NCellular Mechanisms Involved in Metabolic Regulation

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- Flux through metabolic pathways needs to be controlled. Different tissues need different patterns of metabolism according to their roles in the body. In addition, metabolic pathway flux needs to change with time, for instance to adapt to storing nutrients after a meal or mobilizing them between meals.
- Mechanisms for regulating metabolic flux might be divided into:

(1.) features specific to individual tissue

(2.) short-term dynamic changes (over periods of minutes or hours)

(3.) longer-term changes (over periods of days or longer). Longer-term changes usually involve changes in the amount of proteins present in cells.

- Many key metabolic enzymes exist in different isoforms (coded for by different genes), expressed in different tissues. Usually the isoforms catalyze the same reaction but the regulation is different.
- The flow of substrates across membranes is a potential site for regulation. Families of transporter proteins exist for all major "energy metabolites": glucose, fatty acids, amino acids; also for cholesterol and glycerol, and even water. Tissue-specific expression of different isoforms of these transporters confers metabolic specificity on tissues.
- Short-term metabolic regulation often involves covalent modification of enzymes, especially phosphorylation/dephosphorylation. It may also involve allosteric effects, or translocation of proteins within a cell.
- Much of short-term metabolic regulation is governed by hormones, "signal molecules" that travel through the bloodstream and act through specific cellular receptors. Binding of the hormone to its

receptor is usually followed by a chain of intracellular events linking it to the target metabolic process.

- Hormone signaling chains are usually complex. Hormones signaling to mobilize stored fuels often signal via the small molecule cyclic adenosine 3 ,5 - monophosphate (cyclic AMP or cAMP).

Movement of Substances Across Membranes

The cell membrane, and membranes within cells, are formed from a phospholipid bilayer. Most biological molecules, especially polar molecules and ions, will not diffuse freely across such a membrane. Instead, there are specific proteins embedded in the membranes, which "transport" molecules and ions from one side to the other. A substance will cross a membrane to move from one solution to another if

(1) the membrane is permeable to the substance.

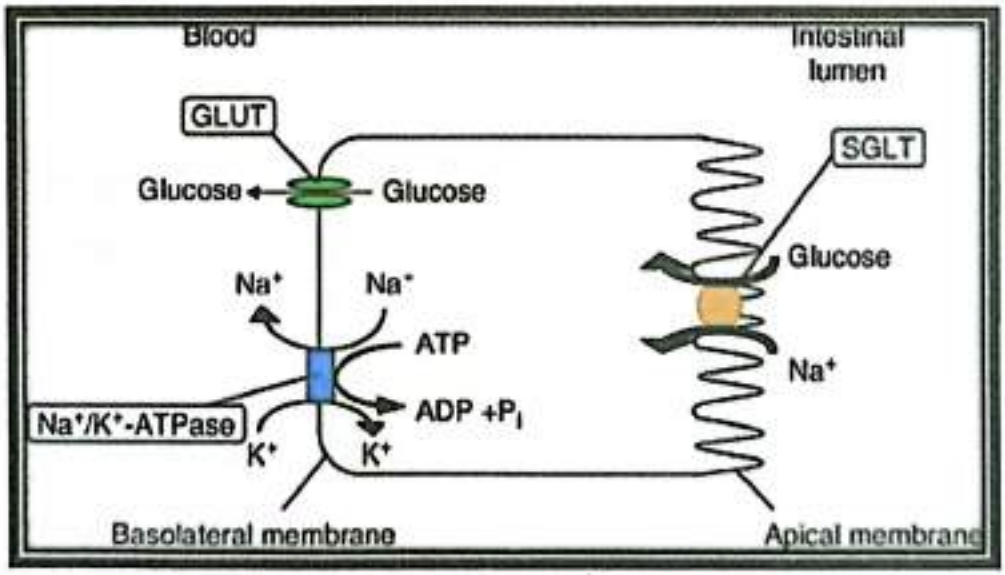
(2) there is a concentration gradient in the appropriate direction: that is, a substance will move from a region of high concentration to a region of lower concentration.

There are two major means by which such movement may occur: free diffusion, that is, unassisted movement by diffusion, brought about simply by the overall effect of random molecular motions, and facilitated diffusion (carrier-mediated diffusion), that is, movement assisted by a specific transporter protein. In addition, there is a third means of movement: active transport, in which substances may move up a concentration gradient – that is, from a lower concentration to a higher one.

1- Glucose Transport

It has long been known that glucose enters cells by carrier-mediated diffusion (facilitated diffusion) rather than by free diffusion across the cell membrane. There are two families of glucose transporters. The more widespread family consists of passive transporters, allowing the movement of glucose across cell membranes only down a concentration gradient. They are called GLUTn, where n is a number distinguishing different members.

The other family consists of active transporters, enabling glucose to move up a concentration gradient (i.e., it may be concentrated by the transporter) because sodium ions, cotransported with the glucose, are moving down a concentration gradient (Figure 2.2). These are known as the sodium-glucose cotransporter family, SGLTn.



2- Amino Acids

The concentrations of most amino acids are considerably higher inside cells than. This implies the existence of active transporters to move amino acids into the cells up a concentration gradient. In fact, like glucose in the

small intestine, amino acids are mostly actively transported by sodium-linked carriers. Again, therefore, energy is required to pump the sodium ions out and maintain their concentration gradient.

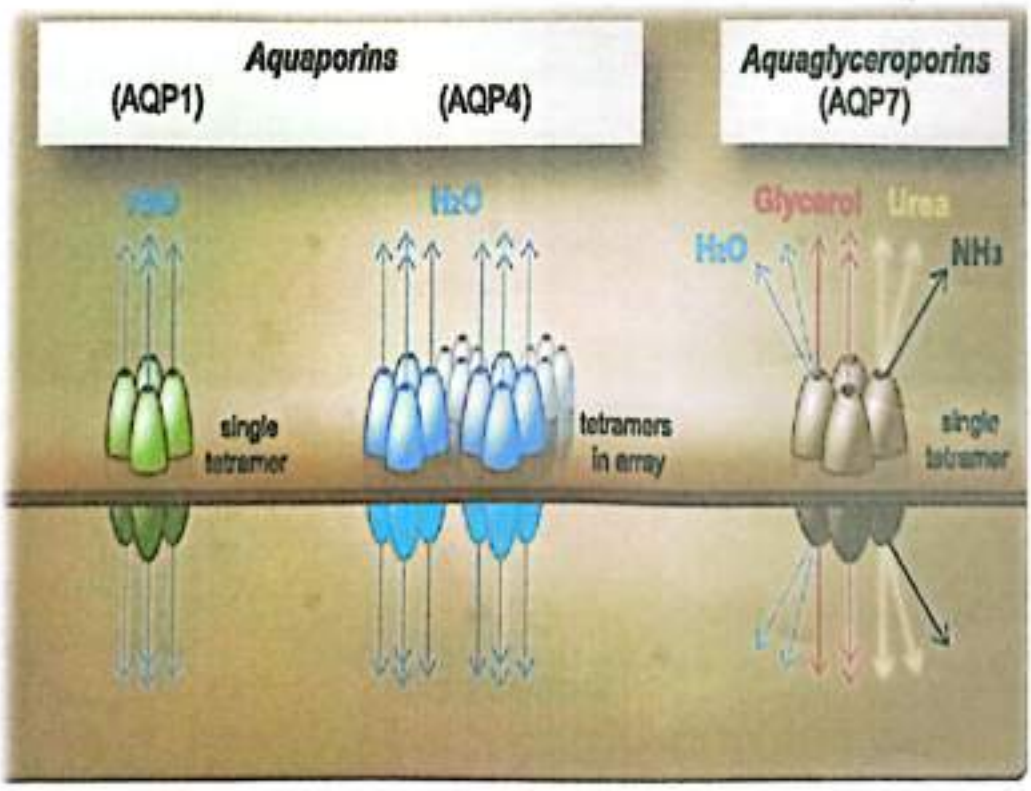
3- Fatty Acids

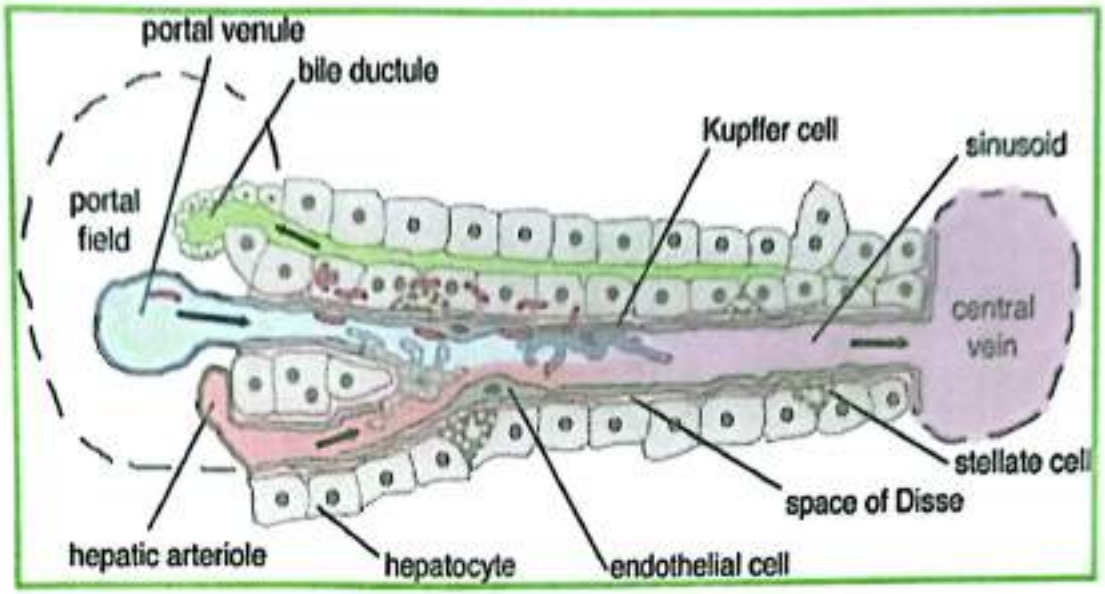
Fatty acids arrive at cells in two ways. They may come in the form of non-esterified fatty acids that have been carried through the plasma bound to albumin. Alternatively, they may be liberated from triacylglycerol in the plasma by the enzyme lipoprotein lipase attached to the endothelial cells that line the capillaries. They cross the endothelial cell lining and enter cells (e.g., liver, skeletal muscle, cardiac muscle, adipose tissue) down a concentration gradient, which is generated by avid binding to specific fatty acid binding proteins within the cells. The gradient is maintained because the fatty acids are utilized for further metabolism within the cells. The first step in this process is always esterification to coenzyme A to form acyl-CoA thioesters. This step is sometimes called activation. It requires ATP and releases AMP and pyrophosphate, PPi. Most of the non-esterified fatty acids in plasma are bound to albumin, and the concentration actually free in solution, and available to enter cells, is much lower. Hence, there may also be a need for active transport mechanisms.

There is still debate about how fatty acids cross cell membranes. They may do so by passive diffusion using a movement usually called "**flip-flop**", in which the polar carboxyl group enters the polar face of the membrane, the hydrophobic fatty tail flips into the lipid bilayer, and then a reversal takes it out of the other side.

4- Water and Glycerol

Water itself is a polar molecule. We should not imagine that water will cross cell membranes by diffusion. In 1991 the first specific "water channel," or aquaporin, was discovered. There is now known to be a family of related **aquaporins**. These channels are abundant in cell membranes. It is not clear, however, that they play much of a role in energy metabolism. Other closely related proteins (the **aquaglyceroporins**) are carriers for glycerol, a molecule with similar physicochemical properties to water. The aquaglyceroporins are important in fat cell (adipocyte) function, since glycerol is released from the adipocyte during the process of fat mobilization and in the liver, which removes glycerol from the blood for use as a substrate for glucose synthesis.





Metabolic functions of the liver

The morphological and functional integrity of the liver is vital to the health of the human organism. This essentially depends upon constant maintenance of the numerous biochemical functions of the liver and the diverse metabolic processes occurring in the hepatocytes and sinusoidal cells.

The liver ensures that approximately 70 partial functions within 12 major metabolic areas proceed either continuously or in biological (e.g. circadian) rhythms, or vary according to specific requirements.

1. Bilirubin metabolism
2. Porphyrin metabolism
3. Bile acid metabolism
4. Amino acid and protein metabolism
5. Carbohydrate metabolism

6. Lipid and lipoprotein metabolism

7. Hormone metabolism

8. Vitamin metabolism

9. Trace elements and the liver

10. Biotransformation and detoxification function

11. Alcohol degradation

12. Acid-base balance

Metabolic processes utilize a variety of differing and contrasting biochemical routes to enable synthesis of degradation and activation or deactivation of substances; in addition, they facilitate cellular uptake and excretory mechanisms. Moreover, there are various links between different metabolic pathways and functional processes. Intermediate chemical products generated in the course of metabolic reactions may be taken up by other pathways or cycles. Substrates are shifted between subcellular structures, and the metabolic end-products of one process are often used as the original substrate for new syntheses.

Regulatory metabolic mechanisms

(1.) Regulation may occur at the **molecular level** for example:

- through negative feedback, whereby the end-product of a metabolic reaction inhibits the activity of the enzyme which determines the speed of reaction. This affords a rapid adaptation of specific chemical reactions in response to alterations in metabolic conditions.
- through changes in the actions of activators and inhibitors;
- through modulation of enzyme activities;

- through changes in the rate of enzyme synthesis or degradation.

(2.) Regulation can take place within the **organelles** for example:

- Protein synthesis occurs in the ribosomes of the rough endoplasmic reticulum by contrast, the process of protein degradation occurs in the lysosomes.
- Fatty acids are synthesized in the smooth endoplasmic reticulum, but they are broken down in the mitochondria.

(3.) Regulation may be effected at the **cellular level** for example:

- Hepatocytes display metabolic heterogeneity according to their zonal location within the acinus.
- Hepatocytes interact closely with the sinusoidal cells and Kupffer cells (e. g. in the breakdown of erythrocytes and the degradation of pyrimidine nucleotides).
- Hepatocytes and sinusoidal cells are influenced by vegetative nerve fibre endings in Disse's space.