Biochemical aspects of kidney function

by

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Introduction

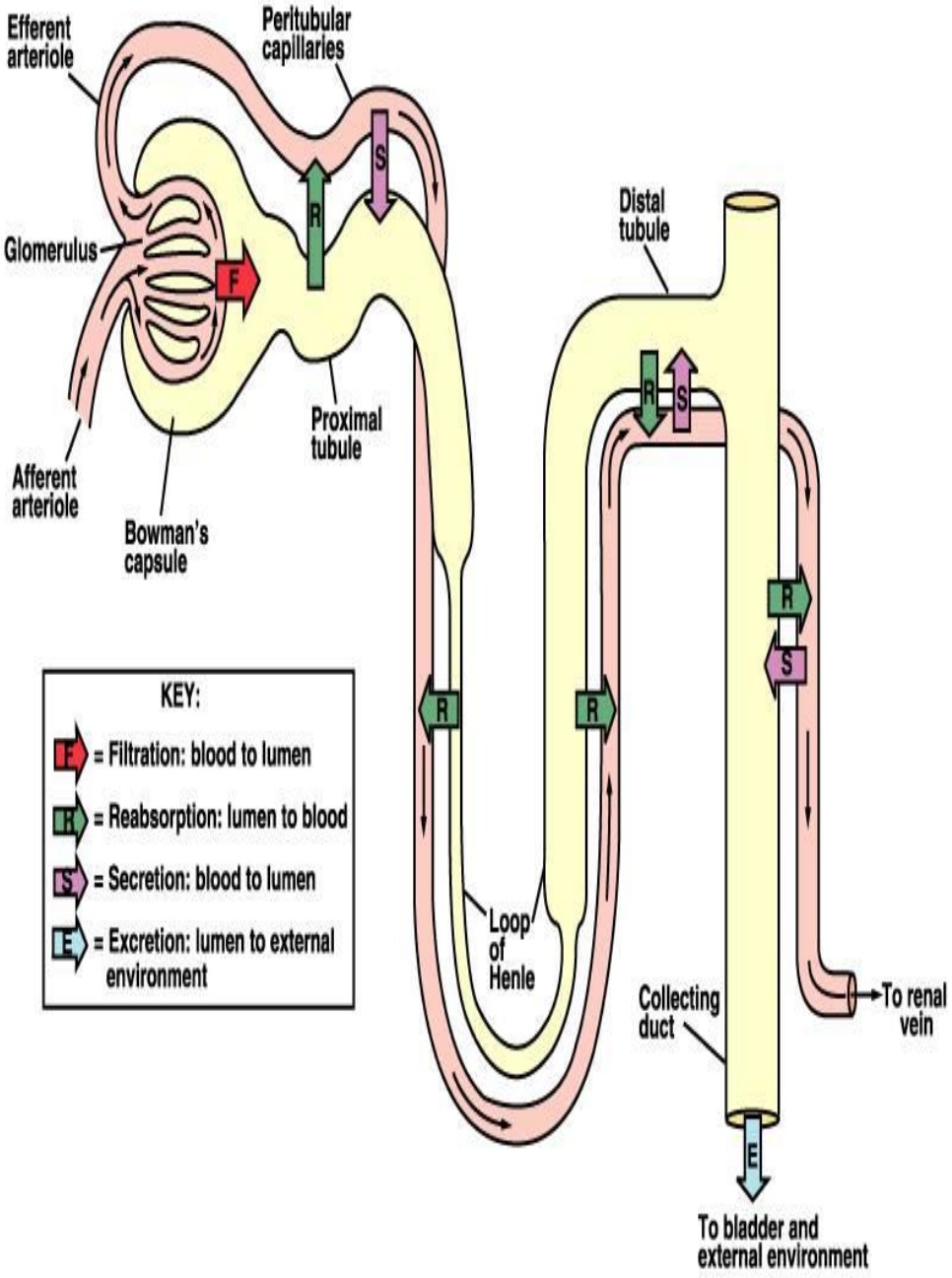
Urine formation

Structures responsible for the urine formation:

- glomeruli.
- proximal convoluted tubule.
- distal convoluted tubule.

Mechanism of urine formation:

- filtration
- reabsorption
- secretion



Glomeruli: site of filtration

- Substances with molecular mass **below** ***40,000 Da*** pass through the membrane of glomerulus.
- About **120 mL/min** or ***180 L/day*** of blood is filtrated.
- Filtration – ***passive process***.
- After filtration – **primary urine** (180 L/day)

TUBULES FUNCTION:

1. Proximal convoluted tubule:

- **Reabsorption**
  - substances from the glomerular filtrate:

  - ¾ of Na and water. - totally glucose. - most of amino acids. - varied amounts of electrolytes (Mg, Ca, K, Cl, HCO_3^-) and small molecules (proteins, uric acid, urea)
- **Secretion:**
  - K^+, H^+, ammonia, uric acid, certain organic bases, medicines (penicillin).

2. Distal Convoluted Tubule: here the final stage of optimal concentration control takes place for the balance of fluids and electrolytes.

- Reabsorption: small amounts of salt, water, bicarbonates
- Secretion: uric acid, ammonia, H^+
- This is the action place for
  - **aldosterone** - ↑ reabsorption of Na and secretion of K
  - **ADH** - ↑ permeability and water reabsorption.

3. Collector Duct:

- **ADH** controls water reabsorption - determines urine concentration
- **Aldosterone** controls Na reabsorption

Intercalated cells

- There are **two types of intercalated cells** identified as type A (alpha) and type B (beta):
- **Principal cells:** reabsorb Na^+ and excrete K^+. Principal cells are the major cell types that respond to the actions of **aldosterone**.

1. **Type A:** intercalated cells reabsorb K^+ and HCO_3^- and excrete H^+.
2. **Type B:** intercalated cells function in opposition to type A cells such that they secrete HCO_3^- and reabsorb H^+.

- The differences in function between type A and type B intercalated cells is due, in part, ***to the opposing distributions of various transporter proteins.***

Kidney metabolism
1. Carbohydrate: a. Glycolysis

- Utilization of glucose in cortex and medulla differs one from another.
- Dominant type of glycolysis:

➢ **In cortex** is ***aerobic*** and CO_2 formed in result.

➢ **In medulla** is ***anaerobic*** and glucose converted to lactate by lactate dehydrogenase (LDH).

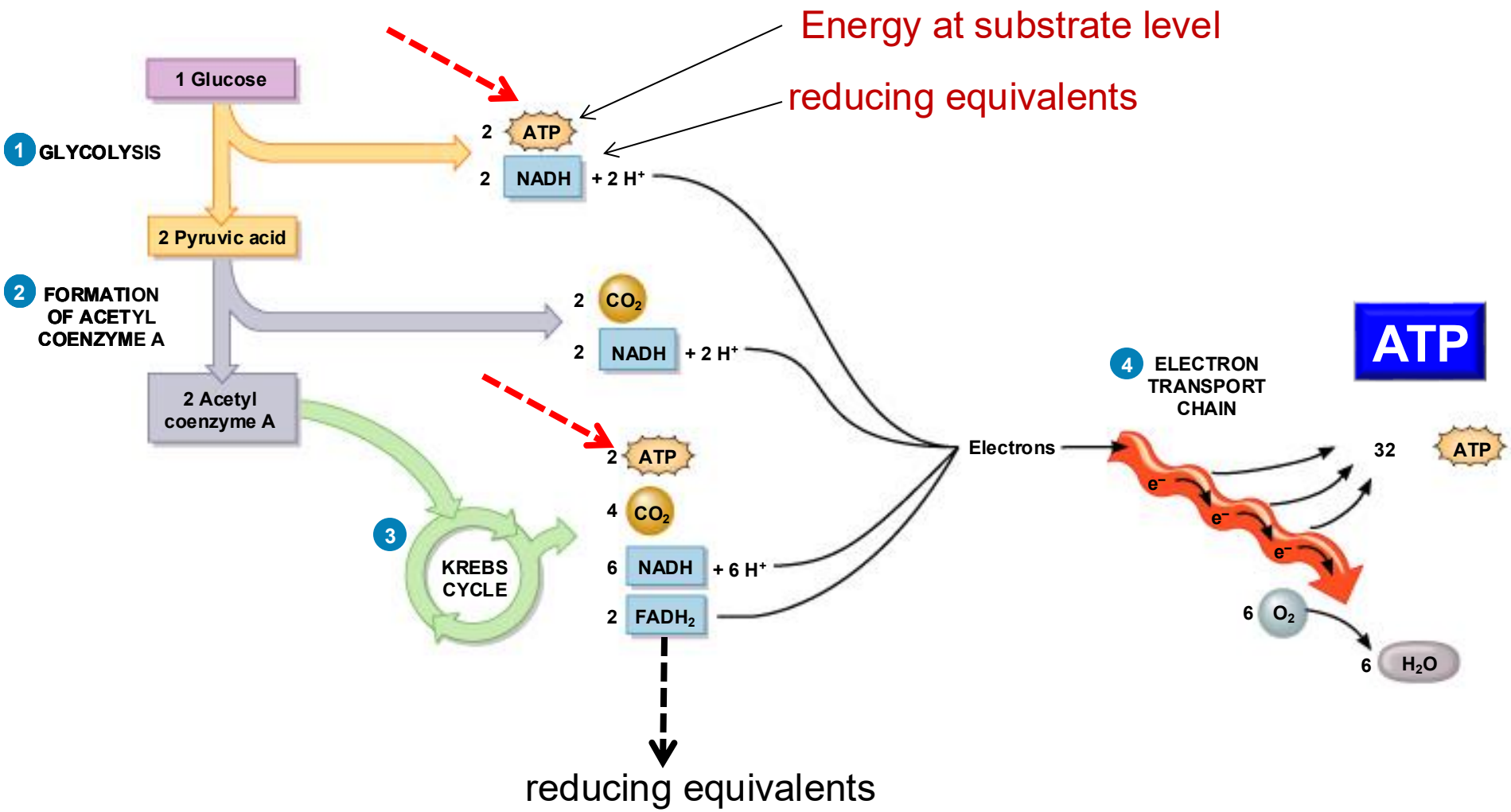
b. Gluconeogenesis:

- ***Kidney cortex*** like ***liver*** appear to be unique in that it possess the enzymatic potential for both:

➢ glucose synthesis (gluconeogenesis).

➢ glucose degradation (glycolysis).

Glucose oxidation



b. Gluconeogenesis:

Definition: synthesis of glucose from ***non-carbohydrate*** precursors such as: 1- lactate. 2-glucogenic amino acids (Gln, Ala). 3-glycerol.

4-propionate.

Site: in ***liver*** (90%) & ***kidney cortex*** (10%)

Importance:

1. Gluconeogenesis is important when the dietary supply of glucose does not satisfy the metabolic demands.

- Under these conditions, glucose is required by the ***CNS***, the ***RBC***, ***renal medulla*** and possibly, other tissues which cannot obtain all their energy requirements from fatty acids or ketone body oxidation.

2. gluconeogenesis may be important in the removal of excessive quantities of glucose precursors from the blood (lactic acid after severe exercise for example).

- The ability of the kidney to convert certain organic acids to glucose, a neutral substance, is an example of a ***nonexcretory mechanism in the kidney for pH regulation***.

Gluconeogenesis: liver vs renal cortex

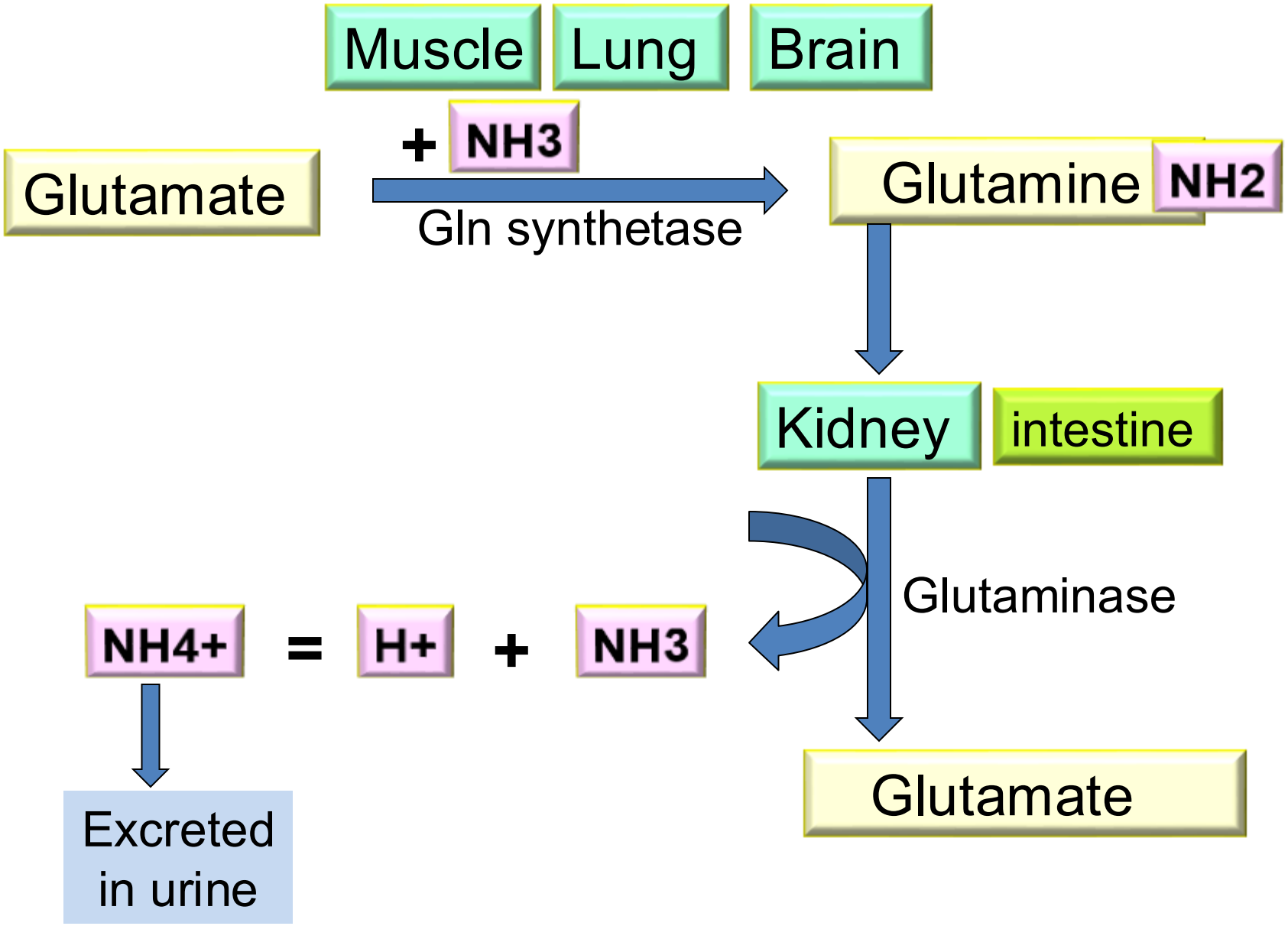
- Although the biosynthetic pathways are similar, there are several important differences in the factors, which regulate gluconeogenesis in the two organs.

1. The **liver** utilizes predominately pyruvate, lactate and ***alanine.*** The **kidney cortex** utilizes pyruvate, lactate, and ***glutamine***.
2. ***Hydrogen ion*** activity has little effect upon hepatic gluconeogenesis, but it has marked effects upon renal gluconeogenesis.

- Thus, when intracellular fluid pH is reduced (acidosis), the rates of gluconeogenesis in slices of renal cortex are markedly increased.

Kidney metabolism: 2. protein
a. glutamine & ammonia

- Gln is generated mainly in the skeletal muscle and also by the lungs and brain for the removal of NH_4^+.
- Cells with rapid turnover rate (tubular cells in kidney, enterocytes, cells of the immune system) are the major sites of Gln uptake
- Here, Gln serves as a fuel and a nitrogen donor for synthetases; in the kidney, the glutaminase reaction is particularly important
- Much of the unused nitrogen from Gln is built into Ala which carries the nitrogen to the liver where it is converted to urea.


Muscle
Lung
Brain
+ NH3
Glutamate
Gln synthetase
Glutamine NH2
Kidney
intestine
Glutaminase
NH4+ = H+ + NH3
Excreted in urine
Glutamate

Protein metabolism: a. Glutamine & ammonia.

Sources of blood ammonia:

1.From amino acids :

- Transdeamination
- Oxidative deamination
- Non-oxidative deamination .

2.From glutamine:

- Renal glutaminase
- Intestinal glutaminase

3.From amines :

- dietary amine
- monoamine hormones by amine oxidase.

4. From catabolism of purines and pyrimidines .

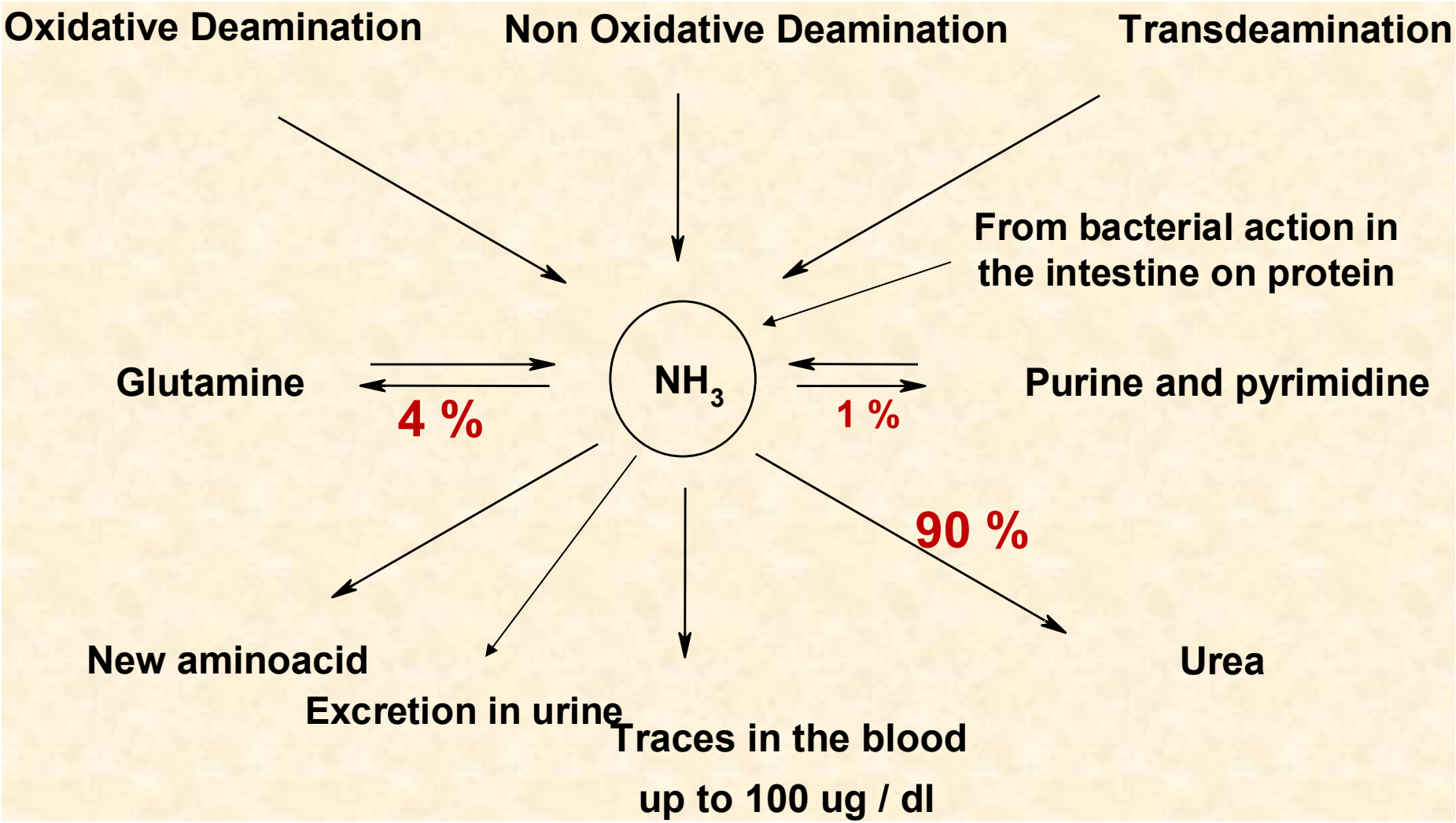
5.From bacterial action in the intestine either from

- dietary protein residue
- urea diffuses into the intestine.

Protein metabolism: a. Glutamine & ammonia.

Fates **of blood ammonia:**

- ***Amination*** of α-ketoacid to form non-essential amino acids and other biosynthetic reactions.
- ***Glutamine synthesis*** in the brain, liver, muscle and renal tissues (4%).
- The majority of NH_3 (90%) will produce ***urea*** in the liver by urea cycle.
- Traces in ***blood*** (up to 100 ug / dl).
- Excretion in ***urine.***



Sources and Fates of blood ammonia

Protein metabolism: a. Glutamine & ammonia.

Renal ammonia:

- **Two sources contribute to the renal ammonia:**

1. ***blood*** ammonia (is about one-third of excreted ammonia).
2. ammonia formed in the ***kidney*** through:

- *Glutaminase.*
- *Glutamate dehydrogenase.*

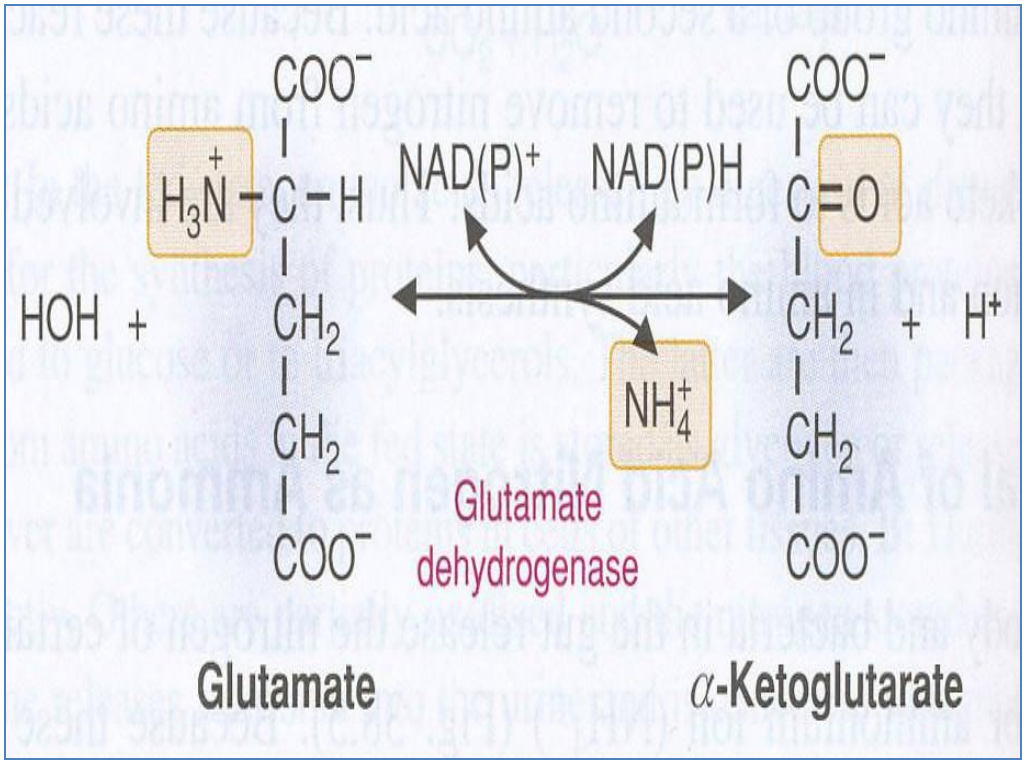
Ammonia secretion

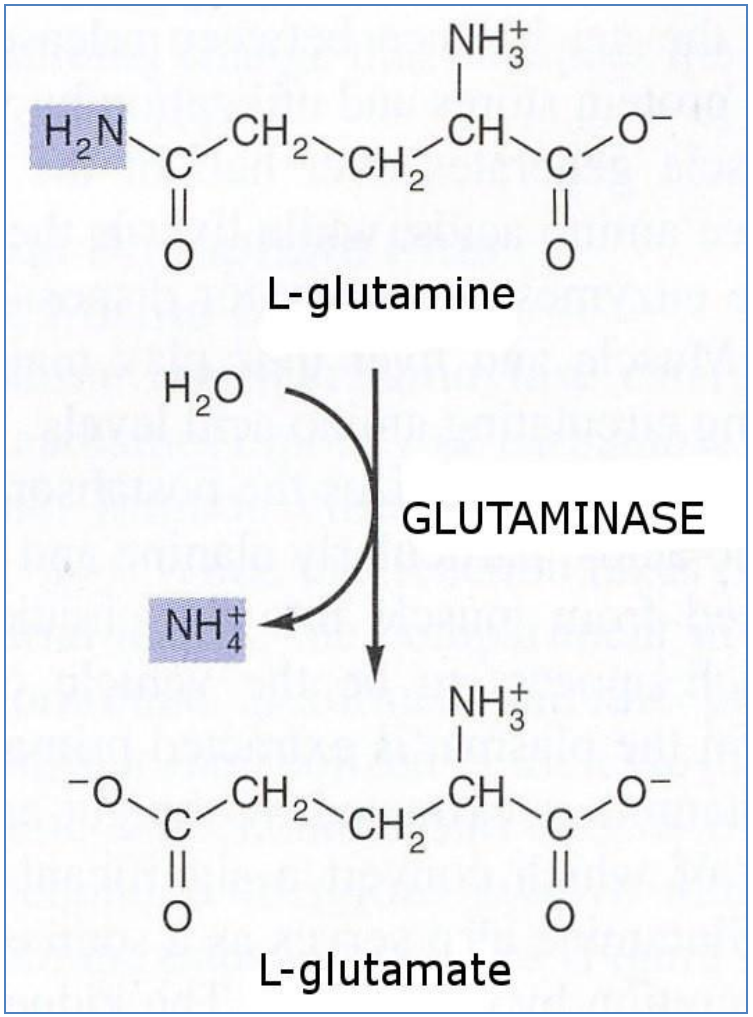
- Ammonia is secreted into the tubular lumen throughout the ***entire length*** of the nephron.
- Secretion occurs both during ***normal acid-base balance*** and in chronic acidosis.
- ***Metabolic acidosis*** is accompanied by an adaptive increase in renal ammonia production with a corresponding increase in urinary ammonium excretion.

Ammonia release in the kidney

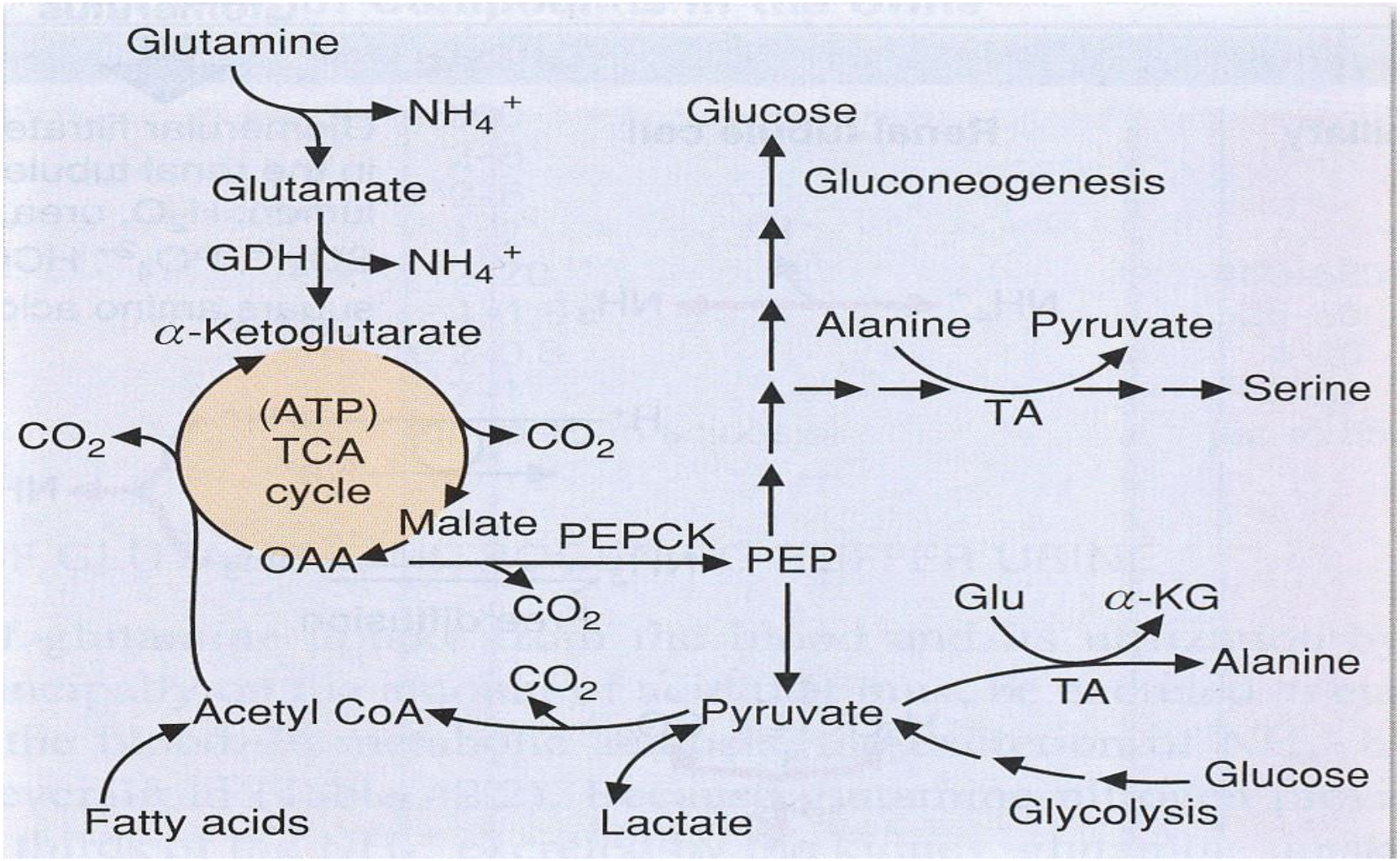
- Ammonia production:

1) By glutaminase
2) By glutamate dehydrogenase





Glutamine as a fuel for the kidney



Protein metabolism: b. Creatine: **synthesis**

- It is present in muscle as creatine phosphate **(CP)** which is a high-energy phosphate compound.

Synthesis: It is synthesized from:

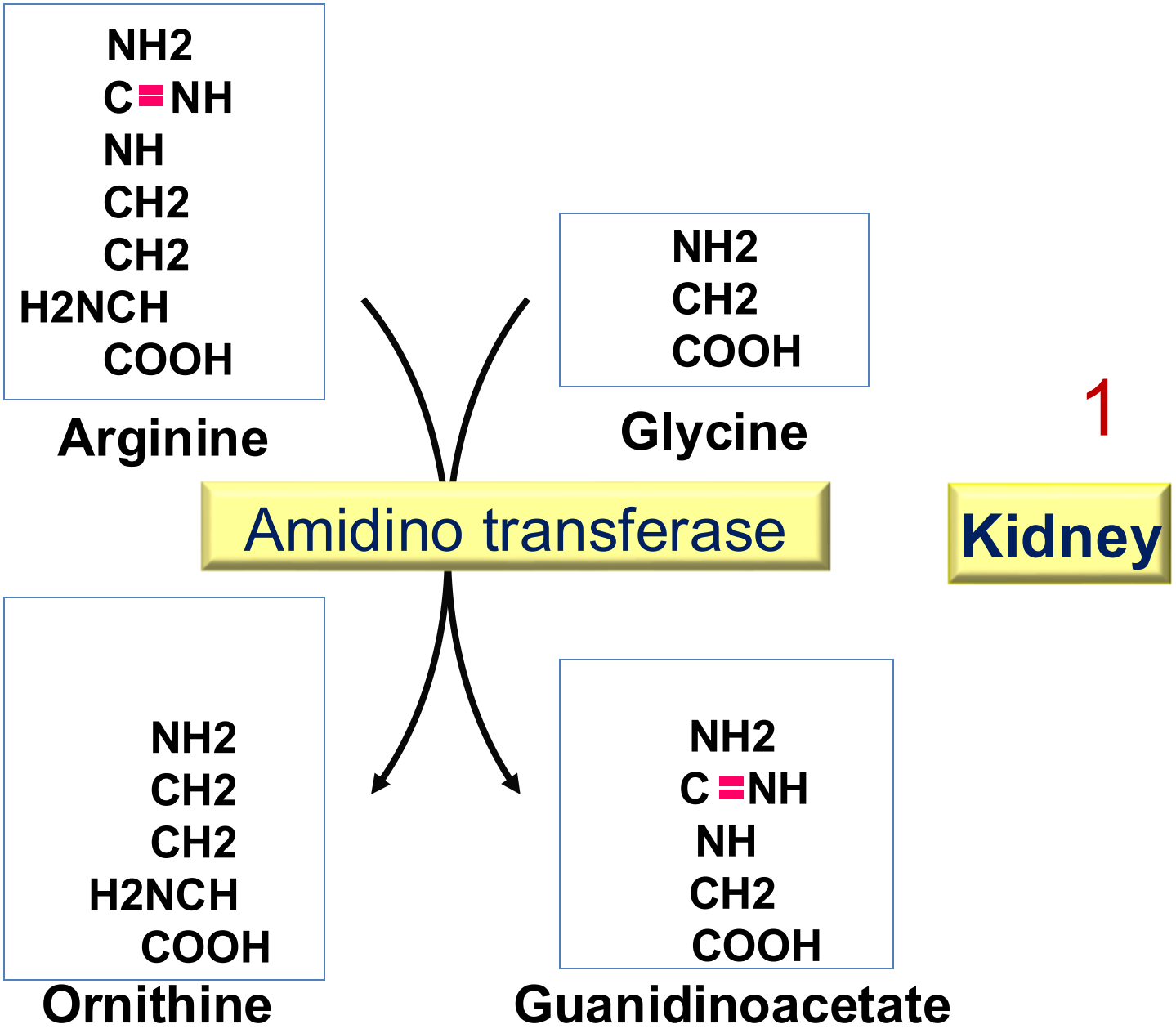
1. ***Glycine.***
2. The guanidino group of ***arginine***.
3. The methyl group of S-adenosylmethionine ***(SAM).***

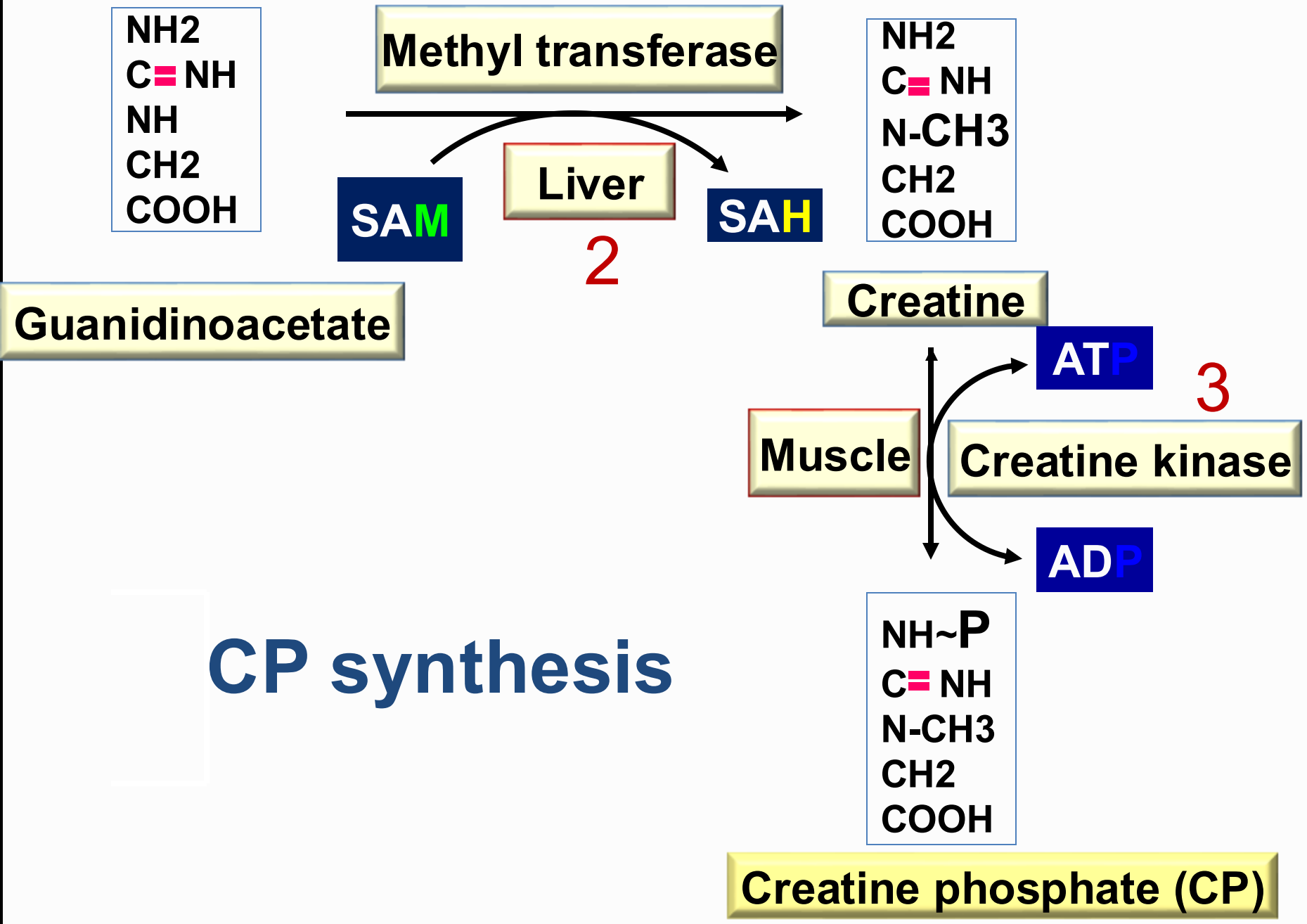
- Creatine formed in the ***liver*** is transported by blood to muscles where it is phosphorylated to phosphocreatine (phosphagen).

➢ During ***rest*** (relaxed muscle), creatine is phosphorylated to store energy.

➢ In ***contracting muscle*** the reaction is reversed to supply ***ATP*.**

Synthesis of Creatine Phosphate: 1





CP synthesis

Protein metabolism: b. Creatine.

Function of CP

- It provides a small but ***rapidly mobilized reserve of high-energy phosphates*** to maintain the intracellular level of ATP during the first few minutes of severe muscle contraction.
- CP acts as a store of energy in the **muscle** because muscle can not store ATP which is used as an immediate source of energy for the contracting muscle.
- The amount of CP in the body is ***proportional*** to muscle mass i.e. the amount of CP increases as the muscle mass increases.

Protein metabolism: b. Creatine.

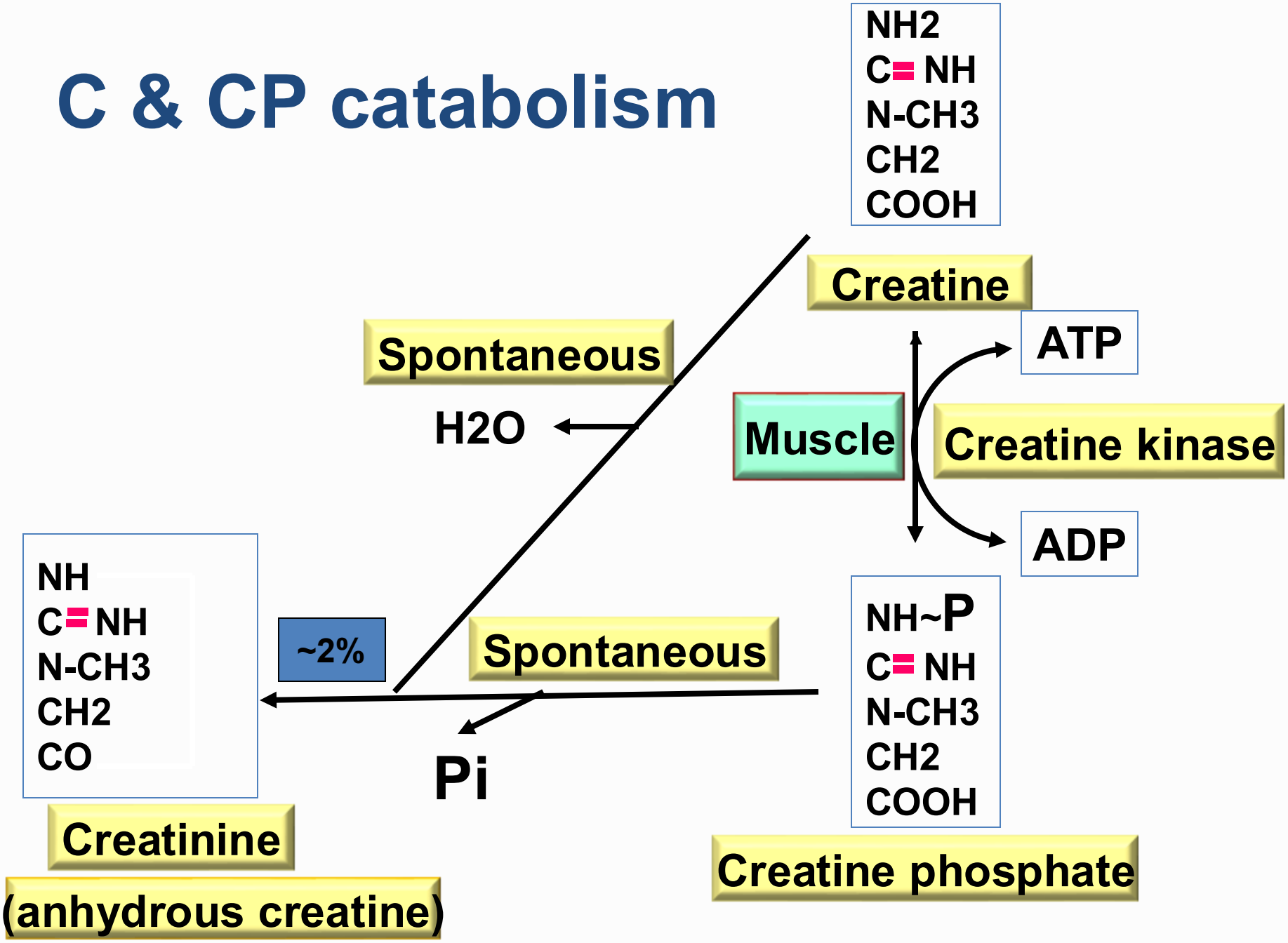
Catabolism

- A low but constant percentage ***(~ 2%)*** of creatine and creatine phosphate is converted to creatinine which is excreted in urine.
- Therefore, the amount of creatinine excreted in urine is proportional to the total CP content of the body, and thus can be used to estimate ***muscle mass***.

Creatinine:

- Creatinine is normally rapidly removed from blood and excreted in urine therefore, blood creatinine is used as ***a sensitive marker of kidney function***.
- high blood creatinine indicates kidney dysfunction.

C & CP catabolism



Plasma levels of creatine & creatinine

- normal plasma **creatine** level is **0.2 to 0.9 mg/dl**
- normal **creatinine** is **0.5 to 1.2 mg/dl.**
- Plasma **creatinine** level is a good index for **renal function** as its level is not affected by diet.

Creatinine clearance: it is calculated as:

Clearance creatinine = U/S x V

where:

- U is the urine concentration of creatinine.
- S is the serum creatinine concentration.
- V is the volume of urine excreted per minute.
- U and S are measured in the same units (mg/dl or SI units).

The clearance is expressed in **ml/minute** and is practically the same as the glomerular filtration rate.

Creatine in urine

- At normal plasma levels, **creatine** is almost completely reabsorbed by renal tubules, thus it is not excreted in significant amounts in urine of normal adult.
- Under normal physiological and some pathological conditions, creatine excretion in urine increases.

Causes of physiological creatinuria:

- In ***young children***. - In ***pregnant*** females and early postpartum period. - prolonged administration of ***androgens***, which reflects increased muscle mass.

Causes of pathological creatinuria:

- All conditions of **muscle wasting** as in:

- Starvation. ***- Hyperthyroidism.*** ***- Diabetes mellitus.***

- Fevers. - Degenerative muscle diseases ***(myopathies)***

Creatine kinase (CK)

- The plasma levels of *CK* are commonly determined in the diagnosis of ***myocardial infarction.***
- They are particularly useful when the ECG is difficult to interpret, such as when there have been previous episodes of heart disease.
- *CK* occurs as three isoenzymes.
- Each isoenzyme is a dimer composed of two polypeptides (B and M subunits)

➢ Appearance of ***CK2*** **(MB)** isoenzyme in plasma is specific for infarction of the ***myocardium.***

- CK isoenzyme shows a characteristic electrophoretic mobility.