Overview of Metabolism & the Provision of Metabolic Fuels

Metabolism is the term used to describe the interconversion of chemical compounds in the body, the pathways taken by individual molecules, their interrelationships, and the mechanisms that regulate the flow of metabolites through the pathways.

Metabolic pathways fall into three categories.

(1) Anabolic pathways, which are those involved in the synthesis of larger and more complex compounds from smaller precursors (for example, the synthesis of protein from amino acids and the synthesis of reserves of triacylglycerol and glycogen). Anabolic pathways are endothermic.

(2) Catabolic pathways, which are involved in the breakdown of larger molecules, commonly involving oxidative reactions; they are exothermic, producing reducing equivalents, and, mainly via the respiratory chain, ATP.

(3) Amphibolic pathways, which occur at the "crossroads" of metabolism, acting as links between the anabolic and catabolic pathways, for example, the citric acid cycle.

Knowledge of normal metabolism is essential for an understanding of abnormalities that underlie a disease. Normal metabolism includes adaptation to periods of fasting, starvation, and exercise, as well as pregnancy and lactation.

Abnormal metabolism may result from nutritional deficiency, enzyme deficiency, abnormal secretion of hormones, or the actions of drugs and toxins.

A 70-kg adult human being requires about 1920-2900 kcal from metabolic fuels each day, depending on physical activity. Growing children have a proportionally higher requirement to allow for the energy cost of growth. For human beings, this energy requirement is met from carbohydrates (40%-60%), lipids (mainly triacylglycerol, 30%-40%), and protein (10%-15%), as well as alcohol. The mix of carbohydrate, lipid, and protein being oxidized varies, depending on whether the subject is in the fed or fasting state, and on the duration and intensity of physical work.

There is a constant requirement for metabolic fuels throughout the day. However, most people consume their daily intake of metabolic fuels in two or three meals, so there is a need to form reserves of carbohydrate (glycogen in liver and muscle), lipid (triacylglycerol in adipose tissue), and proteins stores during the period

following a meal, for use during the intervening time when there is no intake of food.

If the intake of metabolic fuels is consistently greater than energy expenditure, the excess is stored, largely as triacylglycerol in adipose tissue, leading to the development of obesity and its associated health hazards. By contrast, if the intake of metabolic fuels is consistently lower than energy expenditure, there are negligible reserves of fat and carbohydrate, and amino acids arising from protein turnover are used for energy-yielding metabolism rather than replacement protein synthesis, leading to emaciation, wasting, and, eventually, death.

In the fed state, after a meal, there is a plentiful supply of carbohydrate, and the metabolic fuel for most tissues is glucose. In the fasting state, glucose must be spared for use by the central nervous system (which is largely dependent on glucose) and the red blood cells (which are wholly dependent on glucose). Therefore, tissues that can use fuels other than glucose do so; muscle and liver oxidize fatty acids and the liver synthesizes ketone bodies from fatty acids to export to muscle and other tissues. As glycogen reserves become depleted, amino acids arising from protein turnover are used for gluconeogenesis (and ketogenesis).

The formation and utilization of reserves of triacylglycerol and glycogen, and the extent to which tissues take up and oxidize glucose, are largely controlled by the hormones insulin and glucagon. In diabetes mellitus, there is either impaired synthesis and secretion of insulin (type I diabetes, previously known as juvenile onset, or insulin-dependent diabetes) or impaired sensitivity of tissues to insulin action (type II diabetes, sometimes called adult onset or noninsulin-dependent diabetes), leading to severe metabolic derangement.

Levels of organization of metabolic pathways

In addition to studies in the whole organism, the location and integration of metabolic pathways is revealed by studies at two levels of organization. At ***the tissue and organ level***, the nature of the substrates entering and metabolites leaving tissues and organs can be measured. At ***the subcellular level***, each cell organelle (eg, the mitochondrion) or compartment (eg, the cytosol) has specific roles that form part of a subcellular pattern of metabolic pathways.

At the Tissue & Organ Level

Products of digestion (amino acids, glucose and triacylglycerol) are absorbed via the hepatic portal vein.

Liver

Taking up glucose in excess of immediate requirements and using it to synthesize glycogen (***glycogenesis***) or fatty acids (***lipogenesis***).

Between meals, the liver acts to maintain the blood glucose concentration by breaking down glycogen (***glycogenolysis***) and, together with the kidney, by converting noncarbohydrate metabolites such as lactate, glycerol, and amino acids to glucose (***gluconeogenesis***).

Partial oxidation of fatty acids in the liver leads to ketone body production (***ketogenesis***). Ketone bodies are exported to extrahepatic tissues, where they provide a fuel in prolonged fasting and starvation.

The liver also ***synthesizes the major plasma proteins*** (eg, albumin) and ***deaminates amino acids*** that are in excess of requirements, synthesizing ***urea***, which is transported to the kidney and excreted.

Note: Unlike glucose and amino acids absorbed from the small intestine, triacylglycerol is not taken up directly by the liver. It is first metabolized by tissues that have lipoprotein lipase, which hydrolyzes the triacylglycerol, releasing fatty acids that are incorporated into tissue lipids or oxidized as fuel. ***The remnants are cleared by the liver***.

Skeletal muscle

It stores glycogen (***glycogenesis***) as a fuel for use in muscle contraction during prolong fasting or starvation (***glycogenolysis***).

It ***synthesizes muscle protein*** from plasma amino acids. Muscle accounts for approximately 50% of body mass and consequently represents a considerable store of protein that can be drawn upon to ***supply amino acids for gluconeogenesis*** in starvation.

Adipose tissue

Triacylglycerol is the main fuel reserve of the body. It is hydrolyzed (***lipolysis***) and glycerol and non-esterified (free) fatty acids are released into the circulation.

Glycerol is a substrate for gluconeogenesis. The fatty acids are transported bound to serum albumin; they are taken up by most tissues (but not brain or erythrocytes) and either esterified to triacylglycerols for storage or oxidized as a fuel.

At the Subcellular Level

Compartmentation of pathways in separate subcellular compartments or organelles permits integration and regulation of metabolism. Not all pathways are of equal importance in all cells.

Pathways occurring in the mitochondria

The citric acid cycle, β-oxidation of fatty acids, ketogenesis, as well as the respiratory chain and ATP synthase.

Pathways occurring in the cytosol

Glycolysis, the pentose phosphate pathway, and fatty acid synthesis.

Pathways with some reactions occurring in the cytosol and others in the mitochondria

Gluconeogenesis and urea cycle

Pathway occurring in the membranes of the endoplasmic reticulum

Triacylglycerol synthesis

Pathway occurring the ribosomes

Protein synthesis

Regulation of the Flux of Metabolites through Metabolic Pathways

In a reaction at equilibrium, the forward and reverse reactions occur at equal rates, and there is therefore no net flux in either direction. In practice, there are normally one or more nonequilibrium reactions in a metabolic pathway. The enzymes catalyzing nonequilibrium reactions are usually present in low concentration and are subject to a variety of regulatory mechanisms.

Note: most reactions in metabolic pathways cannot be classified as equilibrium or nonequilibrium, but fall somewhere between the two extremes.

The flux-generating reaction can be identified as a nonequilibrium reaction in which the K_m of the enzyme is considerably lower than the normal concentration of substrate. The first reaction in glycolysis, catalyzed by hexokinase, is such a flux-generating step because its K_m for glucose of 0.05 mmol/L is well below the normal blood glucose concentration of 3 to 5 mmol/L.

Factors regulating the flux of metabolites through metabolic pathways

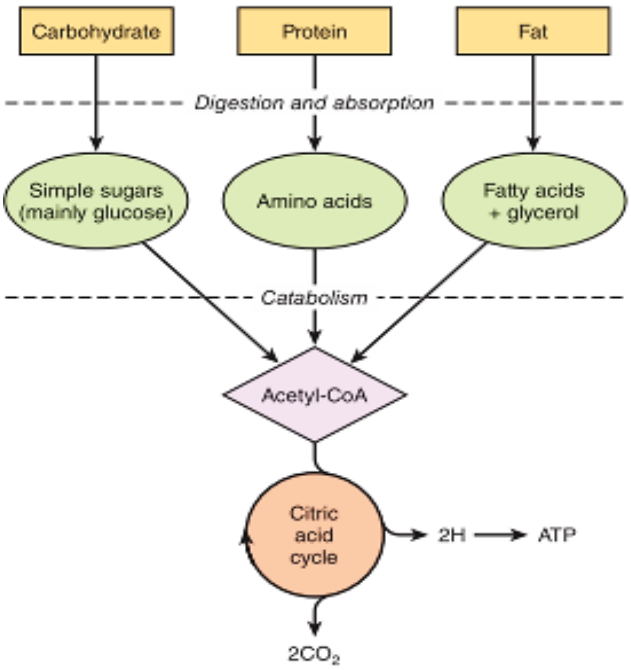
The flux through this pathway can be regulated by the ***availability of the initial substrate***. This depends on its supply from the blood, which in turn depends on either *food intake* or key *reactions that release substrates from tissue reserves* into the bloodstream, for example, glycogenolysis in liver and lipolysis in adipose tissue. It also depends on the *transport of the initial substrate into the cell*. Muscle and adipose tissue only take up glucose from the bloodstream in response to the hormone insulin.

Flux is also determined by ***removal of the end product*** and the ***availability of cosubstrates or cofactors***. Enzymes catalyzing nonequilibrium reactions are often allosteric proteins subject to the rapid actions of "feed-back" or "feed-forward" control by allosteric modifiers, in immediate response to the needs of the cell. Frequently, the end product of a biosynthetic pathway inhibits the enzyme catalyzing the first reaction in the pathway.

Other control mechanisms depend on the action of ***hormones*** responding to the needs of the body as a whole; they may act rapidly by altering the activity of existing enzyme molecules, or slowly by altering the rate of enzyme synthesis.

Many Metabolic Fuels are Interconvertible

There is a need to process the products of digestion of dietary carbohydrate, lipid, and protein; these are mainly glucose, fatty acids and glycerol, and amino acids, respectively. All the products of digestion are metabolized to a common product, acetyl-CoA, which is then oxidized by the citric acid cycle.



End products (or intermediate product) of a given metabolic pathway can be utilized as a substrate of another. Acetyl-CoA for example can be used interchangeably among many pathways.

Gluconeogenesis utilizes products from lipolysis and from amino acid catabolism.

CLINICAL ASPECTS

In ***prolonged starvation***, as adipose tissue reserves are depleted, there is a very considerable increase in the net rate of protein catabolism to provide amino acids, as substrates for gluconeogenesis. Death results when essential tissue proteins are catabolized and not replaced. In patients with ***cachexia*** as a result of release of cytokines in response to tumors and disease, there is an increase in the rate of tissue protein catabolism, as well as a considerably increased metabolic rate, so they are in a state of advanced starvation. Again, death results when essential tissue proteins are catabolized and not replaced.

In pregnancy and lactation, the high demand for glucose by the fetus, and for lactose synthesis in lactation, can lead to ketosis. This may be seen as mild ketosis with hypoglycemia in human beings.

In ***poorly controlled type 1 diabetes mellitus***, patients may become hyperglycemic, both as a result of lack of insulin to stimulate uptake and utilization of glucose, and because in the absence of insulin to antagonize the actions of glucagon, there is increased gluconeogenesis from amino acids in the liver. At the same time, the lack of insulin to antagonize the actions of glucagon results in increased lipolysis in adipose tissue, and the resultant nonesterified fatty acids are substrates for ketogenesis in the liver.

In uncontrolled diabetes, the ketosis may be severe enough to result in pronounced acidosis (ketoacidosis); acetoacetate and 3-hydroxybutyrate are relatively strong acids.

Coma results from both the acidosis and also the considerably increased osmolality of extracellular fluid (mainly as a result of the hyperglycemia, and diuresis resulting from the excretion of glucose and ketone bodies in the urine).