جامعة الملك سعود
King Saud University

"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Biochemistry437

Vitamin B6 & B12

Biochemistry Team 437

Color index:
Doctors slides
Doctor's notes
Extra information
Highlights

Neuropsychiatry block

Revised By
Hadeel Alwarthani & Abdullah AlOmar

MED437
KING SAUD UNIVERSITY

Objectives:

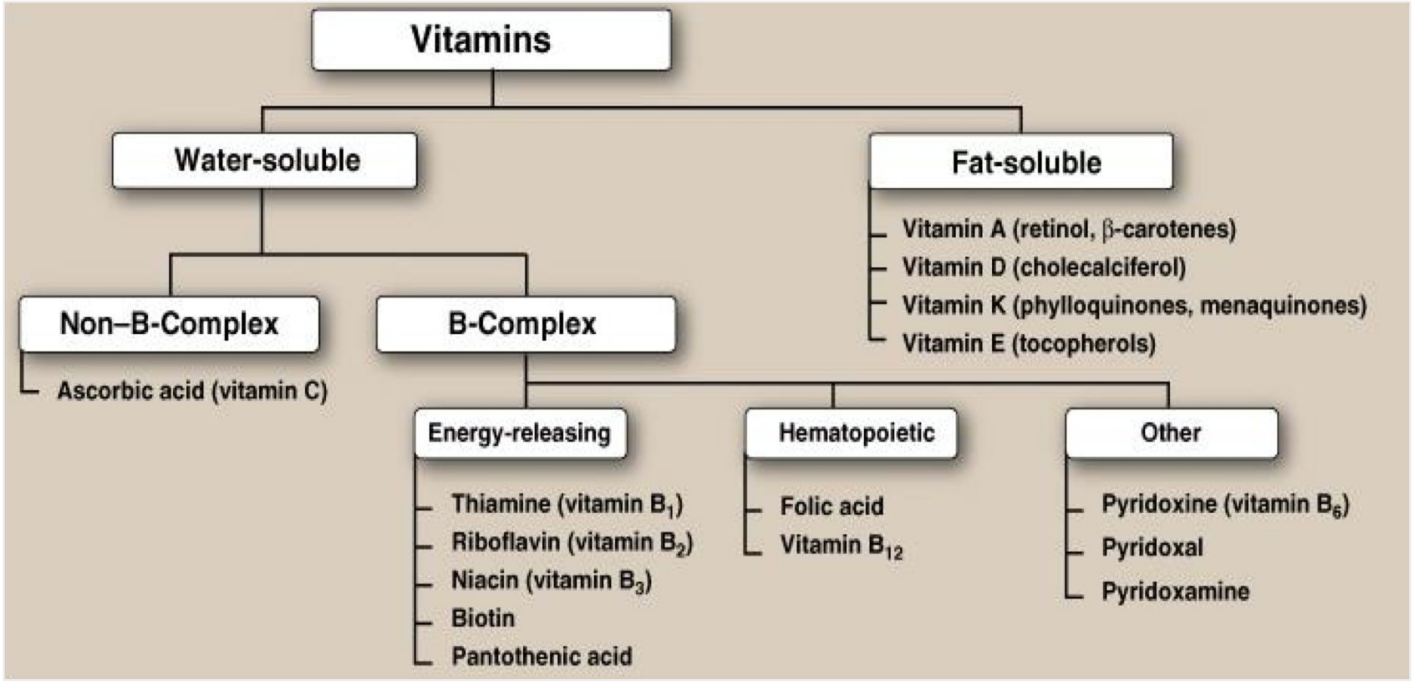
By the end of this lecture the Second Year students will be able to:

- Understand the types and functions of vitamins B6 and B12
- Recognize the role of these vitamins in maintaining the myelin sheath of nerves and their function
- Discuss the consequences of vitamin B6 B12 and deficiency that can lead to nerve degeneration and irreversible neurological damage

Overview

- Types and functions of vitamins B6 B12
- Disorders due to Vitamins B6 and B12 deficiency
- Vitamin B12 deficiency and folate trap
- Demyelination, neuropathy and neuropsychiatric symptoms of vitamin B12 deficiency

Classification of Vitamins



Water-Soluble Vitamins

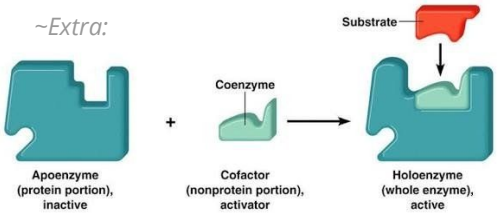
B vitamins:

- Thiamin (B1)
- Riboflavin (B2)
- Niacin (B3)
- Pantothenic acid (B5)
- Pyridoxine (B6)
- Biotin (B7)
- Cobalamin (B12)
- Folate

Vitamin B Complex:

- Present in small quantities in different types of food
- Important for growth and good health
- Help in various biochemical processes in cell
- Function as coenzymes [1]
- Not significantly stored in the body, **Except** Vit B12 "cobalamin" which is stored in the liver
- Must be supplied regularly in the diet
- Excess excreted [2]

~Extra:



1- An organic compound that binds to the enzymes active site to catalyze a reaction but are not degrades or considered substrates.
2- It is rare to develop toxicity.

Vitamin B_6

Three forms:

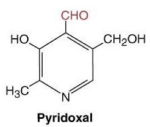
- Pyridoxine (Plant sources)
- Pyridoxal (Animal sources)
- Pyridoxamine (Animal sources)

All 3 are converted to their Active form: pyridoxal phosphate (PLP)

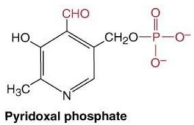
Structures: EXTRA:

Pyridoxine

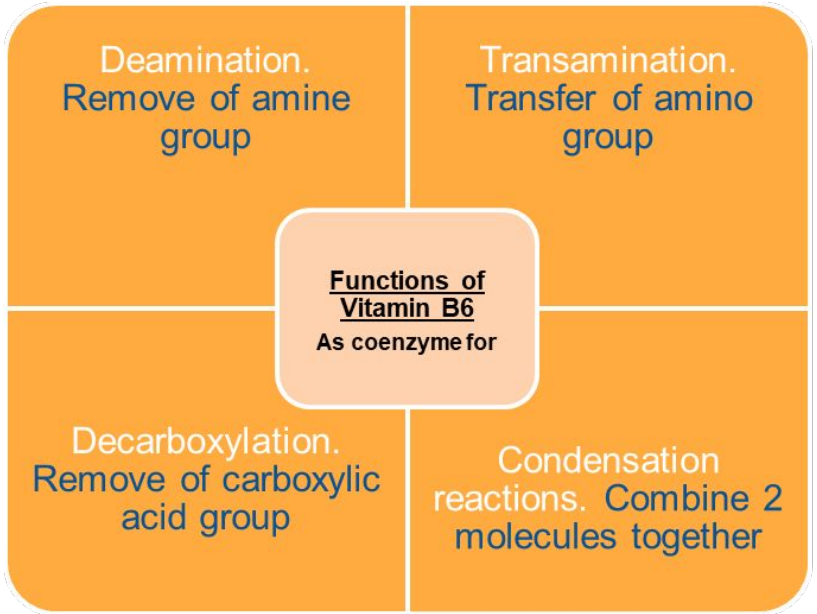
Pyridoxamine



Pyridoxal



Pyridoxal phosphate



Vitamin 6 (PLP) is required for:

- Amino acid synthesis and breakdown
- Glycogen metabolism
- Heme synthesis

This is just an overview, what you need to memorize is mentioned in the following slides

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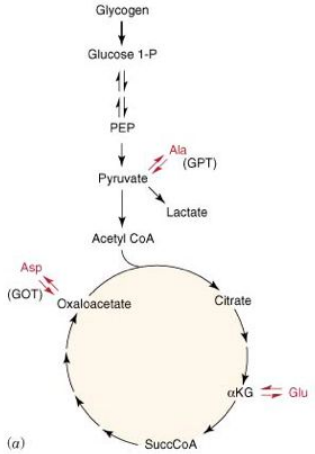
Some metabolic roles played by pyridoxal phosphate "vit B6" in metabolism:

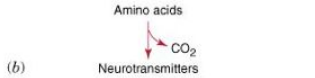
A) During krebs cycle you need PLP for:

- Conversion of alanine to pyruvate and vice versa
- Conversion of alpha ketoglutarate to glutamate and vice versa
- Conversion of aspartic acid to oxaloacetate and vice versa

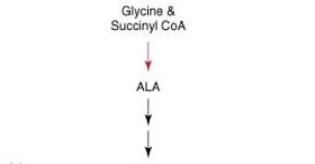
All of these reactions are transamination



B) Amino acids are decarboxylated with the help of PLP to synthesize neurotransmitters

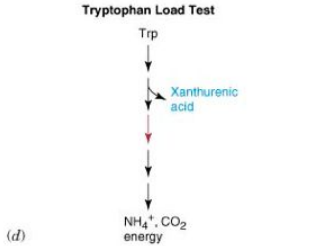


C) Glycine and succinyl CoA are conjoined together with the help of PLP to ultimately make heme



D) Tryptophan load test:

- While degrading tryptophan "an amino acid" the body makes Xanthurenic acid in one of the steps
- To degrade Xanthurenic acid, the body requires vit B6
- So in case of vit B6 deficiency, there will be accumulation of XAnthurenic acid
- So using this information, if we want to test for vit B6 deficiency, we give the patient a big load of tryptophan, then measure the Xanthurenic acid they produce,accumulation of it points to vit B6 deficiency



You have to know the substrates, products, and the role of enzymes on these reactions

Condensation Reaction

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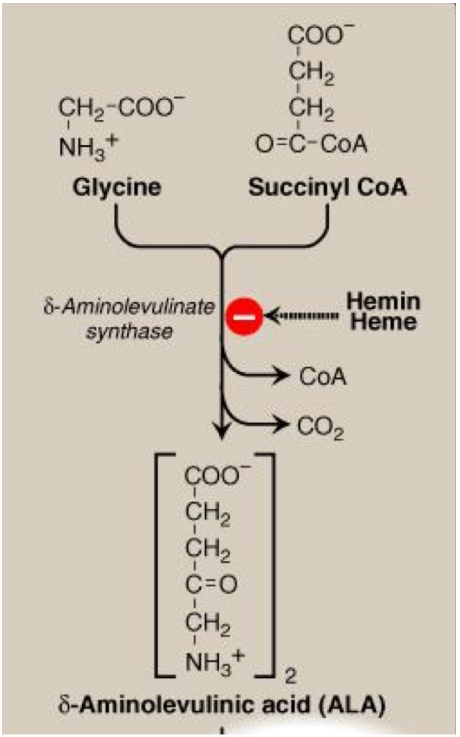
Formation of ALA by ALA synthase, The regulatory step in hemoglobin synthesis

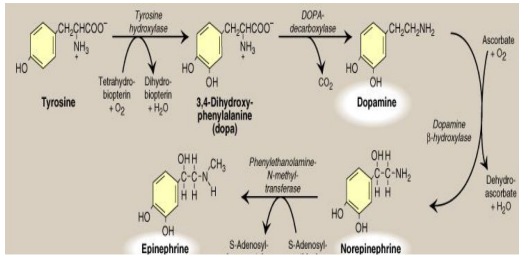
- Glycine and succinyl CoA condense in the presence of the enzyme alpha aminolevulinate synthase (ALA synthase) to form alpha aminolevulinic acid (ALA)
- This step is important in the synthesis of heme
- Deficiency of B6 will lead to inhibition of heme synthesis → Hemoglobin deficiency → Anemia
- This anemia is called **Sideroblastic anemia**



Decarboxylation Reaction (Reaction of Vitamin B_6)

The enzyme is decarboxylase in all of these reactions

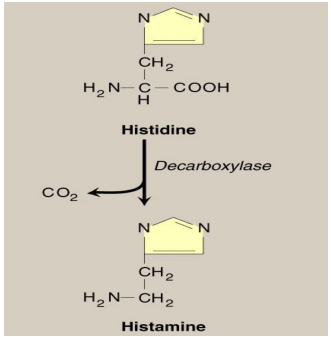
Formation of Catecholamines



(Neurotransmitters) Dopamine, norepinephrine and epinephrine

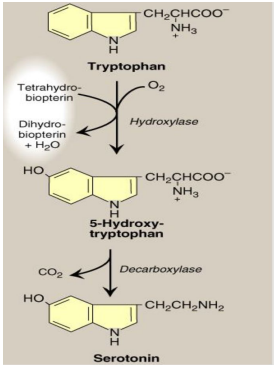
- Tyrosine is decarboxylated to dopamine,which requires vit B6
- Dopamine gets converted to epinephrine and norepinephrine
- deficiency of vit B6 leads to deficiency of the 3 catecholamines

Formation of Histamine



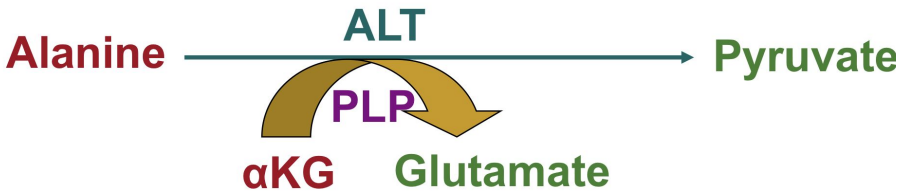
Decarboxylation of histidine to histamine requires vit B6

Formation of Serotonin



Decarboxylation of tryptophan to serotonin requires vit B6

Transamination Reaction (Reaction of Vitamin B_6)



PLP: Pyridoxal Phosphate (active form of Vit B6)
ALT: Alanine Transaminase
αKG: alpha Ketoglutarate

- Alanin transfer its amino group to alpha ketoglutarate which then turns alpha ketoglutarate into glutamate, and alanine to pyruvate
- Pyruvate then is converted to acetyl CoA and it enters TCA cycle
- This reaction is catalyzed by ALT “alanine transaminase” which needs PLP

Disorders of Vitamin B_6 Deficiency

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Dietary deficiency is rare, but it is observed in:

- Newborn infants fed on formulas low in vit. B
- Women on oral contraceptives
  Because it disturbs carbohydrates metabolism
- Alcoholics
- Isoniazid Treatment for tuberculosis can lead to vit. B6 deficiency by forming inactive derivative with PLP
  Isoniazid makes a complex with pyridoxal phosphate and inactivates it

In these two cases, there is impairment of vit B6 absorption

Disorders of Vitamin B_6 Deficiency

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- Deficiency leads to poor activity of PLP-dependent enzyme causing:
  - Deficient amino acid metabolism
  - Deficient lipid metabolism
  - Deficient neurotransmitter synthesis: Serotonin, epinephrine, norepinephrine and gamma-aminobutyric acid (GABA)

- PLP is involved in the synthesis of sphingolipids "in ceramide synthesis"
  - Its deficiency leads to demyelination of nerves and consequent peripheral neuritis "MS like symptoms"

- Mild deficiency leads to: "mostly psychiatric symptoms"
  - Irritability
  - Nervousness
  - Depression

- Severe deficiency leads to: "mostly neurological symptoms"
  - Peripheral neuropathy
  - Convulsions

Vitamin B_{12}

Forms of Vitamin B_{12} (Cobalamin)[1]

- Cyanocobalamin[2]
- Hydroxocobalamin[2]
- Adenosylcobalamin (major storage form in the liver)
  The only water soluble vitamin that can be stored
- Methylcobalamin (mostly found in blood circulation)
  Bound to vit. B binding protein or to trans-cobalamin

1: Called cobalamin because it has cobalt in it
2: Commercially synthesized form
-These forms can be converted to each other

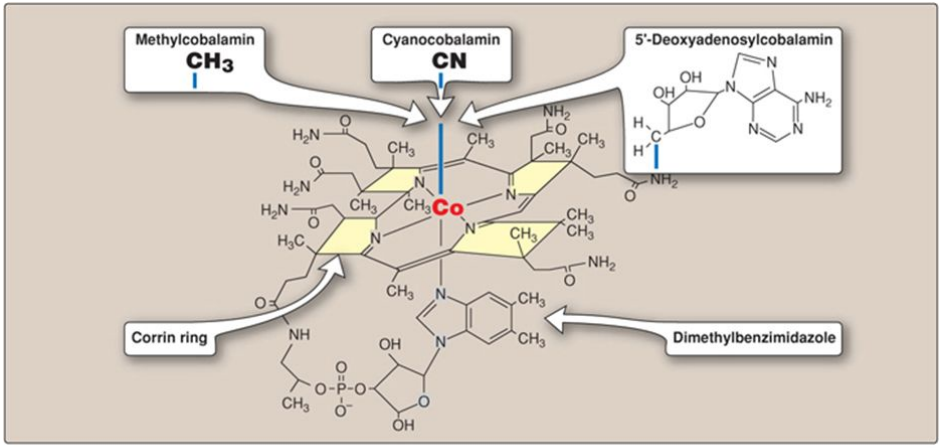
Coenzyme Forms of Vitamin B_{12} (Cobalamin)

- Adenosylcobalamin and Methylcobalamin
  - Coenzymes for metabolic reactions
- Body can convert other cobalamins into active coenzymes

Vitamin B_{12} (Cobalamin)

Structure of cobalamin:

- corrin ring with a cobalt in the center
- the cobalt has a valency of 6 “can make 6 bonds”
- 4 of these bonds are with the pyrrole nitrogen of the corrin ring
- one bond with dimethylbenzimidazole (DMZ)
- the last bond is either with:
    - a methyl group to make methylcobalamin
    - cyanide to make cyanocobalamin
    - deoxyadenosine to make 5-deoxyadenosylcobalamin

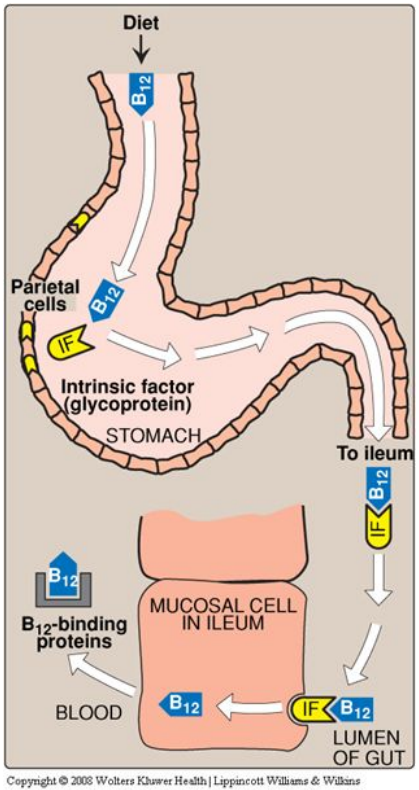


- Mainly found in animal liver
  Not found in plants, it is mainly synthesized by the bacteria present in guts
- Bound to protein as:
    - Methylcobalamin or
    - 5’-deoxyadenosylcobalamin
- These two forms are stored in the liver
- Essential for normal nervous system function and red blood cell maturation.
- We can store a huge amount of vit B12 to the point where symptoms of deficiency will take few years to start showing

Vitamin B_{12} (Cobalamin)

- Not synthesized in the body and must be supplied in the diet.
- Binds to intrinsic factor and absorbed by the ileum.
- Intrinsic factor is a protein (glycoprotein) secreted by cells in the stomach, and is required for the proper absorption of the vitamin B12, so deficiency of intrinsic factor will lead to deficiency of vitamin B12.

- While eating, our salivary glands secrete a protein called R protein.
- When the food reaches the stomach, the acidity of the stomach allows the R protein to bind to vitamin B12.
- In the intestine, the pancreatic enzymes act on the R protein and remove it from vitamin B12.
- Now that the vitamin B12 is free, it binds to the intrinsic factor, which is released from the parietal cells of the stomach.
- Now vitamin B12 is ready for absorption.
- Vitamin B12 and intrinsic factor complex bind to their special receptors present on the intestinal epithelial cells and it is taken inside the enterocytes.
- From there the vitamin is thrown into the general circulation, bound to trans-cobalamin “B12 binding protein”.
- After that it goes to the liver to be stored.



Vitamin B_{12} Storage

- Liver stores vitamin B_{12} (4-5 mg)
- Other B vitamins are not stored in the body
- Vitamin B_{12} deficiency is observed in patients with IF (Intrinsic Factor) deficiency due to autoimmunity* or by partial or total gastrectomy
- clinical deficiency symptoms develop in several years

*They have antibodies against the parietal cells of the stomach, so synthesis of IF stops

Functions of Vitamin B_{12}

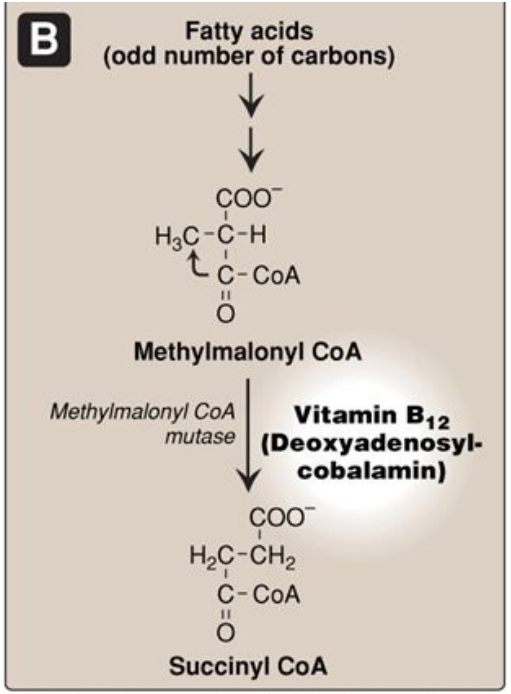
There are Two reactions that require B_{12} :

1- Conversion of propionyl-CoA to succinyl-CoA
"during fatty acid with odd number of carbons metabolism"

The enzyme in this pathway [methylmalonyl-CoA mutase], requires B_{12}

Steps:

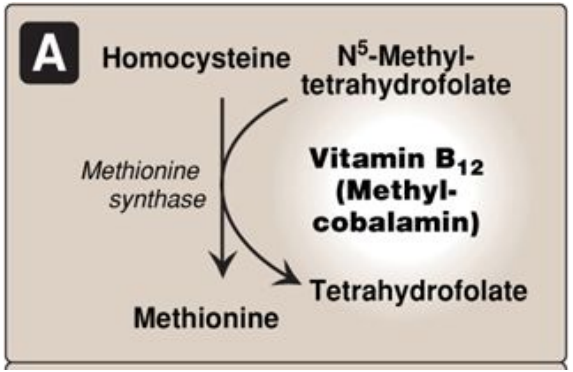
- Usually when fatty acids are being metabolized or broken down, they are broken down into 2 carbon molecules " during β-oxidation".
- If I have an odd number of carbons in a fatty acid, I will end up with a 3 carbon molecule called propionyl- CoA.
- Propionyl-COA gets converted to methylmalonyl COA.
- Methylmalonyl CoA is converted to succinyl CoA by the enzyme methylmalonyl CoA mutase, this enzyme requires vitamin B12 in the form of deoxyadenosyl-cobalamin" for its activity.
- Deficiency in this vitamin will lead to deficiency in succinyl CoA and accumulation of methylmalonyl-CoA in the membrane of neurons.



Functions of Vitamin B_{12}

2- Conversion of homocysteine to methionine "amino acid" which is catalyzed by Methionine synthase.

This enzyme requires B_{12} in converting homocysteine to methionine



- Homocysteine receives a methyl group and gets converted to methionine. now where does this methyl group come from?
  - It comes from a molecule called N^5-methyltetrahydrofolate
  - when N^5-methyltetrahydrofolate gives its methyl to homocysteine it gets converted to tetrahydrofolate, the biologically active form of folic acid
- In case of deficiency of vitamin B12:
  - tetrahydrofolate will not be synthesized, which will lead to:
    - folic acid deficiency
    - and the synthesis of purine and thiamine stops, which in turn stops DNA synthesis. this greatly affects Red blood cell synthesis, and the patient gets **megaloblastic anemia**
    - Accumulation of N^5-methyltetrahydrofolate
      - Which is also called folate trap, because folate is trapped in that form and is not converted to tetrahydrofolate the active form, so the body cant use it. "explained next slide"

Vitamin B_{12} Deficiency and Folate Trap

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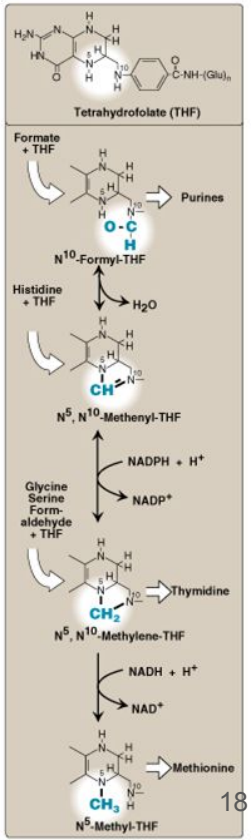
- Homocysteine re-methylation reaction is the only pathway where N^5-methyl TH4 can be returned back to tetrahydrofolate pool.
- Hence folate is trapped as N^5-methyltetrahydrofolate (folate trap)
- This leads to folate deficiency and deficiency of other TH4 derivatives:
- (N^5 -N^{10}methylene TH4 and N^{10} formyl TH4) required for purine and pyrimidine synthesis.
    - N^{10} formyl TH4 is required for purine synthesis
    - N^5 -N^{10}methylene TH4 is required for thymidine synthesis
    - N^5-methyl TH4 is required for methionine synthesis

TH4: Tetrahydrofolate
- Due to trapping of TH4 all of these reactions can't go on
- The functional form of folate is tetrahydrofolate.
- Folate is trapped because it can not be converted to the active form while it exists as inactive form

Interconversion between TH4 carrier of "one-carbon units"



Disorders of Vitamin B_{12} Deficiency

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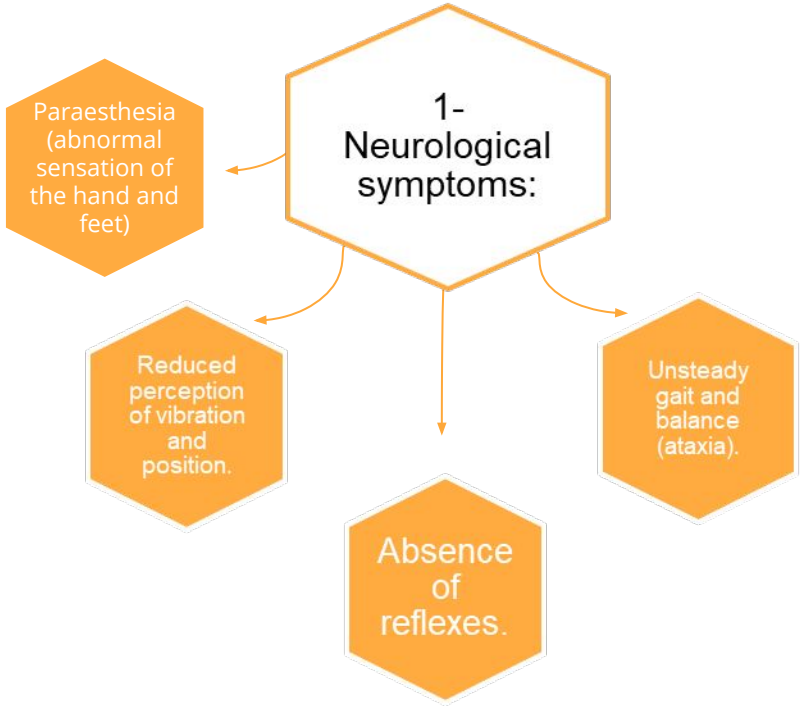
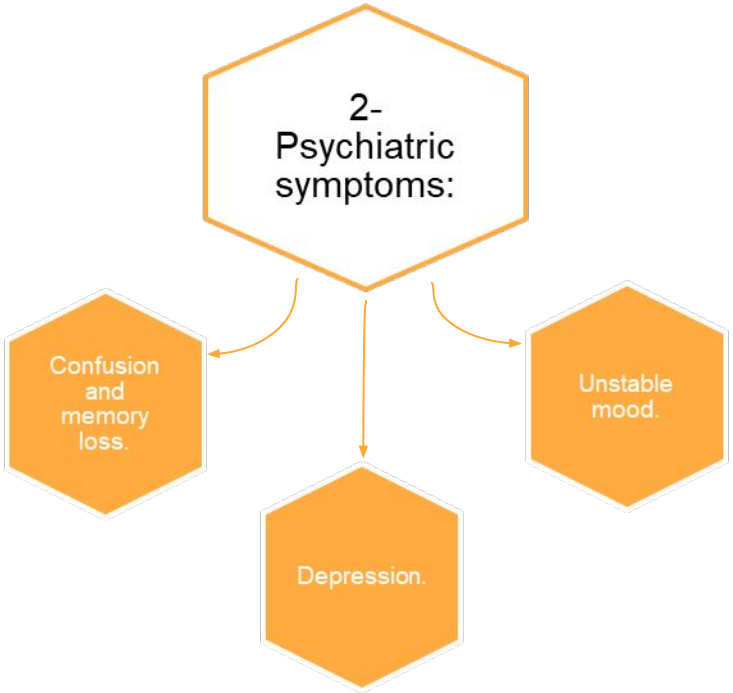
01	Pernicious anemia	Megaloblastic anemia. Vitamin B12 deficiency is mainly due to the deficiency of intrinsic factor.
02	Demyelination	Myelin sheath of nerves is chemically unstable and damaged "because of accumulation of methylmalonyl-CoA - slide 17- "
03	Neuropathy Peripheral nerve damage	Causes of neuropathy: • Deficiency of vitamin B12 leads to accumulation of methylmalonyl CoA. • High levels of methylmalonyl CoA are used instead of malonyl CoA for fatty acid synthesis. • Myelin synthesized with these abnormal fatty acids is unstable and degraded causing neuropathy . In a normal sphingomyelin contains two fatty acids and they are synthesized by malonyl CoA but because of the accumulation of methylmalonyl CoA the sphingomyelin will be made from methylmalonyl CoA making them unstable and degraded causing neuropathy

Symptoms of B_{12} Deficiency





- Anemia is also the most common symptom of vitamin B12 deficiency, if you supply the patient with folic acid you treat the anemia.
- Patients who have done gastric bypass, and those with pancreatic insufficiency are at risk for vitamin B12 deficiency.

Summary

	Vitamin B6	Vitamin B12
Forms	Forms of B6 : •Pyridoxine: From plants. •Pyridoxal: From animal proteins such as eggs and meat. •Pyridoxamine: Same source as pyridoxal. All 3 are converted to pyridoxal phosphate (active form).	Forms of B12 : •Cyanocobalamin •Hydroxycobalamin •Adenosylcobalamin (major storage form in the liver) •Methylcobalamin (mostly found in blood circulation) Three and four are coenzymes for metabolic reactions.
Functions	As coenzyme for: •Transamination. •Deamination. •Decarboxylation. •Condensation reactions.	• Conversion of methylmalonyl-CoA to succinyl-CoA. • Conversion of homocysteine to methionine.
	Deficiency Disorders	**Symptoms**
	•Dietary deficiency : •Newborn infants fed on formulas low in B6. •Women on oral contraceptives. •Alcoholics. •Medication side effect : •Isoniazid treatment for tuberculosis	Neurological : •Paraesthesia (abnormal sensation) of hands and feet. •Reduced perception of vibration and position. •Absence of reflexes. •Unsteady gait and balance (ataxia). Psychiatric : •Confusion and memory loss. •Depression. •Unstable mood.

Summary

	Vitamin B6	Vitamin B12
Deficiency leads to	• Deficiency leads to poor activity of PLP-dependent enzymes causing: • Deficient amino acid metabolism. • Deficient lipid metabolism. • Deficient neurotransmitter synthesis: Serotonin, epinephrine, norepinephrine and gamma aminobutyric acid (GABA) • PLP is involved in the synthesis of sphingolipids and its deficiency leads to demyelination of nerves and consequent peripheral neuritis : • Mild deficiency leads to: Irritability, Nervousness, and Depression. • Severe deficiency leads to: Peripheral neuropathy and Convulsions.	• Pernicious anemia : • Megaloblastic anemia . • Vitamin B12 deficiency is mainly due to the deficiency of intrinsic factor. • Demyelination : • Myelin sheath of nerves is chemically unstable and damaged. • Neuropathy (Peripheral nerve damage) caused by : • Deficiency of vitamin B12 leads to accumulation of methylmalonyl CoA. • High levels of methylmalonyl CoA are used instead of malonyl CoA for fatty acid synthesis. • Myelin synthesized with these abnormal fatty acids is unstable and degraded causing neuropathy.
General Information	-	Vitamin B12 (Cobalamin) is essential for: •Normal nervous system function. •Red blood cell maturation Liver stores vitamin B12 (4-5 mg) while other B vitamins are not stored in the body. Vitamin B12 deficiency is observed in patients with IF (intrinsic factor) deficiency. B12 Deficiency will leads to folate trap or folate deficiency.

Take Home Messages

- Vitamins B6 and B12 are essential in maintaining the nerve function and the central nervous system.
- Various neurological symptoms have been associated with their deficiency

MCQs:

Q1/ Which of the following is a water soluble non-B-complex vitamin ?

A- Vitamin K
B- Vitamin E
C- Vitamin C
D- Vitamin B1

Q2/ Formation of histamine is a..... reaction ?

A- Condensation Reaction
B- Decarboxylation reaction
C- Transamination Reaction
D- Deamination reaction

Q/- Vit B12 is mainly stored in liver in the form of?

A- Adenosyl cobalamin
B- Methylcobalamin
C- Cyanocobalamin
D- Phylloquinone

1. C
2. B
3. A

Team leaders

- رهام الحلبي
- معاذ الحمود

Boys team

- طارق العميم
- محمد الصويغ
- عبدالعزيز العبدالكريم
- صالح الوكيل
- عبد الملك الشرهان
- سعيد القحطاني
- نايف المطيري
- نواف اللويمي
- معن شكر

Girls team

- ريناد الغريبي
- العنود المنصور
- ليلى الصّباغ

Special thank for Dimah Alaraifi

@biochemistry437

teambiochem437@gmail.com