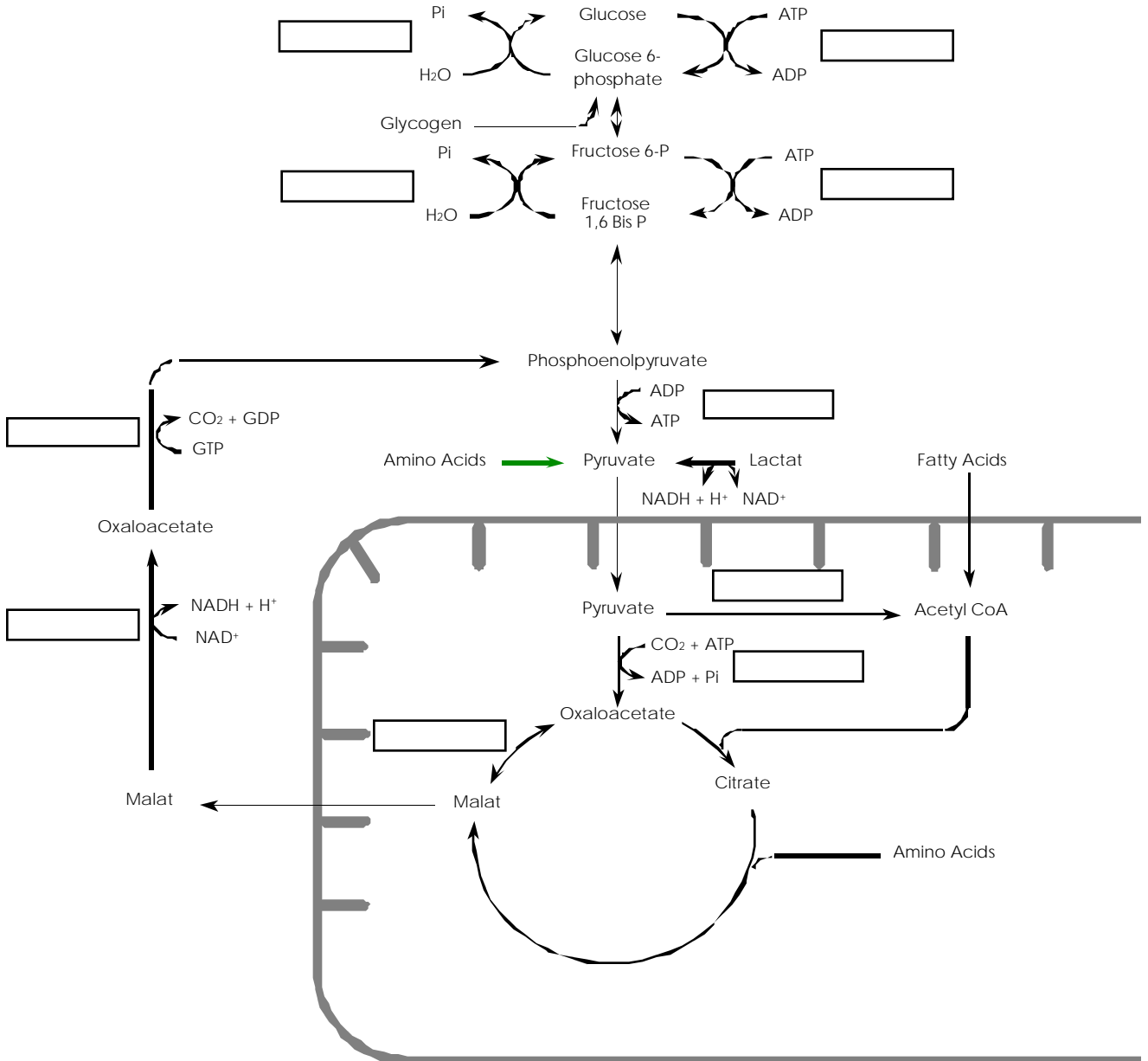


## Gluconeogenesis - Chapter 15

### Gluconeogenesis - Generation of glucose from pyruvate

The principle noncarbohydrate precursors of glucose are lactate, pyruvate, and amino acids. Lactate and amino acids can be converted to glucose by this pathway (gluconeogenic) - NOT Fatty acids

Most amino acids (except leucine and lysine) are converted into oxaloacetate and then metabolized to glucose.



This is only in part a reversal of glycolysis. Remember the irreversible reactions of glycolysis.

- Liver and kidney are only real gluconeogenic tissues although adipose has some capacity (no G6Pase)
- This is how liver can provide most of glucose during fasting state - i.e. after the glycogen is gone.

There are three steps and four enzymes involved in glycolysis.

Step 1 Pyruvate to Phosphoenolpyruvate (2 enzymes)

1. *Pyruvate carboxylase (PC)*

- pyruvate + CO<sub>2</sub> + ATP → oxaloacetate + ADP + Pi
- Pyruvate is carboxylated in the mitochondria and the reaction is driven by ATP hydrolysis
- PC uses biotin as activated CO<sub>2</sub> carrier
- vitamin B - most produced by bacteria in GI
- Biotin binds CO<sub>2</sub> from bicarbonate on enzyme for addition of pyruvate
- CO<sub>2</sub> ~ biotin bond supplies energy for reaction
- OAA must travel out of the mitochondria - via 2 MDH isozymes (cytosolic NADH allows reversal of GAPDH)

2. *Phosphoenolpyruvate kinase (PEPCK)*

- 2 isozymes cytosolic/mitochondrial
- found in liver, kidney and adipose
- OAA + GTP → PEP + GDP + Pi
- potential involvement in SIDS
- in adipose (fat cells) glycerol is produced rather than glucose (via - glycerol 3-phosphate). Used for glycerol backbone of triacylglycerol
- In kidney PEPCK is responsible for decrease ammonia produced via the Krebs cycle. Ultimately responsible for acid base regulation,

Step 2 Fructose 1,6-bisphosphate to fructose 6-phosphate

- *Fructose 1,6-bisphosphatase (FBPase-1)*
- found in cytosol of liver and kidney a little in striated muscle
- hydrolysis of 1-phosphate from fructose

Step 3 Glucose 6-phosphate to glucose

- glucose 6 phosphatase (**G6Pase**)
- 5 subunit enzyme found in endoplasmic reticulum
- Only in liver and kidney
- Hydrolysis of 6-phosphate
- requires transport in and out of ER
- Von Gierke's Disease - missing G6Pase

Control of cycle:

several common factors that increase one pathway will shut off the other.

High energy state → ATP, citrate

Low energy state → ADP, AMP

Fructose 2,6 bisphosphate → increase blood [glucose]

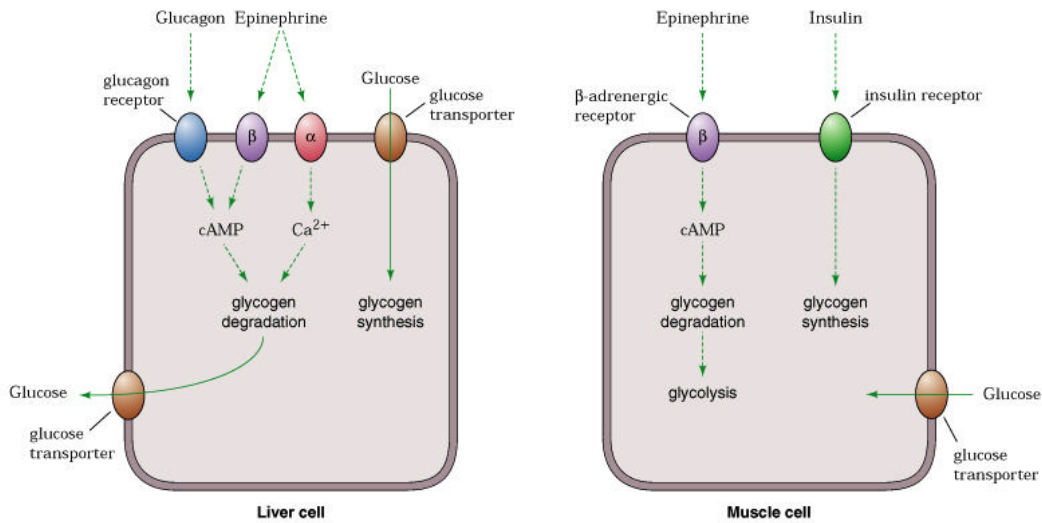
Starvation increases gluconeogenesis

High carbo reduces gluconeogenesis while low carbo diet increases.

Well fed state - decreases gluconeogenesis and increases glycolysis - how?

Two main focus points - Fructose phosphate metabolism and PEPCK gene regulation

Quick review of insulin, glucagon and epinephrine



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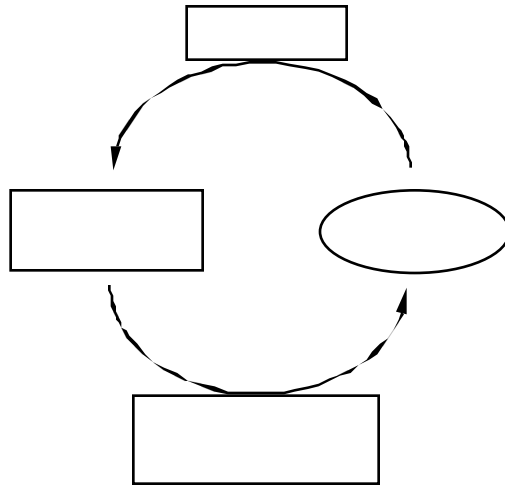
	Released by	Affects	Results on Blood Glucose Levels
Insulin -			
Glucagon -			
Epinephrine -			



Gluconeogenesis and glycolysis are reciprocally regulated in the liver. The principal allosteric regulator is fructose-2,6-bisphosphate (F2,6P), which is a potent activator of PFK-1 and inhibitor of FBPase-1.

F2,6P is formed and degraded by a different enzyme with two different activities.

- The enzyme is called PFK-2/FBPase-2. (also the bifunctional enzyme)
- So the production and breakdown of F2,6P is controlled by a different enzyme than the F1,6P.
- Regulation of the bifunctional enzyme is under the control of PKA. When the bifunctional enzyme is phosphorylated the PFK-2 activity is inactive and the phosphatase activity is on. The reverse is true when the enzyme is dephosphorylated. -> this favors gluconeogenesis
- In heart muscle, the situation is reversed so that phosphorylation activates PFK-2, which facilitates the muscle's ability to extract energy from glucose via glycolysis.



#### Transcriptional control of PEPCK gene

- promoter region of gene - ultimately controls protein levels
- PEPCK is quickly degraded
- several hormones can effect the concentration of PEPCK in cell through the promoter including insulin, cAMP, glucorticoids, thyroid hormones
- this all leads to an increase in gluconeogenesis w/long term starvation

#### Ethanol inhibits gluconeogenesis -> brings about hypoglycemia

- two metabolic pathways of ethanol - major path in liver (alcohol dehydrogenase).  

$$\text{EtOH} + \text{NAD}^+ \rightarrow \text{acetaldehyde} + \text{NADH}$$
- results in a high NADH/NAD<sup>+</sup> ratio
- shifts equilibrium of LDH and GAPDH in cytosol and decreases citric acid cycle at malate dehydrogenase
- low blood sugar affects brain and results in up to a 2°C loss of body heat - don't drink to warm up!
- Alcohol just dilates the vasculature which results in even more heat loss