Great moments in evolution

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Dr. Hans Krebs

Product of Kreb's cycle

One Cycle  Two Cycles  Energy
1. Three CO₂  Six CO₂  
2. 4 NADH₂  8 NADH₂  24 ATP  
3. 1 FADH₂  2 FADH₂  4 ATP  
4. 3 H₂O  6 H₂O  
5. 1 GTP  2 GTP  2 ATP  

C₆H₁₂O₆ + 6O₂ + 6H₂O ⇌ 6CO₂ + 12H₂O

Total 30 ATP for Kreb Glycolysis
8 ATP 6 are from NADH
Peter Dennis Mitchell

Born: 29-Sep-1920
Birthplace: Mitcham, Surrey, England
Died: 10-Apr-1992
Location of death: Bodmin, Cornwall, England
Cause of death: unspecified
Gender: Male
Occupation: Chemist
Nationality: England

Executive summary: ADP to ATP conversion in mitochondria
Father: Christopher Gibbs Mitchell (civil servant, OBE)
Mother: Kate Beatrice Dorothy Taplin
Brother: Christopher John Mitchell

University: Queens College, Taunton
University: PhD, Jesus College, Cambridge University (1950)
Professor: Zoology and Biology, University of Edinburgh (1955-63)

Nobel Prize for Chemistry 1978
Copley Medal 1981
Royal Society 1974
The Nernst equation is used in physiology for finding the electric potential of a cell membrane with respect to one type of ion.

\[ E = E^0 - \frac{RT}{nF} \ln \frac{a_{\text{Red}}}{a_{\text{Ox}}} \]
For a cell **membrane potential** with respect to one **positive** ion - cation (for a negative ion (anion) the sign before the logarithm is changed to a minus!)

\[
E = E^0' + \frac{0.0591}{n} \log \frac{\text{ion out of cell}}{\text{ion inside cell}}
\]

\[
E^0' = E^0 - \frac{RT}{nF} \ln \frac{\gamma_{\text{Red}}}{\gamma_{\text{Ox}}}
\]

*R is the **universal gas constant**, equal to 8.314510 J K\(^{-1}\) mol\(^{-1}\)*

*T is the **temperature** in **kelvins**. (Kelvins = 273.15 + °C.)*

*F is the **Faraday constant** (the charge per a mole of electrons), equal to 9.6485309*10\(^4\) C mol\(^{-1}\)*

*n is the number of **electrons** transferred in the **half-reaction**.*

*[Red]* is the concentration of **oxidizing agent** (the reduced species).*

*[Ox]* is the concentration of **reducing agent** (the oxidized species).*

*E0'* is the formal electrode potential

*γ is the **activity coefficient**
At 25°C, $2.3RT/F = 59$ mV, and substituting this value into the foregoing expression results in the most commonly used equation for proton motive force which is expressed in millivolts:

$$\Delta \mu = \frac{\Delta \tilde{\mu}_{H^+}}{F} = \Delta E + \frac{2.3RT}{F} \left( \log \frac{[H^+]^i}{[H^+]^o} \right)$$

$$\frac{\Delta \tilde{\mu}_{H^+}}{F} = \Delta p = \Delta E - \frac{2.3RT}{F} \Delta \text{pH}$$

At 25°C, $2.3RT/F = 59$ mV, and substituting this value into the foregoing expression results in the most commonly used equation for proton motive force which is expressed in millivolts:

$$\Delta p = \Delta E - 59\text{mV}\Delta \text{pH}$$
Let's consider the example of a cell bathed in a solution of 1 mM KCl and 1 mM sucrose. Proton pumping by an H\textsuperscript{+}-ATPase results in a membrane potential of -120 mV and a pH difference between the inside and the outside of the cell of 2 pH units. Thus:

\[
\Delta p = -120 \text{mV} - 59(2) \text{mV} = -238 \text{mV}
\]
How much K\(^+\) can the cell take up by using this $\Delta p$?

Because potassium is positively charged and the membrane potential difference across the cell membrane is negative inside, potassium will be taken up through ion channels by the electrical component of $\Delta p$, which equals -120 mV.

Using the Nernst equation, we can calculate that an external K\(^+\) concentration of 1 mM and a $\Delta E$ value of -120 mV will equilibrate with an internal K\(^+\) concentration of 100 mM. Thus, if the electrical component of $\Delta p$ is used, the cell can generate a 100-fold K\(^+\) gradient across the membrane.
The proton motive force can also be used to take up sucrose against a concentration gradient, usually via a proton–sucrose symporter.

Because sucrose is co-transported with a proton, both components of the gradient of electrochemical potential (−238 mV in our example) can be used for sucrose uptake (Harold 1986).

At equilibrium, $\Delta H^+$ will be equal to $F(\Delta p)$; thus we can calculate that an external sucrose concentration of 1 mM and a $\Delta p$ of −238 mV will equilibrate with an internal sucrose concentration of 10 M.
In real life, however, such concentration gradients would not exist: Sucrose would diffuse back out of the cell, and regulatory mechanisms at the membrane would repress the function of the symporter after certain critical concentrations were attained.
TRUE/FALSE QUESTION

A carbon in a glucose molecule that enters the Krebs cycle may find itself at some later time as CO$_2$ or as the amino acid aspartic acid.
Amino Acid Biosynthesis

- Glucose → Ribose-5-phosphate → Histidine
- 3-Phosphoglycerate → Erythrose-4-phosphate → Tyrosine
- Serine → Cysteine → Glycine
- Phosphoenolpyruvate → Pyruvate → Acetyl CoA → Acetoacetyl CoA
- Oxaloacetate → Malate → Fumarate → Citrate
- Aspartate → Asparagine → Methionine
- Glycine, Threonine → Isoleucine
- Lysine, Threonine → Glutamate
- Glutamine, Proline, Arginine
- Alanine, Valine, Leucine, Lysine
- Leucine
Glutamate \[\xrightarrow{\text{ATP, NADPH}}\] Glutamic \[\xrightarrow{\gamma-\text{semialdehyde}}\] Δ1-Pyrroline-5-carboxylate

\[\xrightarrow{\text{Transaminase}}\] Ornithine

\[\xrightarrow{\text{H}_2\text{O}}\] Arginine

\[\xrightarrow{\text{NADPH}}\] Proline
The metabolic precursors are in blue, amino acids which serve as precursors for other amino acids are in red, and the essential amino acids are underlined.
Most transaminases have a $K_{eq}$ close to 1. Whether they run backwards or forwards is largely determined by the relative concentrations of substrates, so they can be used both anabolically to make amino acids, and catabolically, to degrade them.
Ammonium can be added directly to alpha-ketoglutarate to produce glutamate by glutamate dehydrogenase:

\[
\text{α-Ketoglutarate} + \text{NH}_4^+ + \text{NADPH} + H^+ \rightleftharpoons \text{Glutamate} + \text{NADP}^+ + H_2O
\]
Glutamine synthetase has a higher affinity for ammonium than glutamate dehydrogenase, and is therefore the enzyme which is used for nitrogen assimilation when ammonium levels are low.

\[
\text{NH}_4^+ + \alpha\text{-ketoglutarate} + \text{NADPH} + \text{ATP} \rightarrow \text{glutamate} + \text{NADP}^+ + \text{ADP} + \text{P}_i
\]

Note that this reaction sequence uses both NADPH and ATP to incorporate one molecule of ammonium - the extra energy expenditure is necessary to assimilate nitrogen under limiting conditions.
\[
\text{Glutamate} + \text{NH}_4^+ + \text{ATP} \rightarrow \text{Glutamine} + \text{ADP} + P_i + H^+
\]

\[
\text{\(\alpha\)-Ketoglutarate} + \text{Glutamine} + \text{NADPH} + H^+ \rightarrow 2 \text{Glutamate} + \text{NADP}^+
\]

\[
\text{NH}_4^+ + \text{\(\alpha\)-Ketoglutarate} + \text{NADPH} + \text{ATP} \rightarrow \text{glutamate} + \text{NADP}^+ + \text{ADP} + P_i
\]
Bacteria which possess both pathways of nitrogen assimilation need to regulate them so that when ammonium levels are high glutamate dehydrogenase is active and glutamine synthetase (GS) and glutamate synthase (GOGAT - glutamate:oxo-glutarate aminotransferase) are not.

Conversely, the GS-GOGAT system needs to be activated when ammonium levels are low. This is accomplished through a series of covalent enzyme modifications in response to the relative levels of alpha-ketoglutarate and glutamine.
This is a starch gel of the isozyme malate dehydrogenase (MDH). The numbers indicate first the MDH locus, and next the allele present (ie. 3-18 is locus 3 allele 18). Some bands are heterodimers (intralocus or interlocus).
"Name that Beast"
The End