Integration of metabolism

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اللهم لا سهلا إلا ما جعلته سهلا وأنت تجعل الحزن إذا شئت سهلا
ربي اشرح لي صدري ، ويسر لي أمري ، واحلل العقدة من لساني ، يفقهوا قولي

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 as **Metabolism**. Metabolism serves the following purposes:

1. Chemical energy is obtained from the degradation of energy-rich nutrients.
2. Food materials are converted into the building block precursors of cellular macromolecules. These building blocks are later made into macromolecules, such as proteins, nucleic acids, polysaccharides, etc.

   Biomolecules required for specialized functions of the cell are synthesized.

3. Metabolic pathways are taking place with the help of sequential enzyme systems. These pathways are regulated at three levels:
   a. Regulation through the action of allosteric enzymes, which increase or decrease the activity under the influence of effector molecules.
   b. Hormonal regulation. Hormones are chemical messengers secreted by different endocrine glands.
   c. Regulation at the DNA level; the concentration of the enzyme is changed by regulation at the level of synthesis of the enzyme.

→ enzymes are proteins that are presented on genes so changes from the dna regulates the synthesis of the enzyme.

Types of Metabolic Pathways

A. **Catabolic** (degradation) pathways, where energy rich complex macromolecules are degraded into smaller molecules. Energy released during this process is trapped as chemical energy, usually as ATP.

→ exergonic reaction makes ATP

Examples of Catabolic pathways includ glycolysis, the citric acid cycle

B. **Anabolic** (biosynthesis) pathways. The cells synthesise complex molecules from simple precursors. This needs energy.

→ endergonic reaction needs ATP

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

C. **Amphibolic** pathways are seen at cross-roads of metabolism, where both anabolic and catabolic pathways are linked.

→ a lot of examples as TCA cycle
* like citrate which is broken down to acetyl coA/oxaloacetate {catabolic reaction which are used to make fatty acids and amino acid { anabolic reaction }

- 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 or Phases of Metabolism

The degradation of foodstuffs occurs in three stages.

i. In the first stage, digestion in the gastrointestinal tract converts the macromolecules into small units. For example, proteins are digested to amino acids. This is called **primary metabolism.**

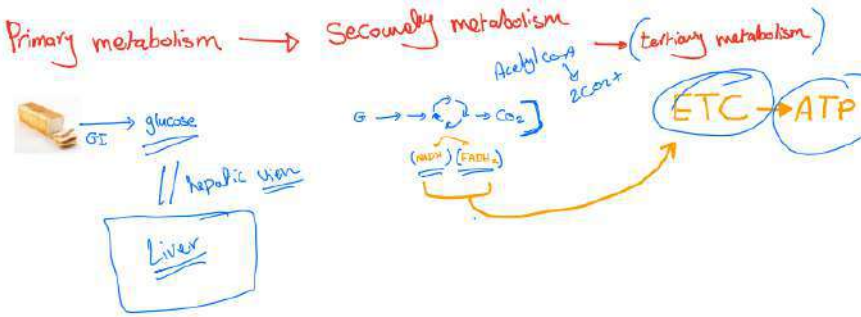
ii. Then these products are absorbed, catabolized to smaller components, and ultimately oxidized to CO_2. The reducing equivalents are mainly generated in the mitochondria by the final common oxidative pathway, citric acid cycle. In this process, NADH or $FADH_2$ are generated. This is called **secondary or intermediary metabolism**.

iii. Then these reduced equivalents enter into the **electron transport** chain (ETC, or Respiratory chain), where energy is released. This is the **tertiary metabolism** or Internal respiration or cellular respiration (see Fig. 20.1).

+ primary stage ♂ makes the building blocks

+ secondary stage ♂ Makes NADH / $FADH_2$

+ tertiary stage ♂ Makes ATP from NADH / $FADH_2$ by ETC



Glucose enters glycolysis pathway, converted to acetyl CoA and are oxidized in the citric acid cycle. Carbohydrate metabolism is centered around glucose, and is mainly used for provision of energy to the body (see Chapter 9).

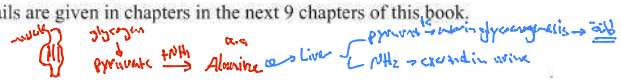
Lipid metabolism is centered around fatty acids, which are also used for provision of energy (see Chapter 12).

→ Provision of energy

Amino acids are mainly meant for body building purpose. However, most of the amino acids are eventually transaminated, the carbon skeletons are oxidized. This will provide some energy. (see Chapter 15). But energy production is not the main purpose of amino acid metabolism.

→ Building Purpose. But can provide energy in Starvation

Carbohydrate, lipid and amino acid metabolisms are inter-related and details are given in chapters in the next 9 chapters of this book.



لا تُفكّر، لها مُدّبر .

كم كُربةٍ ضاق الفتى لنزولها ... للهُ في أعطافها ألطاف

أُوحِ تستسلم بسرعة !
الحياة ، هي عايزة حدّ شجاع
يواجهها !

اللهم إنك عفوّ تحب العفو فاعفُ عنا

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.

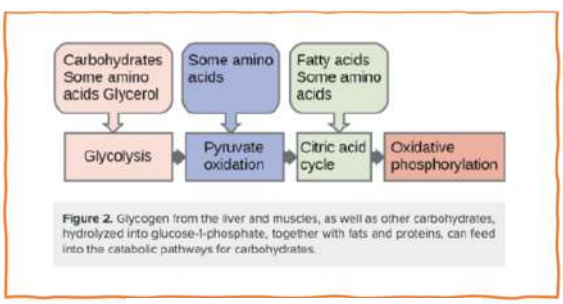


Figure 2. Glycogen from the liver and muscles, as well as other carbohydrates, hydrolyzed into glucose-1-phosphate, together with fats and proteins, can feed into the catabolic pathways for carbohydrates.

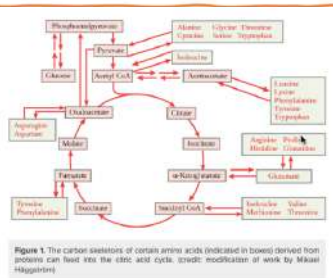
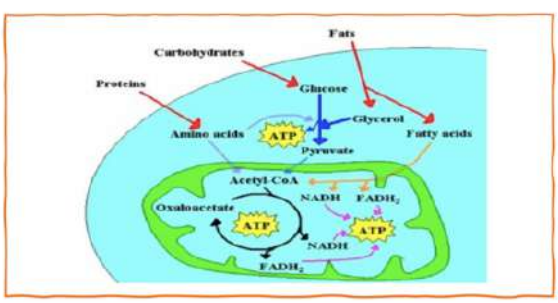
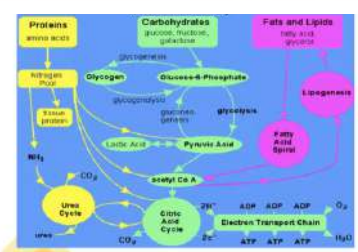


Figure 1. The carbon skeletons of certain amino acids (indicated in boxes) derived from proteins can feed into the citric acid cycle. (credit: modification of work by Mikael Häggström)

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**.





METABOLIC PROFILE OF ORGANS

The metabolic pattern or metabolic profile of different organs is different depending on its function. Moreover, the organs are able to adapt to metabolic alterations in fed state and starvation. The storage forms of fuels are shown in Table 8.1.

TABLE 8.1: Energy reserves of man

Percentage to total fuel reserve	*Stored fuel*	*Weight (in gram)*	*Energy equivalent (in kilo calories)*
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	6,000	24,000

نلاحظ أن أكبر كمية بتفس الوزن أقل
(1 gram of fat = 9 Kcal)
(1 gram of protein or carbohydrate = 4 Kcal)

- each organ uses different type of metabolic pathway and different macromolecules as fuel. ← Depending on it's function

- different energy sources stored in body
notice how because of the muscle weight it has more glycogen
and note how the brain doesn't have anything stored in it

liver → 1.5 - 2 Kg
2 Kg
70 g → glycogen

Muscles → 45% of total body weight
45 Kg
120 g → glycogen

Liver

- First pass of nutrients from GI tract
- Glycogenesis/glycogenolysis
- Gluconeogenesis (& kidney)
- Lipogenesis
- Ketogenesis
- Protein synthesis
- Deamination, urea synthesis
- Mostly uses fatty acids for fuel

Brain

- Glucose for fuel
  - CANNOT use fat!
- Can adapt to ketones for fuel

No influence of insulin in brain to uptake glucose

Muscle

- Glycogenesis/glycogenolysis
- Glucose, fatty acids or ketones for fuel
  - Mostly fatty acids at rest, mostly glucose during exercise
- Lactic Acid System

Adipose

- Lipolysis, releases fatty acids into blood
- Lipogenesis
- Major site of triglyceride storage (TAGs)
- Mostly glucose as fuel, can use fatty acids

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

i. Although brain represents only 2% of adult body weight, it needs 10–20% cardiac output. About 750 mL of blood circulates through the brain per minute. Neurons can survive only a few minutes without blood supply. Occlusion of blood supply to brain causes unconsciousness within 10 seconds.

ii. There is **no stored fuel** in the brain. Glucose, the preferred fuel for the brain, should be in continuous supply. Glucose can freely enter the brain cells.

iii. The total consumption of glucose by 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 brain. In children, this may be as high as 50%.

* brain cannot store any fuel
* that is why there must be a continues supply of fuel
* the brain prefers glucose (number 1 fuel for the brain)
  - because it can freely pass the blood brain barrier
* unlike fatty acids that cannot pass it because of it's attachment to albumin.
* in people with diabetic keto acidosis (no insulin) glucose can't be utilized by cells so the brain can use aceto acetate simple keto acid as fuel

Blood glucose level below 30 mg/dL is fatal.

v. **Brain and acetoacetate:** The brain is unable to utilize fatty acids as a source of fuel since the fatty acids complexed to albumin are unable to traverse the blood brain barrier. But, brain can effectively utilize acetoacetate. This is again a survival technique in diabetic and starvation ketosis.

Simplest beta Keto acid

vi. **Brain and starvation:** During starvation, a significant part (60–70%) of the energy requirement of the brain is met by ketone bodies (Fig. 8.1).

* during starvation when glucose level is very low brain uses Ketone bodies to make energy until glucose level is back to normal

- 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.

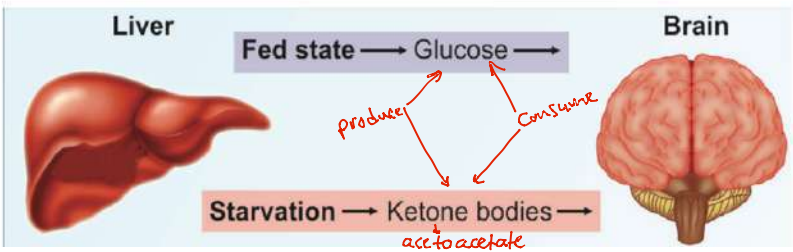
Note
* Fed state → 4 hours after meal
* fasting state → last meal - 24 hours
* Starvation → 24 hours - 24 days
* Prolonged Starvation → 24 days - 40 days

Summary: brain uses 2 pathways to make energy

Brain
- Can't store fuel (Gluconeogenesis)
- Glucose main fuel
- during starvation it uses Ketone bodies (aceto acetate)

1. the primary one: glucose
2. the secondary one: Ketone bodies

and it can use aceto acetate in some patients



Skeletal Muscle

i. The skeletal muscle forms about 45% of the total weight of the body. About 0.5% muscle weight is due to glycogen content. Following a meal, the muscle glycogen content increases by about 1% of the total weight.

ii. **Muscle metabolism after a meal:** The uptake and storage of glucose by the skeletal muscle is under the influence of insulin. Following a meal, the level of the glucose and insulin are high. So glycogen synthesis is enhanced. (Fig. 8.2). The resting muscle uses fatty acids as a major fuel (85%).

iii. **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 liver to undergo gluconeogenesis (Cori's cycle in Chapter 9). Muscle however uses fatty acid as fuel for aerobic exercise and long distance running.

iv. **Muscle metabolism during starvation:** 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 (Table 8.3).

v. **During prolonged starvation**, muscle protein breakdown occurs and alanine is released to the bloodstream. It is transported to liver to provide substrate for gluconeogenesis (glucose-alanine cycle in Fig. 9.30). The metabolic fuel during prolonged fasting is **ketone bodies**. **Branched chain amino acids** are utilised by the skeletal muscle (Fig. 8.3 and Table 8.2).

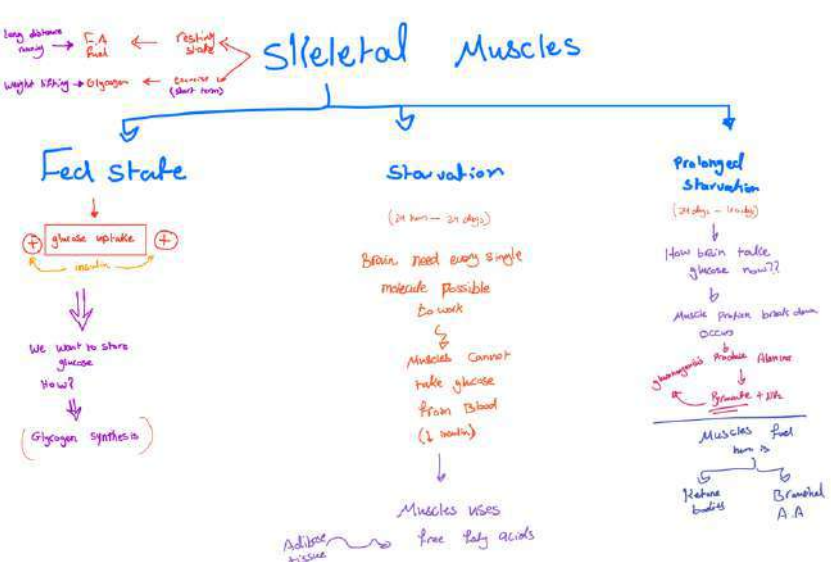
* after meals glycogen almost doubles in muscles
* muscles use the free ADP lying in it to make energy with the use of creatine phosphate.
* it will also use the glucose from meals to make glycogen and store it
* at rest the muscle will use fatty acids as fuel

* during exercise it will use the stored glycogen to make ATP / lactate {during anaerobic exercise}

if it's an aerobic exercise {which long not that strenous exercise} we use fatty acid

* during starvation & glucose is used for brain so we keep using free fatty acid
* prolonged starvation & we use Amino acids (alanine) and convert it to pyruvate to make glucose
* prolonged fasting & Ketone bodies and branched amino acids are used to make energy

Summary & Sm uses fatty acids / glycogen / ketone bodies / amino acids



Lipo protien = F.A + protien

chylomicrons

VLDL (Very low density Lipo protien)

DHAP → Glycerol

TAG

Adipose Tissue

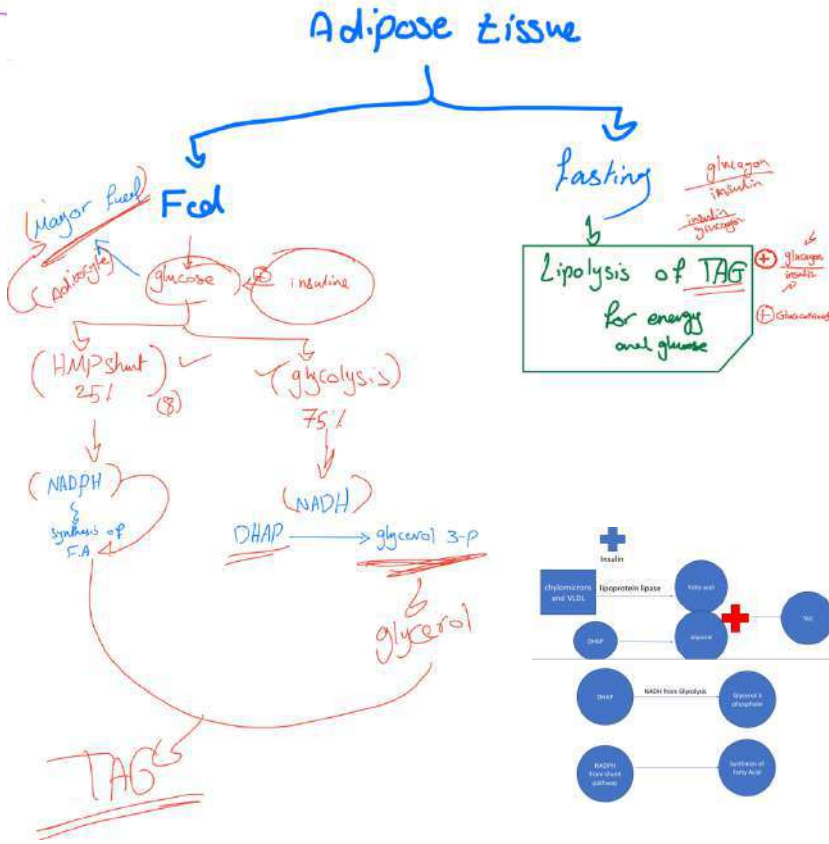
It is the **storehouse of energy** in the body (about 1,35,000 kcal) (Table 8.1). The energy is stored in the concentrated form, triacylglycerol. The chylomicrons and VLDL are hydrolyzed by lipoprotein lipase present on capillary walls. It is activated by insulin. The fatty acids are re-esterified to form triacylglycerol (see Chapter 11). The glycerol is derived from dihydroxy acetone phosphate (DHAP), an intermediate of glycolysis. Therefore, for storage of triacylglycerol, both fatty acid synthesis and glycolysis should operate. The uptake of glucose, glycolysis and lipogenesis are all favored by insulin.

About 25% of glucose taken up by adipose tissue is metabolized by the HMP shunt pathway, and the rest by glycolysis. The NADPH generated from the shunt pathway is used for the synthesis of fatty acids. The NADH produced during glycolysis is used to reduce the DHAP to glycerol-3-phosphate. Table 8.3 shows the major metabolic fuels of different organs during various physiological conditions.

During fasting, triacylglycerols in the adipose tissue are hydrolyzed. Cyclic AMP mediated activation of hormone sensitive lipase occurs in response to the high glucagon-insulin ratio. Glucocorticoids also have a stimulant lipolytic effect during fasting.

- Adipose tissue uses DHAP to make glycerol which is then used with 3 fatty acid to make TAG

Glucose taken by adipose tissue is metabolized by :
① HMP shunt to primarily make NADPH which is used in fatty acid synthesis
② glycolysis and the NADH made used in reducing DHAP to glycerol 3 phosphate



During fasting ∴ fat is used as fuel in Adipose tissue & this is mediated by insulin / glucagon / glucocorticoid.

- 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

Liver

i. The liver plays a central role in metabolism by providing adequate quantities of metabolic fuel for other organs.

fuel → Brain, Adipocyte: glucose, lipid, ketone bodies, proteins
muscle in work
secondary fuel for brain
muscle in starving

Almost all the metabolic pathways operate in the liver; a notable exception being ketolysis.

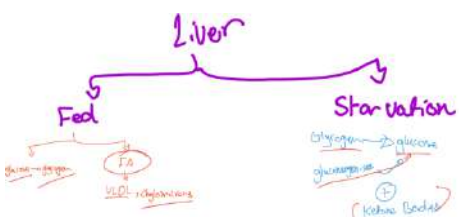
ii. **Liver metabolism in fed state:** Under well-fed conditions, the liver takes up glucose from circulation and stores it as **glycogen**. Similarly the fatty acids synthesised by the liver are incorporated into **VLDL** and secreted into bloodstream (Fig. 8.2). Liver is the major site of degradation of amino acids and detoxification of ammonia into urea (see Chapter 15).

iii. **During starvation**, liver provides glucose by **glycogenolysis** and later by **gluconeogenesis** so that the obligatory requirements of the brain are met (Fig. 8.3). Moreover, liver also produces the **ketone bodies**, an alternate source of fuel. But the liver cannot use ketone bodies as its own fuel. Table 8.3 shows the major metabolic fuels of different organs during various physiological conditions.

Ketolysis is the only metabolic pathway that doesn't happen in liver.

during fed state ∴ takes glucose and stores it as glycogen and the fatty acids synthesised by it will pass to the bloodstream

during starvation ∴ breaks glycogen to glucose and gives it to the brain
it also produces ketone bodies but can't use it & liver uses fatty acids for energy



Summary ∴ →

- **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.

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

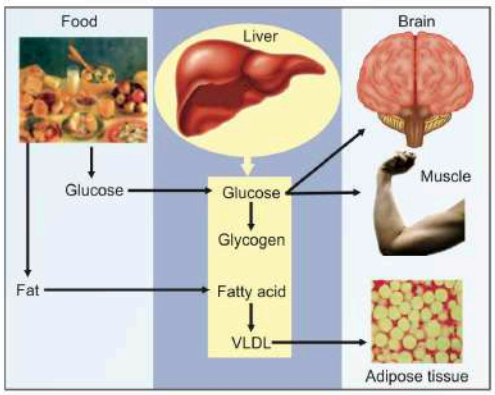


Fig. 8.2: Metabolism in well-fed state

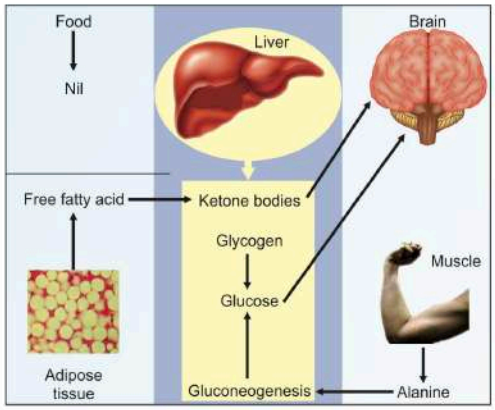


Fig. 8.3: Metabolism in fasting state

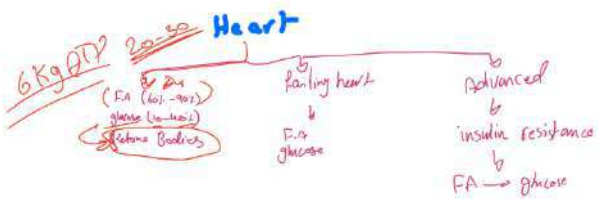
Cardiac Muscle

Heart consumes more energy than any other organ. It utilizes about 6 kg of ATP per day, 20-30 times of its own weight. Cardiac muscle derives its energy by oxidative metabolism of fatty acids (60–90%) and glucose 10–40%. Ketone bodies are also normally metabolized.

In addition, energy transfer to heart's myofibrils occurs by creatine kinase catalyzed energy shuttle. Phosphocreatine being a smaller molecule than ATP can easily diffuse into the myofibrils from mitochondria. The myofibrillar creatine kinase catalyzes the reformation of ATP. The free creatine diffuses back. The creatine kinase system acts as an energy buffer, by keeping ATP level constant. When ADP level increases due to a fall in phosphocreatine, it inhibits intracellular enzymes causing failure of the heart's contracting mechanism. In a failing heart, the uptake and utilization of fatty acids and glucose occurs. In advanced heart failure, insulin resistance also develops, further decreasing the glucose utilization. At the same time, the metabolism of a hypertrophied heart switches from fatty acid utilization to glucose.

Table 8.4 shows the activity of key enzymes under well-fed conditions, fasting and starvation and their regulators.

- heart consumes most energy
- brain consumes most glucose



Creatine phosphate is smaller than ATP so it passes to the heart → the phosphate from it is used to convert ADP → ATP in the heart and then creatine goes back out of the heart { this when heart has enough creatine p }

- when it falls it uses fatty acids / glucose.

- in advanced heart failure glucose is used to make energy but at the same time insulin resistance occures { organ doesn't respond to insulin }

still contracts { passive tone }

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	Fatty acids, branched chain amino acids and ketone bodies utilized

TABLE 8.3: Major fuels in different organs

	Brain	*Skeletal muscle*	*Cardiac muscle*	*Adipose tissue*
After a meal	Glucose	Glucose, Fatty acids	Glucose, pyruvate	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	

1 E.P.

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	

سبحان الله وبحمده, عدد خلقه, و زنة عرشه, ومداد كلماته

Effect of Exercise on Metabolic Profile

Long distance running is the typical example of aerobic exercise, where as sprinting or weight lifting exemplifies anaerobic exercise. 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.

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. The respiratory quotient (RQ) falls during long distance running since there is a progressive change from glycogenolysis to fatty acid oxidation to meet the energy demands. Muscles start oxidizing fatty acids and the high AMP level which activates AMP kinase and low malonyl CoA that

Box 8.2: Long distance runners do not compete with sprinters!!

Long distance running is 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.

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.

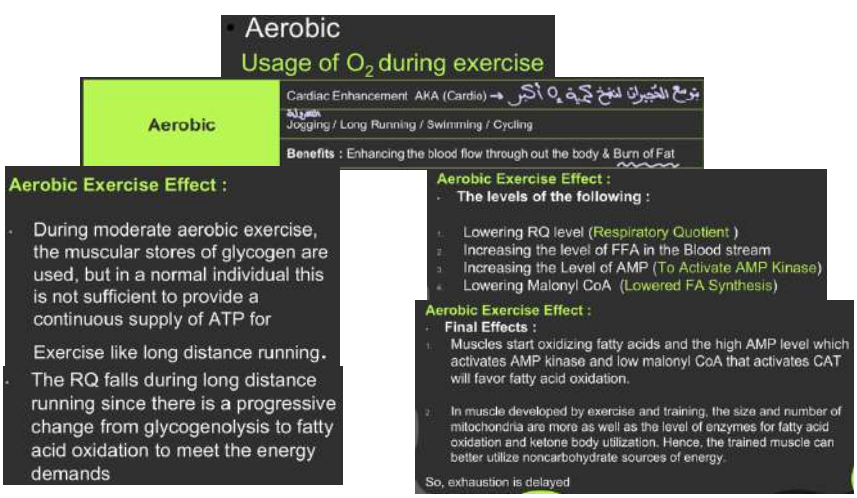
↑ aerobic exercise ∴ any long term non strenous exercise

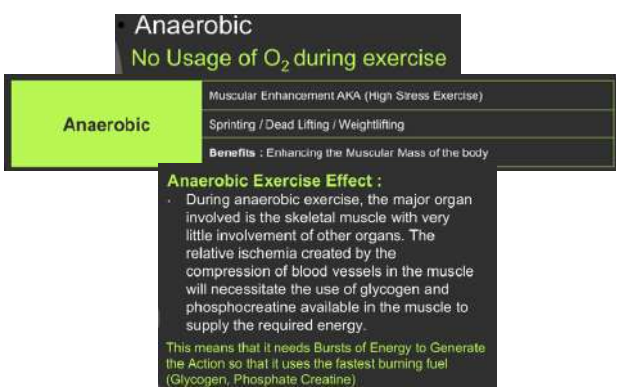
↑ anaerobic ∴ any exercise that requires specific muscle to work on it's own or strongues for short period

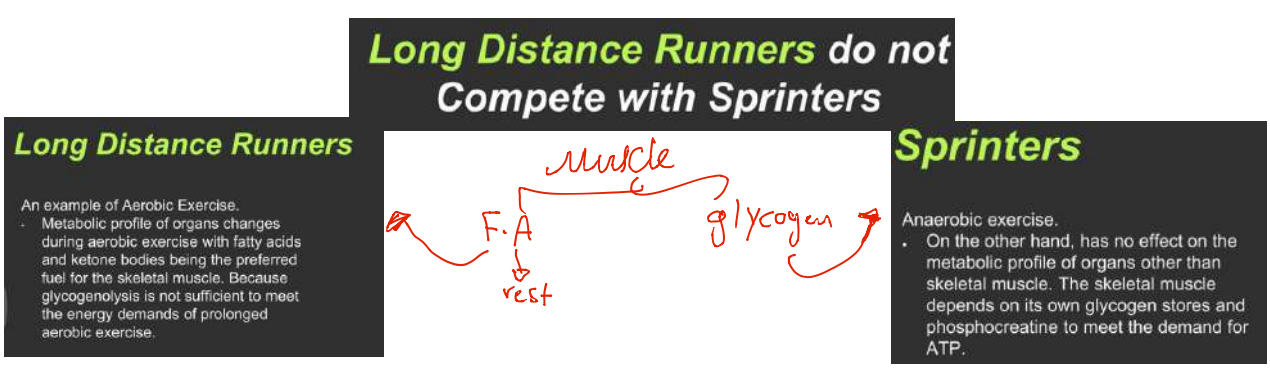
during long runs ∴ body has time to breakdown fat and make fatty acids to use

during weight lifting ∴ muscles use it's own glycogen to make energy in short time

or use free ADP and creatine phosphate







During exercise whether its aerobic or unaerobic our body concentrating our blood to the sites of exercise like skeletal muscles by VD and reduce the amount of blood in area thats not use in exercise like GIT by action of a1 receptors (VC)

so drinking high amount of water during exercise will lead to loss of VC and increase amount of blood in GIT and this will reduce the amount of blood going to the areas of exercise so will lead to

weakness of these area i.e weakness of skeletal muscles

Metabolic Adaptations During Starvation

When blood glucose levels decline as in starvation, it is normalized by intrahepatic glycogenolysis and gluconeogenesis. Once the glycogen and gluconeogenesis are utilized, fatty acids, ketone bodies and finally body proteins are utilized for energy production.In early fasting the effect of short-term regulation by altering the activity of existing enzymes (fine control) is more significant. When starvation is prolonged (>3 days), long-term adaptation sets in, e.g. brain starts metabolizing ketone bodies deriving about 30% energy from ketone bodies.

First Stage: Glycogenolysis

Second Stage: Gluconeogenesis

Third Stage: Lipolysis

Fourth Stage: Acidosis

Fifth stage: Death from Starvation

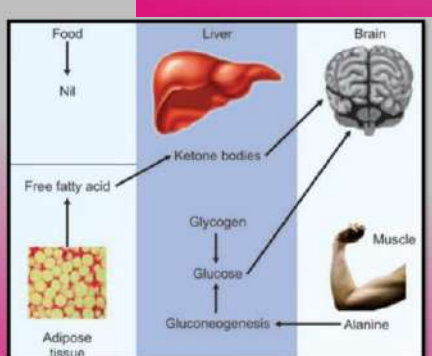
First stage: Glycogenolysis

- 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.

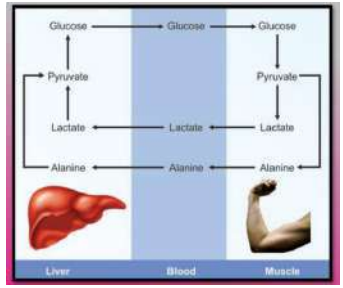
-When starvation is prolonged (>3 days), long term adaptation sets in, brain starts metabolising ketone bodies deriving about 30% energy from ketone bodies.

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 (Figs 8.3 and 8.4). The amino acids released from muscle form the major substrate for gluconeogenesis. The amino nitrogen is transferred from other amino acids to pyruvate to form alanine. Thus the amino group reaches the liver as alanine where it is transaminated to give pyruvate for gluconeogenesis. This glucose alanine cycle (see Fig. 9.30) serves to transport the amino nitrogen of other amino acids to liver in a harmless form. Glutamic acid also serves as an important mode of transport of amino acids to liver (see Chapter 15).

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 bloodstream. The plasma level of branched chain amino acids reaches a peak by 5th day of starvation.

→ liver can't metabolise them

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Third Stage: Lipolysis

The prevailing state of high glucagon-insulin ratio stimulates cAMP-mediated lipolysis by increasing the activity of hormone sensitive lipase. 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). Inactivation of pyruvate dehydrogenase by phosphorylation is the basis of this change. The stimulation of the activity of CAT by glucagon favors increased rate of beta oxidation. 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.

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.

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Key enzymes under well fed, fasting and starvation conditions

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

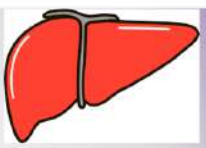
Location: Liver and muscles

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)

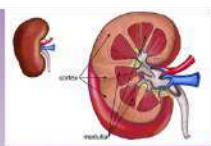
Location: All cells

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

اللهم إني أستودعك ما درست وقرأت وحفظت وفهمت.. فرُدَّه لي عند حاجتي إليه