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Review Article

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Biochemistry of Nutritional Sciences

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Introduction

Biochemistry comprises four main chapters, which can be described by chemical reactions:

1. Common principles of life from pluripotent cells to differentiated tissues;

2. Energy production from food supply and storage of transformed energy;

3. Biosynthesis of suitable bricks for anabolism;

4. Adaption and response to the environmental circumstances.

Vital phenomena can be explained by traits of molecules and physiology can be reduced to biochemical reactions involved in a phenomenon. Although living systems are diverse, biochemical pathways are common to cells and complex organisms, to pluripotent cells up to highly differentiated tissues, and reveal the common ancestry within the tree of life. Nature seems to conserve successful molecular patterns and reaction principles no matter how specialized an organism may be [1].

Common Principles of Life: Genetic Code and Expression of Genetic Information

Prebiotic atmosphere

Before life on earth could appear, organic molecules had to be formed. An electric discharge (lightning) in an atmosphere of CH_4, NH_3, H_2O, and H_2 (Urey-Miller experiment) has been shown to be able to generate key organic compounds such as the amino acids glycine and alanine in about 2% yield, as well as glutamic acid and leucine in smaller amounts. Hydrogen cyanide (HCN) formed is able to condense with further energy (heat, light) to form adenine, one of the nucleic acid bases. In prebiotic conditions, sugars such as ribose can be formed from aldehyde [1].

Transcription and translation of the genetic code

Evolution requires reproduction, variation, and selection. One of the most mysterious secrets of life was unraveled in 1953 by Watson and Crick, who later won the Nobel Prize laureates in 1962. The discovery of the double helix structure of DNA had a huge impact on further research on genetic code, expression and information. The Human Genome Project is one of the most important results having been arisen from Watson and Crick's model. It was started in 1984 on a proposal and funding by the US government and declared complete in 2003 [2].

The specific pairing in DNA is assured by guanine (G) together with cytosine (C) and adenine (A) together with thymine (T). The pairing is stabilized by hydrogen bonds resulting in a double helical structure. In this way the two complementary strands are readily unzipping for easy replication. In this way, the information of the original DNA double helix is distributed to two newly formed cells.

The genetic code is expressed by means of transcription and translation into functional molecules. The sequence of bases along a DNA strand defines a messenger RNA (m-RNA) sequence (transcription), which in turn defines the amino acid chain of a protein (translation). The genetic code consists of codons which are formed from three nucleotides and which are decoded by a ribosome and base-paired to amino acids carrying transfer RNA (t-RNA). The 4 bases, arranged by groups of 3, would yield 64 possible codons (43 combinations). This means that to encode the twenty standard amino acids, more than one codon can be attributed to most amino acids. UAA, UGA, and UAG mean stop codons labeling the end of the coding region.

Applications of genetic coding techniques

Biochemistry provides knowledge about commonality principles, explains particularities of individuals, and discloses targets for therapeutic approaches. Although common biochemical pathways have been conserved during evolution, and although molecules and pathways have been generated based on existing ones, a one-fits-all medicine is about to be more and more replaced by personalized medicine. The declared objective of personalized medicine is to either predict a person's risks for developing a disease or to treat a patient according to his or her metabolic predisposition and capacity, genetic mutations, or polymorphisms. The genotype of a person can hint at imminent risks and prevent the outbreak of diseases if lifestyle or behavior is changed according to the risk profile. The phenotype does not only describe proteins, enzymes and metabolites from the expression of the person's genes, but provides data to recognize patterns belonging to an existing or eventually silent disease which can be treated effectively (Figure 1) [1].

Applications of genetic coding techniques include:

I. **Genetic engineering and molecular biology**

1. DNA purification from organisms.

2. Polymerase Chain Reaction (PCR).

Recombinant DNA technology in pharmaceutical manufacturing of active ingredients such as monoclonal antibodies or in agricultural production.

II. **Forensics**

1. DNA profiling from blood, semen, skin, saliva or hair of an individual "genetic fingerprint".

2. DNA profiling to identify bodies and victims of mass casualty incidents or accidents.

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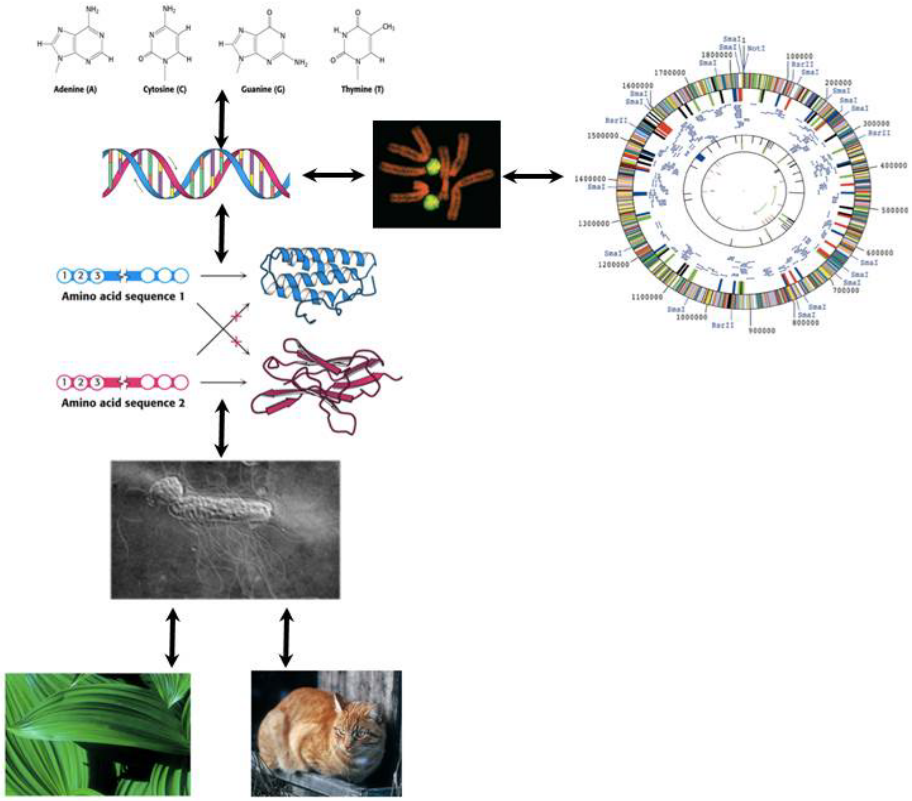


(**Note:** Biochemistry as life science making out commonality of successful biochemical principles. Biosynthesis is constructing cells, tissues and organisms according to genetic information. Analysis is disassembling bodies, tissues, and cells into molecules. The analysis of the genome is the science of genomics, of proteins the science of proteomics, and of metabolites issued from enzymatic reactions the science of metabolomics).

Figure 1: Biosynthesis of cells, tissues and organisms according to their genetic information.

III. **Bioinformatics**

1. Data mining of biological data, e.g. to identify specific mutations, to study phylogenetic relationships and protein function, or to compare entire genomes.

IV. **History and Anthropology**

1. Evolutionary biology (History of particular populations).

Stereo-specificity

Nature is stereospecific, requiring natural enantiomers as substrates of biochemical reactions. Chiral systems exist on several dimensions:

I. Asymmetric C-atoms leading to L-/D-amino acids or –monosaccharides.

II. Double bonds, spiro (or ring) systems, which are hindered to rotate around a chemical bond due to bulky substituents, leading to cis-/trans- or Z-/E-conformation.

III. Complex 3-dimensional molecules with ansa bridging structure such as rifamycin.

Different enantiomers are agonists or antagonists when reacting with receptors at cell surfaces or in the nucleus of a cell, leading to a physiological or therapeutic effect, or to a block of the physiological effect. There are also olfactory characteristics arising from enantiomers, e.g. terpenoid flavorings:

I. R-(+)-limonene has an orange aroma

II. S-(-)-limonene has a lemon aroma

III. S-(+)-carvone has a caraway aroma

IV. R-(-)-carvone has a mint aroma

Proteins, enzymes, or receptors consist of chains of L-amino acids. Isolated amino acids are chiral. A chain of amino acids is a two component symmetry (as if left hands were linked to form a chain) and thus not chiral. However, as soon as the system is three-dimensionally-organized as enzymes or as receptors at cell surfaces or in the cell nucleus, chirality is regained and brings with it the stereospecificity of their interactions with substrates.

Nutrient absorption

The most common way of ingesting nutrients is the GI tube. Membranes, such as the GI tube, are barriers and separate compartments of different densities and hydrophilic/lipophilic balances. Membranes can be overridden by passive or active transport:

I. **Passive transport**

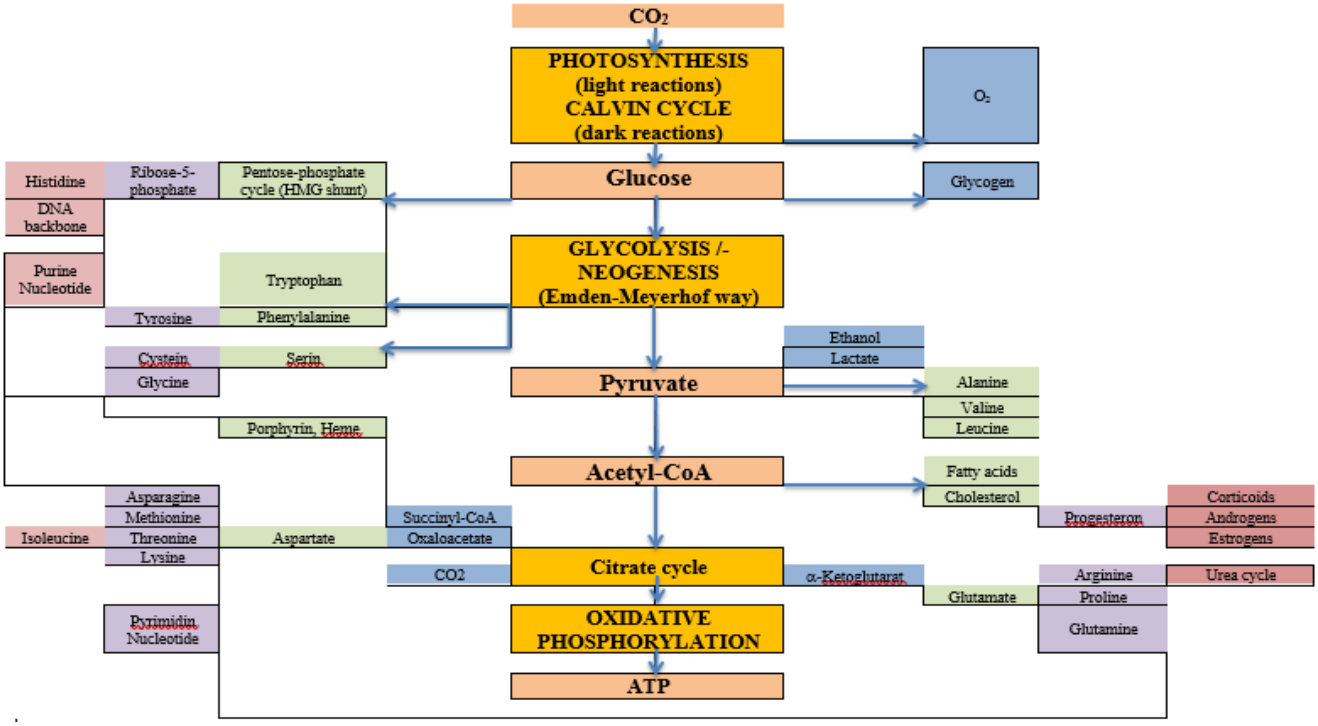
1. Passive diffusion along a concentration gradient.

2. Ion pair absorption.

3. Diffusion through pores.

II. **Active transport (ATP-dependent)**

1. Transport with carrier against a concentration gradient.



(**Note:** Carbohydrates, proteins, and lipids liberated from the food matrix, are digested to glucose, amino acids, and fatty acids which are made available for anabolic reactions and for energy production).

Figure 2: Biochemical backbone reaching from glucose to energy production.

2. Pump such as bidirectional symporter, Na^+/K^+-ATPase.

3. Facilitated diffusion (i.e., a carrier not needing energy such as vitamin B12 absorption).

4. Corpuscular absorption such as phagocytosis, persorption, pinocytosis).

Individuality

As humans are not ISO-normed constructs, metabolism can follow biochemical principles, but is individually diverse according to genetic information, age, gender, race, and environmental circumstances (epigenetics). Thus, response to primary and secondary nutrients (comparable to keys) is an individual matter as well as their reaction with target receptors (comparable to keyholes) after having passed the intestinal wall. Receptors are located not only on the cell surfaces, but also in the nucleus, cytosol or freely in various compartments such as blood. Cell surfaces receptors are denominated seven-transmembrane helix receptors, which change conformations in response to ligand binding. Such ligands can be α- and β-adrenergic amines, neurotransmitters, glucagon, parathyroid hormones, acetylcholine, photons, thrombin, et cetera. The signal triggered by substrate binding is converted into a downstream chemical signal transduced across the cell membrane, where it is received by GDP-bound G Proteins at the inner side of the cell membrane. GDP is activated to GTP, which amplifies the signal by passing it further to second messengers such as cAMP (cyclic adenosin monophosphate), cGMP (cyclic guanosin monophosphate), calcium ions, IP3 (Inositol 1,4,5-triphosphate), DAG (Diacylglycerol), or Na^+ and H+ exchange. Second messengers can lead to phosphorylation of target proteins by activating protein kinases or to expression of protein biosynthesis (Figure 1). Defects in signaling pathways can lead to cancer and other diseases. Examples of excessive signaling are cholera, adenoma of pituitary, thyroid, adrenal, ovary, or essential hypertension, those of deficient signaling night blindness, pertussis, et cetera.

Taste is a response to substrate binding to receptors. Sweet compounds bind to seven-transmembrane helix receptors, whereas salty and sour tastes are transmitted by sodium cations or protons passaging through ion channels. Glutamate's umami taste however is detected by a special form of glutamate receptor.

Energy production and Storage

Energy in various forms has to be transformed to be a suitable resource for living systems, as well as to be stored in a suitable manner to be readily available in times when a response to environmental circumstances is needed. To attain this metabolic target, many coupled interconnecting reactions exist. They can be parted into the following partial metabolisms:

1. Metabolism of complex and simple carbohydrates.

2. Metabolism of complex and simple lipids.

3. Metabolism of proteins and amino acids.

4. Metabolism of cofactors and vitamins.

5. Nucleotide metabolism.

6. Energy metabolism.

7. Metabolism of other substances.

As humans are not able to biosynthesize some important substrates

such as glucose, unsaturated fatty acids, vitamins or oligoelements as plants do, these substrates have to be supplied. Eating provides energy for endothermic reactions and bricks for construction of cells and tissues. However, carbohydrates, proteins, and lipids must be extracted from their food matrix first and broken down to suitable simple molecules by digestion, before useful energy can be produced. Some substrates have to be converted to glucose to be loaded into metabolism (Figure 2). For instance, galactose would be highly hepato- and/or brain-toxic, if it were not transferred by galactose 1-phosphate uridyl transferase. Cataract would develop due to galactitol formation by an aldose reductase.

Absorption from food is gender dependent and quantitatively and qualitatively influenced by pH and by motility. Anatomical and physiological gender differences exist all along the gastric tube. Mean gastric fasting pH is 2.15 for men and 2.8 for women corresponding to a nearly 5-fold excess of gastric protons and a higher prevalence of duodenal ulcers in men. A sufficiently acid pH <3.5 is essential for pepsin activation and thus for protein digestion. Gastric and intestinal liquid volume is bigger in men than in women. Gastric emptying and colon transit times are shorter in men, since gastrointestinal motility is decreased due to estrogen and progesterone regulation. Gastrin, bicarbonate as well as further endocrine secretion tend to be increased in the moment of an afflux of substrates in women, whereas in men secretion is maintained in a more permanent manner.

Biochemical Pathways of Glucose

Plasma glucose levels give a signal for insulin secretion by the pancreas' β cells (islets of Langerhans). Insulin reacts with the receptors on the surface of target cells in muscle and liver to signal the need for glucose uptake. Several glucose transporters (GLUT) are known:

I. GLUT1 (in all mammalian tissues).

II. GLUT2 (in liver and pancreatic β cells.

III. GLUT3 (in all mammalian tissues).

IV. GLUT4 (in muscle and fat cells).

V. GLUT5 (in small intestine).

Insulin resistance is characterized by the interruption of this cell signaling. The insulin stimulus should translocate GLUT4 from cytosol to the cell membrane to facilitate glucose uptake. However, insulin resistance impairs GLUT4 translocation and glucose not taken up.

Glucose is exploited for anabolic reactions in the following major pathways (Figure 2):

1. Glycogen synthesis and storage in the liver and muscle cell.

2. Pentose-phosphate cycle (HMG shunt) yielding 5-ribose-phosphate essential for DNA double helix.

3. Pyruvate formation in the aerobic glycolysis followed by decarboxylation to acetate.

4. Lactate is the product of anaerobic glycolysis.

5. Oxidative decarboxylation of pyruvate leads to acetyl-CoA which can enter into the citrate cycle (also referred to as Tricarboxylic acid cycle or Krebs cycle) and be used for anabolic reactions such as:

i. Biosynthesis of glutamate, other amino acids and purines from α-ketoglutarate.

ii. Porphyrins, heme, or chlorophyll (in plants) from succinyl CoA.

iii. Aspartate, other amino acids, purines, or pyrimidines from oxaloacetate.

6. Pyruvate is transported to the mitochondrial matrix by the antiporter pyruvate carrier where it is oxidatively decarboxylated to acetyl-CoA by the pyruvate dehydrogenase complex in an irreversible reaction.

7. Excess glucose can be converted to fatty acids and sterols via acetoacetyl-CoA.

Stored forms of glucose are readily available by glycogenolysis and gluconeogenesis. From the citrate cycle, oxaloacetate can branch off to reconstruct glucose via phosphoenolpyruvate in times of need (hunger metabolism, cachexia, et cetera), to warrant primarily brain function. For this, ketoplastic amino acids such as leucine, isoleucine, lysine, phenylalanine, tryptophane, and tyrosine will form acetoacetyl CoA and acetyl CoA as substrates for the citrate cycle. Other points of entry are α-ketoglutarate, succinyl-CoA, fumarate, and oxaloacetate (Figure 2).

Amino acids from protein stores in the muscle and from plasma proteins such as albumin are available in amounts of 100'000 kJ from muscles and 1700 kJ from the liver to effectively maintain the glucose plasma level at nearly 4 mM. Glycogen from muscles can provide 5'000 kJ of readily available energy, the liver 1700 kJ. The fatty acids plasma level is slowly increasing for 4 days approximately from 0.3 mM to 1.2 mM. Ketones increase after two days of starvation to reach plasma levels of 5 mM approximately. A catabolic state is obvious if acetone is exhaled. Adipose tissue can provide up to 560'000 kJ of energy.

Glycogen breakdown requires the interplay of several enzymes. It is initiated by adrenalin, i.e., the stress hormone, and glucagon, i.e., the antagonist of insulin. Glycogen diseases are:

1. Von Gierke disease (A glucose-6-phosphate defect. Located in liver and kidney. Massive liver enlargement, hypoglycemia, ketosis, hyperuricemia, hyperlipidemia).

2. Pompe disease (A lysosomal α-1,4-glucosidase defect. Cardiorespiratory failure. Death before age 2).

3. Cori disease (An amylo-1,6-glucosidase defect. Located in liver and muscle. Liver enlargement, hypoglycemia, ketosis, hyperuricemia, hyperlipidemia).

4. Andersen disease (A branching enzyme α-1,4 -> α-1,6 defect. Located in liver and spleen. Progressive liver cirrhosis and failure. Death before age 2).

5. McArdle disease (A phosphorylase defect. Located in muscle. Limited ability to perform exercise due to painful muscle cramps).

6. Hers disease (A phosphorylase defect. Located in the liver. Liver enlargement, hypoglycemia, ketosis, hyperuricemia, hyperlipidemia).

7. Phosphofructokinase defect (located in muscle. Limited ability to perform exercise due to painful muscle cramps).

8. Phosphorylase defect (located in liver. Mild liver enlargement and hypoglycemia).

Biochemical Pathways of Lipids

Dietary lipids are transported in chylomicrons compounded from cholesterol and triacylglycerols. Triacylglycerols from food are a highly concentrated energy source which serves birds to best gain energy for long migration flights. Chylomicrons and their remnants

have receptors on the surface of hepatocytes which metabolize lipids. Lipoproteins circulate in the entero-hepatic circulation. As fatty acids are released from lipoproteins, very low density lipoproteins (VLDL) are transformed to intermediate (IDL) and low density lipoproteins (LDL). LDLs have receptors on hepatocytes and on muscle cells which are to metabolize the components. Release of cholesterol transforms IDL and LDL finally to high density lipoproteins (HDL) which are not related to cardiovascular risk factors.

Fatty acids are synthesized and degraded by different pathways. Elongation and unsaturation of fatty acids are accomplished by accessory enzyme systems bound in the membranes. Acetyl-CoA carboxylase plays a key role in controlling fatty acid metabolism. The utilization of fatty acids as fuel from adipose tissues requires three processing steps, i.e., c-AMP regulated lipases, linkage to CoA before being oxidized and carnitine-mediated transport of activated fatty acids into the mitochondria. Additional isomerization and reduction steps are needed for oxidative degradation of unsaturated fatty acids. Odd-chain fatty acids yield propionyl CoA instead of acetyl CoA in the final step. Formation of Acetyl-CoA from pyruvate is less direct than from fatty acids. Plants and some microorganisms are able to grow on acetate and to bypass the decarboxylation steps of the citric acid cycle. This option is called glyoxylate pathway. Ketone bodies are formed from acetyl-CoA when fat breakdown predominates. Acetoacetate and 3-hydroxybutyrate are major fuels of respiration. These ketones raise dangerously up to life-threatening concentrations in type I diabetes related diabetic ketosis.

Starting from acetoacetyl-CoA Apart from fatty acids, sterols are biosynthesized. Three of the two carbon bricks yield hydroxyl-methyl-glutaryl-CoA (six carbon), which is converted by HMG-CoA-reductase to mevalonic acid (five carbon). The latter will condense to a thirty carbon sterol and lead to twenty-seven carbon cholesterol, from which gluco- and mineralocorticoids as well as sex hormones will be biosynthesized. HMG-CoA is active during night's rest under influence of the parasympathic part of the central nervous system. Thus, statins, which are inhibitors of HMG-CoA-reductase, should be administered at night [3,4].

Fatty acids, mainly the unsaturated, together with cholesterol, are recombined to phospholipids such as phosphatidyl choline, phosphatidyl inositol, cardiolipin, sphingomyelin, or cerebrosid, are determinant for membrane's fluidity.

Eicosanoid hormones derived from arachidonate comprise leucotrienes, prostaglandins, prostacyclin and thromboxanes. Prostaglandins play a major role in inflammation. They are formed by induced cyclooxygenase (COX) and be inhibited by nonsteroidal anti-inflammatory drugs (NSAID) such as ibuprofen or mefenamic acid. Acetylosalicylic acid (Aspirin®) inhibits thrombocytes' aggregation too. It has a double effect of COX-1 and COX-2 inhibition. This is an important feature for patients receiving anti-inflammation treatment if they have an increased thrombosis risk. With COX-2 inhibition only (e.g. by celecoxib, rofecoxib), the risk for adverse cardiovascular events increases. This was the reason why rofecoxib as one of the first COX-2 specific NSAID was withdrawn from the market.

Biochemical Pathways of Amino Acids

Proteins have primary, secondary, tertiary and quaternary structures, beginning with the sequence, going to two- and three dimensional structures and to assembling subunits to functional clusters. Amino acids can be provided by uptake from food protein or synthesized under participation of metabolic cycles such as glycolysis, pentose-phosphate cycle, or citrate cycle. The metabolism of glucose-6-phosphate by the pentose phosphate pathway is coordinated with glycolysis. NADPH and five carbon sugars are produced in this cycle.

Important amino acid stores are muscle proteins and albumin. In a catabolic state of hunger or of cachexia, sarcopenia, or consuming diseases such as COPD, HIV or cancer, it is essential to provide amino acids by food in order to fill stores of at least those amino acids which are involved in the metabolic cycles. However, reversal of catabolism in these diseases is difficult to achieve and only successful in combination with anti-inflammation, anabolics, and physical activity. Supplementation is particularly important for arginine and glutamine, which are essential key substrates in critically ill patients with protein-energy-malnutrition and hard-to-heal wounds when arginine stores may become depleted. A wounded tissue heals only if it is perfused and obtains substrates such as oxygen and growth factors to induce angiogenesis. In this situation, arginine is consumed by two competing enzymatic reactions, i.e., arginase and nitric oxide synthase. Arginine is the precursor of angiogenetic nitric oxide ($NO^{\cdot}$), formerly known as endothelial derived relaxing factor. Apart from arginine, glutamine and hydroxyproline are essential amino acids for wound healing. Glutamine needs ATP to be biosynthesized from glutamate. As this is lacking in wounded critically ill patients, it needs to be substituted. Hydroxyproline as key amino acid in keratin needs ascorbic acid for being produced from proline. Thus, in wound healing, the right amino acids (arginine, proline, glutamine), co-factors (e.g. copper for the Fenton reaction), and co-enzymes (ascorbic acid), as well as energy and oxygen, must be provided [5].

The first step in amino acid degradation is the direct removal of nitrogen (from serine and threonine) or by transamination from other amino acids, with pyridoxal (= vitamin B6) as co-enzyme. Ammonium is converted to urea (carbamide) in the urea cycle. Ornithine binds ammonium as carbamoyl phosphate and passed on via citrulline to arginine which excretes urea and is recycled to ornithine (Figure 2). The fragments of amino acids emerge as major metabolic intermediates after entering the Citric acid cycle at α-ketoglutarate as the point of entry.

Inborn errors of metabolism can disrupt amino acid degradation. Hyperammonemia is detected soon after birth in lethargic and frequently vomiting babies. Coma and irreversible brain damage may follow as a result of accumulation of glycine and glutamine. A diet of phenylacetate and benzoate can help to bypass the genetic defect and excrete ammonium as hippurate and phenylacetylglutamine.

Energy Metabolism

The final conversion of the initial glucose substrate to into a usable form of energy, i.e., to activated molecules such as adenosine triphosphate (ATP) or guanosine triphosphate (GTP), happens in the respiratory chain and the oxidative phosphorylation in mitochondria. The respiratory chain consists of four complexes, i.e., three proton pumps and a physical link to the Citric acid cycle. A proton gradient powers the synthesis of ATP and many shuttles allow movements across the mitochondrial membranes. Oxidative phosphorylation describes the formation of ATP as a result of electron transfer from NADH or $FADH_2$ built in the citrate cycle to oxygen. It takes place in the mitochondria. For this reason mitochondria are considered as the power plant of the cell.

The net ATP yield per glucose molecule from glycolysis (conversion

of glucose to pyruvate in the cytosol, -1-1+2+2), the conversion of puyruvate into acetyl CoA and citric acid cycle (inside mitochondria, +2), and the oxidative phosphorylation (inside mitochondria, +3+5+3+15) is +30.

In cancer cells, respiratory chain and ATP production is inhibited due to altered ATPase function (Warburg effect). Instead, ATP from glycolysis has to replace mitochondrially produced energy. The lack of oxygen induces reduction to lactate instead of pyruvate oxidation. This is an inefficient way of producing two molecules of ATP from one molecule glucose and leads to consumption of major amounts of glucose. Glucose accumulation is used to diagnose tumor tissues by positron emission tomography (PET). The glucose analogue fluorodeoxyglucose (^{18}F-FDG) represents the positron emitting radionuclide (tracer) which is accumulated by cancer tissues and metastases.

Metabolism of Other Substances

Metabolic reactions of xenobiotics and secondary plant components are predominantly executed by the cytochrome P450 superfamily. 57 human CYP450 isoenzymes are known. They are active in hepatocytes, epithelial tissues, skin, kidneys, intestines, lungs, nasal epithelium and brain. Substrates are converted to more hydrophilic products by the monoxygenase function. In men, the isoenzymes CYP1A2, CYP2C9, CYP2E1 have a higher activity, CYP1A2 up to 40-fold. In women, CYP3A4,5,7, CYP2A6, CYP2B6, or CXP2D6 are more expressed, CYP2D6 only in the fertile phase, CYP3A4,5,7 as a function of menstrual cycle with top level before ovulation and in pregnancy. CYP450 isoenzymes are key players for drug-drug and food-drug interactions.

Adaption and Response to the Environmental Circumstances

Metabolism is regulated by positive or negative feedback, i.e., activation or inhibition of entire enzymatic reaction cascades. Products from substrates are synthesized as long as there is a need. As soon as this one is satisfied, the trigger is withdrawn. The endocrine system regulates on several levels:

I. Releasing or release inhibiting hormones such as liberines in the hypothalamus.

II. Glandotrophic hormones produced by the pituitary gland.

III. Endocrine secretion by placenta, testes, ovaries, pancreas, thyroid, kidneys, or tissues in the GI tube.

To regulate the activity of enzymes, mainly four principles are applied, i.e.,

Allosteric control/induced fit

The binding of a substrate changes the conformation of a receiving molecule and activates its function. Subunits cooperate to increase the activity. Products formed give a feedback signal to inhibit the enzyme's activity by reconversion to the original conformation. An example for such conformational changes is hemoglobin when binding and releasing oxygen.

Isoenzymes (also referred to as isozymes)

A family of enzymes such as the cytochrome P450 superfamily includes multiple forms of enzymes, sometimes tissue-specific. Isoenzymes are specialized in their function to metabolize specific substrates or which are polyvalent to detoxify undesirable substrates in a fast and effective way. Critical enzymes are controlled by regulation of the rate of protein synthesis and degradation by feedback inhibition and activation. Vitamins and oligoelements are often precursors to co-enzymes and co-factors providing one or two carbon fragments, or electrons for metabolic reactions.

Phosphorylation

The catalytic properties of many enzymes depend on the covalent binding of a phosphoryl group mediated by kinases. The removal of this group is catalyzed by phosphatases. An example of activation upon phosphorylation would be the blood-clutting cascade.

Proteolysis

Proenzymes have to be cleaved at a defined site to be activated, e.g. digestive enzymes such as pepsin emerging of a pepsinogen precursor, or caspases from procaspases to activate regulated cell death, or factors in the blood coagulation cascade such as prothrombin/thrombin or fibrinogen/fibrin. The idea is to activate these enzymes upon need only rather than to all-time activity.

Living cells and beings have to adapt to changing environmental circumstances. They do so by differentiation from plural potency of cell groups to high specificity of tissues, organs and bodies and by regulation of gene expression to sensory systems used by living beings. If the need to adapt is satisfied and survival in the environment succeeds, the adapted organism is passively selected for further generation of individuals of the species.

The mechanism of epigenetic impact is to methylate nucleic acids and to induce a change in response to an environmental pressure. Genetic codes and epigenetic response cannot explain every individual phenotype. There seems to be a fetal programming during the first trimester of pregnancy, which can be emerging up to many years later in adult or even elderly life.

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