Energy sources for muscle contraction & creatinine metabolism

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Why is energy required for skeletal muscles?

ATP is required for contraction-relaxation cycle of skeletal muscle being essential for activity of key enzymes involved in:

1. **Membrane excitability (<u>Na^+/K^+ ATPase</u>),**
2. **Myofilament cross-bridge cycling (<u>myosin ATPase</u>)**
3. **Sarcoplasmic reticulum calcium handling (<u>Ca^{2+} ATPase</u>)**

Energy sources for skeletal muscles:

ATP can be generated from:
1. Glycolysis,
2. Oxidative phosphorylation,
3. Creatine phosphate,
4. 2 ADP by adenylyl kinase

ATP in skeletal muscle is only sufficient to provide energy for a few seconds, so ATP must be constantly renewed from one or more of these sources, depending upon metabolic conditions.

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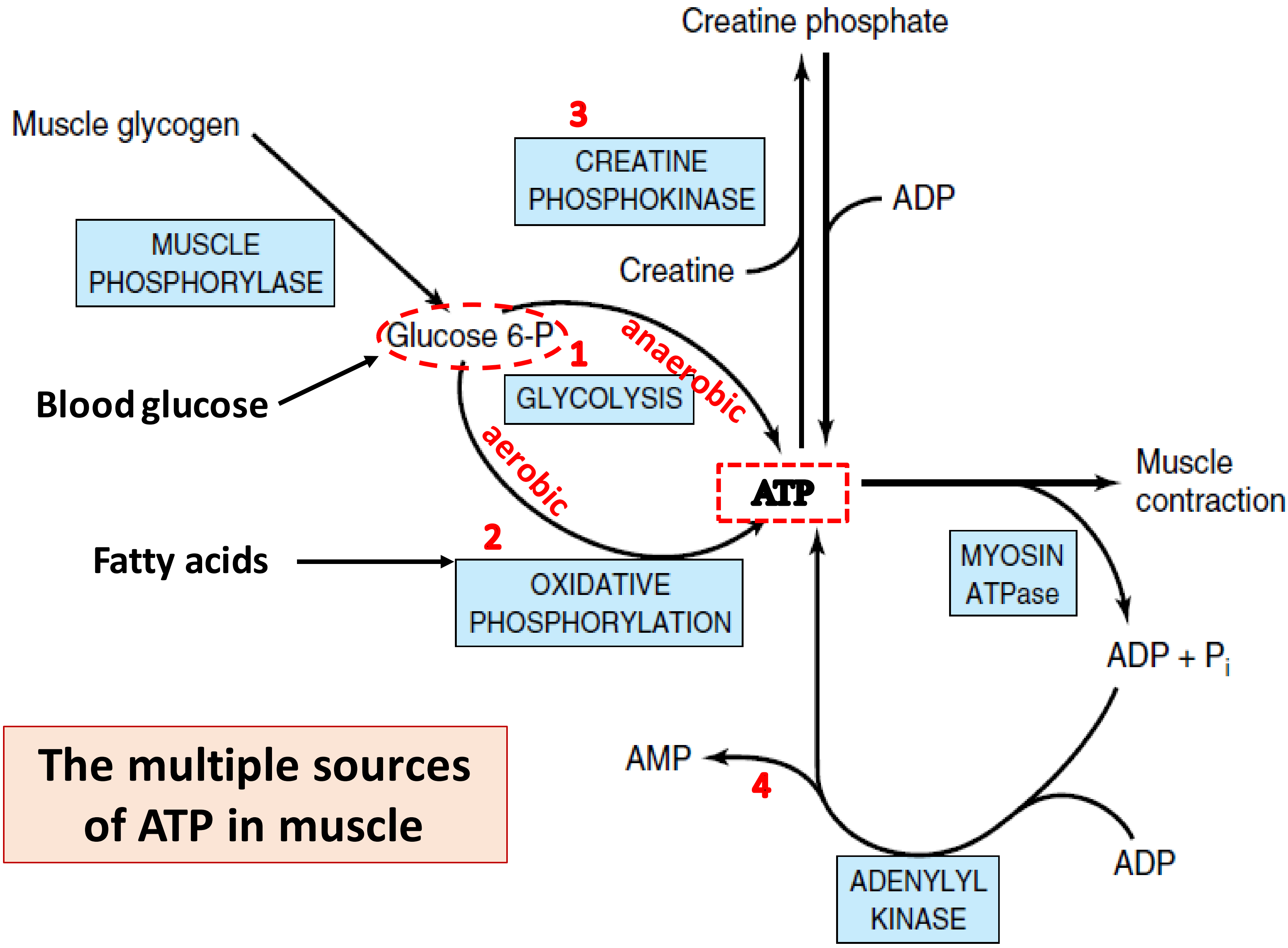

The multiple sources of ATP in muscle

(1) Glycolysis (aerobic or anaerobic):

- Glucose is supplied from **blood glucose**, **endogenous muscle glycogen** or **gluconeogenesis** by liver.

- Insulin increases glucose uptake from blood by **GLUT4**
- In the fed state, most glucose → **glycogen**, which is a **store** for use in exercise, "**preloading**" with glucose.
- **Muscle glycogen phosphorylase** is activated by **Ca^{2+}, epinephrine & AMP but it is not activated by glucagon (no glucagon receptors in muscles)**.
- **Muscle glycogen phosphorylase** is deficient in **McArdle disease,** one of the glycogen storage diseases.

(2) Oxidative phosphorylation:

- **Aerobic glycolysis** → pyruvate → **acetyl CoA** → krebs´ → ETC (electron transport chain)
- **Oxidation of fatty acids** → **acetyl CoA** → krebs´ → ETC

(3) Creatine phosphate:

- Creatine phosphate is formed at times the muscle is **relaxed**. It prevents **the rapid depletion of ATP.**

(4) Two molecules of ADP by adenylyl kinase.

$$2\ ADP \xrightarrow{\text{adenylyl kinase}} ATP + AMP$$

Resting Muscle

- The major fuels of skeletal muscle are **glucose (fed state)** & **fatty acids (fasting state)**
- **Ketone bodies** may be used in **prolonged fasting or starvation**

Active muscle

- Active muscle uses **glycogen & triglycerides** stores. Blood glucose and free fatty acids also may be used.
- The fuel used in muscle contraction depends on the:

1. **Magnitude** of exercise **(high intensity or moderate)**
2. **Duration** of exercise **(sustained prolonged or short)**
3. **Type of muscle fibers** **(slow or fast twitch fibers)**

Active muscle

- **Proportion of 2 types of fibers** varies **depending on function:**

I. **Slow twitch (type I):**

- **Aerobic, slow to fatigue.**
- Primarily in **posture-maintaining** **(leg muscles)** **&** **in long distance runners** **(marathons).**

II. **Fast twitch (type II):**

- **IIA (both Aerobic & anaerobic**) and **IIB** (**anaerobic**)
- Primarily in **short-term, high-intensity exercise** **(sprinters & weight lifters).**

Types of muscle fibers and major energy sources used by a marathon runner and a sprinter

Marathon Runner (km)	Sprinter (100 m)
Type I (oxidative) fibers are used predominantly.	Type II (glycolytic) fibers are used predominantly.
ATP is the major energy source throughout.	Creatine phosphate is the major energy source during the first 4–5 seconds.
Blood glucose and free fatty acids are the major fuel sources.	Glucose derived from muscle glycogen and metabolized by anaerobic glycolysis is the major fuel source.
Muscle glycogen is slowly depleted.	Muscle glycogen is rapidly depleted.

Some biochemical features of Skeletal Muscles:

1. Skeletal muscle **glycogen** **cannot** contribute directly to <u>blood glucose</u> (it does not contain **glucose- 6 –phosphatase**)
2. **Lactate** of anaerobic metabolism in skeletal muscle passes to liver → **glucose** → muscle (**Cori cycle**).
3. Major amino acids emerging from muscle are **alanine** (**glucose-alanine cycle**).
4. Skeletal muscle is the principal site of metabolism of **branched-chain amino acids**, used as an energy source.
5. **Proteolysis** of muscle during starvation (prolonged fasting > 18 hrs) → amino acids for **gluconeogenesis**.

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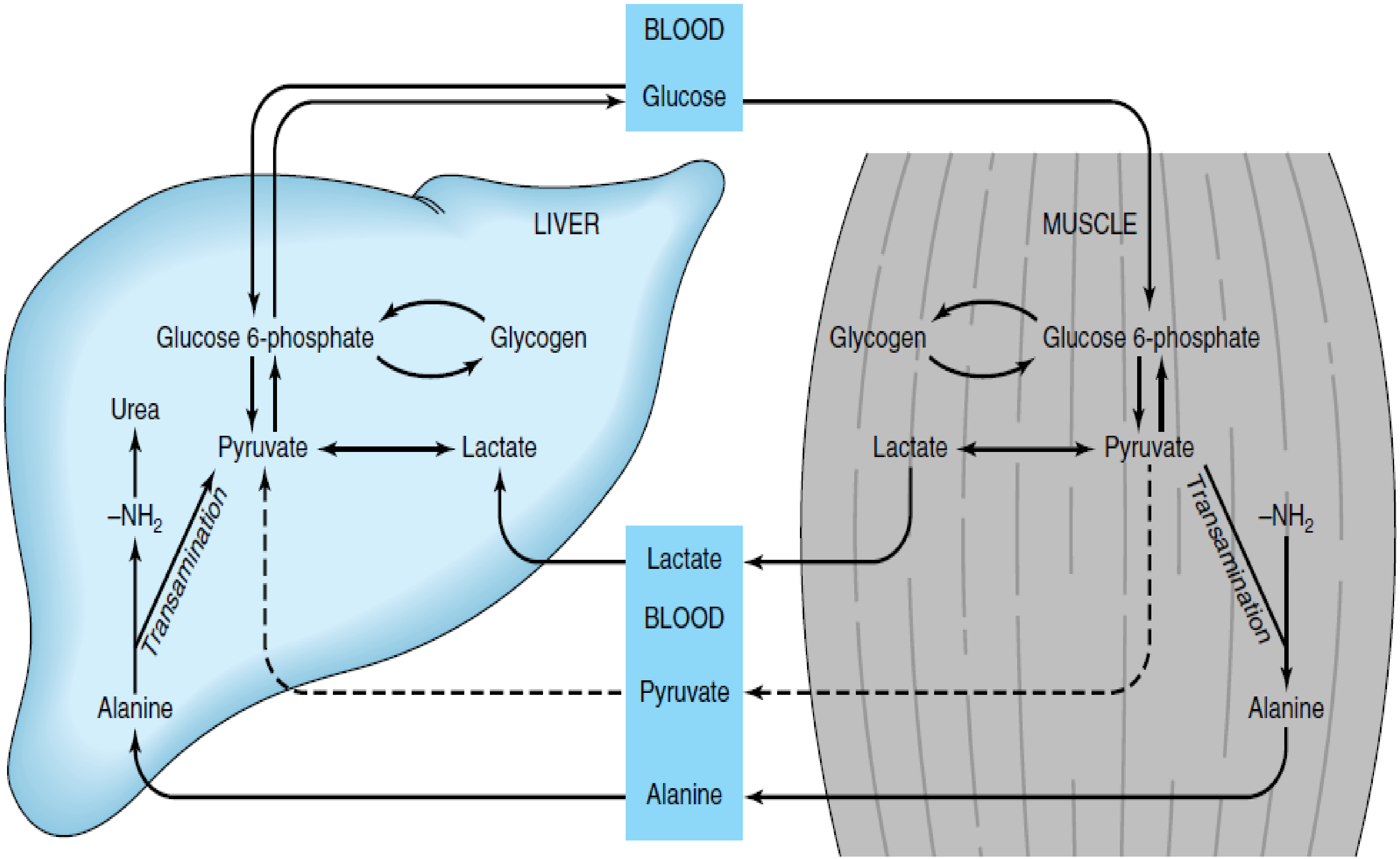


The lactic acid (Cori) cycle and glucose-alanine cycle

Creatinine metabolism

GAM

Creatine is formed from 3 aa (**glycine, arginine & methionine**)

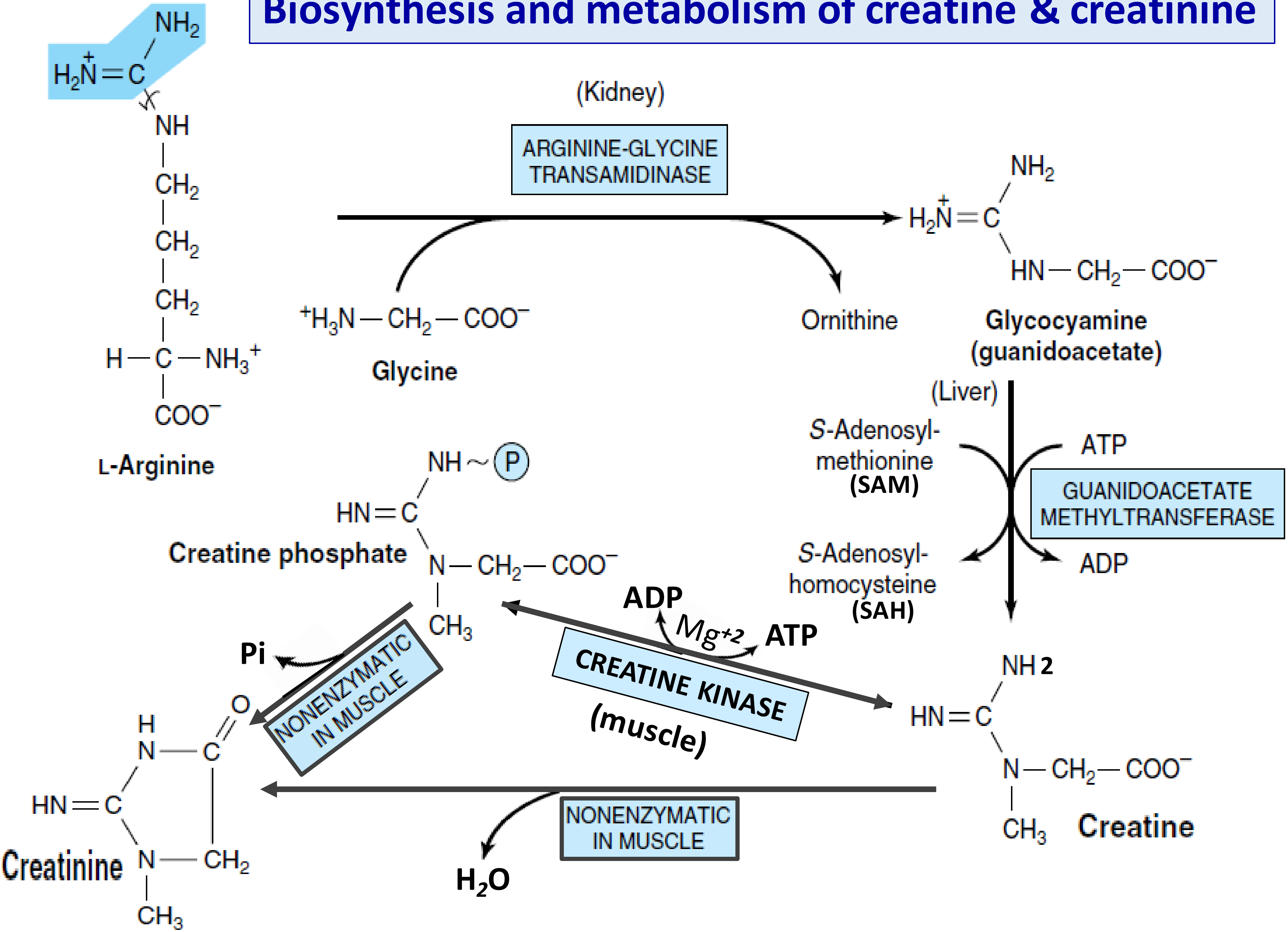
1. Glycine + arginine → **guanidoacetate in the kidney by arginine glycine transamidinase**
2. **Guanidoacetate** is **methylated (using SAM) in the liver** to form **creatine** by **guanidoacetate methyl transferase.**

3. **Creatine** goes via blood to various tissues, chiefly to **muscles**.

- **Creatine uptake & retention by muscles is ↑ by androgens (androgen deficiency → creatinuria & ↓ muscle creatine).**

- Phosphorylation of creatine by **creatine kinase** (CK), a muscle-specific enzyme with clinical importance in **muscle diseases**.

Biosynthesis and metabolism of creatine & creatinine



Functions of creatinine phosphate:

- Creatine phosphate (phosphocreatine), is a high-energy compound that can reversibly donate a phosphate group to ADP to form ATP in a reversible reaction catalyzed by creatine kinase (creatine phosphokinase)(CK or CPK).

- Creatine phosphate provides **a small but rapidly** mobilized store of **high-energy phosphate**. It can be used to maintain the intracellular level of ATP during the **first few seconds** of intense muscular contraction, by reversal of CK reaction.

- The ***amount of creatine phosphate*** in the body is ***proportional to the muscle mass***.

Fate and Excretion of creatinine phosphate:

4. **Creatinine** is formed in muscle by **irreversible**, spontaneous or **non-enzymatic** loss of phosphate from creatine phosphate or from dehydration of creatine (at a slower rate).

- The two reactions result in the steady production of a constant amount of creatinine that is proportional to the total amount of phosphocreatine and creatine in the body, which is in turn proportional to the **muscle mass.**

- The creatinine formed goes via the blood to the kidneys to be excreted in the urine.
- 24-hour urinary excretion of creatinine is proportionate to muscle mass.

Fate and Excretion of creatinine phosphate

- Normal plasma creatine: 0.2-0.9 mg/dl.
- The normal plasma creatinine level varies **0.6 *and* 1.2 mg/dl in adult male**, depending on ***muscle bulk*** being higher in males than in **females (0.5 – 1.1 mg/dl).**

- Higher plasma levels are observed in ***renal failure.***

- Plasma creatinine level is a more ***accurate marker of kidney function*** than urea, as creatinine is not affected by diet.