Amino Acid Metabolism & Urea Cycle

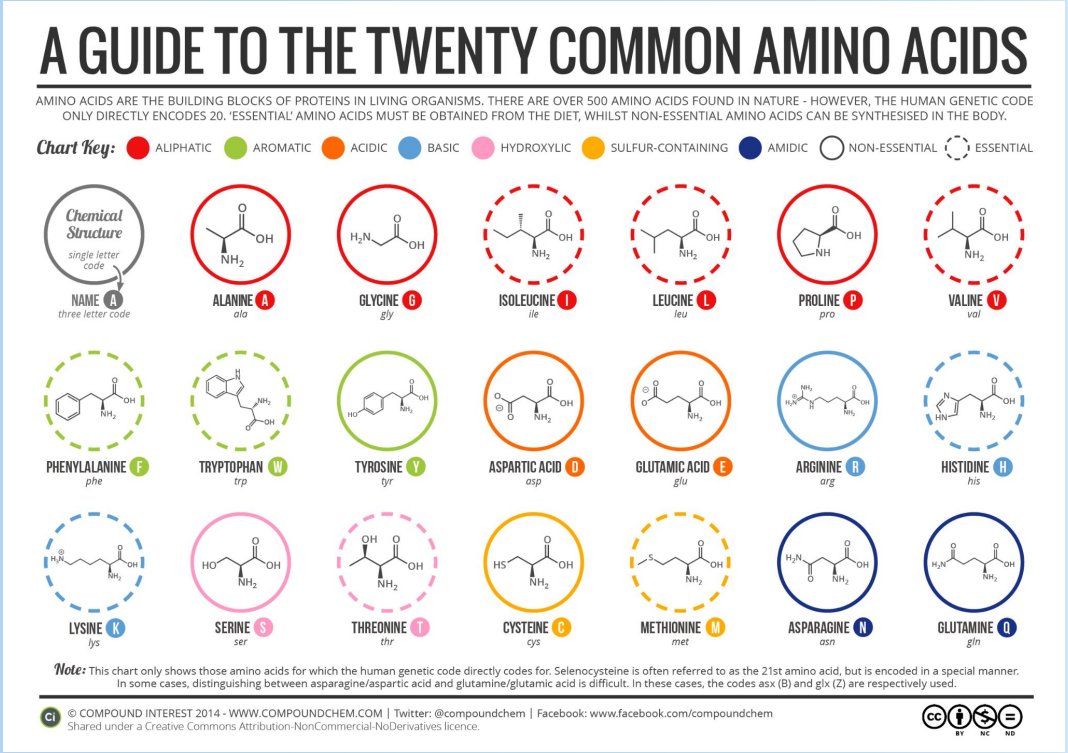
Karolina Orocz

Amino acid metabolism

Table of contents

Amino acid classifications

Amino acid structures



Essential vs non-essential amino acids

10 essential amino acids: “PVT TIM HALL”

- PVT:
  - Phenylalanine
  - Valine
  - Tryptophan
- TIM:
  - Threonine
  - Isoleucine
  - Methionine
- HALL:
  - Histidine
  - Arginine
  - Leucine
  - Lysine

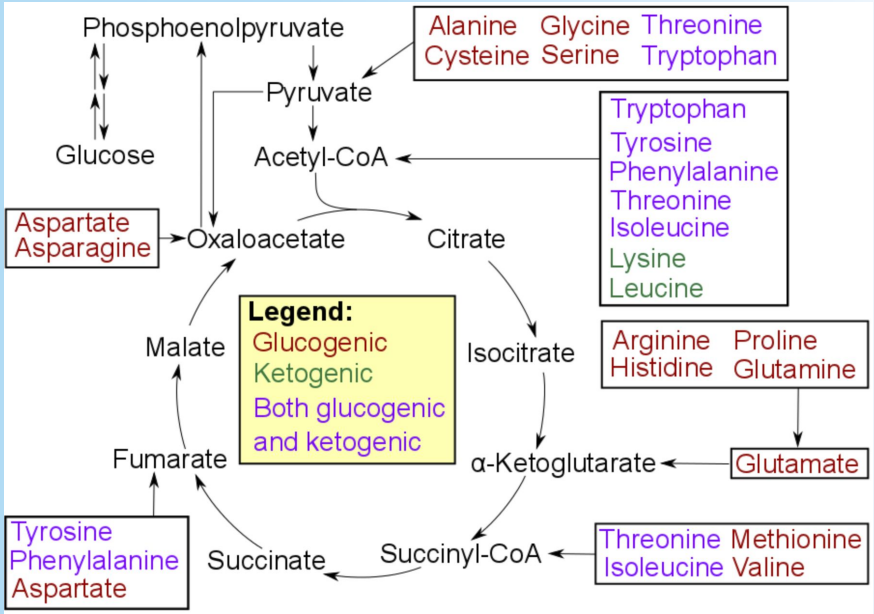
Glucogenic vs ketogenic amino acids

Glucogenic:

Can be converted into glucose via gluconeogenesis

Ketogenic:

Can be converted into acetyl-CoA in order to make ketone bodies



https://en.wikipedia.org/wiki/Glucogenic_amino_acid#/media/File:Amino_acid_catabolism_revised.png

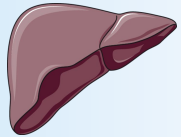
Ketogenic a.a: “Ls”	BOTH: “PITTT”	Gluconeogenic a.a:
Leucine Lysine	Phenylalanine Isoleucine Tyrosine Tryptophan Threonine	Everything else

General amino acid catabolism

Definitions:

1) **Transamination:** Transfer of an amino group from an amino acid
2) **Deamination:** Removal of an amino group from an amino acid, resulting with ammonia as a byproduct
3) **Urea cycle**: Neutralizes ammonia to be excreted as urea

All occurs in the liver!



Transamination

↓

Deamination

↙ **Oxidative**

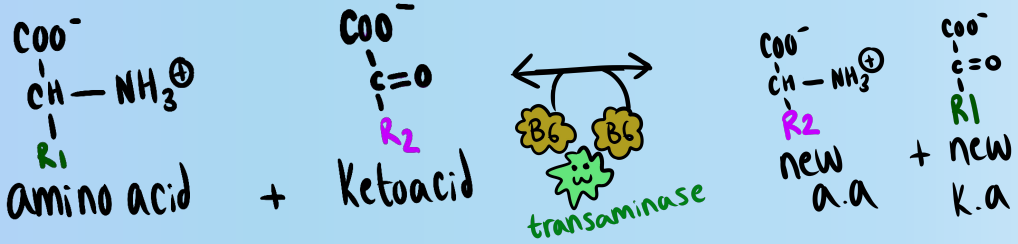
↘ **Non-oxidative**

↘ ↙

Urea cycle

Transamination

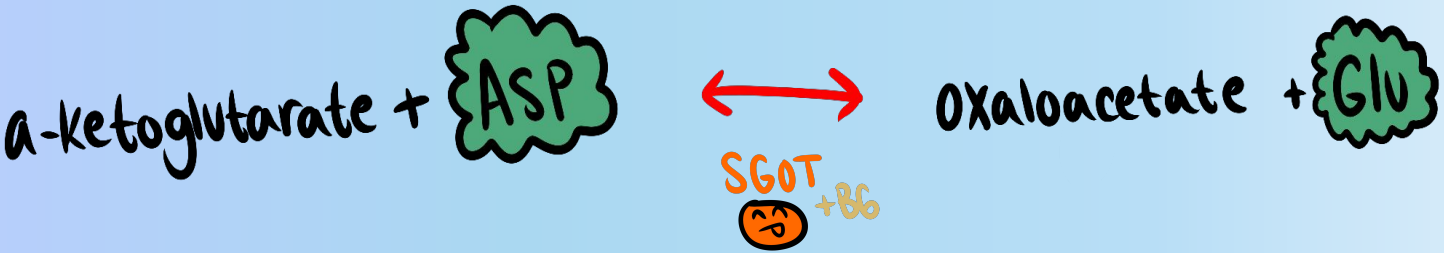
- Transferring an amino acid's amino group (NH3+) to its partner keto acid to make a new amino acid
- Done via aminotransferases/transaminases
  - Vitamin B6 (PLP/pyridoxine) dependent
- Main focus: Make glutamate (especially will be important for oxidative deamination)

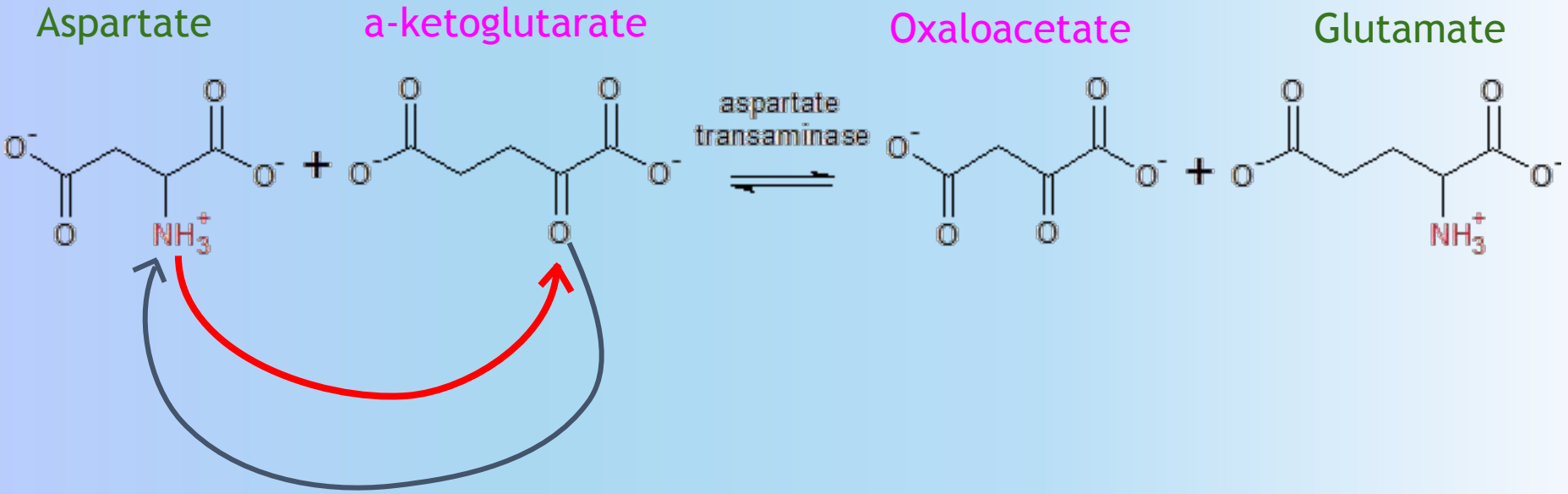


Examples of transamination

Serum glutamic oxaloacetic transferase (SGOT):

- Aka aspartate transferase (AST)
- Liver enzyme: Found in the hepatocyte cytosol and mitochondria

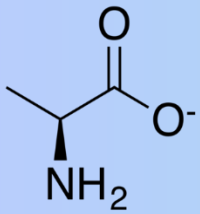




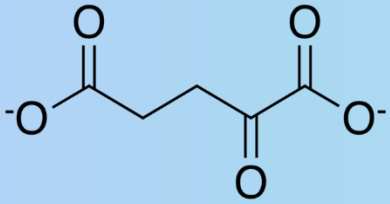
https://en.wikipedia.org/wiki/Aspartate_transaminase#/media/File:Aspartate_aminotransferase_reaction.png

Serum glutamic pyruvic transferase (SGPT):

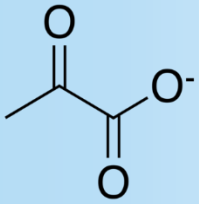
- Aka alanine transferase (ALT)
- Liver enzyme: Found in the hepatocyte cytosol



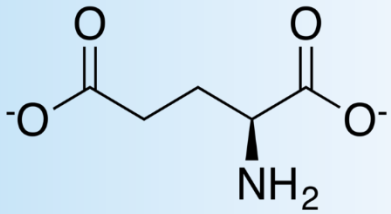
Alanine



a-ketoglutarate



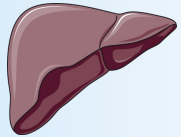
Pyruvate



Glutamate

https://en.wikipedia.org/wiki/Alanine_transaminase#/media/File:Alanine_transaminase.png

All occurs in the liver!



Transamination

Deamination

Oxidative

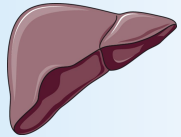
Non-oxidative

Urea cycle

Deamination

- Removal of an amino group from an amino acid
- Results in the release of ammonia
  - Ammonia is toxic, so must be neutralized via the urea cycle
- Occurs primarily in the liver, but also some in the kidney
- Two types:
  - Oxidative
  - Non-oxidative

All occurs in the liver!



Transamination

Deamination

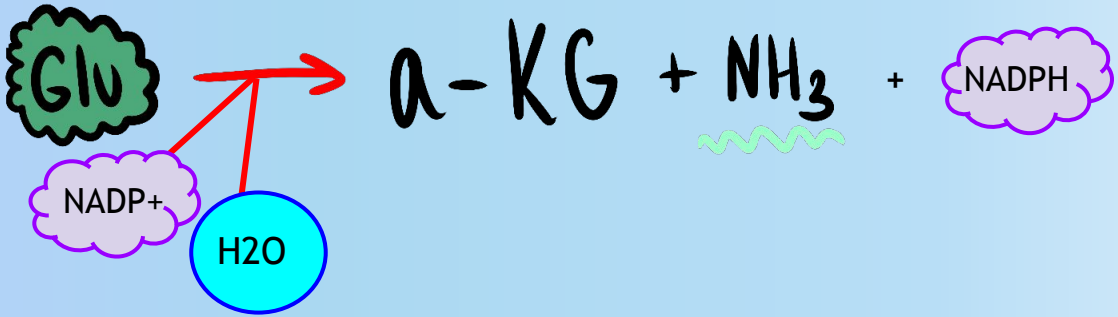
Oxidative

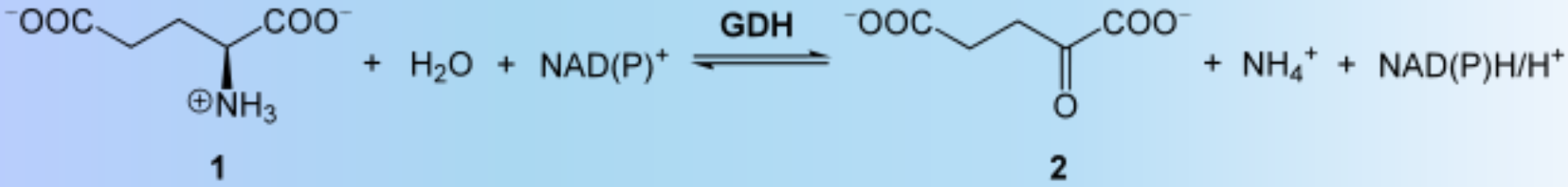
Non-oxidative

Urea cycle

Oxidative deamination

- Occurs with glutamate
- Oxidative: Glutamate donates a H+ to NADP+
- Enzyme: Glutamate dehydrogenase
- Products: alpha-ketoglutarate (keto acid), ammonia, & NADPH



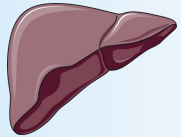


Glutamate

a-ketoglutarate

https://commons.wikimedia.org/wiki/File:Glutamate_dehydrogenase_reaction.svg

All occurs in the liver!



Transamination

Deamination

Oxidative

Non-oxidative

Urea cycle

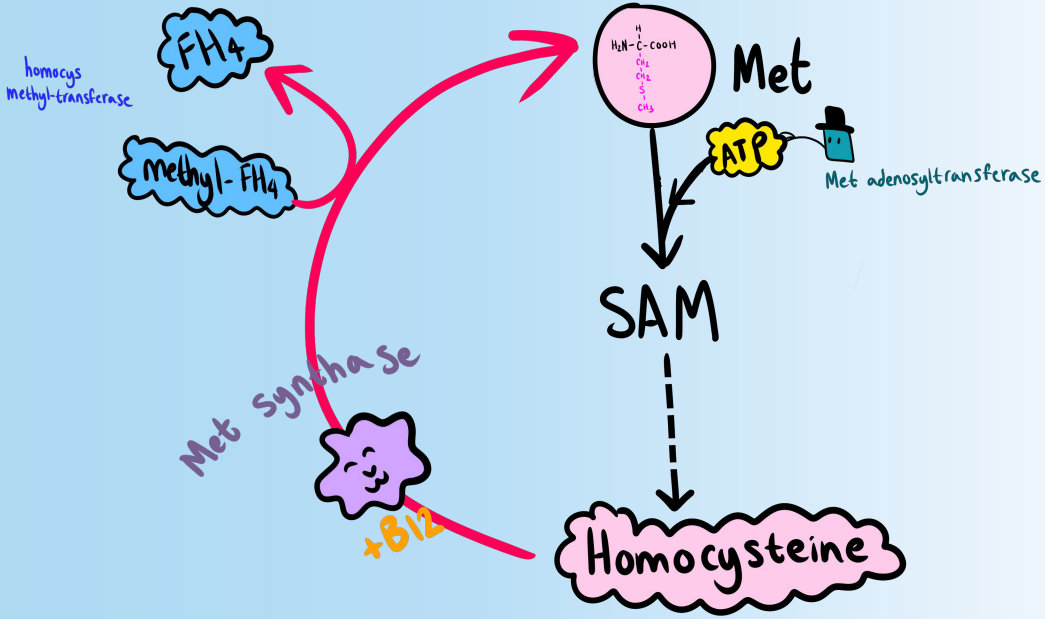
Non-oxidative deamination

- Non-Oxidative: No donation of H+ is involved
- Serine:
  - Enzyme: Serine dehydratase/deanimase
  - Vitamin B6 (PLP/pyridoxine) dependent
- Threonine:
  - Enzyme: Threonine dehydratase/deanimase
  - Vitamin B6 (PLP/pyridoxine) dependent
- Products: Ammonia, a keto acid, and water

Specific amino acid metabolisms & correlated diseases

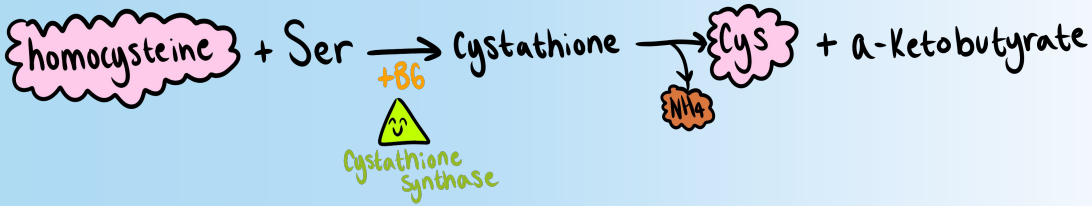
Methionine

- Methionine: sulfur-containing, essential amino acid
- Methionine makes homocysteine, and homocysteine can be converted back into methionine
- SAM: S-adenosylmethionine
- Methionine synthase requires vitamin B12 (cobalamin)
    - During methionine synthase reaction, a methyl group is taken from methyl-FH4 and given to homocysteine; this results in FH4 (aka THF/tetrahydrofolate) as a byproduct

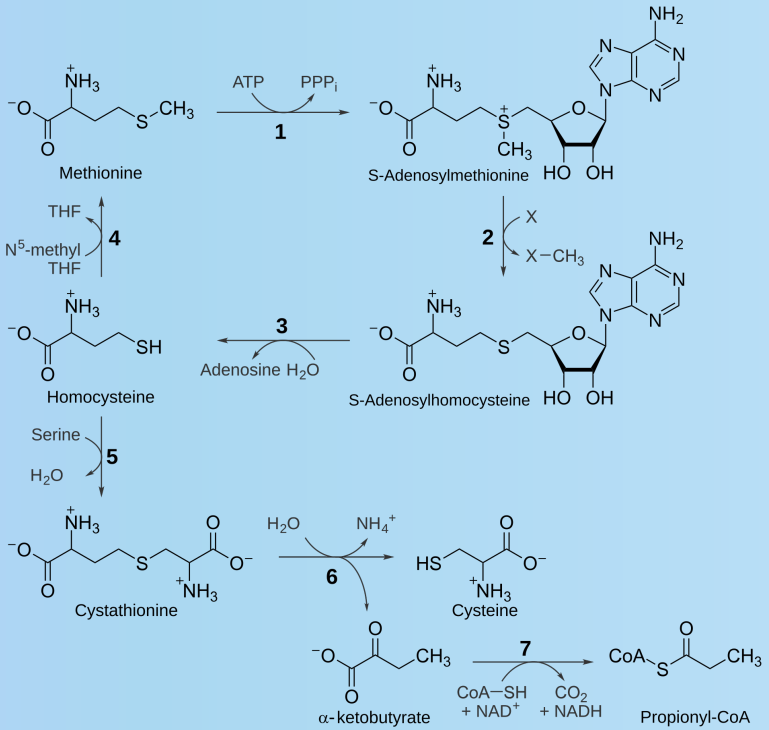


Homocysteine

- Homocysteine can be converted into cystathionine and cysteine
- Cystathionine synthase is vitamin B6 (PLP/pyridoxine) dependent
- Cysteine: Sulfur-containing, non-essential amino acid

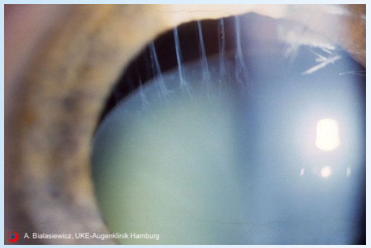


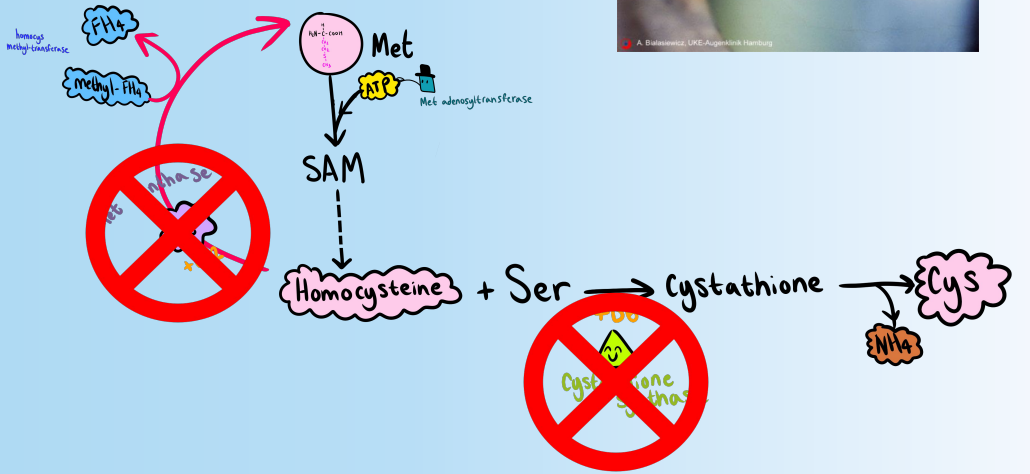
Methionine & homocysteine metabolism



Clinical correlation: Homocystinuria

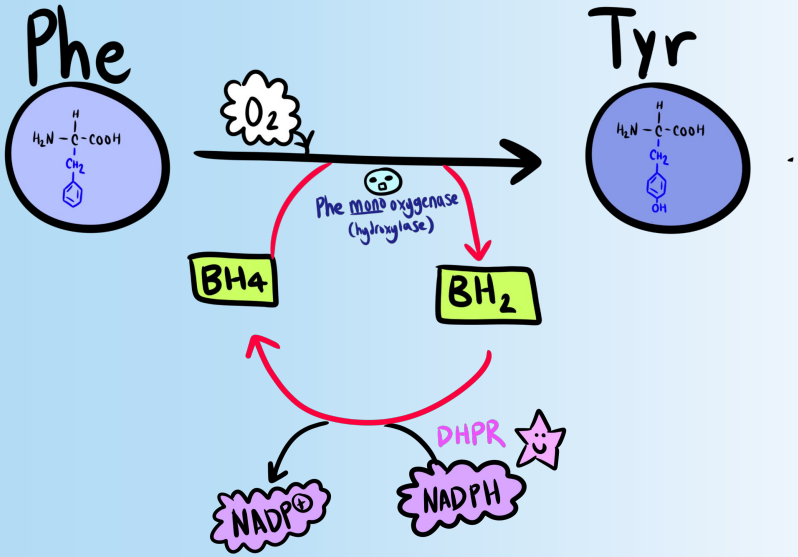
- **General:**
  - Deficiency of methionine synthase or cystathionine synthase
  - Homocysteine build up in blood & urine
- **Symptoms:**
  - Lens dislocation
  - Marfanoid habitus: Long limbs, pectus excavatum, etc…
  - Intellectual disability
- **Tx:**
  - Restriction of methionine intake
  - B6, B12, and/or folate supplementation





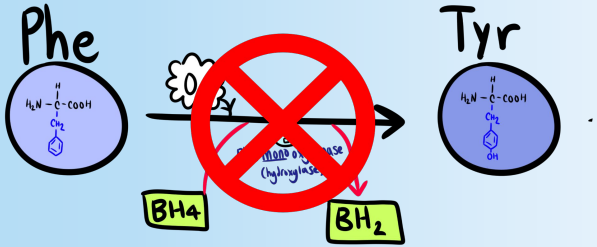
Phenylalanine

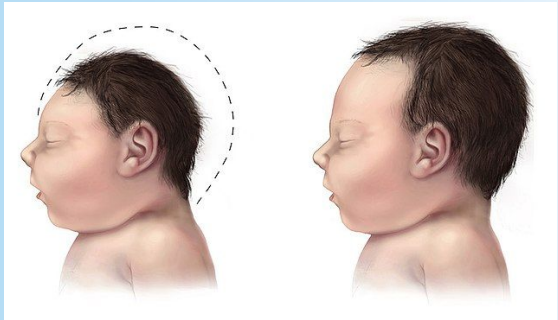
- Phenylalanine: Aromatic, essential amino acid
- Phenylalanine can be converted into tyrosine
- Phenylalanine monooxygenase/hydroxylase is tetrahydrobiopterin (BH4) dependent
- BH4 is regenerated by the help of dihydropteridine reductase (DHPR)



Clinical Correlation: Phenylketonuria (PKU)

- **General:**
  - Deficiency of phenylalanine monooxygenase/hydroxylase
  - Can range from mild to severe deficiency
  - Phenylalanine gets converted into phenylpyruvate (acid) instead of tyrosine
  - Phenylalanine/phenylpyruvate build up in blood and urine
- **Symptoms:**
  - Musty urine odor
  - Less skin pigment: due to less tyrosine
  - Severe intellectual disability, developmental delay, microcephaly
- **Tx:**
  - Lifelong restriction of Phe

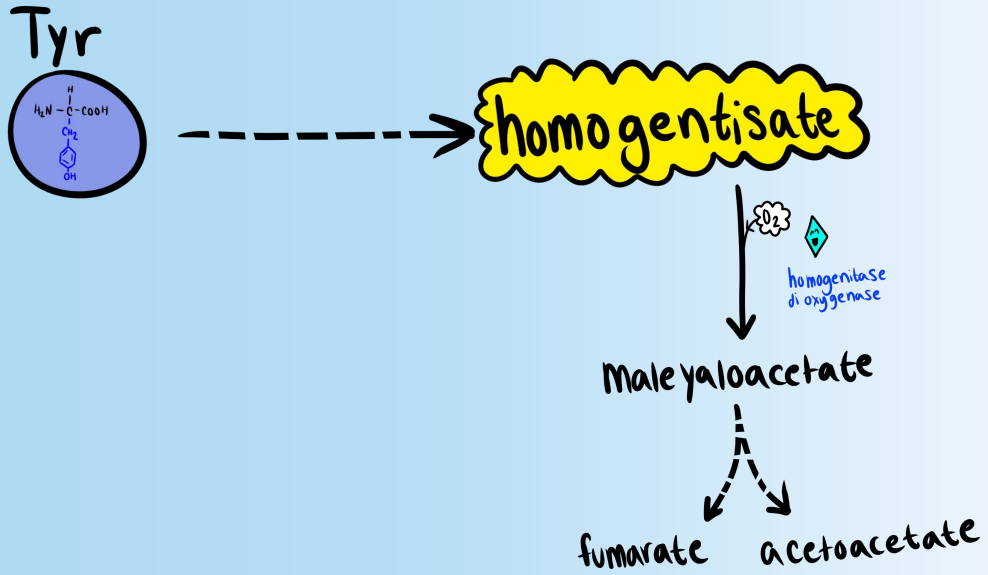




https://www.cdc.gov/ncbddd/birthdefects/images/microcephaly-comparison-500px.jpg

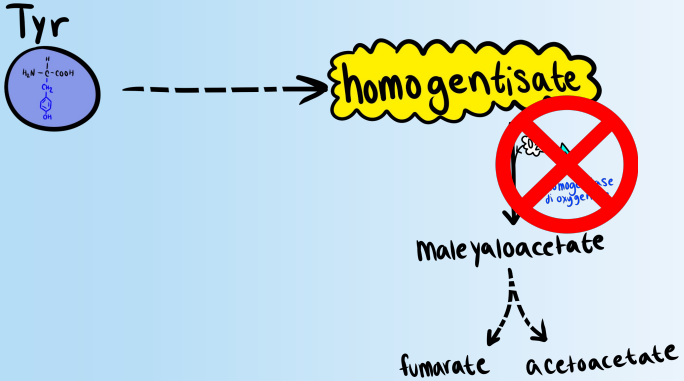
Tyrosine

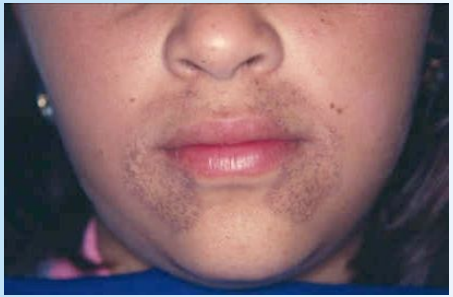
- Tyrosine: Aromatic, non-essential amino acid
- Homogentisate/homogentisic acid: intermediate catabolite of tyrosine & phenylalanine
- Homogentisate dioxygenase: converts homogentisate into maleylacetoacetate, which is later converted into fumarate & acetoacetate



Clinical Correlation: Alkaptonuria

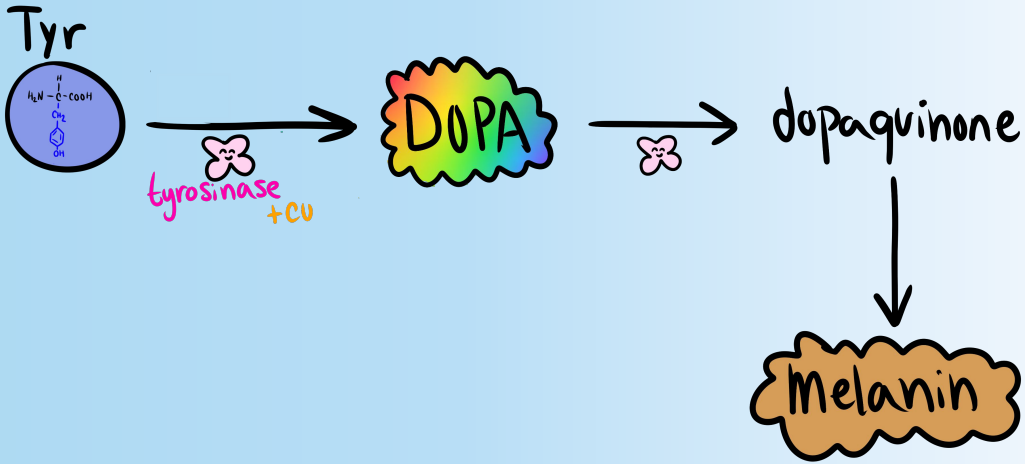
- **General:**
  - Deficiency of homogentisate dioxygenase
  - Homogentisate & tyrosine buildup in blood & urine
  - Majority of symptoms start ~ age 40
- **Symptoms:**
  - Black, spotted pigment on skin and eyes
  - Black urine (due to aciduria)
  - Large joint arthritis
- **Tx:**
  - Restriction of tyrosine and phenylalanine





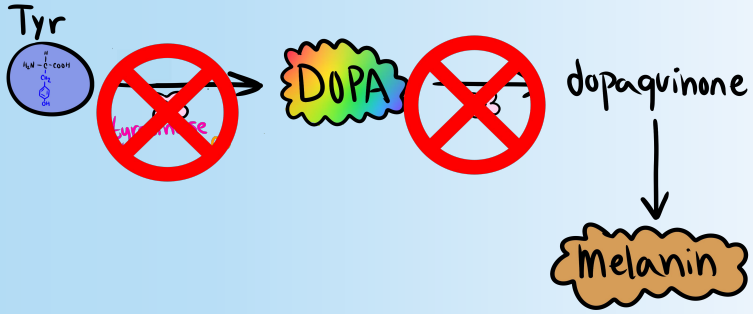
Tyrosine

- Tyrosine makes melanin, a oligomer/polymer that provides pigment for skin and hair
- Enzyme: tyrosinase
    - Is copper dependent



Clinical Correlation: Albinism

- **General:**
  - Deficiency of tyrosinase
  - Little or lack of melanin
  - Inheritance: AR or X-linked
    - AR: Oculocutaneous & some ocular albinism types
    - X-linked: ocular albinism
- **Symptoms:**
  - Loss of skin, hair, & eye pigmentation
  - Vision defects
  - Increased risk of skin cancer

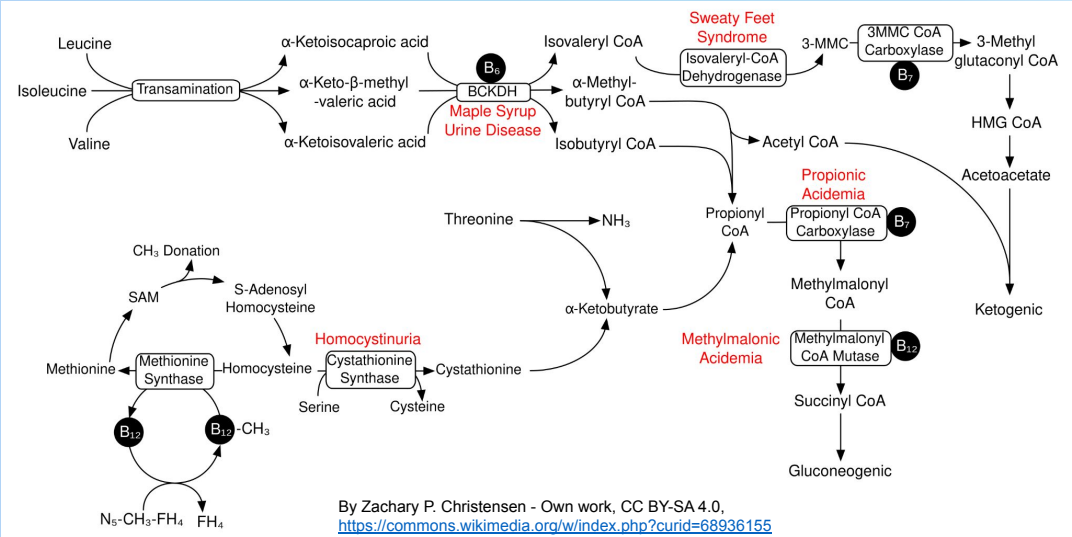


Karen Grønskov, Jakob Ek, and Karen Brondum-Nielsen: Oculocutaneous albinism Orphanet J Rare Dis. 2007; 2: 43. doi: 10.1186/1750-1172-2-43.

BCAAs

- Leucine, Isoleucine, Valine: Essential amino acids with an aliphatic side chain (only contains **H** or **C**)
- Are predominantly metabolized in the liver and skeletal muscles
- Products are substrates that can be used in the Krebs cycle (directly or indirectly)

BCAA: "I love Bailey's"	Product
Isoleucine	Acetyl-CoA, Propionyl-CoA/Succinyl-CoA
Leucine	Acetyl-CoA, Acetoacetate
Valine	Propionyl-CoA/Succinyl-CoA



By Zachary P. Christensen - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=68936155

Clinical Correlation: Maple Syrup Urine Disease

- **General:**
  - Deficiency of BCKA dehydrogenase (BCKD)
  - BCAAs & BCKAs build-up in the blood & urine
  - Inheritance: AR
- **Symptoms:**
  - In Classic MSUD, onset of symptoms within 48 hrs of birth
  - Ketoacidosis
  - Neurotoxicity
  - “Maple syrup” odor of urine
  - Fatal if not treated
- **Tx:**
  - Restriction and close monitoring of BCAAs

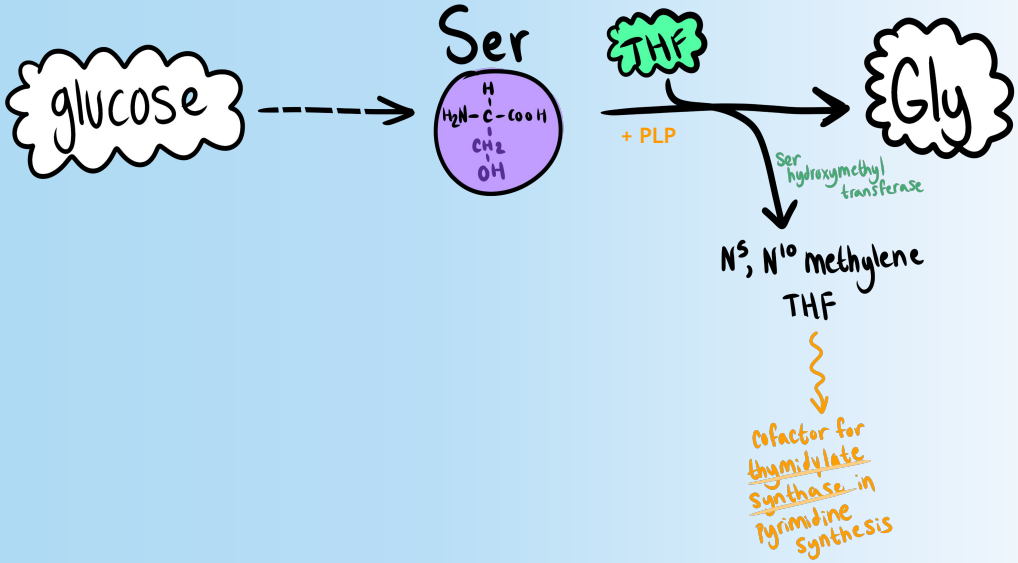
Summary

Disorder:	Cause:	Main symptoms:
Homocystinuria	- Deficiency of methionine synthase or cystathionine synthase - Buildup of homocysteine	- Lens dislocation - Marfanoid habitus - Intellectual disability
Phenylketonuria	- Deficiency of Phenylalanine monooxygenase/hydroxylase - Buildup of phenylalanine and its metabolites	- Musty urine odor - Fair skin & hair - Intellectual disability
Alkaptonuria	- Deficiency of homogentisate dioxygenase - Buildup of homogentisic acid	- Black spots on skin & eyes - Black urine when exposed to air - Arthritis
Albinism	- Deficiency of tyrosinase - Lack of melanin	- Loss of pigmentation - Vision defects - Increased risk of skin cancer
Maple syrup urine disease	- Deficiency of BCKA dehydrogenase - Buildup of BCAA and BCKAs	- Acidosis - Sweet urine odor - Neurotoxicity

Extra amino acid metabolisms

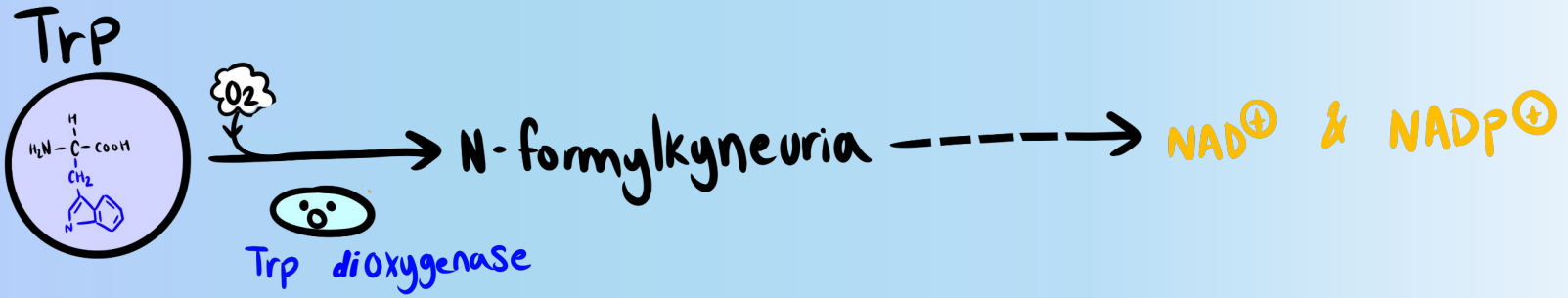
Serine

- Serine: Hydroxylic (-OH), non-essential amino acid
- Gluconeogenic molecule
- Can be converted into glycine
- Enzyme: Serine hydroxymethyl transferase
    - Dependent on Vitamin B6 (PLP/pyridoxine)

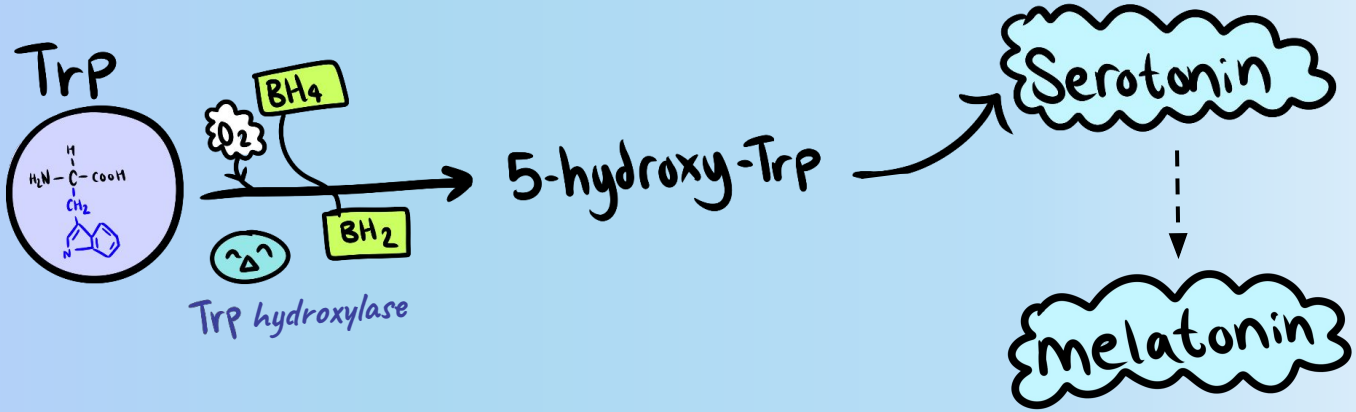


Tryptophan

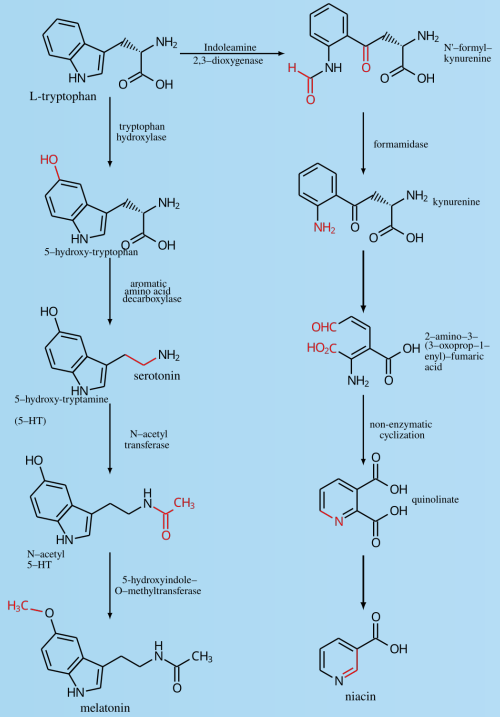
- Tryptophan: Aromatic, essential amino acid
- Tryptophan makes NAD & NADP
- Enzyme: Tryptophan dioxygenase



- Tryptophan makes serotonin & melatonin
- Enzyme: Tryptophan hydroxylase
    - Dependent on BH4 (tetrahydrobiopterin)



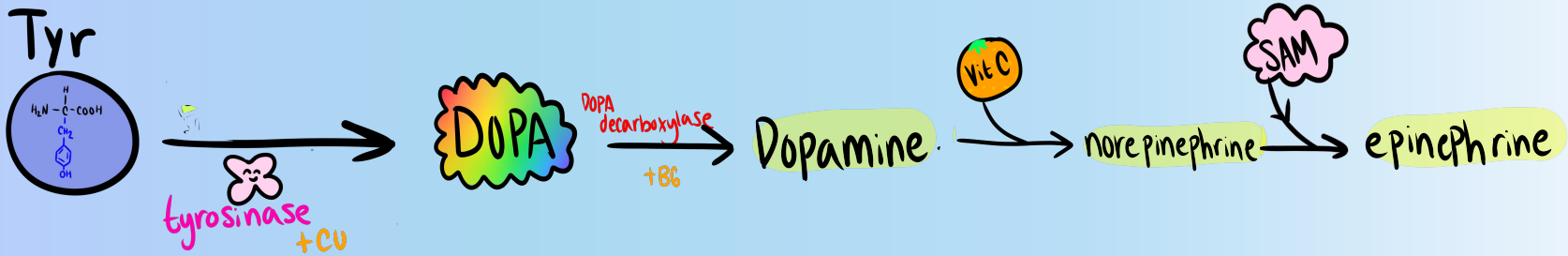
Tryptophan metabolism



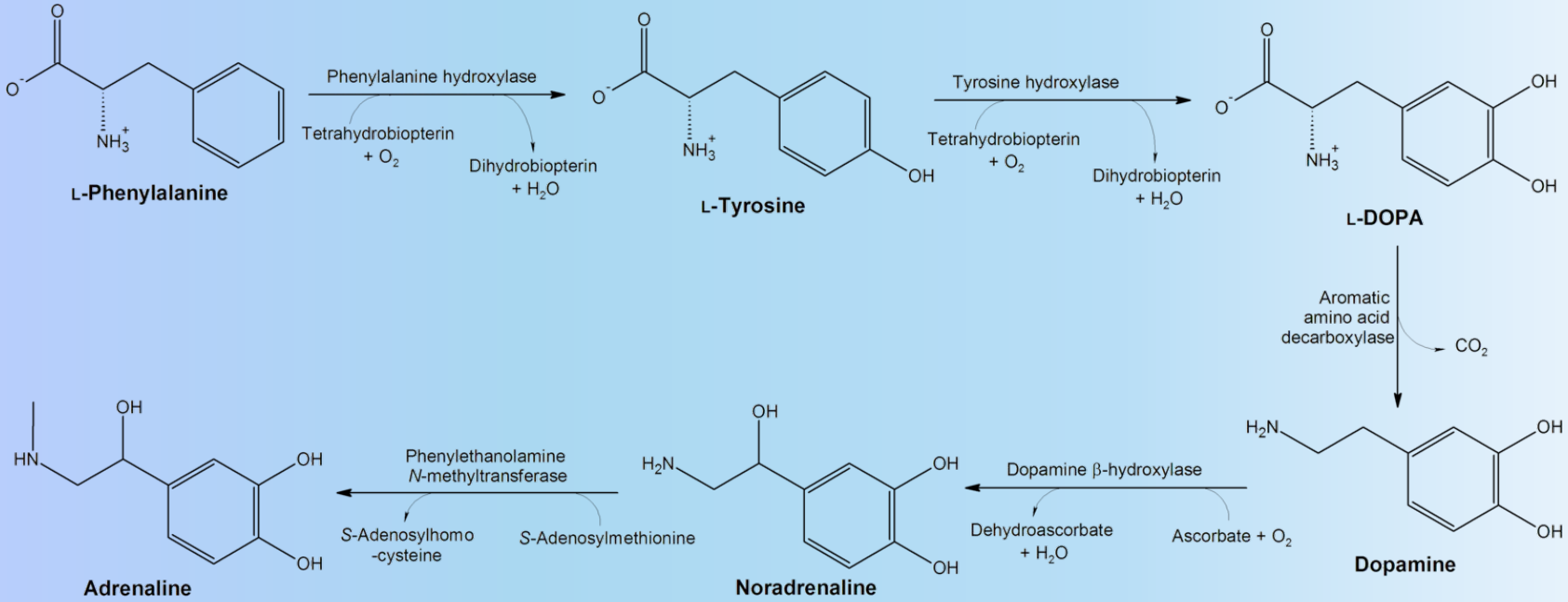
https://en.wikipedia.org/wiki/Tryptophan#/media/File:Tryptophan_metabolism.svg

Tyrosine

- Tyrosine: Aromatic, non-essential amino acid
- Tyrosine makes dopamine, norepinephrine, and epinephrine
- Dopamine & norepinephrine: neurotransmitters
    - Parkinson's disease: loss of dopamine-producing neurons in substantia nigra
    - Norepinephrine synthesis requires vitamin C
        - Scurvy: vitamin C deficiency
- Epinephrine: adrenal hormone involved in the sympathetic nervous system
    - Synthesis of epinephrine requires SAM (same SAM as in the methionine-homocysteine cycle)



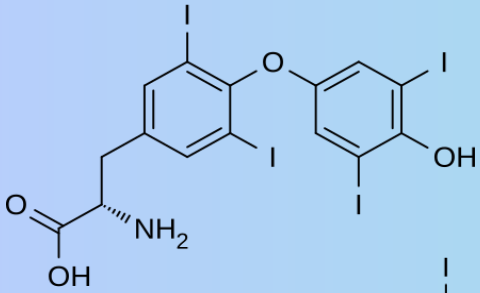
Phenylalanine/tyrosine metabolism



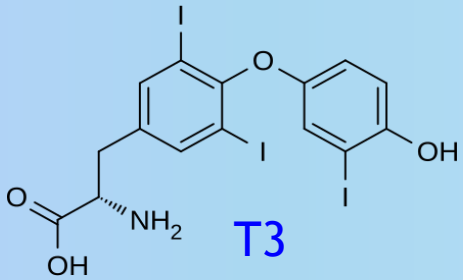
https://en.wikipedia.org/wiki/Tyrosine#/media/File:Conversion_of_phenylalanine_and_tyrosine_to_its_biologically_important_derivatives.png

Tyrosine

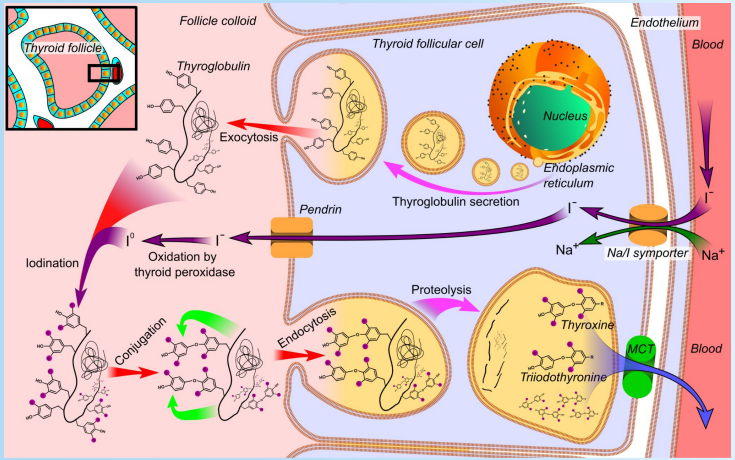
- Tyrosine makes thyroid hormones
- Thyroglobulin: Carries tyrosine, in which tyrosines are then partnered with iodine to make thyroid hormones



T4



T3

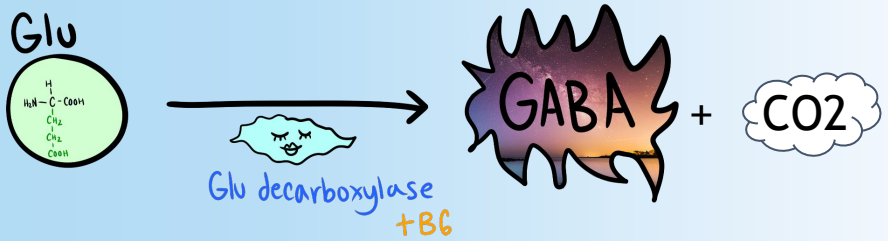


https://en.wikipedia.org/wiki/File:Thyroid_hormone_synthesis.png

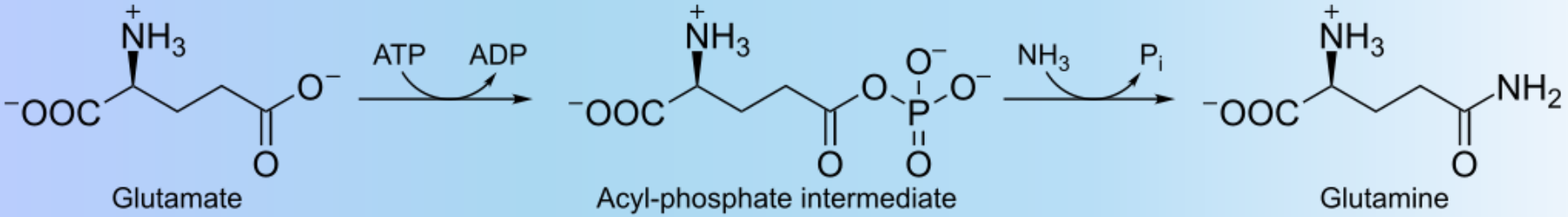
studyaid

Glutamate

- Glutamate: Acidic, non-essential amino acid
- Glutamate makes GABA
- GABA:
  - AKA y-aminobutyric acid
  - Inhibitory neurotransmitter in the central nervous system (CNS)
- Enzyme: Glutamate decarboxylase
  - Vitamin B6 (PLP/pyridoxine) dependent



- Glutamate can be converted into glutamine by adding a NH3+ to glutamate
- Enzyme: glutamine synthetase
- Especially important for uptaking excess ammonia (NH3) in astrocytes in the brain



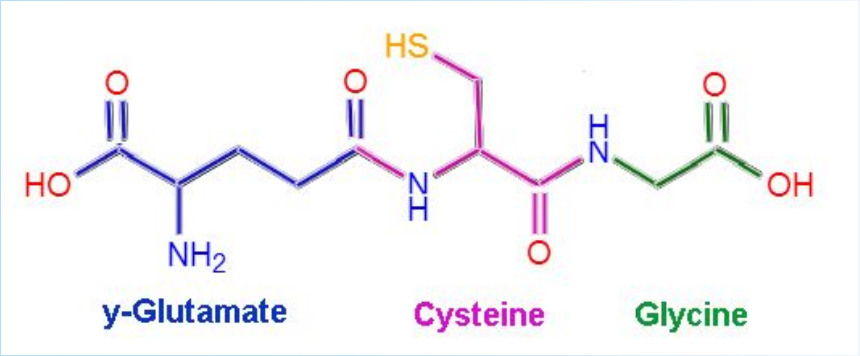
https://commons.wikimedia.org/wiki/File:Glutamine_synthetase_reaction.svg

Glutathione

- Glutathione:
  - Antioxidant
  - Re-oxidizes reduced glutathione in order to convert H2O2 (a reactive oxygen species) into H2O
- Glutamate + cysteine + glycine yields glutathione

Glu + Cys + Gly = glutathione

"γ-glutamylcysteinylglycine"

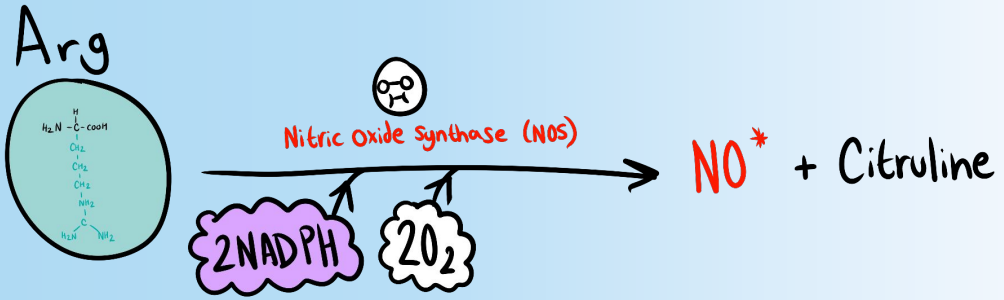


https://commons.wikimedia.org/wiki/File:Glutathione_structure.png

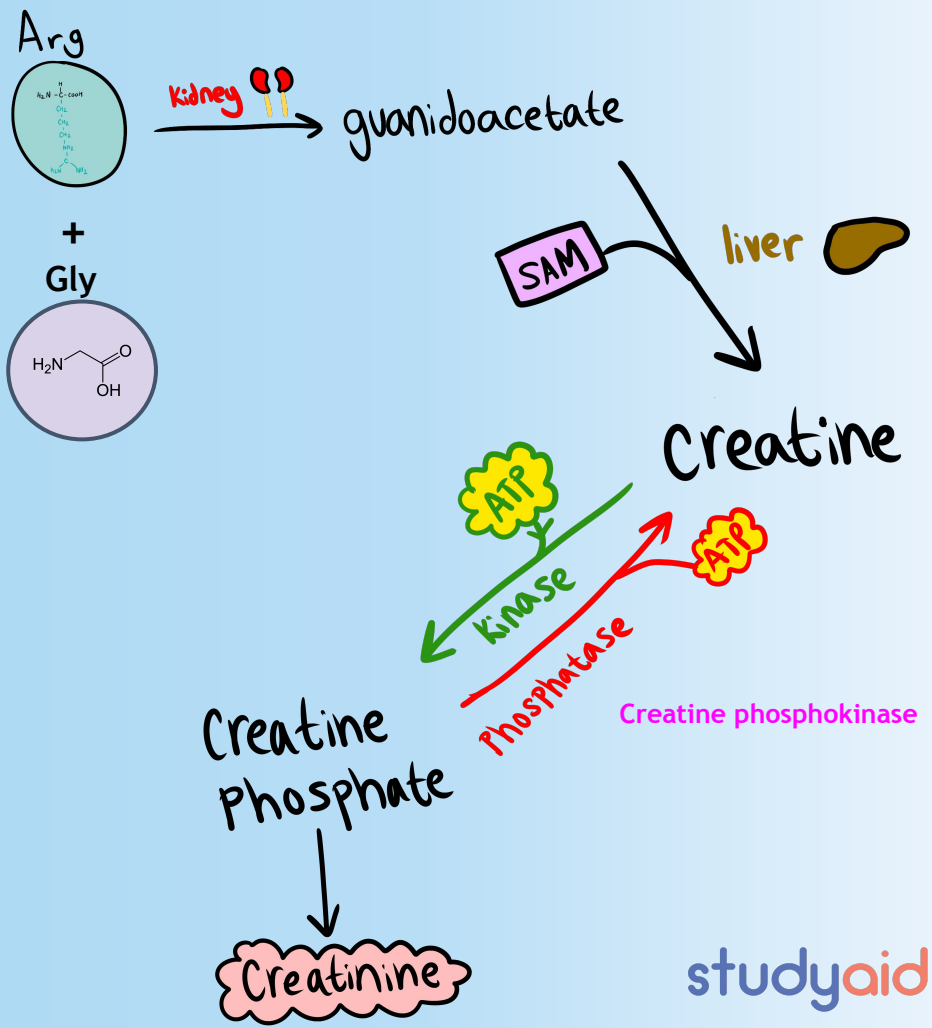
studyaid

Arginine

- Arginine: Basic, non-essential amino acid
- Arginine makes nitric oxide
- Nitric oxide (NO*): free radical
    - For vasodilation
    - For macrophage respiratory burst
- NOS enzyme:
    - nNOS: for neurons
    - iNOS: cytokine-inducible NOS
    - eNOS: for endothelial cells



- Arginine + glycine + methionine make creatine
- **Creatine phosphate:**
  - Stores phosphate, a very high energy molecule, in the muscles
  - We have enough ATP in the body? Make creatine phosphate!
  - Don't have enough ATP in the body? Break down creatine phosphate!
- **Creatinine:**
  - Waste product of the muscles
  - Kidneys filter our creatinine
    - Marker of kidney function
    - High creatinine in the blood means that kidneys are not filtering well

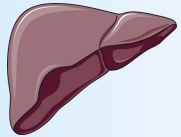


Molecule	Products
Methionine	- SAM - Homocysteine
Homocysteine	- Cysteine - A-ketobutyrate
Tryptophan	- NAD + NADP - Serotonin - Melatonin
Phenylalanine	- Tyrosine - Phenylpyruvate (acid in PKU)

Molecule	Products
Tyrosine	- Homogentisate - DOPA - Melanin - Dopamine - Norepinephrine - Epinephrine - Thyroid hormones
BCAAs	- Branched chain keto acids - Acyl-CoA derivatives
Arginine	- Nitric oxide - Creatine & creatinine

Urea Cycle

All occurs in the liver!



Transamination

Deamination

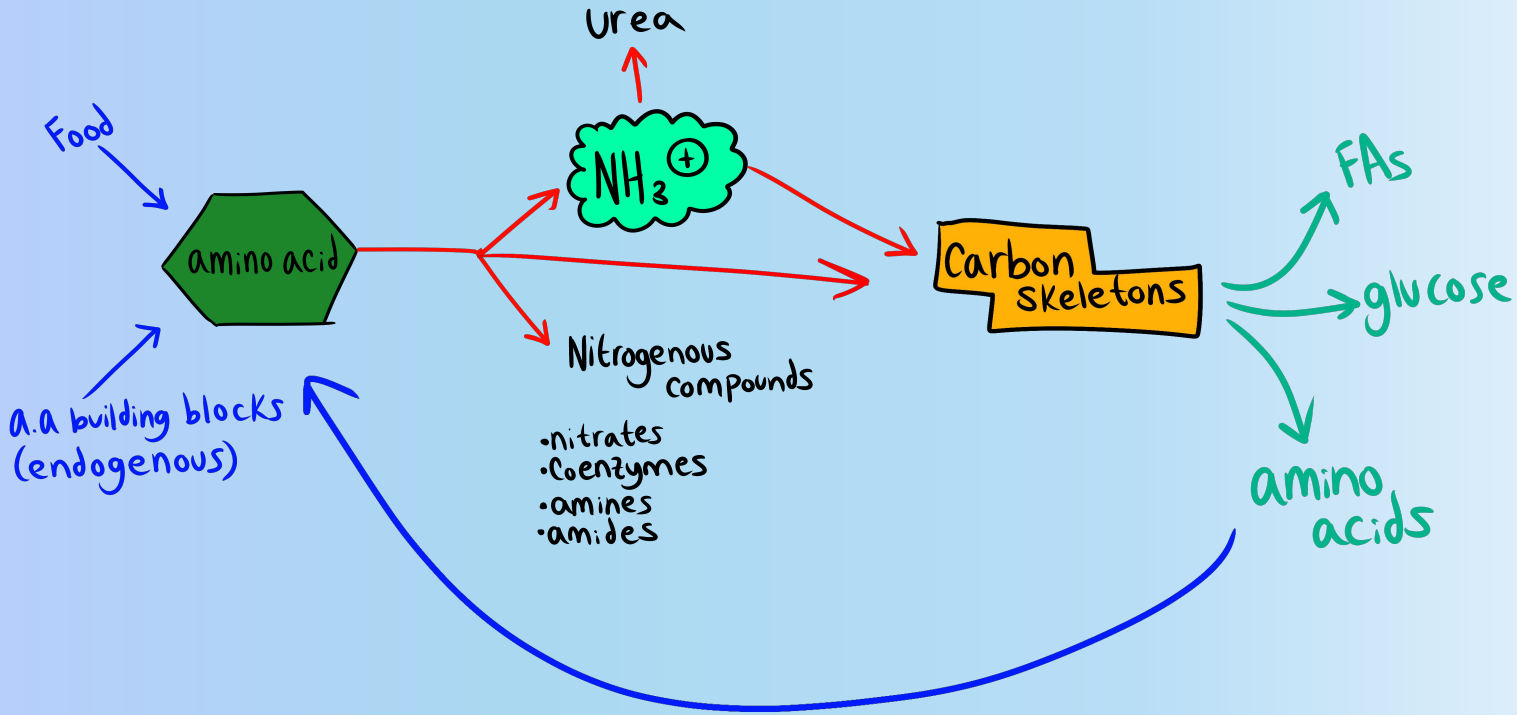
Oxidative

Non-oxidative

Urea cycle

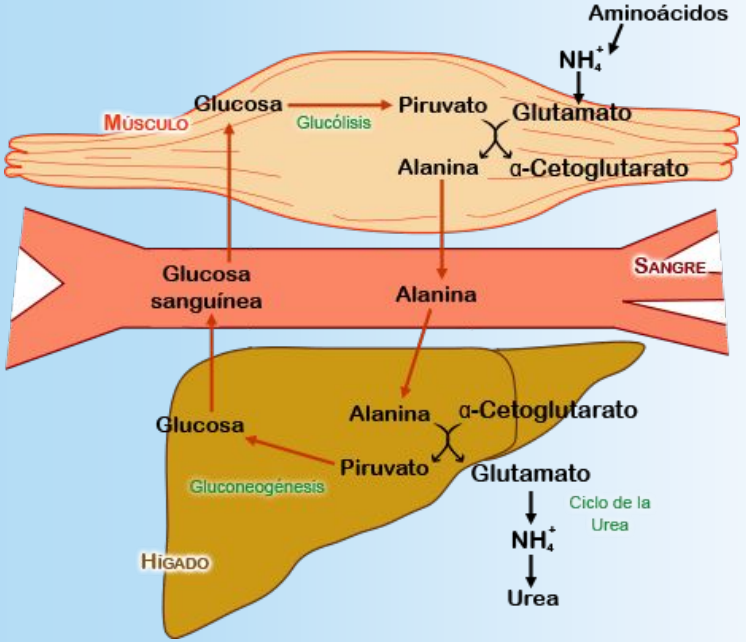
Table of contents:

Nitrogen cycling: General



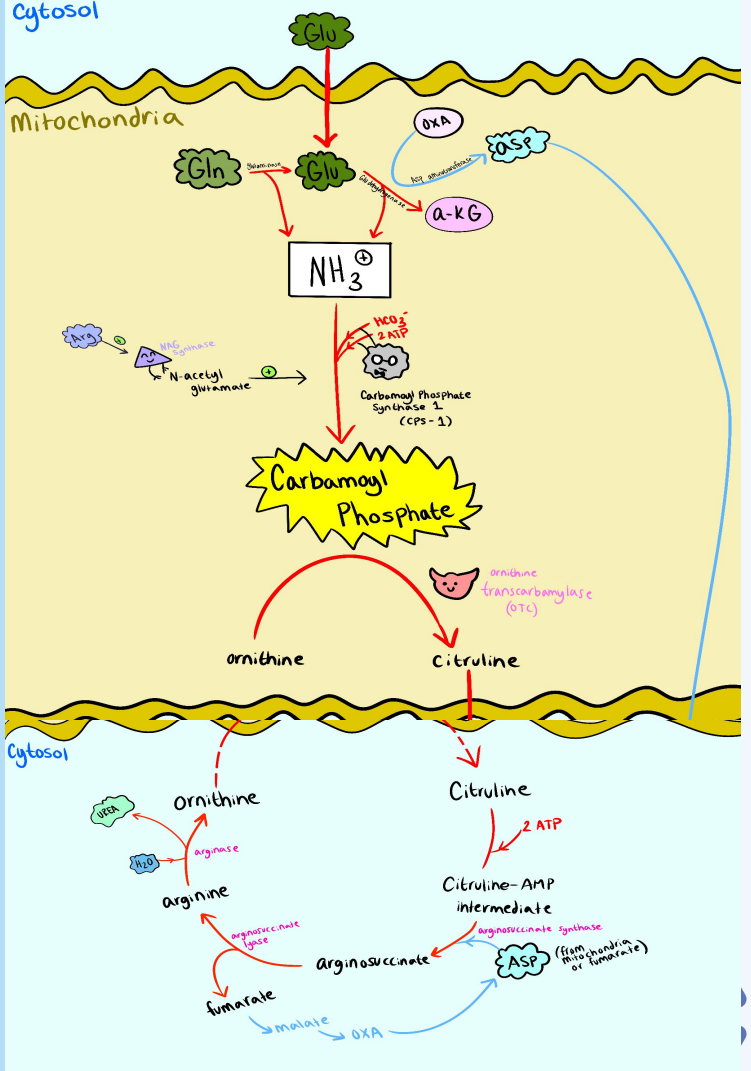
NC: Cahill Cycle

- Tissues and muscles make ammonia (NH3/NH4+), which is toxic and needs to be get rid of
- NH3 from muscles is transported via alanine to the liver
- Alanine lets go of NH3 and turns into pyruvate
    - Liver turns NH3 into urea via urea cycle, which is then excreted by the kidneys
    - Pyruvate can be turned into glucose via gluconeogenesis and used as energy in the muscle



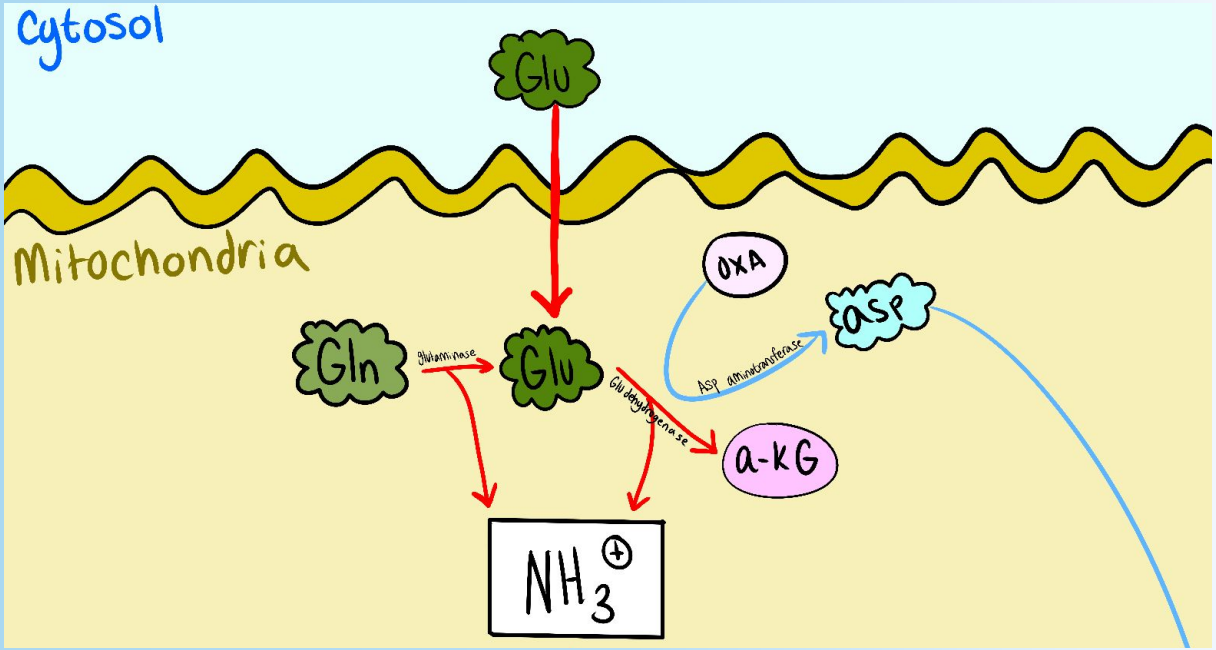
What is the urea cycle?

- Detoxification method
- Converts ammonia (NH3/NH4+, toxic) into urea (H2NCONH2, nontoxic)
- Only occurs in the liver
- Three most important enzymes:
  - Carbamoyl phosphate synthetase 1 (CPS-1)
  - Ornithine transcarbamylase (OTC)
  - Arginase



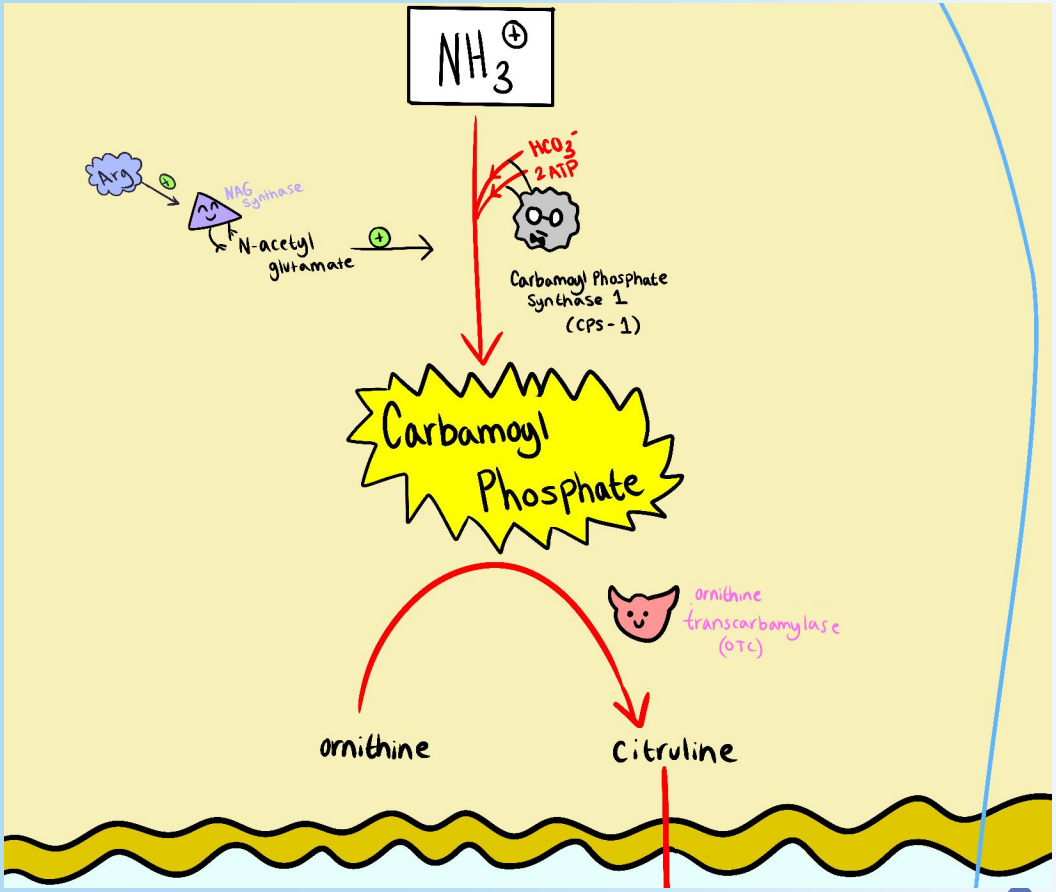
Urea cycle: Step 1

- Glutamate and glutamine release ammonia (NH3+)
- Aspartate is later used when the urea cycle occurs in cytosol



Urea cycle: Step 2

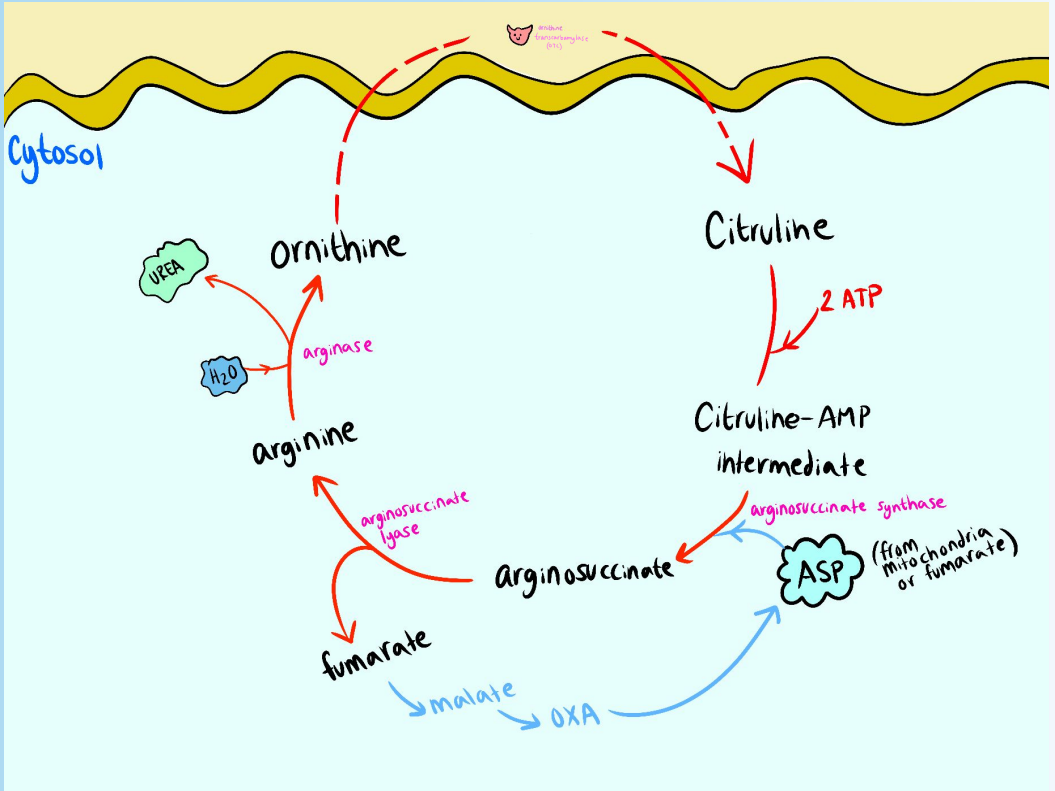
- CPS-1 uses bicarbonate and ATP to make carbamoyl phosphate
- CPS-1 is a rate limiting enzyme
- CPS-1 is activated by N-acetyl-glutamate, which is made by N-acetyl-glutamate synthase (NAGS), which is activate by arginine
- Carbamoyl phosphate helps power OTC by turning ornithine into citrulline, two key urea cycle substrates in the cytosol



studyaid

Urea cycle: Step 3

- Citrulline + aspartate = argininosuccinate
- Argininosuccinate - fumarate = arginine
    - Fumarate can be converted back into aspartate via krebs cycle (fumarate to oxaloacetate) and via glutamate oxaloacetate transaminase (oxaloacetate to aspartate)
- When converting arginine into ornithine, finally you make urea!
- Ornithine is converted back into citrulline via ornithine transcarbamylase inside the mitochondria

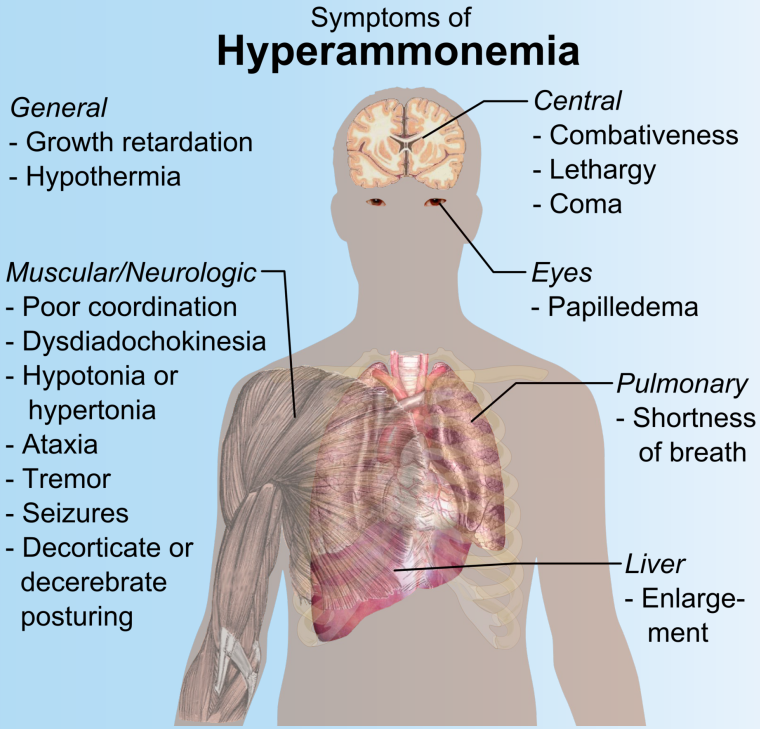


studyaid

Clinical Correlation: Hyperammonemia

- When you have too much ammonia in the blood
- Primary causes (ex: enzyme deficiency) or secondary (ex: hepatic cirrhosis)
- Primary causes:
  - **NAGS** deficiency
  - **CPS-I** defect
  - **OTC** defect
    - Most common
    - Increased orotic acid
    - Tx: Sodium benzoate (nitrogen scavenging agent)

- Symptoms:
  - Vomiting
  - Ataxia
  - Seizures
  - Encephalopathy
  - Coma
- If not treated, can be fatal



By Mikael Häggström
https://commons.wikimedia.org/w/index.php?curid=6703007