Biochemistry of Cardiac Muscle-2_231108_094214

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Biochemistry of Cardia...

Biochemistry of Cardiac Muscle-2

Myosin head has ATPase that consumes ATP (($ATP \rightarrow ADP$)) to induce muscle contraction.

PC gives its phosphate group to ADP to compensate for ATP loss : $PC + ADP \rightleftharpoons ATP + Cr$

The PC-CK system in cardiomyocytes

- CK synthesizes PC from creatine and a phosphate group from ATP in a reversible reaction, acting as a functional ATP reserve.
- CK associated with myofilaments catalyzes the transference of the phosphate from phosphocreatine towards ADP, replenishing ATP in ATPase active sites, such as myosin heads.

- The PC-CK system represents the first line of energetic reserves in cardiomyocytes, providing a quick source of ATP and favoring its transportation to its utilization sites, especially myofilaments.

- The disruptions in the PC-CK system have been linked to impaired myocardial contractility and increased risk for arrhythmias. Moreover, alterations in the functionality of CK have been identified as an independent risk factor for heart failure.

Life span for ATP is short thats why we depend on PC as a storage form of energy

Characteristics of PC :

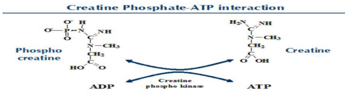
- longer life span than ATP
- faster than ATP
- gives energy by a single reaction
- 1 PC = 1 ATP
- gives the explosive force
- بيخلص ب 30 ثانية
- Produced in myofilaments

- CK is composed of dimers, which consist of subunits M and B, and originate three isozymes: CKMM, -MB and -BB.

Skeletal muscle Cardiac Muscle Brain

- A fourth isozyme is found in mitochondria (mi-CK) and accounts for 20%-40% of all CK activity in the heart.

- The mi-CK isoform is coupled to the external surface of the internal mitochondrial membrane, near the ATP/ADP translocases.


Creatine Phosphate-ATP interaction
Phospho creatine
Creatine
ADP
ATP
Creatine phospho kinase

CK has ATPase Activity wich results in loss of ATP's Phosphate group to join Creatine to make PC

$ATP + Creatine \xrightarrow{CK} PC + ADP$

- During oxidative phosphorylation, the ATP generated in the mitochondrial matrix is exported by ANT (Adenine nucleotide translocase) to the inter-membrane space and transphosphorylated by mi-CK to PC and ADP, with the latter being immediately available for oxidative phosphorylation, stimulating cellular respiration.

- In a healthy heart, approximately two thirds of all creatine is phosphorylated by CK to yield PC.
- In heart failure, the level of PC is lower in relation to the concentrations of ATP, with a lower PC/ATP index. = 4/1 ⇒ Concentration of PC is 4 times the concentration of ATP

- Lower values of this index have been related to increased mortality. High mortality rate

ATP should leave mitochondria after it's synthesis, If ATP doesn't leave this will inhibit ETC.

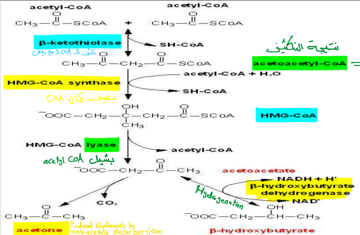
Ketone bodies

- A special source of fuel and energy for certain tissues.
- Some of the acetyl-CoA produced by FAs oxidation in liver mitochondria is converted to acetone, acetoacetate and β- hydroxybutyrate.
- Source of fuel for brain, heart and muscle.
- Major energy source for brain during starvation.
- Liver is the only organ to Synthesize them without being able to use them.

In ketogenesis:

- Large amounts of acetyl CoA accumulate.
- Two acetyl CoA molecules combine to form acetoacetyl CoA.
- Acetoacetyl CoA hydrolyzes to acetoacetate, a ketone body.
- Acetoacetate reduces to β-hydroxybutyrate or loses CO_2 to form acetone, both ketone bodies.

Reactions of Ketogenesis


acetyl-CoA
acetyl-CoA
β-ketothiolase
كثف ال 2 COA مع بعض
SH-CoA
نتيجة التكثيف
acetoacetyl-CoA
HMG-CoA synthase
بضيف كمان CoA
acetyl-CoA + H₂O
SH-CoA
HMG-CoA
HMG-CoA lyase
بشيل acetyl CoA
acetyl-CoA
acetoacetate
NADH + H⁺
β-hydroxybutyrate dehydrogenase
NAD⁺
Hydrogenation
CO₂
acetone
Produced spontaneously by acetoacetate decarboxylation
β-hydroxybutyrate

diapetic Coma ((acetone smell))

acetoacetyl-CoA ⟹ this intermediate is found Also in Cholesterol Synthesis

Extra note: Acetone is a Volatile Compound

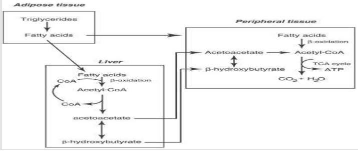
Diabetic Patient may go into 2 types of Coma:

- Diabetic
- hypoglycemic: charachterized by sweating ((more dangerous))
  may be caused by insulin injection on empty stomach.

Production

- Ketone bodies are produced mainly in the mitochondria of liver cells.
- Their synthesis occurs in response to low glucose levels in the blood and after exhaustion of cellular carbohydrate stores, such as glycogen.
- Fatty acids are enzymatically broken down in β-oxidation to form acetyl-CoA.
- Under normal conditions, acetyl-CoA is further oxidized and its energy transferred as electrons to NADH, $FADH_2$, and GTP in TCA cycle.
- The production of ketone bodies is then initiated to make available energy that is stored as fatty acids.

- However, if the amounts of acetyl-CoA generated in fatty acids β-oxidation exceeds the capacity of the TCA cycle or if activity in the TCA cycle is low due to low amounts of intermediates such as oxaloacetate, acetyl-CoA is then used instead in biosynthesis of ketone bodies via acetoacyl -CoA ß-hydroxy-ß- methylglutaryl - CoA (HMG-CoA), which is also an intermediate in the synthesis of cholesterol.


Adipose tissue
Triglycerides
Fatty acids
Peripheral tissue
Fatty acids
β-oxidation
Acetoacetate
Acetyl-CoA
β-hydroxybutyrate
TCA cycle
ATP
CO₂ + H₂O
Liver
Fatty acids
β-oxidation
CoA
Acetyl-CoA
CoA
acetoacetate
β-hydroxybutyrate

Ketosis or keto-Acidosis

- A large accumulation of ketone bodies is dangerous, because it leads to profound metabolic acidosis. Life threatening
- The physiologic ketogenesis (In Fasting state) of fasting and the adaptive ketosis in starvation never progress to acidosis.

adaptive ⟹ In Starvation cases.

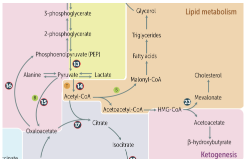
because those 2 States Are not Continuous

Ketonemia

- It is increased concentration of ketone bodies in blood due to increased their production by the liver rather than to a deficiency in their utilization by extra hepatic tissues.
- The production of ketone bodies occurs at a relatively low rate during normal feeding and under conditions of normal physiological status.
- Normal physiological responses to carbohydrate shortages cause the liver to increase the production of ketone bodies from the acetyl-CoA generated from fatty acid oxidation.

When Acetyl COA levels increase it will biosynthesize:-

1- FAs
2- Ketone bodies
3- Cholesterol


3-phosphoglycerate
2-phosphoglycerate
Phosphoenolpyruvate (PEP)
Alanine
Pyruvate
Lactate
Acetyl-CoA
Oxaloacetate
Citrate
Isocitrate
Glycerol
Triglycerides
Fatty acids
Malonyl-CoA
Acetoacetyl-CoA
HMG-CoA
Cholesterol
Mevalonate
Acetoacetate
β-hydroxybutyrate
Lipid metabolism
Ketogenesis
13
14
15
16
17
23
T
B
B

Causes of ketosis:

- Uncontrolled diabetes mellitus ⟶ Pathological
- Starvation ⟶ Physiological
- Chronic alcoholism ⟶ Pathological because of it's Chronicity
- Von Gierke's disease ⟶ Pathological considered one of Glycogenosis ((Problem in glucose 6 Phosphatase))
- Heavy exercise ⟶ Physiological
- Low carbohydrate diet ⟶ Physiological
- Phosphorylase kinase deficiency
- Pyruvate carboxylase deficiency
- Prolonged ether anesthesia
- Toxemia of pregnancy
- Nonpathologic due to high-fat feeding and
- After severe exercise in the post absorptive state

((acute alcholism doesn't Produce Ketosis))

Starvation induced ketosis

In prolonged fasting:

-There will be drop in the levels of plasma glucose, amino acids, triacylglycerols and decline in insulin level and an increase in glucagon release (decreased insulin /glucagon ratio), makes this period of nutritional deprivation a catabolic state, characterized by glycogenolysis, triacylglycerol and protein degradation.

-There will be an exchange of substrates between liver, adipose tissue, muscle and brain that is guided by two priorities:

1- The need to maintain glucose level to sustain the energy metabolism of brain, red blood cells and other glucose requiring cells, and;

In Well-fed state Insulin takes Control
- it increases glucose intake by the Cells
- increases glucose Storage
- increases glucose Oxidation
- increases storage of FAs

Diabetogenic hormones : Glucagon - epinepherin - Cortisol - Growth hormone

In starving state : gluconeogenesis, glycogenolysis, lipolysis ((opposing affect to insulin
Protien Proteolysis ⇒ in advanced states of starvation.

2- To supply energy to other tissues by mobilizing fatty acids from adipose tissues and converting them to ketone bodies to supply energy to other cells of the body.

- In early stages of starvation , heart and skeletal muscle consume primarily ketone bodies to preserve glucose for use by the brain.
- After several weeks of starvation, ketone bodies become the major fuel of the brain.

Months of starvation might lead to diabetic Ketoacidosis.

normally we have low Concentrations of Ketone bodies in the blood ((not 0))

In starving : Organs will depend on Ketone bodies to leave the glucose for erythrocytes and Brain.

Diabetic ketoacidosis (DKA)

- It is a state of inadequate insulin levels resulting in high blood sugar and accumulation of ketone bodies in the blood.
- It is a potentially life-threatening complication.
- It happens predominantly in type 1 diabetes mellitus, but can also occur in type 2 under certain circumstances, which may be due to intercurrent illness (pneumonia, influenza, gastroenteritis, a urinary tract infection), pregnancy, inadequate insulin intake , myocardial infarction, eating disorder , stroke or the use of drugs. Precipitating factors of Ketoacidosis
- DKA results from relative or absolute insulin deficiency combined with counter regulatory hormone excess (glucagon, catecholamines, cortisol, and GH). Anti-insulin hormones.
- In 5% of cases, no cause for the DKA is found.

normally the upperhand in the Post-absorbtive state is for insulin and insulin Keeps blood glucose level in a normal level

Insulin Actions (Again) :

- ↑ Cellular uptake by ↑ GLUT4 expression
- Stimulates regulatory steps in glycolysis to break glucose
- initiate Glycogenesis
- Convert extra glucose to TAG
- Stimulates GlycoProtien synthesis

Insulin inhibits any mechanism that could lead ↑ Glucose in blood

Insulin inhibits : Glycogenolysis + lipolysis + Gluconeogenesis

- Decreased ratio of insulin/glucagon ratio promotes gluconeogenesis, glycogenolysis, and ketone bodies formation in the liver, as well as increases in substrate delivery from adipose and muscle tissues (free fatty acids, amino acids) to the liver Physiological pH is 7,35 to 7,45

-The ketone bodies have a low pH → metabolic acidosis.

-The body initially buffers these with the bicarbonate buffering system, and other mechanisms to compensate for the acidosis, such as hyperventilation (Kussmaul respiration) to ↓ blood CO_2 levels.

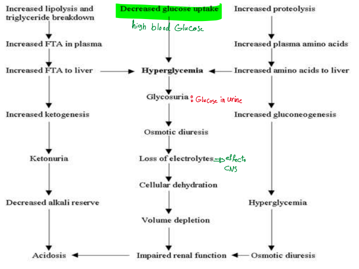
- Ketone bodies lead to electrolyte losses due to osmotic diuresis.
- Diabetic ketoacidosis may be diagnosed when the combination of hyperglycemia, ketones on urinalysis and acidosis are demonstrated.

we have 3 compensatory mechanism for the pH drop :

1- bicarbonate buffer ((Alkaly reserve)) : this buffer has limited volume ((55 - 70 mmol/L)) wich is considered as a disadvantage because if we had severe DKA it might lead to depletion of Alkali reserve

2- Respiraty hyperventilation : CO_2 wash

3- Phosphate buffer : this is the main buffer in the Kidneys
this mechanism will result in ↑ urine acidity wich could lead to crystal urine wich might lead to urinary stones


Increased lipolysis and triglyceride breakdown
Decreased glucose uptake
high blood Glucose
Increased proteolysis
Increased FTA in plasma
Increased plasma amino acids
Increased FTA to liver
Hyperglycemia
Increased amino acids to liver
Glycosuria : Glucose in urine
Increased ketogenesis
Increased gluconeogenesis
Osmotic diuresis
Ketonuria
Loss of electrolytes ⇒ effects CNS
Cellular dehydration
Decreased alkali reserve
Hyperglycemia
Volume depletion
Acidosis
Impaired renal function
Osmotic diuresis

uncontrolled DKA might lead to skeletal muscle wasting
the reason for that is CathePsin

CathePsin : enzyme wich is inactive in normal pH and gets activated after a pH drop to start working as a Proteolytic enzyme

Glucagon : stimulates lipolysis by HSL enzyme, uncontrolled diabetic Patient will show loss of adipose tissue

we dont depend on urine to diagnose DM
because there is a certain threshold for plasma Glucose to appear high in urine ((threshold is 180))
Example : if we took urine sample from diabetic Patient with lower Plasma Glucose than 180 you would notice a normal urine

For the following up of DM
it's better not to use fasting blood Glucose
but use HbA1C ((glycosylated Hb))

Regulation

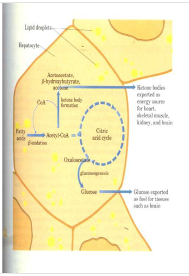
- Ketogenesis may or may not occur, depending on levels of available carbohydrates in the cell or body.

-This is closely related to the paths of acetyl-CoA:

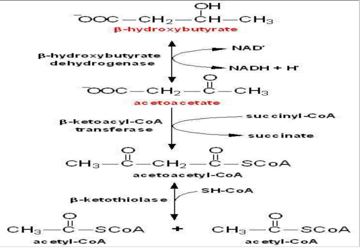
1- When the body has ample carbohydrates available as energy source, glucose is completely oxidized to CO2; acetyl-CoA is formed as an intermediate in this process, first entering the citric acid cycle followed by complete conversion of its chemical energy to ATP in oxidative phosphorylation.

2- When the body has excess carbohydrates available, some glucose is fully metabolized, and some of it is stored by using acetyl-CoA to create fatty acids. (CoA is also recycled here).

3- When the body has no free carbohydrates available, fat must be broken down into acetyl-CoA in order to get energy. Acetyl-CoA is not being recycled through the citric acid cycle because the citric acid cycle intermediates (mainly oxaloacetate) have been depleted to feed the gluconeogenesis pathway, and the resulting accumulation of acetyl-CoA activates ketogenesis.


Lipid droplets
Hepatocyte
Acetoacetate, β-hydroxybutyrate, acetone
CoA
ketone body formation
Fatty acids
β oxidation
Acetyl-CoA
Citric acid cycle
Oxaloacetate
gluconeogenesis
Glucose
Ketone bodies exported as energy source for heart, skeletal muscle, kidney, and brain
Glucose exported as fuel for tissues such as brain

Ketolysis


β-hydroxybutyrate
β-hydroxybutyrate dehydrogenase
NAD⁺
NADH + H⁺
acetoacetate
β-ketoacyl-CoA transferase
succinyl-CoA
succinate
acetoacetyl-CoA
β-ketothiolase
SH-CoA
acetyl-CoA
acetyl-CoA

under Physiological conditions
glucagon stimulates Ketogenesis
but insulin Keeps Ketone bodies
within a very small range
because it inhibits lipolysis
wich means no AcetylCoA.

Ketolysis (ketone body utilization)

-Tissues that can use fatty acids can generally use ketone bodies in addition to other energy sources.
-The exceptions are the liver and the brain.
-The liver synthesizes ketone bodies, but has little α-ketoacyl-CoA transferase, and therefore little ability to convert acetoacetate into acetyl-CoA.
-The brain does not normally use fatty acids, which do not cross the blood-brain barrier; under ordinary circumstances, the brain uses glucose as its sole energy.
- The metabolic rate of the brain is essentially constant.
-While other tissues reduce their metabolic requirements during starvation, the brain is unable to do so.

- After a few days of fasting, the brain undergoes metabolic changes to adapt to the decreased availability of glucose.
- One major change is increased amounts of the enzymes necessary to metabolize ketone bodies.
-The utilization of ketone bodies requires one enzyme not present in the ketone body biosynthetic pathway, β - ketoacyl-CoA transferase (thiophorase), converts acetoacetate to acetoacetyl-CoA.
-The lack of thiophorase in the liver prevents the futile cycle of synthesis and breakdown of acetoacetate.
-The β- ketoacyl-CoA transferase uses succinyl-CoA as the CoA donor, forming succinate and acetoacetyl-CoA

ما شرحه الدكتور

-This reaction bypasses the succinyl-CoA synthetase step of the TCA cycle, although it does not alter the amount of carbon in the cycle.
-This implies that the TCA cycle must be running to allow ketone body utilization; a fact which is necessarily true, because the TCA cycle is necessary to allow generation of energy from acetyl-CoA.
-The other enzymes of the ketone body utilization pathway, β hydroxybutyrate dehydrogenase and thiolase, are identical to the enzymes used for ketone body synthesis.

DHAP is intermediate in Glycolysis
that could work in TAG formation

برضه ما شرحه

Some aspects of myocardial biochemistry of heart failure

→ Left ventricular hypertrophy
Left ventricular HF

- Heart failure reduces the capacity to transduce the energy from foodstuff into ATP.

HF results in lesser blood Pumping

- In the advanced stage of HF→ → →
  - Down regulation in F.A.s oxidation;
  - Increased glycolysis and glucose oxidation
  - Reduced respiratory chain activity.

* most dangerous MI is inferior MI.

Cardiac muscle and Ischemia

- Coronary artery occlusion → ischemia → significant change in cell structure, chemistry and function
  - Loss of contractile function
  - Arrhythmias
  - Cell death
  - Depletion of ATP
  - ↑ in AMP and ADP

مشكلة الـ MI بأنه الجزء اللي صارله
occlusion تحول من muscular لـ Fibrous

-The decrease of the ATP / ADP, the accumulation of AMP, inorganic phosphate, metabolic products are removed (lactate).

-The rapid decline in creatine phosphate (only short-term mechanism to compensate for reduced ATP production in mitochondria)

- Even mild ischemia reduces the concentration of ATP and creatinephosphate, increases the level of inorganic phosphate → activation of glycolysis (glucose needed from the bloodstream into the heart cells) → increase in the concentration of pyruvate → conversion by LDH to lactate.

- Prolonged ischemia - the accumulation of substrates (lactate, $NADH^+$ and H^+) → inhibition of glycolysis at the level of PFK-1 and glyceraldehyde-3-dehydrogenase.

ADP and AMP are stimulators

lactate + $NADH^+$ + H^+ are inhibitors

to Solve the Problem we Should balance between inhibitory and stimulatory factors to Save the cardiac muscle.