بیوشیمی عمومی

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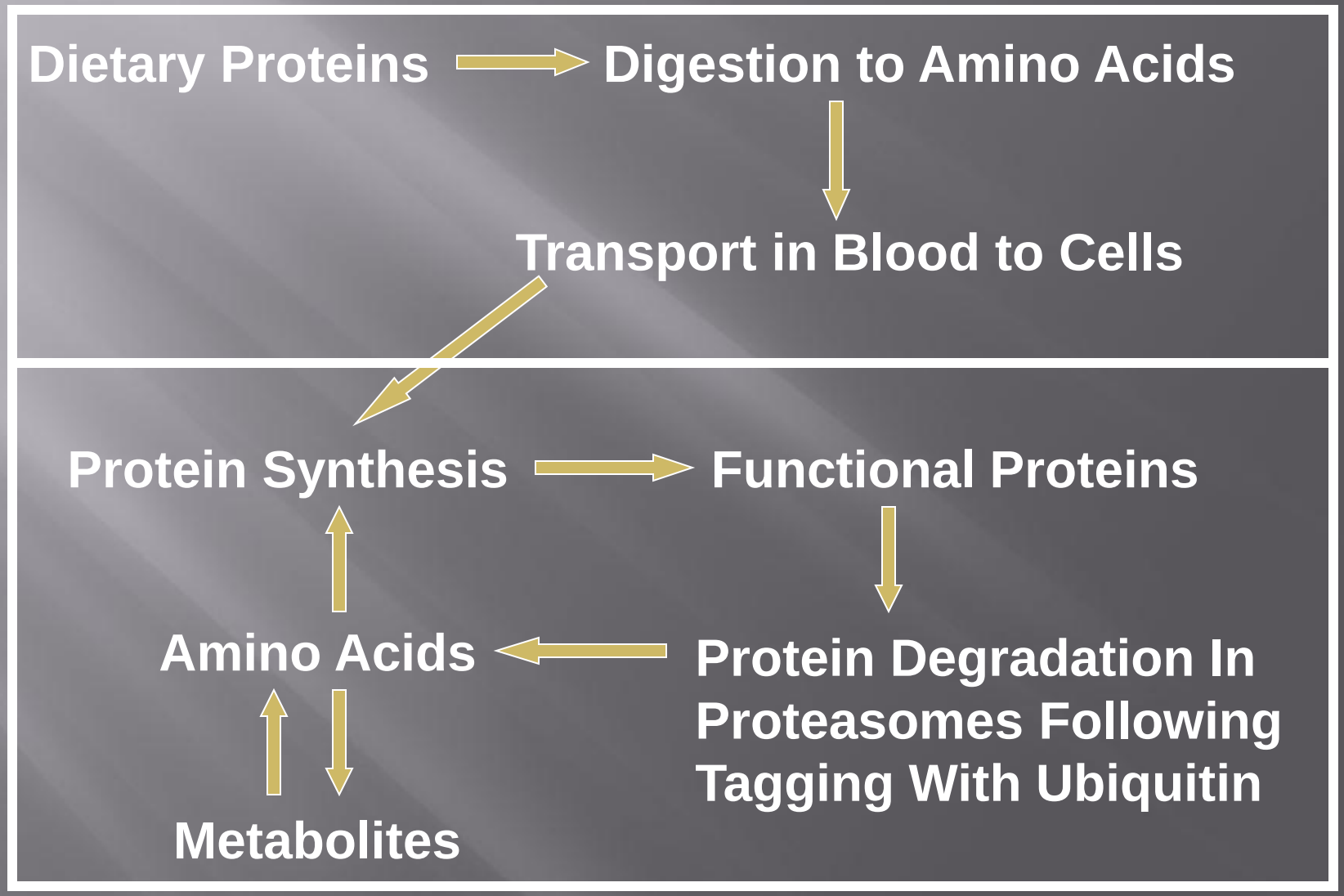
دکتر مختار خواجوی

AMINO ACID METABOLISM

Dynamics of Protein And Amino Acid Metabolism



Digestion of Proteins

Stomach: Pepsinogen → Pepsin (max. act. pH 2)

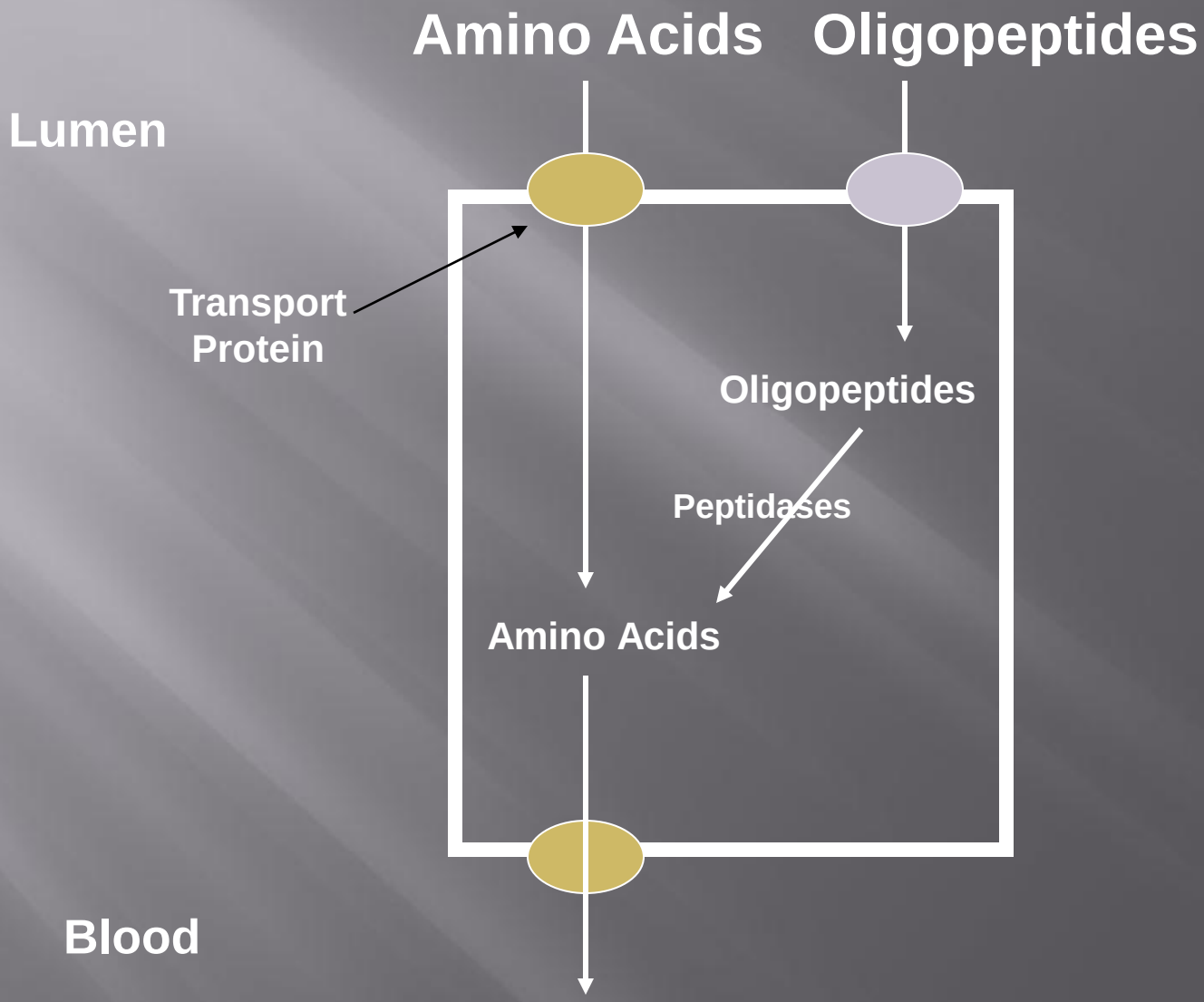
Small Intestine: Trypsinogen —Enteropeptidase→ Trypsin

Trypsin cleaves:

- **Chymotrypsinogen to chymotrypsin**
- **Proelastase to elastase**
- **Procarboxypeptidase to carboxypeptidase**

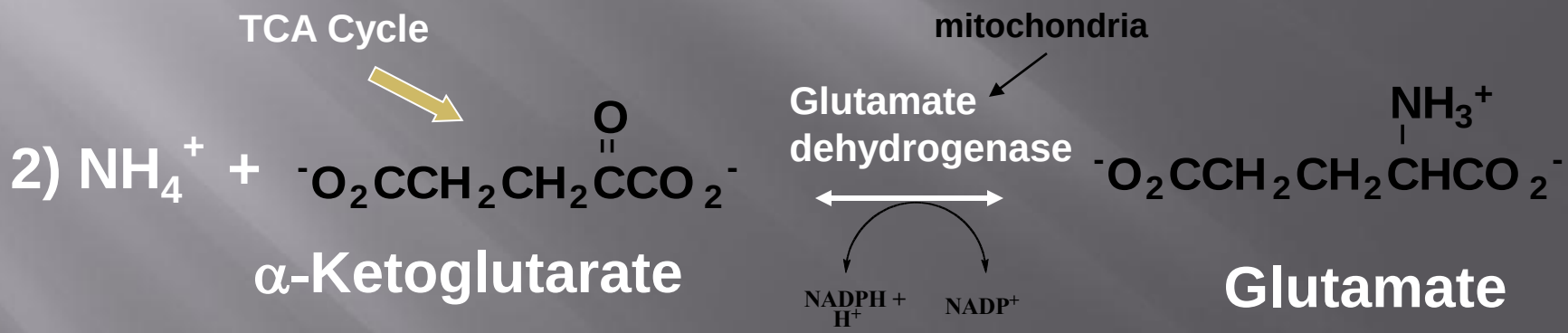
Aminopeptidases (from intestinal epithelia)

Intestinal Absorption



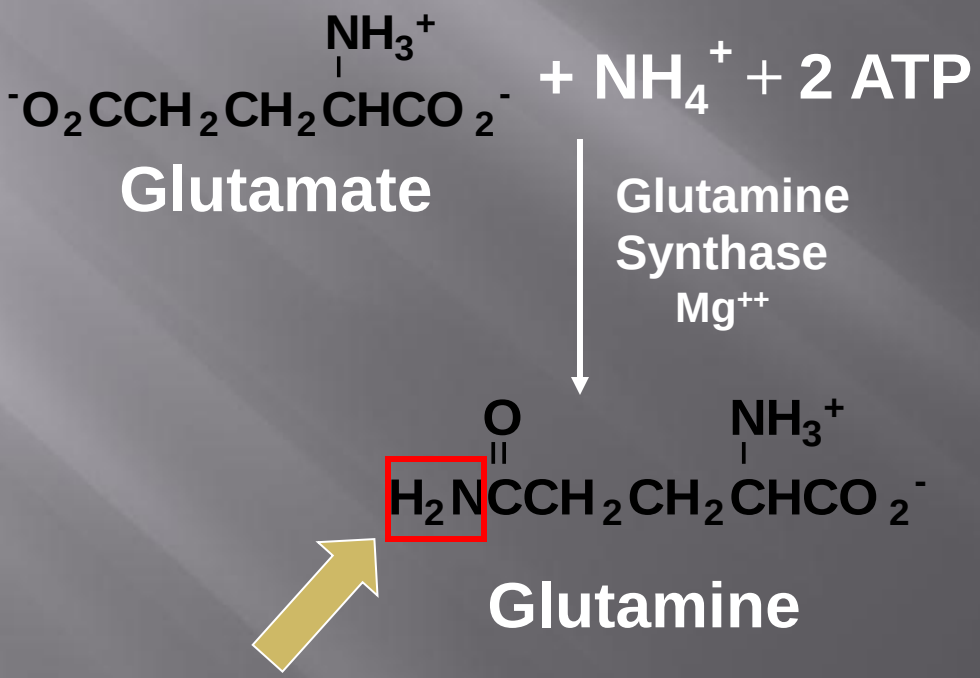
Incorporation of NH_4^+ Into Organic Compounds

1) $NH_4^+ + HCO_3^- + 2\ ATP \xrightarrow[\text{Synthase I (CPS-I)}]{\text{Carbamoyl Phosphate}} NH_2CO_2PO_3^{-2}$ (Carbamoyl Phosphate) $+ 2\ ADP + P_i + 2\ H^+$



Incorporation of NH_4^+ Into Organic Compounds (Cont.)

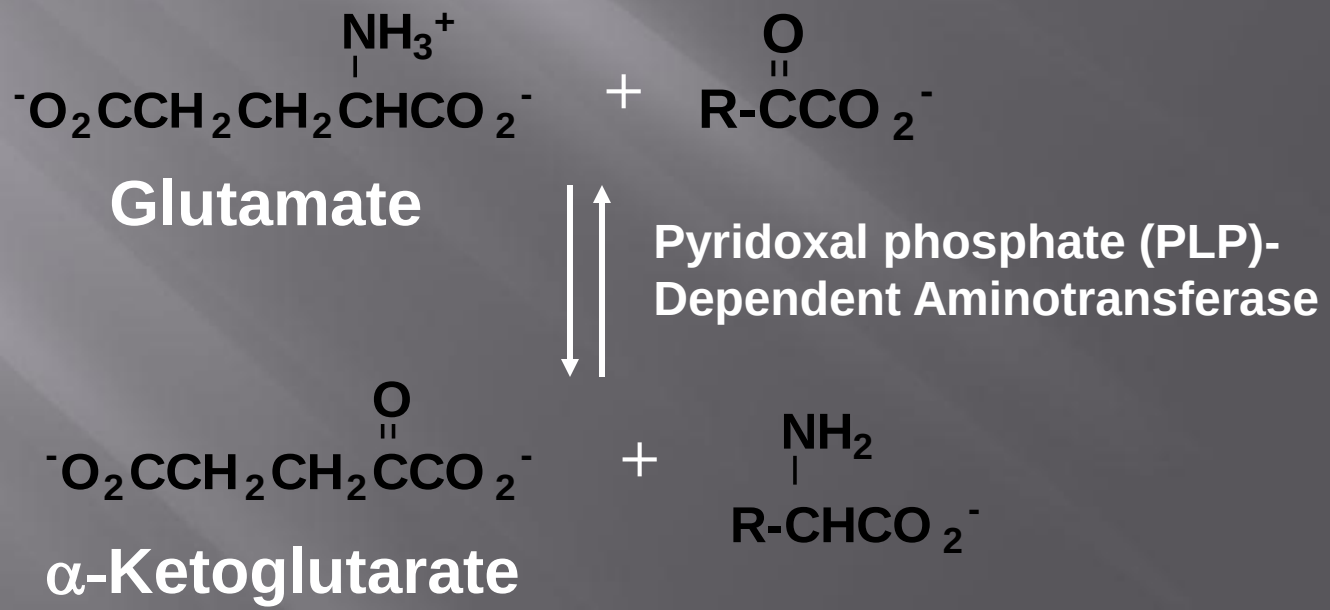
3)

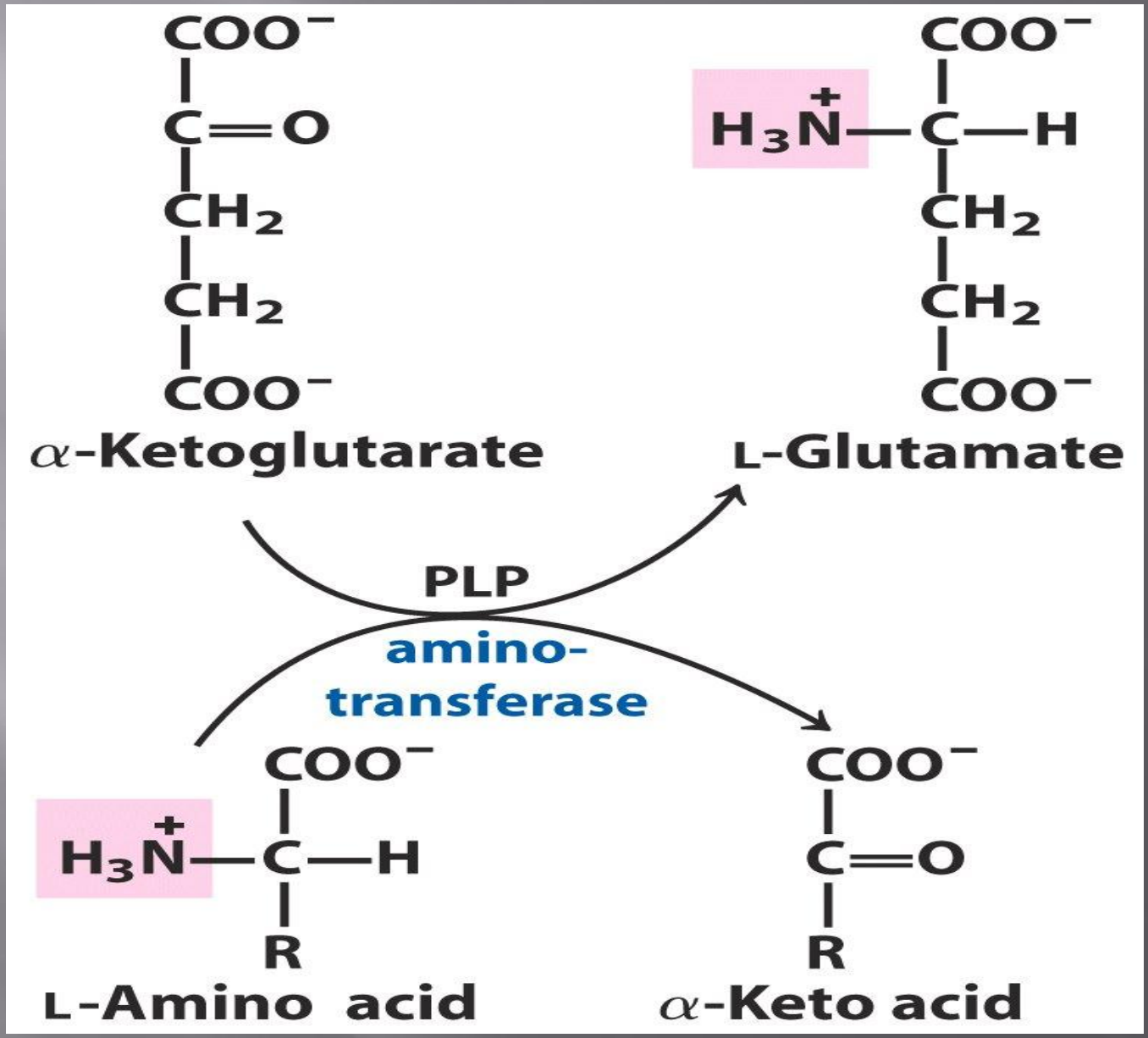


N of glutamine donated to other compounds in synthesis of purines, pyrimidines, and other amino acids

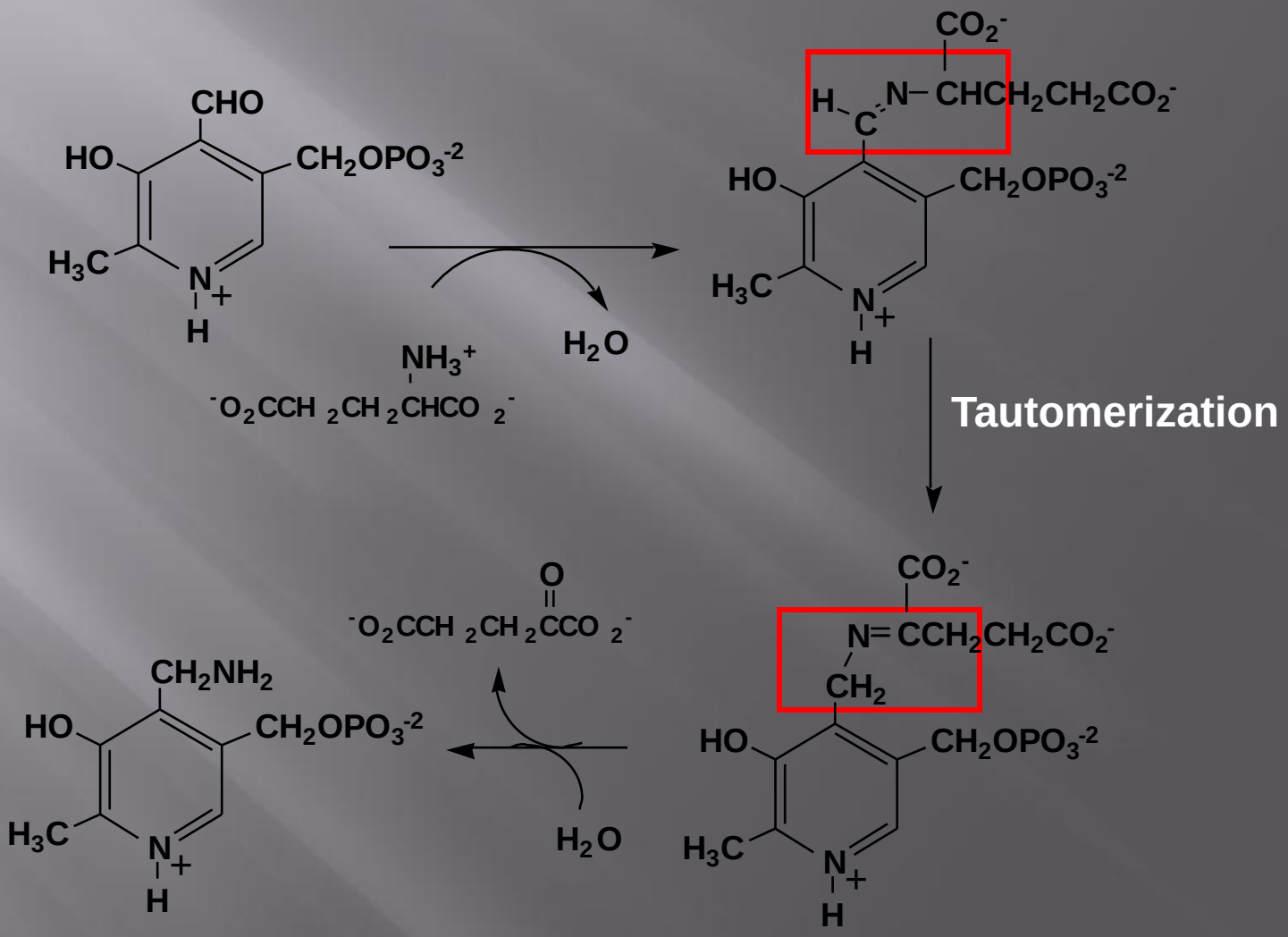
Biosynthesis of Amino Acids: Transaminations

Amino Acid$_1$ + α-Keto Acid$_2$ $\rightleftharpoons$ Amino Acid$_2$ + α-Keto Acid$_1$

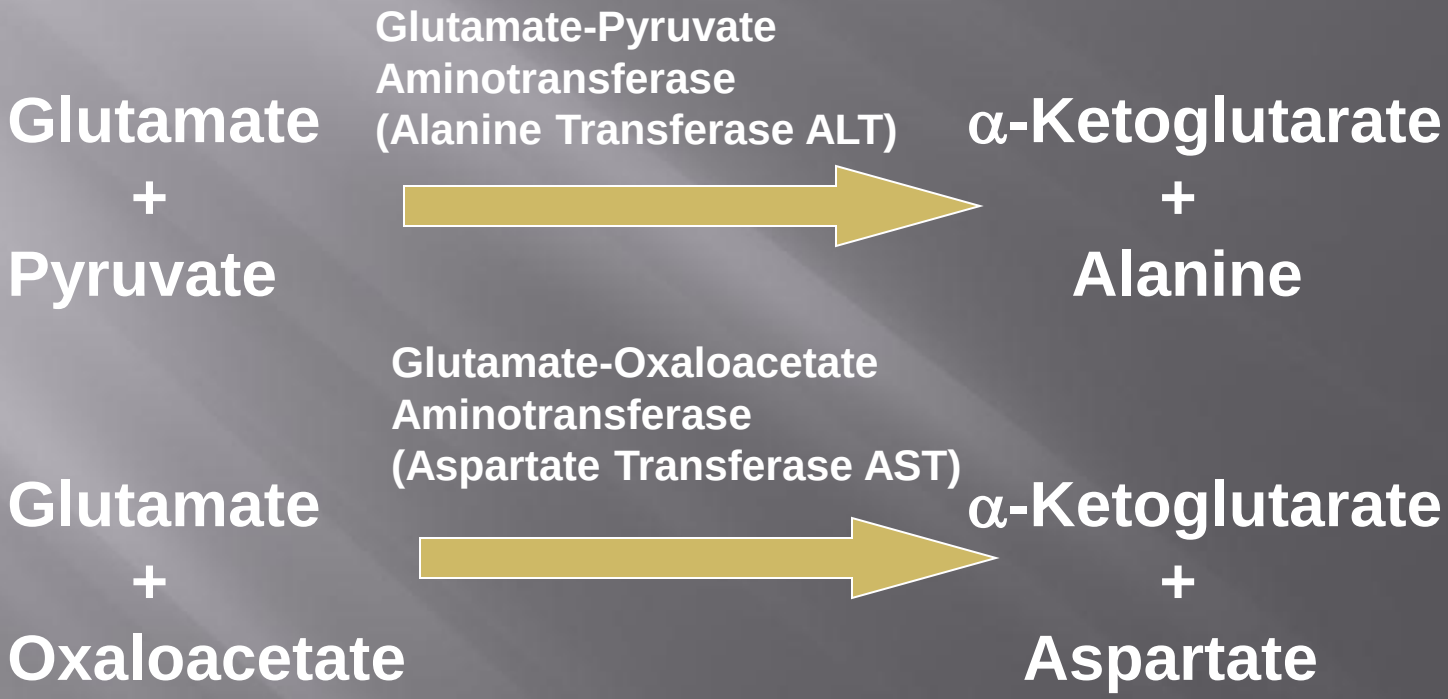



α-Ketoglutarate
L-Glutamate
PLP
amino-
transferase
L-Amino acid
α-Keto acid

Transaminations: Role of PLP



Transaminations



Blood levels of these aminotransferases, also called transaminases, are important indicators of liver disease

Metabolic Classification of the Amino Acids

- **Essential and Non-essential**
- **Glucogenic and Ketogenic**

Non-Essential Amino Acids in Humans

- **Not required in diet**
- **Can be formed from α-keto acids by transamination and subsequent reactions**

- **Alanine**
- **Asparagine**
- **Aspartate**
- **Glutamate**
- **Glutamine**
- **Glycine**
- **Proline**
- **Serine**
- **Cysteine (from Met*)**
- **Tyrosine (from Phe*)**

*** Essential amino acids**

Essential Amino Acids in Humans

- Required in diet
- Humans incapable of forming requisite carbon skeleton

- Arginine*
- Histidine*
- Isoleucine
- Leucine
- Valine
- Lysine
- Methionine
- Threonine
- Phenylalanine
- Tryptophan

* Essential in children, not in adults

Glucogenic Amino Acids

- Metabolized to α-ketoglutarate, pyruvate, oxaloacetate, fumarate, or succinyl CoA

→ Phosphoenolpyruvate → Glucose

- Aspartate
- Asparagine
- Arginine
- Phenylalanine
- Tyrosine
- Isoleucine

- Methionine
- Valine
- Glutamine
- Glutamate
- Proline
- Histidine

- Alanine
- Serine
- Cysteine
- Glycine
- Threonine
- Tryptophan

Ketogenic Amino Acids

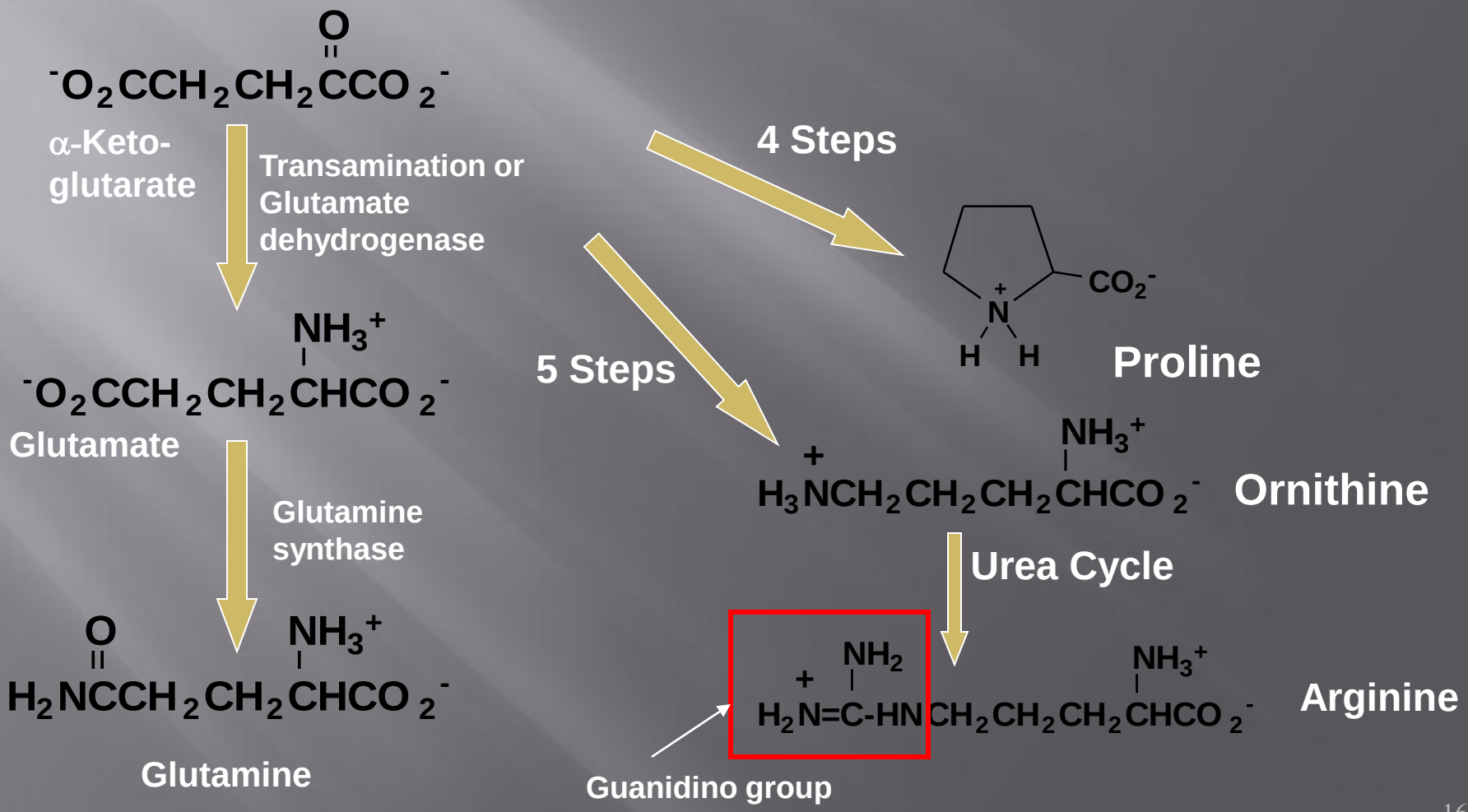
- **Metabolized to acetyl CoA or acetoacetyl CoA**

Animals cannot convert acetyl CoA or acetoacetyl CoA to pyruvate

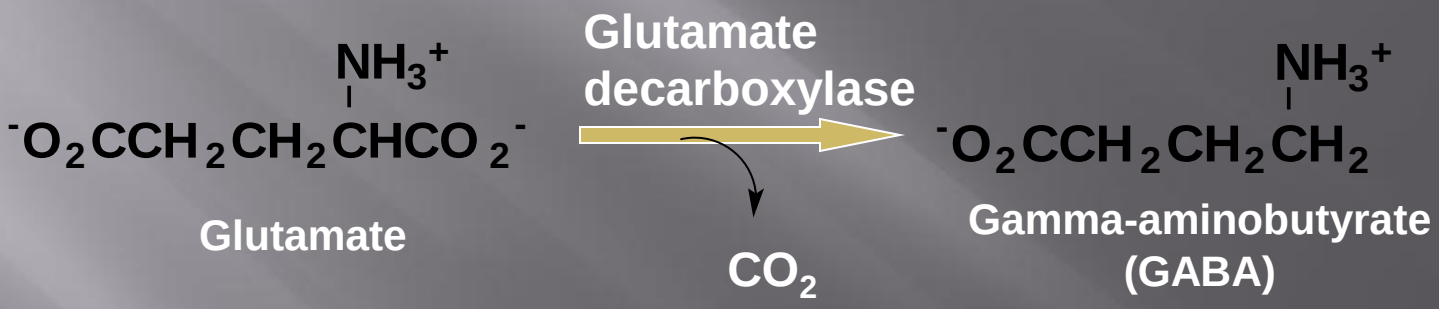
- **Isoleucine**
- **Leucine ***
- **Lysine ***
- **Threonine**
- **Tryptophan**
- **Phenylalanine**
- **Tyrosine**

*** Leucine and lysine are only ketogenic**

Amino Acids Formed From α-Ketoglutarate



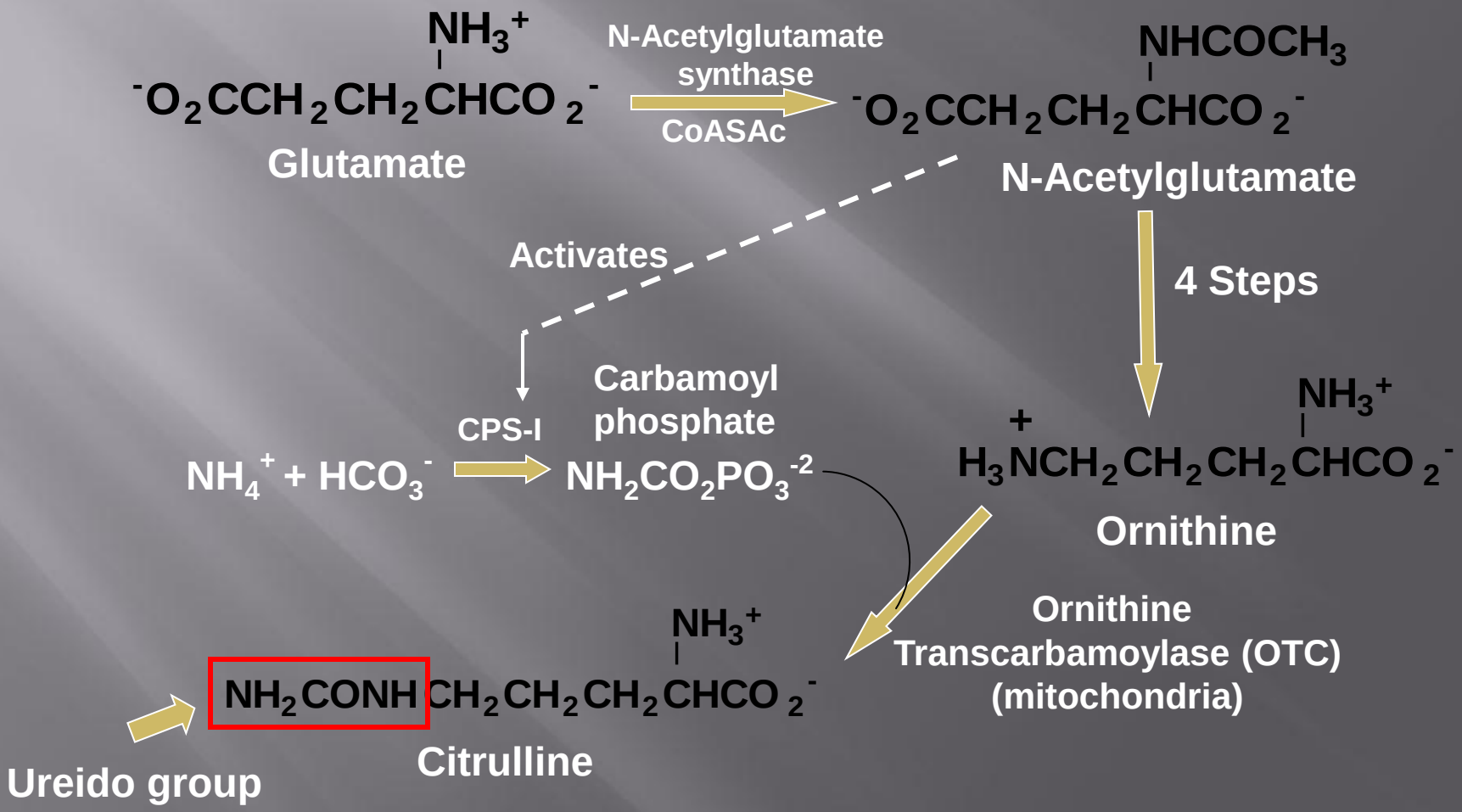
GABA Formation



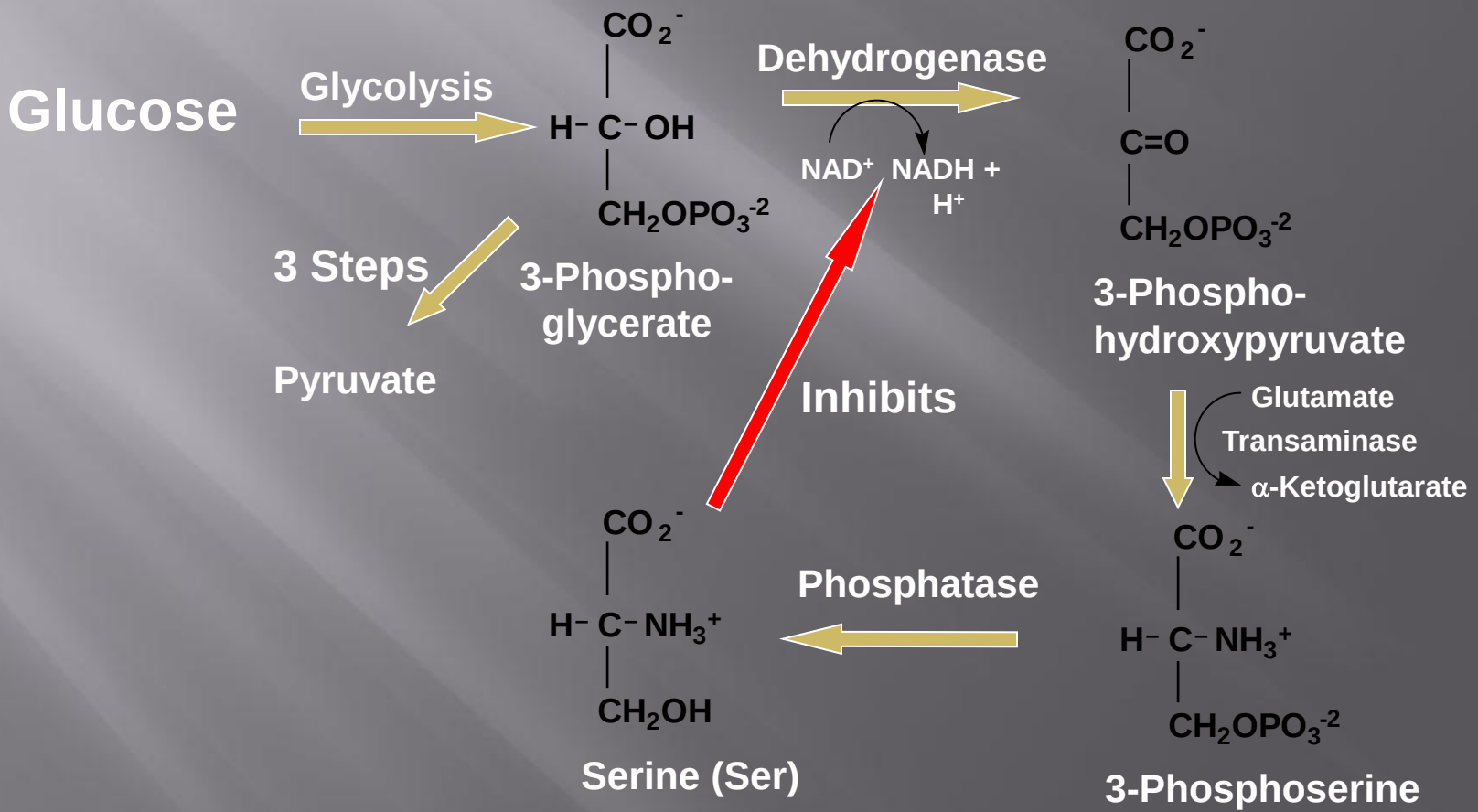
GABA is an important inhibitory neurotransmitter in the brain

Drugs (*e.g.*, benzodiazepines) that enhance the effects of GABA are useful in treating epilepsy

Arginine Synthesis: The Urea Cycle



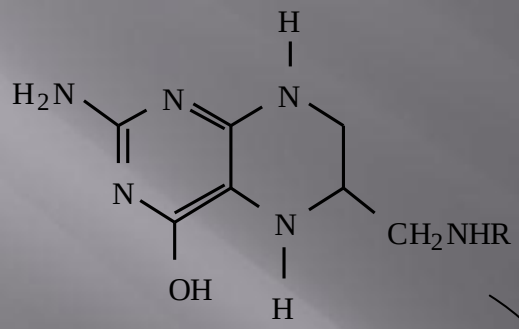
Formation of Serine



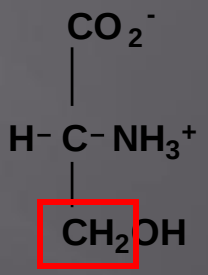
Conversion of Serine to Glycine

Folate

Dihydrofolate reductase

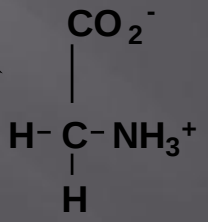


Tetrahydrofolate (FH_4)



Serine

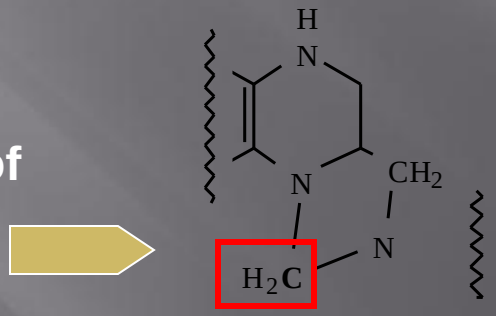
Serine hydroxymethyl transferase (PLP-dep.)



Glycine

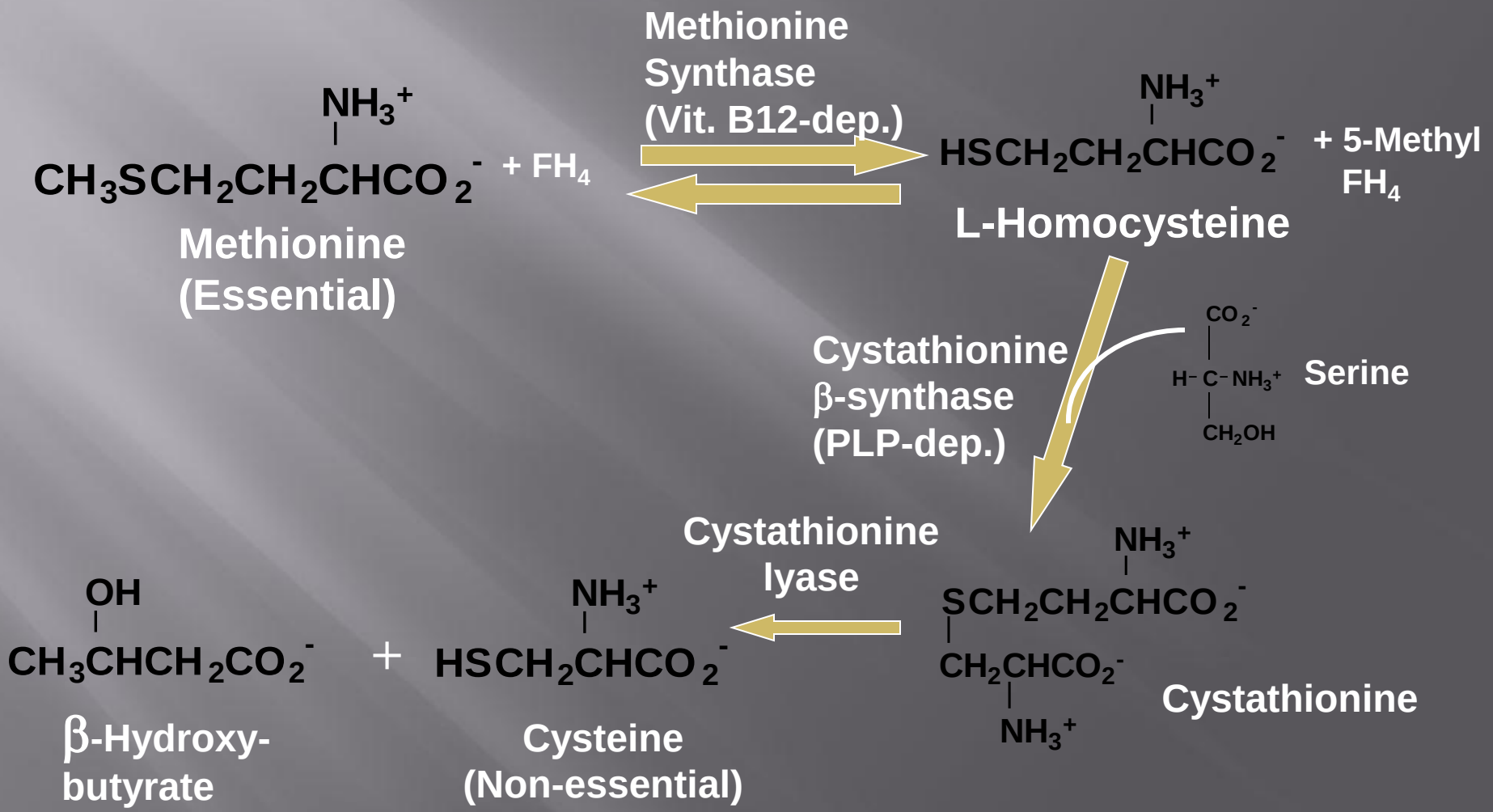
Important in biosynthesis of heme, porphyrins, and purines

Key intermediate in biosynthesis of purines and formation of thymine



N^5, N^{10}-Methylene FH_4

Sulfur-Containing Amino Acids



Homocysteine

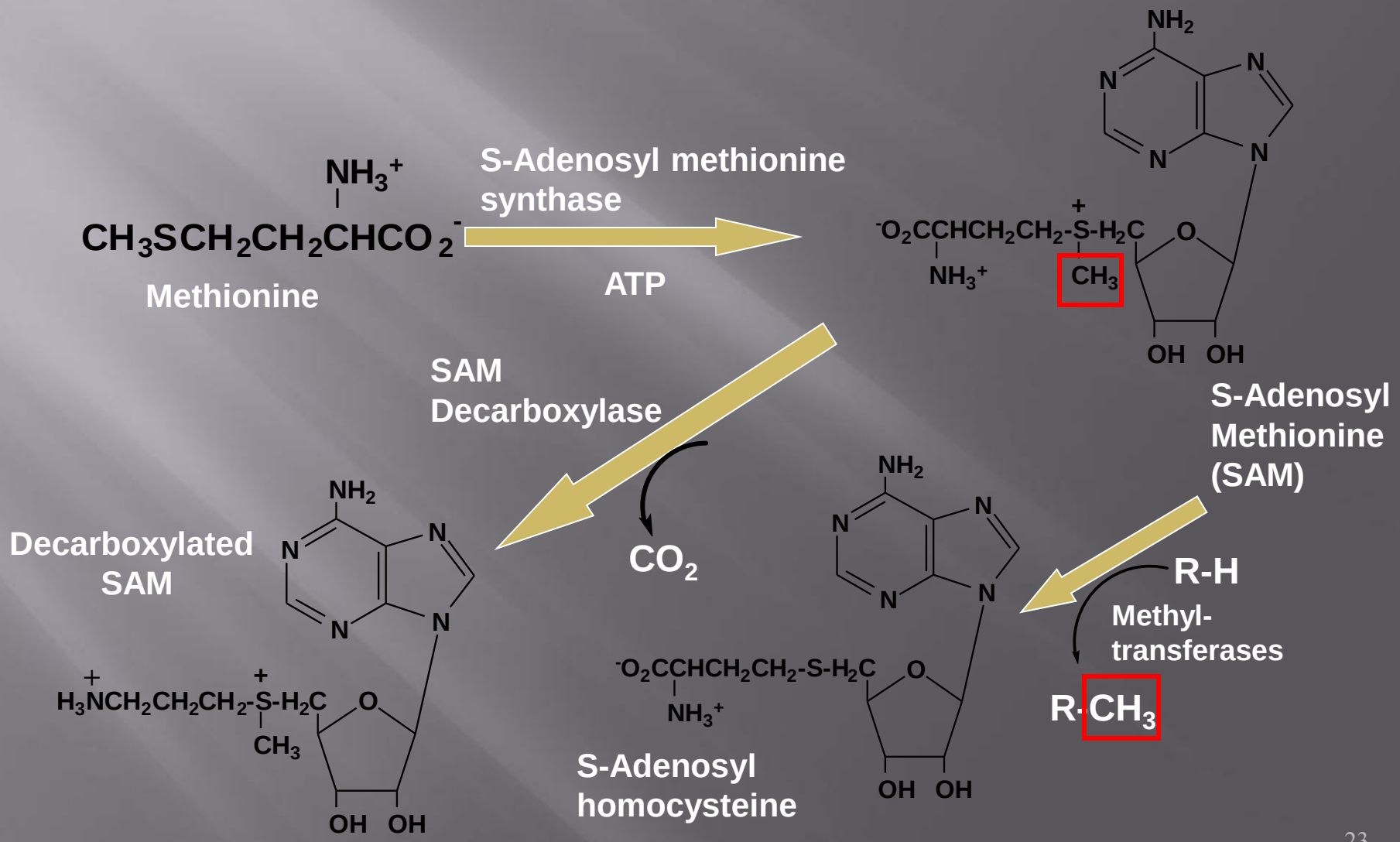
Homocysteinuria

- **Rare; deficiency of cystathionine β-synthase**
- **Dislocated optical lenses**
- **Mental retardation**
- **Osteoporosis**
- **Cardiovascular disease → death**

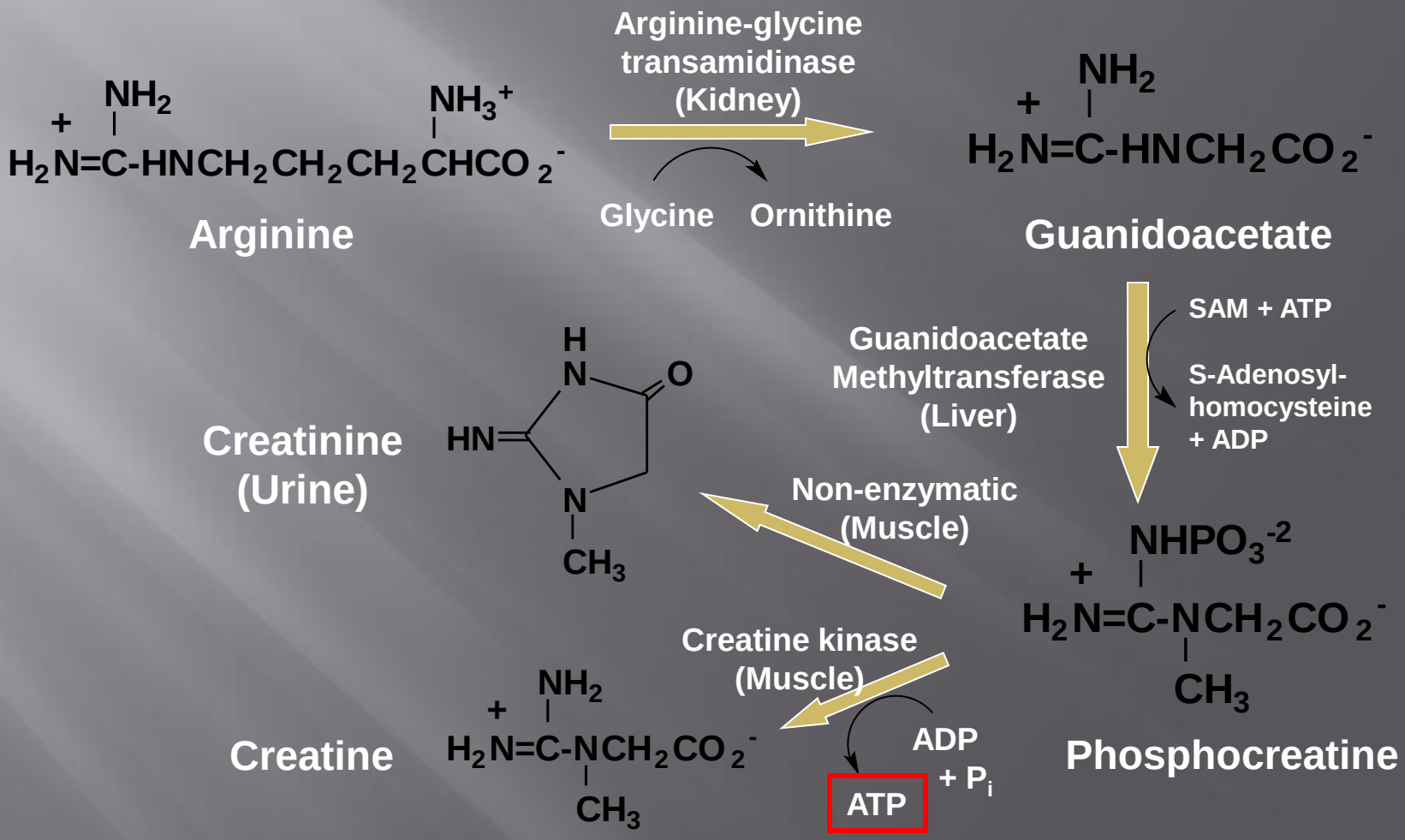
High blood levels of homocysteine associated with cardiovascular disease

- **May be related to dietary folate deficiency**
- **Folate enhances conversion of homocysteine to methionine**

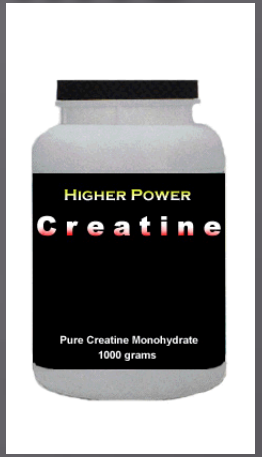
Methionine Metabolism: Methyl Donation



Creatine and Creatinine



Creatine and Creatinine



Creatine:

- Dietary supplement
- Used to improve athletic performance

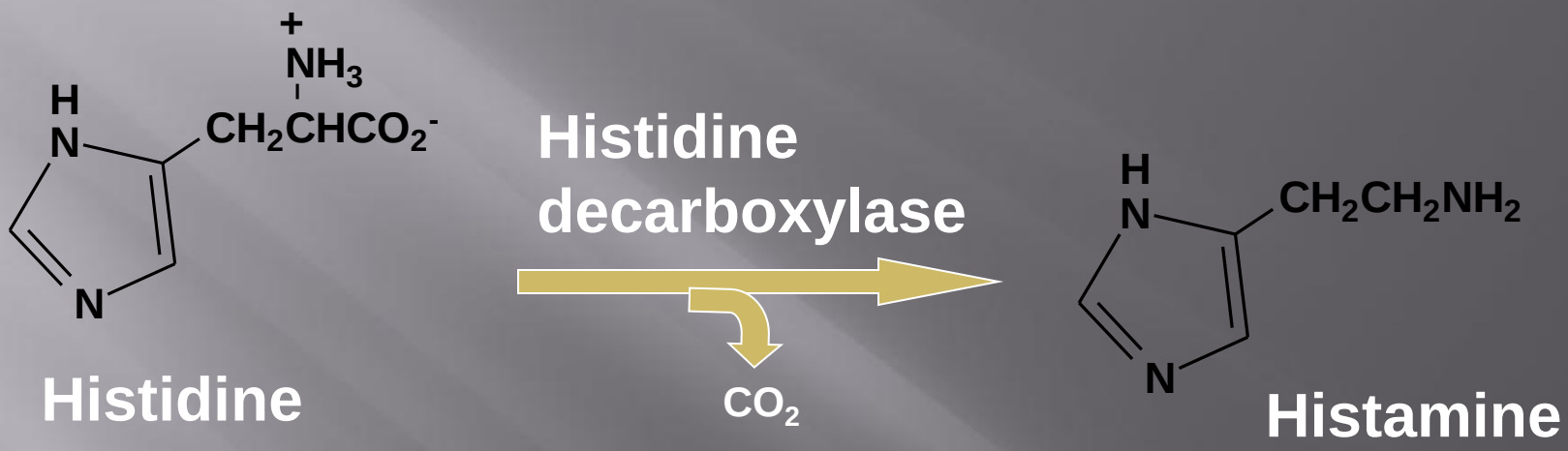
Creatinine:

- Urinary excretion generally constant; proportional to muscle mass

Creatinine Clearance Test:

- Compares the level of creatinine in urine (24 hrs.) with the creatinine level in the blood
- Used to assess kidney function
- Important determinant in dosing of several drugs in patients with impaired renal function

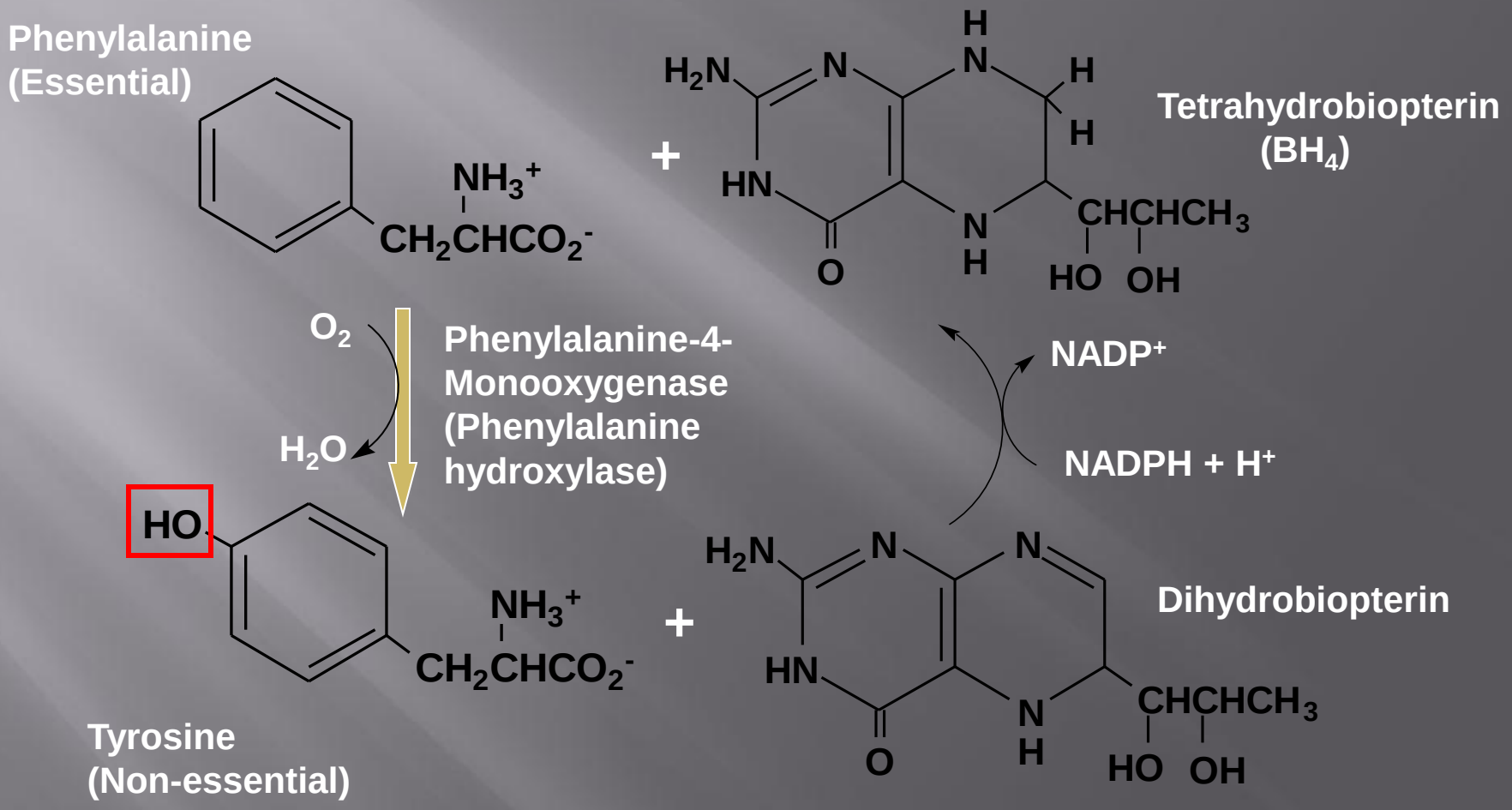
Histidine Metabolism: Histamine Formation



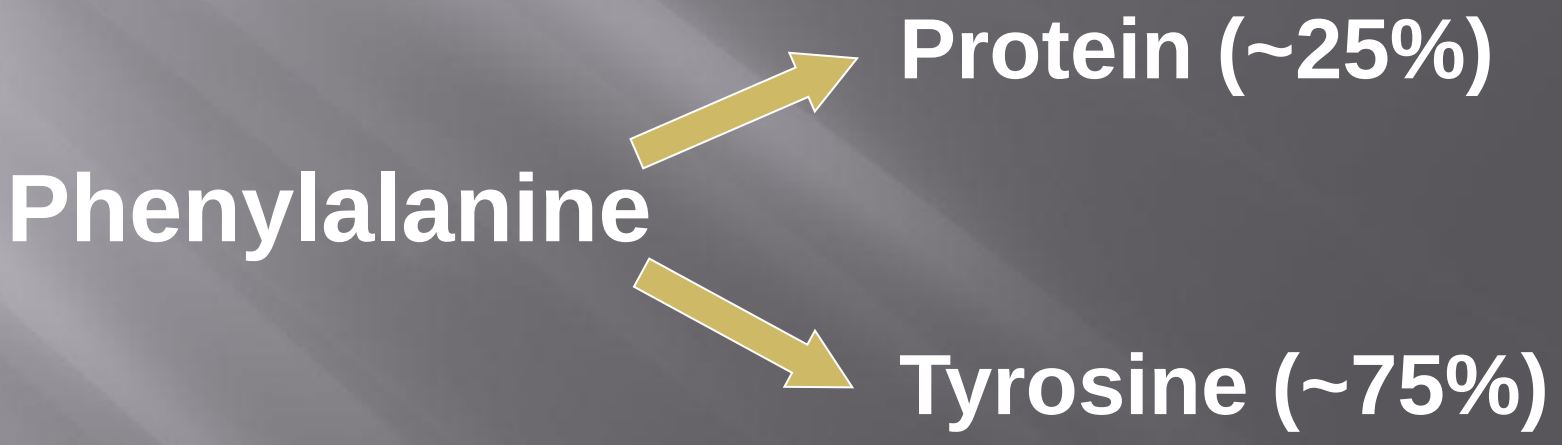
Histamine:

- Synthesized in and released by mast cells
- Mediator of allergic response: vasodilation, bronchoconstriction (H_1 receptors)
  - H_1 blockers: Diphenhydramine (Benadryl)
    Loratidine (Claritin)
- Stimulates secretion of gastric acid (H_2 receptors)
  - H_2 blockers: Cimetidine (Tagamet); ranitidine (Zantac)

Phenylalanine and Tyrosine

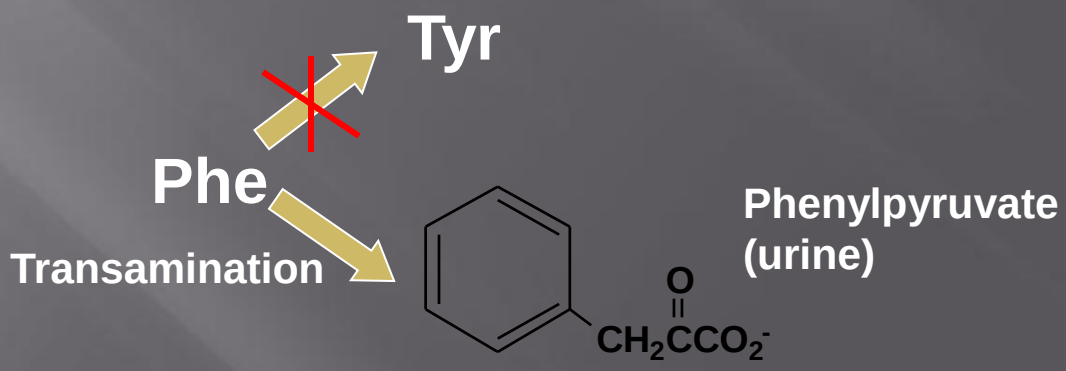


Normal Utilization of Phenylalanine

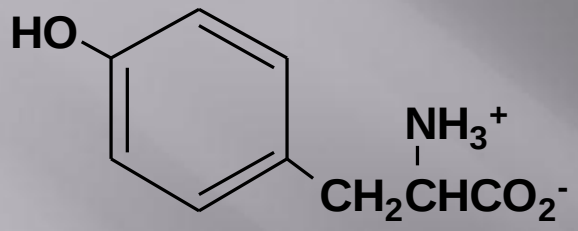


Phenylketonuria (PKU) Disease

- Deficiency of Phe hydroxylase
- Occurs in 1:20,000 live births in U.S.
- Seizures, mental retardation, brain damage
- Treatment: limit phenylalanine intake
- Screening of all newborns mandated in all states



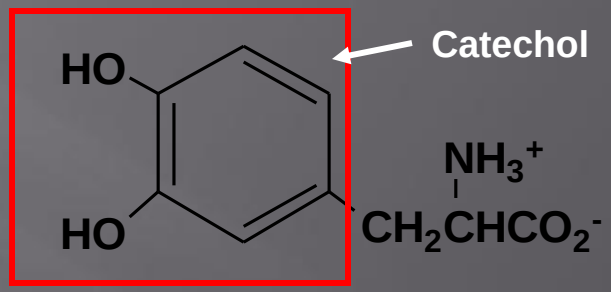
Catecholamine Biosynthesis



Tyrosine

Tyr hydroxylase

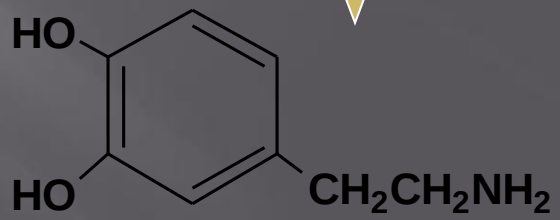
O_2



Dihydroxyphenylalanine (DOPA)

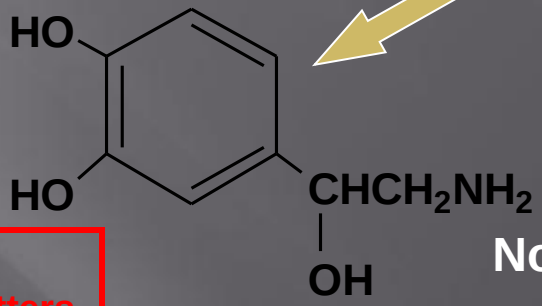
DOPA decarboxylase

CO_2



Dopamine

Dopamine hydroxylase

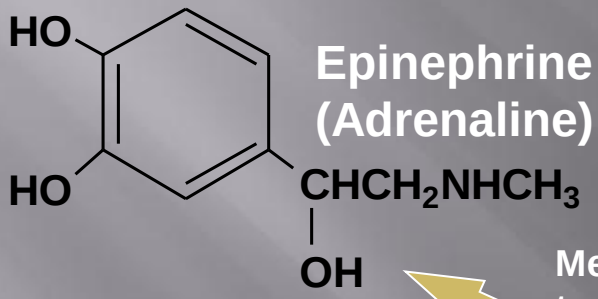


Norepinephrine

Methyl transferase

S-Adenosyl-homocysteine

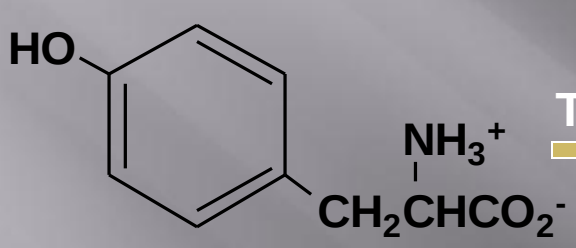
SAM



Epinephrine (Adrenaline)

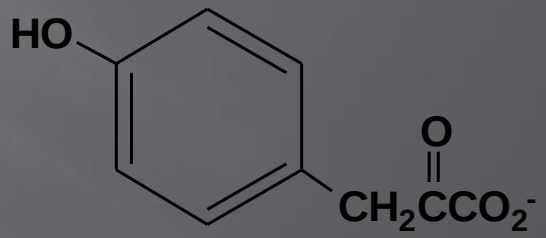
DOPA, dopamine, norepinephrine, and epinephrine are all neurotransmitters

Tyrosine catabolism



Tyrosine

Transamination



p-Hydroxyphenyl-pyruvate

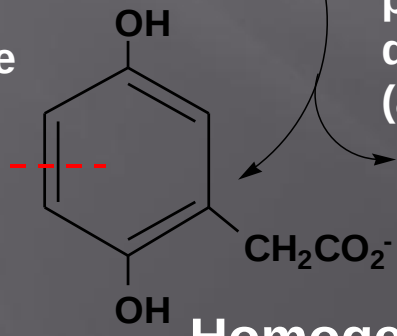
O_2

p-Hydroxyphenyl-pyruvate dioxygenase (ascorbate-dep.)

CO_2

Deficient in alkaptonuria

Homogentisate dioxygenase



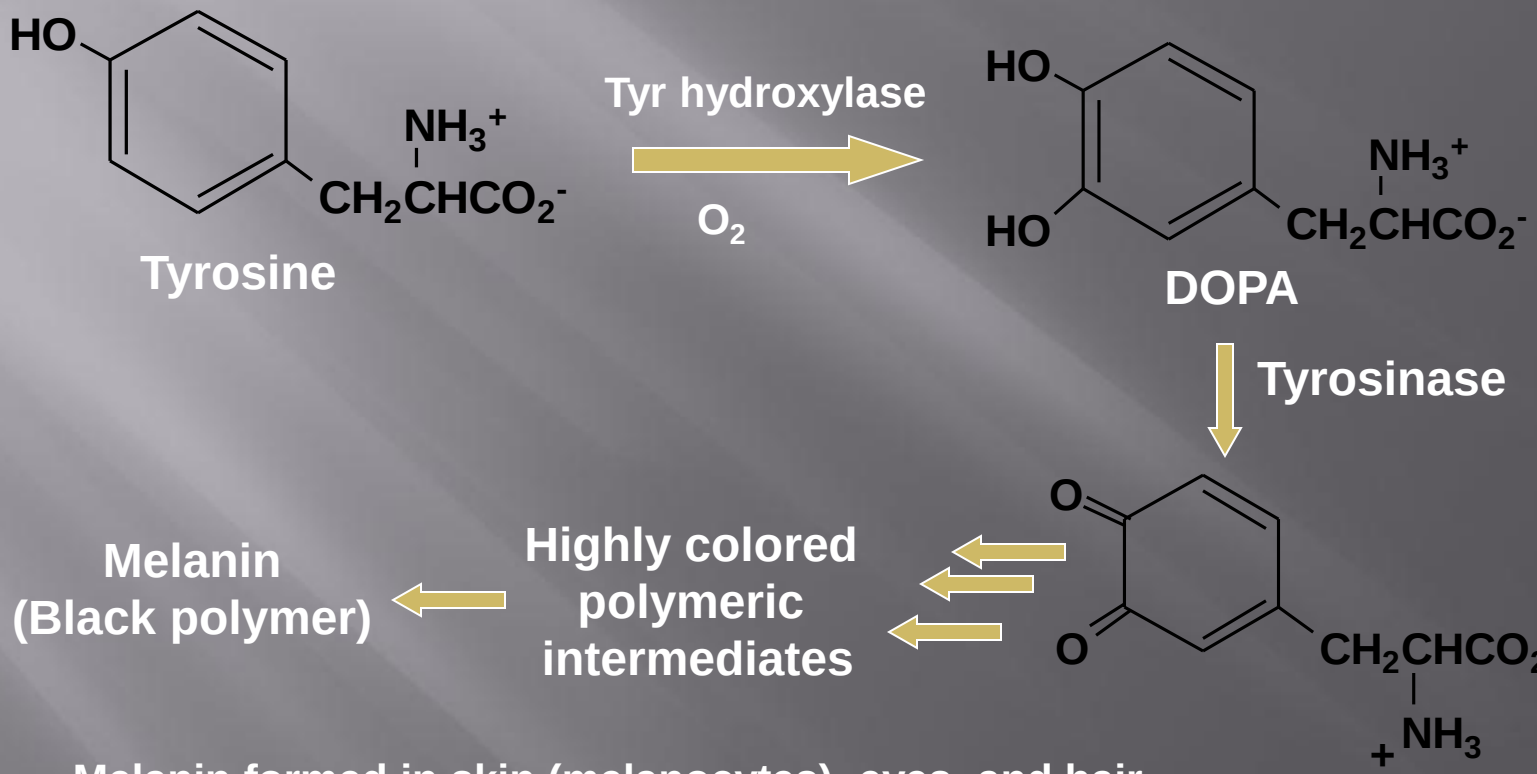
Homogentisate

O_2

Cleavage of aromatic ring

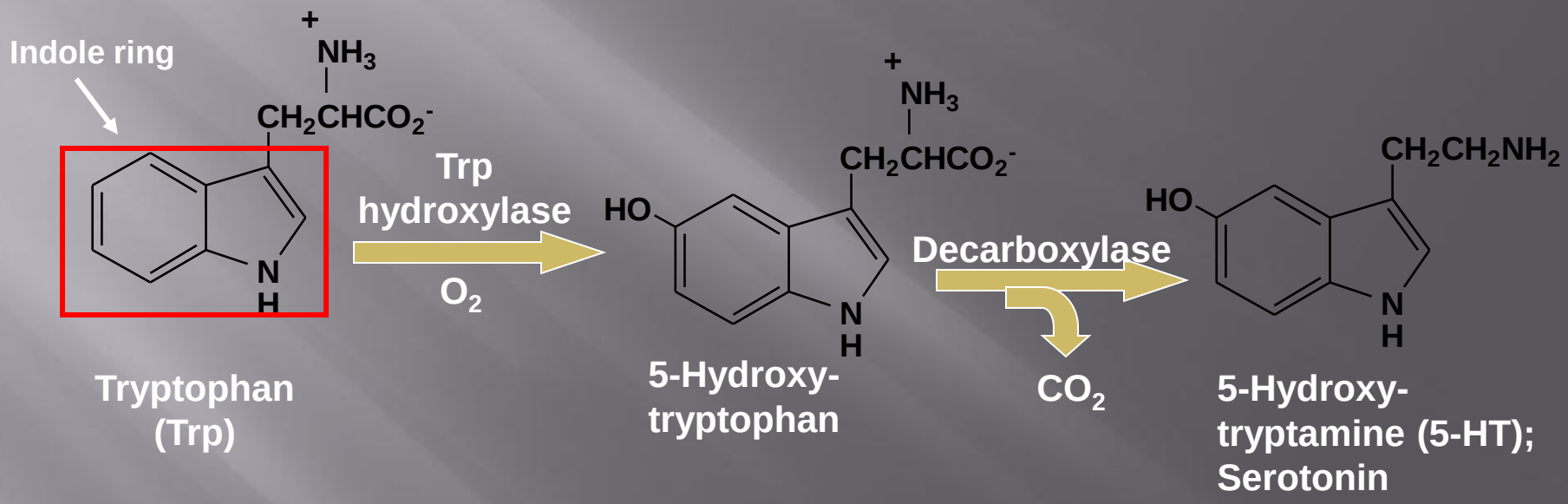
Fumarate + acetoacetate

Melanin Formation



Melanin formed in skin (melanocytes), eyes, and hair
In skin, protects against sunlight
Albinism: genetic deficiency of tyrosinase

Tryptophan Metabolism: Serotonin Formation



Serotonin

- Serotonin formed in:
  - Brain (neurotransmitter; regulation of sleep, mood, appetite)
  - Platelets (platelet aggregation, vasoconstriction)
  - Smooth muscle (contraction)
  - Gastrointestinal tract (enterochromaffin cells - major storage site)

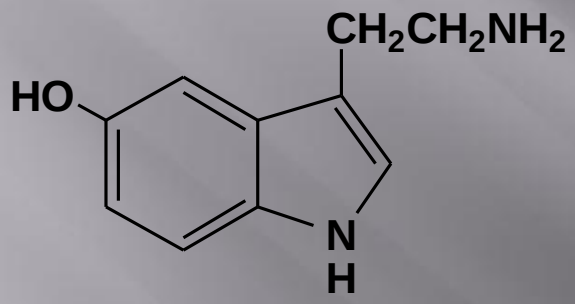
- Drugs affecting serotonin actions used to treat:
  - Depression
    - Serotonin-selective reuptake inhibitors (SSRI)
  - Migraine
  - Schizophrenia
  - Obsessive-compulsive disorders
  - Chemotherapy-induced emesis

- Some hallucinogens (*e.g.*, LSD) act as serotonin agonists

L-Tryptophan

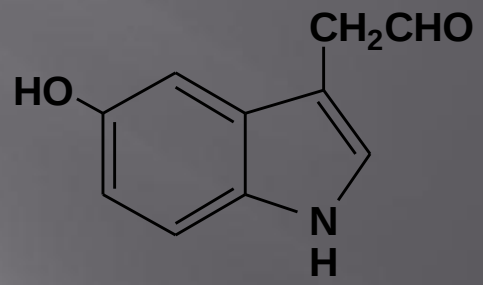
- Food supplement promoted for serotonin effects
- L-Tryptophan disaster (1989):
  - Eosinophilia-myalgia syndrome (EMS)
    - Severe muscle and joint pain
    - Weakness
    - Swelling of the arms and legs
    - Fever
    - Skin rash
    - Eosinophilia
    - Many hundreds of cases; several deaths
    - Traced to impurities

Serotonin Metabolism: 5-HIAA

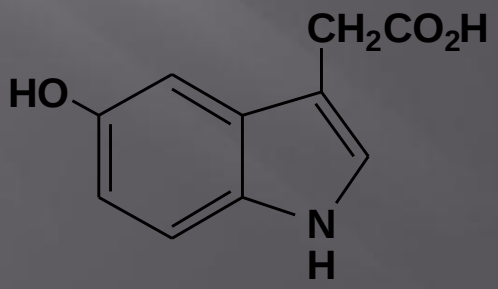


Serotonin

MAO



Dehydrogenase

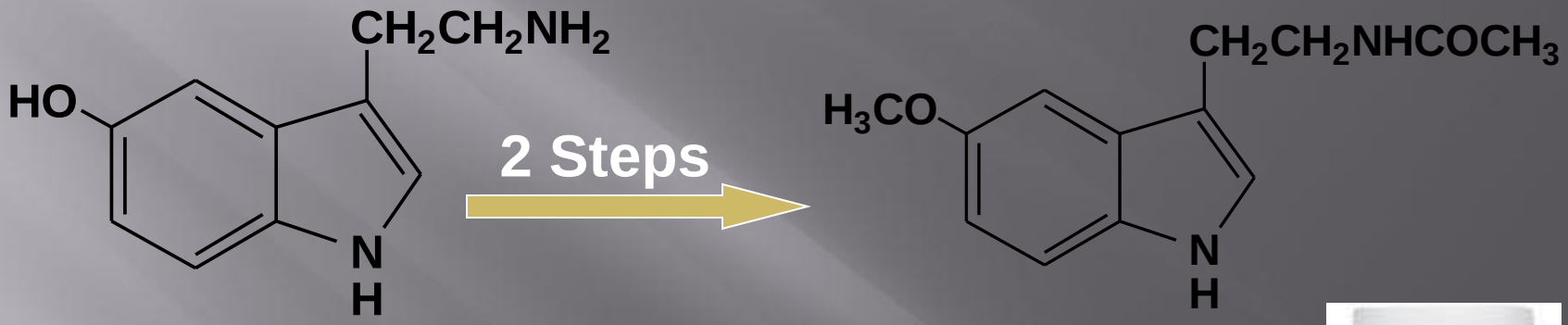


5-Hydroxyindole acetic acid (5-HIAA) (Urine)

Carcinoid tumors:

- Malignant GI tumor type
- Excretion of large amounts of 5-HIAA

Serotonin Metabolism: Melatonin



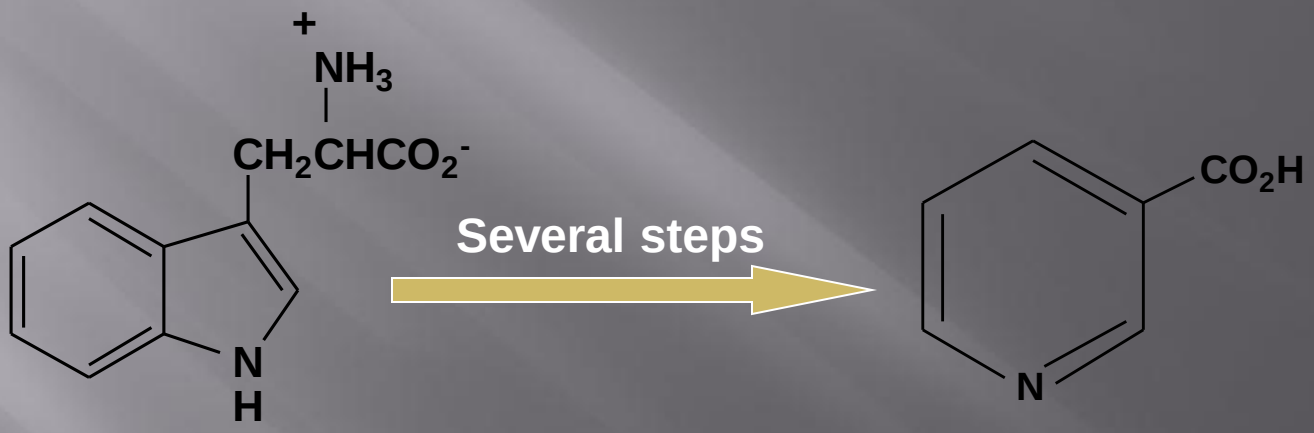
Serotonin

Melatonin

Melatonin:

- Formed principally in pineal gland
- Synthesis controlled by light, among other factors
- Induces skin lightening
- Suppresses ovarian function
- Possible use in sleep disorders

Tryptophan Metabolism: Biosynthesis of Nicotinic Acid



Tryptophan → **Several steps** → **Nicotinic acid (Niacin)**

↓

Nicotinamide adenine dinucleotide (NAD)