The Conc. Of Serum Glucose is constant!

Before eating: 5 mM
After eating: 10 mM.

The conc. of glucose is buffered.

**WHY?**

Brain, CNS & RBC use glucose exclusively as energy source.

Brain consumes ~ 120 gm glucose/day

Glycogen reserves: ~ 190 gm.

During Fasting and extreme exertion (e.g. marathon) the available glucose is rapidly depleted.

So:

Glucose is kept available for energy!

In addition:

Glucose is main precursor of
Amino sugars
Complex polysaccharides
Glycoproteins
Glycolipids
The buffering mechanism

High Glucose

Glycogen $\rightleftharpoons$ Glucose $\rightarrow$ Pyruvate $\rightarrow$ Acetyl CoA $\rightarrow$ Fatty Acids

Low Glucose

Glycogen $\rightarrow$ Glucose $\leftarrow$ non–sugar precursors

(but not fatty acids)

A Problem.

Glycolysis is EXERGONIC!

($\Delta G' \sim -96 \text{ kJ/mole} \; \{-23 \text{ kcal}\}$).

3 Reactions of Glycolysis are irreversible!

<table>
<thead>
<tr>
<th>Reaction</th>
<th>$\Delta G'$ (kJ/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hexokinase</strong></td>
<td>$\ll 0$</td>
</tr>
<tr>
<td>Phosphoglucoisomerase</td>
<td>$\sim 0$</td>
</tr>
<tr>
<td><strong>Phosphofructokinase</strong></td>
<td>$\ll 0$</td>
</tr>
<tr>
<td>Aldolase</td>
<td>$\sim 0$</td>
</tr>
<tr>
<td>Triose P isomerase</td>
<td>$\sim 0$</td>
</tr>
<tr>
<td>Glyceraldehyde-3-P dehydrogenase</td>
<td>$\sim 0$</td>
</tr>
<tr>
<td>Phosphoglycerate kinase</td>
<td>$\sim 0$</td>
</tr>
<tr>
<td>Phosphoglycerate mutase</td>
<td>$\sim 0$</td>
</tr>
<tr>
<td>Enolase</td>
<td>$\sim 0$</td>
</tr>
<tr>
<td><strong>Pyruvate kinase</strong></td>
<td>$\ll 0$</td>
</tr>
</tbody>
</table>

Gluconeogenesis is not Glycolysis in Reverse!
The secret of gluconeogenesis

a) Hexokinase is replaced by Glucose-6-Phosphatase

\[
G + ATP \Rightarrow G6P + ADP
\]
\[
\text{HK}
\]
\[
G6P \Rightarrow G + P
\]
\[
\text{G6Pase}
\]

b) Phosphofructokinase is replaced by Fructose1,6 bisphosphatase

\[
F6P + ATP \Rightarrow F1,6P + ADP
\]
\[
\text{PFK1}
\]
\[
F1,6P \Rightarrow F6P + P
\]
\[
\text{FBPase}
\]

c) Pyruvate kinase is replaced by a complex sequence!

1. Make oxalacetate (by a variety of ways).
2. Convert OAA to PEP (PEPCK (anaplerotic reactions))

These reactions occur mainly in the liver.
MAIN REACTIONS.

Pyruvate $\Rightarrow$ Oxalacetate

$$\text{CH}_3\text{-CO-COOH} + \text{ATP} + \text{CO}_2 \iff \text{COOH-CH}_2\text{-CO-COOH} + \text{ADP} + \text{Pi}$$

Pyruvate carboxylase
(biotin)

Oxalacetate $\Rightarrow$ PEP

$$\text{COOHCH}_2\text{COCOOH} + \text{GTP} \iff \text{CH}_2\text{=OP-COOH} + \text{GDP} + \text{Pi} + \text{CO}_2$$

PEPCK (Mn; mito or cyto)

Both PC & PEPCK were covered in anaplerotic reactions!
Glycerol $\Rightarrow$ DHAP $\Rightarrow$ Glyceraldehyde-3-P

Consider

$$\text{G} + \text{ATP} \Rightarrow \text{G6P} \Rightarrow \text{G} + \text{P}.$$  

A machine for burning ATP-a **futile** cycle.

So…..Enable

- glycolysis
- OR
- gluconeogenesis

**but not both.**

The control of glucose metabolism.

Organizing Principles

1. Molecules are synthesized by different pathways (tho many shared reactions).

2. Corresponding pathways controlled by 1 (or more) early steps.
3. Synthesis rendered exergonic via excess ATP & NADPH

Three mechanisms.

Allosteric activators/inhibitors

Covalent Modification (phosphorylation).

Protein synthesis.

**Allosteric Controls**

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Activated by:</th>
<th>Inhibited by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexokinase</td>
<td>------</td>
<td>G6P</td>
</tr>
<tr>
<td>G6Pase</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>PFK-1</td>
<td>AMP, <strong>F2,6P</strong></td>
<td>ATP, citrate</td>
</tr>
<tr>
<td>FBPase</td>
<td>------</td>
<td>AMP, <strong>F2,6P</strong></td>
</tr>
<tr>
<td>Pyruvate kinase</td>
<td>F1,6P</td>
<td>Alanine, ATP</td>
</tr>
<tr>
<td>Pyruvate carboxylase</td>
<td>acetyl CoA</td>
<td></td>
</tr>
<tr>
<td>PEPCK</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>PFK-2</td>
<td>AMP, F6P</td>
<td>citrate</td>
</tr>
<tr>
<td>FBPase-2</td>
<td>glycerol-3-P</td>
<td>F6P</td>
</tr>
</tbody>
</table>
F2,6P a potent regulator of the interconversion of F6P and F1,6P.

Product of *phosphofructokinase-2*

\[
\text{F6P} + \text{ATP} \Rightarrow \text{F2,6bisP} + \text{ADP}
\]

PFK–2……….An enzyme with 2 activities

Enz: KINASE
Enz-P: PHOSPHATASE

\[
\text{Enz} + \text{ATP} \Leftrightarrow \text{Enz-P} + \text{ADP}
\]

*Protein kinase*

Low blood sugar ⇒ Glucagon ⇒ cAMP
Enzyme modification caused by Protein Kinase

Specific PKs controlled by cAMP/Insulin

INACTIVE

+ 2 cAMP

ACTIVE

Protein-SerOH + ATP → Protein-SerP + ADP

Enzyme Phosphorylation

Inactivates
Pyruvate Kinase.
PFK-2

Activates
FBPase-2
lactate → pyruvate ← alanine

pyruvate → OAA → PEP

OAA ← malate

malate → PEP

humans, rabbit, pigeon

humans, rat

OAA → PEP