Amino Acid Metabolism & Urea Cycle

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Amino acid classifications

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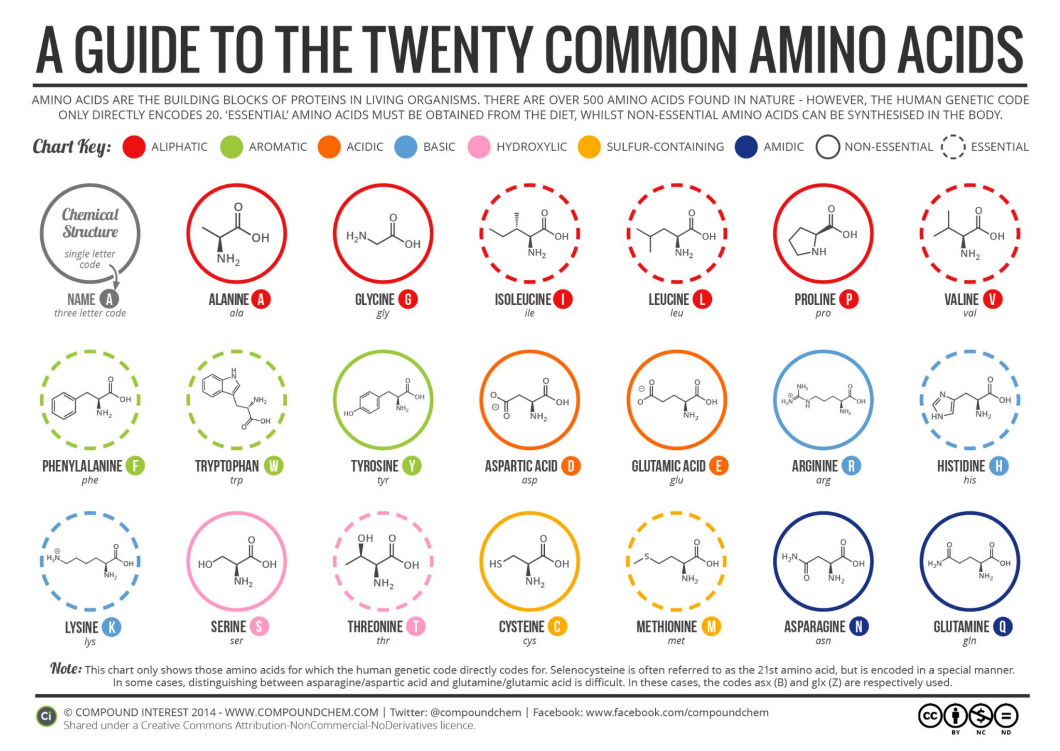
Amino acid structures



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



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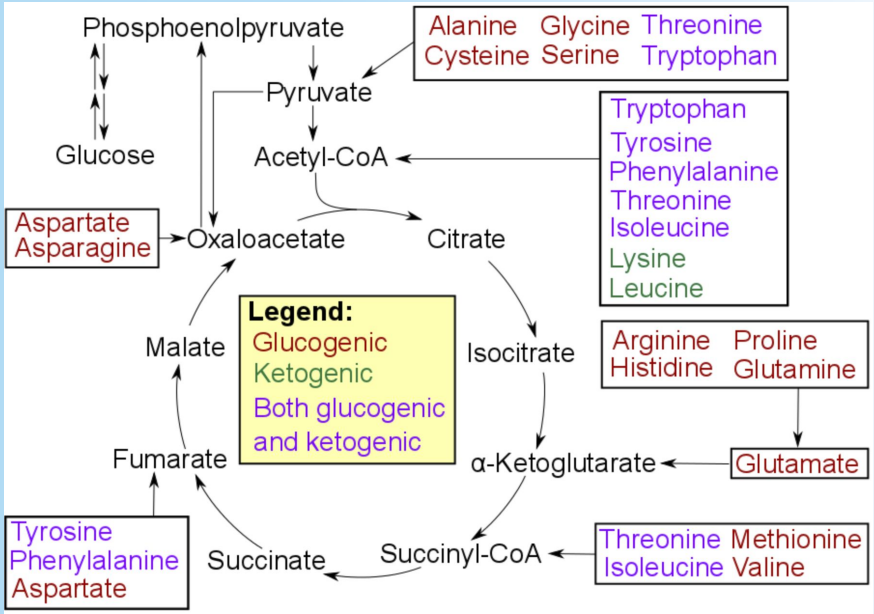
Glucogenic vs ketogenic amino acids

Glucogenic:

Can be converted into substrates used in gluconeogenesis, which eventually makes glucose

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

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





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Biochemical reactions of amino acid metabolism

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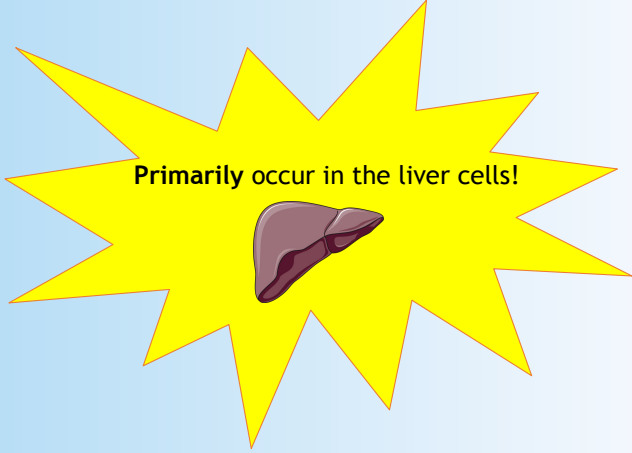
Definitions:



1) **Transamination:** Transfer of an amino group from an amino acid to its partner keto-acid

2) **Deamination:** Removal of an amino group from an amino acid, resulting with ammonia as a byproduct

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Transamination

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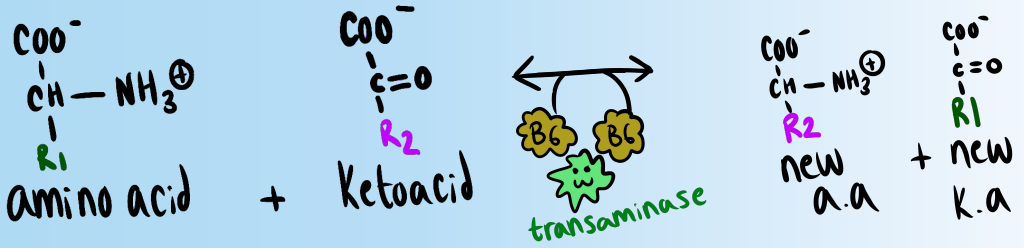
What is transamination?

- **What is it:** Transferring an amino acid's amine group (NH3+) to its partner keto acid to make a new amino acid
- **Enzyme:** aminotransferases/transaminases
  - Vitamin B6 (PLP/pyridoxine) dependent
- **Goal:** Make glutamate (especially will be important for oxidative deamination)



1st important example of transamination

Serum glutamic oxaloacetic transferase (SGOT):

- A.k.a aspartate transferase (AST)
- Liver enzyme: Found in the hepatocyte cytosol and mitochondria



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Aspartate

a-ketoglutarate

Oxaloacetate

Glutamate



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2nd important example of transamination

Serum glutamic pyruvic transferase (SGPT):

- A.k.a alanine transferase (ALT)
- Liver enzyme: Found in the hepatocyte cytosol



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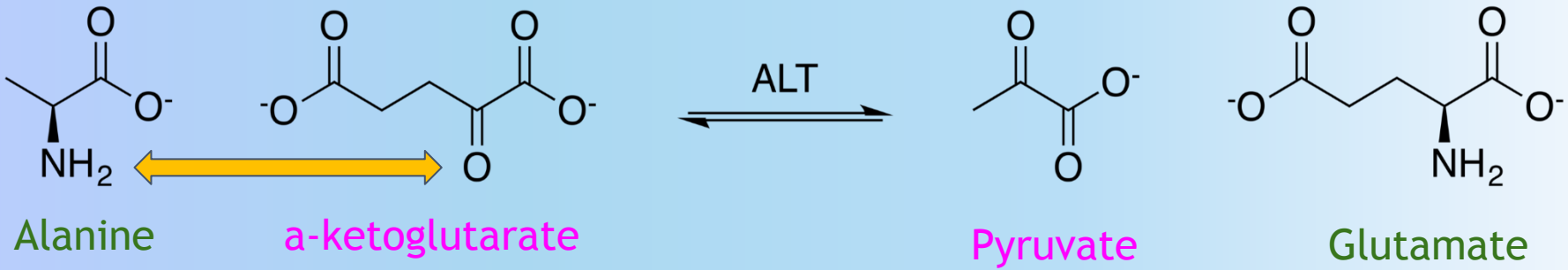

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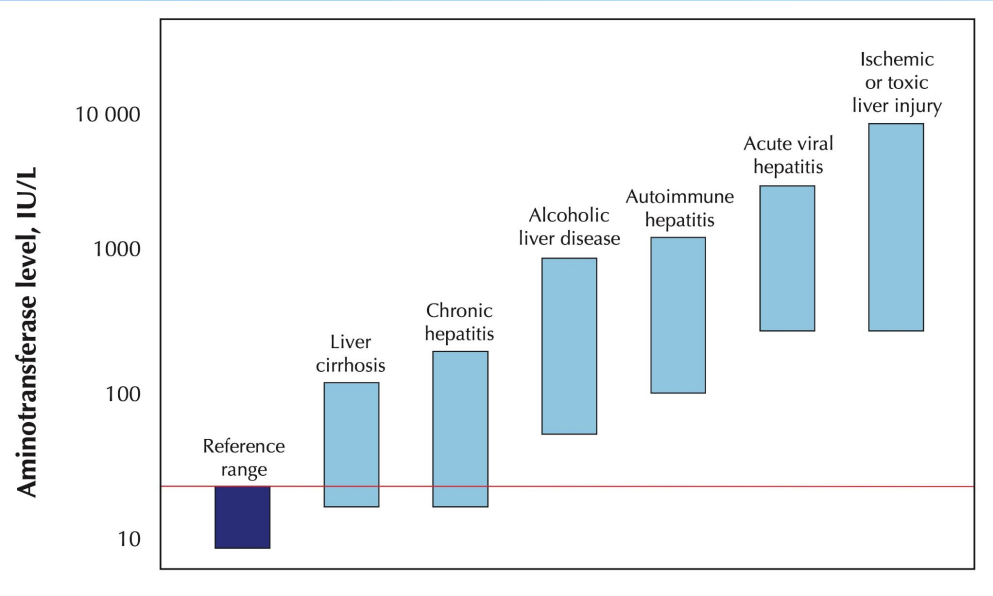
Clinical correlation: ALT & AST

ALT & AST are biomarkers of liver damage because when liver cells die, they release these enzymes into the bloodstream



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Deamination

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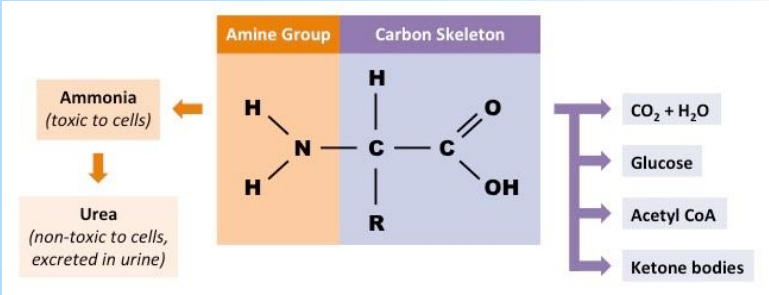
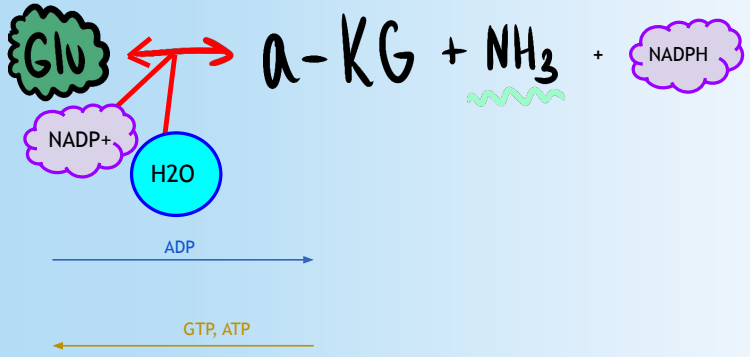
What is deamination?

- Removal of an amino group from an amino acid → release of ammonia
  - Ammonia is toxic, but the urea cycle neutralizes it
- Occurs primarily in the liver
- Two types of deamination:
  - Oxidative
  - Non-oxidative



Oxidative deamination

- Occurs with glutamate
- Enzyme: Glutamate dehydrogenase
  - Reversible reaction
  - Oxidative: glutamate donates a H+ to NADP+
- Products: alpha-ketoglutarate (keto-acid), ammonia & NADPH
- Regulation: Depends if we want to do Krebs Cycle because a-KG is a krebs cycle substrate
    - **Activator** from **Glu → a-Kg:** ADP
      - Signifies low energy, so want to do Krebs cycle to make more ATP
    - **Activator** from **a-Kg → Glu:** GTP, ATP
      - Signifies high energy, so don't want to do Krebs cycle



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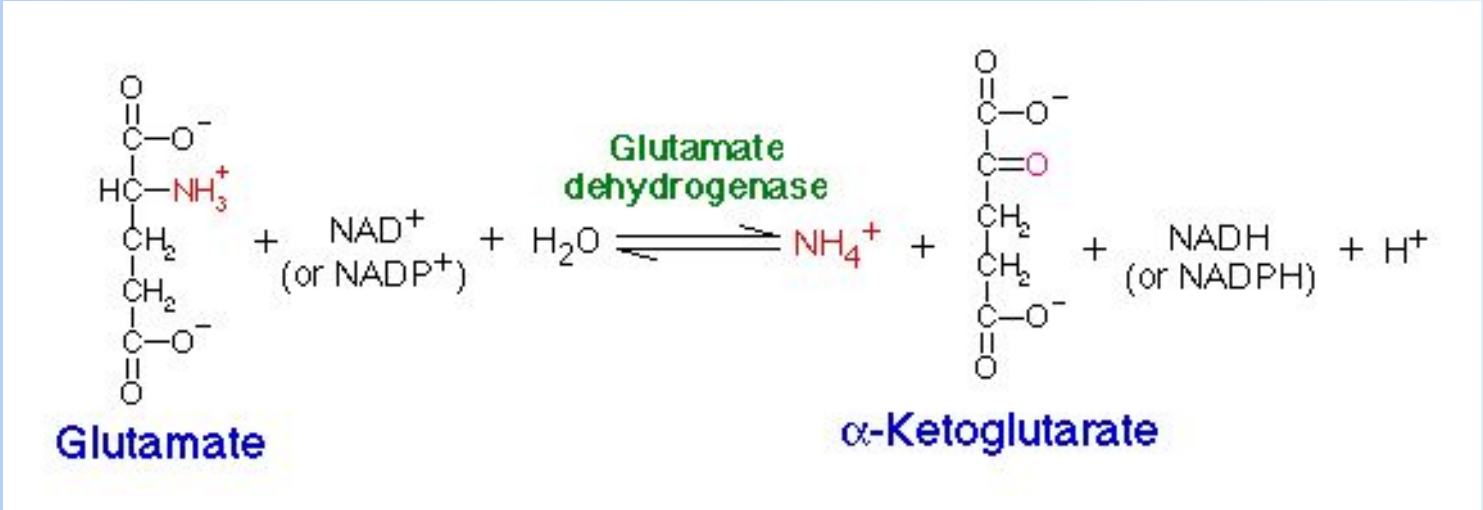
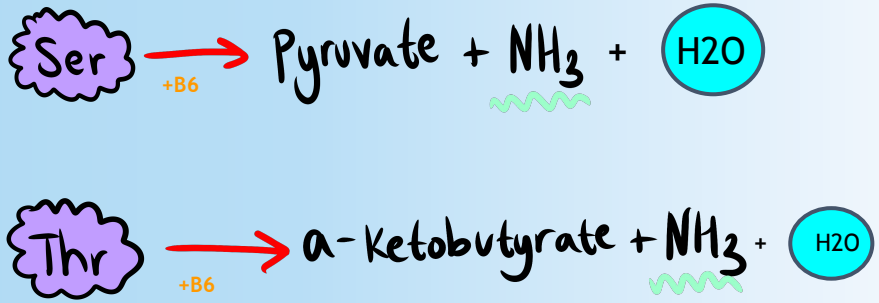

Glutamate dehydrogenase
NAD+ (or NADP+)
H2O
NH4+
NADH (or NADPH)
H+
Glutamate
α-Ketoglutarate

Non-oxidative deamination

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



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Specific amino acid metabolisms & correlated diseases

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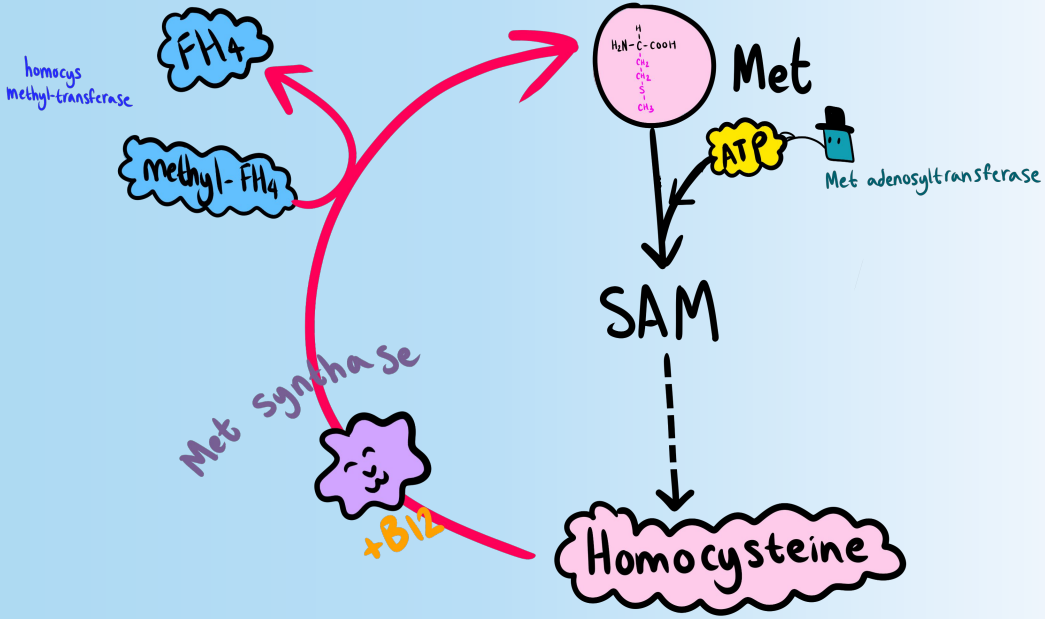
Methionine

- 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



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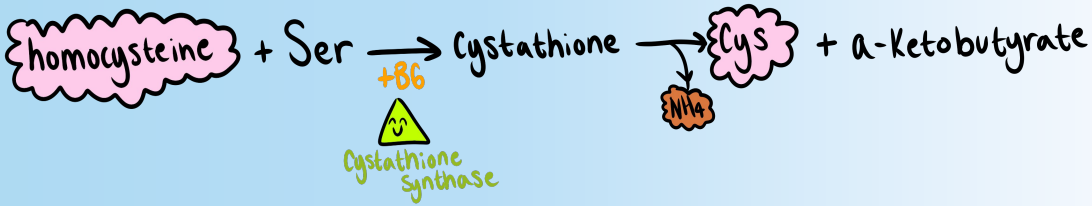
Homocysteine

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



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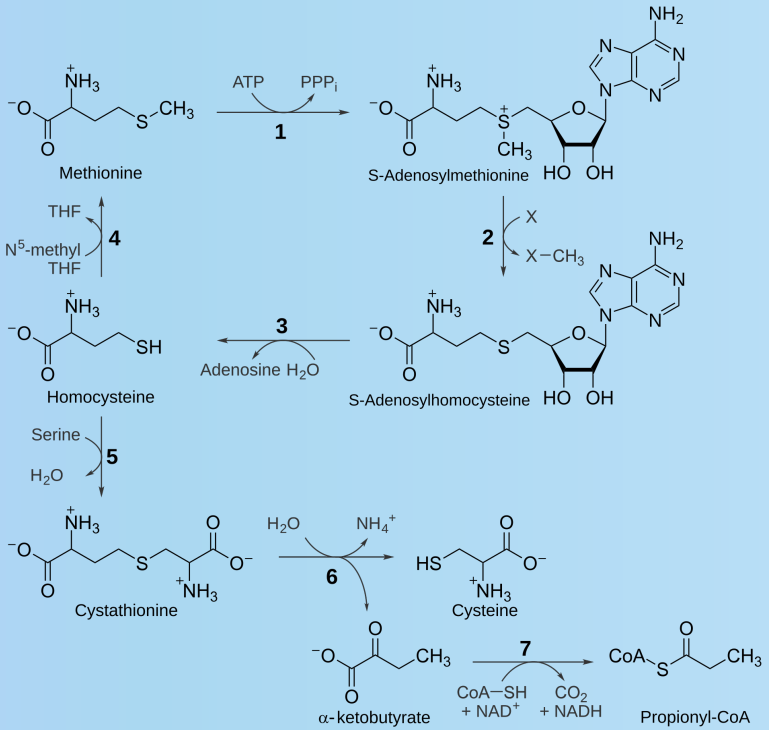
Methionine & homocysteine metabolism



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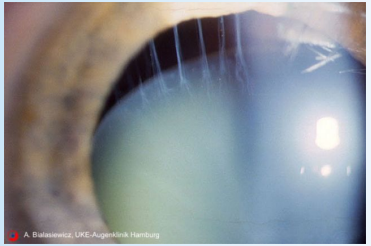
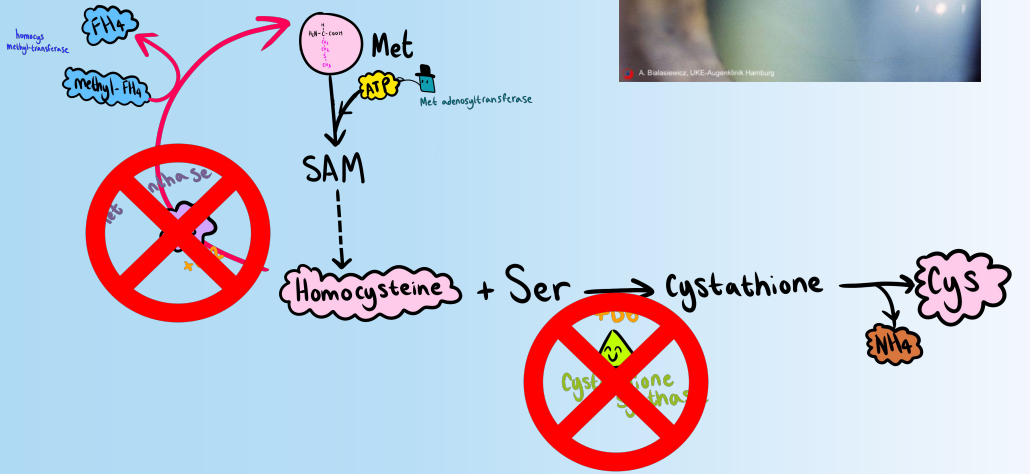
Clinical correlation: Homocystinuria

- **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





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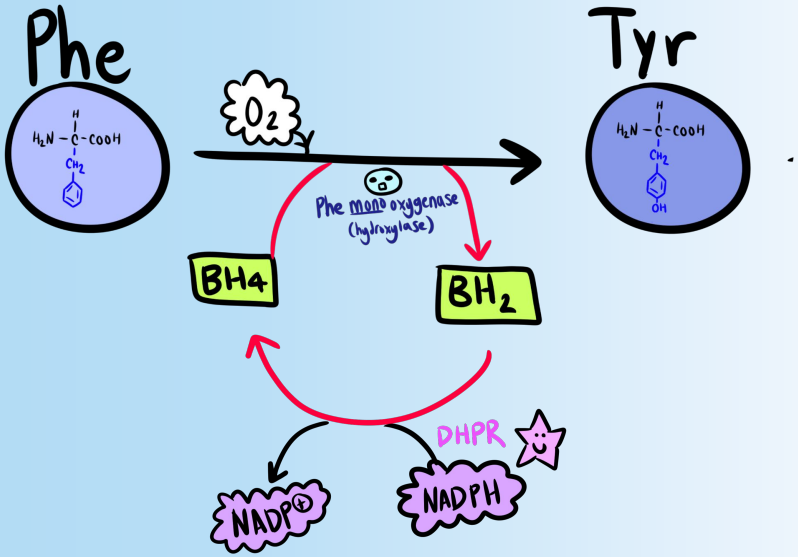
Phenylalanine

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



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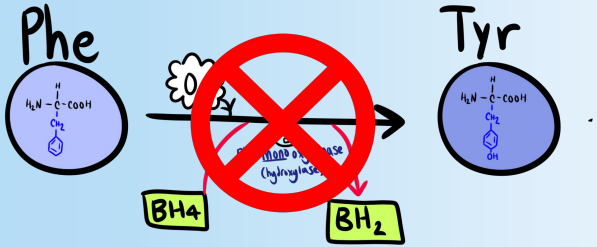
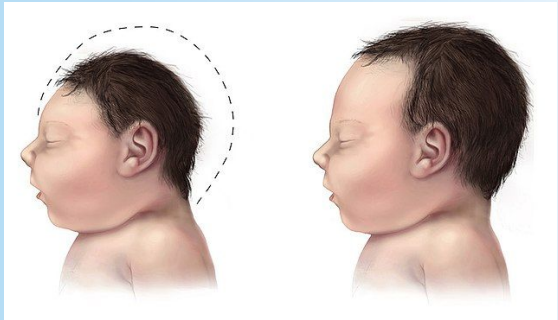
Clinical Correlation: Phenylketonuria (PKU)

- **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

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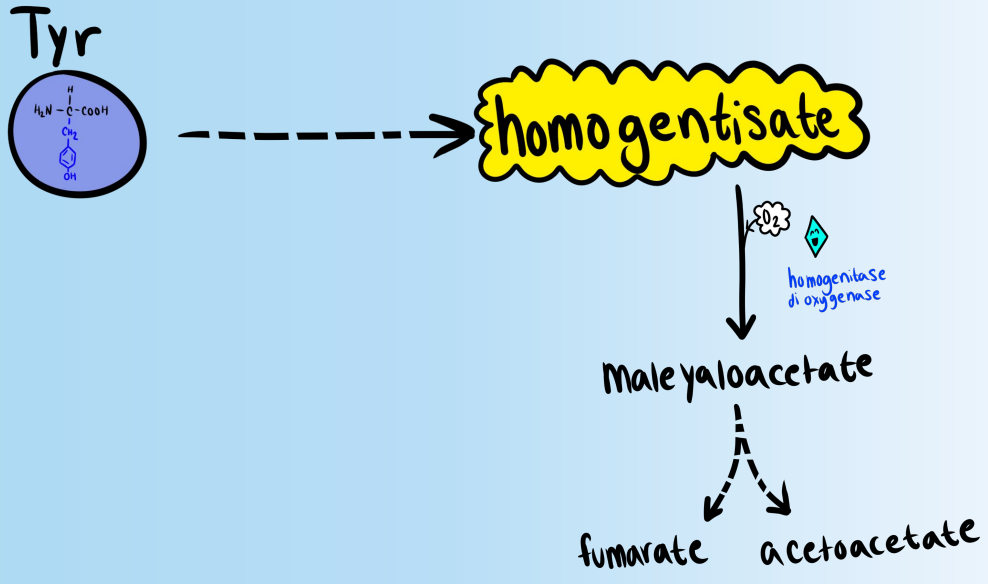
Tyrosine

- 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



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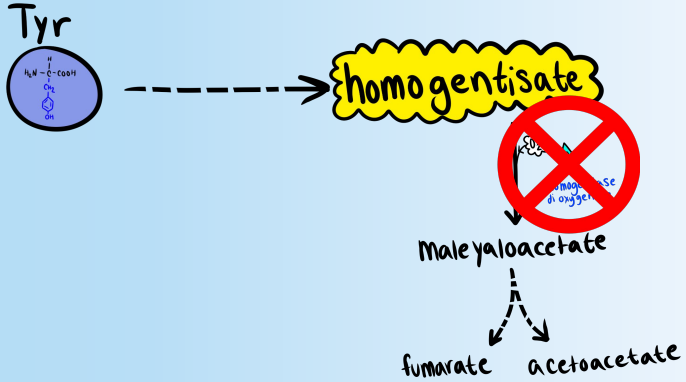
Clinical Correlation: Alkaptonuria

- **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





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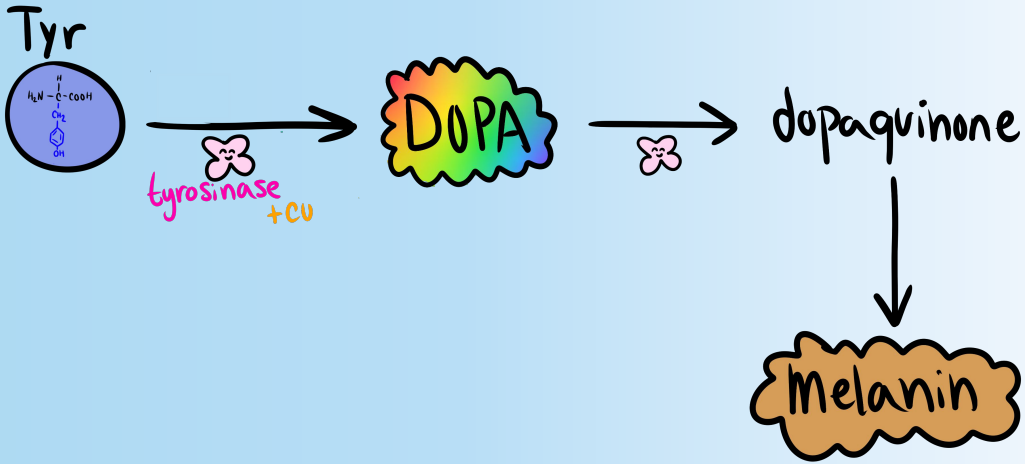
Tyrosine

- Tyrosine makes melanin, a oligomer/polymer that provides pigment for skin and hair
- **Tyrosinase:** copper dependent



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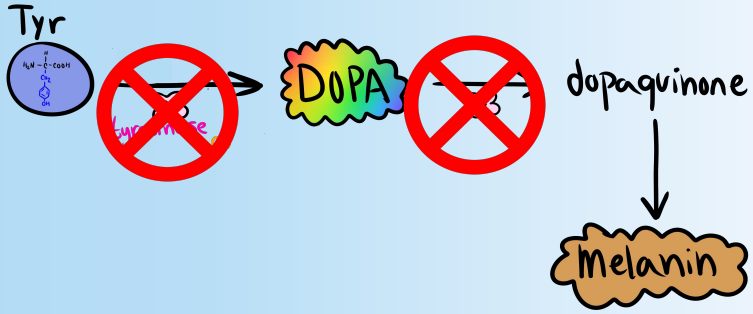
Clinical Correlation: Albinism

- **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.

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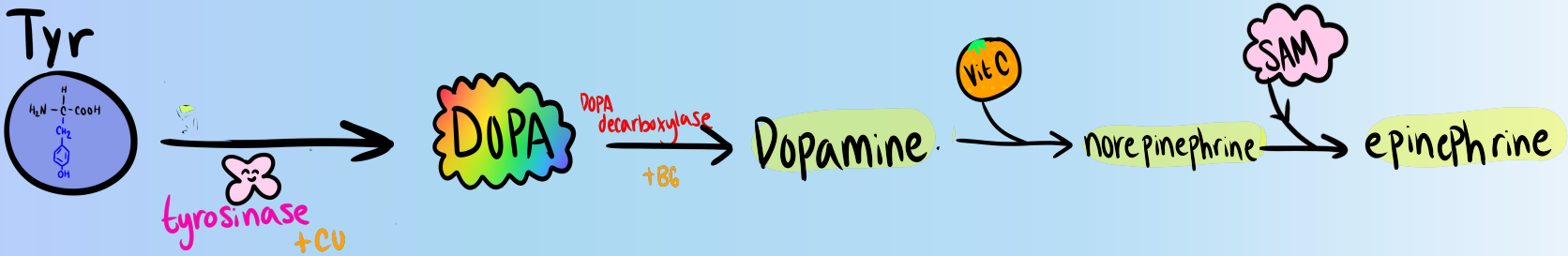
Tyrosine

- **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)



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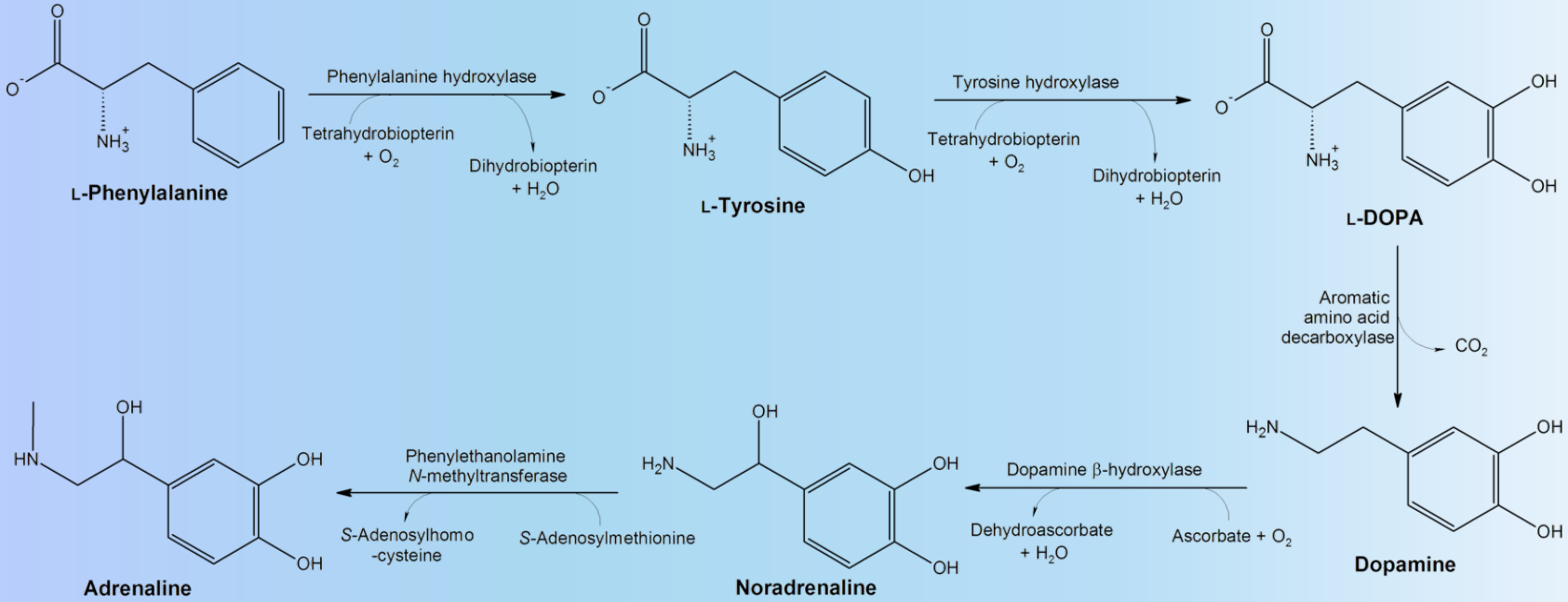
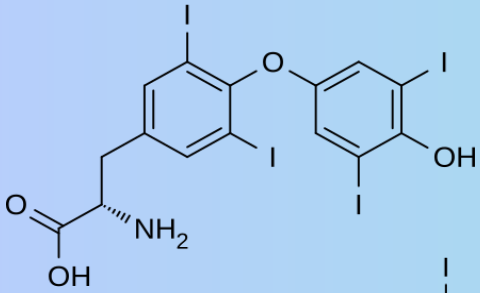
Phenylalanine/tyrosine metabolism

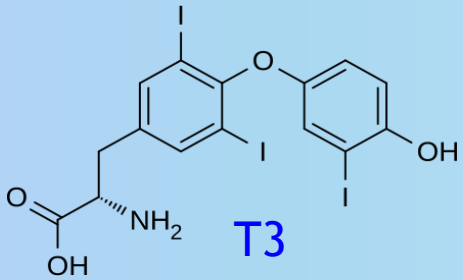


Tyrosine

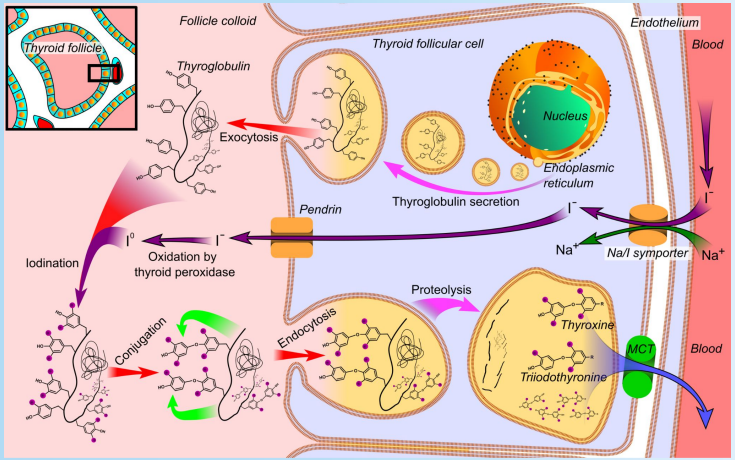
- **Tyrosine**: makes thyroid hormones
- **Thyroglobulin:** Carries tyrosine, in which tyrosines are then partnered with iodine to make thyroid hormones



T4



T3



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

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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)



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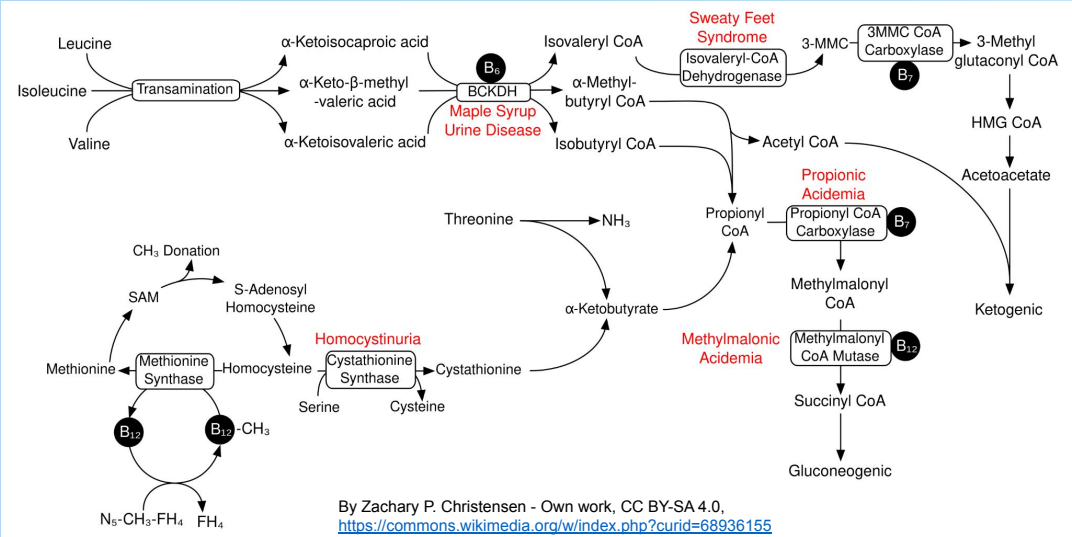
BCAA: "I love Bailey's"	Product
Isoleucine	Acetyl-CoA, Propionyl-CoA/Succinyl-CoA
Leucine	Acetyl-CoA, Acetoacetate
Valine	Propionyl-CoA/Succinyl-CoA



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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



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Summary of a.a metabolic diseases

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

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Extra (but high yield) amino acid metabolisms

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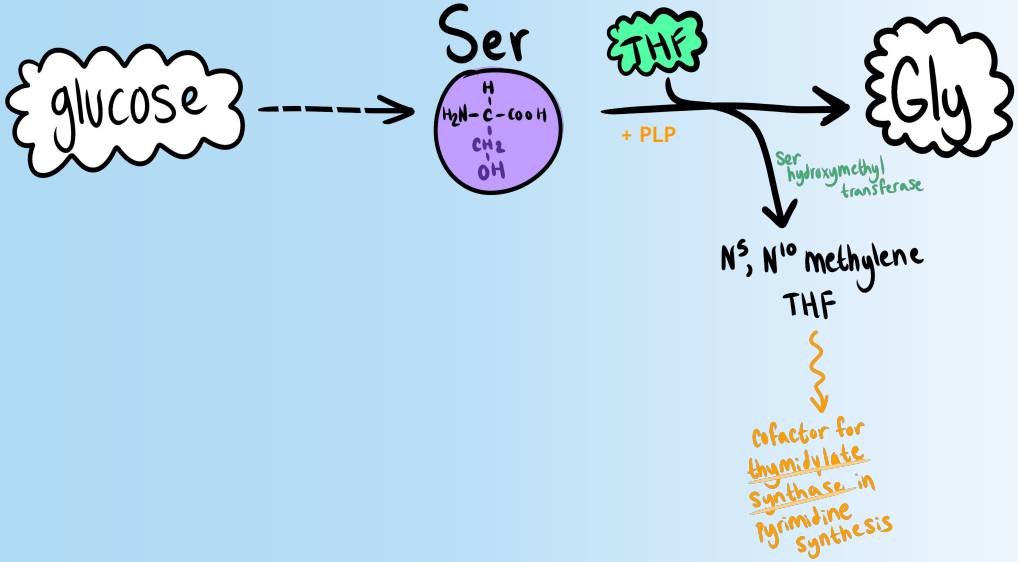
Serine to glycine

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



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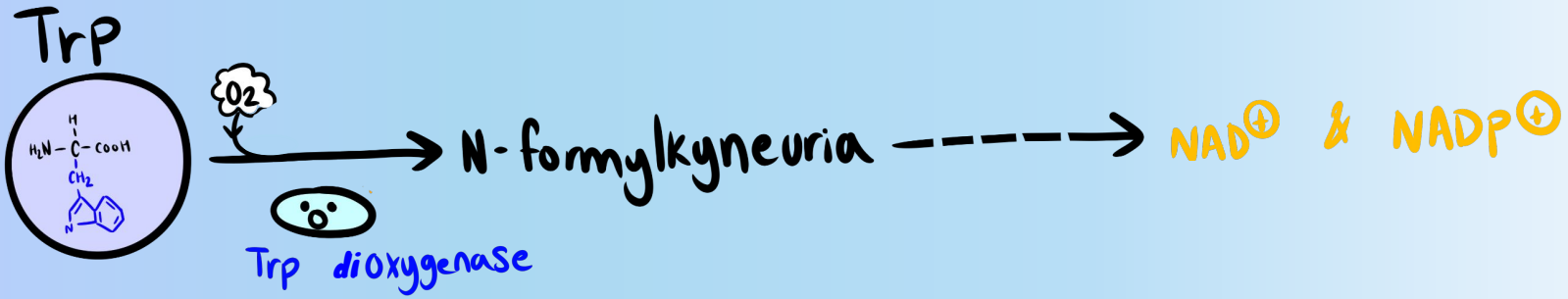
Tryptophan metabolism

- Tryptophan: Aromatic, essential amino acid
- Tryptophan makes NAD+ & NADP+
- **Tryptophan dioxygenase:** uses O2



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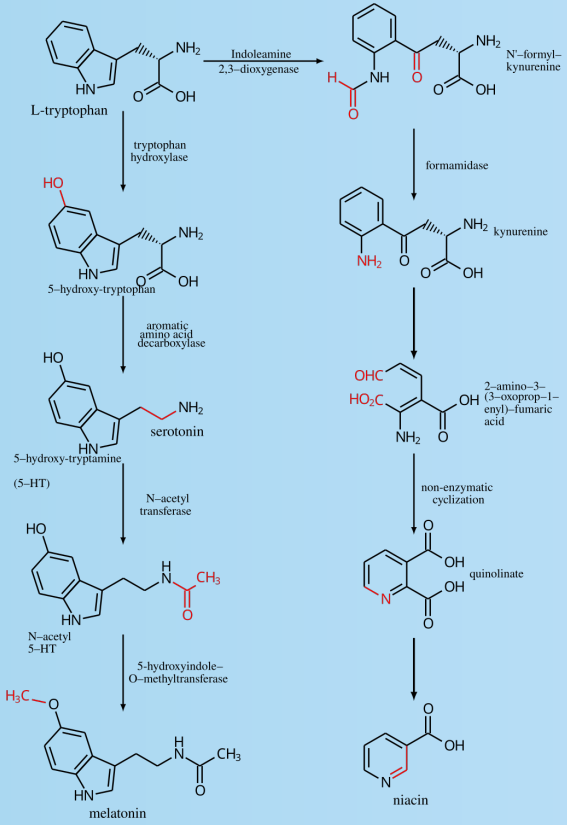
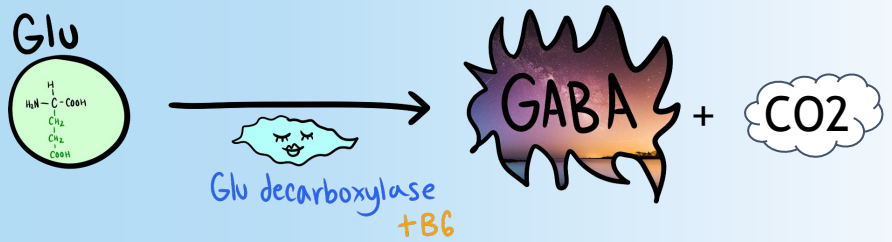
Tryptophan metabolism



Glutamate to GABA

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



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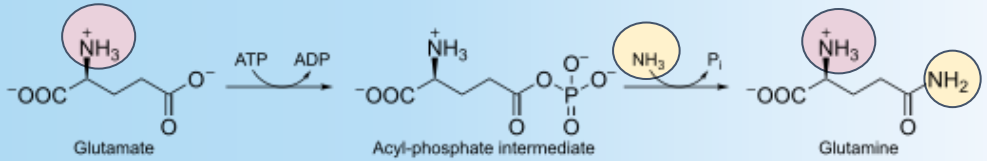
Glutamate to glutamine

- **Glutamine synthetase**
  - Adds an ammonia to glutamate
  - Especially important for uptaking excess ammonia (NH3) in the brain
  - ATP dependent
- Reverse reaction: **glutaminase**



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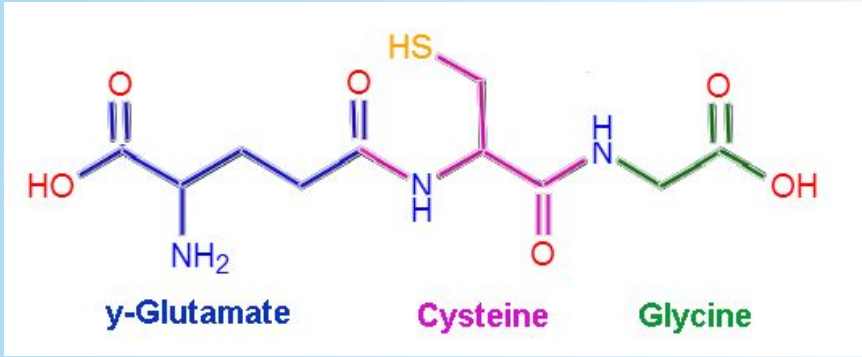
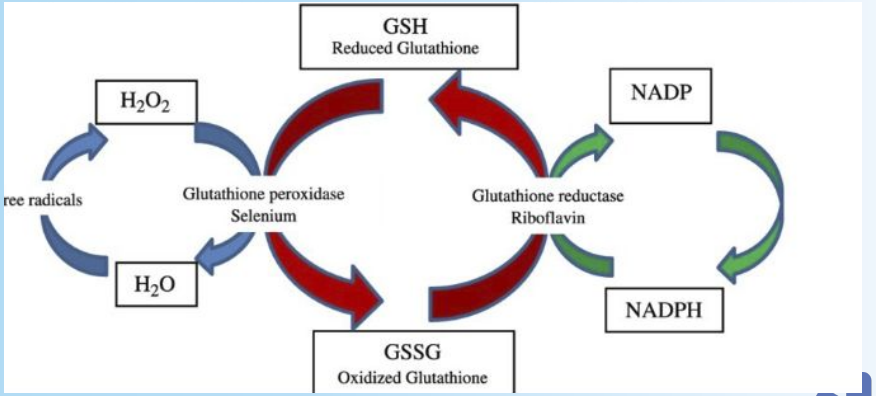
Glutathione

Glu + Cys + Gly = glutathione

"γ-glutamylcysteinylglycine"

- **Glutathione:**
  - Antioxidant
  - Reduced glutathione that is reoxidized helps convert H2O2 (a reactive oxygen species) into H2O (water)
    - Important to keep red blood cells from getting destroyed by reactive oxygen species
- **Glutamate + cysteine + glycine** yields glutathione





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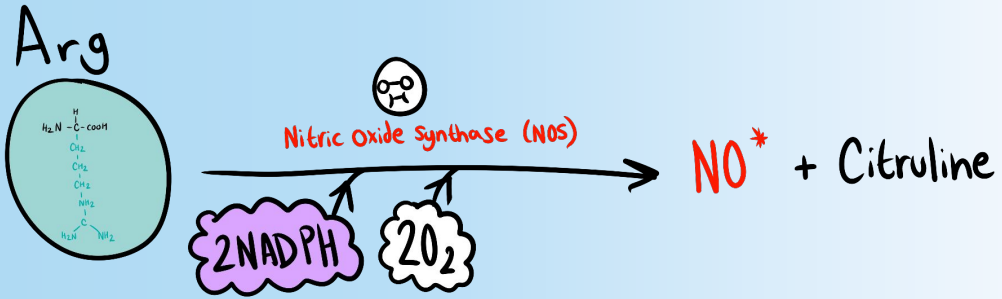
Arginine to nitric oxide

- **Arginine:** Basic, non-essential amino acid
- Arginine makes nitric oxide
- **Nitric oxide (NO*):** free radical
  - For vasodilation
  - For macrophage respiratory burst: helps kill pathogens eaten by macrophages
- **NOS enzyme:**
  - nNOS: for neurons
  - iNOS: cytokine (inflammation)-inducible NOS
  - eNOS: for endothelial (organ-lining) cells



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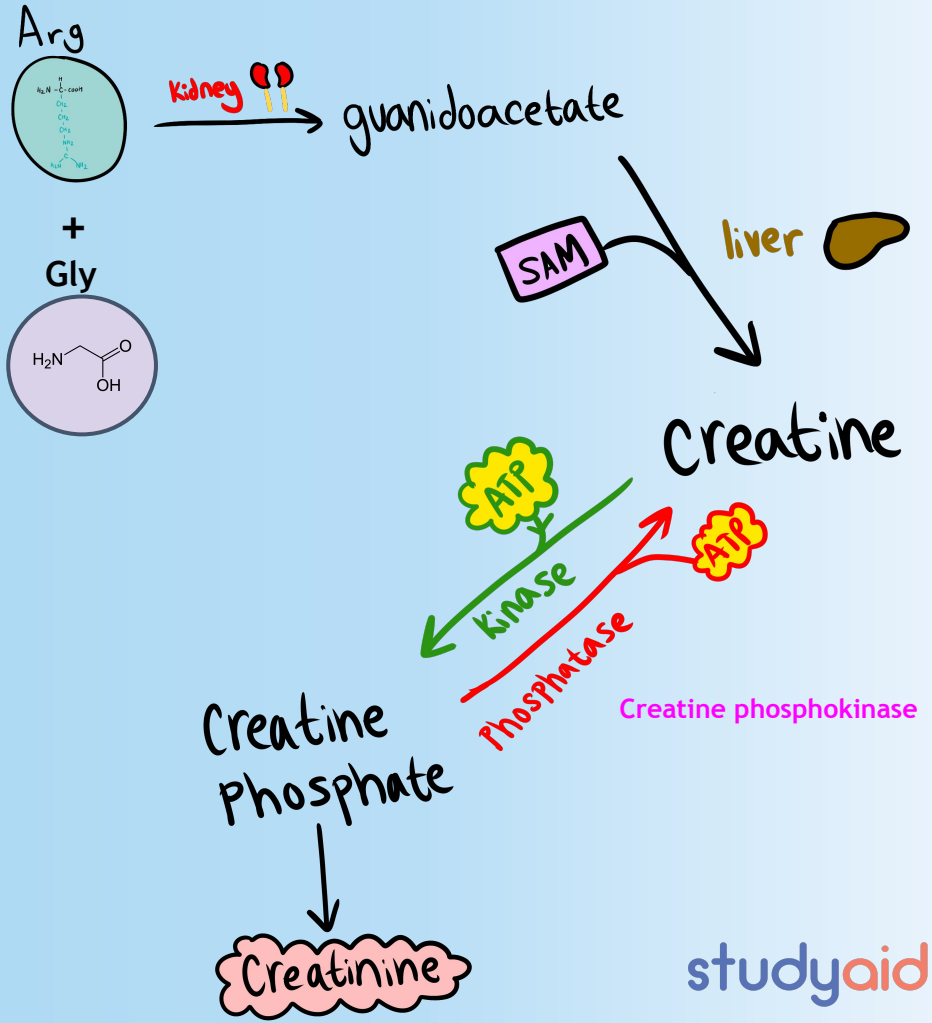
Arginine to creatine

- Arginine + glycine + methionine make creatine (like the gym supplement)
- **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 out our creatinine
    - Marker of kidney function
    - High creatinine in the blood means that kidneys are not filtering well



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Amino Acid Metabolism to Products

Amino acid	Products
Methionine	- SAM - Homocysteine
Tryptophan	- NAD + NADP - Serotonin - Melatonin
Phenylalanine	- Tyrosine - Phenylpyruvate (acid in PKU)

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Amino Acid Metabolism to Products

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

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Which enzyme uses which cofactor?

Enzyme	Cofactor	Which pathway?
Transaminases (ALT, AST)	Vitamin B6	Transamination
Glutamate dehydrogenase	NADP+, H2O	Oxidative deamination
Deaminases	Vitamin B6	Non-oxidative deamination
Methionine synthase	Vitamin B12, methyl-THF	Homocysteine → methionine
Cystathionine synthase	Vitamin B6	Homocysteine → cystathionine → cysteine
Phenylalanine monooxygenase/hydroxylase	BH4	Phenylalanine → tyrosine

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Which enzyme uses which cofactor?

Enzyme	Cofactor	Which pathway?
Tyrosinase	Copper	Tyrosine → melanin
DOPA decarboxylase	Vitamin B6	DOPA → dopamine
Dopamine b-hydroxylase	Vitamin C	Dopamine → norepinephrine
Phenylethanolamine N-methyltransferase (PNMT)	SAM	Norepinephrine → epinephrine
Glutamate decarboxylase	Vitamin B6	Glutamate → GABA
Nitric oxide synthase	2 NAPH, 2 O2	Arginine → NO* & citrulline

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Urea Cycle

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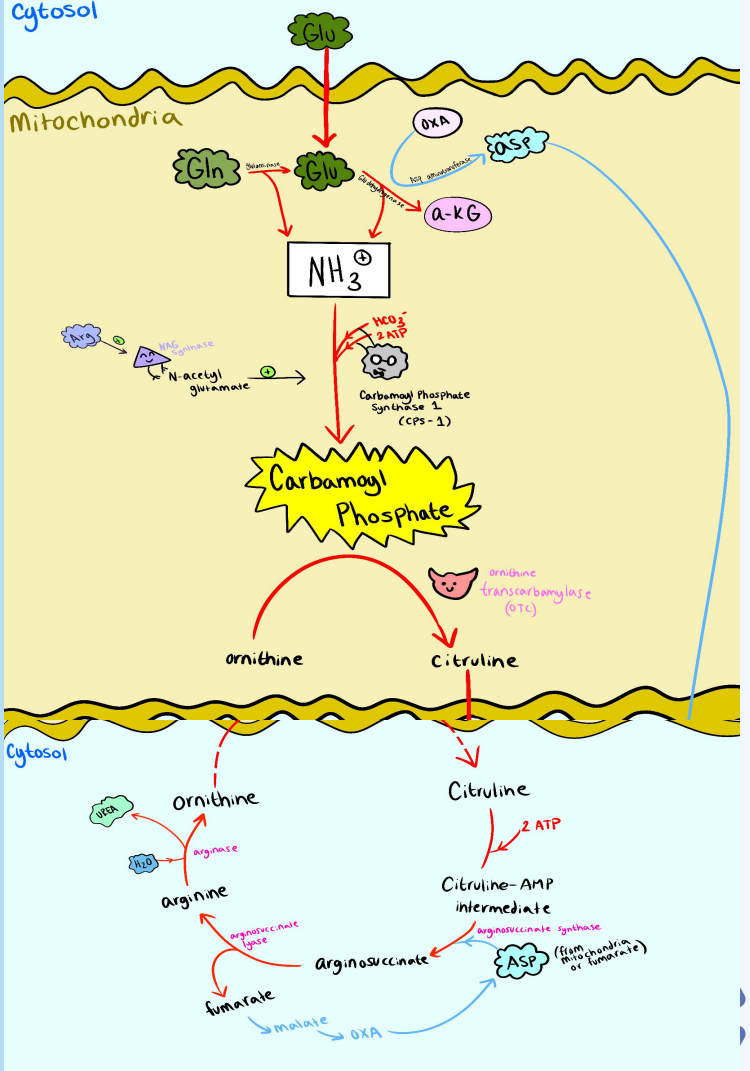
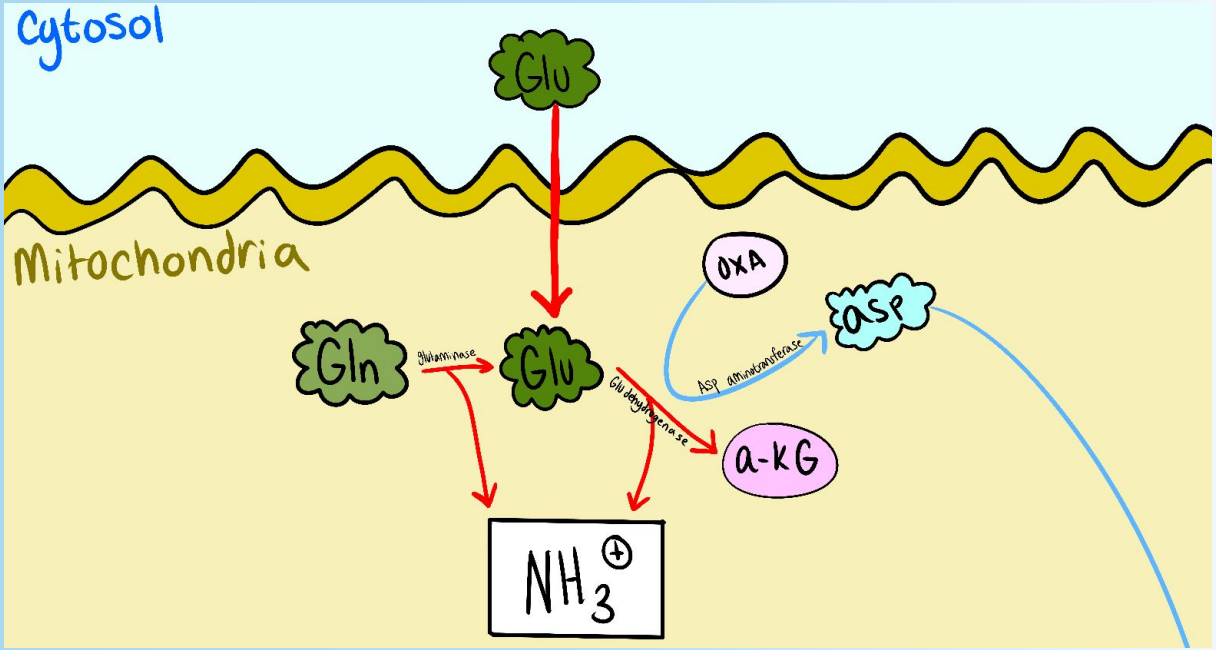
What is the urea cycle?

- 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



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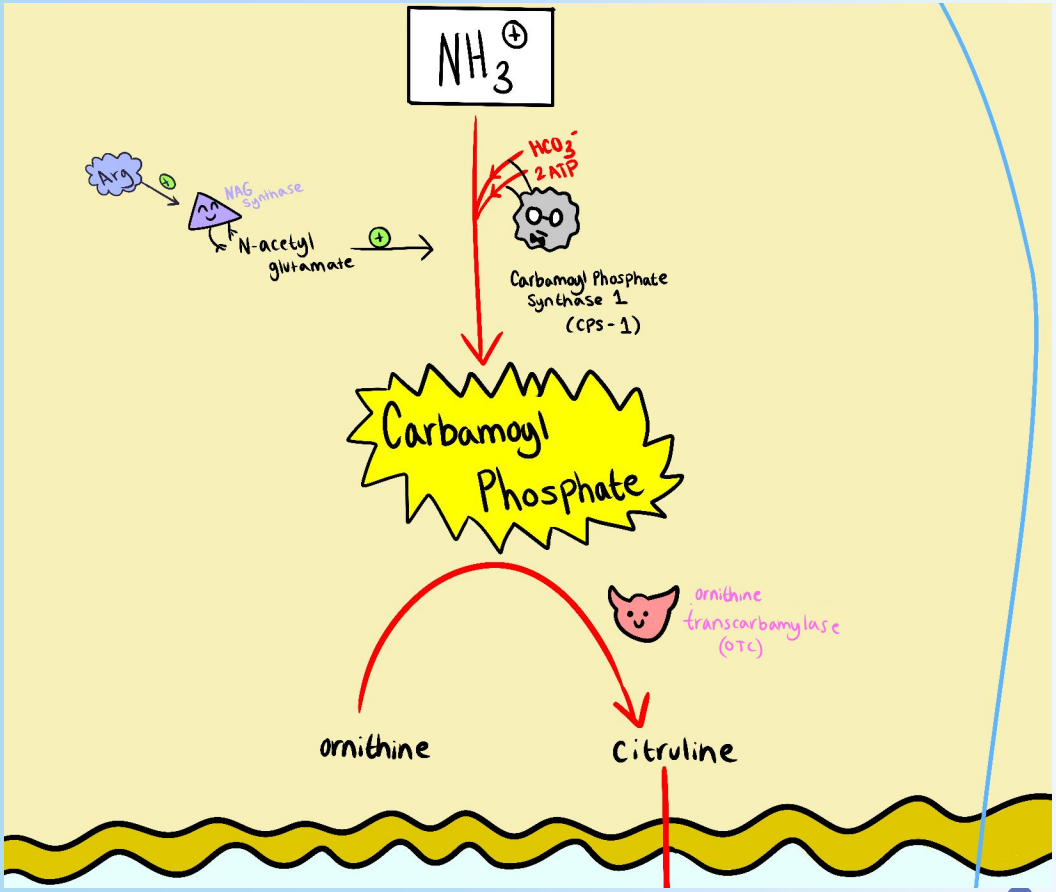
Urea cycle: Step 2

- 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



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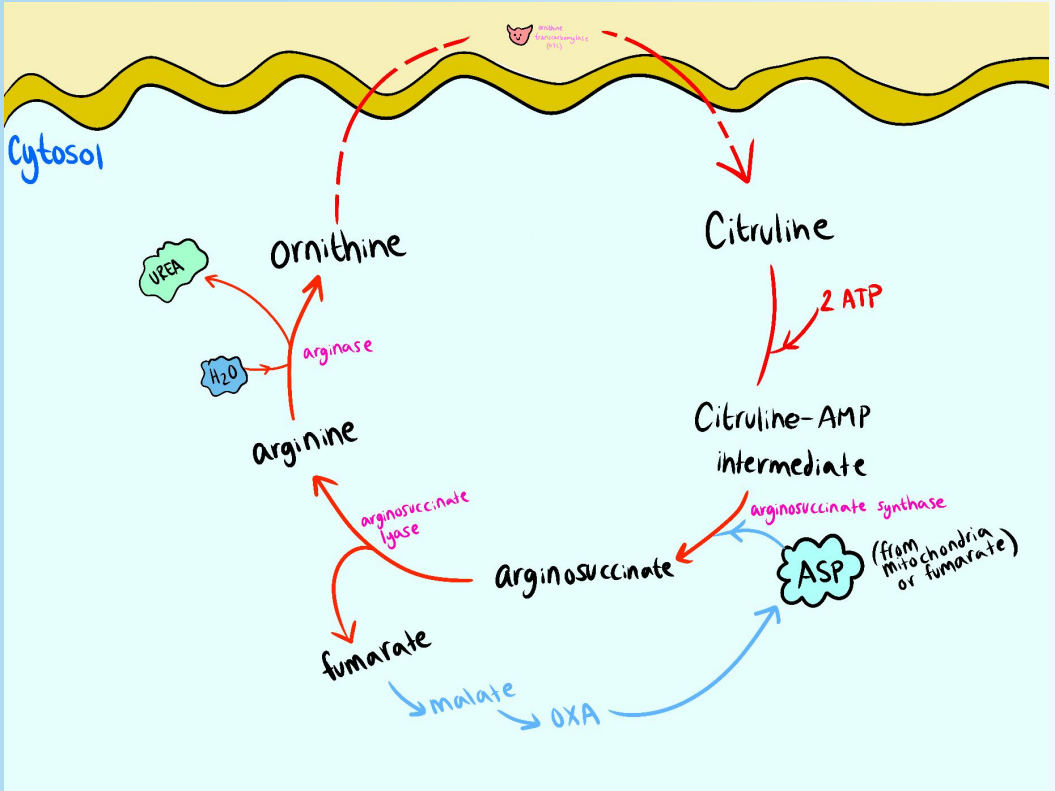
Urea cycle: Step 3

- 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



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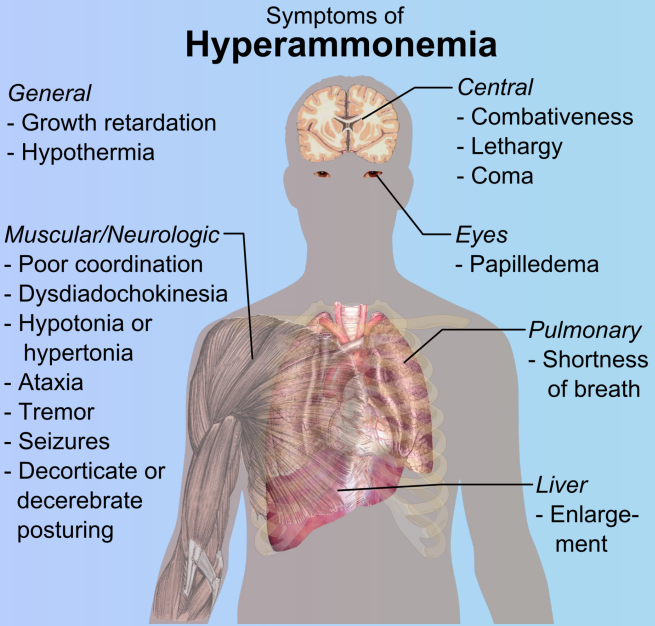
Clinical Correlation: Hyperammonemia



If not treated, can be fatal

- 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)

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