Revised & Approved

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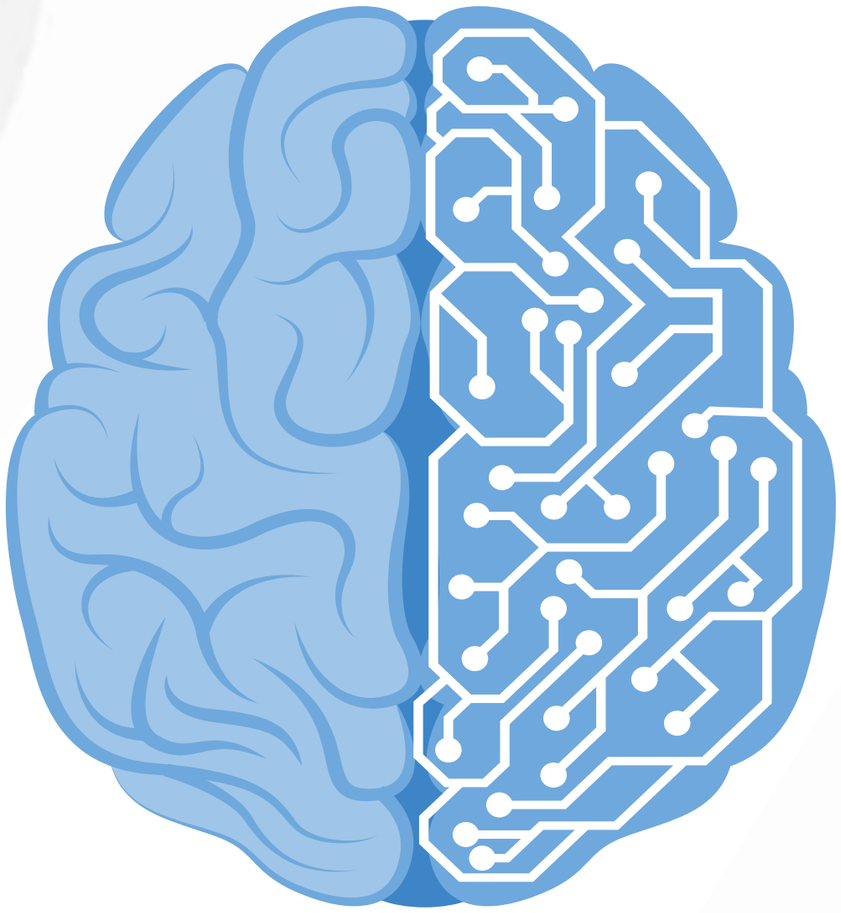
BIOCHEMISTRY TEAM
439

MED439
KING SAUD UNIVERSITY



Vitamins B6 and B12

Editing File

Color Index

- Main Text
- Important
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- Dr.'s Notes
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- Boys slides

Objectives

Click on the objective to go to the related slide

- 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 and B12 deficiency that can lead to nerve degeneration and irreversible neurological damage.

Level 2 (with each lecture you will level up and it will get harder to find the scientist)
Hello my name is Richard Kuhn, Find me in this lecture!
Then click me for more info about what I discovered.

Click the number between the [ ] to see the related notes.

Objective: 1

Classification of Vitamins [1]

Click on the diagram for more info

- **Water-soluble** [2]
  - **Non-B-complex**
    - Ascorbic acid (Vitamin C)
  - **B-complex**
    - **Energy-releasing**
      - Thiamine (vitamin B1)
      - Riboflavin (vitamin B2)
      - Biotin (vitamin B7)
      - Niacin (vitamin B3)
      - Pantothenic acid (B5)
    - **Hematopoietic**
      - Folic acid
      - Cobalamin (Vitamin B12)
    - **Other**
      - Pyridoxine (vitamin B6)
      - Pyridoxal
      - Pyridoxamine
- **Fat-soluble** [3]
  - Vitamin A (retinol, B-carotenes)
  - Vitamin D (cholecalciferol)
  - Vitamin K (phylloquinones, menaquinones)
  - Vitamin E (tocopherols)

Water-Soluble (B vitamins)

- Thiamin (B_1)
- Riboflavin (B_2)
- Niacin (B_3)
- Pantothenic acid (B_5)
- Pyridoxine (B_6)
- Biotin (B_7)
- Folate (B_9)
- Cobalamin (B_{12})

B Vitamins

Vitamin B complex

- Present in small quantities in different types of food

Vitamin B complex

- Help in various biochemical processes in cell
- Important for growth and good health

Vitamin B complex

- **Function as coenzymes**

Coenzyme: a non-protein compound that is necessary for the functioning of an enzyme.

Water-Soluble Vitamins

- Not significantly stored in the body
- Excess excreted

Water-Soluble Vitamins

- Must be supplied [4] regularly in the diet

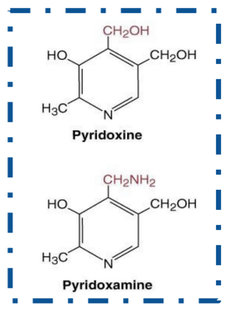
Click the number between the [ ] to see the related notes.

Objective: 1

Don't memorize the structure, just know which form is the biologically active

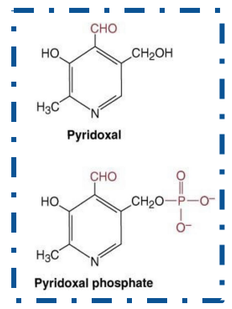
Three forms of Vitamin B6 [5]

Pyridoxine | Pyridoxal [6] | Pyridoxamine



All three forms converted to Active form

Pyridoxal phosphate (PLP)



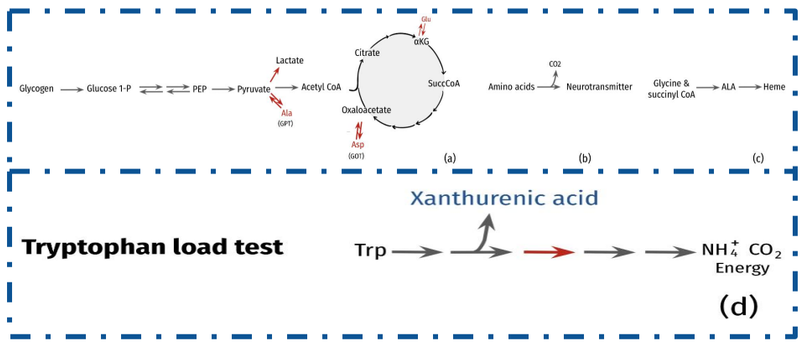
Functions of Vitamin B6

You need to know three things: (substrate , final product , type of reaction).

As coenzyme for: [7]

1. **Condensation reactions**
2. **Decarboxylation**
3. **Transamination**
   Transfer of amino group
4. **Deamination**
   Removal of amino group

[25]



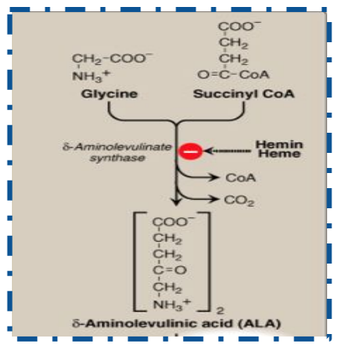
1. Condensation reactions

Formation of ALA by ALA synthase, ALA = AminoLevulinic Acid

The regulatory step in hemoglobin synthesis

Condensation reaction: A reaction in which two or more molecules combine to form a larger molecule, with the simultaneous loss of a small molecule

[8]

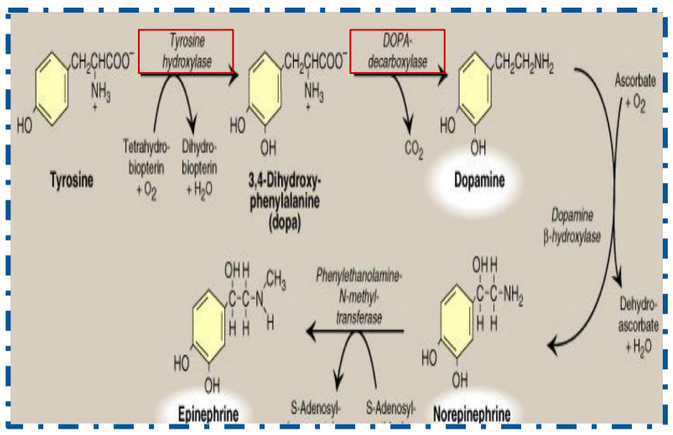


2. Decarboxylation reactions

Removal of CO2 group

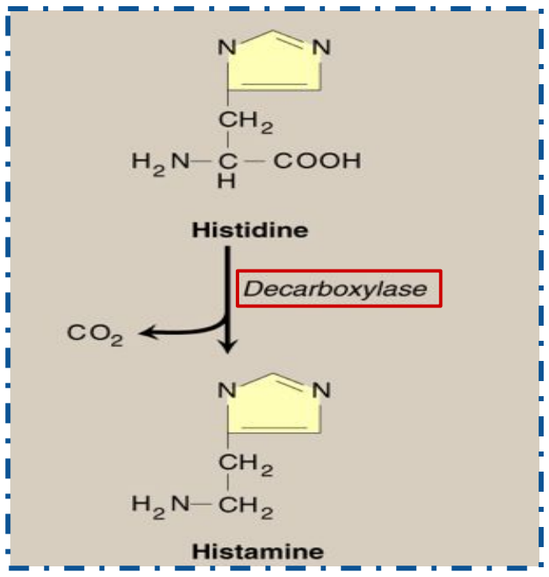
Click on the pictures for more info

Formation of Catecholamines : [9]
Dopamine, norepinephrine and epinephrine

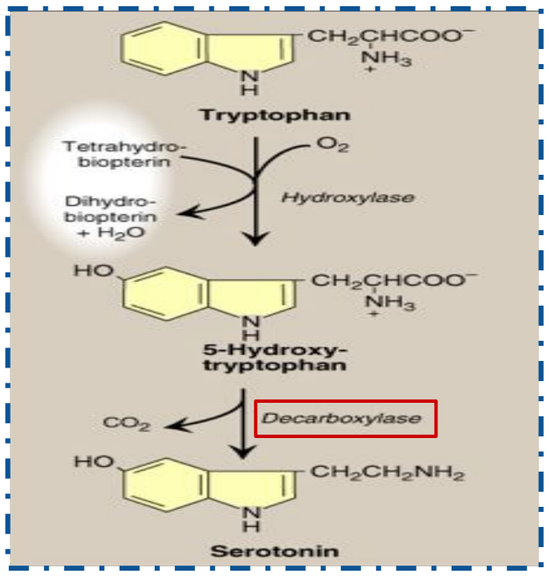


Don't have to memorize the intermediates just know the conversion of tyrosine to dopamine requires a decarboxylase enzyme

Formation of Histamine



Formation of Serotonin

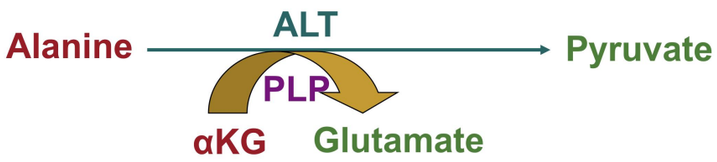


Click the number between the [ ] to see the related notes.

Objective: 2&3

3. Transamination Reaction [10]

-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 (krebs cycle).
-This reaction is catalyzed by ALT "alanine transaminase" which needs PLP.



Disorders of Vitamin B6 deficiency [11]

Dietary deficiency is rare, but it was observed in:
-Newborn infants fed on formulas low in B6 [12]
-Women on oral contraceptives [13]
-Alcoholics

Isoniazid treatment for tuberculosis can lead to vitamin B6 deficiency by forming inactive derivative with PLP [14]

PLP = Pyridoxal phosphate

Deficiency leads to poor activity of PLP-dependent enzymes Causing:
1-Deficient amino acid metabolism [15]
2-Deficient lipid metabolism
3-Deficient neurotransmitter synthesis:
[serotonin, epinephrine, norepinephrine and gamma amino butyric acid (GABA)]

PLP is involved in the synthesis of sphingolipids -> Its deficiency leads to demyelination of nerves and consequent peripheral neuritis

Mild deficiency leads to:
- Irritability
- Nervousness
- Depression

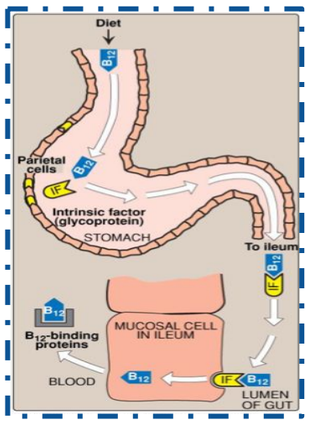
Severe deficiency leads to:
- Peripheral neuropathy
- Convulsions

Vitamin B12 (cobalamin) [16]

Click on the picture for more info

- Mainly found in animal liver bound to protein as **Methylcobalamin** or **5'-deoxyadenosylcobalamin**
- Essential for:
  -Normal nervous system function
  -Red blood cell maturation
- Not synthesized in the body and must be supplied in the diet
- Binds to intrinsic factor (IF: is a protein secreted by cells in the stomach) and absorbed by the ileum.

Intrinsic Factor (IF) has an important role in the absorption of vitamin B12 in the intestine. [27]
تجري عملية امتصاص فيتامين ب12 في المعدة بمساعدة العامل الداخلي الذي يرتبط بجزيئات هذا الفيتامين، ممّا يساعد على امتصاصه في الدم وخلايا الجسم.



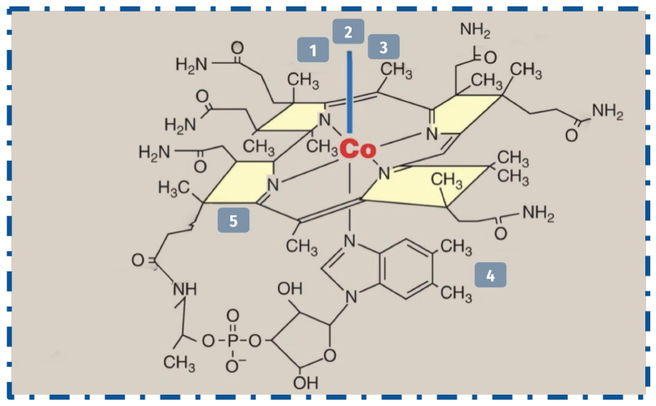
Forms of Vitamin B12	Coenzyme forms of Vitamin B12
Cyanocobalamin [17]	Body can convert other cobalamins into active coenzymes
Hydroxocobalamin [17]	
Adenosylcobalamin (major storage form in the liver)	Adenosylcobalamin and Methylcobalamin[18] (Coenzymes for **metabolic reactions**)
Methylcobalamin (mostly found in blood circulation)	

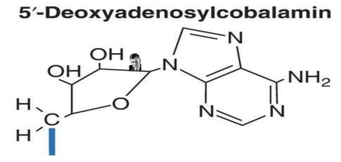
Click the number between the [ ] to see the related notes.

Objective: 3

Forms of Vitamin B12

Click on the picture for more info



1	Methylcobalamin CH_3
2	Cyanocobalamin CN
3	5′-Deoxyadenosylcobalamin 
4	Dimethylbenzimidazole
5	Corrin ring

Vitamin B12 storage

Liver stores vitamin B12 (4-5 mg) [19]

Other B vitamins are not stored in the body

Vitamin B12 Deficiency:

- Vitamin B12 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 [20]

Functions of Vitamin B12

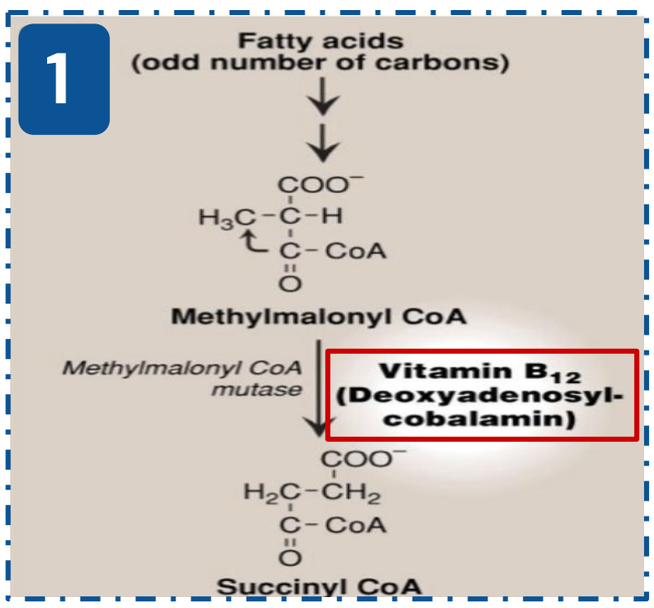
★ **Very important**

Two reactions require B12:

1 Conversion of propionyl-CoA to succinyl-CoA [21]

The enzyme in this pathway, **methyl-malonyl CoA mutase**, requires B12

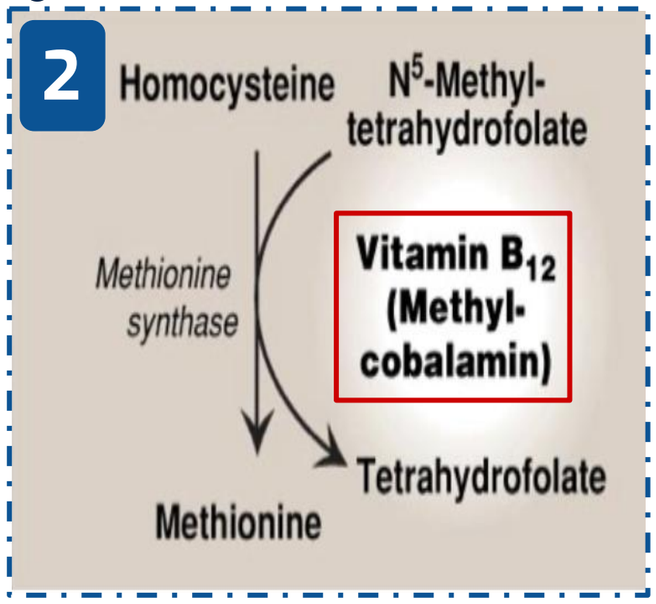
Click on the picture for more info



2 Conversion of homocysteine to methionine [22]

Methionine synthase requires B12 in converting homocysteine to methionine

Click on the picture for more info



Click the number between the [ ] to see the related notes.

Objective: 3

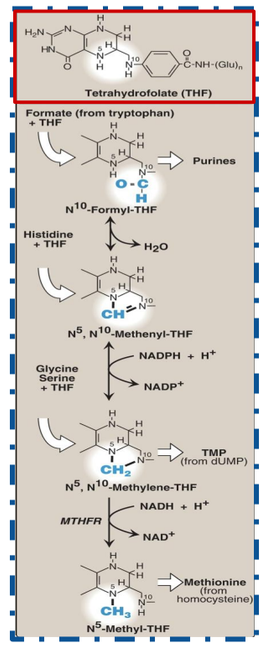
B12 deficiency and folate trap [23]

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 (N^5-methyl TH4) (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 syntheses
TH4: Tetrahydrofolate

Click on the picture for more info



Interconversion between TH4 carrier of "one-carbon units"

Disorders of Vitamin B12 Deficiency

Pernicious anemia

- **Megaloblastic anemia** [26]
- **Vitamin B12 deficiency is mainly due to the deficiency of intrinsic factor**

Demyelination

- Myelin sheath of neurons is [24] chemically unstable and damaged

Neuropathy

- Peripheral nerve damage

Disorders of Vitamin B12 deficiency

Causes of neuropathy	Neurological symptoms	Psychiatric symptoms
• Deficiency of vitamin B12 leads to **accumulation of methylmalonyl CoA.**	• **Paraesthesia (abnormal sensation) of hands and feet** (tangling of hands and feet)	• Confusion and **memory loss**
• High levels of **methylomalonyl CoA** are used instead of malonyl CoA for **fatty acid synthesis.**	• Reduced perception of **vibration** and **position**	• Depression
• **Myelin** synthesized with these **abnormal fatty acids is unstable and degraded causing neuropathy** (due to methyllalonyl CoA)	• Absence of reflexes	• Unstable mood
	• **Unsteady gait** and balance (ataxia)	

Doctors' Notes

Click the note to go back to the related slide

[1] vitamins are coenzymes that are required in body processes such as energy releasing and formation of Heme.

[2] Water soluble vitamins aren't stored and absorbed so they are less likely to cause toxicity except for B12 (stored in liver), they must be supplied in daily diet .

[3] Fat soluble vitamins require fat to be transported and absorbed in the body , it cross the membrane so it's stored in the (liver and adipose tissue), and they are more likely to develop toxicity.

[4] Your body can't synthesize all of these vitamins so you have to obtain them from the diet.

[5] B6 could be obtained from plant sources like pyridoxine, or it could be obtained from animal sources like pyridoxal & pyridoxamine.
Vitamin B6 comes from different sources so it has 3 forms differ in the group

[6] All forms of B6 has to be converted to pyridoxal first then phosphorylated to pyridoxal phosphate (the active form).

[7] from all the reactions you need to know three things: (substrate , final product , type of reaction).

[8] Delta aminolevulinic acid is the first step in the synthesis of heme.

[9] Pyridoxal phosphate is a coenzyme for dopa decarboxylase which is essential for catecholamines synthesis.

[10] Alanine is converted to pyruvate with the help of ALT and Pyridoxal phosphate.

[11] Food is rich in B6 so deficiency is rare.

[12] Newborn infants who drink formulas instead of breast milk might develop deficiency if the formula isn't rich in B6, or they don't have access to food.

[13] Oral contraceptives (OCs) can increase excretion of B6 and poor absorption of the vitamin which leads to a deficiency in the vitamin among females using OCs.

[14] Isoniazid can binds to pyridoxal phosphate and it becomes inactive.

[15] Deficiency in B6 mainly affects metabolism.

[16] VitB12 (cobalamin) named cobalamin because there's cobalt in its structure, B12 can't be absorbed directly, first it binds to R which release the B12 from the protein that's bound with(older ages don't have acidic secretions and R compound so they develop B12 deficiencies) , then it binds intrinsic factor then it reabsorbed from ileum, it's a big molecule with a high molecular weight.

[17] they are commercial drugs found in the pharmacy but can be converted into biological B12

[18] Both adenosylcobalamine and methylcobslamine are present in liver and blood, but adenosylcobalamine is more abundant in liver, and methylcobalamine is more abundant in blood.

[19] we need B12 in micrograms and the liver stores 4-5 mg so it's enough for 3-5 years, a deficiency won't produce any symptoms for years.

[20] patients with **total** gastroctomy can develop symptoms of B12 deficiencies in months.

[21] B12 involved in the degradation of fatty acids containing odd number of carbon to convert it into propionyl CoA into methylmalonyl CoA which's then converted into succinyl-CoA (the last step requires methylmalonyl CoA mutase which requires B12), **without vit B12 there'll be methylmalonyl CoA accumulation and Succinyl Coa deficiency.**

Doctors' Notes

Click the note to go back to the related slide

[22] the only way for N5 methyltetrahydrofolate to be converted to THF (Tetra Hydro Folate) is with the help of B12 in the conversion of homocysteine to methionine, which is why a deficiency in B12 can lead to a folate deficiency in THF, THF isn't actually deficient it's trapped so it can't be used by the body this is called Folate trap.

[23] in this part you just have to know:

- Tetrahydrofolate is the functional form of folic acid.
- N10-formyl-THF is the form of folic acid that is required in purine synthesis.
- N5-N10-methylene-THF is the form of folic acid that is required for thymidine synthesis.
- N5-methyl-THF is the form of folic acid that is required for methionine synthesis.
- **N5-methyl-THF is the form of folic acid that is accumulated during folate trap. Imp**
- N10-formyl-THF & N5-N10-methylene-THF are deficient in case of tetrahydrofolate deficiency.

So folic acid has:

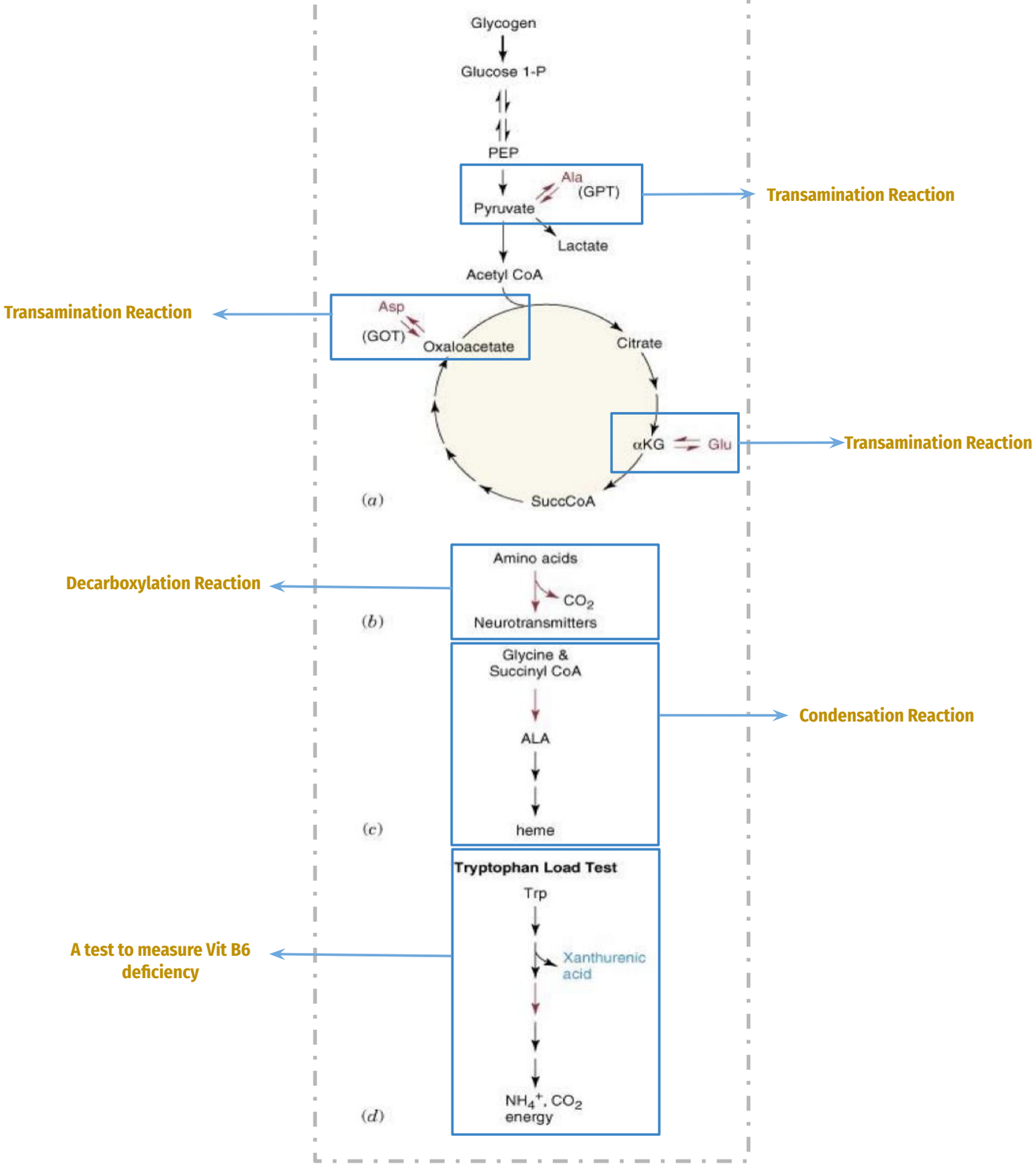
1- 4 functional forms.

2- 1 form accumulated in folate trap.

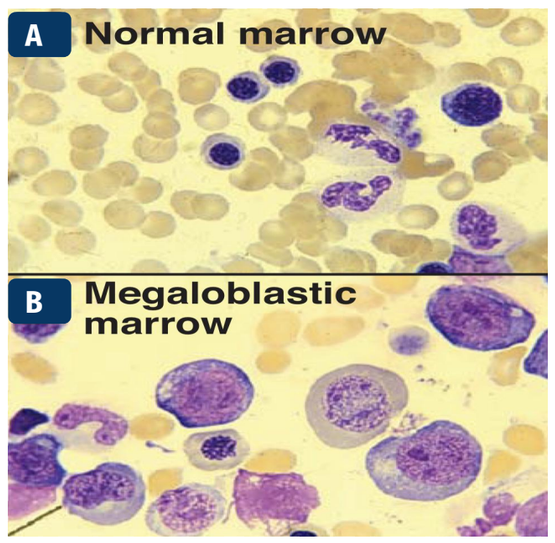
3- 2 forms are deficint in tetrahydrofolate deficiency.

[24] B12 maintains the myelin sheath.

[25]



[26] Extra



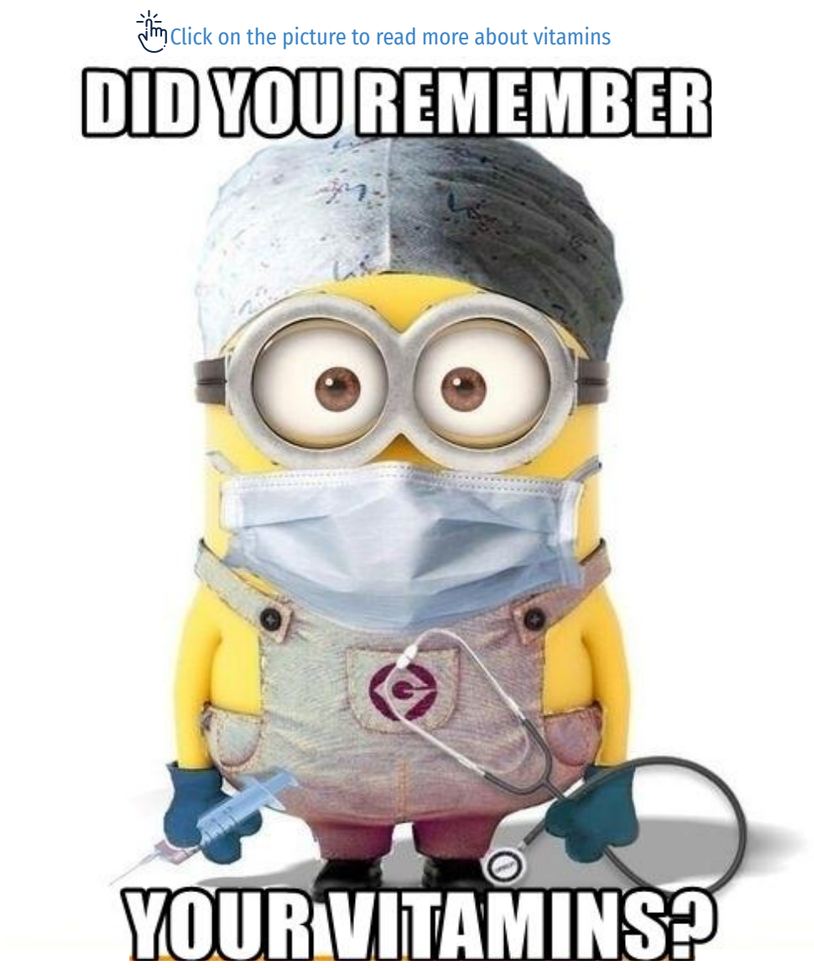
[27]

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**

Click on the picture to read more about vitamins



Summary

Vitamins

Water soluble

Cobalamin (B12)

Forms

1- Cyanocobalamin
2- Hydroxycobalamin
3- Adenosylcobalamin (Active form)
4- Methylcobalamin (Active form)

Function

1- Normal nervous system function and red blood cell maturation
2- Coenzyme for:
A- Conversion of propionyl-CoA to succinyl-CoA
B- Conversion of homocysteine to methionine

Storage

B12 in the liver Other B vitamins are not stored in the body

Deficiency

Folate Trap

Leads to:
1- Pernicious anemia
2- Demyelination
3- Neuropathy

Thiamin (B1)

Riboflavin (B2)

Niacin (B3)

Pantothenic acid (B5)

Folate (B9)

Deficiency

Leads to:
1- Poor activity of PLP-dependent enzymes
2- Sphingolipids deficiency
Severe:
1- Peripheral neuropathy
2- Convulsions
Mild:
1- Irritability
2- Nervousness
3- Depression

Function

Coenzyme for:
1- Transamination
2- Deamination
3- Decarboxylation
4- Condensation reactions

Pyridoxine (B6)

Forms

1- Pyridoxine
2- Pyridoxal
3– Pyridoxamine

Active form:
pyridoxal phosphate (PLP)

Lipid soluble (AKED)

Mnemonic

The Ronaldo Nd Paolo Played for Biochester Football Club

B1 - Thiamine B2 - Riboflavin B3 - Niacin B5 - Pantothenic acid B6 - Pyridoxine B7 - Biotin B9 - Folic acid B12 - Cobalamin

MCQs

1-which of the following vitamins known as cobalamin:
A- vit B6
B- vit B2
C-vit B12
D- vit B2

2-A 57 year old man post gastrectomy developed loss of joint position and vibration. What is the most probable diagnosis?
A- IDA
B- Cobalamin deficiency
C- Folic acid deficiency
D- Vit B6 deficiency

3-Vitamin B12 bound to protein as:
A-Methylcobalamin
B-Cyanocobalamin
C-5'-deoxyadenosylcobalamin
D-Both A & C

4-The major storage form of vitamin B12 in the liver:
A-Hydroxocobalamin
B-Methylcobalamin
C-Adenosylcobalamin
D-Cyanocobalamin

5-Formation of histamine is a ..... reaction?
A-Condensation
B-Decarboxylation
C-Transamination
D-Deamination

6-Mild deficiency of Pyridoxine leads to which of the following?
A-Convulsions
B-Irritability
C-Peripheral neuropathy
D-Both A & C

Answers key

1- C 2- B 3- D 4- C 5- B 6- B

🧠 SAQs

1- What are The two reactions that require vitamin B12?

Conversion of:
- homocysteine to methionine (Methionine synthase)
- propionyl-CoA to succinyl-CoA (methylmalonyl-CoA mutase)

2- Mentions 2 neurological & psychiatric symptoms of vitamin B12 deficiency.

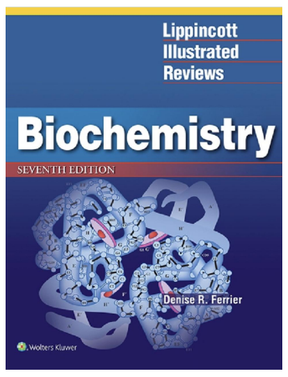
- Neurological symptoms:
  1- Paraesthesia of hands and feet
  2- Reduced perception of vibration & position
  3- Absence of reflexes
  4- Unsteady gait and balance (ataxia).
- Psychiatric symptoms:
  1- Confusion & memory loss
  2- Depression, Unstable mood.

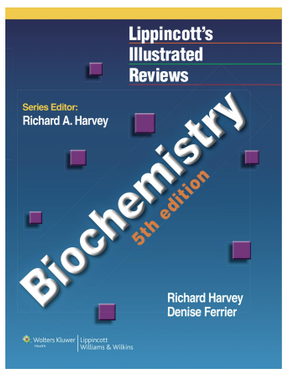
3- List some of the mild and severe manifestations of pyridoxine deficiency?

- In mild cases:
  1- irritability
  2- nervousness and depression.
- In severe cases:
  1- Peripheral neuropathy
  2- convulsions

Resources

Click on the book to download the resource





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Special thanks to Fahad AlAjmi for designing our team's logo.