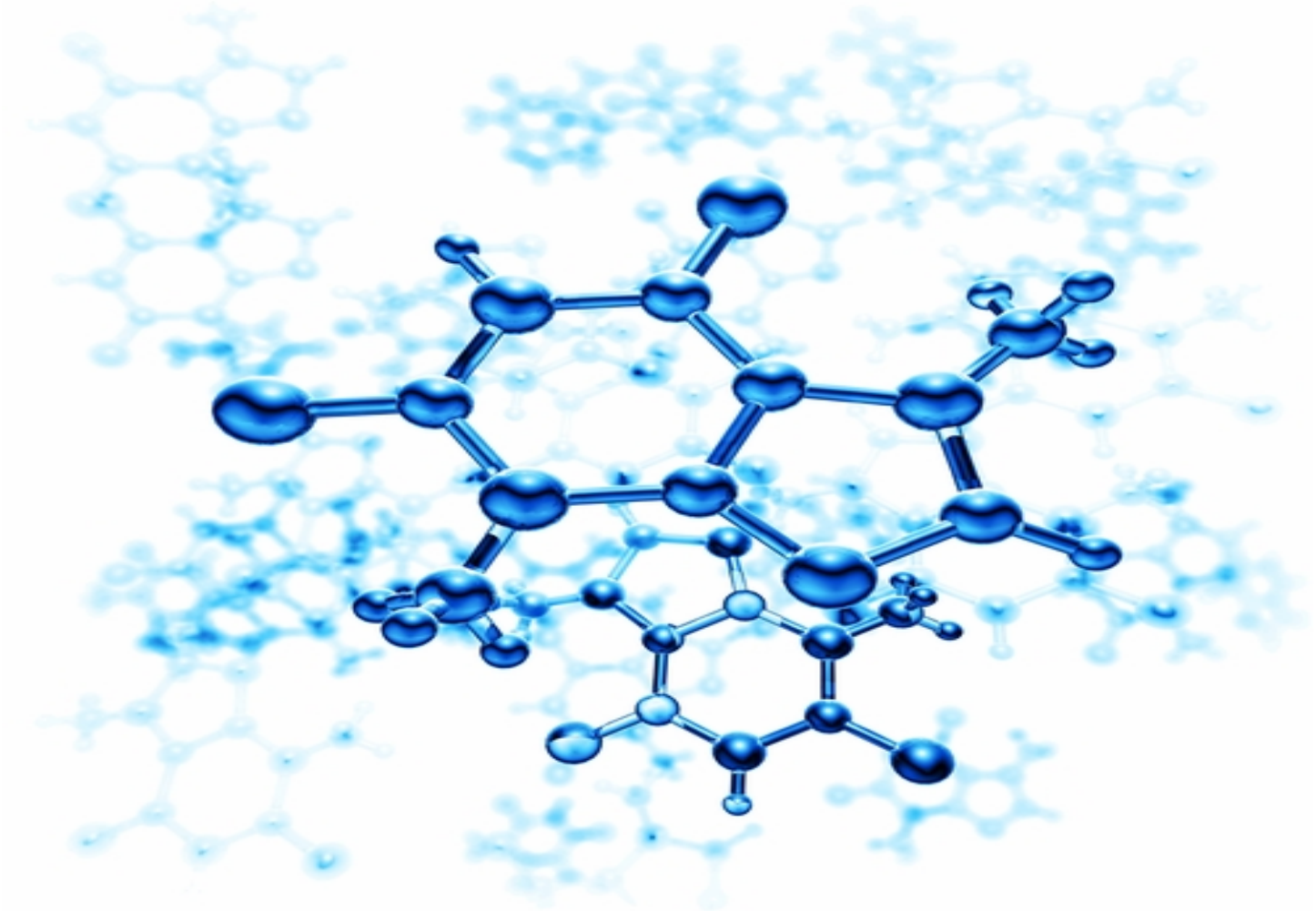
SMASHUSMLE Biochemistry Lecture Notes

BIOCHEMISTRY



USMLE made simple

Introduction of vitamins

"Vita"+ "Mins" = Essential minerals for the body

Two types

Fat soluble	Water soluble
A-Retinol	B Vitamins
D-	B1- Thiamine
E-	B2- Riboflavin
K-	B3- Niacin
Need pancreas and terminal ileum to be reabsorbed back in the body	B5- Pantothenic acid
Bile acids absorb them by formation of micelles.	B6- Pyridoxine
Toxicity caused due to nature to accumulate within the body. **Steatorrhea- fats eliminated in feces and occurs in-** - **Cystic fibrosis** - **Sprue disease**	B7- Biotin
	Vitamin C Folate / B12
	Except Vitamin B12 and folate rest all can be washed out through urine in case of excess. Vitamin B12 and folate are stored in liver.

Vitamin A

- As called as Retinol.
- It is a carotene compound and comes in forms- retinal, retinoic acid and retinol.

Functions of Vitamin A

- Antioxidant
- Essential for growth, maintenance and epithelial cells
- Differentiation of epithelial cells into pancreatic cells or mucus secreting cells.
- Vision- Retinal in rods and cones. Rods are responsible for low light vision.
- Used in treatment of acute myelogenous leukemia (AML) M3 subtype- all transretinoic acid is administered which induces the differentiation of myeloblasts.

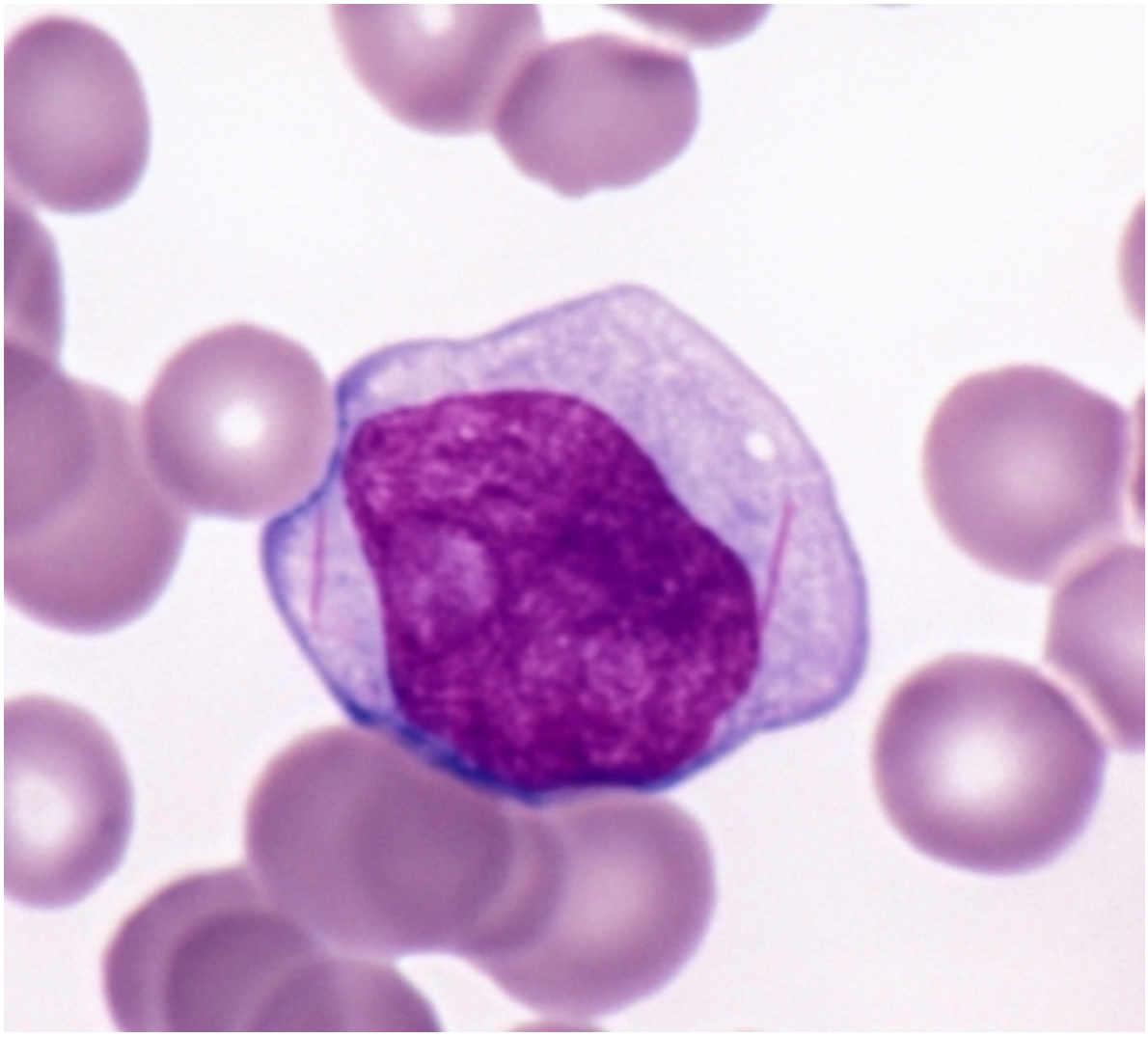


Image showing Auer rods inside cytoplasm

AML has Auer rods which are dark colored peroxidase positive cytoplasmic inclusions. Retin A causes the release of Auer rods from myeloblasts to outside the cytoplasm. This may cause DIC (Disseminated Intravascular Coagulaopathy).

- Used in treatment of Measles.
- Measles caused by Paramyxo virus
- Characterized by 3 Cs- Cough, Conjunctivitis and Coryza
- Koplik's spots
- Descending maculopapular rash

- Used in treatment of Acne in the form isotretinoin. Contraindicated in pregnancy due to teratogenic effects, cause cleft palate and cardiac abnormalities. Low concentration of Vitamin A decreases sebum production, hence no substrate for the acne causing bacteria to thrive on. This way the acne reduces.

Source of Vitamin A- Liver and vegetables

Deficiency of Vitamin A-

- Night blindness
- Dry skin

Vitamin A toxicity

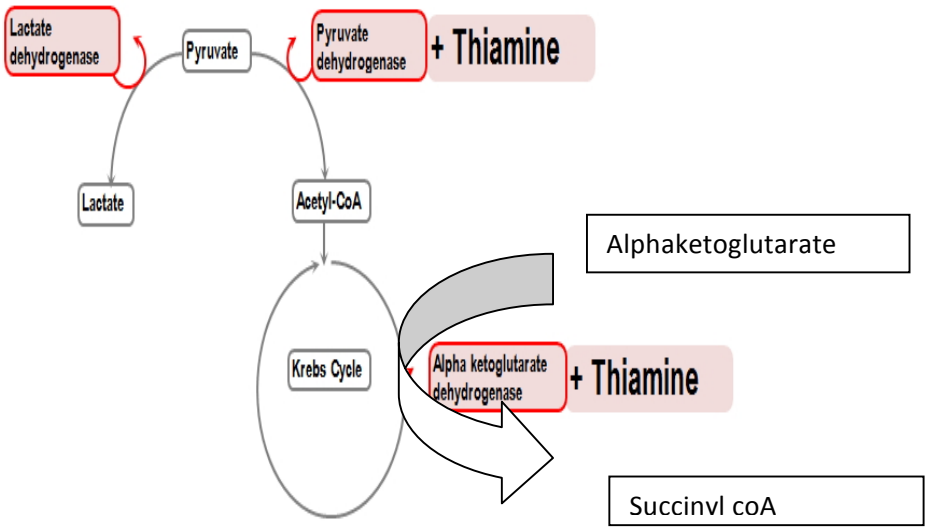
- Headache
- Papilledema- Blurred vision
- Cerebral oedema
- Benign intracranial hypertension
- Arthralgias
- Alopecia
- Sore throat
- Fatigue
-

Vitamin B1 (Thiamine)

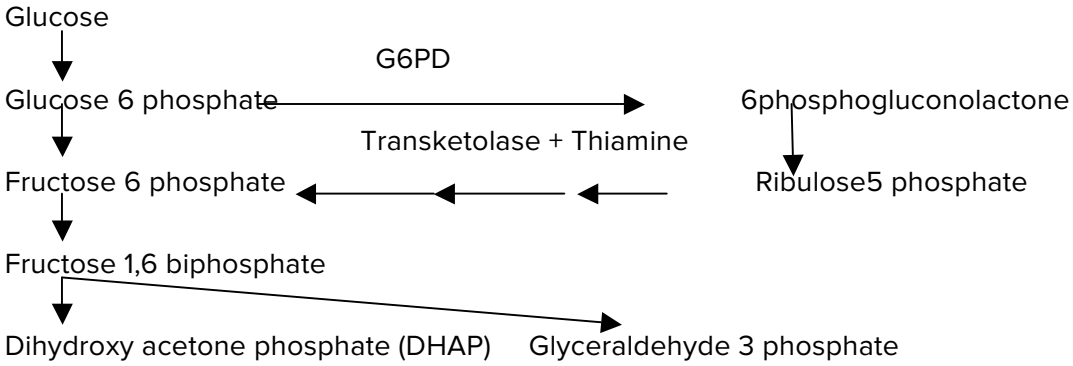
- Involved in biochemical reactions in the form of co-factors.
- Also known as TPP (Thiamine PyroPhosphate)

First pathway-Pyruvate dehydrogenase in glycolysis

- Glucose converts to pyruvate.
- Pyruvate converts to acetyl coA that is utilized in Kreb's cycle.
- Pyruvate conversion to acetyl coA needs pyruvate dehydrogenase and thiamine



- ***Second pathway- TCA cycle***
- Conversion of alphaketoglutarate to succinyl coA under the action of alphaketoglutarate dehydrogenase which needs thiamine
- ***Third pathway- HMP (Hexose Monophosphate) Shunt***
- Transketolase needs thiamine for the conversion of ribulose5 phosphate to fructose6 phosphate.



- ***Fourth pathway- Branch chain AA dehydrogenase***

Deficiency

- **Wernicky Korsakoff's syndrome**- found in **alcoholics** and causes neurologic damage
- The syndrome is seen in people with **malnutrition or malabsorption.**
- Symptoms**- Cerebellar damage, Ophthalmoplegia, Nystagmus, confabulation, memory loss, psychosis**
- **COPS – C (Cerebellar damage, confabulation)**
    - **O (Ophthalmoplegia, Nystagmus)**
    - **P (psychosis) S**
- **BERI BERI**
- Two types- dry and wet
- Dry beriberi- polyneuritis- Loss of sensation, pain and tingling in feet, muscle wasting,
- Wet beriberi- High output cardiac failure (dilated cardiomyopathy), pitting oedema, S3 sound on auscultation.

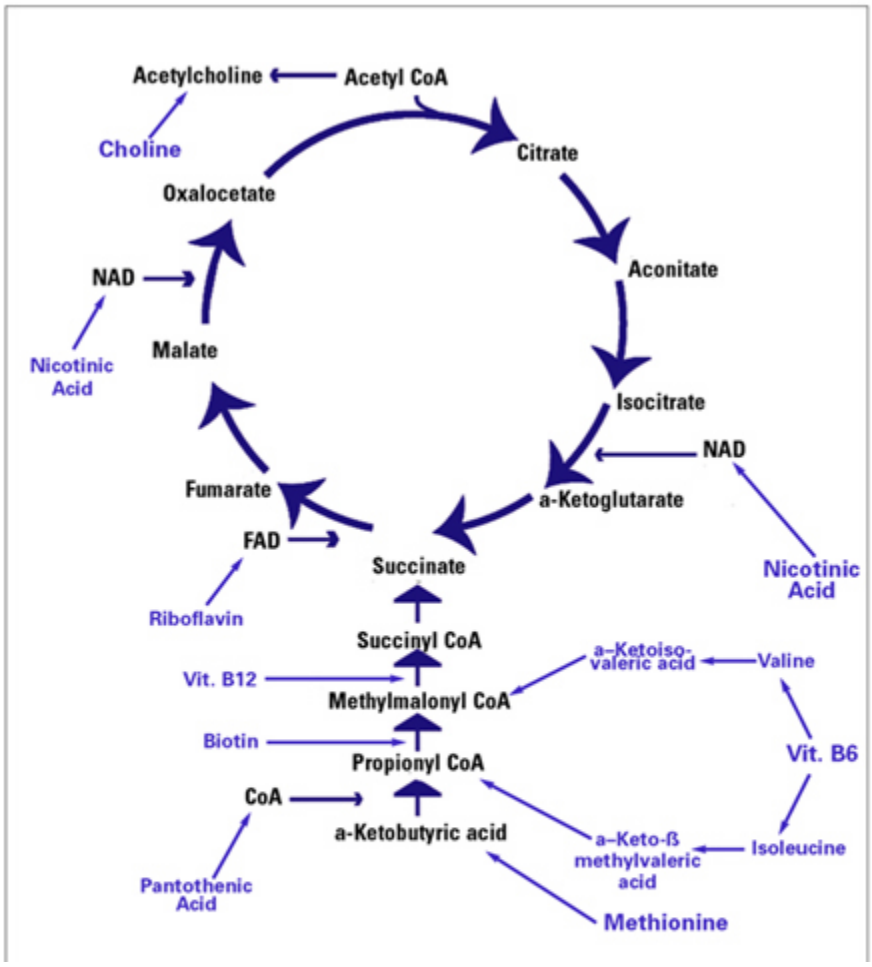
Treatment

Administration of Vitamin B1 supplements

Vitamin B2 and B3

Vitamin B2 (Riboflavin)

- Cofactor for succinate dehydrogenase

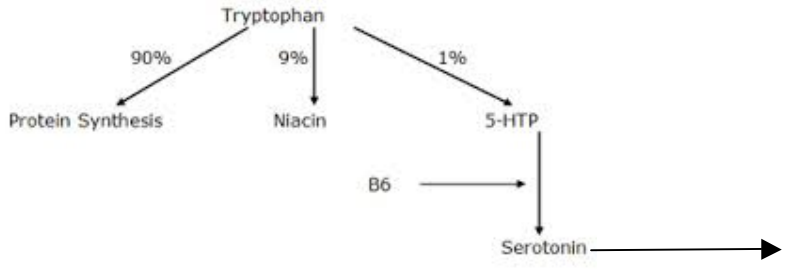


Deficiency of Vitamin B2- **c**heilosis

- Redness
- Scaling and fissures
- Sores
- Cracklings
- Angular cheilitis
- **C**orneal vascularisation
- 2 C's syndrome

Vitamin B3 (Niacin)

Tryptophan is amino acid from which niacin is made in presence of Vit B6 (pyridoxine)



Melatonin (Pineal gland)

Deficiency

- Initially glossitis
- Pellagra – rough thick skin
- 3D's
- **D**ermatitis- inflammation of skin in sun-exposed area (lizard skin)
- **D**ementia – neuronal degeneration of brainstem
- **D**iarrhea- Atrophy of colonal epithelium
- Death- severe 3D's can cause death

Hart nup disease

- Due to renal malabsorption of tryptophan- genetic abnormality

Carcinoid tumor

- Tumor inside appendix
- Uses up tryptophan to make serotonin.
- Cause Vitamin B3 deficiency

Isoniazid (INH) treatment- should be given VitB6- peripheral neuropathy

- They will have Vit B6 deficiency hence Vitamin B3 deficiency

Niacin

- increases HDL by 35%
- and decreases Triglycerides by at least 50 %
- low HDL patients are given Niacin
- also called as nicotinic acid
- side effects of niacin- flushing due to vasodilation

Vitamin B6 (Pyridoxal phosphate)

- Converted to its co-factor called pyridoxal phosphate (used as co-factor in transamination reaction in liver)

- ***First pathway***- Homocysteine pathway
  Homocysteine ⟶ (Cystathione synthase (VitB6)) cystathione ⟶ cysteine

  Homocystinuria- Elevated levels of Homocysteine in urine due to deficiency of Vit B6 or cystathione synthase.

  Symptoms –
- Mental retardation
- Tall stature
- Lens subluxation
- Atherosclerosis (stroke, MI)- damage to endothelial walls due to homocysteine

- ***Second pathway***- Tryptophan ⟶ (Vit. B6) Niacin (Vit B3)

- ***Third pathway***- Histidine ⟶ (Vit. B6) Histamine

- ***Fourth pathway***- Glycine ⟶ (Vit. B6) Porphyrin ⟶ Heme
  Sideroblastic anemia due to iron build up as no heme molecule produced in absence or deficiency of vitamin B6.

- ***Fifth pathway-*** Glutamate ⟶ (Vit. B6) GABA ⟶ Glutathione

- ***Sixth pathway***-
  Phenylalanine ⟶ Tyrosine ⟶ DOPA ⟶ (Vit B6, DOPA decarboxylase) Dopamine ⟶ Norepinephrine ⟶ (VitC) Epinephrine

Deficiency of Vitamin B6

- Sideroblastic anemia
- Convulsions, seizures and
- Hyperirritability
- INH- Isoniazid- causes hepatotoxicity and Vit B6 level depletes causing peripheral neuropathy.
- Oral contraceptive pills

Vitamin B7 (Biotin)

- Cofactor for carboxylation enzymes (CO_2 added)

- **Gluconeogenesis in liver**

  Pyruvate ——(Pyruvate carboxylase)——▶ oxaloacetate

- **Fatty acid synthesis (citrate shuttle)**

  Acetyl CoA ——(Acetyl CoA Carboxylase)——▶ Malonyl CoA ——▶ fatty acids

- **Propionate metabolism**

  Odd chain fatty acids ——▶ propionyl CoA ——(Propionyl CoA carboxylase (Biotin and ATP))——▶ methyl malonyl CoA ——(mutase)——▶ MMCoA

  (Vit.B12)

  Glucose ◀—— Oxaloacetate ◀—— Citric acid cycle ——▶ Succinyl CoA

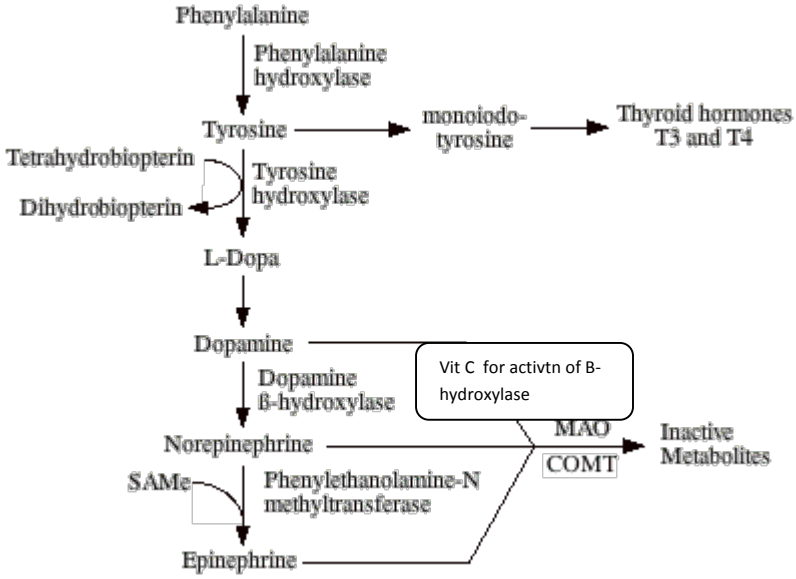
  B7 deficiency can cause high levels of propionyl CoA.

Symptoms of deficiency of Vit. B7

- This is a very rare condition
- Dermatitis is the most common symptom.
- Alopecia
- Enteritis
- **Raw eggs ingestion excessively can cause biotin deficiency due to Avidin binding to Vit.B7**
- **Antibiotics can cause Vit B7 deficiency.**

Vitamin C (Ascorbic acid)

- Fruits and vegetables (oranges)
- Antioxidant
- Increases iron absorption Fe3+ to Fe2+
- Hydroxylation of proline and lysine in collagen synthesis.
- Phenylalanine to epinephrine pathway



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Deficiency of Vitamin C

Scurvy

- Swollen gums
- Easy bruising
- Prolonged bleeding time
- Hemarthrosis- bleeding in the joints
- Poor wound healing
- Anemia
- Depression in severe VitC deficiency
- Weak immune response

Vitamin C toxicity

- Nausea
- Vomiting
- Diarrhea
- Fatigue and sleep problems
- Iron toxicity (caution for hemachromatosis)

Vitamin D

Forms:

D2- Inactive form (Ergocalciferol) plants

D3- Cholecalciferol (Milk, under sun exposed skin)

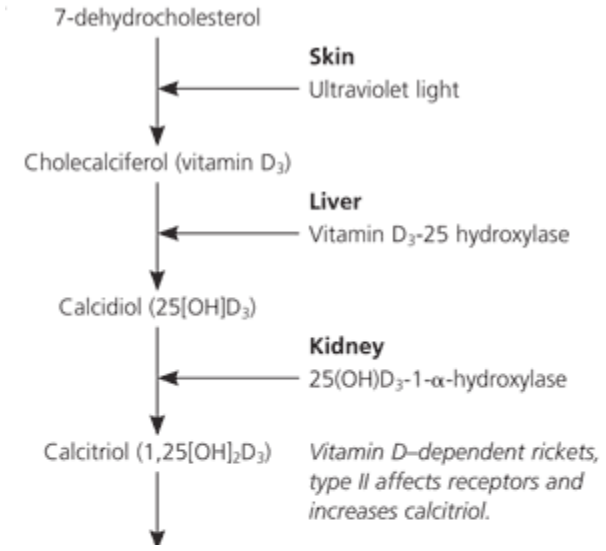
Active form

Storage form

Functions of Vitamin D

- Increase the level of intestinal absorption of calcium and phosphate
- Increase bone resorption

Pathway of Vitamin D



Osteoclasts Ca2+ mineralization

PTH mobilization

Vitamin D deficiency

- Rickets in children, osteomalacia in adults (soft bones)
- Hypocalcemic tetany

- Alcoholic with liver cirrhosis cannot be given D2 and D3 as it cannot be metabolized
- In renal failure, patients develop secondary hyperparathyroidism.- renal osteodystrophy

Vitamin D toxicity

- Hypercalcemia
- Hypercalciuria
- Loss of appetite
- Sarcoidosis (epitheloid macrophages are activated)
- Breast milk does not contain Vitamin D or K

Vitamin E

- Antioxidant (protects RBCs)
- Peroxidation of fatty acids on cell membranes

Deficiency of vitamin E

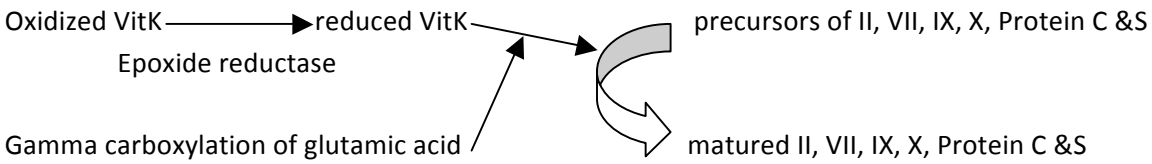
- Due to malnutrition
- In premature infant
- Fat malabsorption as Vit E is fat soluble vitamin

Clinical features

- They are prone to hemolytic anemia. RBCs undergo acanthocytosis in the presence of free radicals.
- Neural dysfunction- nerves get demyelinated and patient gets loss of position and vibratory senses,
- Deficiency affects Spinocerebellar tracts – causes ataxia
- Friedreich's ataxia mimics Vit E deficiency
- Muscle weakness
- E stands for erythrocytes- hemolytic anemia
- Damage to retina- retinitis pigmentosa

Vitamin K

- Responsible for activating clotting factors.
- Vit K pathway



- When a baby is born, Vitamin K is injected as it doesn't have it at birth and this way **neonatal hemorrhage** is prevented.
- **Prolonged antibiotic** use can kill the bacteria in gut so develop VitK deficiency.
- **Warfarin**- VitK antagonist

Malnutrition

Kwashiorkor

- Protein malnutrition
- Skin lesions
- Edema- proteins maintain oncotic pressure within capillaries
- Liver malfunction – due to fatty change
- Pot belly like belly due to fluid accumulation in third space
- Anemia
- Pneumonic – no good MEAL (Malnutrition; Edema; Anemia; Liver dysfunction)

Marasmus

- Energy malnutrition
- Muscle wasting is the primary symptom
- Skinny arms and legs
- Loss of subcutaneous fat
- Variable edema
- Due to complete starvation unlike Kwashiorkor where food is available.

Introduction to metabolism

- Sites where metabolism occurs.
- Cytoplasm
- Glycolysis,
- Fatty acid synthesis
- Hexose Monophosphate Shunt Pathway

Endoplasmic reticulum

- Rough surface- protein synthesis
- Smooth surface- Steroid synthesis

Mitochondria

- Beta oxidation of fatty acids
- Acetyl CoA production
- TCA cycle
- Oxidative phosphorylation

Both mitochondria and cytoplasm

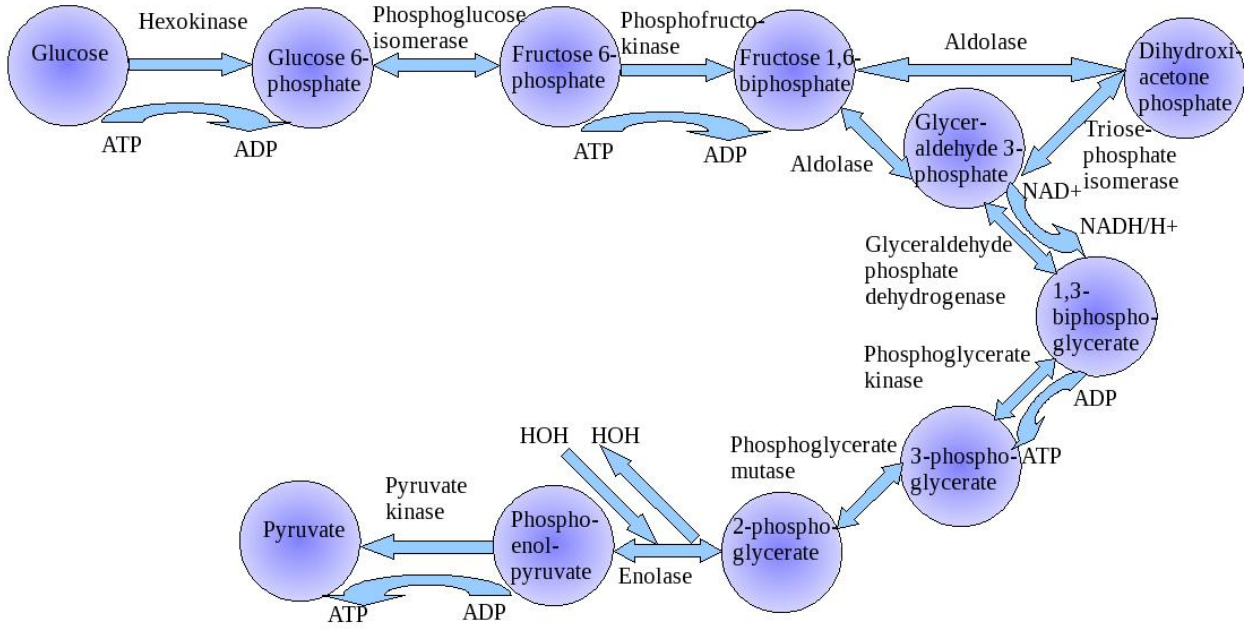
- Heme synthesis
- Urea cycle
- Gluconeogenesis

Enzyme- name based on function

- ***Kinases***- uses ATP
  PFK- phosphofructokinase- catalyses the conversion of fructose 6 p to fructose 1,6 P
- ***Phosphorylase***- add inorganic P to Substrate without ATP. Eg- glycogen phosphorylase
- ***Phosphatase***- remove phosphate groups from a substrate.
- ***Dehydrogenase***- catalyses oxidation-reduction reaction
- ***Carboxylase***- Add CO_2 with the help of Biotin / VitB7. Eg- pyruvate carboxylase

Glycolysis

Definition- Breakdown of glucose occurring in cytoplasm



6 C ----------3C----------2 Pyruvate (3C)----------Acetyl CoA----Kreb's cycle

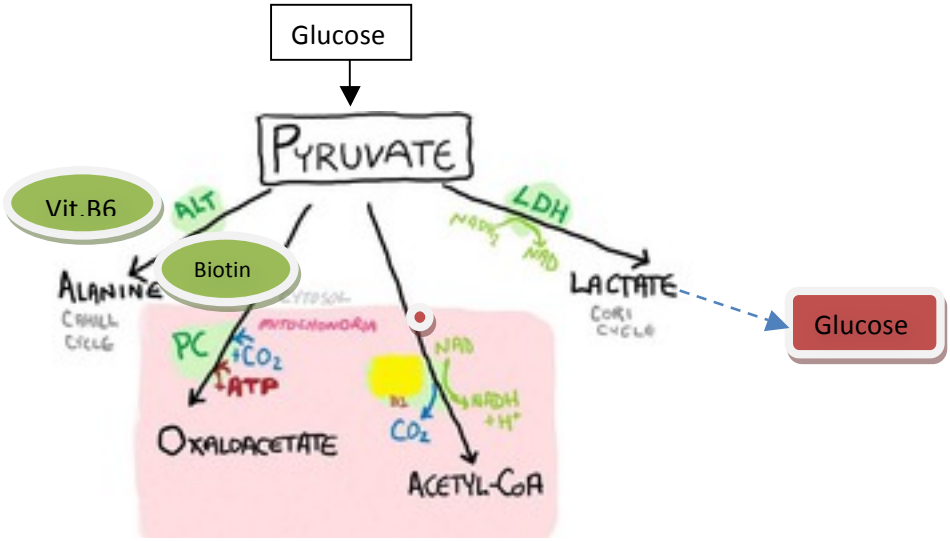
2 ATP 4ATP (NADH made in the process)

Insulin receptors present in skeletal muscle, adipose tissue and cardiac muscle.

Glut-4 receptors transport Glucose

Hexokinase/ Glucokinase- an important enzyme

Pyruvate metabolism



Pyruvate dehydrogenase

- 5 different cofactors used by PDH- Tender Loving Care For Nancy (**TLCFN**)
- **T**hiamine pyrophosphate -Vit B1
- **L**ipoic acid
- **C**oenzyme A- Vit B5
- **F**AD – Riboflavin –Vit B2
- **N**ADH- Niacin- Vit B3
- RBCs use pyruvate to make lactate as they do not have mitochondria. Apart from that other tissues that use pyruvate similarly in anaerobic respiration are leukocytes, Kidney medullar cells, Testes and retina.

Deficiency of pyruvate DH complex

- Infant feels **lethargic** due to absence of ATP, neurologic defects and vomiting.
- LDH becomes active hence lactic acidosis due to excess of lactate.
- E1 Alpha sub-unit- this is where the genetic mutation occurs on X chromosome.
- Treatment from lactic acidosis- done with the help of proteins/amino acids- lysine and leucine rich diet as they are the only ketogenic amino acids.

Arsenic toxicity

- Arsenic inhibits lipoic acid.
- Symptoms- rice water stool, garlic breath, vomiting

Alpha keto glutarate ⟶ succinyl coA

Alpha KG DH

This reaction has the same set of cofactors TLCFN

Hypoxia- pyruvate DH does not act LDH acts instead. So lactic acidosis occurs.

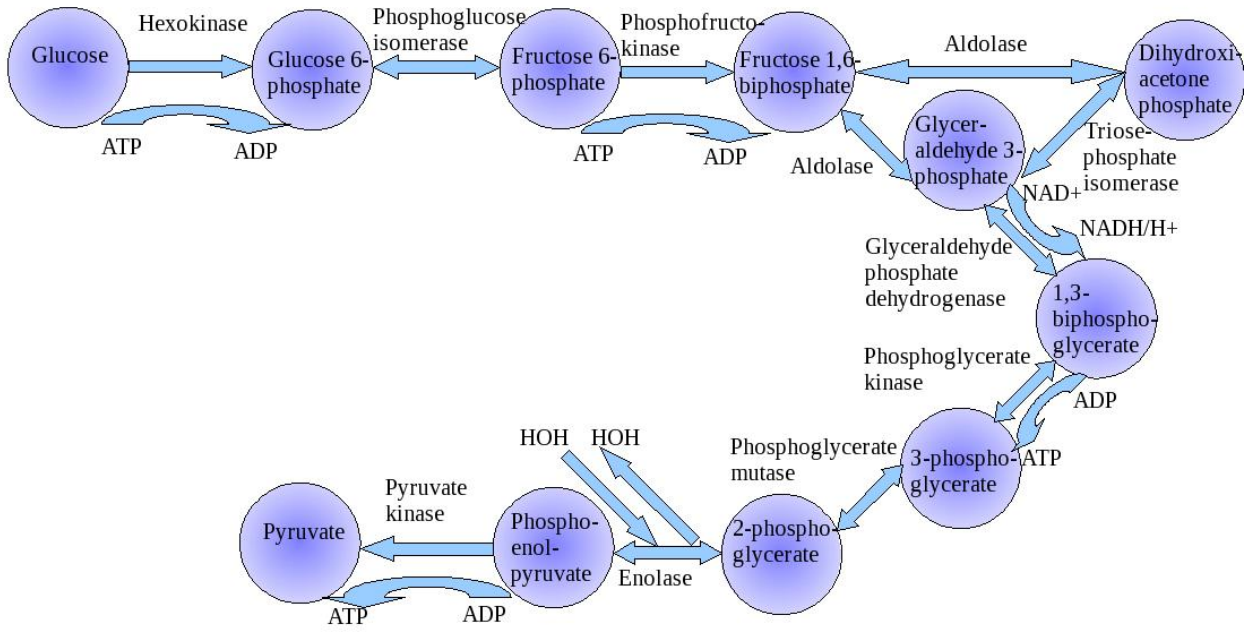
Activators of PDH

Exercise activates the below mentioned cofactors as more ATP is required.

1. Increased NAD/NADH RATIO
2. Increased ADP
3. Increased Ca2+

Alcoholics have thiamine deficiency so PDH does not function thereby lactate production increases. In case of chronic alcoholics, thiamine should be given first and then the person should be given glucose so that glucose enters Kreb's cycle.

Pyruvate kinase deficiency



- RBCs depend upon glycolysis and hexose monophosphate shunt pathway for ATP due to absence of any organelle.
- Pyruvate kinase def is autosomal recessive genetic mutation.
- 3 characteristic-
- i. Hemolytic anemia
- ii. Increase in 2,3 bisphosphoglycerate
- iii. Heinz bodies absent in RBCs
- If ATP is not produced, Na/K ATPase pump does not work, Na accumulates within RBC and water follows it, thereby RBCs swell up. In the spleen , these RBCs get destroyed to form Burr cells. So hemolytic anemia occurs. High levels of bilirubin from heme destruction.

NADH

- Electron carrier.
- Fe3+ converts to Fe2+ in presence of NADH.
- In the absence of NADH, Fe3+ increases in concentration and leads to methemoglobinemia
- RBCs cannot carry oxygen then
- 1,3 Bisphosphoglycerate partial pyruvate kinase def. 2,3 Bisphosphoglycerate

2,3 bisphosphoglycerate decrease O2 affinity in RBCs- increased oxygen unloading

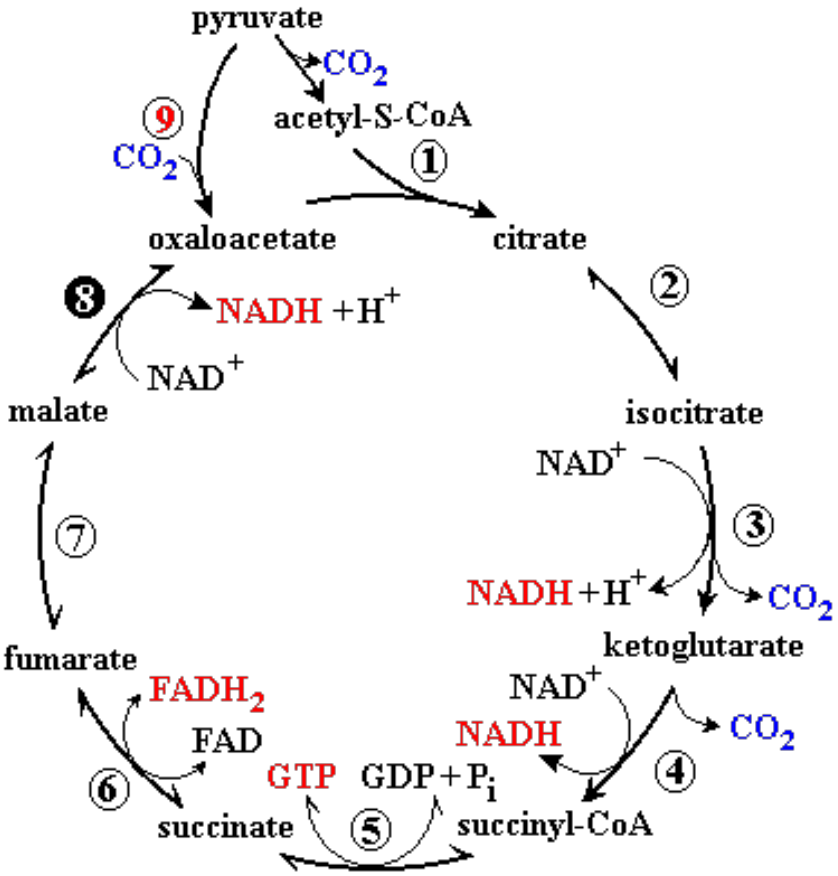
HMP pathway

- Glucose used to form glutathione.
- NADPH is formed which is an antioxidant.

Hemolytic anemia is caused by G6 Pd deficiency and Pyruvate DH deficiency.

Kreb's cycle (TCA cycle)

- Tricarboxylic acid cycle or citric acid cycle (starts with citric acid)
- Glycolysis converts glucose to pyruvate
- Most important cycle for life as ATP is produced.



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- More ATP and NADH can inhibit isocitrate dehydrogenase, ADP activates it.
- Alpha ketoglutarate dehydrogenase- dehydrogenases requires cofactors. TLCFN are required as cofactors
- A lot of succinyl CoA, NADH or ATP inhibit alpha ketoglutarate dehydrogenase
- **Succinate dehydrogenase** is another important enzyme as it needs a cofactor – Vitamin B2

Summary

8 NADH × 3	= 24 ATP
2 FaDH2 × 2	= 4 ATP
Kreb's cycle- 2ATP	= 2 ATP
	30 ATP

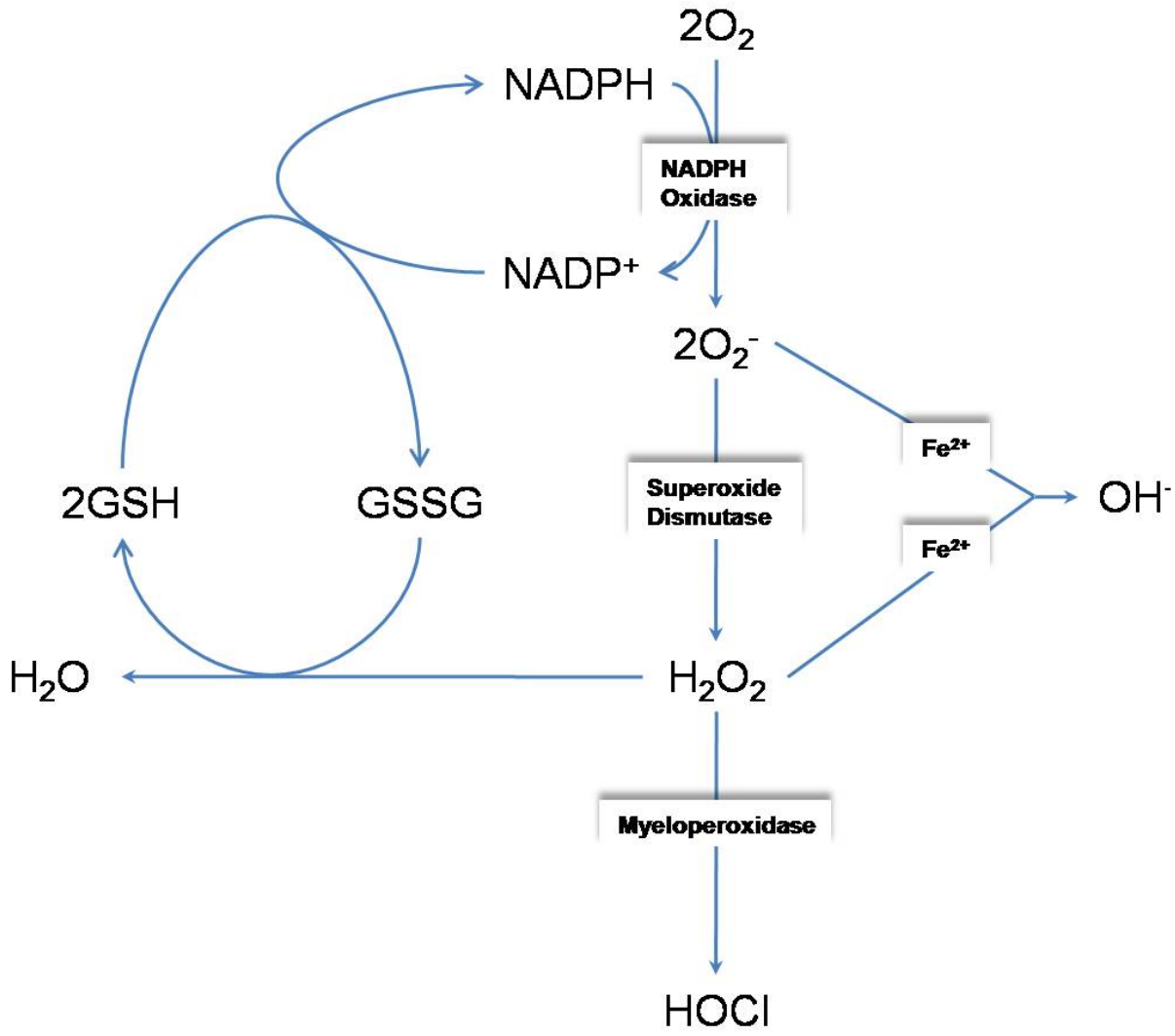
Glycolysis	2 ATP
2 NADH × 2 ATP	= 4 ATP
Total	36 ATP

Pneumonic – **C**itrate **I**s **K**rebs **S**tarting **S**ubstrate **F**or **M**aking **O**xaloacetate

Pathway between I and K is irreversible as the process goes on if isocitrate dehydrogenase is activated.

Respiratory burst

- Also called as oxidative burst
- Neutrophils use myeloperoxidase pathway to kill bacteria. It is oxygen dependent
- Inside the phagolysososme-



Hypochlorite destroys bacterial cells.

- Bacterial cells also produce Hydrogen peroxide but under the action of catalase it is converted to O2 and water.
- Inside phagocytes, Hydrogen peroxide is neutralized through Hexose Mono Phosphate shunt.

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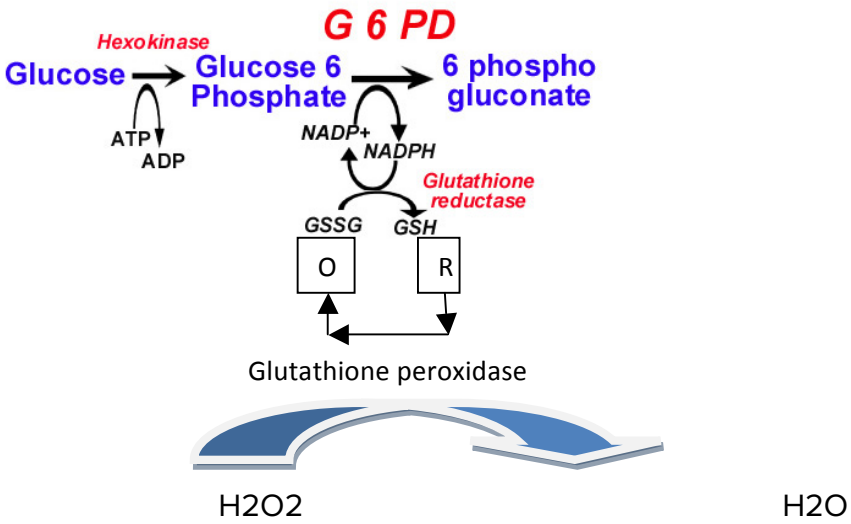
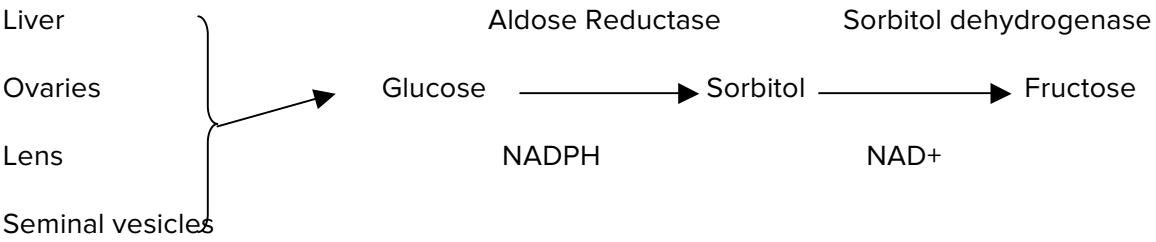


Chronic Granulomatos Disease (CGD)

- A deficiency in NADPH oxidase
- Neutrophils cannot kill bacteria- exposed to bacterial infections
- **Catalase positive** organisms cannot be killed by CGD patients.
- **Recurrent pulmonary infection** in lungs, skin (staph and strep), lymphatic tissue, hepatic infection
- **Bacteria-** Staph aureus, Pseudomonas aeroginosa, Nocardia species, Aspergillus and Burkholderia cepacia.
- Fever **triggered by IL-1, PG E2, TNF- alpha.**
- The oxygen-hemoglobin curve shifts towards the right. Hence hb releases more oxygen for WBCs to perform their function of phagocytosis.

Sorbitol

Organs



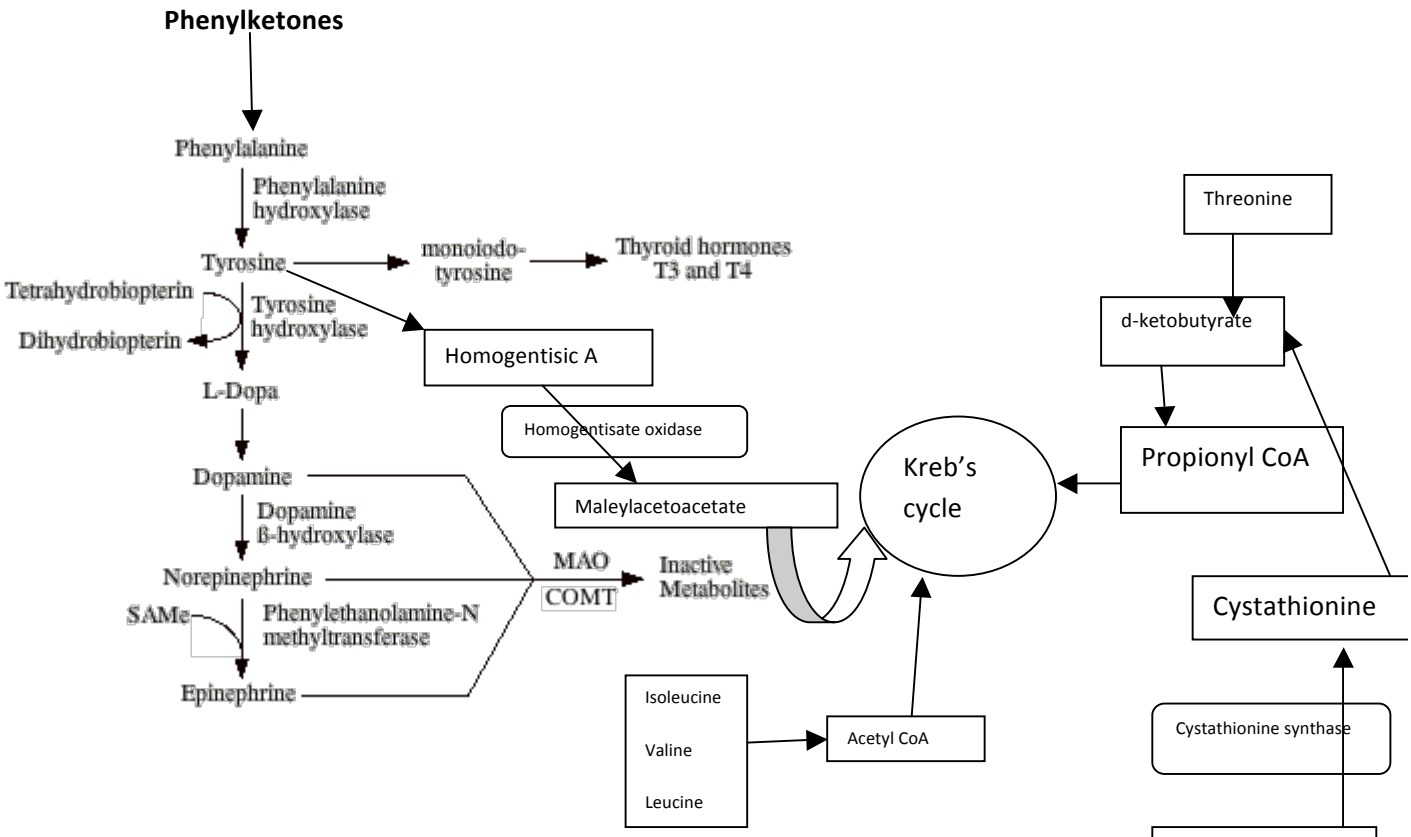
Schwann cells, kidney and retina do not have sufficient sorbitol dehydrogenase to convert sorbitol to fructose.

Sorbitol is osmotically active. Cells swell up or get damaged- chronic diabetics

In lens- this leads to –

i. Cataracts
ii. Retinopathy
iii. Peripheral neuropathy

Amino acid metabolism



VOMIT pathway

V- Valine

O- Odd chain fatty acids

M- Methionine

I – Isoleucine

T- Threonine

Urea cycle

- This takes place in liver to remove excess of ammonium ions (coming after amino acid metabolism), the deposition of which can lead to problems like encephalopathy, confusion and tremors.
- Urea structure

NH2 from NH4+

C=O from CO2

NH2 from aspartate

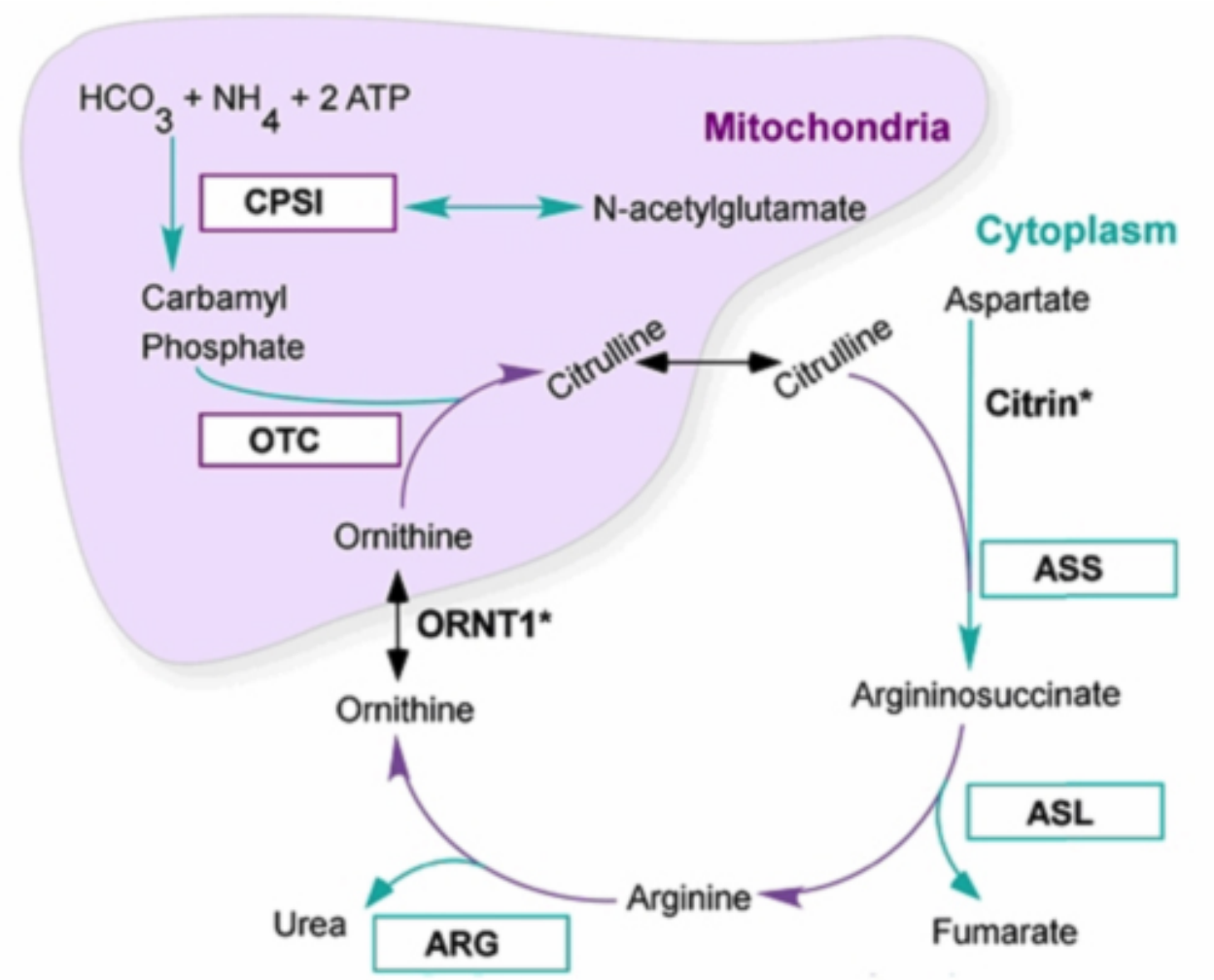


Image reference: http://drmhanna.com/urea-cycle-defects/

- Blood Urea Nitogen- If BUN is low there is problem in liver, if high problem is in kidneys.

- Deficiency of enzymes like CPS1 and OTC cause symptoms like
- 1. Ammonium ions level elevated so hyperammonemia
- 2. Elevated level of glutamine
- 3. Decrease level of urea hence BUN
- 4. Cerebral oedema
- 5. Lethargic, coma, seizures and death
- 6. High levels of orodic acid (uracil)- deficiency of OTC

Hyperammonemia

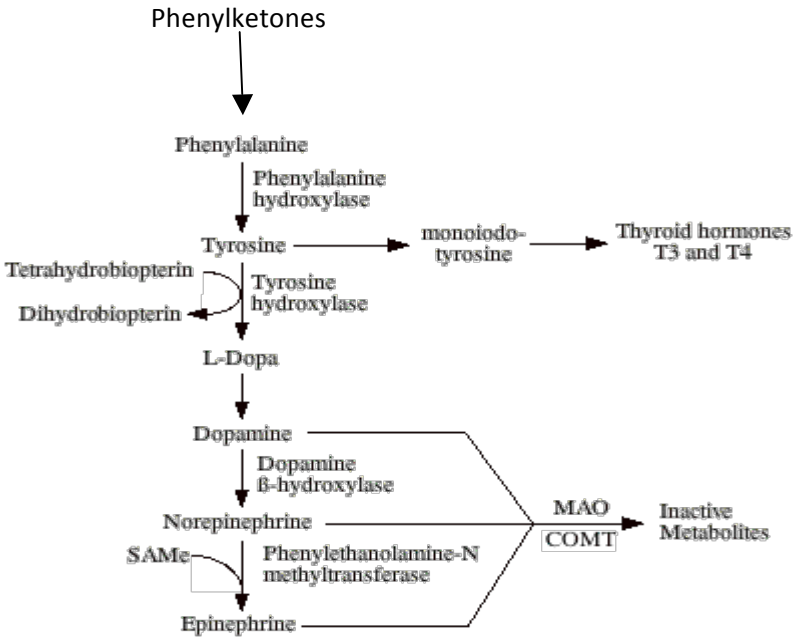
Can be from acquired liver disease (Hep B and C, chronic alcoholics) or hereditary liver disease (inheritance of enzyme deficiency like arginase deficiency)

In high protein diet, N acetyl glutamate is activated and that causes CPS1 to convert ammonium ions to kidneys.

Catecholamine synthesis

Definition

Catecholamines are epinephrine and norepinephrine and are made inside the adrenal gland.



Pheochromocytoma

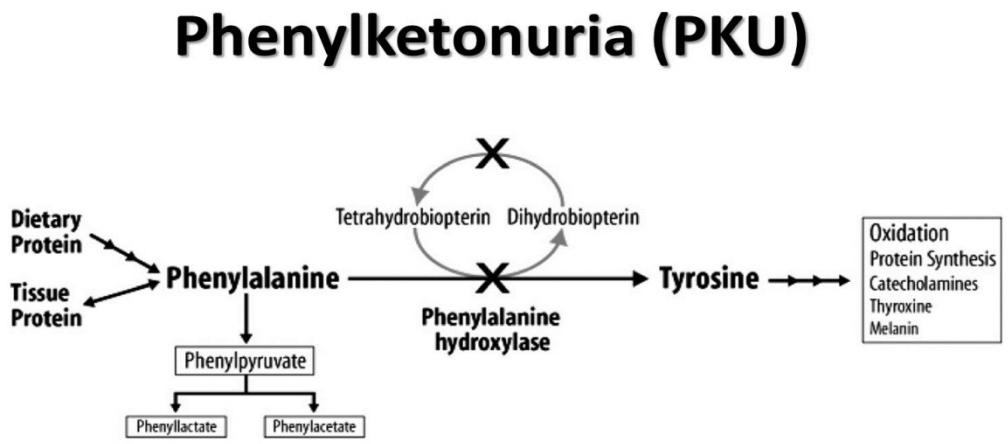
- Tumor of the adrenal gland so excess production of sympathomimmetics.
- Tachycardia, hypertension, increased cardiac output, increased heart rate, palpitation, headaches and perspiration and pallor.
- Urinary VMA (Vanillylmandelic Acid)- high levels. It is a product of epinephrine and norepinephrine.
- High levels of plasma catecholamines.
- Neurofibromatosis type I and MEN Type 2A/2B

Neuroblastoma

- Most common adrenal gland tumor in children.
- Affect anywhere along the sympathetic chain (T1 to L2)
- Elevated levels of HVA (Homovanillic acid)- breakdown of dopamine
- Overexpression of N-MYC oncogene- tumor is aggressive

Phenylketonuria

- It is an autosomal recessive disease
- Incidence- 1 in 10,000
- Screening done as this leads to mental retardation
- Elements of phenylalanine and breakdown products in urine of babies.- phenylacetate and phenylpyruvate
- Due to deficiency of phenylalanine hydroxylase.



- Low levels of tetrahydrobiopterin (malignant PKU) can cause phenylketonuria

- **Symptoms**
- Mental retardation
- Growth retardation
- Seizures
- Fair skin
- Eczema
- Musty body odor (disorder of aromatic amino acids)

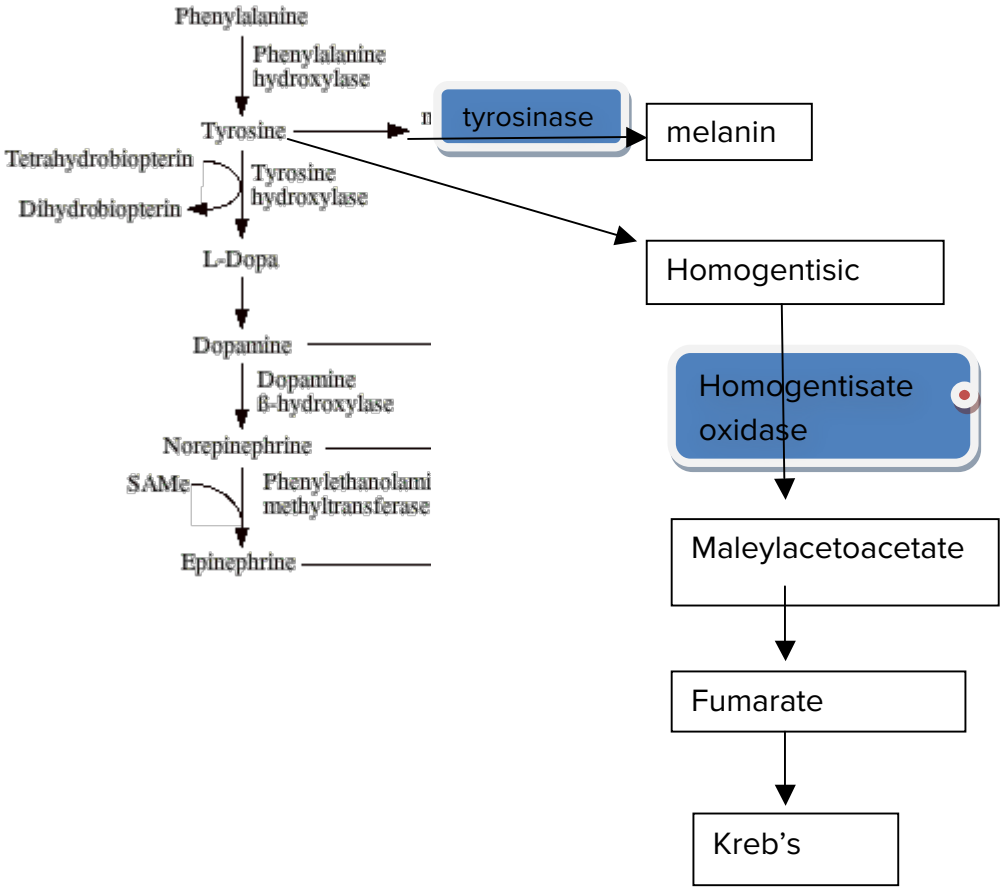
- **Treatment**
- Decrease phenylalanine in diet
- No aspartame and Nutra sweet
- Increase tyrosine levels as tyrosine becomes an essential amino acid for these kids.

Maternal PKU

- Because of lack of dietary supplements
- The baby has high chances of getting problems like microencephaly, growth retardation, mental retardation and congenital heart defects.

Alkaptonuria (Onchronosis)

- Benign autosomal recessive disease
- Due to deficiciency of homogentisate oxidase.
- Patients have dark colored urine.
- Brown pigmented sclera
- Dark connective tissue
- Debilitating arthralgias due to deposition in bone and joints.
- Develop arthritis in early adults.

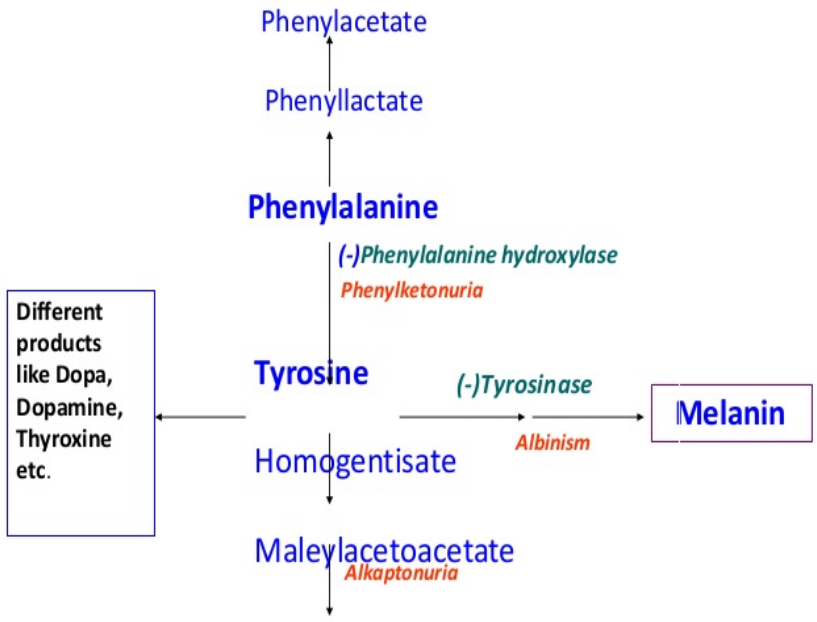


Albinism

Definition

Congenital deficiency in tyrosinase- Autosomal recessive deficiency

Tyrosinase converts tyrosine to melanin.



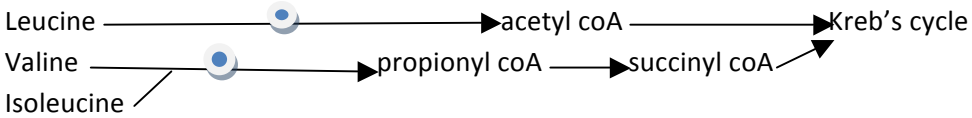
Melanin protects the skin from the penetration of UV rays from sunlight that might cause DNA damage. Hence, loss of melanin increases the susceptibility of an individual to have cancers like melanoma.

It can be due to deficiency in tyrosine transporter.

It can be due to lack of migration of neural crest cells.

Maple syrup urine disease

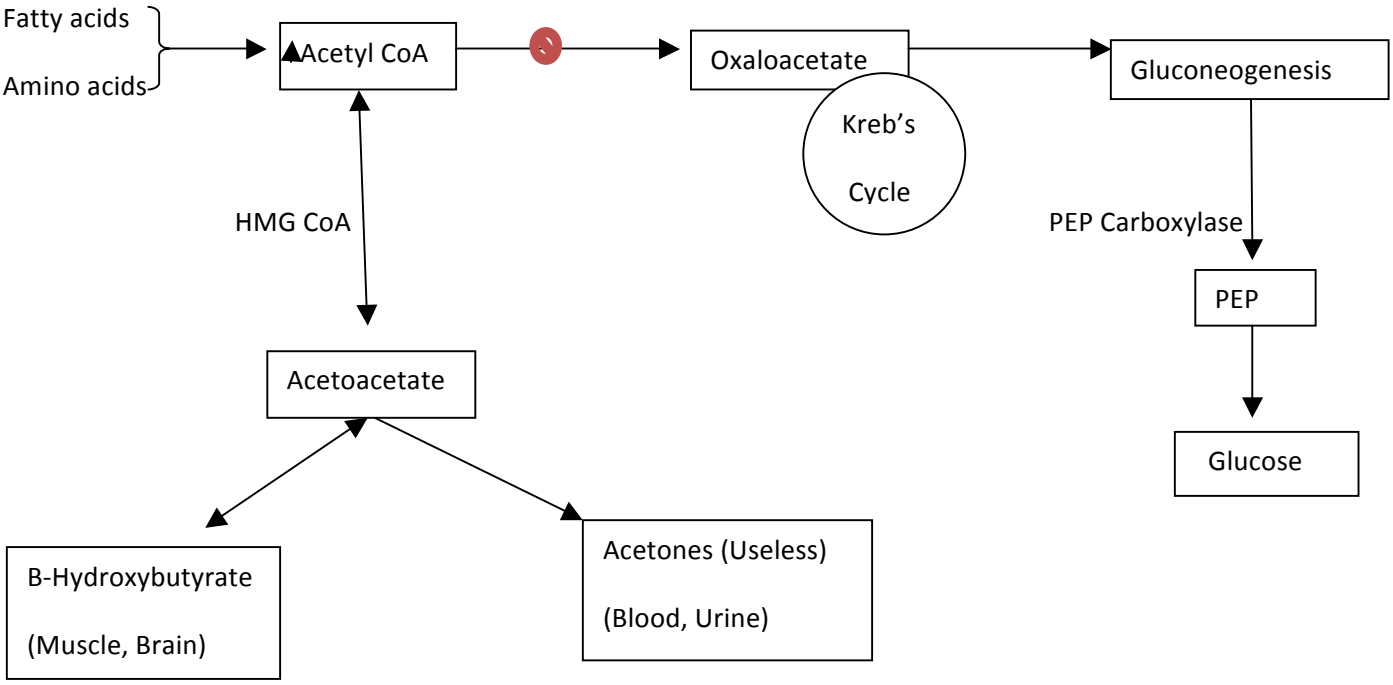
- Urine smells like Maple syrup.
- Autosomal recessive disease
- Branch chain of alpha ketoacid dehydrogenase.



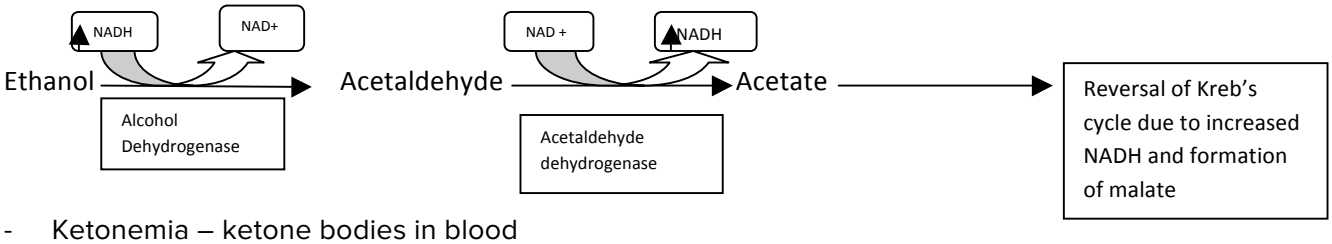
- Leucine and isoleucine are ketogenic acids.
- Branch chain of alpha ketoacid dehydrogenase needs 5 cofactors to function which are TLCFN
- Thiamine, Lipoic acid, CoA, FAD, Niacin (B3)
- **Symptoms**
- CNS defects
- Mental retardation
- Death
- **Diagnosis**
- Urine with maple syrup smell
- I LOVE VERMONT MAPLE SYRUP
- I – Isoleucine
- L- Leucine
- V - Valine

Ketone bodies

- Ketone bodies are made inside the liver and the process is not under hormonal control.
- Mitochondria of hepatocytes
- Occurs in starvation, chronic alcoholism or DKA (diabetic ketoacidosis)
- Body switches to fatty acids and amino acids.



- Chronic alcoholism-



- Ketonemia – ketone bodies in blood
- Ketonuria- ketone bodies in urine
- Nail polish type smell because of release of acetones in breath.

- Lactic acidosis in DKA.

- Thiophorase- an important enzyme found in extrahepatic tissues for utilization of ketones for energy production.

Lactase deficiency

- Lactose (galactosyl 1,4 glucose) ⟶ glucose + galactose
- Lactose is a disaccharide.
- Due to lactase deficiency, lactose remains as such in the GI tract.
- Since it is osmotically active so draws water from cells- osmotic diarrhea
- In African Americans and Asians
- Symptoms- bloating, cramps and osmotic diarrhea
- Treatment – add lactase enzyme or pills to diet or avoid dairy products

Lysosomal storage diseases

Ceramide- a waxy lipid

- Made out of fatty acids and sphingosine
- Ceramides help in cellular signaling as in differentiation, proliferation and apoptosis.
- Ceramide synthesis pathway