Regulation of Metabolism

Chapter 15 from Nelson and Cox’s Lehninger’s Biochemistry
Rates of a biochemical reactions depend on many factors

- Concentration of reactants
- **Activity of the catalyst**
  - Concentration of the enzyme
  - Intrinsic activity of the enzyme
- **Concentrations of effectors**
  - Allosteric regulators
  - Competing substrates
  - pH, ionic environment
- Temperature
### Table 15–3
Equilibrium Constants, Mass Action Coefficients, and Free-Energy Changes for Enzymes of Carbohydrate Metabolism

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>$K'_{eq}$</th>
<th>Mass action ratio, $Q$</th>
<th>Reaction near equilibrium in vivo*</th>
<th>$\Delta G'^\circ$ (kJ/mol)</th>
<th>$\Delta G'$ (kJ/mol) in heart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexokinase</td>
<td>$1 \times 10^3$</td>
<td>$2 \times 10^{-2}$</td>
<td>$8 \times 10^{-2}$</td>
<td>No</td>
<td>$-17$</td>
</tr>
<tr>
<td>PFK-1</td>
<td>$1.0 \times 10^3$</td>
<td>$9 \times 10^{-2}$</td>
<td>$3 \times 10^{-2}$</td>
<td>No</td>
<td>$-14$</td>
</tr>
<tr>
<td>Aldolase</td>
<td>$1.0 \times 10^{-4}$</td>
<td>$1.2 \times 10^{-6}$</td>
<td>$9 \times 10^{-6}$</td>
<td>Yes</td>
<td>$+24$</td>
</tr>
<tr>
<td>Tissue phosphate isomerase</td>
<td>$4 \times 10^{-2}$</td>
<td>—</td>
<td>$2.4 \times 10^{-1}$</td>
<td>Yes</td>
<td>$+7.5$</td>
</tr>
<tr>
<td>Glyceraldehyde 3-phosphate dehydrogenase + phosphoglycerate kinase</td>
<td>$2 \times 10^3$</td>
<td>$6 \times 10^2$</td>
<td>$9.0$</td>
<td>Yes</td>
<td>$-13$</td>
</tr>
<tr>
<td>Phosphoglycerate mutase</td>
<td>$1 \times 10^{-1}$</td>
<td>$1 \times 10^{-1}$</td>
<td>$1.2 \times 10^{-1}$</td>
<td>Yes</td>
<td>$+4.4$</td>
</tr>
<tr>
<td>Enolase</td>
<td>$3$</td>
<td>$2.9$</td>
<td>$1.4$</td>
<td>Yes</td>
<td>$-3.2$</td>
</tr>
<tr>
<td>Pyruvate kinase</td>
<td>$2 \times 10^4$</td>
<td>$7 \times 10^{-1}$</td>
<td>$40$</td>
<td>No</td>
<td>$-31$</td>
</tr>
<tr>
<td>Phosphoglucose isomerase</td>
<td>$4 \times 10^{-1}$</td>
<td>$3.1 \times 10^{-1}$</td>
<td>$2.4 \times 10^{-1}$</td>
<td>Yes</td>
<td>$+2.2$</td>
</tr>
<tr>
<td>Pyruvate carboxylase + PEP carboxykinase</td>
<td>$7$</td>
<td>$1 \times 10^{-3}$</td>
<td>—</td>
<td>No</td>
<td>$-5.0$</td>
</tr>
<tr>
<td>Glucose 6-phosphatase</td>
<td>$8.5 \times 10^2$</td>
<td>$1.2 \times 10^2$</td>
<td>—</td>
<td>Yes</td>
<td>$-17$</td>
</tr>
</tbody>
</table>

*Source: $K'_{eq}$ and $Q$ from Newsholme, E.A. & Start, C. (1973) Regulation in Metabolism, Wiley Press, New York, pp. 97, 263. $\Delta G'$ and $\Delta G'^\circ$ were calculated from these data.

*For simplicity, any reaction for which the absolute value of the calculated $\Delta G'$ is less than 6 is considered near equilibrium.
Active Protein Molecules have a Finite Lifespan

• Different proteins in the same tissue have very different half-lives
  – less than an hour to about a week for liver enzymes
  – The stability correlates with the sequence at N-terminus
• Some proteins are as old as you are
  – Crystallins in the eye lens
<table>
<thead>
<tr>
<th>Tissue</th>
<th>Half-life (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>0.9</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.7</td>
</tr>
<tr>
<td>Heart</td>
<td>4.1</td>
</tr>
<tr>
<td>Brain</td>
<td>4.6</td>
</tr>
<tr>
<td>Muscle</td>
<td>10.7</td>
</tr>
</tbody>
</table>

Table 15-1
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Phosphorylation of Enzymes Affects their Activity

- Protein phosphorylation is catalyzed by protein kinases
- Dephosphorylation is spontaneous, or catalyzed by protein phosphatases
- Typically, hydroxyl groups of Ser, Thr, or Tyr are phosphorylated
Control of Glycogen Synthesis

• **Insulin** signaling pathway
  – increases glucose import into muscle
  – **stimulates** the activity of muscle **hexokinase**
  – activates glycogen synthase

• Increased hexokinase activity enables activation of glucose

• Glycogen synthase makes glycogen for energy storage
Figure 15-10
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Figure 15-13
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Rate of Reaction Depends on the Concentration of Substrates

- The rate is more sensitive to concentration at low concentrations
  - Frequency of substrate meeting the enzyme matters

- The rate becomes insensitive at high substrate concentrations
  - The enzyme is nearly saturated with substrate
Figure 15-5
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Regulation of Phosphofructokinase-1

- The conversion of fructose-6-phosphate to fructose 1,6-bisphosphate is the commitment step in glycolysis
- ATP is a negative effector
  - Do not spend glucose in glycolysis if there is plenty of ATP
Regulation of Phosphofructokinase 1 and Fructose 1,6-Bisphosphatase

- Go glycolysis if AMP is high and ATP is low
- Go gluconeogenesis if AMP is low
Regulation by Fructose 2,6-Bisphosphate

• F26BP activates phosphofructokinase (glycolytic enzyme)
• F26BP inhibits fructose 1,6-bisphosphatase (gluconeogenetic enzyme)
Fructose 2,6-bisphosphate
Figure 15-16a
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Figure 15-16b
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Regulation by Fructose 2,6-Bisphosphate

• Go glycolysis if F26BP is high
• Go gluconeogenesis if F26BP is low
Gluconeogenesis

ATP

Fructose 6-phosphate

PFK-1

ADP

Fructose 1,6-bisphosphate

F26BP

Fructose 1,6-bisphosphatase-1

P_i

H_2O

Glycolysis
Stimulates glycolysis, inhibits gluconeogenesis

Insulin

\[ P_i \]

\[ H_2O \]

phosphoprotein phosphatase

PKF-2 (active)

FBPase-2 (inactive)

OH

cAMP-dependent protein kinase

ATP

ADP

glucagon (↑ [cAMP])

PKF-2 (inactive)

FBPase-2 (active)

↓[F26BP]

Inhibits glycolysis, stimulates gluconeogenesis

↑[F26BP]

Figure 15-17b
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Regulation of Pyruvate Kinase

• Signs of **abundant energy** supply allosterically **inhibit** all **pyruvate kinase** isoforms

• Signs of **glucose depletion** (glucagon) **inactivate liver pyruvate kinase** via phosphorylation
  – Glucose from liver is exported to brain and other vital organs
Two Alternative Fates for Pyruvate

• Pyruvate can be a source of new glucose
  – Store energy as glycogen
  – Generate NADPH via pentose phosphate pathway
• Pyruvate can be a source of acetyl-CoA
  – Store energy as body fat
  – Make ATP via citric acid cycle
• Acetyl-CoA stimulates glucose synthesis by activating pyruvate carboxylase
Figure 15-25
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Dealing with Branch Points in Glycogen

- **Glycogen phosphorylase** works on non-reducing ends until it reaches four residues from an \((\alpha 1\rightarrow 6)\) branch point
- **Debrancing enzyme** transfers a block of three residues to the non-reducing end of the chain
- **Debrancing enzyme** cleaves the single remaining \((\alpha 1\rightarrow 6)\) –linked glucose
Figure 15-35
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