

Intermediary metabolism

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In humans, chemical unity in diversity prevails as metabolic pathways are coordinated, regulated, and integrated to protect the body against metabolic catastrophes. The end product of one metabolic pathway is connected to another metabolic pathway of the same or another metabolite. A basic understanding of the normal metabolic pathways and their abnormality is the foundation in the management of patients subjected to the stress of anaesthesia and surgery. Objective clinical evaluation, investigations, and perioperative risk stratification of patients are based on understanding the fundamentals of intermediate metabolism.

Keywords: intermediary metabolism, essential intracellular chemical processes

Introduction

Metabolism refers to the hormonal coordinated, multistep enzyme-mediated chemical reactions and energy transformation occurring in a living organism.¹ Intermediary metabolism refers to the sum of essential intracellular chemical processes and pathways by which nutritive material (carbohydrates, proteins, and fats), post-digestion and absorption, is converted into cellular components.^{1,2} The basic high potential substrates, such as glucose from carbohydrates, amino acids (AA) from proteins, free fatty acids (FFA) and glycerol from fats, undergo oxidation (process of oxygen + substance combination with electron/hydrogen removal) to substrate at lower potential. In the mitochondria, under aerobic conditions, the tricarboxylic acid (TCA) cycle /citric acid cycle occurs, consuming glucose and fat breakdown products such as acetyl-CoA and AA.

Reduced coenzymes, such as nicotinamide adenine dinucleotide (NAD⁺), nicotinamide adenine dinucleotide phosphate (NADP⁺), and flavin adenine dinucleotide (FAD), pick up the removed hydrogen from oxidation in the process called electron transport chain.¹ The final product of the metabolic process yields CO₂, H₂O, and energy essential for survival. Less energy can also be generated anaerobically via glycolysis with the production of lactate. The high energy phosphate (PO₄³⁻) bonds in adenosine triphosphate (ATP) make it the energy currency of the cell.¹

Energy requirements

Energy balance describes the difference between caloric intake and energy output. During positive energy balance (caloric intake > energy expenditure from thermogenesis and work), the body stores energy increasing the risk of weight gain. In a fasted state and starvation, caloric intake do not meet energy requirements (i.e. negative energy balance); endogenous stores such as glycogen, body protein, and fat are catabolised.³ Energy production is constantly required for multiple cellular functions in a living organism.

Energy units are calories or kilocalories (kcal); 1 kcal = 1 000 calories. Kilojoules (kJ) are other units of energy (1 kcal = 4.18 kJ). The basal energy expenditure (BEE), also called basal metabolic rate (BMR), is about 200 kcal/day for an average-sized man. The BEE falls by about 10% during sleep and goes up by 40% during exercise.¹

Intermediary metabolism has pathways that are anabolic and catabolic in nature.^{1,3} The starve-feed cycle, energy availability, and regulatory mechanism for the metabolism determine the direction of the intermediary metabolic pathway to a catabolic or anabolic state.¹

Anabolic pathways

These pathways require energy (endergonic), are involved in compound synthesis, and are divergent in nature with simple precursors built into large and complex molecules.

Catabolic pathways

These metabolic pathways are involved in the release of energy and most of them are convergent.

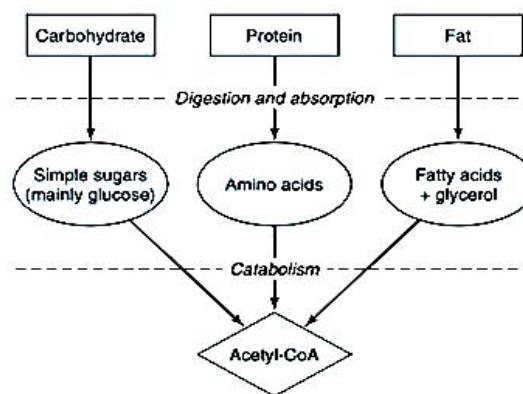


Figure 1: Steps in catabolic processes converging to acetyl-CoA³

Major intermediates

The main intermediates of metabolism formed from carbohydrate, protein, and fat catabolism converge at acetyl-CoA (Figure 1).³

Other important intermediates of metabolism are pyruvate, succinyl-CoA, and oxaloacetic acid (OAA). Cofactors such as vitamins are required for efficient enzyme functions in metabolic pathways.³

Carbohydrate metabolism

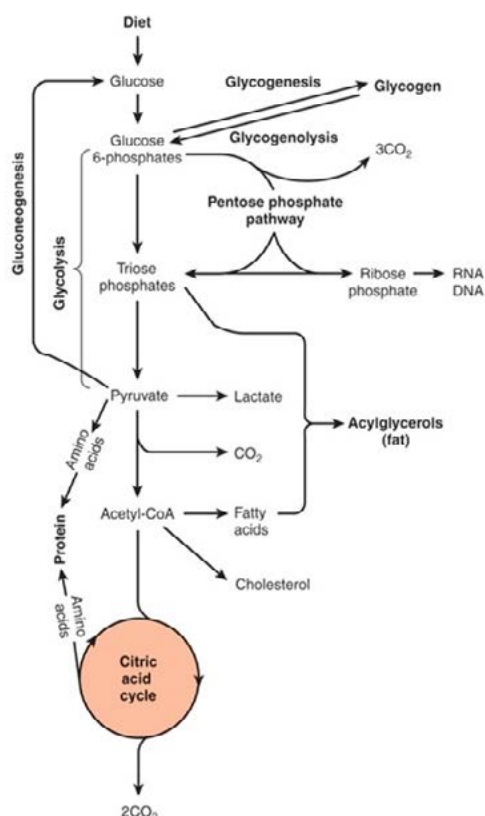
Major dietary carbohydrates in the human diet are polysaccharides (starch, plant storage form of carbohydrate), disaccharides (sucrose, table sugar, and lactose, milk sugar), and monosaccharides (glucose and fructose). Cellular respiration refers to combined reactions that lead to the oxidation of glucose, producing CO₂, H₂O, and ATP.⁴ Energy produced per gram of carbohydrates equals 4 kcal/g.

Glycogenesis

The enzyme-mediated conversion of excess glucose to glycogen, a branched polymer of glucose at α-1,4 and α-1,6 links.

Glucose-6-phosphate → glucose-1-phosphate → glycogen

Glycogen is stored in the muscle, liver, and minimally in the brain at 400 g, 100 g, and only 3–12 μmol/g of brain tissue for minute supply, respectively. Glycogen synthetase is the enzyme that initiates glucose conversion to glycogen and is stimulated by high blood glucose levels and insulin.^{1,5}



Glycogenolysis

The breakdown of glycogen to glucose in times of glucose deficiency.

Glycogen → glucose-1-phosphate → glucose-6-phosphate

Glycolysis

The conversion of glucose to pyruvate (figure 2a). Pyruvate is further converted to acetyl-CoA under aerobic conditions (presence of oxygen), which is essential for the citric acid cycle. During anaerobic respiration (absence of oxygen), lactate is formed from pyruvate. The other important fate of glucose-6-phosphate is the pentose phosphate pathway producing the ribose-5-phosphate sugar used to make deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) (see figure 2b).

Gluconeogenesis

The pyruvate and citric acid cycle intermediates are converted to glucose from non-carbohydrate precursors, see figure 2a.

Protein metabolism

Proteins are linear chains resulting from AA joined together. Their structures contain approximately 16% nitrogen in addition to carbon, hydrogen, and oxygen. The AA are produced from the digestion of proteins from exogenous and endogenous sources. The complete oxidation of AA produces CO₂, H₂O, and NH₃. The amount of energy produced per gram of protein is 4 kcal. There are essential (these are only obtained from exogenous sources) and non-essential AA (these can be endogenously produced in protein synthesis).⁶

Transamination

Transfer of an amine group from AA to alpha-ketoglutaric acid, thereby transforming it to glutamic acid.

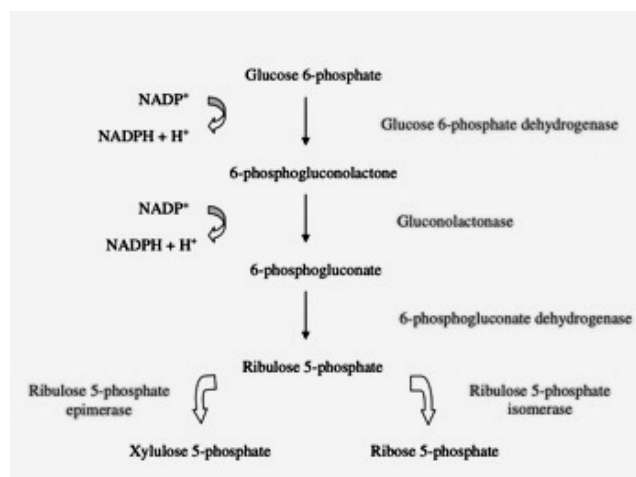


Figure 2a (left), 2b (right): Simplified multiple fates of glucose metabolism and pentose phosphate pathway^{3,4}

Oxidative deamination

The removal of an amine group from glutamic acid as ammonia and regenerating alpha-ketoglutaric acid.

Proteolysis

AA can be converted to glucose via gluconeogenesis or may help in the synthesis of non-essential AA. In the liver, $\text{NH}_3 + \text{HCO}_3^- + \text{ATP}$ forms carbamoyl phosphate, which is further converted to urea in the urea cycle.^{3,6}

Fat metabolism

Fat (triacylglycerol/triglycerides) in the adipose tissue is the largest form of energy reservoir in the body. Other important biological lipids are phospholipids, steroid hormones, and cholesterol. The triglycerides containing no double bonds are called saturated fats compared to unsaturated fats, which contain double bonds. Polyunsaturated fats such as linoleic, linolenic, and arachidonic acids are essential precursors of prostaglandins.³

Fats catabolism

Involves complete oxidation of triacylglycerol (TAG) to CO_2 , H_2O and heat with 9 kcal/g of energy produced (see figure 4).

Lipolysis

Breakdown of lipids to fatty acids and glycerol.

Beta (β) oxidation

Conversion of fatty acids to acetyl-CoA.

Ketogenesis

Alternative energy production from fatty acids and certain ketogenic AA. Excess acetyl-CoA is converted to acetoacetyl-CoA and further converted to acetoacetate in the liver. The derivatives of acetoacetate are acetone and β-hydroxybutyrate (figure 3 and 4). Commonly formed ketone bodies (figure 3) are acetoacetate, acetone, and β-hydroxybutyrate.⁷

Fats anabolism

Lipogenesis

The formation of lipids from acetyl-CoA and glyceraldehyde phosphate occurs in the cytosol (figure 4). Important cofactors for this process are biotin and nicotinamide adenine dinucleotide (NADPH). Other important fat anabolism pathways lead to cholesterol genesis and subsequent steroidogenesis; all essential for organism survival.

The tricarboxylic acid cycle/Krebs cycle/citric acid cycle

This cycle (figure 5) occurs in the mitochondria and is at the core of energy production, CO_2 , and some reduced coenzymes from the acetyl-CoA.³ Biochemical homeostasis is maintained

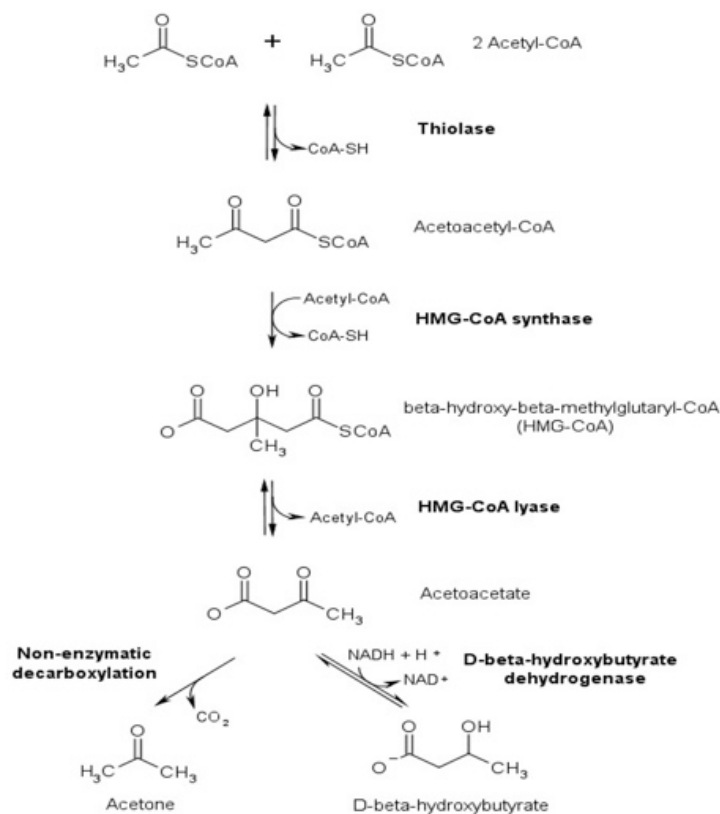


Figure 3: Steps of ketone body production⁷

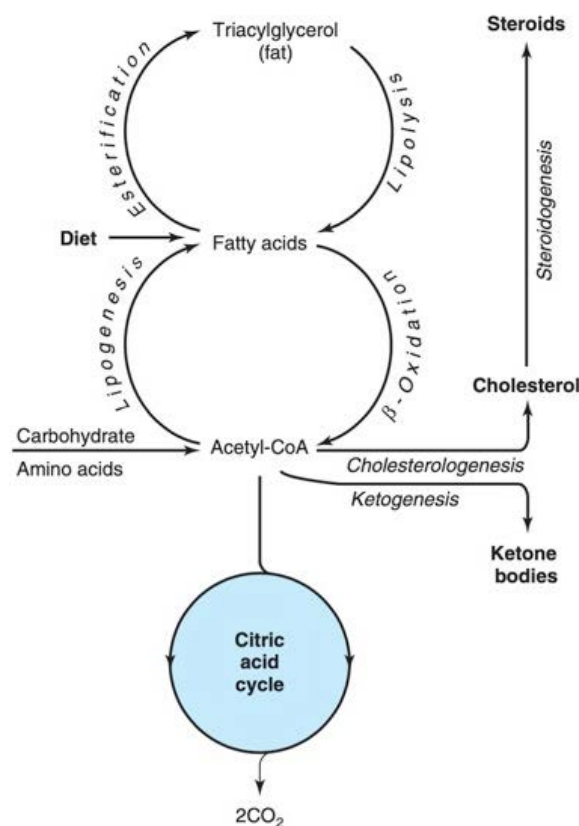


Figure 4: Simplified lipolysis, esterification, lipogenesis, and β-oxidation³

by mitochondrial influxes and effluxes of intermediates as per cellular needs. The TCA intermediates are used for glucose, AA, fatty acids, and heme synthesis, among others. The other essential efflux of the TCA intermediate is key in the urea cycle.

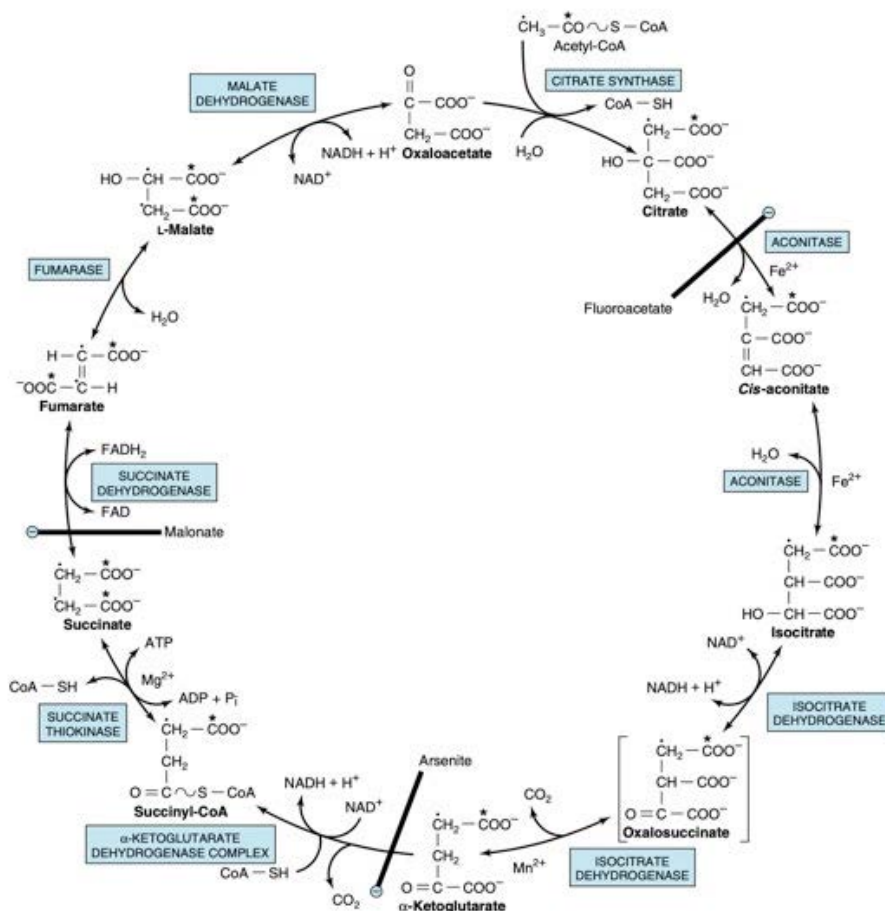


Figure 5: TCA cycle showing the multisteps involved in energy production³

Regulation of metabolism

The enzymes involved in all metabolic pathways are regulated by hormones. The hormones either inhibit or stimulate the regulatory enzyme. The enzymatic regulation can be allosteric regulation or covalent modification. The substrate availability, such as citrate levels, fructose-2,6-biphosphate levels, and ATP/AMP ratio, also plays a role in regulating metabolism.⁸ Low ATP levels stimulate enzymes of glycolysis, while high ATP levels stimulate TCA enzymes. High citrate levels stimulate acetyl-CoA carboxylase leading to fatty acid biosynthesis. A high level of fructose-1,6-bisphosphate stimulates phosphofructokinase (PFK) of glycolysis and inhibits fructose-1,6-bisphosphates of gluconeogenesis.

Fasting

The prescribed complete voluntary abstinence (nil per os) from caloric intake perioperatively has an impact on intermediary metabolism. During fasting periods, the body lives on reserves. The plasma levels of glucose, AA, and triacylglycerol (TAG) decrease. The insulin secretion declines and glucagon hormone secretion increases to initially stimulate glycogenolysis and later glycolysis, gluconeogenesis, fat oxidation, and ketogenesis take over as fat stores can last longer. The fuel storage in an average 70 kg male is distributed as fats 15 kg, protein 6 kg, and carbohydrates of about 2 kg.

Exercise

During exercise, the body requires added energy production. The cardiovascular system, respiratory system, and endocrine system, among others, need to adjust to meet the increase in intermediate metabolism and energy requirements.

Comorbid diseases

In the context of anaesthesia, there are relevant diseases associated with intermediary metabolism. Perioperatively, the impact on patients with these conditions and knowledge of their metabolic status is necessary for their safe management. Any molecule metabolism (i.e. carbohydrate, protein, lipid, nucleic acid, minerals, and vitamins) can be affected by a disease process.

Other comorbidities, such as hypo/hyper thyroids, lipid storage diseases, hemochromatosis, and sickle cell disease, contribute to intermediary metabolism and may affect the response to anaesthesia.

Diabetes mellitus (DM)

Both type 1 and type 2 DM resulting from insulin deficiency or resistance may lead to abnormal glucose metabolism. Perioperative glycaemic control will affect patient outcomes.

Metabolic syndrome

Obesity resulting from abnormal positive caloric balance may result in complications during anaesthesia, such as difficult airway management and obstructive sleep apnoea.

Inborn errors of metabolism (IEM)

Inherited defects in the activity of an enzyme that affect a wide variety of metabolic processes may result in specific diseases such as galactosemia and phenylketonuria. The pathogenesis is that of either accumulation of toxic precursors, or deficiency in the product of metabolic pathway.

Anaesthesia implications include patient-specific dietary restrictions, fasting time prescriptions, and the risk of triggering these diseases with the associated perioperative stress response.

Glycogen storage diseases

Patients known with this condition are prone to hypoglycaemia during fasting.

Alcoholism

Chronic alcohol use may lead to alcoholic liver diseases, thereby disrupting liver metabolism pathways. Nutrients, toxins, and drugs metabolise abnormal in these patients and therefore require special attention to anaesthetic drug doses.

Cancer cachexia

In advanced cancer, patients develop metabolic abnormalities leading to cachexia, a condition characterised by weight loss and muscle wasting. Patients with this condition may present with a low body mass index and may require preoperative nutritional rehabilitation to improve their metabolic reserves and clinical outcomes.

Intermediate metabolism-relevance in patient investigations

Blood gases

Respiratory quotient (RQ) is the ratio of oxygen consumed versus carbon dioxide produced for the energy yield from nutrients (e.g. for carbohydrates it is 1, lipids 0.7, and protein 0.8). Acid-base disorders, such as acidosis, lead to an increase in RQ while RQ is decreased in alkalosis. Maintaining acid-base balance and

optimum temperature is essential for the enzymatic functions involved in intermediate metabolism.

Cardiopulmonary exercise testing (CPET)

CPET is a dynamic test that can identify cardiac or pulmonary disease in patients with borderline abnormal diagnostic tests. Data collected include electrocardiogram (ECG), heart rate, oxygen uptake (essential for aerobic respiration), and carbon dioxide output (major intermediate metabolism byproduct).

Metabolic equivalent of task (METs)

This refers to the amount of oxygen consumed per kilogram per minute. One MET equals 3.5 ml of oxygen/kg/min⁻¹. The higher the METs, the better the patient can tolerate perioperative stress, and hence have a better outcome.^{9,10}

Intensive care unit (ICU) feeding

To calculate caloric requirements, basic intermediary metabolism knowledge and the use of indirect calorimetry help meet patient nutritional requirements to improve patient outcomes in this time of stress associated with critical illness.

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