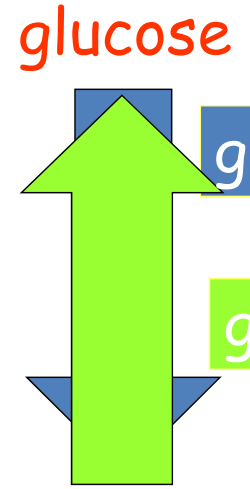
# gluconeogenesis

**Dr. Bariaa Ali Maki**




gluco neo genesis

sugar (re)new make/
create

# Gluconeogenesis

- Mainly occurs in cytosol
- Some precursors are produced in mitochondria
- Takes place in liver and kidney
- Synthesis of glucose or glycogen from non carbohydrates like pyruvate, lactate ,glucogenic amino acids, glycerol .
- Pathway involves steps of TCA cycle and reversal of glycolysis
- The irreversible steps of glycolysis are catalysed by
- Hexokinase
- Phosphofructokinase and
- Pyruvate kinase
- These three stages bypassed by other enzymes specific to gluconeogenesis
- They are called as key enzymes of gluconeogenesis

1. Pyruvate carboxylase
2. Phosphoenolpyruvate carboxykinase (PEPCK)
3. Fructose 1,6- Bis phosphatase
4. Glucose 6-phosphatase

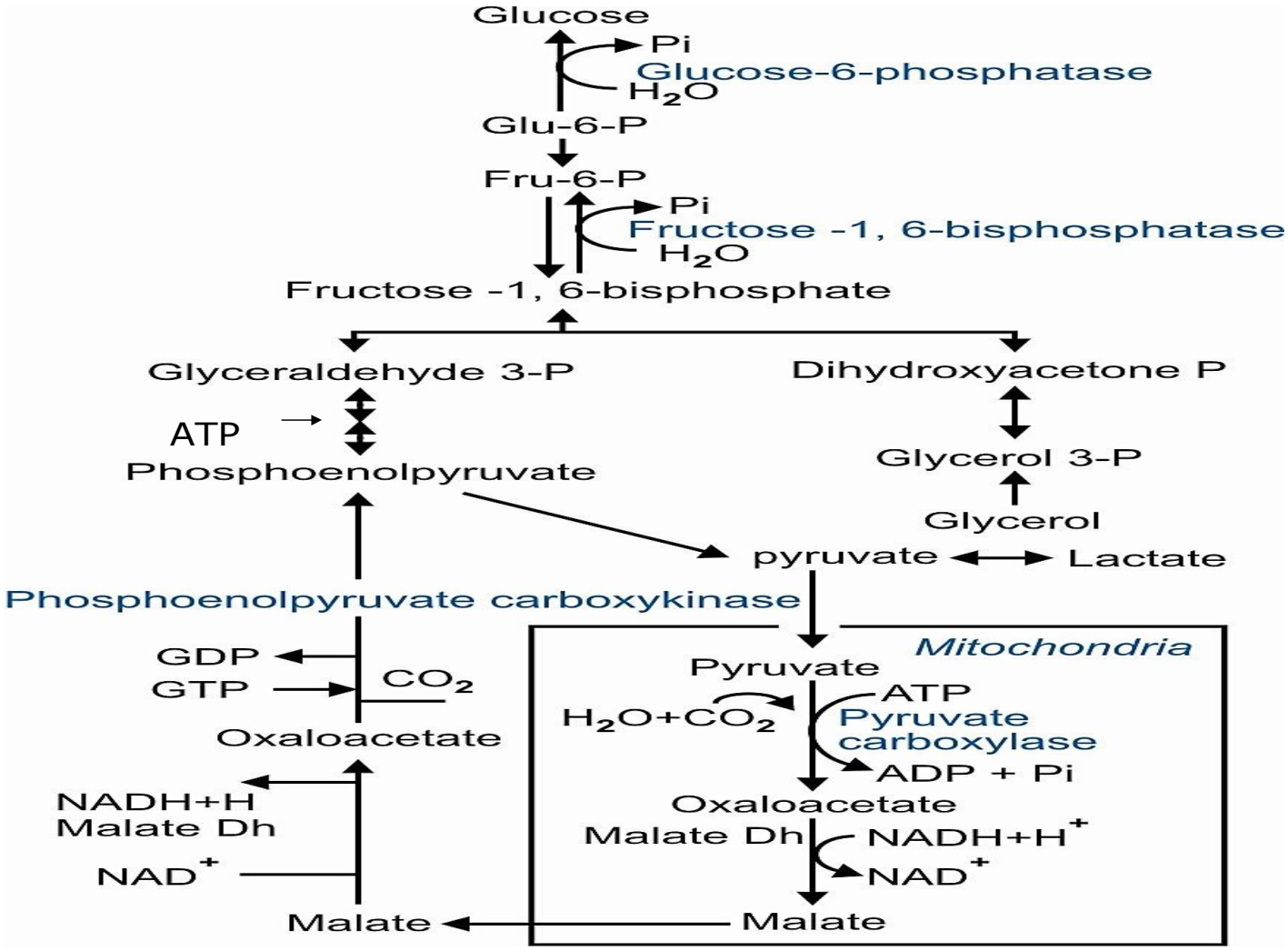
The pathway give the needs of the body for glucose

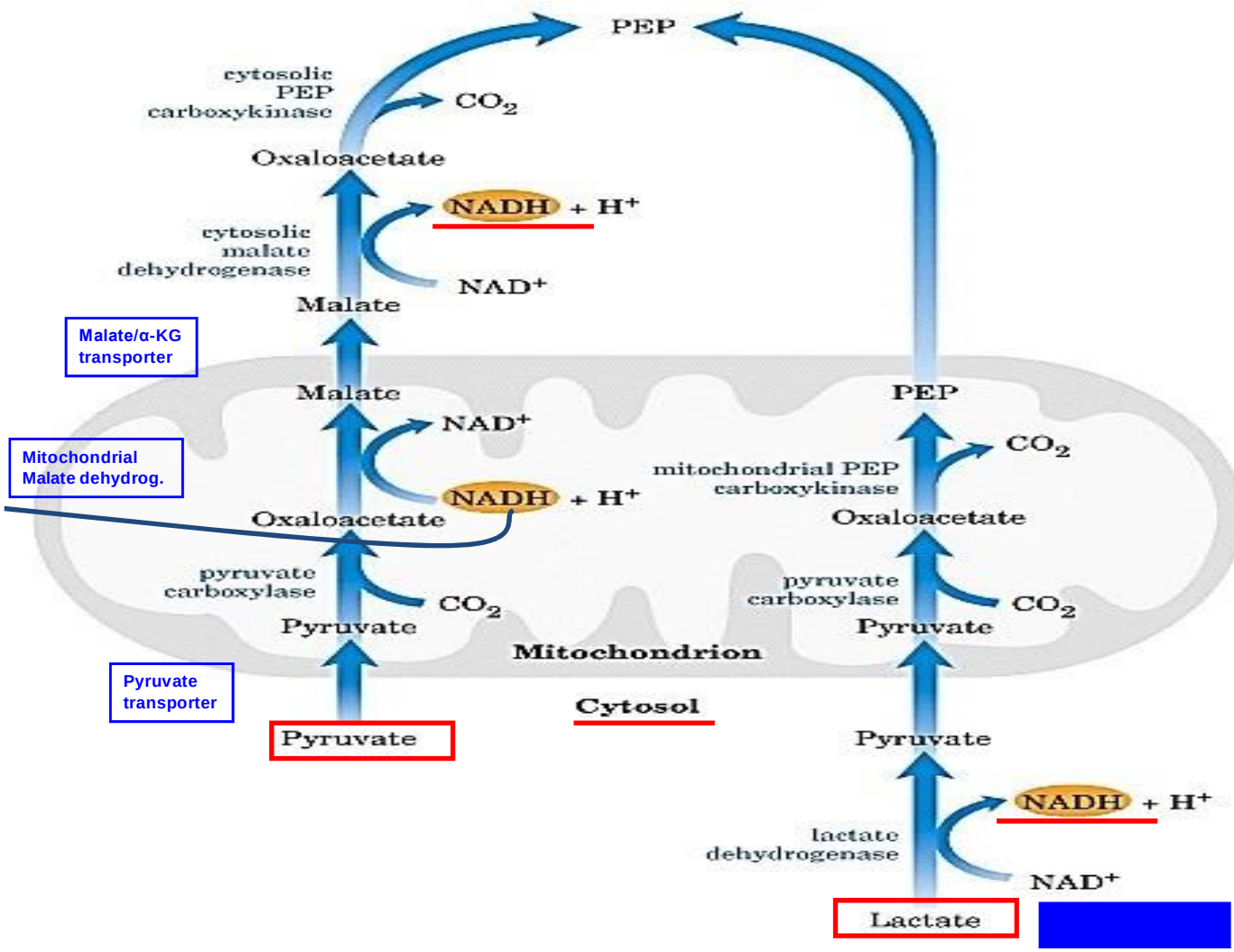
Continuous supply of glucose required as a sourc of energy for the CNS, Brain, RBC and skeletal muscle during starvation

The de novo synthesis of glucose and its role in preventing hypoglycemia

# In which kind of situation do we need gluconeogenesis?

- ✓ Normal physiology situation:
  - -Between meals and during sleep
  - -Exercise/work
- ✓ After heavy exercise or work (recycling of lactate)
- ✓ After protein-rich diet (glucogenic amino acids)
- ✓ Starvation (glucogenic amino acids)






## First Bypass Reaction: Conversion of Pyruvate to Phosphoenolpyruvate

**Requires participation of both mitochondrial and cytosolic enzymes.**

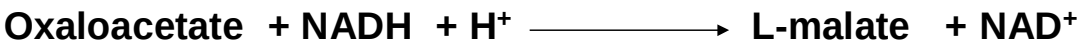
**Step 1: Pyruvate is transported from the cytosol into mitochondria via the mitochondrial pyruvate transporter OR pyruvate may be generated within mitochondria via deamination of alanine.**

**Step 2: Pyruvate is converted to OAA by the biotin-requiring enzyme *pyruvate carboxylase* as follows:**

$$\text{Pyruvate} + HCO_3^- + \text{ATP} \longrightarrow \text{oxaloacetate} + \text{ADP} + \text{Pi} + H^+$$

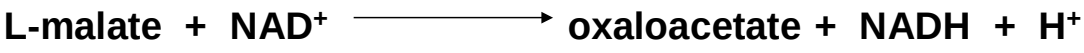
***Pyruvate carboxylase* is a regulatory enzyme. .**

**Step 3:** Oxaloacetate is reduced to malate by mitochondrial *malate dehydrogenase* at the expense of mitochondrial NADH.



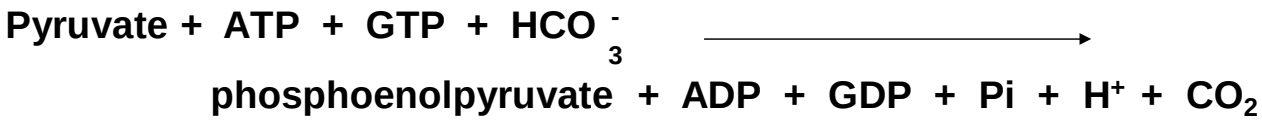

**Step 4:** Malate exits the mitochondrion via the malate/α-ketoglutarate carrier.

**Step 5:** In the cytosol, malate is reoxidized to oxaloacetate via cytosolic *malate dehydrogenase* with the production of cytosolic NADH.




**Step 6:** Oxaloacetate is then converted to phosphoenolpyruvate (PEP) by *phosphoenolpyruvate carboxykinase* in the reaction:


The overall equation for this set of bypass reactions is:




Thus the synthesis of one molecule of PEP requires an investment of 1 ATP and 1 GTP.

**Note:** when either pyruvate or the ATP/ADP ratio is high, the reaction is pushed toward the right (i.e., in the direction of biosynthesis).

## Second Bypass Reaction: Conversion of Fructose 1,6-bisphosphate to Fructose 6-phosphate

**The second glycolytic reaction (i.e., the phosphorylation of fructose 6-phosphate by *PFK1*) is irreversible.**

**Hence, for gluconeogenesis fructose 6-phosphate must be generated from fructose 1,6-bisphosphate by a different enzyme: *fructose 1,6-bisphosphatase.***

**This reaction is also irreversible.**

**Fructose 1,6-bisphosphate + $H_2O$ ⟶ fructose 6-phosphate + Pi**

## Third Bypass Reaction: Glucose 6-phosphate to Glucose

**Because the hexokinase reaction is irreversible, the final reaction of gluconeogenesis is catalyzed by a different enzyme, namely *glucose 6-phosphatase.***

**Glucose 6-phosphate + $H_2O$ ⟶ glucose + Pi**

**Glucose 6-phosphatase is present in the liver, but absent in brain and muscle.**

**Thus, glucose produced by gluconeogenesis in the liver, is Take by the bloodstream to brain and muscle.*****

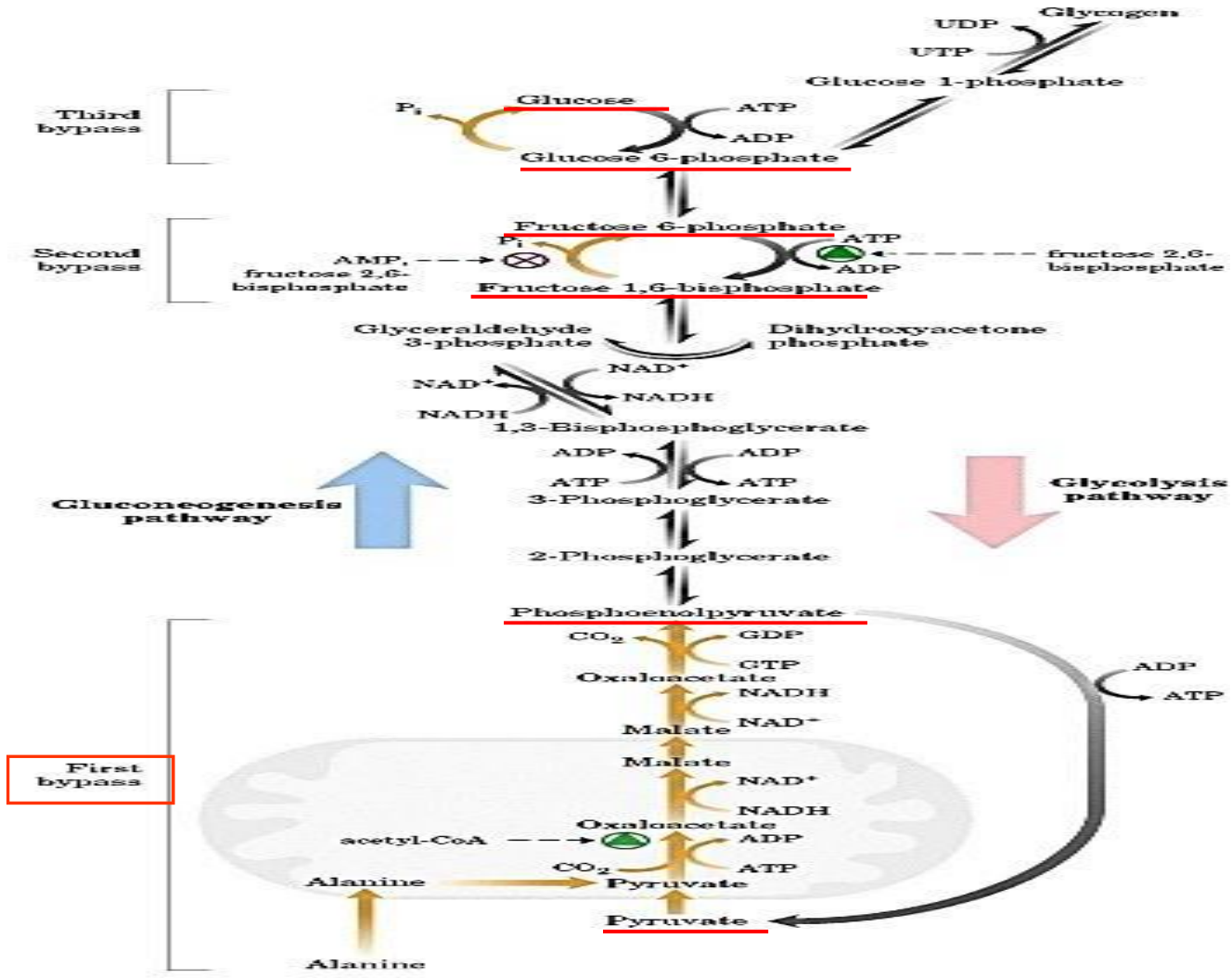
## The overall equation for gluconeogenesis is:

**2 pyruvate + 4 ATP + 2 GTP + 4 $H_2O$ ⟶**

**glucose + 4 ADP + 2 GDP + 6 Pi + 2 $H^+$**

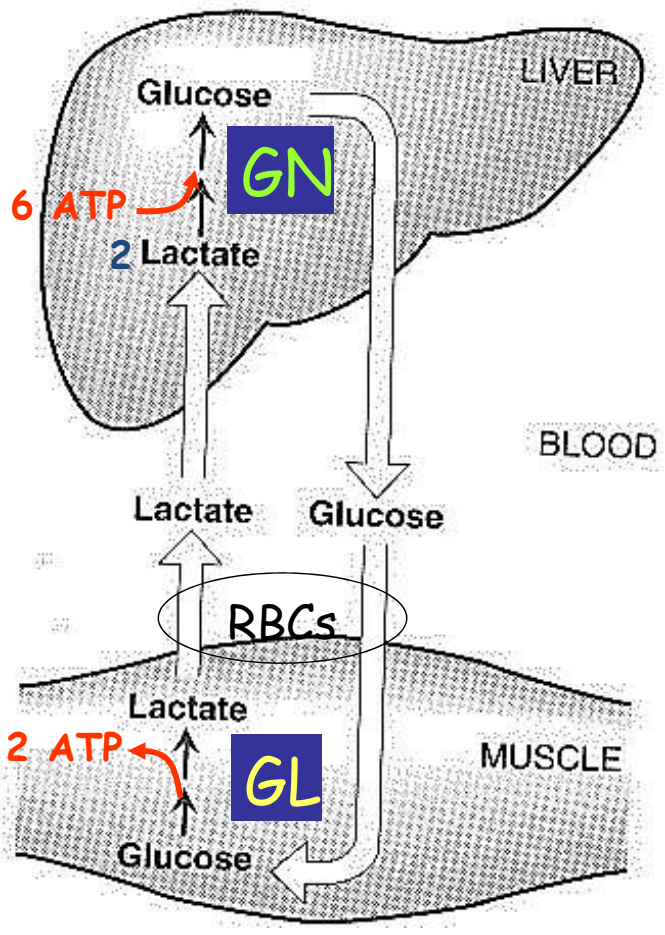
**For each molecule of glucose produced, 6 high energy phosphate groups**

## Thus "Gluconeogenesis Costs".



# Precursers for gluconeogenesis

1. Pyrovat
2. Lactate
3. Amino acid
4. glycerol

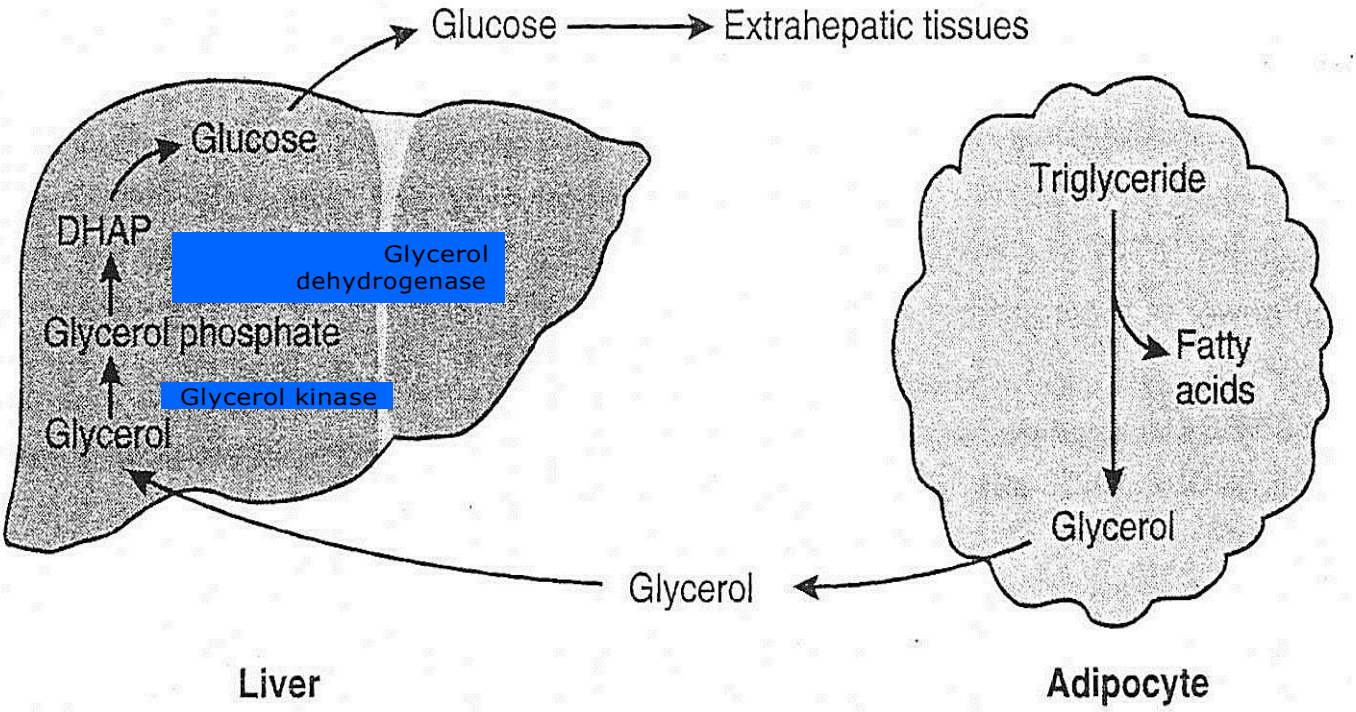



## The Cori Cycle

Lactate and glucose shuttle between active muscle/RBC and liver (glucagon/insulin )

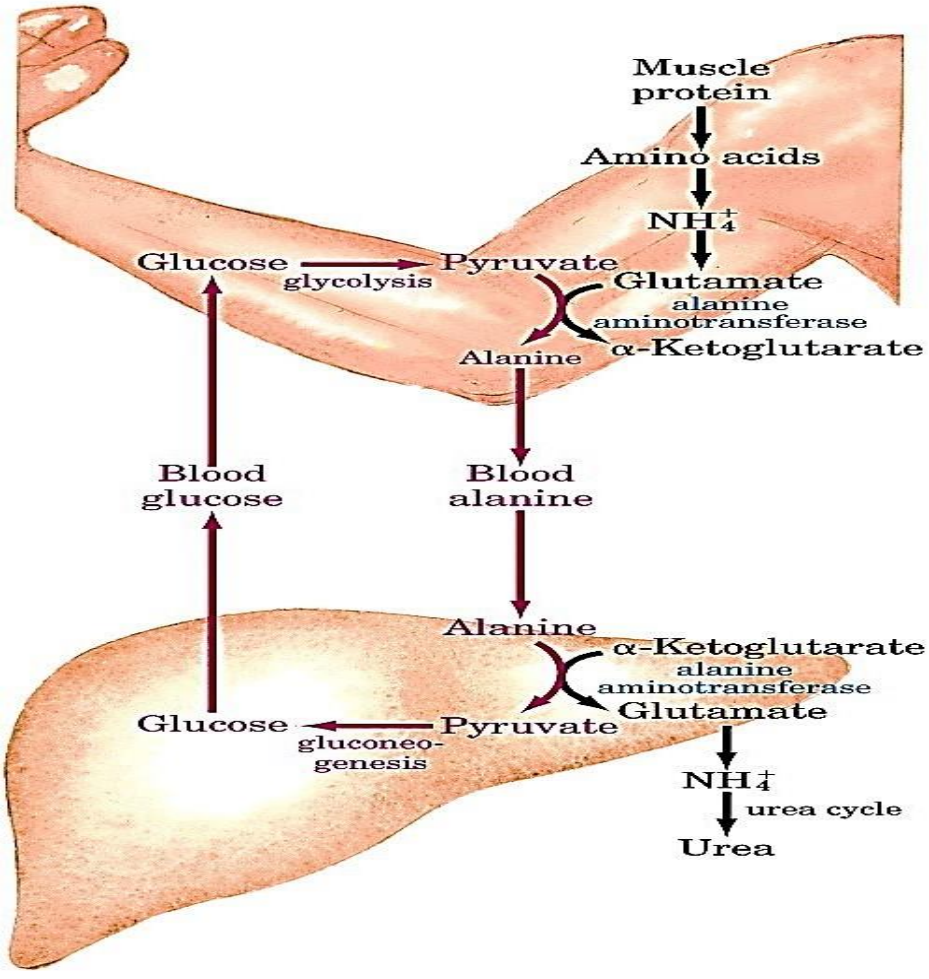
*Note: the brain fully oxidizes glucose, so it does not funnel back lactate

- Glycerol
  - derived from adipocyte lipolysis
  - hepatic glycerol kinase

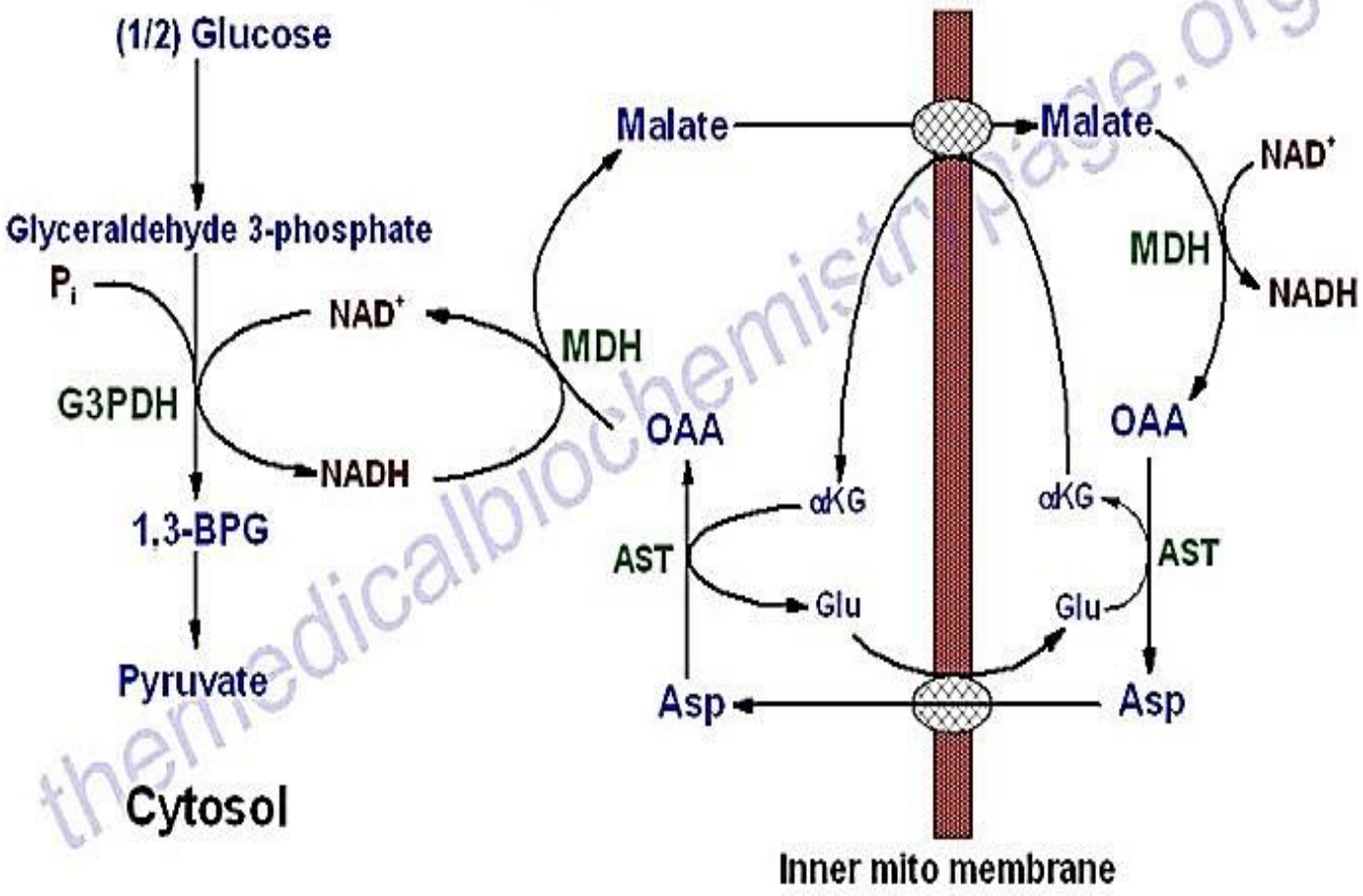



## The Alanine Cycle

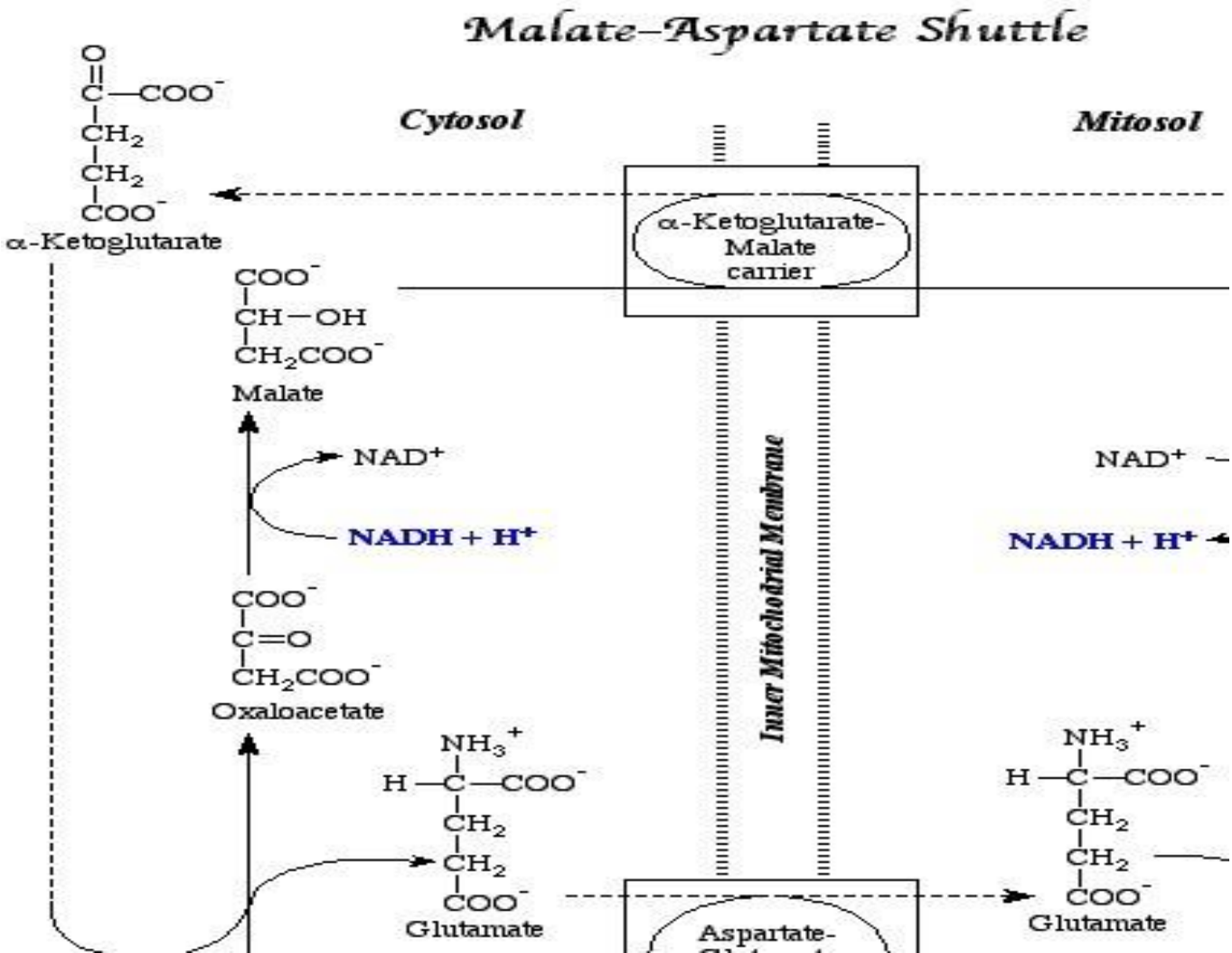
The liver can also use the amino acid Alanine similarly to Lactate



# Malate-Aspartate Shuttle





# Glycerol Phosphate Shuttle