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:

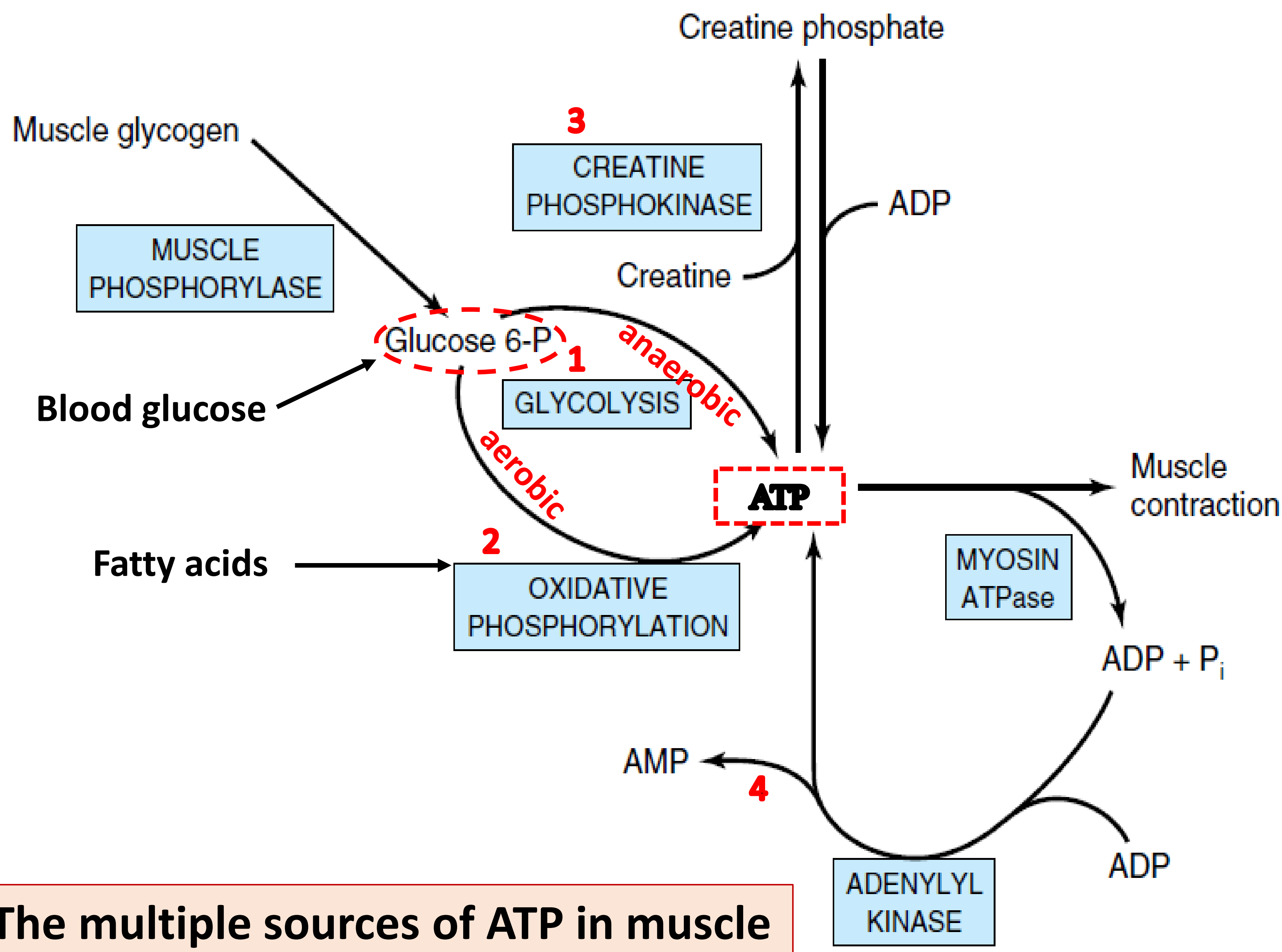
1. **Membrane excitability (Na^+/K^+ ATPase),**
2. **Myofilament cross-bridge cycling (myosin ATPase)**
3. **Sarcoplasmic reticulum calcium handling (Ca^{2+} ATPase)**

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.



The multiple sources of ATP in muscle

(1) Glycolysis (aerobic or anaerobic):

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

- Insulin increases glucose uptake from blood by **GLUT4**

- The sarcoplasm of skeletal muscle contains large stores of **glycogen** that releases **glucose 1- P** by muscle **glycogen phosphorylase** (activated by **Ca^{2+}, epinephrine & AMP).**

- **Muscle glycogen phosphorylase** b is inactive 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.**
- The enzyme catalysing the phosphorylation of creatine is **creatine kinase** (CK), a muscle-specific enzyme with clinical importance in acute or chronic **muscle diseases**.

(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** & **fatty acids**

Fed state	Fasting state
• **Glucose uptake** to be oxidized & to replenish **glycogen** stores • **Amino acid uptake** for **protein** synthesis	• It uses **free fatty acids** from blood. • **Ketone bodies** may be used if fasting is **prolonged.**

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)**

Characters of type I & type II fibers of skeletal muscles

	Type I Slow Twitch	Type II Fast Twitch
Myosin ATPase	Low	High
Energy utilization	Low	High
Mitochondria	Many	Few
Color	Red	White
Myoglobin	Yes	No
Contraction rate	Slow	Fast
Duration	Prolonged	Short

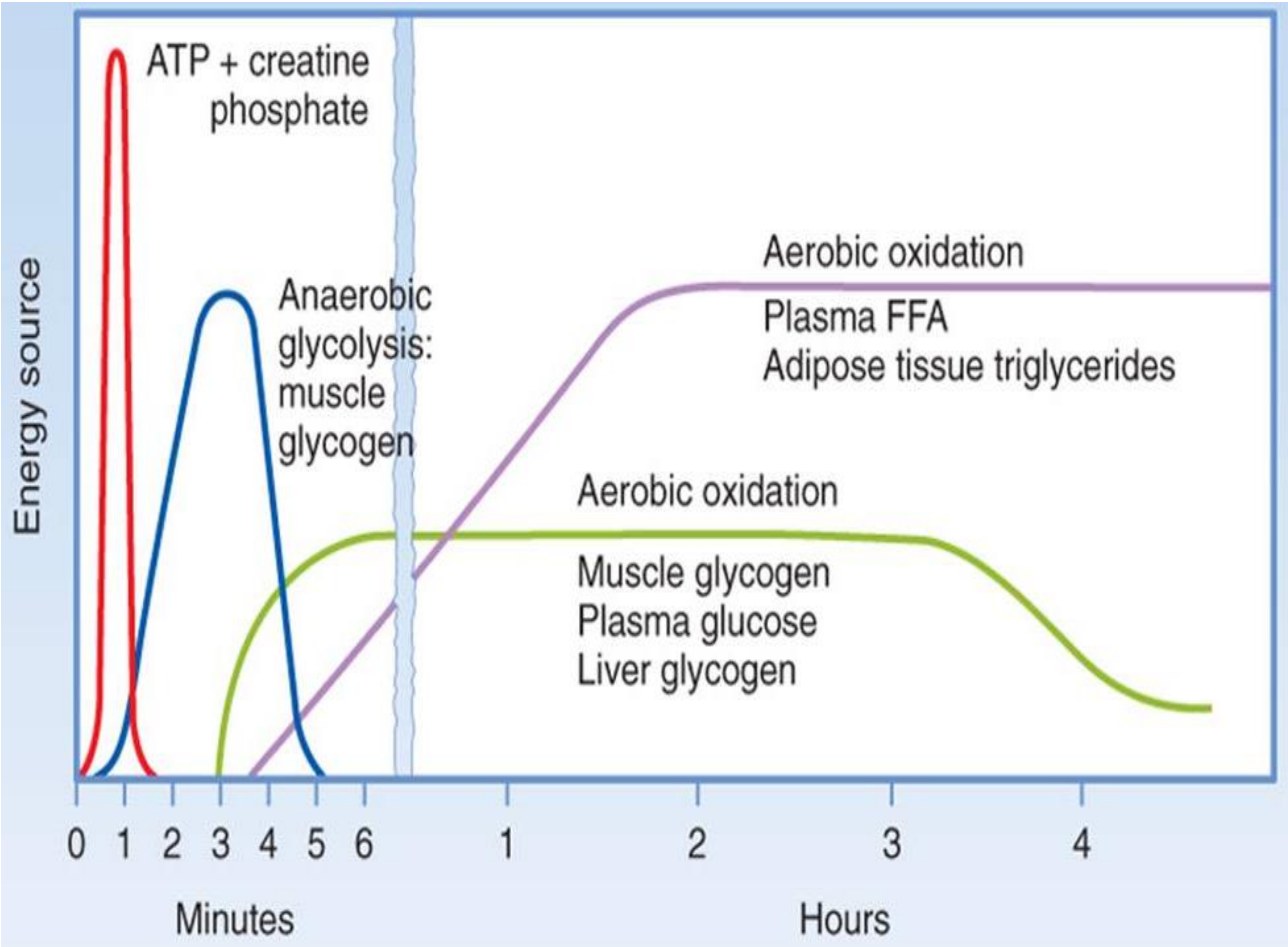
- The **proportion of the two types of fibers** varies among muscles of the body, **depending on function**.

- Fast twitch fibers are involved **primarily** in **short-term, high-intensity exercise** **(sprinters & weight lifters).**

- Slow twitch fibers are involved **primarily** in **posture-maintaining muscles** **(leg muscles)** **& in long distance runners** **(marathons).**

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.
Control sites	**HSL, PDH, TCA & at glycogenolysis**	**Glycogen phosphorylase & at PFK-1**


ATP + creatine phosphate
Anaerobic glycolysis: muscle glycogen
Aerobic oxidation
Plasma FFA
Adipose tissue triglycerides
Aerobic oxidation
Muscle glycogen
Plasma glucose
Liver glycogen
Energy source
0 1 2 3 4 5 6
Minutes
1 2 3 4
Hours

Summary of Biochemical features of Skeletal Muscles:

1. Skeletal muscle functions in **aerobic** (resting) & **anaerobic** (sprinting) conditions, so both aerobic & anaerobic glycolysis operate, depending on conditions.

2. Skeletal muscle contains **myoglobin** as a **reservoir of O_2**

3. The **different types of skeletal muscle fibers** primarily suited to anaerobic (**fast twitch fibers**) or aerobic (**slow twitch fibers**) conditions.

Summary of Biochemical features of Skeletal Muscles:

4. **Insulin** acts on skeletal muscle to increase glucose **uptake**

5. In the fed state, most glucose → **glycogen**, which is a **store** of glucose for use in exercise, "**preloading**" with glucose.

6. **Epinephrine** stimulates **glycogenolysis** in skeletal muscle, but **glucagon does not** because of absence of its receptors.

7. Skeletal muscle **glycogen** **cannot** contribute directly to blood glucose (it does not contain **glucose- 6 –phosphatase**)

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Summary of Biochemical features of Skeletal Muscles:

8. **Lactate** of anaerobic metabolism in skeletal muscle passes to liver → glucose → muscle (the **Cori cycle**).

9. Major amino acids emerging from muscle are **alanine** (mainly for gluconeogenesis in liver and forming part of the **glucose-alanine cycle**).

10. Skeletal muscle is the principal site of metabolism of **branched-chain amino acids**, used as an energy source.

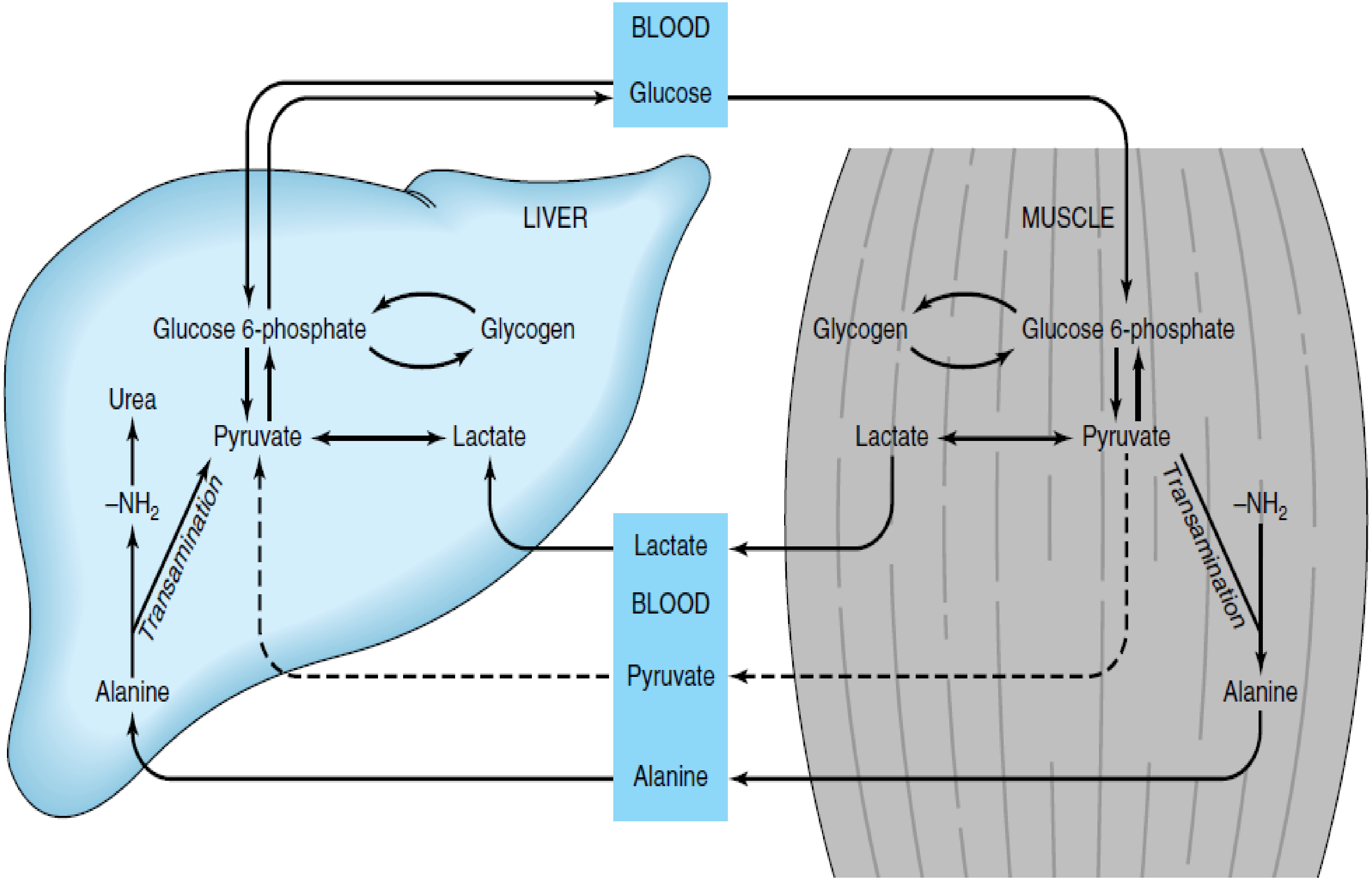
Summary of Biochemical features of Skeletal Muscles:

11. Skeletal muscle can utilize **ketone bodies during starvation**.

12. **Free fatty acids** in plasma are a major source of energy, particularly in **marathons & prolonged starvation**.

13. Skeletal muscle contains **phosphocreatine**, which acts as an energy store for short-term (seconds) demands.

14. **Proteolysis** of muscle during starvation (prolonged fasting > 18 hrs) → amino acids for **gluconeogenesis**.



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

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Creatinine metabolism

GAM

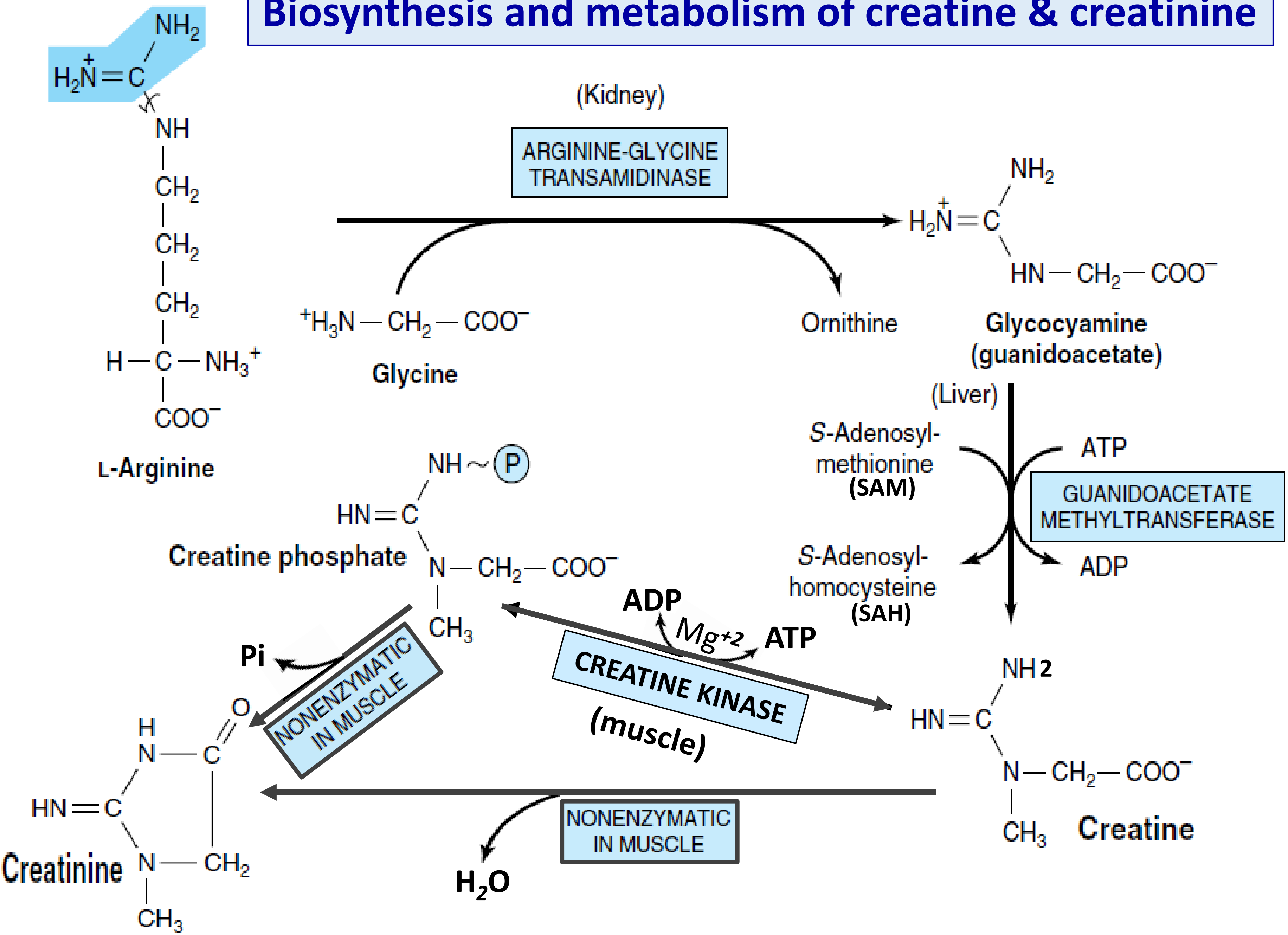
Creatine is formed from 3 aa (**glycine, arginine & methionine**)

1. Glycine accepts amidine group from arginine to form **glycocyamine (<u>guanidoacetate</u>) in the <u>kidney</u> by <u>arginine glycine amidinotransferase</u>)**
   arginine glycine transamidinase
2. **Guanidoacetate** is **methylated in the <u>liver</u>** to form **<u>creatine</u>** by **<u>guanidoacetate methyl transferase</u>**

- The creatine formed in the liver goes via the blood to various tissues, chiefly to muscles.
- **Creatine uptake & retention by muscles is increased by androgens (androgen deficiency → <u>creatinuria</u> & ↓ muscle creatine).**

- Creatinine is formed in muscle by irreversible, **non-enzymatic** loss of phosphate from creatine phosphate or by dehydration of creatine.
- 24-hour urinary excretion of creatinine is proportionate to muscle mass.

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:

- Creatine phosphate spontaneously and irreversibly loses phosphate, forming creatinine. Creatine itself loses water to form creatinine, but 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.

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 measurement is a more ***accurate marker of kidney function*** than urea, as its level is not affected by diet.