Integration of Metabolism I

Pathways

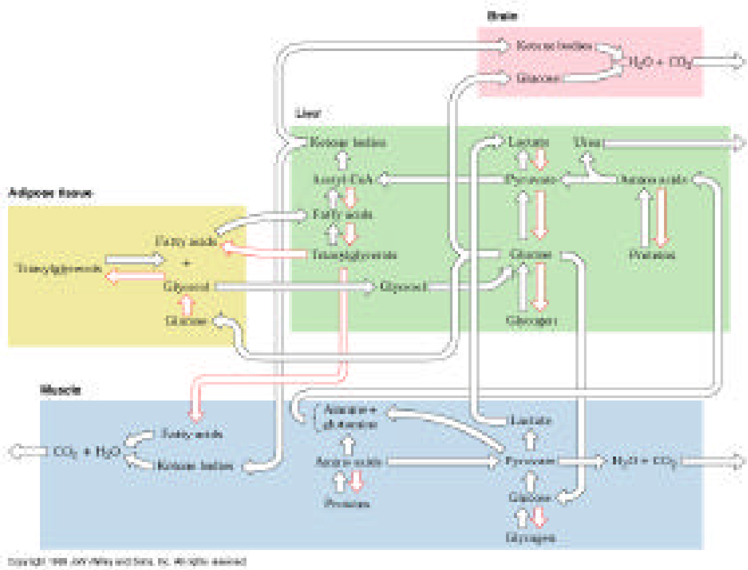
We have studied various pathways - all based on the production and usage of Metabolic energy.

- -glucose homeostasis
- - fatty acids, carbohydrates, amino acids all involved
- - Put together the different pathways and identify the key points

Several common / key metabolic intermediates (cross road metabolites)

- - glucose 6 phosphate
- - pyruvate
- - acetyl CoA

Which are the key enzymes?
Which pathways take place in which tissue



The biochemical pathways for synthesis and breakdown of the three major metabolic fuels (carbos, fats and protein) converge in the above mentioned metabolites. In mammals, the liver is one of the few organs that can carry out almost all of the various pathways.

Organs and their metabolism

The liver is key in homeostasis of circulating fuel molecules for use of all tissues. It acts as a blood glucose buffer. To understand the role of liver as a producer of glucose for other tissues we need to revisit hexokinase. Glucokinase has a high Km (around 5 mM) makes it sensitive to changes in glucose concentration over the physiological range (~5mM). This is very different to the Km for hexokinase which is found in muscle and other tissue (there are actually at least five different HK isozymes) whose affinity is much higher for glucose (Km = 0.01 mM). The result is a saturated enzyme whose activity is high until appreciable amounts of product are generated.

- Liver – gluconeogenesis, glycolysis, glycogenesis, glycogenolysis, fatty acid biosynthesis, fatty acid oxidation, ketogenesis, protein synthesis, amino acid degradation, PPP, TCA cycle and urea cycle

Some organs do not synthesize fuel molecules but are only involved in the use or break down. The brains primary fuel source is normally glucose. This energy is used to restore ion gradients for neural function. The brain uses 10 fold more energy by weight than other tissues! The brain stores no glycogen and therefore relies primarily on glucose from the bloodstream. After long term fasting the body expends glycogen reserves within about 24 hours. After 48 hours of fasting. The liver then moves from glycogenesis to gluconeogenesis and ketogenesis. Peripheral tissues including the brain moves from glucose as the main fuel to ketone bodies. Skeletal and heart muscles rely on fatty acids when resting and use glucose from glycogen or the bloodstream during exercise. Heart tissue is rich in mitochondria and is mostly an aerobic tissue and also utilizes ketone bodies when blood glucose becomes low.

- Brain - glycolysis, TCA cycle, ketone body utilization
- Muscle - glycogenesis, glycogenolysis, glycolysis, TCA cycle, FA oxidation, protein synthesis, proteolysis, ketone body utilization

Adipose tissue is largely involved in the long-term storgae of fatty acids. It releases fatty acids in response to various hormones which cause an increase in cAMP. The synthesis of TAGs requires the catabolism of glucose to glycerol 3-phosphate to which fatty acids are esterified. During starvation the low blood glucose concentration leads to low glycerol3-P and few of the fatty acids are re-esterified and are thus catabolized.

- Adipose - fatty acid synthesis, fat storage, lipolysis, PPP, glycolysis

The kidney in many aspects is similar to liver except that little glucose is transported to the bloodstream for peripheral tissue use. Instead, the bulk of the oxidized metabolitic energy is used for in the filtration and ion transport functions.

- Kidney - gluconeogenesis, glycolysis, TCA cycle, fatty acid oxidation, ketogenesis, ketone body utilization

The red blood cells are relatively simple cells that can be thought of as an organ for this purpose. There are no mito or nuclei in most mammalian RBCs and they simply rely on glycolysis for energy and reducing equivalents for the maintenance of glutathione and other reducing agents.

- RBC - glycolysis

Metabolic effects of endrocrines - three or four major hormonal controlling factors

- insulin - released by increase in blood glucose
- glucagon - inversely proportional to blood glucose
- epinepherine - respond / released by stress and low blood glucose
- glucocorticoids - made in adrenal cortex - cholesterol based steroid hormone - many effects including inhibition of inflammation. Similar to glucagon except for glycogen metabolism leads to formation of glycogen.