Metabolism of cardiac muscle

Dr. Mamoun Ahram
Cardiovascular system, 2014

Resources:
This lecture
Mark's Basic Medical Biochemistry, 4th ed., p. 890-891
Hand-out

What is heart failure?

- Heart failure is “a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood”.

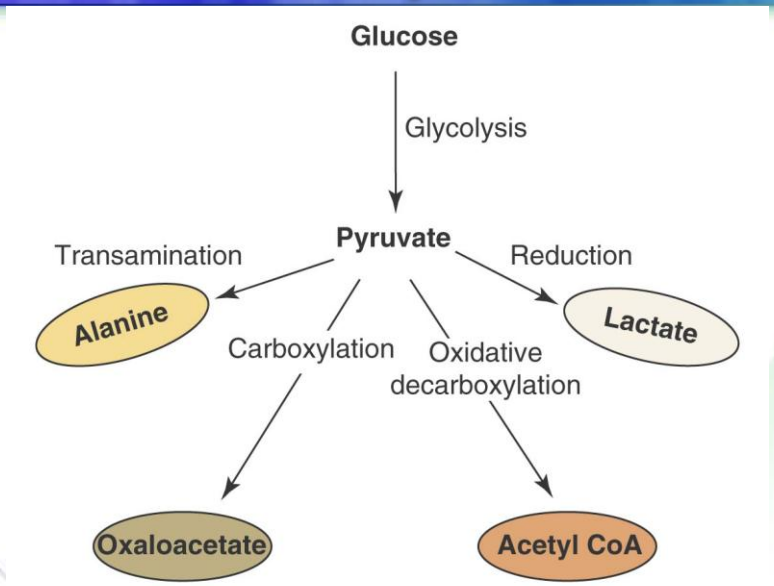
Why is this topic important?

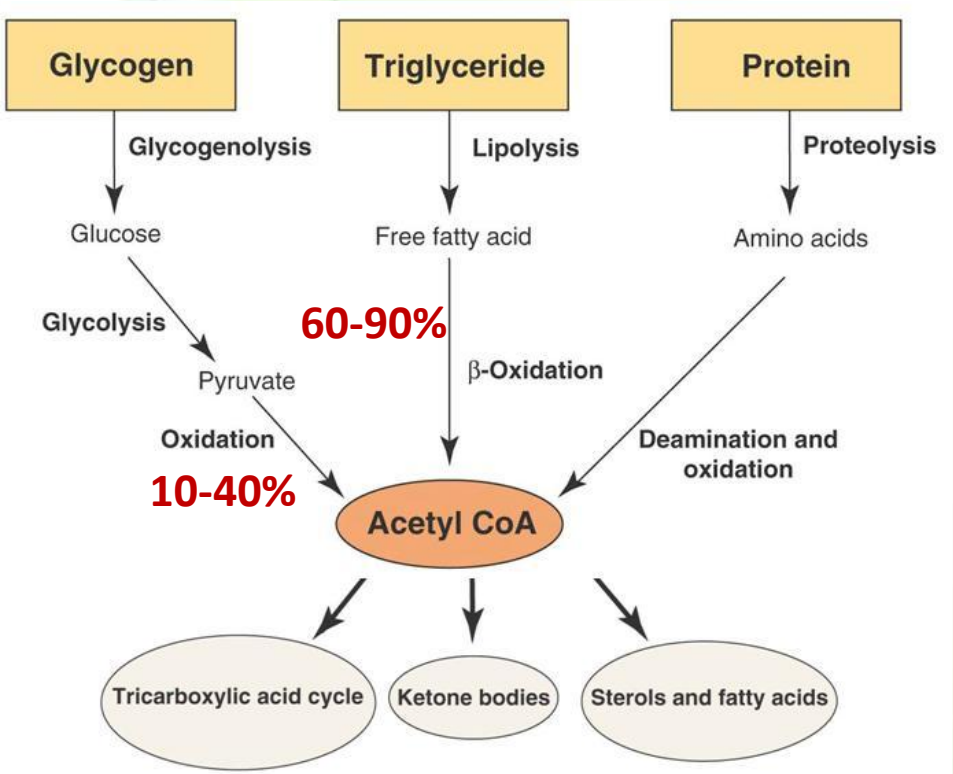
- It is currently a leading cause of death and disability across the globe.
- Heart failure (HF) is associated to changes in metabolic profile.
- 20-30% of HF patients are diabetic indicative of a connection.
- Optimization of substrate metabolism improves cardiac function.

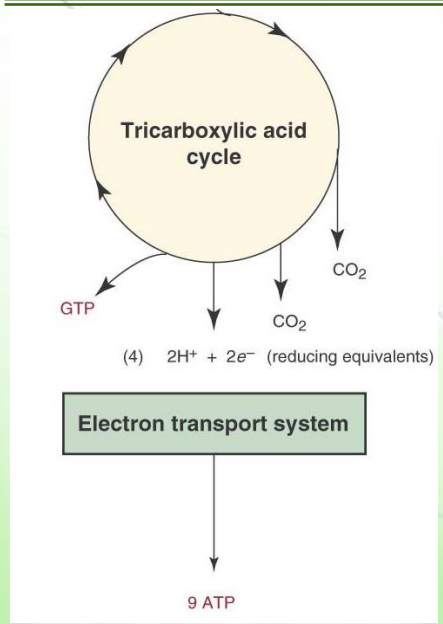
Lecture outline

- Metabolic profile in cardiomyocytes
- Alteration in metabolic profile during ischemia and reperfusion
- Therapeutic targets
- Biomarkers of heart failure

Pathways







- **>95% of ATP comes from oxidative phosphorylation**
- **Complete ATP turnover every 10s (constant)**
- **60–70% of ATP hydrolysis fuels contractile power., and the rest is used for maintaining ionic homeostasis.**
- **Fatty acid oxidation requires a greater oxygen consumption per produced ATP compared to glucose oxidation.**

Preferential substrates

- Sufficient oxygen:
  - Fatty acids (50-70%)
  - Glucose (30%)
    - Glycolysis produces 5% of ATP.
- Increased muscular activity and under ischemic conditions
  - Glucose and lactate
- Pathological conditions and starvation:
  - Ketone bodies and amino acids

Fatty acid metabolism

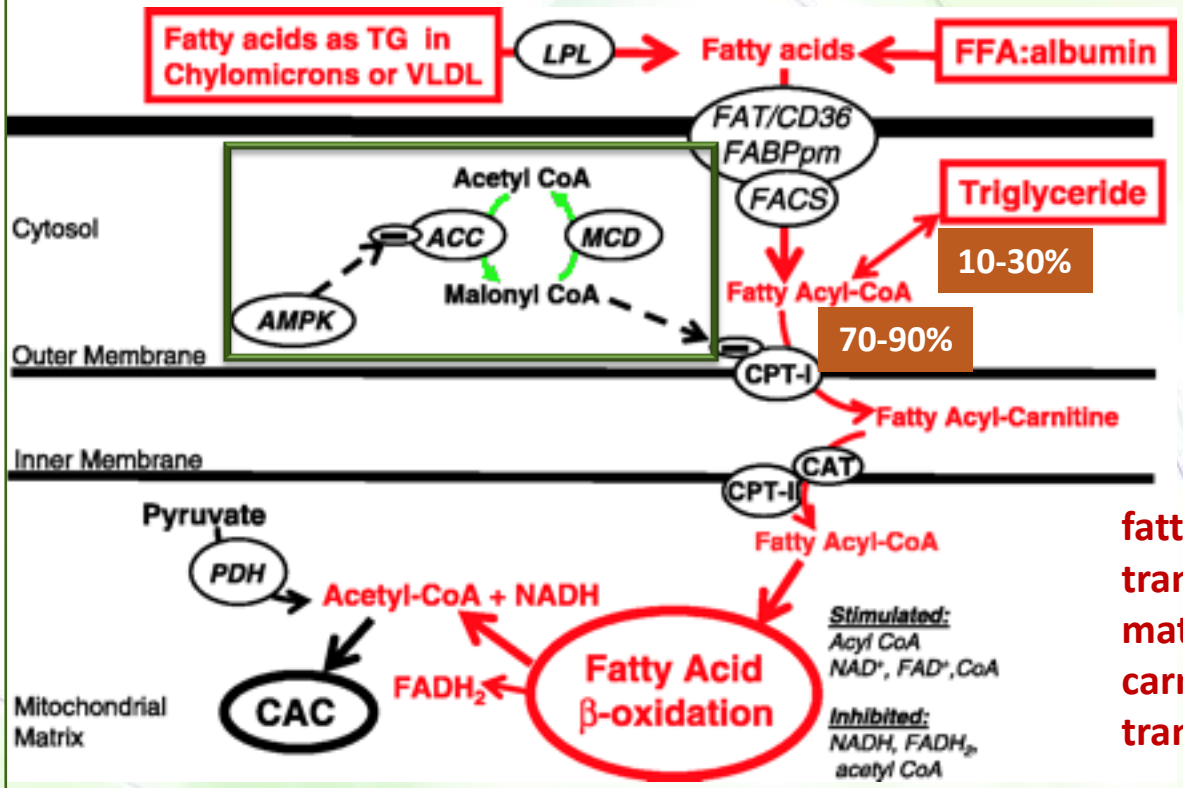
Malonyl-CoA is formed from carboxylation of acetyl-CoA by ACC.

The activity of CPT-I is strongly inhibited by malonyl-CoA.

MCD converts malonyl-CoA back to acetyl-CoA and CO2.

The activity of ACC is inhibited by phosphorylation by AMPK.

Fatty acids enter the cardiomyocyte by either passive diffusion or by either FAT or FABPpm



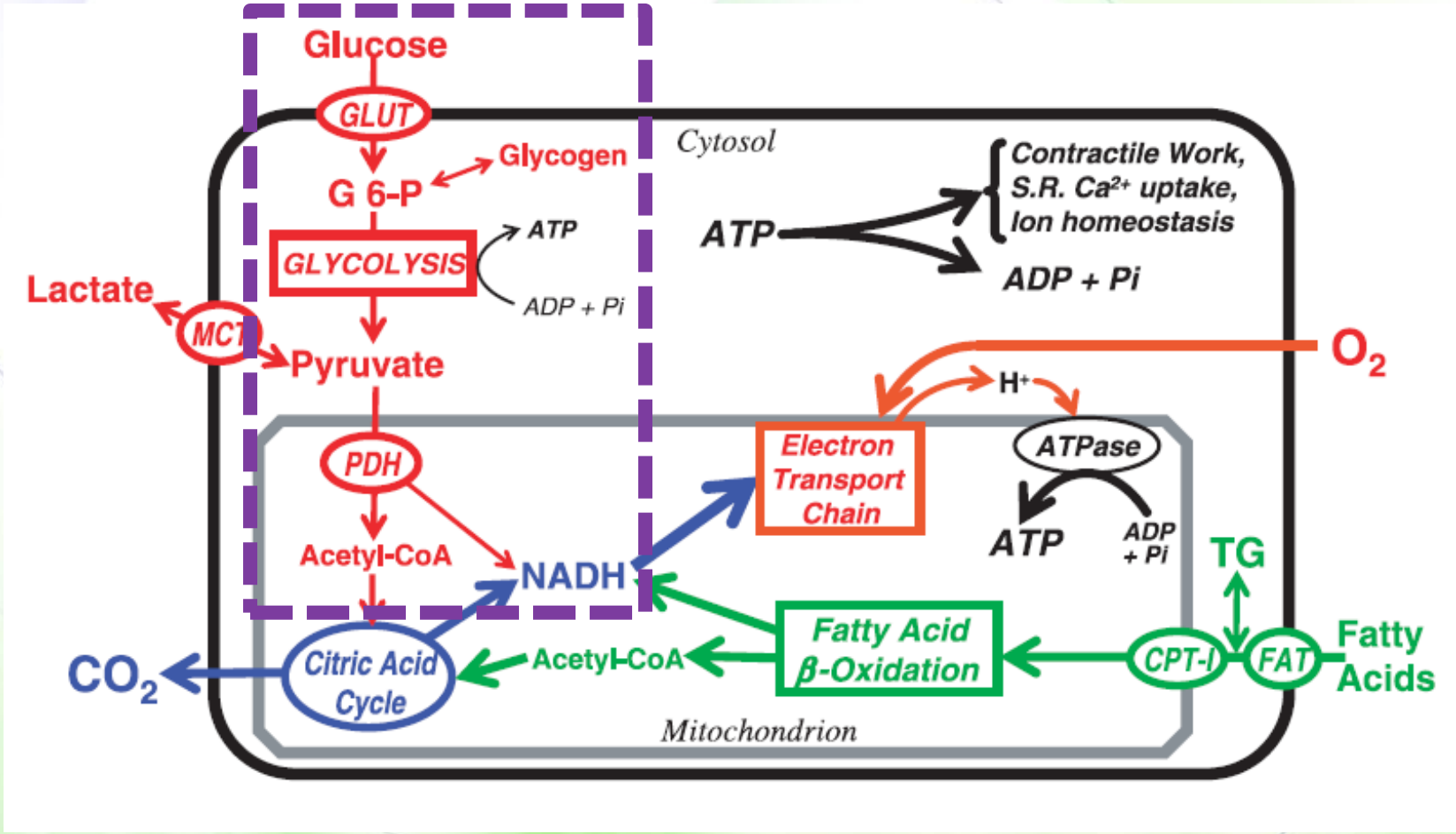
FAs are esterified into fatty acyl-CoA by FACS

fatty acyl molecule is transferred into the matrix by a carnitine-dependent transport system.

ACC, acetyl-CoA carboxylase; CAT, carnitine acyltranslocase; CPT-I, carnitine palmitoyltransferase; FABPPM, plasma membrane fatty acid binding protein; FAT, fatty acid transporter; LPL, lipoprotein lipase; MCD, malonyl-CoA decarboxylase.

Glucose and glycogen

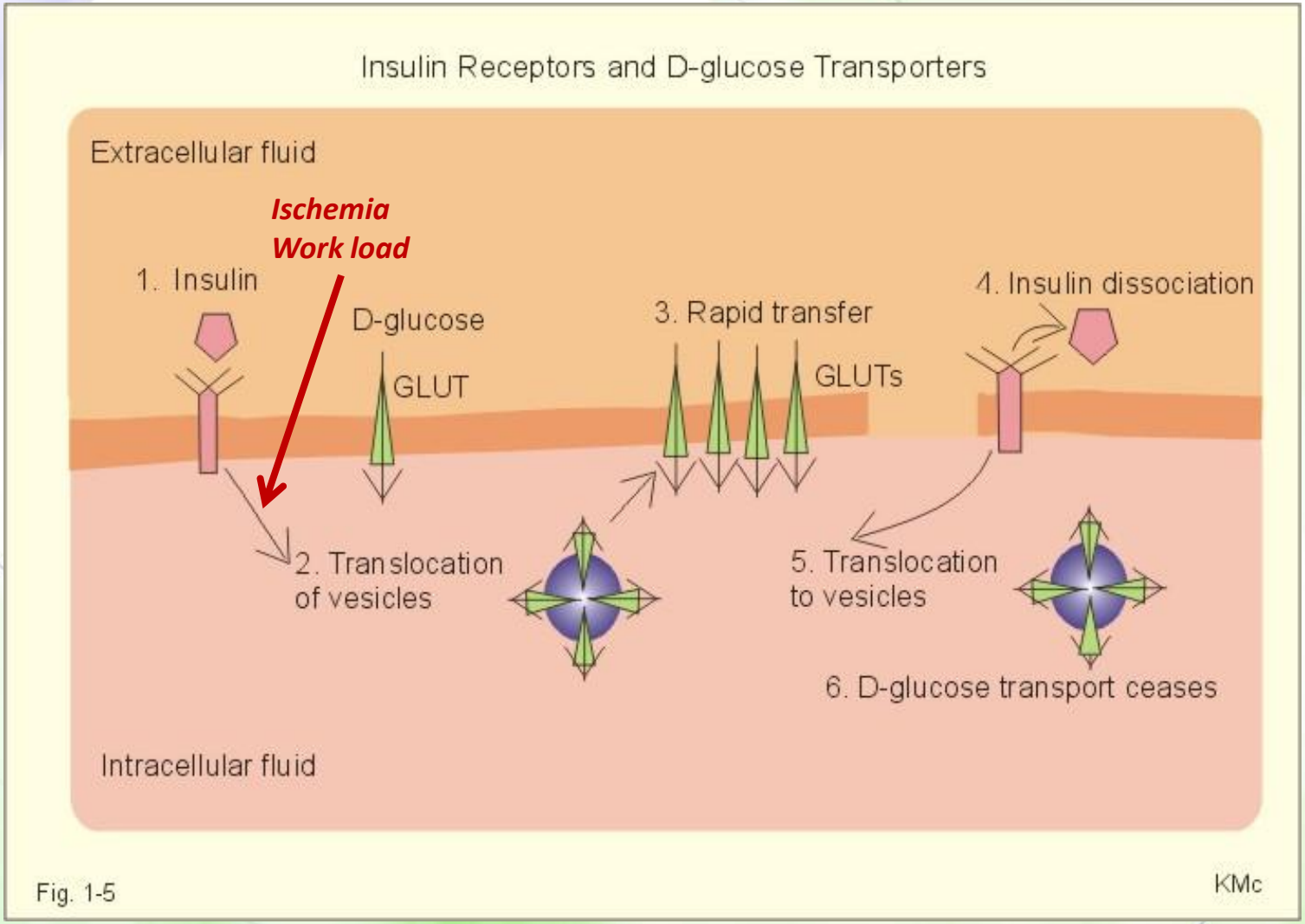
Glycolytic substrate is derived from exogenous glucose and glycogen stores.



Glucose transporters

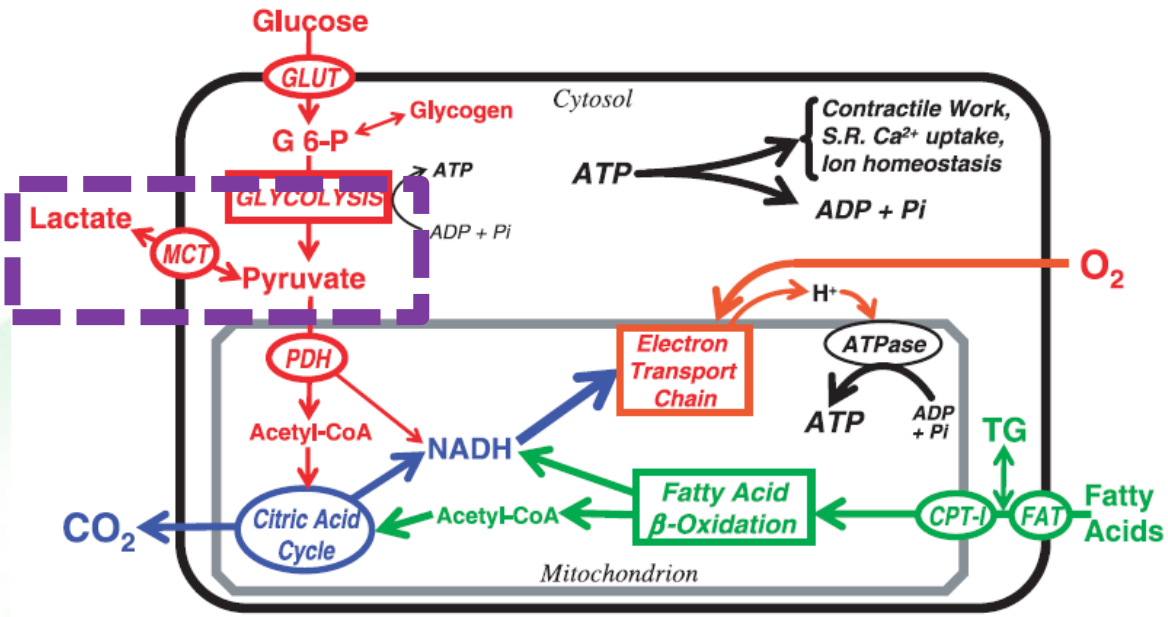
Tansporter	Major Sites of Expression	Characteristics
GLUT-1	Brain, erythrocyte, endothelial cells, fetal tissues	Transports glucose and galactose, not fructose Low Km (~ 1 mM)
GLUT-2	Liver, pancreatic beta cell, small intestine, kidney.	Transports glucose, galactose and fructose Low affinity, high capacity glucose transporter High Km (15–20 mM)
GLUT-3	Brain, placenta and testes	Transports glucose (high affinity; and galactose, not fructose Low Km (<1 mM)
GLUT-4	**Skeletal and cardiac muscle, adipocytes**	**Insulin-responsive; High affinity for glucose Medium Km (2.5–5 mM)**
GLUT-5	Small intestine, sperm, brain, kidney, adipocytes and muscle	Transports fructose, but not glucose or galactose Medium Km (~ 6 mM)

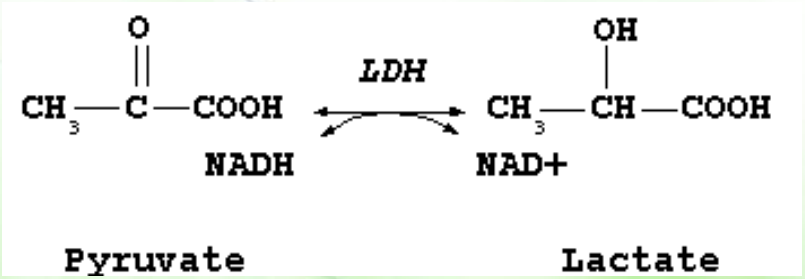
GLUT-4 translocation



Lactate transport and metabolism

- **A healthy nonischemic heart is a net consumer of lactate.**
- **It becomes a net lactate producer under accelerated glycolysis and impaired oxidation of pyruvate (as in ischemic conditions)**

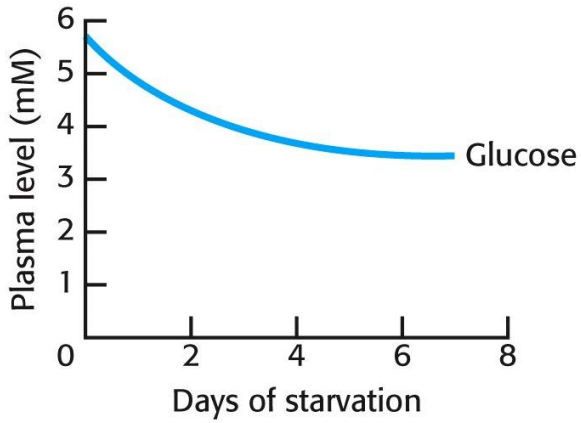


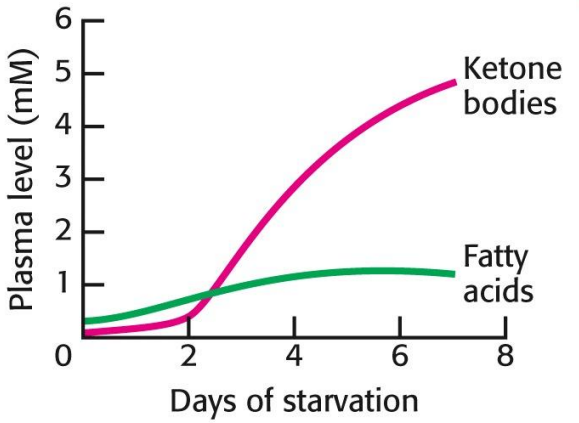


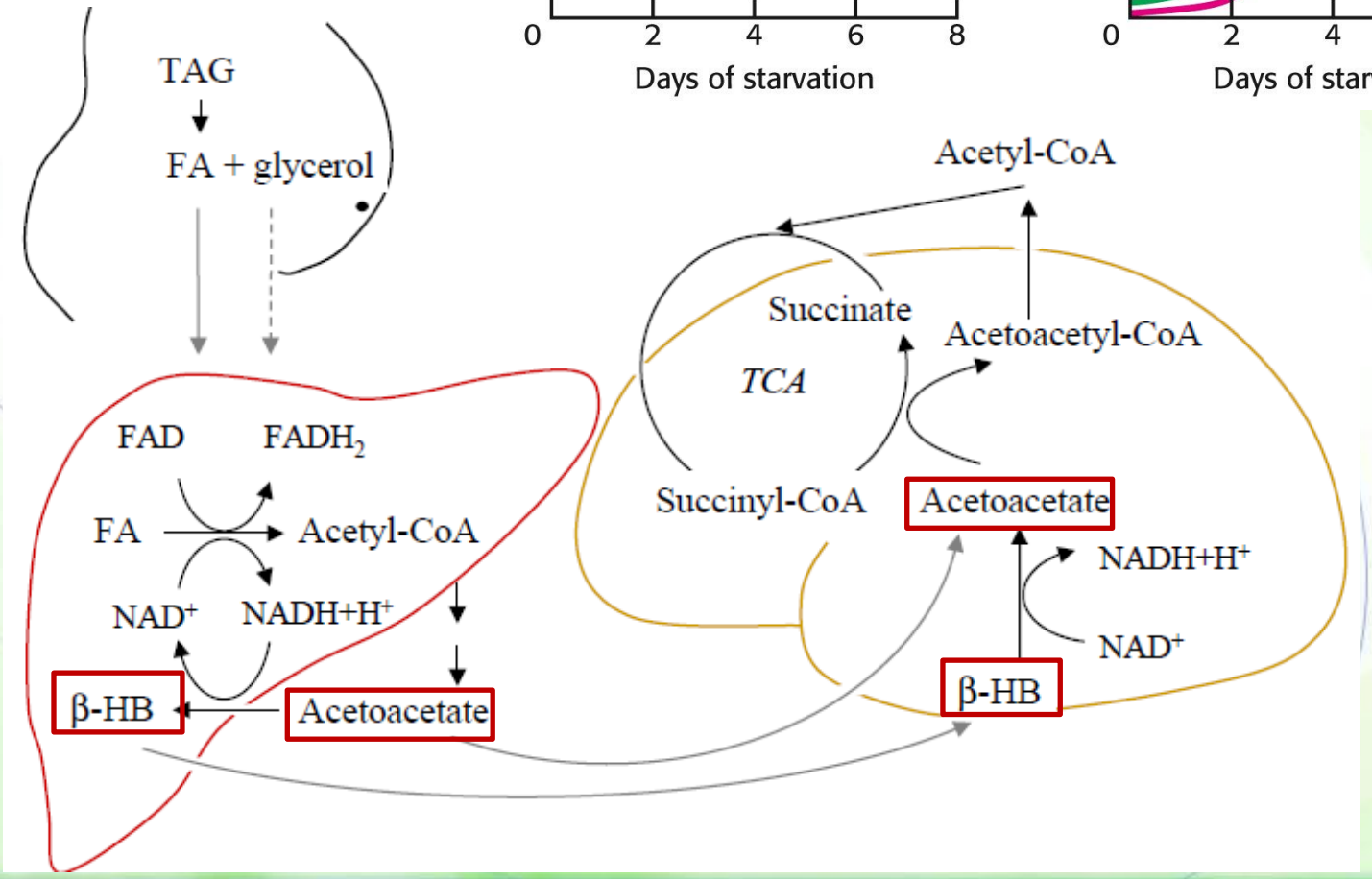
The all H4 isozyme

- functions aerobically
- Reduces lactate into pyruvate
- low Km for lactate
- inhibited by pyruvate

Production of ketone bodies

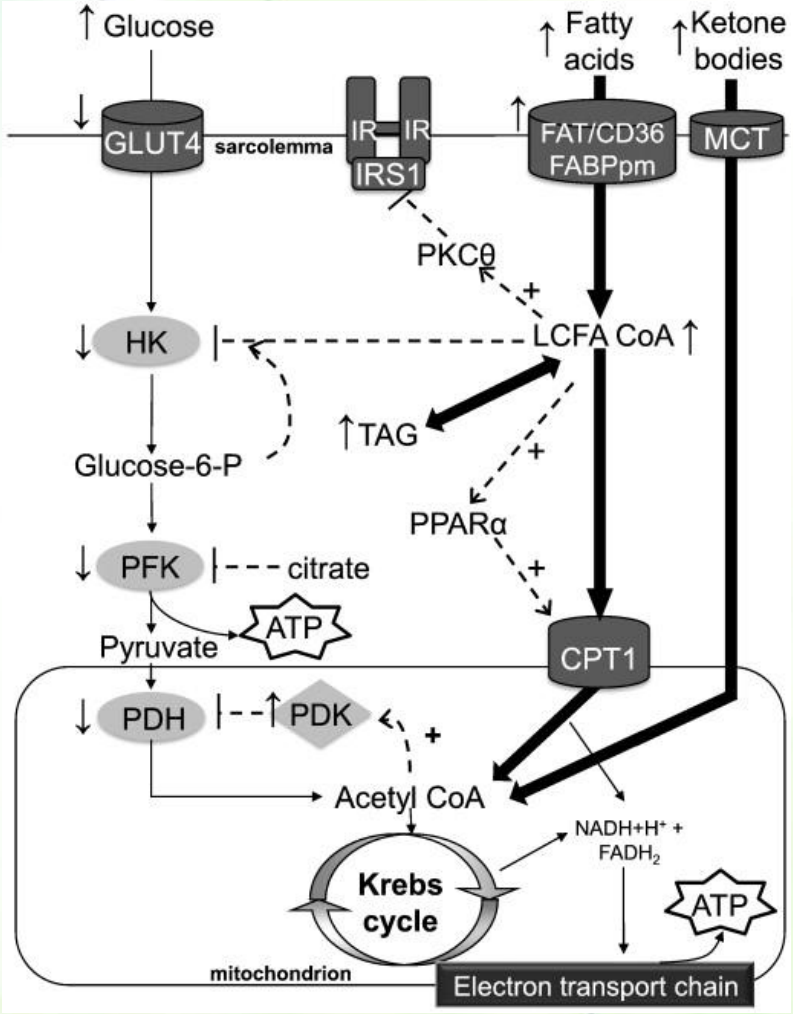






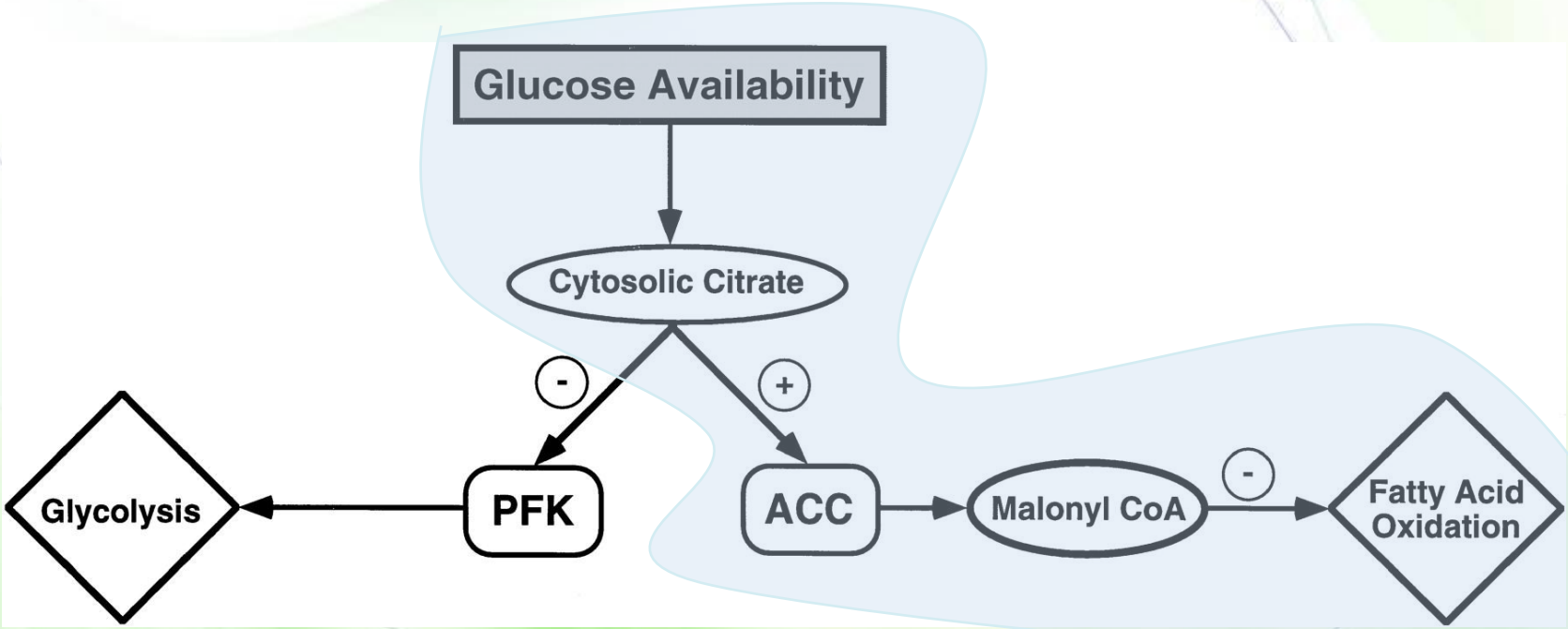
Regulation of glucose metabolism by FFA and ketone bodies

- Ketone bodies metabolism increases
  - acetyl CoA, which activates PDK inactivating PDH
  - citrate, which inhibits PFK
- Fatty acids metabolism increases:
  - LCFAs that inhibit HK
  - NADH/NAD+ ratio, which inhibits PDH
  - acetyl CoA and citrate (see above)



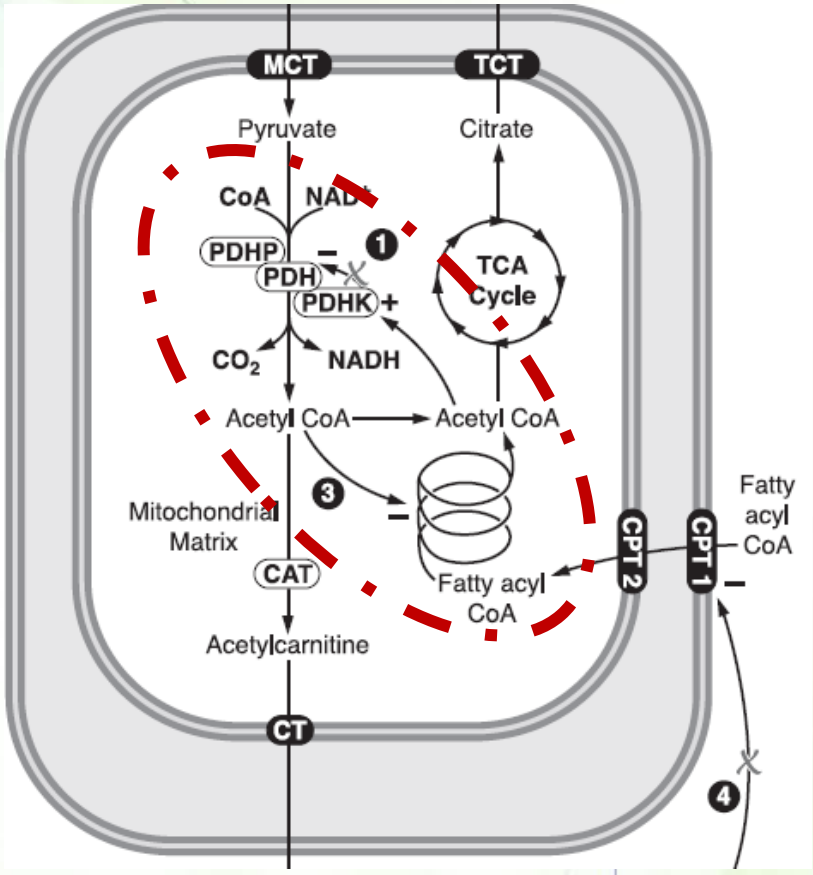
Regulation of fatty acid metabolism by glucose

- Glucose oxidation produces citrate, which can be converted to malonyl-CoA by acetyl-CoA carboxylase (ACC).
- Malonyl-CoA then can bind to and inhibit CPT1 blocking fatty acid oxidation.



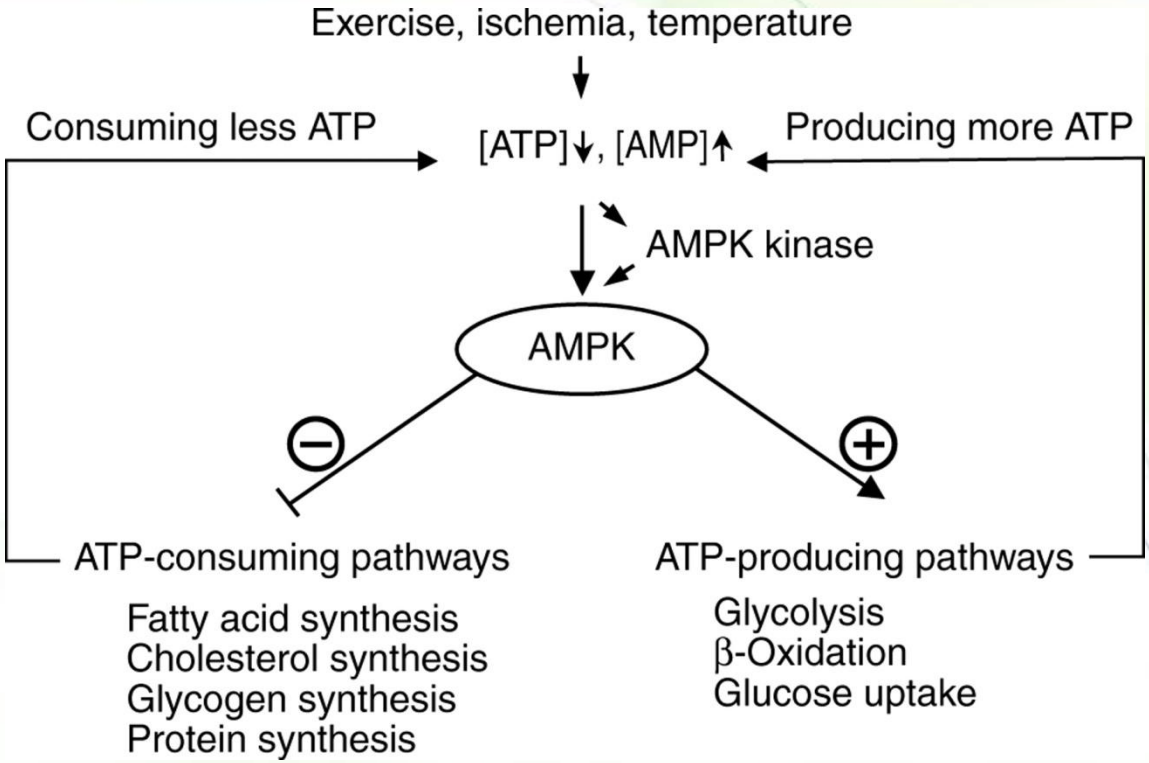
The glucose-fatty acid (Randle) cycle

- The Randle cycle describes the reciprocal relationship between fatty acid and glucose metabolism.
- The increased generation of acetyl CoA derived from fatty acid-oxidation decreases glucose (pyruvate) oxidation.
- The increased generation of acetyl CoA derived from glucose (pyruvate) oxidation inhibits fatty acid oxidation.



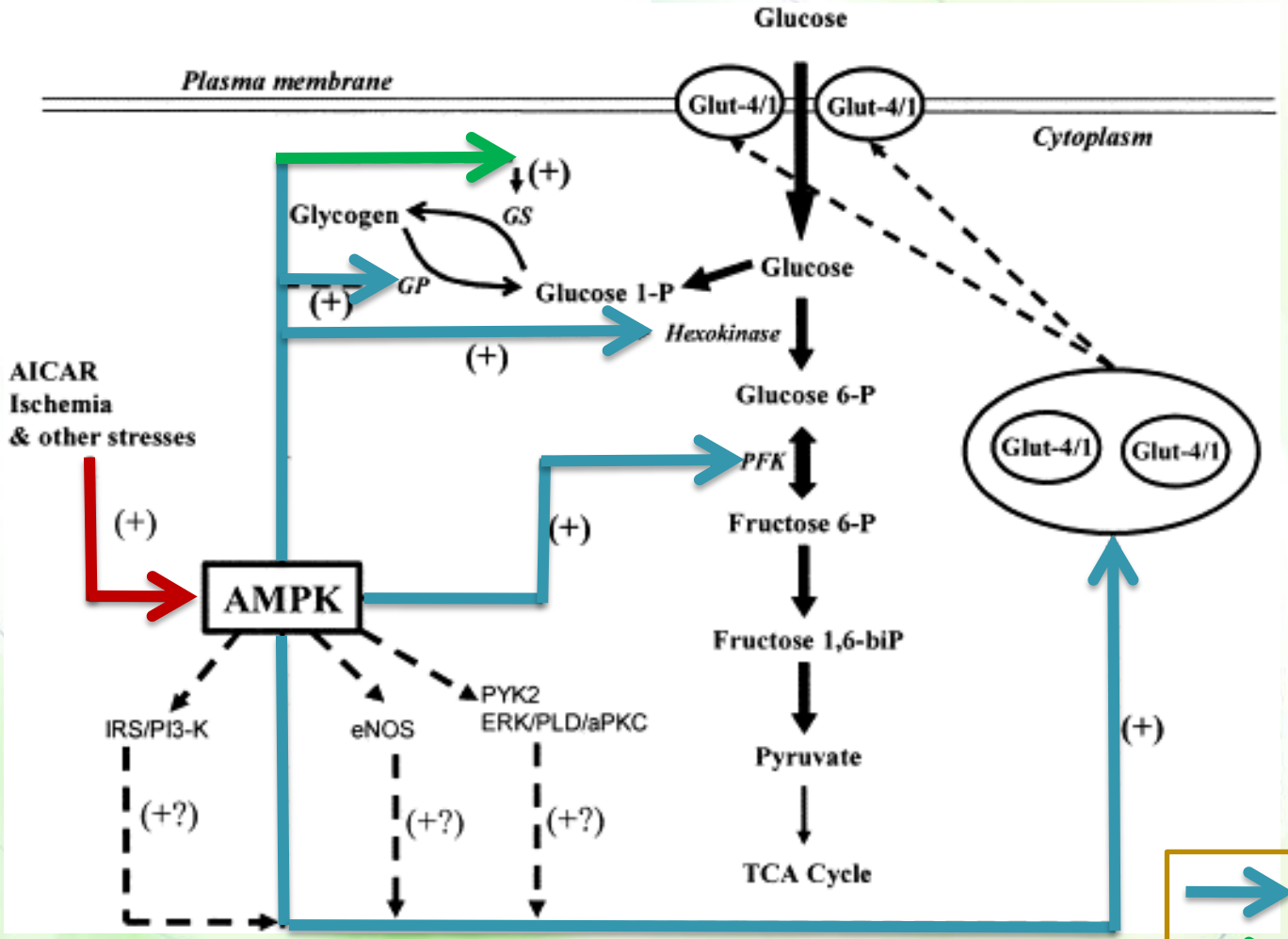
In the heart, inhibition of glucose utilization by fatty acids is a form of glucose intolerance that resembles, or may lead to, insulin resistance.

Metabolic regulation by AMPK



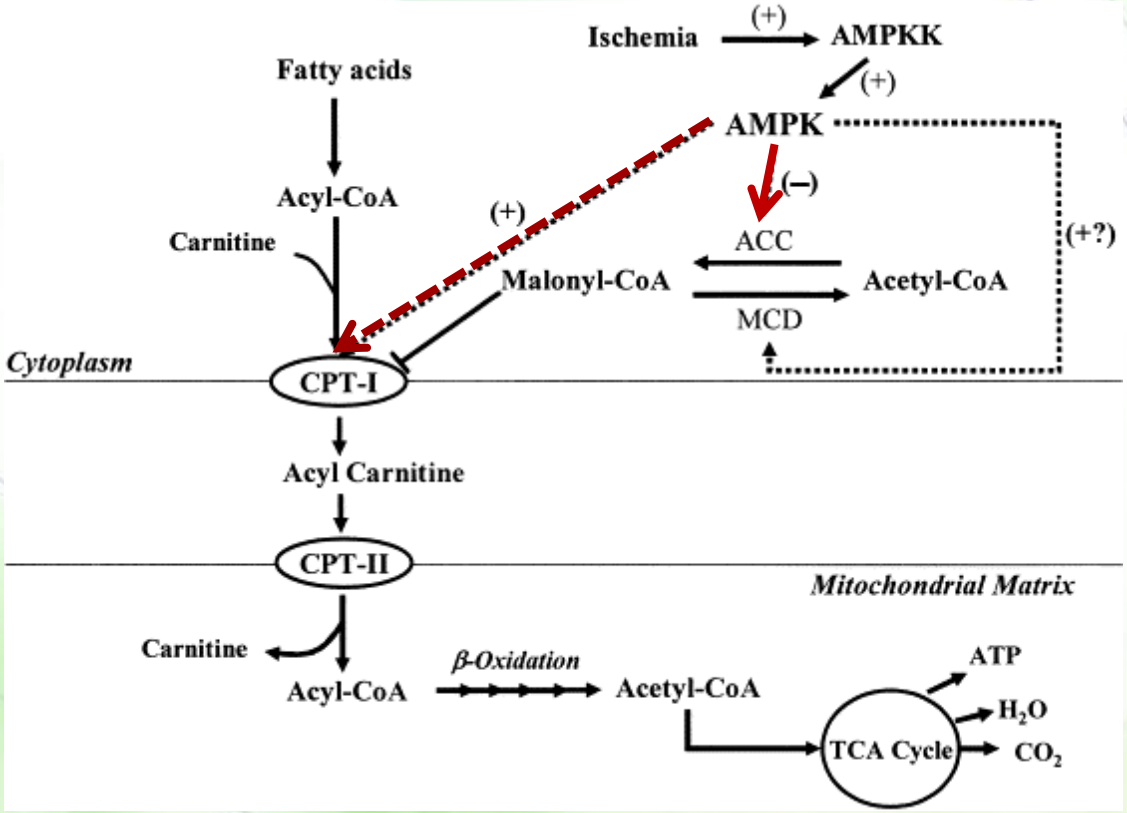
- AMPK
  - Activates GLUT-4 translocation into membrane
  - Stimulates glycolysis by activating hexokinase and phosphofructokinase
  - Activates glycogenolysis
  - Inactivates glycogenesis

AMPK and glucose metabolism



AMPK and fatty acid oxidation

- **AMPK activates fatty acid oxidation by inhibiting formation of malonyl CoA and activating CPT-1**



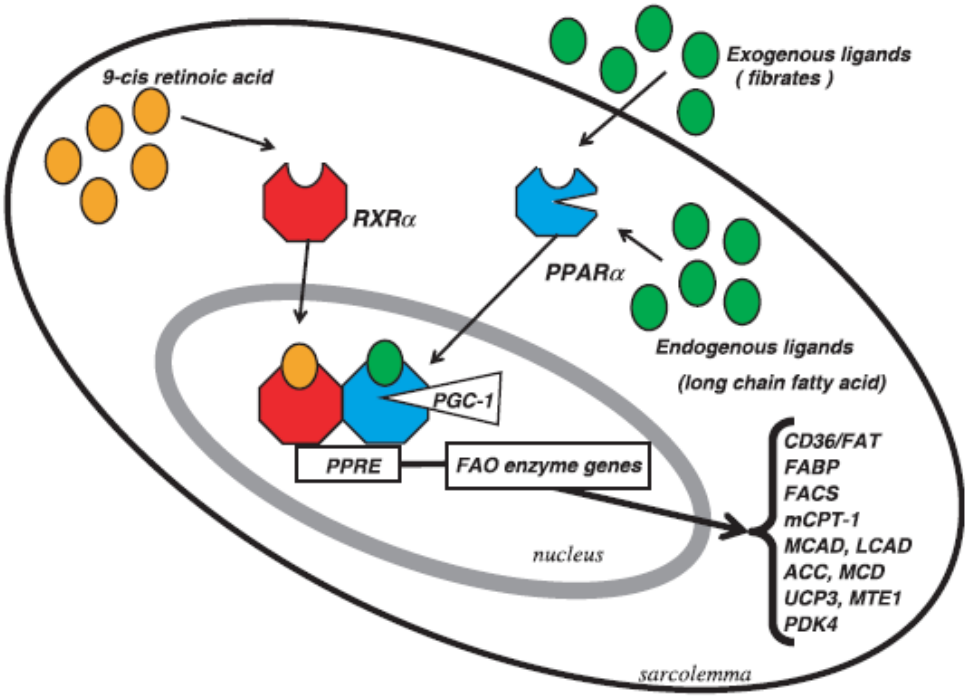
Peroxisome proliferator activated receptor (PPAR)

- PPAR isoforms
  - PPAR-α >> PPAR-β >> PPAR-γ

Heart, skeletal muscle, and liver

skeletal muscle

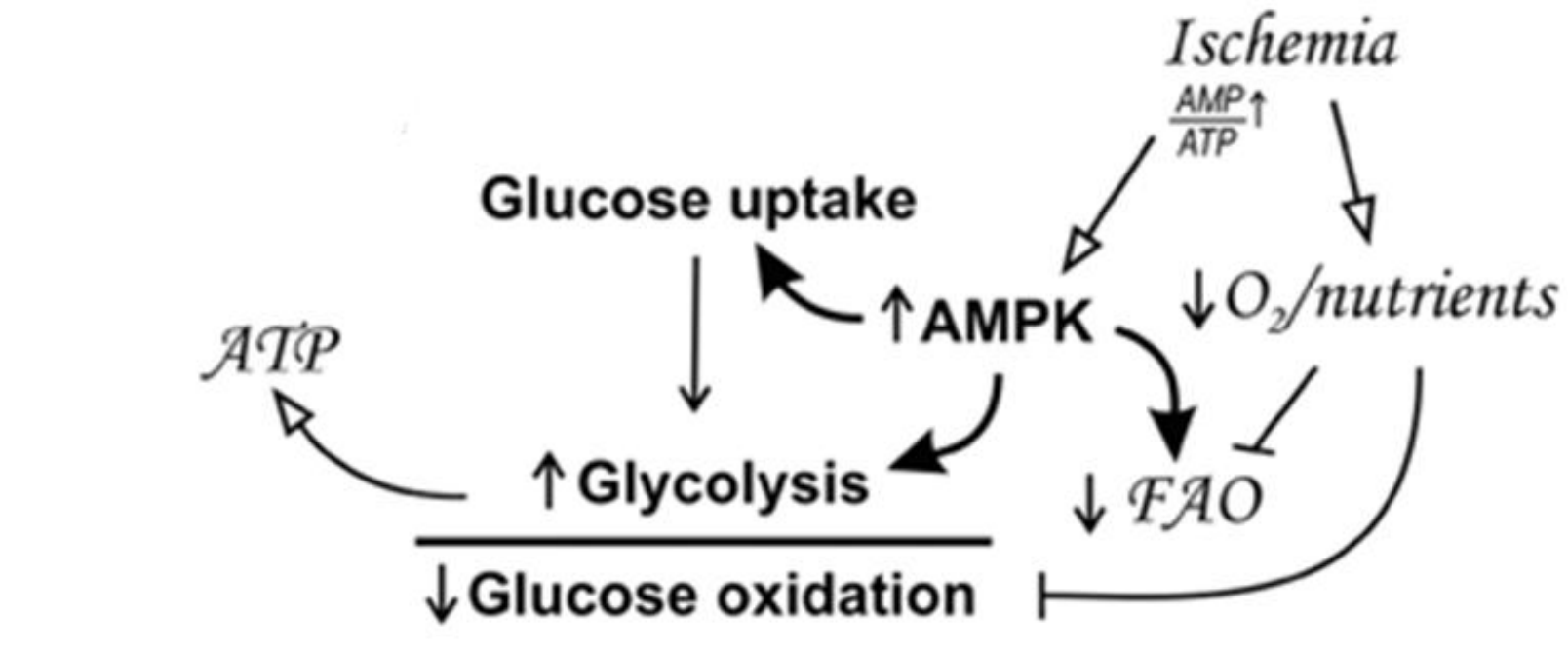
adipose tissue



- **PPAR-α increases the expression of inducers of fatty acid oxidation (uptake, esterification, and oxidation).**
- **PPARs can indirectly regulate fatty acid oxidation by decreasing the fatty acid concentration to which the heart is exposed.**

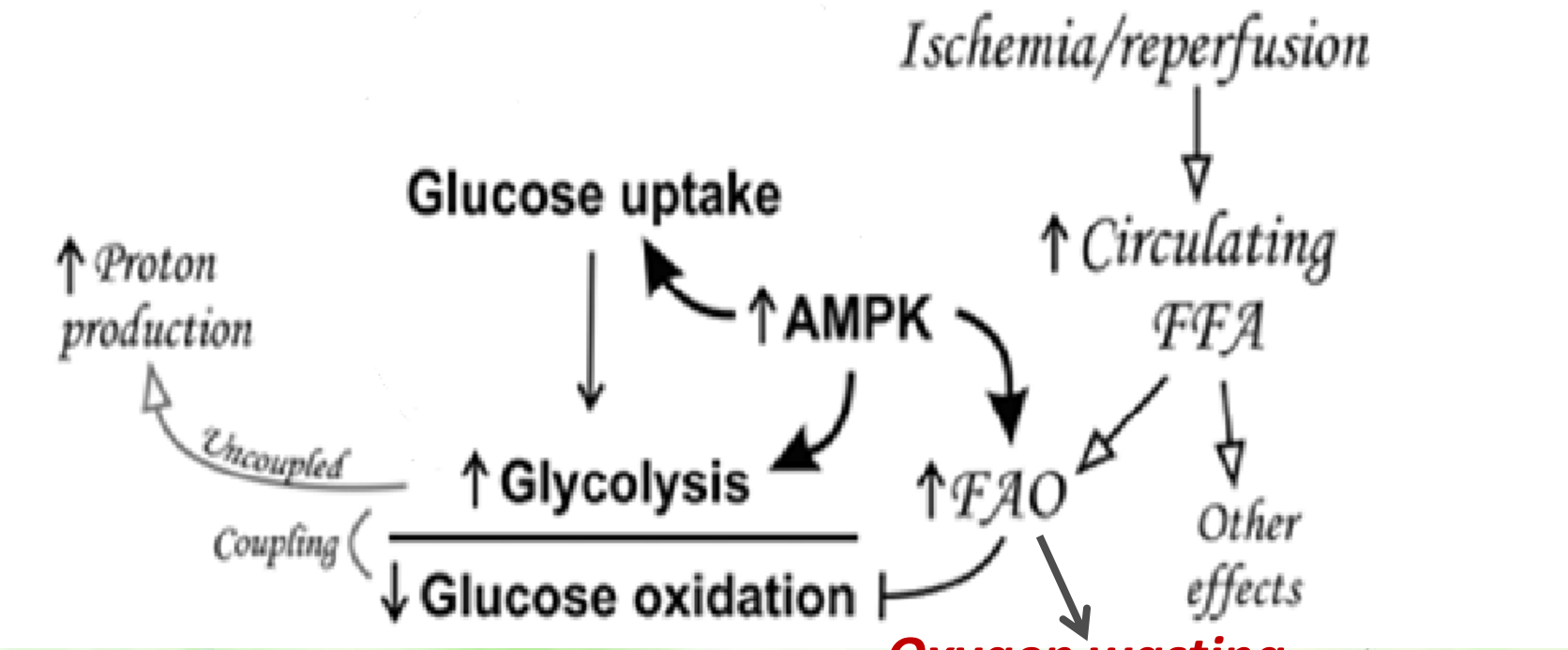
How does ischemia alter metabolic profile?

- Ischemia results in
  - A decrease of O_2 and nutrients, which inhibits oxidation of fatty acid and glucose.
  - An increase in AMP/ATP ratio, which activates AMPK, which activates glucose uptake and glycolysis.



Metabolism during reperfusion

- Fatty acid oxidation resumes, glycolysis continues, but glucose oxidation is inhibited. This is called "lipotoxicity".



Oxygen wasting

1. Fatty acid oxidation
2. Synthesis of uncouplers

Consequences of metabolism during reperfusion

(1) Increased glycolysis and (2) beta oxidation

(3) Activation of AMPK and (4) inhibition of glucose oxidation

(1) Lactate and protons accumulate (acidosis)

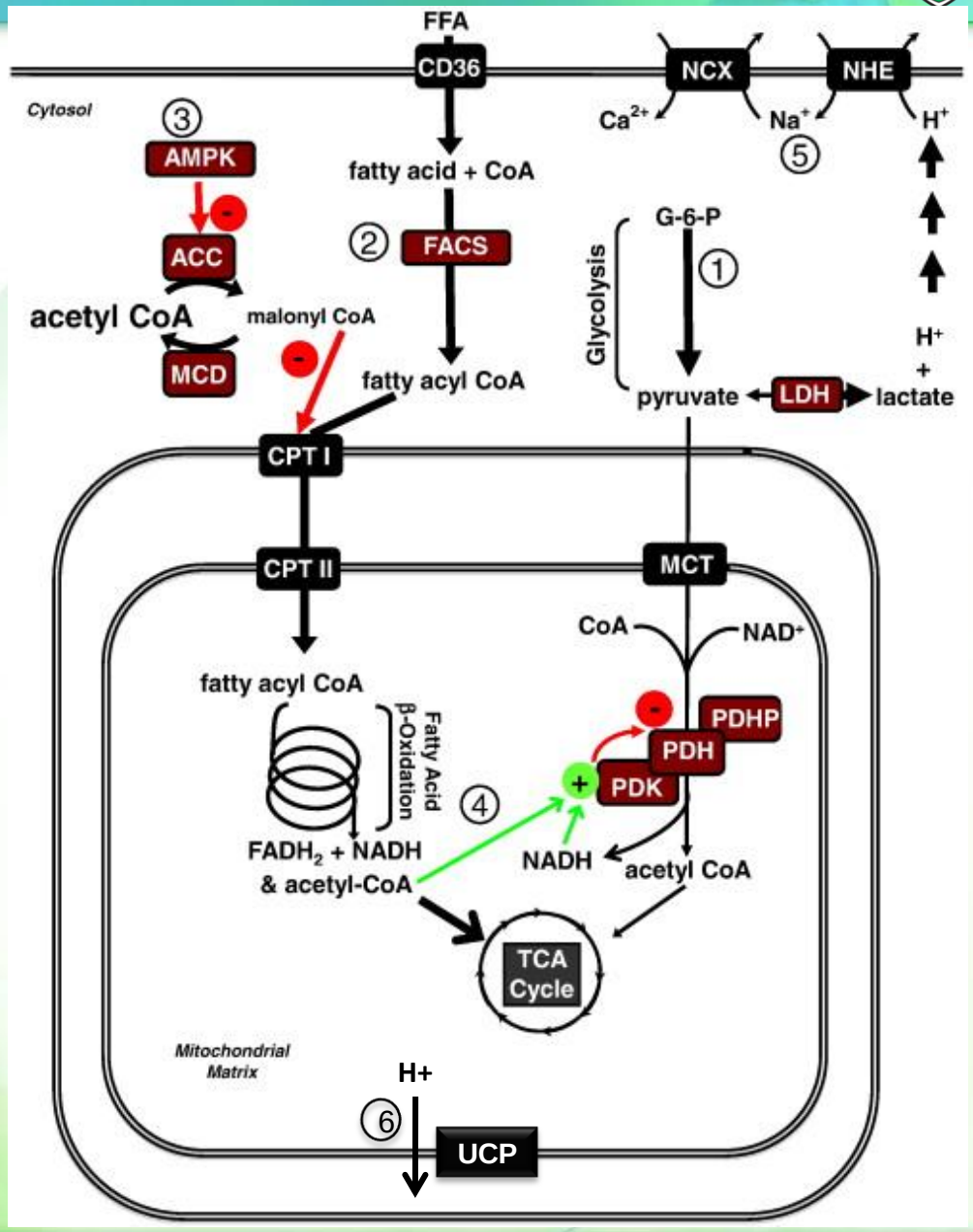
ATP wasting results from:

(5) removal of via H+/Na+ exchanger (Na+ overload) and Na+ ions are removed by Na+/Ca++ exchanger (Ca++ overload)

(6) Increased FFA stimulated synthesis of uncouplers that dissipate the electrochemical gradient across the inner mitochondrial membrane

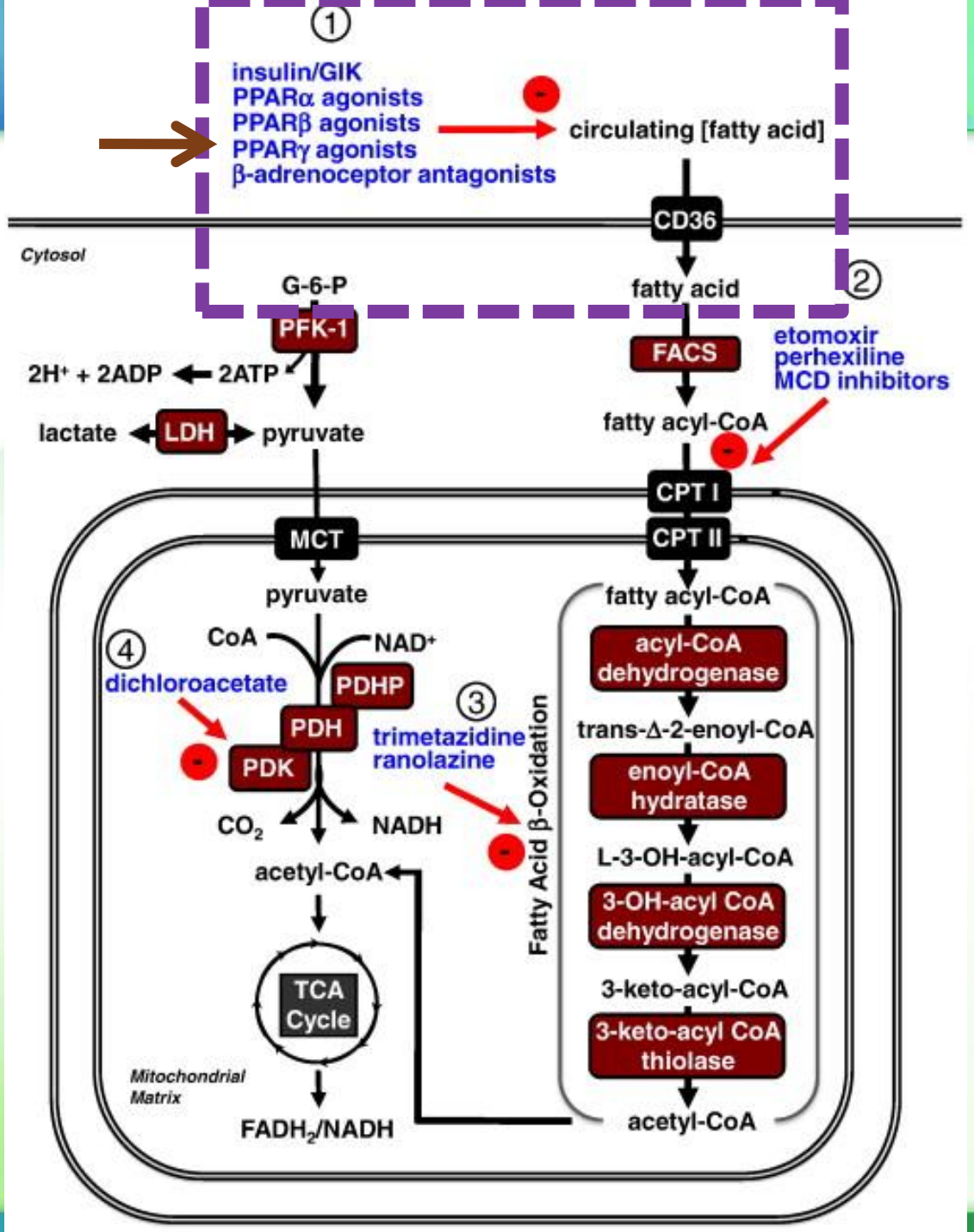
Production of free radicals (mitochondrial damage)

All lead to loss of cardiac contractile power.



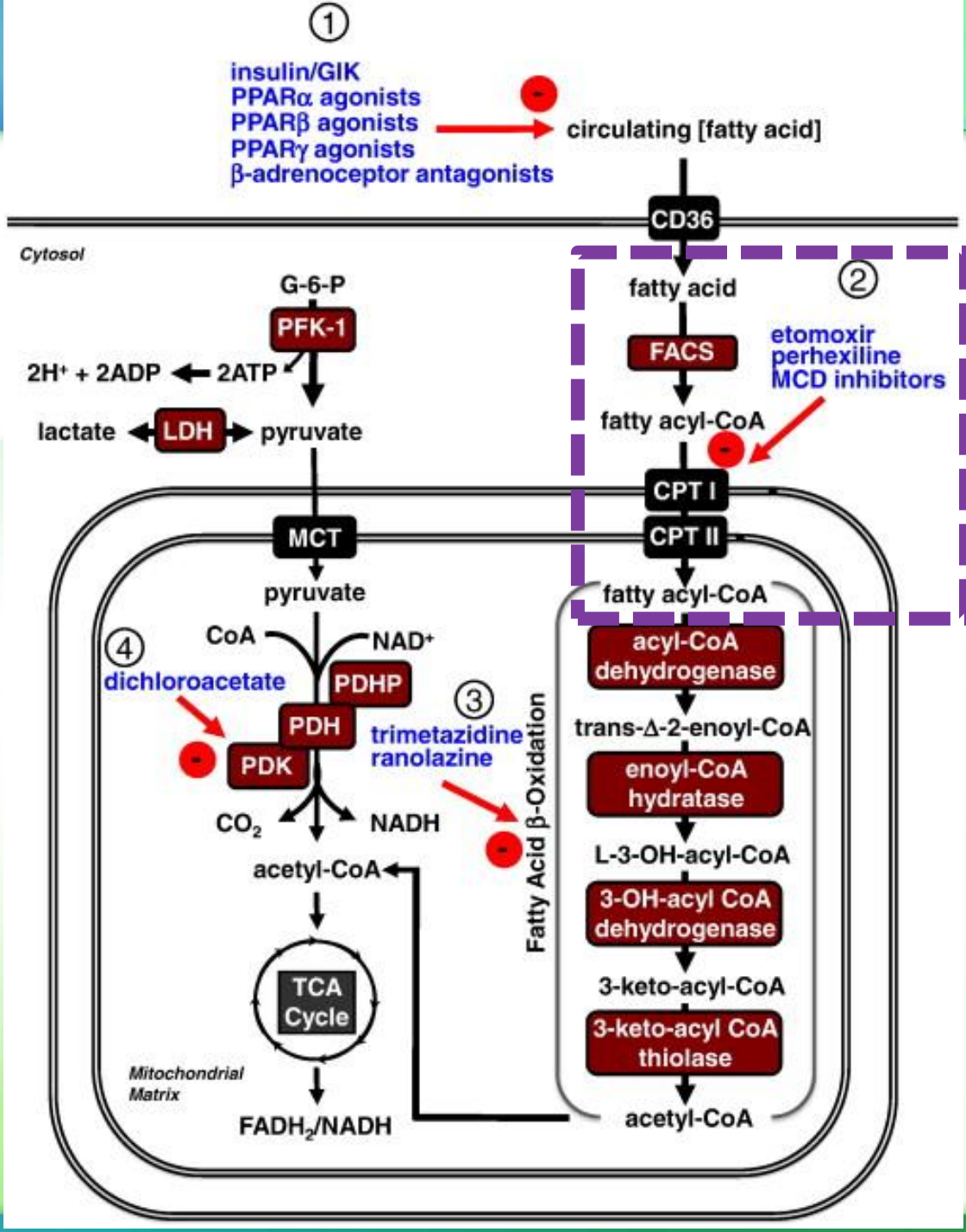
Therapeutic targets (1)

- Glucose–insulin–potassium (GIK) (reduce circulating fatty acid concentrations, while maintaining circulating glucose concentration)
- PPAR agonists (increase beta-oxidation in peripheral tissues)
- β-adrenoceptor antagonists (reduce catecholamine-induced lipolysis)



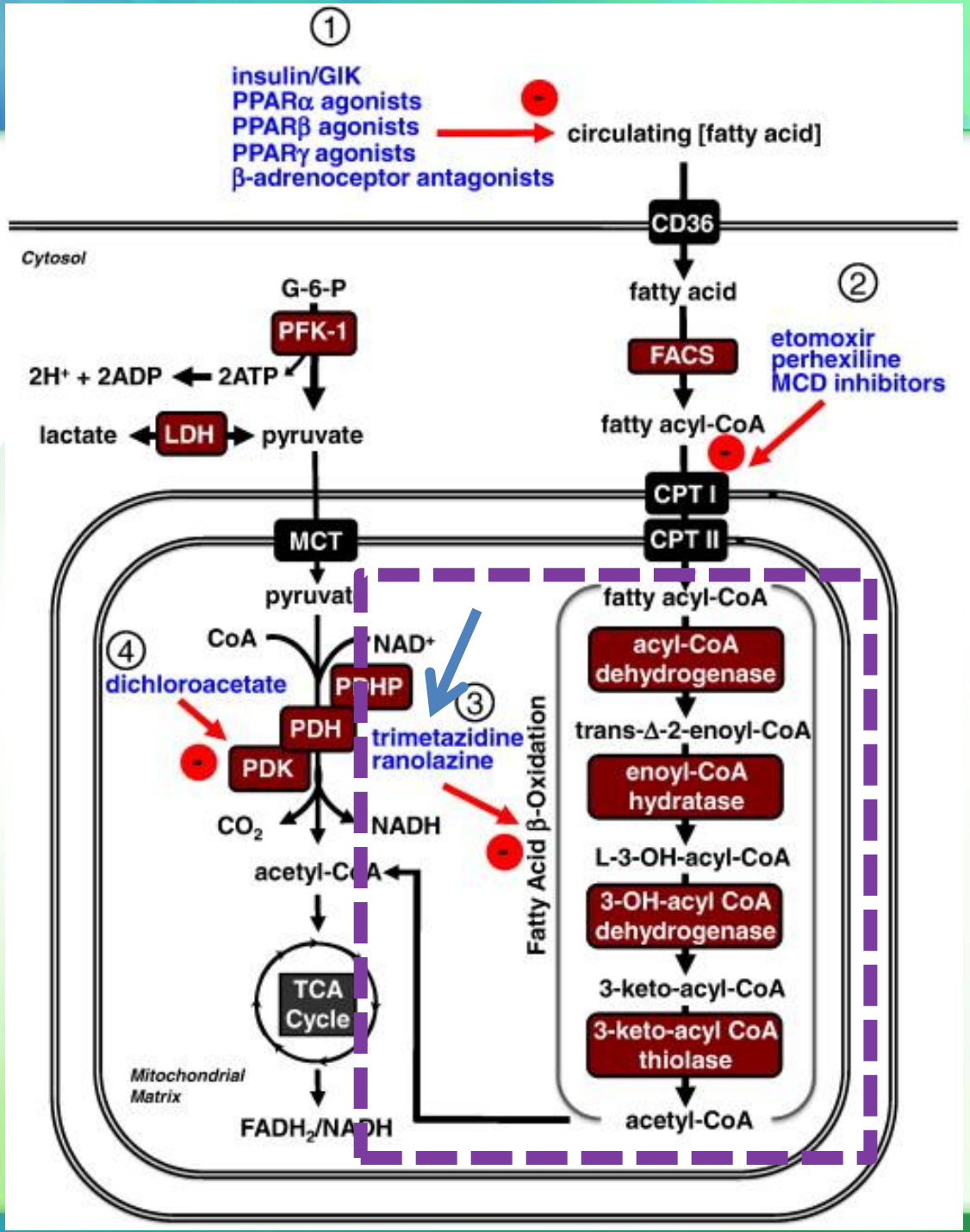
Therapeutic targets (2)

- The mitochondrial uptake of long chain acyl-CoAs can be reduced
  - Carnitine palmitoyl tranferase-I (CPTI)
  - Malonyl-CoA decarboxylase (MCD) inhibitors



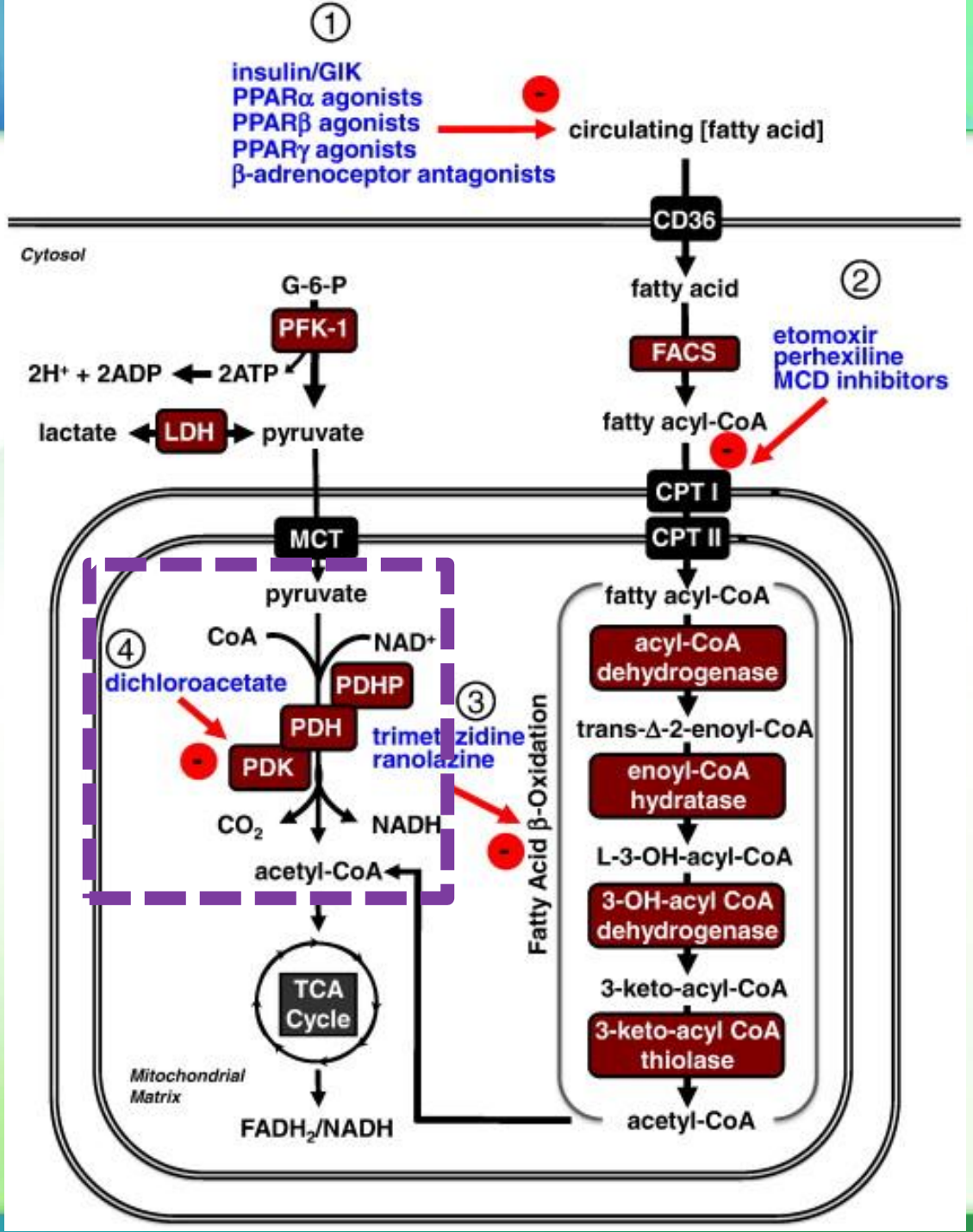
Therapeutic targets (3)

- Fatty acid oxidation inhibitors reduce the rates of myocardial fatty acid oxidation.



Therapeutic targets (4)

- Glucose oxidation can be increased by compounds that
  - increase pyruvate dehydrogenase (PDH) complex activity
  - inhibit PDK



Biomarkers of HF