The Citric Acid Cycle
11/25/2008

The Citric acid cycle

It is called the Krebs cycle or the tricarboxylic and is the “hub” of the metabolic system. It accounts for the majority of carbohydrate, fatty acid and amino acid oxidation. It also accounts for a majority of the generation of these compounds and others as well.

Amphibolic - acts both catabolically and anabolically

3NAD+ + FAD + GDP + Pi + acetyl-CoA →
3NADH + FADH + GTP + CoA + 2CO₂

Overview

The citric acid cycle enzymes are found in the matrix of the mitochondria

Substrates have to flow across the outer and inner parts of the mitochondria

Pyruvate dehydrogenase

A multienzyme complexes are groups of non covalently associated enzymes that catalyze two or more sequential steps in a metabolic pathway.

Molecular weight of 4,600,000 Da

<table>
<thead>
<tr>
<th>E. coli</th>
<th>yeast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyruvate dehydrogenase -- E1</td>
<td>24</td>
</tr>
<tr>
<td>dihydrolipoyl transacetylase -- E2</td>
<td>24</td>
</tr>
<tr>
<td>dihydrolipoyl dehydrogenase -- E3</td>
<td>12</td>
</tr>
</tbody>
</table>

Why such a complex set of enzymes?

1. Enzymatic reactions rates are limited by diffusion, with shorter distance between subunits a enzyme can almost direct the substrate from one subunit (catalytic site) to another.
2. Channeling metabolic intermediates between successive enzymes minimizes side reactions.
3. The reactions of a multienzyme complex can be coordinately controlled.
Covalent modification of eukaryotic pyruvate dehydrogenase

The five reactions of the pyruvate dehydrogenase multi enzyme complex

Induced fit needs binding of oxaloacetate before Acetyl CoA can bind.

Citrate Synthase

Aconitase

The double bond is placed on the Pro-R arm
NAD$^+$- Dependent Isocitrate dehydrogenase

α-Ketoglutarate dehydrogenase

This enzyme is just like pyruvate dehydrogenase, a multi enzyme complex that is specific for longer CoA derivatives

Refresh: The five reactions of the pyruvate dehydrogenase multi enzyme complex

Succinyl-CoA Synthetase or succinate thiokinase

Succinate dehydrogenase

Succinate dehydrogenase is the only membrane bound enzyme in the citrate cycle

The FAD on the enzyme itself is reduced
Regulation of the citric acid cycle

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Enzyme</th>
<th>ΔG°’</th>
<th>ΔG°’</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Citrate synthase</td>
<td>-31.5</td>
<td>Negative</td>
</tr>
<tr>
<td>2</td>
<td>Aconitase</td>
<td>~5</td>
<td>~0</td>
</tr>
<tr>
<td>3</td>
<td>Isocitrate dh</td>
<td>-21</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>α-KG dh</td>
<td>-33</td>
<td>Negative</td>
</tr>
<tr>
<td>5</td>
<td>Succinyl-CoA synthase</td>
<td>-20.1</td>
<td>~0</td>
</tr>
<tr>
<td>6</td>
<td>Succinate dh</td>
<td>+6</td>
<td>~0</td>
</tr>
<tr>
<td>7</td>
<td>Fumarase</td>
<td>-3.4</td>
<td>~0</td>
</tr>
<tr>
<td>8</td>
<td>Malate dh</td>
<td>+29.7</td>
<td>~0</td>
</tr>
</tbody>
</table>

Citric acid cycle intermediates are always in flux

A single molecule of glucose can potentially yield ~38 molecules of ATP
No Lecture Thursday  
11/27/08 Thanksgiving

Next Lecture  
Tuesday 12/02/08  
Pentose phosphate pathway