Shuttle system in Metabolism

Shuttle system is a system that helps in the transfer of electrons from NADH to the electron transport chain.

1. Malate-aspartate Shuttle System

2. Gylcerol 3-Phosphate Shuttle System

Points to remember:

a) This shuttle system is used during glycolysis for the transport of 2NADH (electrons) from cytoplasm to mitochondria matrix for oxidative Phosphorylation.(since the inner mitochondrial membrane is impermeable to NADH).

b) The electrons enter the electron transport chain and help to generate ATP. The net gain during ATP glycolysis depends upon on which the shuttle system is used.

The malate-aspartate (M-A) shuttle provides an important mechanism to regulate glycolysis and lactate metabolism in the heart by transferring reducing equivalents from cytosol into mitochondria. It is the principal mechanism for the movement of NADH from the cytoplasm into the mitochondrial matrix. The electrons are carried into the mitochondrial matrix in the form of **Malate**.

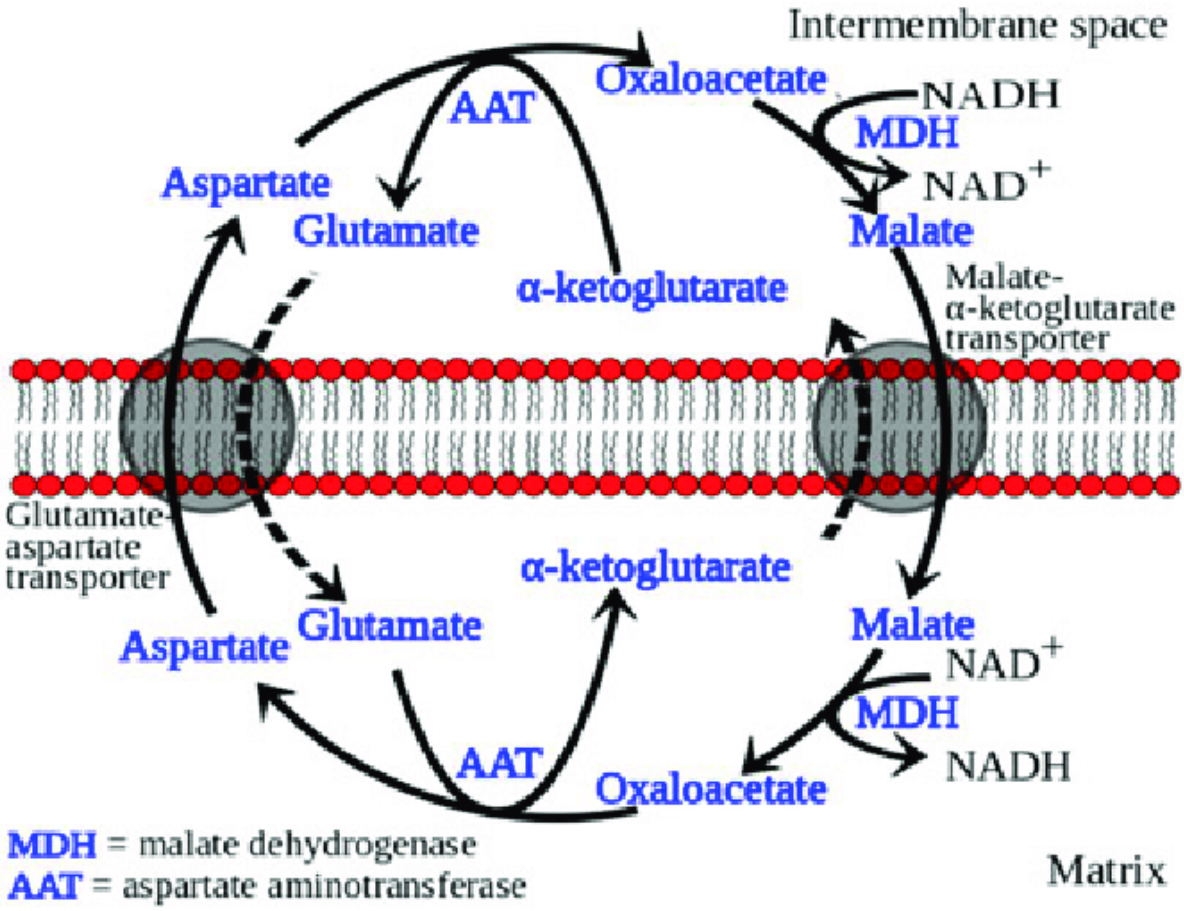
Primary enzyme in the malate-aspartate shuttle is **malate dehydrogenase**. Malate dehydrogenase is present in two forms in the shuttle system: **mitochondrial malate dehydrogenase and cytosolic malate dehydrogenase**. First, in the cytosol, malate dehydrogenase catalyses the reaction of oxaloacetate and NADH to produce malate and NAD^+. Two electrons are generated from NADH, and an accompanying H^+, are attached to oxaloacetate to form malate. There are two antiporter proteins located in the inner membrane of the mitochondria, **the glutamate-aspartate transporter (transporter I) and the malate-α-ketoglutarate transporter (transporter II).**

Once malate is formed, the first antiporter (malate-alpha-ketoglutarate) imports the malate from the cytosol into the mitochondrial matrix and also exports alpha-ketoglutarate from the matrix into the cytosol simultaneously. After malate reaches the mitochondrial matrix, it is converted by mitochondrial **malate dehydrogenase** into oxaloacetate, during which NAD^+ is reduced with 2 electrons to form NADH. Oxaloacetate is then transformed into aspartate (since oxaloacetate cannot be transported into the cytosol) by mitochondrial **aspartate aminotransferase**. Since aspartate is an amino acid, an amino radical needs to be added to the oxaloacetate. This is supplied by glutamate, which in the process is transformed into alpha-ketoglutarate by the same enzyme.

The second antiporter (the glutamate-aspartate antiporter) imports glutamate from the cytosol into the matrix and exports aspartate from the matrix to the cytosol. In the cytosol, aspartate is converted by cytosolic aspartate aminotransferase to oxaloacetate. The M-A shuttle comprises a transport-transamination-redox cycle in both cytosolic and mitochondrial domains.

NADH in the cytosol is oxidized to NAD^+, and NAD^+ in the matrix is reduced to NADH. The NAD^+ in the cytosol can then be reduced again by another round of glycolysis, and the NADH in the matrix can be used to pass electrons to the electron transport chain so ATP can be synthesized.

Since the malate-aspartate shuttle regenerates NADH inside the mitochondrial matrix, it is capable of maximizing the number of ATPs produced in glycolysis (3/NADH), ultimately resulting in a net gain of 38 ATP molecules per molecule of glucose metabolized



Steps of Malate-aspartate shuttle:

1. NADH in the cytosol enters the intermembrane space through openings in the outer membrane (porins), then passes two reducing equivalents to oxaloacetate, producing malate. **2**
2. Malate crosses the inner membrane via the malate–*α*-ketoglutarate transporter.
3. In the matrix, malate passes two reducing equivalents to NAD+, and the resulting NADH is oxidized by the respiratory chain; the oxaloacetate formed from malate cannot pass directly into the cytosol.
4. Oxaloacetate is first transaminated to aspartate, and
5. Aspartate can leave via the glutamate-aspartate transporter.
6. Oxaloacetate is regenerated in the cytosol, completing the cycle, and glutamate produced in the same reaction enters the matrix via the glutamate-aspartate transporter.

Note:

- When body utilises α-glycero-P-shuttle, net ATP produced by glycolysis—TCA cycle per molecule glucose oxidised will be 36 ATP (2 ATP less) and NOT 38 ATP.
- Use of Malate shuttle will form 38 ATP

Shuttle pathways and tissues

- Liver, kidney, and heart utilize malate-aspartate shuttle, and yield 3 ATP per mole of NADH.
- Skeletal muscle and the brain utilize glycerol-phosphate shuttle and liberate 2 ATP from NADH.