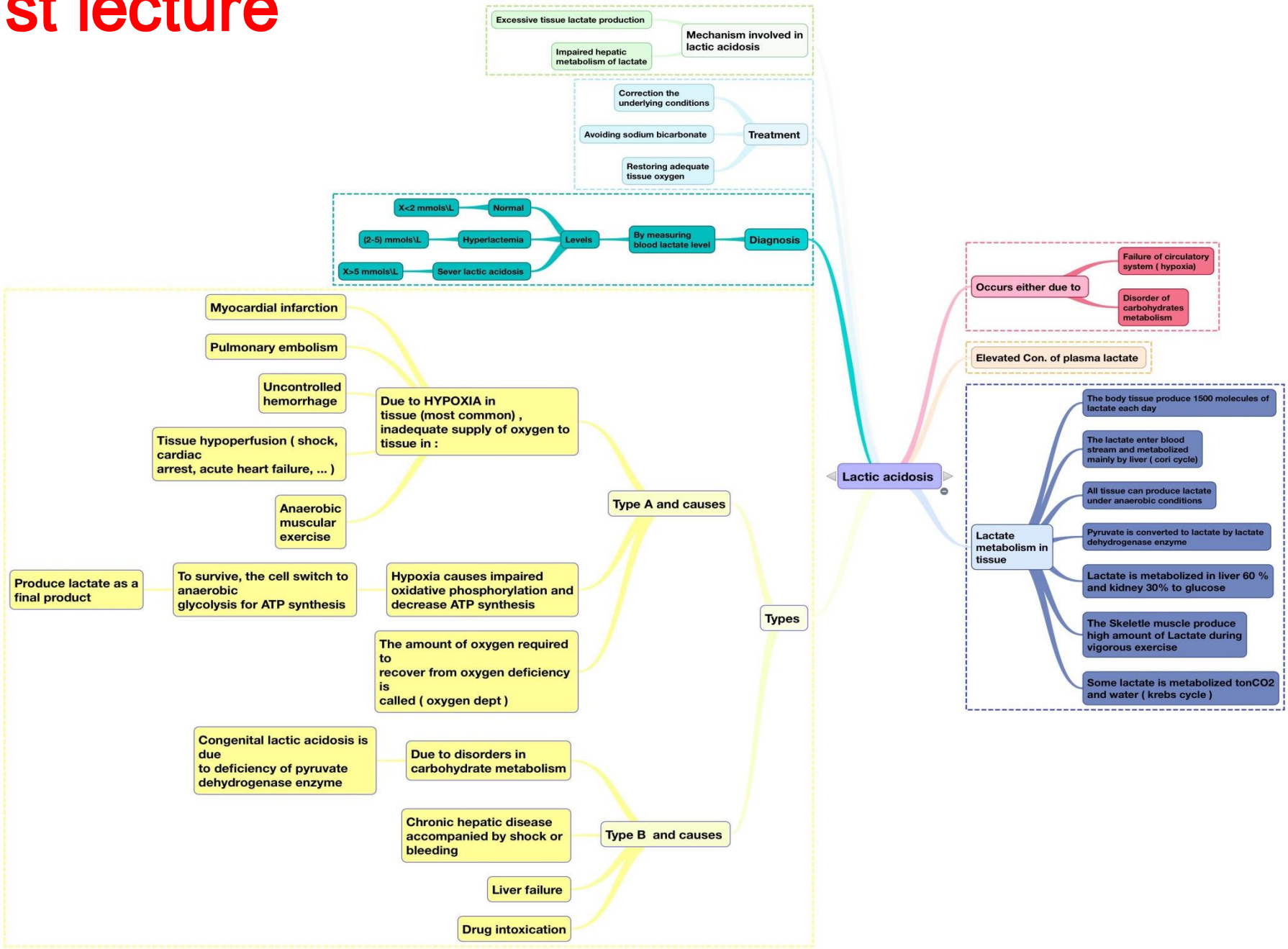
Biochemistry SAQ

Thanks to 435 biochemistry team

Summary of lectures

1st lecture


Lactic acidosis
Occurs either due to
Failure of circulatory system (hypoxia)
Disorder of carbohydrates metabolism
Elevated Con. of plasma lactate
Lactate metabolism in tissue
The body tissue produce 1500 molecules of lactate each day
The lactate enter blood stream and metabolized mainly by liver (cori cycle)
All tissue can produce lactate under anaerobic conditions
Pyruvate is converted to lactate by lactate dehydrogenase enzyme
Lactate is metabolized in liver 60 % and kidney 30% to glucose
The Skeletle muscle produce high amount of Lactate during vigorous exercise
Some lactate is metabolized tonCO2 and water (krebs cycle)
Mechanism involved in lactic acidosis
Excessive tissue lactate production
Impaired hepatic metabolism of lactate
Treatment
Correction the underlying conditions
Avoiding sodium bicarbonate
Restoring adequate tissue oxygen
Diagnosis
By measuring blood lactate level
Levels
X<2 mmols\L
Normal
(2-5) mmols\L
Hyperlactemia
X>5 mmols\L
Sever lactic acidosis
Types
Type A and causes
Due to HYPOXIA in tissue (most common) , inadequate supply of oxygen to tissue in :
Myocardial infarction
Pulmonary embolism
Uncontrolled hemorrhage
Tissue hypoperfusion (shock, cardiac arrest, acute heart failure, ...)
Anaerobic muscular exercise
Hypoxia causes impaired oxidative phosphorylation and decrease ATP synthesis
To survive, the cell switch to anaerobic glycolysis for ATP synthesis
Produce lactate as a final product
The amount of oxygen required to recover from oxygen deficiency is called (oxygen dept)
Type B and causes
Due to disorders in carbohydrate metabolism
Congenital lactic acidosis is due to deficiency of pyruvate dehydrogenase enzyme
Chronic hepatic disease accompanied by shock or bleeding
Liver failure
Drug intoxication

1st lecture

Metabolic acid-base disorders

What are they	Disorders that are caused by changes in bicarbonate concentration in the extracellular fluid (ECF).
occur due to	high concentration **or** loss of **H+ ions.**
Metabolic Acidosis	A reduction in bicarbonate concentration in ECF. - **Leads to:** ⬆ H+ ions conc. & ⬇ HCO3- level. - **causes:** Impaired H+ excretion, Increased H+ production or ingestion, Loss of HCO3−.
Metabolic alkalosis	Increase in bicarbonate concentration in ECF. - **Leads to:** ⬇ H+ ions conc. & ⬆ HCO3- level. - **causes:** Loss of H+ in vomit, Alkali ingestion (NaHCO3) , K+ deficiency due to diuretic therapy.

Metabolic Acidosis & Alkalosis

Acidosis	-**Causes**: Renal disease , renal tubular acidosis , lactic acidosis ,diabetic ketoacidosis, poisoning , chronic Diarrhea. -**Clinical effects** : hyperventilation (stimulated by elevated H+ ions), loss of consciousness, coma, death.
Alkalosis	-**Clinical effects** : Hypovrntilation → increase in PCO2 → respiratory arrest. Confusion , coma ,death.

Anion gap

What is it?	It is the difference between the sum of: cations and anions.
How?	• After calculation the anion gap we check the value: If the value < 3 mEq\L → alkalosis . If the value > 11 mEq\L → Acidosis.

2nd lecture

Cholesterol Metabolism

General information.	1- Most important animal steroid. 2- Maintains membrane fluidity. 3- Insulating effect on nerve fibres
Parent molecule for	**bile acid/salt, steroid hormones and vitamin D3**
Source of liver cholesterol	1- dietary cholesterol → chylomicron remnants. 2- cholesterol synthesized in extrahepatic tissue → HDL 3- de novo synthesis in liver . note: Liver plays a **central role** in cholesterol regulation
Cholesterol leaves the liver as	secreation of VLDL, free cholesterol secreted in bile, or conversion to bile acid/salt

Cholesterol & cholesteryl

Cholesterol	(steroid nucleus with hydrocarbon + HO) - found in membrane, synthesized in all tissue. - major site : liver, adrenal cortex, testes/ovaries, and intestine.
cholesteryl	1- Plasma cholesterol esterified with fatty acid 2- more hydrophobic 3-not found in membrane 4- found in most cells in small amount.

Synthesis of HMG CoA & Mevalonic acid

HMG CoA	Present in both cytosol and mitochondria of liver cells . Acetyl CoA → by thiolase enzyme → acetoacetyl CoA → by HMG CoA synhase → HMG CoA
Mevalonic	HMG CoA → by **HMG CoA reductase** (Rate limiting and key step) →**mevalonic acid** (occur in cytosol)

Cholesterol synthesis

Further steps in synthesis	• Production of 5-carbon unit (Isopentinyl pyrophosphate (IPP) • Condensation to a 30C compound: squalene • Cyclization of squalene to 30C lanosterol • Synthesis of 27-Carbon cholesterol
Defect in 27-carbon synthesis leads to	Smith-Lemli-Opitz Syndrome
Regulation of Cholesterol Synthesis	By HMG reductase
HMG CoA Reductase Regulation	• Sterol-dependent regulation of gene expression (SCAP is the sensor) • Sterol-accelerated enzyme degradation • Sterol-independent phosphorylation/dephosphorylation (low ATP or high AMP) decrease cholesterol. • Hormonal regulation (insulin or thyroxine increase gene expression, glocagon & cortisol do the opposite.)
Excretion of cholesterol	• In bile then transport to intestine for elimination. • note : some cholesterol is converted by bacteria into coprostanol and cholestanol before excretion
Hypercholesterolemia	• High conc. of cholesterol in plasma
Treatment	• Statins drugs(inhibit HMG enzyme activity by competitive inhibition) • b-Sitosterols/ Phytosterols (Block the absorption of dietary cholesterol)

3rd and 4th lectures

In the download center → 435 team work → SAQ (lipoproteins lectures summary)

5th lecture

Oxidative stress

What is it ?	A condition in which cells are subjected to excessive levels of Reactive Species (Oxygen /Nitrative species) & they are unable to counterbalance their deleterious effects with antioxidants
Implicated in	Ageing process & many diseases (e.g.: Atherosclerosis and coronary heart diseases)
Diseases	Inflammatory conditions (Rheumatoid arthritis) Atherosclerosis and coronary artery diseases Obesity Cancers G6PD deficiency hemolytic anemia

Reactive Oxygen Species (ROS)

$$O_2 \rightarrow O_2^{\bullet -} \rightarrow H_2O_2 \rightarrow OH^{\bullet} \rightarrow H_2O$$

Superoxide ($O_2^{\bullet -}$)	Free radicals	Sources: • Ingestion of toxins, chemicals, or drugs. • During course of metabolism:	• auto-oxidation of hemoglobin • xanthine oxidase • partial reduction of molecular oxygen in ETC (to make water)
Hydroxyl radical ($OH^{\bullet}$)			• Fenton reaction (ferric\ferrous) • partial reduction of molecular oxygen in ETC (to make water)
Peroxyl radical ($ROO^{\bullet}$)			-
Hydrogen peroxide (H_2O_2)	Non free radical		• partial reduction of molecular oxygen in ETC(to make water)

Antioxidants

enzymes	Superoxide dismutase	Converts superoxide into oxygen or hydrogen peroxide
	Catalase	Converts hydrogen peroxide into oxygen or water
	Glutathione system	Converts hydrogen peroxide into oxygen or water
vitamins	Vitamin C (ascorbic acid) / Vitamin A and β-carotenes / Vitamin E	
Trace elements	Selenium	

Glutathione system

Glutathione ?	glycine + cysteine (with SH) + glutamate
What happens ?	• Reduced glutathione(2G-SH) donates its hydrogen and gets oxidized into oxidized glutathione (G-S-SG) by glutathione peroxidase (why?) to reduce H_2O_2 into 2 H_2O • Now the oxidized glutathione should be reduced back.. So it takes H from NADPH by glutathione reductase
The NADPH	It is formed in HMP(hexose monophosphate) pathway by glucose-6-phosphate dehydrogenase "so as we said there is an oxidative stress in G-6-PD deficiency hemolytic anemia "

Effects of ROS

Molecular effects	• Lipid peroxidation (especially polyunsaturated fatty acids) • Protein denaturation (inactivation of enzymes - cytoskeletal damage) • DNA damage leading to mutations • Cell signaling effects (e.g.: release of Ca2+ from intracellular stores) • Chemotaxis
Vascular effects	• Altered vascular tone • Increased endothelial cell permeability

Nitric Oxide (NO)

What is it ?	• Free radical gas with very short half-life "it metabolized into nitrates & nitrites in seconds"
synthesis	Enzyme: NO synthase (NOS) — Precursor: L-Arginin
effects	• Relaxes vascular smooth muscle • Prevents platelet aggregation • Bactricidal & Tumoricidal effects of macrophages • Neurotransmitter in brain

The role of NO can be both beneficial and detrimental, depending upon when and where it is released

eNOS	beneficial	• Endothelial NO synthase • improving vascular dilation and perfusion.
nNOS	detrimental	• Neural NO synthase
iNOS		• Induced NO synthase • increased iNOS activity is generally associated with inflammatory processes

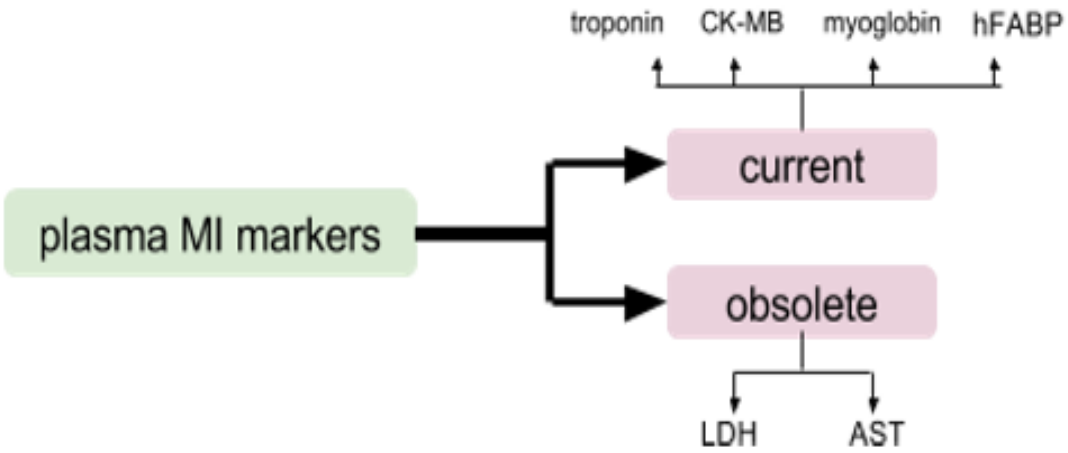
Vasodilators (nitroglycerin) is metabolized into NO and causes vasodilatation

Pathogenesis of atherosclerosis

1	Modified (oxidized) LDL "oxidative stress"	
2	Endothelial injury of arterial wall	
3	Adherence of monocytes to endothelial cells they move into intima and become macrophages	
4	Uptake of oxLDL by macrophage scavenger receptor	Scavenger receptor class A (SR-A) Low-affinity, non-specific & un-regulated receptor
5	Foam cell transformation ➔accumulation of excess lipids inside the cells ➔Atherosclerotic plaque formation	

6th lecture

Criteria for diagnosis of MI	Features of an ideal cardiac marker (*troponin)
To diagnose MI, the presence of at least two of the following characteristics is required: 1. Typical heart attack symptoms 2. Characteristic rise and fall pattern of a cardiac marker in plasma: • Rise and gradual fall of cardiac troponins • More rapid rise and fall of CK-MB 3. Typical ECG pattern	1. High concentration in the myocardium 2. High sensitivity (detected in low concentration at early stages) 3. High specificity (for cardiac tissue damage) 4. Rapid release into plasma 5. Good prognostic value (strong correlation between plasma level and extent of myocardial injury) 6. Easily measured
Blood samples collected after MI	• Baseline (upon admission) • Between 12 and 24 hours after the onset of symptoms



Troponin	CK-MB	Myoglobin	hFABP
• structural proteins in cardiac myocytes and skeletal muscle • "cardiac troponins (cTn) are structurally different from muscle troponins"	• it rises and falls transiently after MI • More than 5 % is indicative for MI	• non-specific because it is elevated in: ★ Muscle disease/injury ★ Acute and chronic renal failure • sensitive marker of cardiac damage	• cytosolic protein involved in fatty acid transport & metabolism • Appears 30 min after acute ischemia early marker for detecting acute ischemia prior to necrosis
↑ specific for MI	sensitive & specific for MI		
• Appear in 3-4 h after MI • Remain elevated for up to 10 days	• Appear in 3-10 h after MI • Returns to normal within 2-3 days	• Appears early (within 1-4 hours)	BNP
After a MI, cytosolic troponins are released rapidly (first few hours) Structurally bound troponins are released later for several days	• Useful for diagnosis of re-infarction • Not highly specific (it is elevated in skeletal muscle damage & in atheletes)	early marker of MI	• produced by the ventricles in response to myocardial stretching and ventricular dysfunction after MI • marker for detecting CHF "differential diagnosis of pulmonary diseases and CHF"

Relative index = CK-MB mass / Total CK x 100

if relative index is More than 5 % , it will indicate for MI