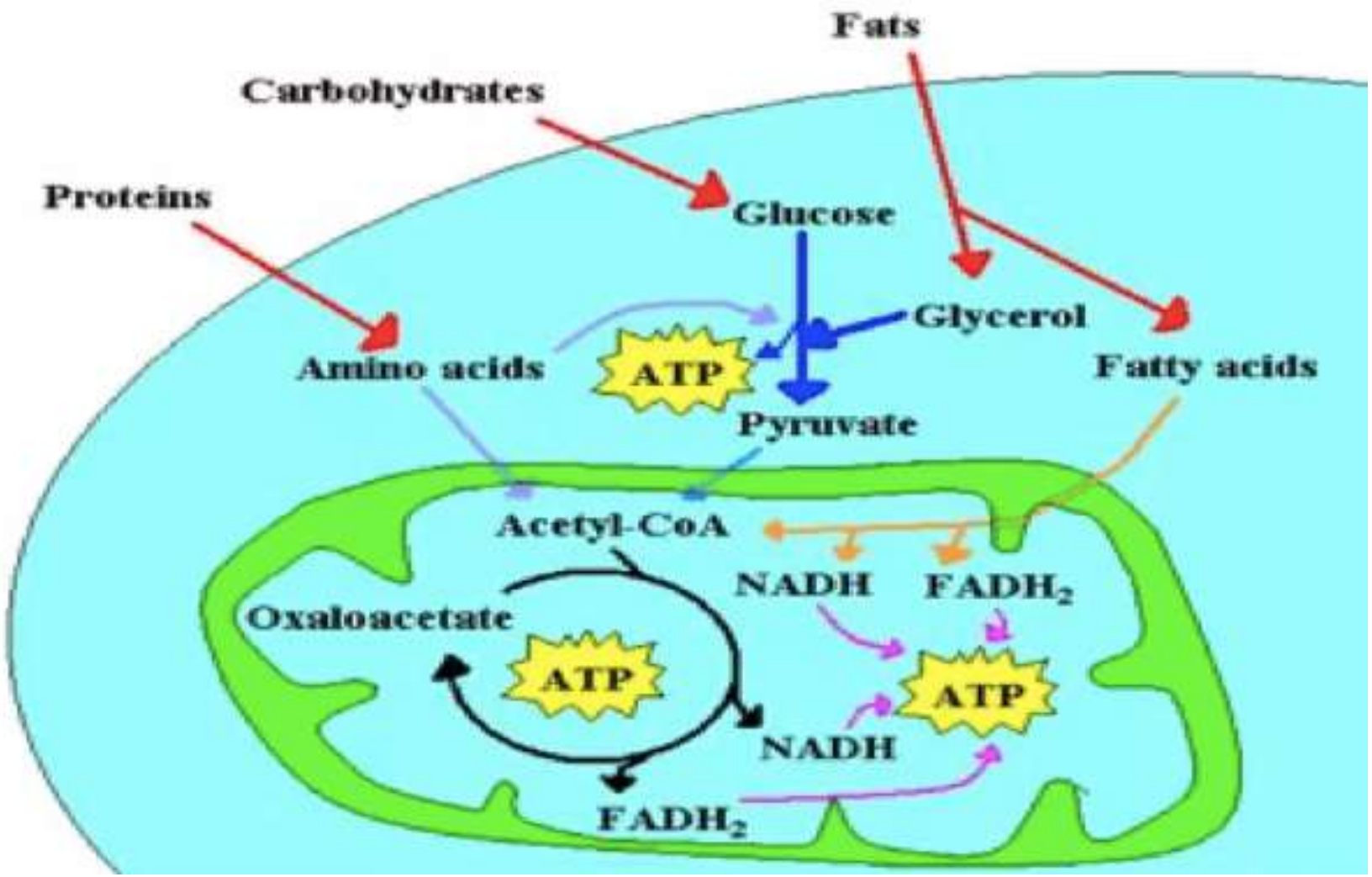


Figure 2. Glycogen from the liver and muscles, as well as other carbohydrates, hydrolyzed into glucose-1-phosphate, together with fats and proteins, can feed into the catabolic pathways for carbohydrates.


Metabolism Summary
Proteins
amino acids
Carbohydrates
glucose, fructose, galactose
Fats and Lipids
fatty acid, glycerol
glycogenesis
Nitrogen Pool
Glycogen
Glucose-6-Phosphate
Lipogenesis
glycogenolysis
tissue protein
gluconeo-genesis
glycolysis
Fatty Acid Spiral
Lactic Acid
Pyruvic Acid
NH3
CO2
acetyl Co A
Urea Cycle
Citric Acid Cycle
2H+
ADP ADP ADP
O2
Electron Transport Chain
urea
CO2
2e-
ATP ATP ATP
H2O


Fats
Carbohydrates
Proteins
Glucose
Glycerol
Amino acids
ATP
Fatty acids
Pyruvate
Acetyl-CoA
NADH
FADH2
Oxaloacetate
ATP
ATP
NADH
FADH2

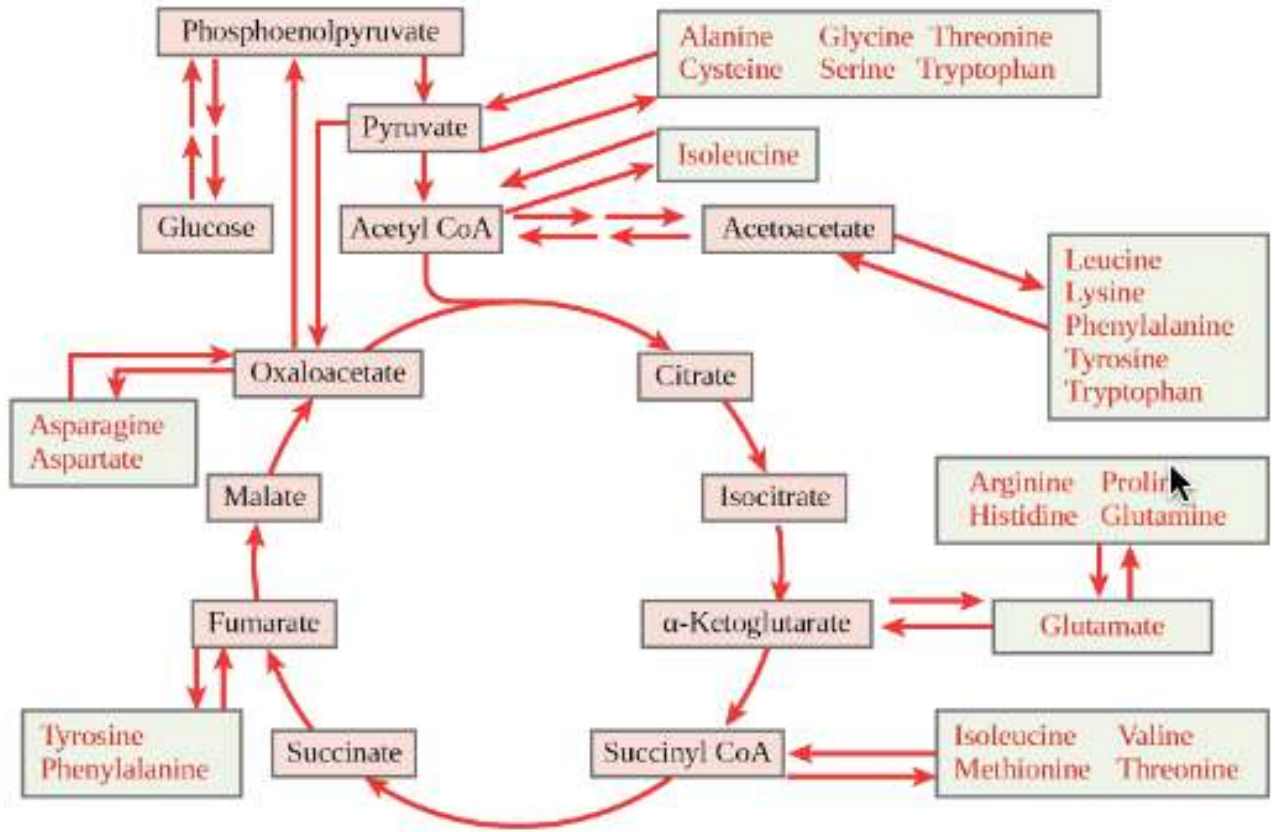


Figure 1. The carbon skeletons of certain amino acids (indicated in boxes) derived from proteins can feed into the citric acid cycle. (credit: modification of work by Mikael Häggström)

Metabolic profile of organs

Made by : yahia yasser

metabolic profile of organs

- The amount of metabolic activity of different organs is different depending on their function.
- moreover, the organs are able to adapt to metabolic alterations in fed state and starvation, and this table shows the storage forms of fuel.

Percentage to total fuel reserve	Stored fuel	Weight(in gram)	Energy equivalent
1%	Glycogen in liver	70	280
	Glycogen in muscle	120	480
	Glucose in body fluids	20	80
85%	Fat in adipose tissue	15 000	135 000
15%	Protein in muscle	6000	24 000

metabolic profile of organs

- Fats stores are mobilized actively only on prolonged fasting, even though adipose tissue fat is undergoing turnover on a daily basis. Caloric homeostasis is maintained regardless of whether a person is well-fed, fasting, or in a state of starvation. Similarly, the metabolic profile of various organs and tissues changes to adapt to physiological and pathological states, so that caloric homeostasis is maintained unless extreme conditions set in.
- The regulation of glycolysis and gluconeogenesis is the major deciding factor in the flux of metabolic intermediates through these pathways.

Brain metabolic profile

- Brain represents 2% of adult body weight but it needs 10-20% of cardiac output, and this equal about 750 ml of blood circulation per minute. Neurons can survive only a few minutes without a blood supply. stoppage of blood supply to the brain causes unconsciousness within 10 seconds.
- There is no stored fuel in the brain. Glucose, the preferred fuel of the brain while it's available, glucose can freely enter the brain cells. The total consumption of glucose by the brain is about 120 g/day (480 Kcal). Thus, about 60% of the total carbohydrate intake by the body is metabolized by the brain. Moreover, about 25% of the oxygen consumed by the adult body is due to glucose oxidation in the brain. In children, this may be as high as 50%. **Blood glucose level below 30 mg/dl is fatal.**

Brain metabolic profile

- The brain is unable to use fatty acids as fuel because the fatty acids can't pass through the blood-brain barrier. But during conditions like diabetes and starvation brain have 60-70% of the energy required for its function by ketone bodies, and one of the most ketone bodies used in the brain is acetoacetate.
- In anoxia (the absence of oxygen) the rate of **lactate production** by glycolysis rises to 5 or 8 times within one minute. The Pasteur effect is the brain's protection against conditions of anoxia.
- Under conditions of partial anoxia, the production of ammonia is increased. This is immediately trapped as glutamine. The NH_2 group of glutamine and glutamate can be used for the synthesis of other amino acids.

Skeletal muscle metabolic profile

- The skeletal muscle forms about 45% of the total weight of the body. About 0.5% of muscle weight is glycogen. Following a meal, the muscle glycogen content increases by about 1% of the total weight.
- The uptake and storage of glucose by the skeletal muscle under the influence of insulin. Following a meal, the level of glucose and insulin are high. So, glycogen synthesis is enhanced.
- Muscle metabolism during exercise: muscle uses glycogen for short active spurts of activity. Glycogen is rapidly broken down to form lactate. The lactate has to be transported to the liver to undergo gluconeogenesis (Cori cycle). Muscle however uses fatty acids as fuel for aerobic exercise and long-distance running.

*__The resting muscle uses fatty acids as major fuel (85%).__

Skeletal muscle metabolic profile

- **During starvation**, maximum glucose is spared for the brain. The free fatty acid (FFA) mobilized from adipose tissue is the preferred fuel for muscle during starvation. FFA does not require insulin, and during fasting insulin level is low.
- **During prolonged starvation**, muscle protein breakdown occur's and alanine is released into the bloodstream. It is transported to the liver to provide substrate for gluconeogenesis (glucose-alanine cycle). The metabolic fuel during prolonged fasting is **ketone bodies**. **Branched chain amino acids** are utilized by the skeletal muscle in prolonged fasting.

Major fuels in different organs

	Brain	skeletal muscle	Cardiac muscle	Adipose tissue
After meal	Glucose	Glucose , fatty acids	Glucose, fatty acids	fatty acids; glucose
Fasting (short term)	Glucose	Fatty acids	Fatty acids	Fatty acids
Fasting(long term)	Glucose ; ketone bodies	Ketone bodies; branched chain aa	Ketone bodies	Fatty acids; ketone bodies
exercise		Glycogen	Fatty acids	

Metabolic profile of adipose tissue, liver and cardiac muscle

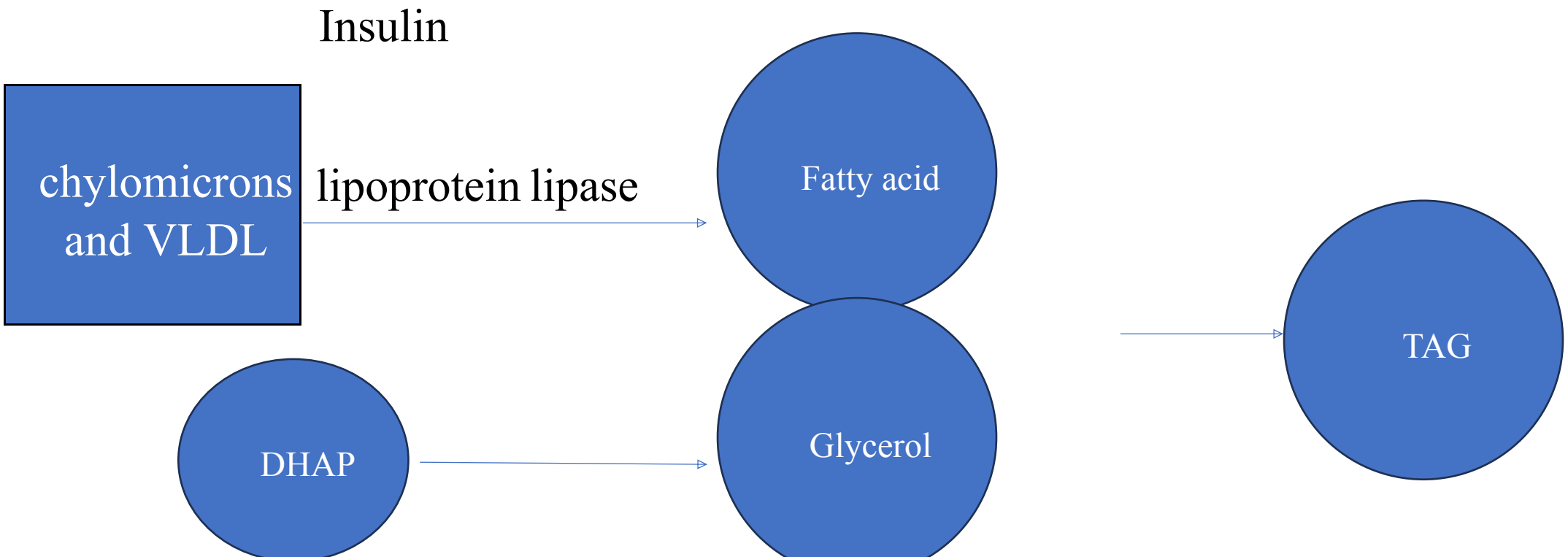
قال النبي صلى الله عليه وسلم:

(إن الله يحب إذا عمل أحدكم عملاً أن يتقنه)

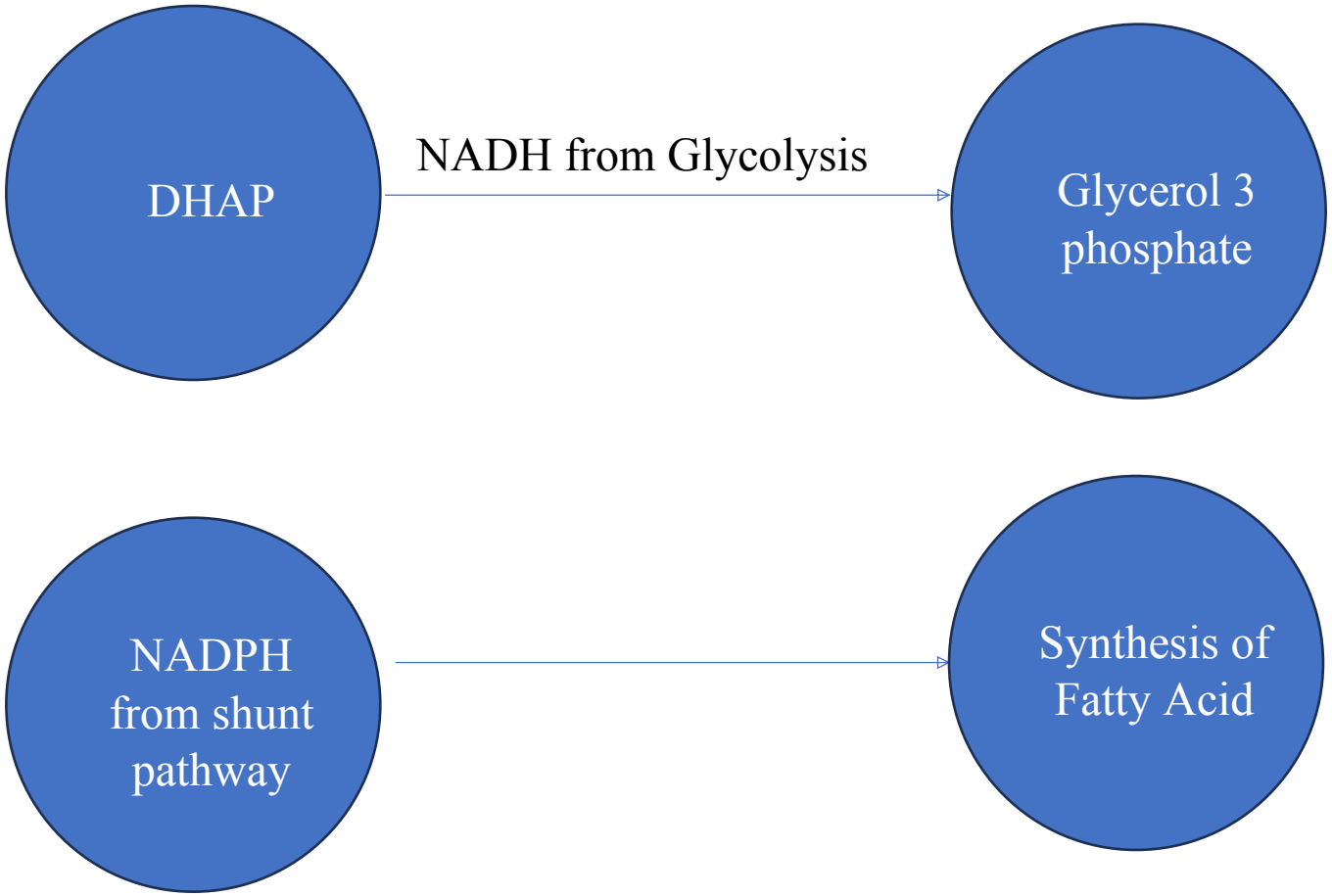
Metabolic profile of adipose tissue

- Adipose tissue It is the storehouse of energy in the body (about 1,35,000 kcal).
- The energy is stored in the concentrated form triacylglycerol.

Metabolic profile of adipose tissue



Metabolic profile of adipose tissue



Metabolic profile of adipose tissue

- **Fasting state:**

1. **Cyclic AMP mediated activation of hormone sensitive lipase occurs in response to the high glucagon-insulin ratio.**
2. **Glucocorticoids also have a stimulant lipolytic effect**

Metabolic profile of the liver

- The liver plays a central role in metabolism by providing adequate quantities of metabolic fuel for other organs.
- Almost all the metabolic pathways operate in the liver; a notable exception being ketolysis.

Metabolic profile of the liver

- **Fed state:**

1. **Glucose from circulation → Glycogen (glycogenesis)**
2. **Fatty Acid. → VLDL → Then, it well be secreted into blood stream.**
3. **Degradation of amino acids.**
4. **detoxification of ammonia into urea.**

Metabolic profile of the liver

- **Starvation state:**

1. **liver provides glucose by glycogenolysis and later by gluconeogenesis.**
2. **liver produces the ketone bodies.**

Metabolic profile of cardiac muscle

- **Heart consumes more energy than any other organ. It utilizes about 6 kg of ATP per day.**

Metabolic profile of the cardiac muscle

- **Cardiac muscle derives its energy by oxidative metabolism of fatty acids (60-90%) and glucose 10-40%.**
- **Ketone bodies are also metabolised in fasting (long term) state.**

Science of Exercise

By : Moath A. Naser & Malek Hassan

Types of Exercise

- Aerobic

  Usage of O2 during exercise
- Anaerobic

  No Usage of O2 during exercise

Aerobic vs. Anaerobic

Aerobic	Cardiac Enhancement AKA (Cardio)
	Jogging / Long Running / Swimming / Cycling
	Benefits : Enhancing the blood flow through out the body & Burn of Fat

Anaerobic	Muscular Enhancement AKA (High Stress Exercise)
	Sprinting / Dead Lifting / Weightlifting
	Benefits : Enhancing the Muscular Mass of the body

Effect on Metabolic profile

Anaerobic Exercise Effect :

- During anaerobic exercise, the major organ involved is the skeletal muscle with very little involvement of other organs. The relative ischemia created by the compression of blood vessels in the muscle will necessitate the use of glycogen and phosphocreatine available in the muscle to supply the required energy.

This means that it needs Bursts of Energy to Generate the Action so that it uses the fastest burning fuel (Glycogen, Phosphate Creatine)

Effect on Metabolic profile

Aerobic Exercise Effect :

- During moderate aerobic exercise, the muscular stores of glycogen are used, but in a normal individual this is not sufficient to provide a continuous supply of ATP for

  Exercise like long distance running.

Effect on Metabolic profile

Aerobic Exercise Effect :

- The RQ falls during long distance running since there is a progressive change from glycogenolysis to fatty acid oxidation to meet the energy demands

Effect on Metabolic profile

Aerobic Exercise Effect :

- **The levels of the following :**

1. Lowering RQ level (Respiratory Quotient)
2. Increasing the level of FFA in the Blood stream
3. Increasing the Level of AMP (To Activate AMP Kinase)
4. Lowering Malonyl CoA (Lowered FA Synthesis)

Effect on Metabolic profile

Aerobic Exercise Effect :

- **Final Effects :**

1. Muscles start oxidizing fatty acids and the high AMP level which activates AMP kinase and low malonyl CoA that activates CAT will favor fatty acid oxidation.

2. In muscle developed by exercise and training, the size and number of mitochondria are more as well as the level of enzymes for fatty acid oxidation and ketone body utilization. Hence, the trained muscle can better utilize noncarbohydrate sources of energy.

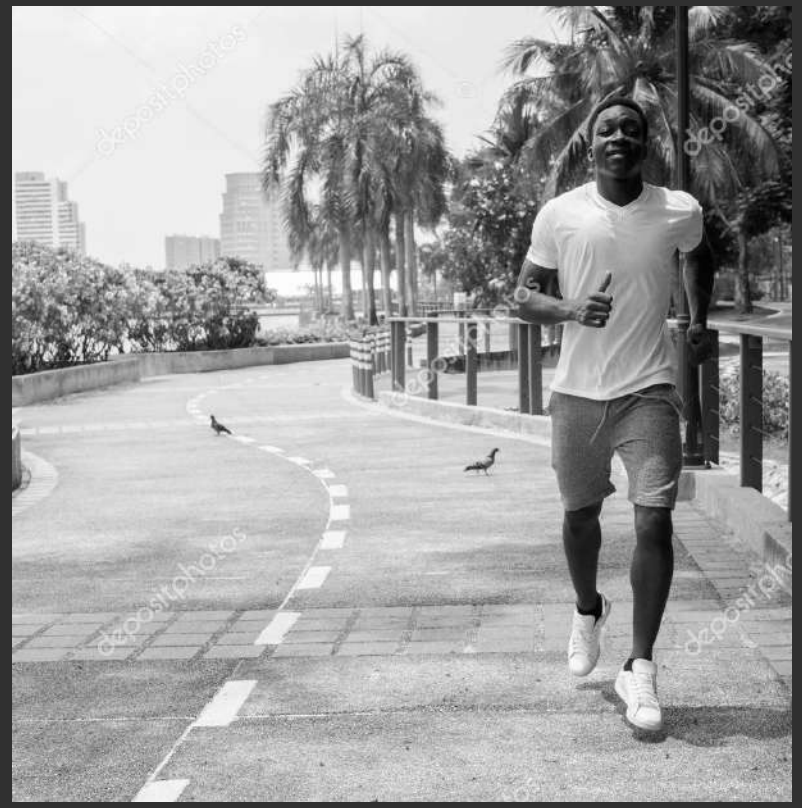
So, exhaustion is delayed

Long Distance Runners do not Compete with Sprinters

Long Distance Runners

An example of Aerobic Exercise.

- Metabolic profile of organs changes during aerobic exercise with fatty acids and ketone bodies being the preferred fuel for the skeletal muscle. Because glycogenolysis is not sufficient to meet the energy demands of prolonged aerobic exercise.



Sprinters

Anaerobic exercise.

- On the other hand, has no effect on the metabolic profile of organs other than skeletal muscle. The skeletal muscle depends on its own glycogen stores and phosphocreatine to meet the demand for ATP.

Questions & Answers

Why is long distance running considered an aerobic exercise?

Because The body Needs more ATP so it undergo Oxidative Phosphorylation
(Goes through ETC)

What is the role of glycogen and phosphocreatine in anaerobic exercise?

Because they are a High Energy Compound that are Easily Broken & used as an Energy source

Questions & Answers

Why does the RQ fall during long distance running?

When switching from Carbohydrates to Fats as a fuel which is a less efficient fuel which use ATP the RQ is lowered

How does training affect the size and number of mitochondria in muscle cells?

The increase in the need to produce more ATP so it responds with an increase in the size & the number of mitochondria in cells to improve its ability in utilizing O2 & producing Energy

Questions & Answers

How does the trained muscle better utilize noncarbohydrate sources of energy?

When doing prolong Activities this increase the usage of fats Which are metabolized by Fatty Acid Oxidation & the Enzymes that are involved in it also the size and number of mitochondria as mentioned before

Metabolic Adaptations During Starvation

Abdulrahman bader

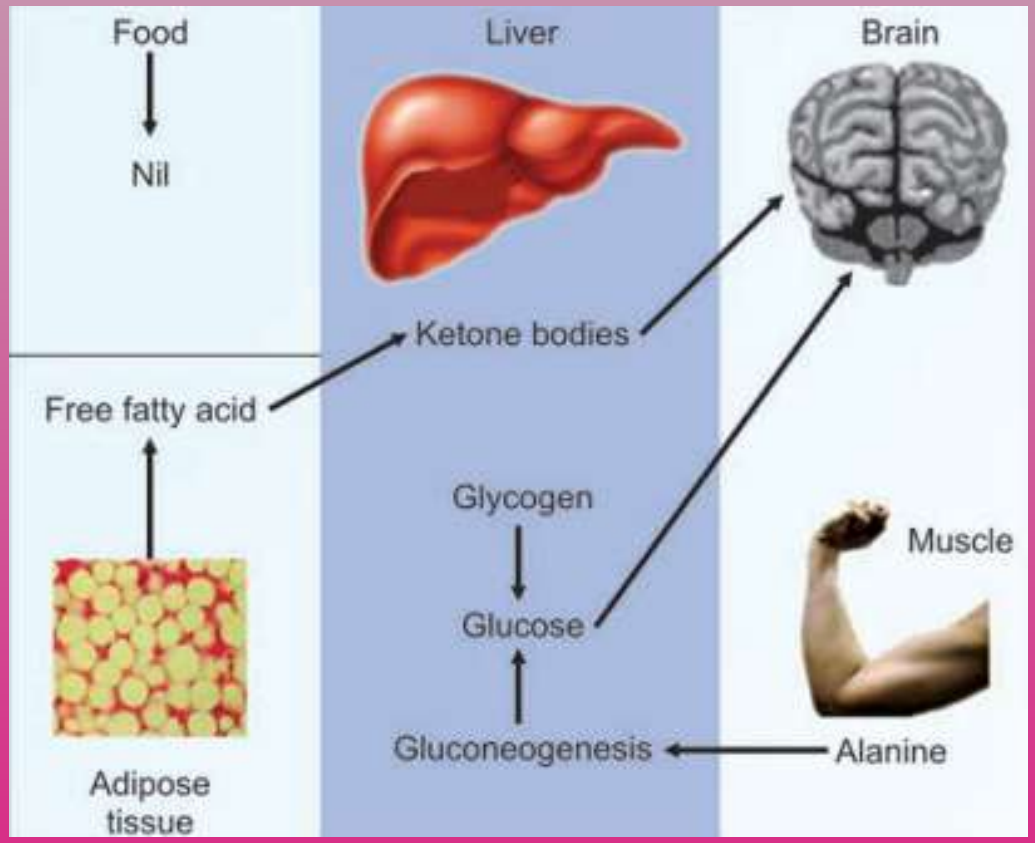
First stage: Glycogenolysis

- At this stage blood glucose level is maintained by hepatic glycogenolysis.
- The glycogen stores are sufficient for about 18 hours.
- The primary requirement for glucose is to meet the demands of the brain.

-When starvation is prolonged (>3 days), long term adaptation sets in, brain starts metabolising ketone bodies deriving about 30% energy from ketone bodies.

Table 8.2. Adaptations during starvation

Fed State	Skeletal Muscle	Cardiac Muscle
Preferred fuel at rest	Fatty acids	FFA, ketone bodies, lactate
Exercise	Glycogen to lactate	Fatty acids
Starvation Adaptations	Protein breakdown; release of amino acids; FFA, ketone bodies and branched chain amino acids utilized	Fattyacids, branched chain amino acids and ketone bodies utilized

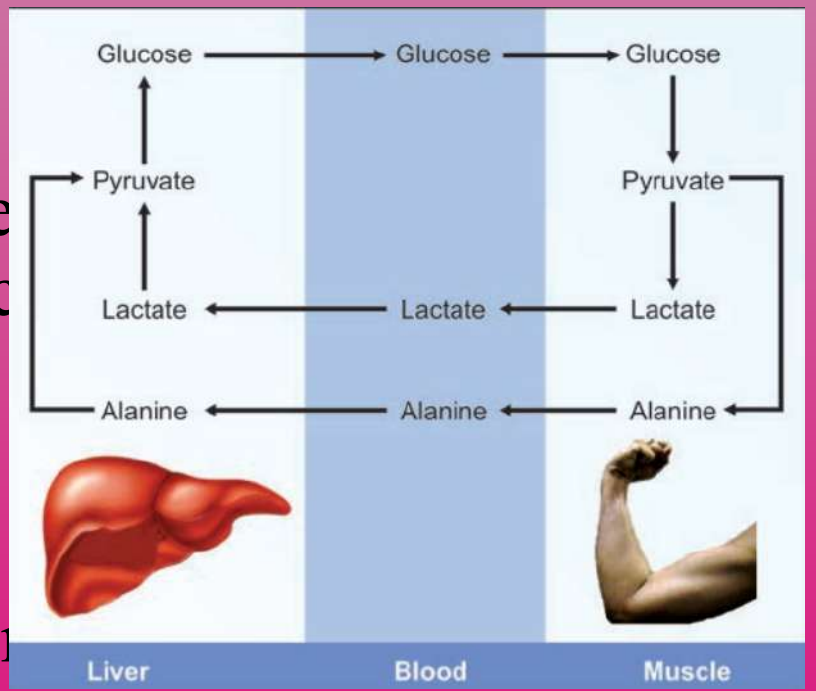


Second Stage: Gluconeogenesis

- Even before the glycogen stores are depleted, gluconeogenesis is accelerated.
- The amino acids released from muscle form the major substrate for gluconeogenesis (Alanine).
- The alanine goes to the liver where it is transaminated to give for gluc

called
alanine cycle.

-Glutamic acid also serves as an important mode of transport of amino acids to liver



Second Stage: Gluconeogenesis(cont..)

- The branched chain amino acids liberated by muscle protein catabolism especially leucine and isoleucine are utilized by the muscle to give energy.
- Brain can preferentially take up the glucogenic valine from the blood stream.
- The plasma level of branched chain amino acids reaches a peak by 5th day of starvation.

Third Stage: Lipolysis

- The prevailing state of high glucagon-insulin ratio stimulates cAMP mediated lipolysis by increasing the activity of hormone sensitive lipase(HSL).
- Then skeletal muscle, heart and kidney will shut down their glucose utilization; and will depend mainly on fatty acids for energy needs (glucose-fatty acid cycle).
- The stimulation of the activity of CAT by glucagon favors increased rate of beta oxidation.

Third Stage: Lipolysis(cont..)

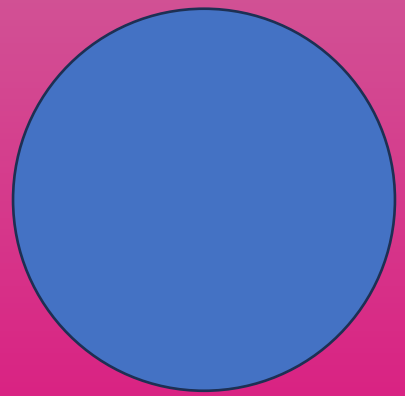
- The increased rate of lipolysis and beta oxidation provides an alternate source of fuel as acetyl CoA and subsequently ketone bodies.
- Ketone bodies provide fuel for tissues like heart muscle, skeletal muscle and to some extent the brain.
- It is seen that brain starts utilizing ketone bodies from 3rd day of starvation. By 10th day of starvation about 60% of energy for brain is derived from ketone bodies.

Fourth Stage: Acidosis

- However, this state cannot continue indefinitely since excessive production of ketone bodies leads to metabolic acidosis. When the bicarbonate buffering capacity is exceeded, the pH falls and hyperventilation occurs as a compensatory mechanism.

Fifth Stage: Death from Starvation

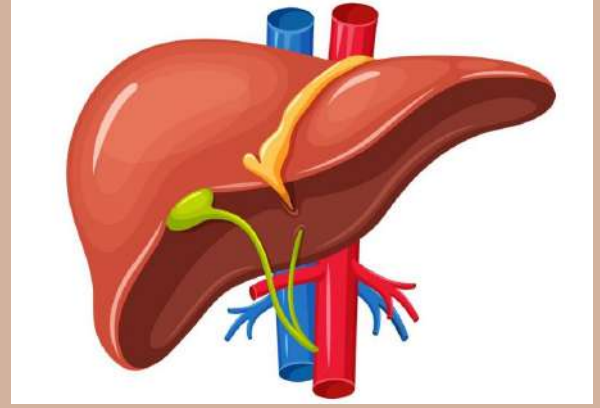
- Metabolic acidosis and dehydration, unless corrected efficiently, will lead to death.
- A normal person has fuel reserves to live up to 45–60 days.



Key enzymes under well fed, fasting and starvation conditions

Omar Debas

Glycogen Phosphorylase



Location: Liver and muscles

Function: Dephosphorylates glucose from glycogen to form G-1-P

Decreases when fed, Increases when fasting

Activated by: Glucagon & AMP
Inhibited by Insulin

Glycogen Synthase

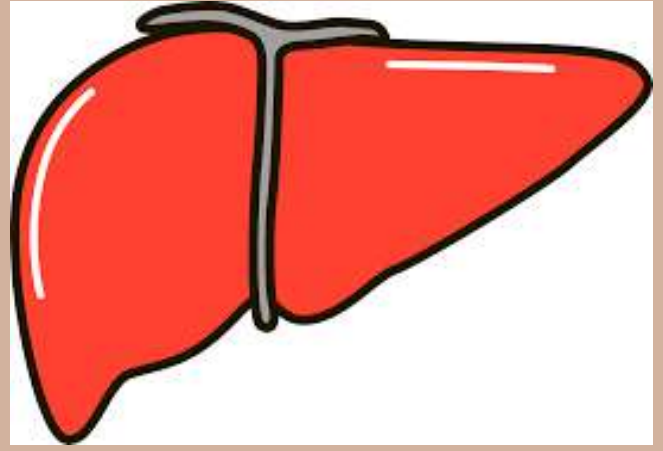
Location: Liver and muscles

Function: Transfers glucose from UDP-Glucose to glycogen

Increases when fed, decreases when fasting or starving

Activated by: Insulin & G-6-P
Inhibited by: Glucagon

Glucokinase (GK)

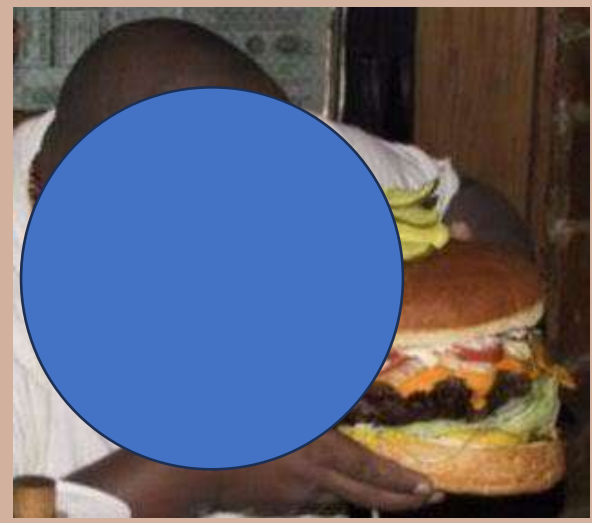


Location: The liver

Function: Phosphorylates Glucose to form G-6-P for glycogen synthesis.

Increases when fed, decreases during fasting and starvation.

Activated by Insulin and glucose
Inhibited by F-6-P (Co-inhibitor with GKRP)



Phosphofructokinase1 (PFK)

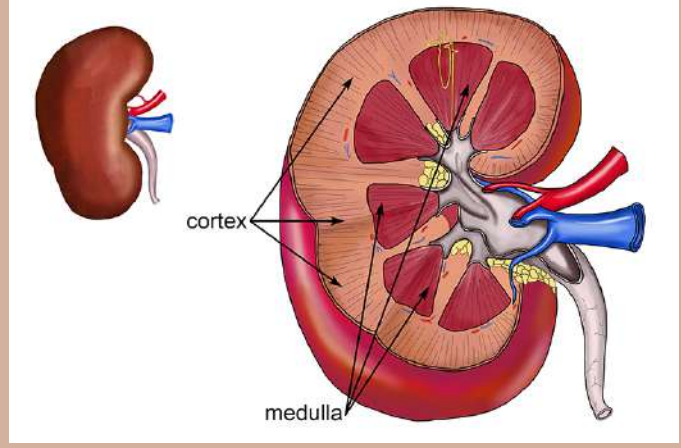
Location: All cells

Function: Phosphorylate F-6-P into F-1,6-BisP

Increases when fed, decreases when fasting and starving.

Activated by: Insulin, F-2,6-BisP & AMP
Inhibited by: Glucagon, ATP & Citrate

Fructose 1,6 Bisphosphatase



Location: Cytosol of the liver and the kidney cortex

Function: Dephosphorylates F-1,6-BisP into F-6-P for gluconeogenesis

Decreases during feeding, increases when fasting or starving

Activated by: ATP and Citrate

Inhibited by: AMP and F-2,6-BisP

Pyruvate Carboxylase

Location: Mitochondria

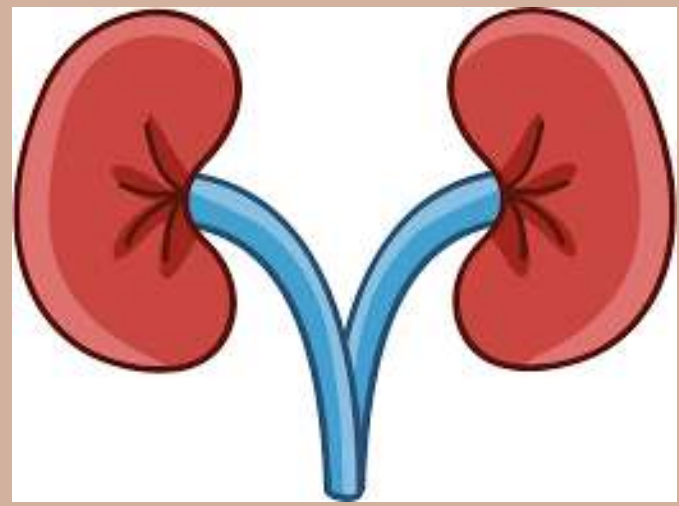
Function: Converts pyruvate to oxaloacetate

Decreases when fed, increases when fasting or starving

Activated by acetyl-CoA

Phosphoenolpyruvate carboxykinase (PEPCK)

Location: Cytosol of the liver and kidneys



Function: Convert Malate into PEP

Decreases when fed, increases when fasting or starving

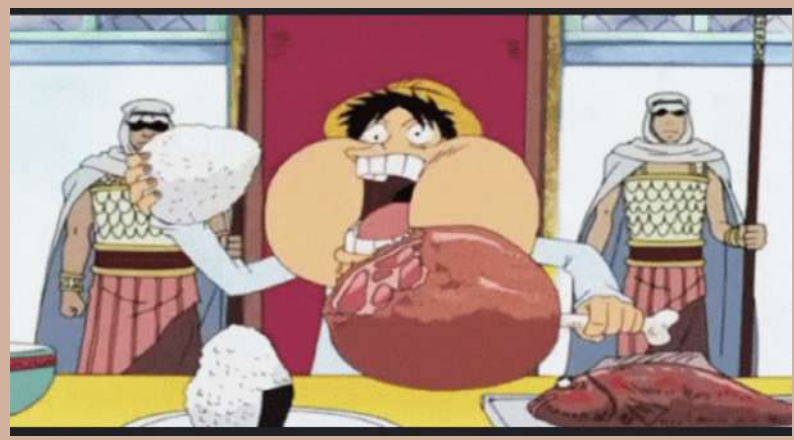
Activated by Glucocorticoids
Inhibited by: Insulin

Acetyl CoA Carboxylase (ACC)

Location: Cytosol of the liver, mammary glands, brain & adipose tissue

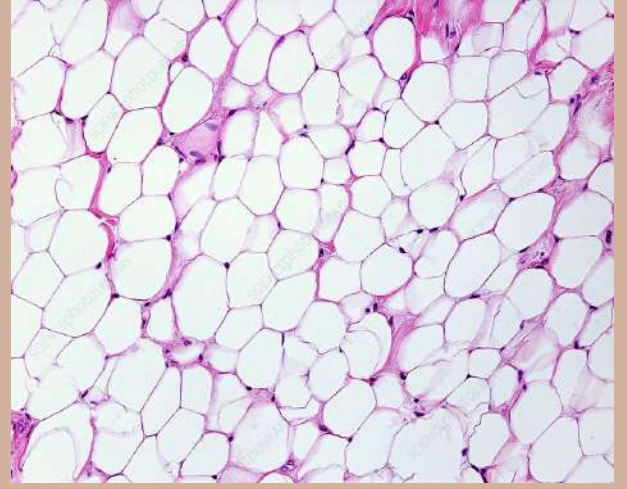
Function: Convert acetyl CoA into Malonyl CoA for FA synthesis

Decreases when fasting or starving



Activated by: Insulin & citrate
Inhibited by: Fatty acyl CoA (mainly Palmitoyl-CoA)

Hormone Sensitive Lipase



Location: Adipose tissue

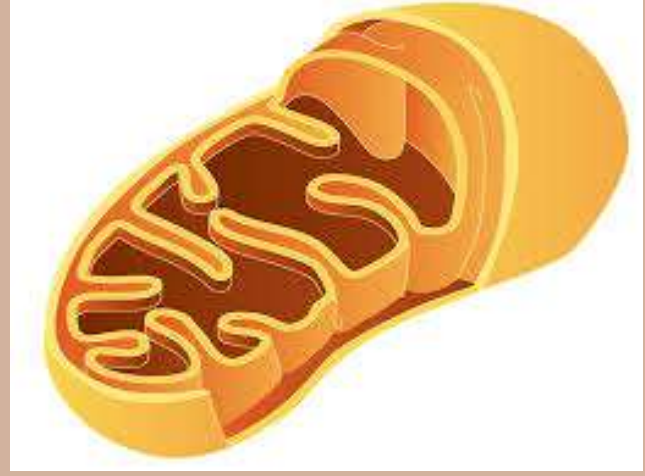
Function: Converts TAG into DAG

Decreases when fed, increases when fasting or starving

Activated by Glucagon
Inhibited by: Insulin

Carnitine acyl transferase (CAT)

Location: Mitochondria of all cells



Function: Transport Fatty acyl-CoA from the cytosol, through the intermembrane space and into the mitochondrial matrix for β-oxidation.

Increases when fasting or starving

Activated by: Glucagon
Inhibited by: Malonyl CoA

Enzyme	Fed	Fasting	Starvation	Activator	Inhibitor
Glucokinase	Increase	Decrease	Decrease	Insulin, Glucose	F-6-P
Phosphofructokinase1	Increase	Decrease	Decrease	F-2,6-bisP, AMP	ATP, Citrate
Fructose 1,6 bisphosphatase	Decrease	Increase	Increase	ATP, Citrate	F-2,6-bisP, AMP
Pyruvate carboxylase	Decrease	Increase	Increase	AcetylCoA	
PEPCK	Decrease	Increase	Increase	Glucocorticoids	Insulin
Glycogen phosphorylase	Decrease	Increase		Glucagon, AMP	Insulin
Glycogen synthase	Increase	Decrease	Decrease	Insulin, G-6-P	Glucagon
Carnitine acyl transferase		Increase	Increase	Glucagon	Malonyl CoA
Acetyl CoA carboxylase	Increase	Decrease	Decrease	Insulin, Citrate	Fatty acylCoA
Hormone sensitive lipase	Decrease	Increase	Increase	Glucagon	Insulin

PEPCK = phospho enol pyruvate carboxy kinase; F-6-P = fructose-6-phosphate; F-2,6-bisP = fructose-2,6-bisphosphate; G-6-P = glucose-6-phosphate