Metabolism

What is the respiratory quotient?

The respiratory quotient (RQ) is the ratio in the steady state of the volume of CO_2 produced to the volume of O_2 consumed per unit of time. It should be distinguished from the respiratory exchange ratio (R), which is the ratio of CO_2 to O_2 at any given time whether or not equilibrium has been reached. R is affected by factors other than metabolism. RQ and R can be calculated for reactions outside the body, for individual organs and tissues and for the whole body. The RQ of carbohydrate is 1.00 and that of fat is about 0.7. This is because H and O are present in carbohydrate in the same proportions as in water, whereas in the various fats, extra O_2 is necessary for the formation of H_2O.

What is metabolic rate?

It is the amount of energy liberated per unit of time. The energy can take the form of work (internal and external) and heat. It is measured by measuring oxygen consumption.

The metabolic rate is increased by exercise and food intake. It is also affected by high or low environmental temperature, height, weight, body surface area, sex, age, growth, reproduction, lactation, emotional state, body temperature, thyroid hormone, catecholamines

Basal metabolic rate is determined at rest in a room at comfortable temperature 12-14 hours after the last meal. This value falls ~10% during sleep and up to 40% during prolonged starvation.

What is ATP?

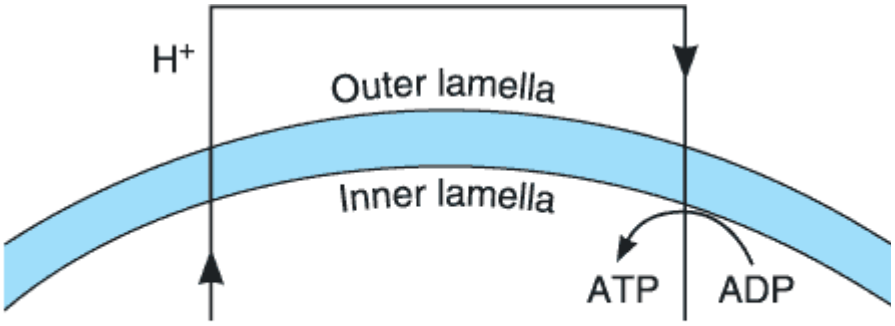
Energy is stored in the bonds between phosphates and organic compounds. When this bond is hydrolysed, large amounts of energy are released. Compounds containing these bonds are called high energy phosphate compounds.

ATP (adenosine triphosphate) is the most important high energy phosphate compound. It is the energy storehouse of the body. It can be hydrolysed to ADP releasing energy for active transport pumps, muscle contraction and synthesis of compounds. Further hydrolysis to AMP releases more energy.

What is oxidative phosphorylation?

It is the process by which ATP is formed in the body. 90% of the O2 consumption in the basal state is mitochondrial and 80% of this is coupled to ATP synthesis.

The following is Ganong's simple diagram of transport of protons across the inner and outer lamellas of the inner mitochondrial membrane by the electron transport system (flaviprotein-cytochrome system) with return movement of protons down the proton gradient, generating ATP.



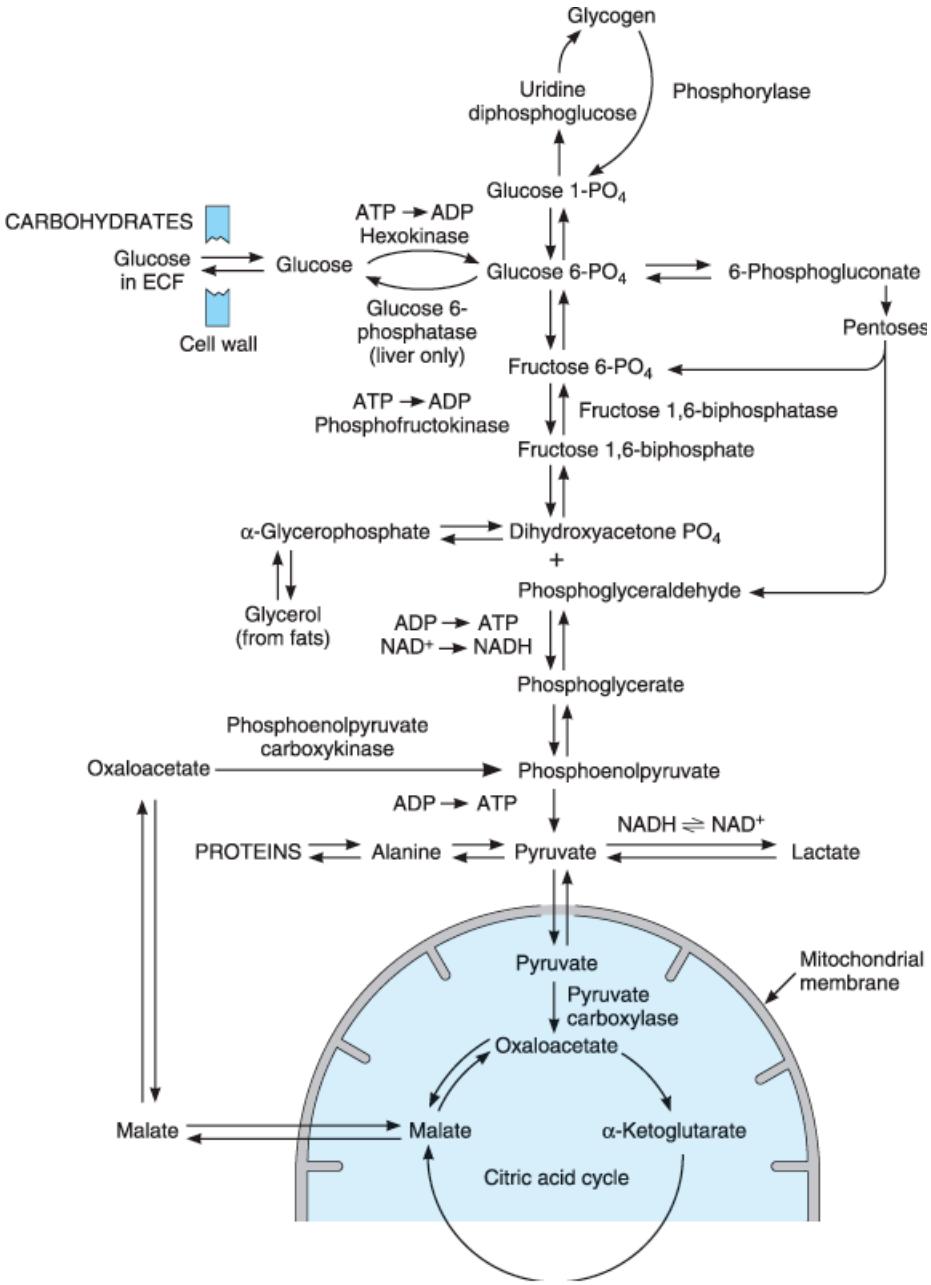
What is the fate of glucose?

Glucose is phosphorylated to glucose 6 phosphate once inside the cell by hexokinase. In the liver there is specific glucokinase that does this. Glucokinase is increased by insulin and decreased in starvation and diabetes whereas hexokinase is not.

G6P can then be polymerized into glycogen for storage (glycogenesis) or catabolised (glycolysis). In glycolysis, the G6P is converted to pyruvate and or lactate by either cleavage to fructose (Embden- Meyehof pathway) or oxidation to pentoses (hexose monophosphate shunt). Fats and protein intermediaries can enter the pathways and move in the opposite direction for gluconeogenesis.

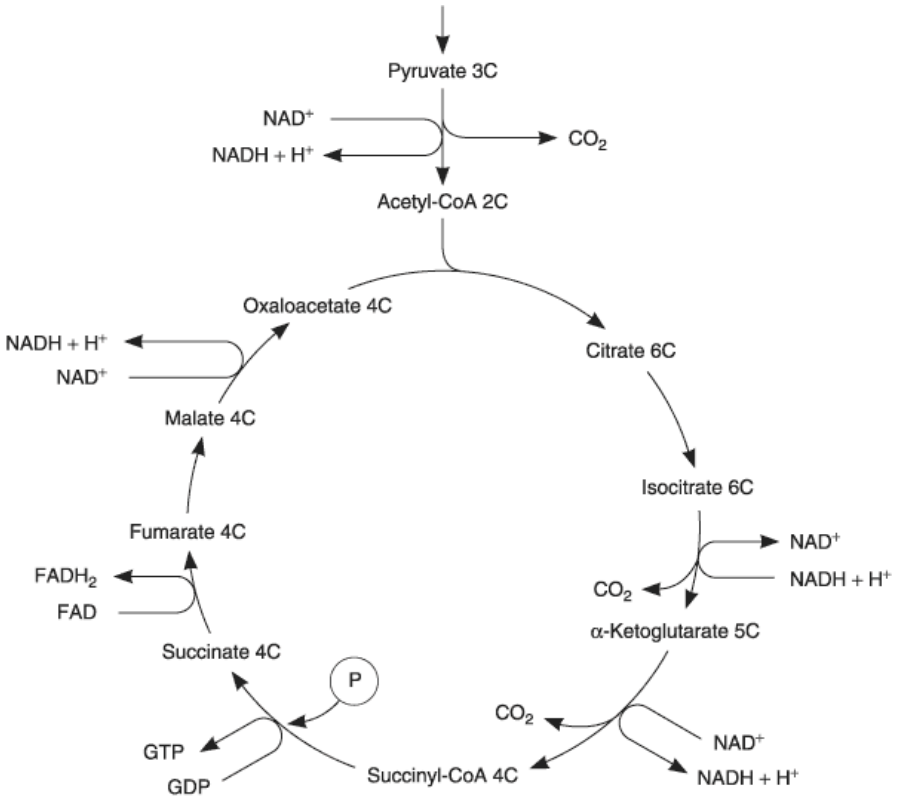
The Embden-meyerhof pathway produces more energy in the form of ATP (38), but the hexose monophosphate shunt generates large amounts of NADPH and the pentoses formed are the building blocks for nucleotides.

Pyruvate is irreversibly converted to Acetyl CoA to enter the citric acid cycle, but can also be converted to fats this way.



What is the citric acid cycle?

The citric acid cycle metabolises acetyl-CoA to CO2 and H+ with production of ATP. It if the common pathway for oxidation of carbohydrate, fat and some amino acids. The citric acid cycle requires O2 and does not function under anaerobic conditions.

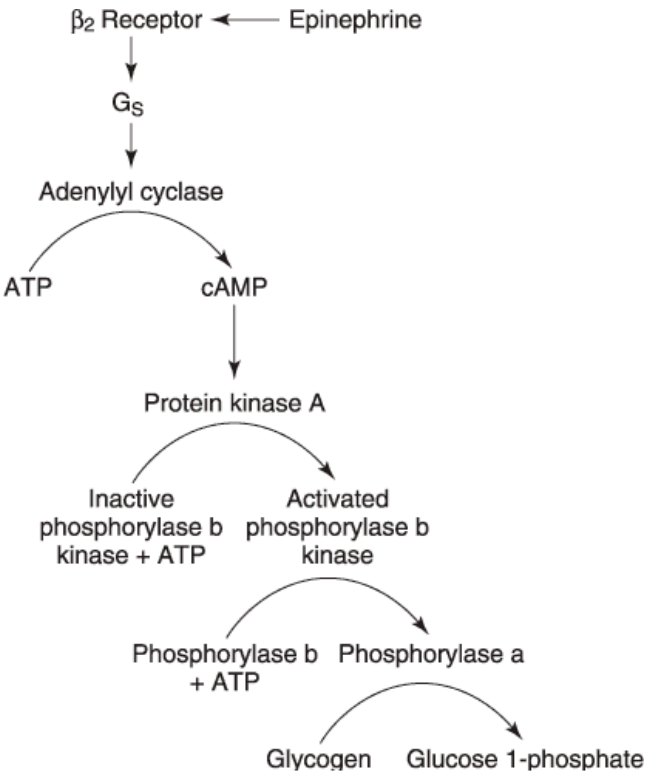


What happens under anaerobic conditions?

Pyruvate formed anaerobically from glucose (Embden-Meyerhof pathway) produces 2mol of ATP per mole of G6P. NAD+ is required for the pathway, and under anaerobic conditions this is supplied by pyruvate accepting a H+ from NADH to form NAD+ and lactate. In this way, glucose metabolism and energy production can continue for a while without O2. The lactate that accumulates is converted back to pyruvate when the O2 supply is restored.

What is phosphorylase?

Phosphorylase is an enzyme that catalyses the breakdown of 1:4 alpha linkages in glycogen. Another enzyme breaks the 1:6 alpha linkages. Phosphorylase is activated by B2 adrenergic receptors in the liver and skeletal muscle.



The liver contains glucose 6 phosphatase so can convert the G6P formed back into glucose for release into the bloodstream.

What is protein?

Chains of amino acids linked by peptide bonds. The order of the amino acids is the primary structure, the way the chain is twisted is the secondary structure and the tertiary structure is the arrangement of the twisted chains into layers or fibres. Quaternary structure describes the arrangements of subunits eg. Hb.

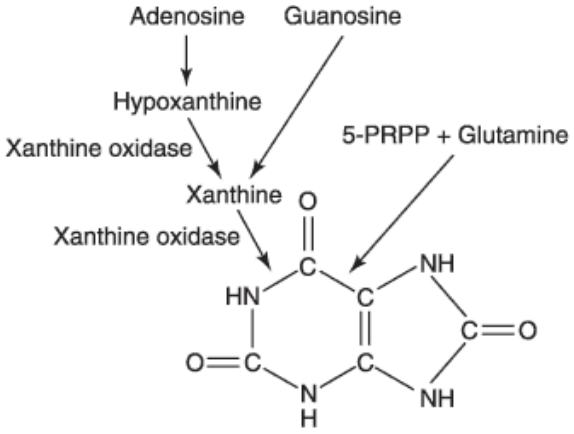
Some of the amino acids are nutritionally essential amino acids, that is, they must be obtained in the diet, whereas others can be synthesised in vivo in amounts sufficient to meet metabolic requirements.

What is uric acid?

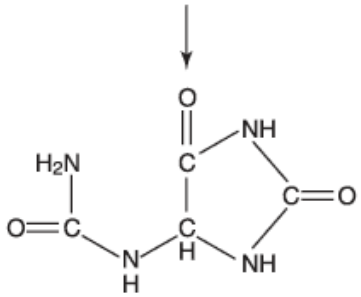
Uric acid is formed from the breakdown of purines. It is freely filtered in the kidneys, 98% reabsorbed and then ~10% secreted in the tubules. Normal blood uric acid level is 0.24mmol/L. Uric acid excretion is halved by going on a purine free diet.

Thiazide diuretics reduce uric acid excretion as does renal disease. Production can be increased by such things as leukaemia and in sepsis with high white cell breakdown.

Xanthine oxidase is competitively inhibited by allopurinol hence reducing uric acid production.
Rasburicase converts uric acid to soluble allantoin which is then readily excreted in the urine.
Colchicine relieves gout by inhibiting the phagocytosis of uric acid crystals by leukocytes.



Uric acid (excreted in humans)



Allantoin (excreted in other mammals)

What are ketone bodies?

Fatty acids can be broken down into acetyl-CoA which can then enter the citric acid cycle. Acetyl-CoA units can condense to form acetoacetyl-CoA and in the liver acetoacetate can be formed. Acetoacetate can be converted to B hydroxybutyrate and acetone. The liver doesn't metabolise these compounds and they enter the circulation. Acetoacetate, B hydroxybutyrate and acetone are called ketone bodies.

Tissues other than the liver can use these compounds for energy. They can transfer CoA from succinyl-CoA to acetoacetate and then metabolise this to CO2 and H2O via the citric acid cycle. There are other pathways as well. The acetone is discharged in the urine and expired in air.

Ketone bodies are normally metabolised as rapidly as they are formed. If Acetyl-CoA entry into the citric acid cycle is depressed by decreased supply of the products of glucose metabolism, or entry is not increased when acetyl-CoA production is increased, then acetyl-CoA accumulates. This leads to more condensation to acetylacetate and then ketone body formation. The ability of the tissues to oxidise the ketones is exceeded and they accumulate in the blood stream (ketosis). Acetoacetate and B hydroxybutyrate are anions of the respective acids. The protons can be buffered only up to a point and then metabolic acidosis occurs.

Deficient intracellular glucose supplies leads to ketoacidosis – starvation, diabetes mellitus and the Atkins diet.

What are the trace elements?

Elements found in tissues in minute amounts that are believed to be essential to life. They are arsenic, chromium, cobalt, copper, fluorine, iodine, iron, manganese, molybdenum, nickel, selenium, silicon, vanadium and zinc.

Digestion and Absorption

What is lactase?

Lactase is an enteric brush border oligosaccharidase that is responsible for hydrolyzing lactose into glucose and galactose so that it can be absorbed. In most mammals, intestinal lactase activity is high at birth and declines with age. In many races, particularly Asians, lactase deficiency can be as high as 100%.
Lactase deficiency results in diarrhoea, bloating and flatulence. Undigested lactose in the bowel is an osmotic load which increases volume in the small bowel and causes diarrhoea. Colonic bacteria break down some of the lactose creating CO2 and H2 gases causing flatulence.
Yogurt is better tolerated than milk as it does contain some bacterial lactase.

How does Na affect the absorption of sugars?

Glucose/galactose and Na share the same cotransporter (SGLT) of which there is SGLT1 and SGLT2. SGLT (mainly 2) is also responsible for glucose transport out of the renal tubule.
Na concentration is low intracellularly, so Na moves down the concentration gradient from the intestinal lumen into the enterocyte using the SGLT. Glucose moves with the Na and is released into the cell. The Na is transported into the lateral intercellular spaces and the glucose is transported by GLUT 2 into the interstitium and then into capillaries.
So this is secondary active transport and the energy for this is provided by the movement of Na out of the cell via NaK ATPase.
The presence of glucose in the intestinal lumen facilitates the reabsorption of Na, hence the physiological basis for the trament of Na and water loss in diarrhoea with oral fluids containing NaCl and glucose.

How is fructose absorbed?

Fructose uses a different mechanism to glucose and galactose. It is independent of Na. It is transported by facilitated diffusion from the intestinal lumen into enterocytes by by GLUT 5 and out of the enterocytes and into the interstitium by GLUT2.

How are proteins digested?

Starts in the stomach where pepsins cleave some of the peptide linkages. Many pepsins are secreted in the stomach as proenzymes (pepsinogens) and are activated by gastric hydrochloric acid. These enzymes are inactived once they hit the relatively alkaline environment of the small intestine. Here, proteolytic enzymes (peptidases) from the pancreas and small intestine take over to liberate amino acids for absorption.

Some dipeptides and tripeptides and actively transported into the intestinal cells by a system requiring H+ and are then hydrolyzed by intracellular peptidases.
There are at least 7 different transport mechanisms for amino acid absorption. Five of these are Na cotransported. Amino acids are then transported out of the enterocytes by a number of different transporters and then enter hepatic blood. Some small peptides also make it into the portal blood.
Protein comes from ingested food (50%) but also from digestive enzymes (25%) and desquamated mucosal cells (25%).
In infants, moderate amount of undigested proteins are absorbed by endocytosis and subsequent exocytosis. This is how protein antibodies (IgA) in maternal colostrum are absorbed. Protein absorption declines with age. Foreign protein ingestion can provoke antibody formation, hence allergic symptoms to some foods. Certain foods are more allergenic than others – mainly seafood, milk, legumes, egg white. Protein antigens are absorbed into M cells that overlie Peyer's patches. The M cells pass these antigens to the lymphoid cells in Peyer's patches and lymphoblasts are actived which subsequently secrete IgA in response to the same allergen.

What happens to water in the GIT?

The GIT is presented with 2000mL ingested fluid/day and 7000mL of water from its own secretions. All of this is reabsortbed except about 200mL which is lost each day in the stool. Water moves in both directions across the mucosa of the small and large bowel in response to osmotic gradients.

What does cholera toxin do?

Cholera vibrio produces a toxin which is absorbed into the enterocyte and binds GTPase inhibiting it. Lack of GTPase results in increased G protein producing prolonged stimulation of adenylyl cylase and a marked increased in intracellular cAMP. Chloride in secreted into the intestinal lumen by protein kinase A which is activated by cAMP. So cholera toxin increases Chloride secretion into the intestinal lumen which drags water and Na with it.
The Na glucose cotransported and Na K ATPase are unaffected, hence the use of glucose and Na containing fluids for resuscitation in cholera diarrhoea.

How is B12 absorbed?

The stomach secretes intrinsic factor which binds B12. This complex is then absorbed in the terminal ileum.

What vitamins are affected by exocrine pancreas deficiency?

ADEK are the fat soluble vitamins. Exocrine pancreas is responsible for lipid digestion and hence absorption, so if this is deficient, ADEK absorption will suffer. Likewise, bile duct obstruction with a lack of bile salts will also adversely affect fat absorption and ADEK.

What is haemosiderin?

Total body stores of iron are regulated by changes in the rate at which it is absorbed from the intestine. Iron is more readily absorbed in the reduced Fe^{2+} state but most dietary iron is in the Fe^{3+} state. Gastric secretions dissolve iron and permit it to form soluble complexes with ascorbic acid for example that aids its reduction to Fe^{2+}. Fe^{3+} reductase is also found in the brush border.
Some of the Fe^{2+} in the enterocyte is oxidized and bound to apoferritin, forming ferritin. This tends to be lost in the stool as the enterocytes are shed.
Fe^{2+} released into the blood binds apotransferrin forming transferrin.
Iron absorption is increased when iron stores are low or erythropoiesis is increased. In iron overload, there is an increase in ferritin in the enterocytes which is then discarded in the shed cells.
Ferritin is also the principle storage form of iron in other tissues. This ferritin may aggregate in intracellular deposits called haemosiderin. Haemosiderin accumulates in the tissues when iron overload is prolonged or severe, producing haemosiderosis. Large amounts can damage the tissues as in haemochromatosis.