15. Energy Metabolism and Temperature Regulation

15.1 Energy Metabolism

Ultimately the body acquires all its energy from outside itself, mostly in the form of food, although thermal energy is also exchanged with the environment. Because energy is neither created nor destroyed,

absorbed food energy = metabolic heat + stored energy
+ external work + energy losses in urine

The *chemical energy of food* can be determined by combusting it with pure oxygen in a bomb calorimeter. Since the final oxidation products of this process are similar to those of human metabolism, at least for carbohydrates and fats, the heat produced by combustion is a measure of the calorific value of the food. The end-products or protein metabolism in man are urea and ammonia, and not the nitrogen or its oxides which are produced in the bomb calorimeter, but a correction can be made for this.

Metabolic Heat

Providing no external work is being performed and body weight is constant, the chemical energy of food is transformed into heat. Even when external work is being done no more than 20% of the total available chemical energy of food is in fact converted to work. It is possible to measure the rate of body heat production (*metabolic rate*) in a whole body calorimeter. However such equipment is not readily available and it is usual to estimate metabolic rate indirectly from respiratory measurements of O_2 uptake and CO_2 production and their ratio, the RQ. For example, the oxidation of 1 mol of glucose requires 6 mol of O_2 and produces 6 mol of CO_2, i.e., the RQ is 1. The total energy produced is 2870 kJ for each mol of glucose utilized. There are thus 480 kJ of energy released for each mol of O_2 involved. For pure carbohydrates, which have an RQ of 1, 21.4 kJ of energy are released for each litre of O_2 measured at STPD that is consumed. This is called the *energetic equivalent of oxygen* and it varies for different substrates. Given the actual RQ and also the urinary nitrogen excretion, the mix of the substrates being metabolized can be estimated and the appropriate energy equivalent of oxygen can be assigned.

For the purposes of comparing individuals the *basal metabolic rate (BMR)* is determined while the subject is resting in a comfortable environment, some 12 h after eating. The BMR is calculated as watts (1 W = 1 J/s) or W/m^2 of body surface because it correlates better with surface area than with weight and height. The resting metabolic rate of a standard 70 kg man is 100 W (equivalent to 1.433 kcal/min, i.e., 58 W/m^2 of surface area), which has been defined as one *met.* Other factors that affect BMR include age, sex, race and disease. It is important that the subject be fasting for at least 12 h because food, particularly protein, increases heat production by its so-called *specific dynamic action (SDA).* Most of this SDA is due to oxidative deamination of amino acids in the liver. Hormones, i.e., adrenaline and thyroxine, also affect the BMR and the determination of BMR was formerly used in the diagnosis of hypothyroidism and hyperthyroidism.

The metabolic rate of a person can increase by as much as fifteen times during severe exercise. Indeed one of the major ways of combating a cold environment is by shivering.

Energy Storage and Utilization

For a given individual, weight remains remarkably constant during adult life and it is clear that there is a very precise control mechanism involved. Over a large population weights vary widely, with a normal distribution. Body composition, however, cannot be determined with the precision that weight can. Thus it is not clear whether or not a constant weight implies a constant composition. The statement that 'within every fat man a thin man is striving to get out' illustrates the concept of a *lean body mass* of muscle, skeleton and essential organs embedded in fat. The lean body mass is related to the amount of regular physical activity whereas the fat represents the stored energy. Fat stores in an average person are equivalent to the amount of energy normally consumed over some 40 days. By comparison carbohydrate stored as glycogen provides for about a day's energy needs and glucose for about one hour's energy needs. The advantage of storing energy in the form of fat is that fat contains about twice as much energy per gram as protein or carbohydrate. Furthermore fat cells contain relatively little water and so the volume in which energy is stored is minimized, and, as we are all aware, there is no apparent limit to the amount of energy that can be stored in this form!

Although the energy stored as carbohydrate represents only about 0.5% of the total, carbohydrate metabolism contributes about half of the basal energy consumed each day. Also, though about 20% of the energy is stored as protein, thee central role of proteins in cellular structure and in skeletal muscle activity precludes the use of these stores to any extent until relatively late in starvation. Without mobility food can not be sought!

Given the preferred role of glucose as an immediate source of energy, and the fact that glucose is stored in cells as glycogen, it is not surprising that several hormones play key roles in regulating carbohydrate metabolism. Principal amongst these are insulin, glucagon, glucocorticoids, adrenaline, growth hormone and thyroxine. Insulin released from pancreatic beta islet cells when blood glucose rises, acts to *lower* blood glucose. It facilitates glucose entry into most cells (other than brain, gut and kidney) and favours carbohydrate storage by stimulating glycogenesis and inhibiting glycogenolysis. In contrast the other hormones, whose secretion is favoured by a decrease in blood glucose (amongst other stimuli), tend to *increase* plasma glucose by collectively inhibiting glucose uptake and facilitating glycogenolysis and gluconeogenesis.

In addition to glucose, metabolism of free fatty acids also provides a substantial proportion of daily energy requirements. Free fatty acids are derived either directly from the diet, or are released from the fat stored in adipose tissue. When plasma glucose levels are high, uptake of fatty acids by adipose tissue is enhanced, as it is by insulin, whereas glucocorticoids inhibit it. Conversely, the release of fatty acids from adipose tissue is inhibited by insulin but stimulated by adrenaline, glucagone and growth hormone. Thus the hormones involved in regulating blood sugar also regulate fat metabolism.

Finally, a dynamic balance is also maintained between protein and amino acid metabolism. Amino acids absorbed in the GIT are resynthesized into new proteins to replace those continually being broken down. This process is stimulated by growth hormone and insulin. In addition some of the amino acids are converted, principally in the liver, to glucose via a variety of intermediates (gluconeogenesis). Once again, glucagon, glucorticoids and growth hormone favour this process, while insulin opposes it.

There is, therefore, a dynamic balance, finely regulated by a variety of hormones, between catabolism and anabolism. When energy is readily available, as after feeding, blood glucose and amino acid levels tend to rise, insulin is secreted and cellular uptake of glucose, glycogenesis, protein synthesis and fat storage are favoured. The secretion of glucagon is suppressed and so too may be that of glucocorticoids, growth hormone and adrenaline. Conversely, when an animal is deprived of food, blood glucose falls, insulin secretion is depressed, and glucose uptake by most cells is inhibited ensuring that what glucose is available is supplied to the cells of the brain. In addition, the hypoglycaemia stimulates secretion of glucagon and perhaps also glucocorticoids, growth hormone and adrenaline. Consequently glycogenolysis and gluconeogenesis are stimulated, increasing the supply of glucose, and fatty acids are released from adipose tissue providing an alternative source of energy to cells deprived of glucose. Furthermore, the sensation of hunger is aroused and food intake thereby encouraged.

Summary of Energy Storage and Utilization

Absorptive State

Energy source for most tissues is glucose.

Energy storage occurs in:

1. Liver and muscle as glycogen and in adipose tissue as triglycerides obtained from:

(i) ingested triglycerides

(ii) triglycerides synthesized from glucose in adipose tissue

(iii) triglycerides synthesized from glucose and amino acids in liver and transported to adipose tissue.

Postabsorptive State

Brain is an obligate user of glucose which is provided in the short term by glycogenolysis and in the long term by gluconeogenesis.

Glycogen in liver gives glucose. Glycogen in muscle gives lactate which in liver gives glucose. Also, amino acids and glycerol in liver give glucose.

Other tissues undergo glucose-sparing reaction and utilize free fatty acids and ketones for their energy needs.

Control of Food Intake

It is generally held that energy intake rather than energy expenditure is regulated to maintain a steady state. Though such regulation has been described in terms of hypothalamic 'satiety' and 'hunger' centres, a more complex picture is emerging. Between meals blood glucose remains remarkably constant, reflecting neural and endocrine matching of hepatic glucose production to peripheral uptake. Sympathetic and parasympathetic pathways from glucose-sensitive neurones in the nucleus solitarius and the vagal nuclei to the endocrine pancreas and adrenals seem to be primarily involved in the neural contribution.

Feeding is initiated by a complex interaction of factors. Experimentally, a fall in blood glucose can be demonstrated several minutes before feeding begins, and this fall may be detected by neurones in the *lateral hypothalamus.* This area also receives a wealth of olfactory, gustatory and visual inputs and is believed to be responsible for initiating food intake. In contrast, the *ventromedial hypothalamic area* appears to regulate the utilization and restoration of body fat stores. When this area is activated sympathetic outflow inhibits pancreatic insulin secretion and stimulates lipolysis in adipose tissue. Destruction of this area, therefore, raises plasma insulin concentration and inhibits lipolysis leading to increased food intake, increased body fat, weight gain and obesity. It is unclear what normally controls the activity of this area and therefore determines the balance between lipolysis and lipogenesis. However it is suggested that the availability of glucose to cells in the area may be critical. With glucose availability diminished, insulin secretion would be inhibited and lipolysis favoured. With sufficient glucose, insulin secretion would be stimulated and lipogenesis would predominate.

Though the lateral hypothalamic area initiates feeding, the amount of food eaten is determined by a variety of factors. These include the palatability of the food and the presence of food in the mouth, stomach and intestine, as well as a range of psychological and learned responses. Eating normally ceases *before* much of the ingested food has been absorbed. Other regions of the CNS also affect food intake.

Obesity

People are regarded as being obese if their adipose tissue is more than 30-40% of the total body weight. The causes of obesity are obscure. Genetic factors play a role in certain strains of obese animals. Hormonal disturbances can sometimes cause obesity. For example, it is common in eunuchs, in hypothyroidism and in hyperadrenocorticalism. The psychological factors are the main cause of obesity. Eating habits are a learned phenomenon and cater for a multitude of sensory and emotional needs over and above energy balance. Obesity is a health hazard because it predisposes to cardiovascular disease and diabetes mellitus.

15.2 Temperature Regulation

Life is a low temperature phenomenon existing in a universe in which temperatures range from near absolute zero to greater than 10^6K. The rate of chemical reaction varies with temperature, increasing about 2.5-fold for each 10 °C rise. However at temperatures above 45 °C the enzymes that catalyse living reactions lose their structural integrity and are said to be denatured. Unlike lower animals which do not regulate their body temperature (*poikilotherms*), mammals and birds derive and advantage by maintaining their body temperature constant (*homoiotherms*) and close to denaturing temperatures. Enzyme reactions of the body function optimally within a narrow range. Conscious intelligence requires an even narrower range of approximately 35-42 °C. Body temperatures below 35 °C are associated with loss of memory and body temperatures greater than 42 °C with delirium and hallucinations.

Heat and Temperature

The concepts of heat and temperature must be clearly distinguished. *Heat* is a form of energy and is measured in joules (J) or in calories (1 kilocalorie = 4184 joules). *Temperature* is a measure of the average kinetic energy per degree of freedom of the constituent molecules. As it is an average, the concept of temperature can only be applied to objects consisting of a large number of molecules.

The *specific heat capacity* is the amount of energy required to be added per unit amount of material to raise the temperature by one unit. At 37 °C the addition of 4.1780×10^3 joules of energy to 1 kilogram of water will raise its temperature by 1 degree (Kelvin or Celsius), i.e., the specific heat capacity of water at 37 °C is 4.1780 kJ/kg. The specific heat capacity of body tissue is about 85% that of water, i.e., 3.6 kJ/kg.

The velocity with which molecules move is dictated by their thermal energy in relation to any attractive forces between molecules. Each change requires an addition of thermal energy (*latent heat*), but while the change is occurring the temperature remains constant. Thus to melt ice 333.7 kJ/kg of thermal energy (*specific heat of fusion*) is required. The evaporation of water requires 2.257 MJ/kg (*specific heat of vaporization*).

Heat Transfer

Heat is lost from the body through (i) conduction, convection, radiation and evaporation of water from the skin, (ii) evaporative loss and direct warming in the upper respiratory tract, and (iii) urination and defaecation. During the resting state about 50% of heat is lost by radiation, about 15% by conduction and convection and up to 30% by evaporation from the skin. Heat lost by respiration and in urine and faeces accounts for about 5%.

Conduction

Within a volume of material the random movement of the molecules results in molecular collisions. These partition the kinetic energy amongst the molecules. In this way the thermal energy diffuses from areas of higher heat concentration, i.e., higher temperature, to those of lower. This is the process of *heat conduction.* Materials differ in the velocity of heat conduction and they can be compared under standard conditions.

Thermal conductivity is the flux of energy per second through a slab of material 1 m^2 in area when the temperature gradient is 1 °C over a distance of 1 m. The units of thermal conductivity are therefore J/sm^2 (°C/m) which reduces to J/sm°C or W/m°C. The thermal conductivity of a slab of fat or muscle is about the same as that of cork.

Thermal insulation (i.e., thermal resistance) is the inverse of thermal conductivity. It is the temperature difference across the slab defined above which will drive unit heat flux and has the units °Cm/W. Those interested in clothing insulation find it more convenient to use the unit called *clo.* The value of 1 clo has been arbitrarily set at 0.155 m^2/W. This enables the insulation of clothing to be given in clo per cm thickness. Clothing with the insulation of 1 clo (about that of a business suit) will maintain a standard 70 kg man, whose metabolic rate is about 100 W, comfortable indefinitely while sitting at rest in an environment of 21 °C, a relative humidity less than 50% and an air movement of 10 cm/s.

Convection

External transfers. A warm object surrounded by cooler fluid transfers heat to the adjacent fluid by conduction. In addition, as the fluid warms it expands lowering its density, and an ascending flow, termed *natural convection,* results. Fluid flow resulting from wind or movement of the object is *forced convection.*

However produced, flow over the skin surface will modify heat transfer between the body and the environment. The amount transferred will depend on the specific heat capacity of the fluid, the total volume flow and the degree of stirring which enhances he removal of heat from the surface. The specific heat of water is 1000 times greater and its heat conductance twenty-five times greater than that of air.

Internal transfers. As most of the body has a very low thermal conductivity its core would become very hot if heat were not redistributed by blood flow. Heat transfer depends on intercapillary distance, thermal conductivity, blood flow per mass of tissue and specific heat capacity of the blood.

Radiation

All molecules, unless at absolute zero temperature, are continuously emitting quanta of energy in the form of electromagnetic energy. They are simultaneously absorbing such energy. In this way energy is transferred at a distance without collision between molecules. The quantity and wavelength of the radiated energy depend on the absolute temperature of the object and also on the ability of the surface to emit radiation, i.e., the emissivity. As the temperature rises the wavelength of the radiated energy falls and, with small temperature differences within the physiological range, the net energy exchange by radiation is directly proportional to the temperature difference.

The quality of the surface determines the fraction of the incident energy which is absorbed and the fraction of the maximum possible radiant energy which is actually emitted. An efficient emitter is also an efficient absorber. The *emissivity* is a measure of this efficiency and is rated as 1 for a surface absorbing all incident radiation (a 'black body') whereas a perfect reflector absorbs no energy and emits no energy, having an emissivity of 0. All real surfaces fall between these. Very dark skin absorbs about 82% of incident solar radiation while very fair skin only 65%. This is modified by any clothing that is being worn.

Not all of the surface area of the naked human body is available to radiate energy. The *effective* surface area varies as body posture changes. The net radiant energy loss is 49 W from a 70 kg person, whose effective surface area is 1.5 m^2 with a skin temperature of 33 °C in an environment at 29 °C, and this is about half of the resting heat production (100 W).

Body Temperature

There is a range of temperatures from the body core to the hands and feet, and core temperature can also vary. Nevertheless over a wide range of environmental conditions there is remarkably little variation in core temperature. This constancy implies a very precise control of heat balance.

Core Temperature

There are only very small temperature differences between the main internal organs and it is their temperature that is referred to as deep body temperature or *core temperature,* usually measured in the rectum. Body temperatures obtained from the mouth and axilla are about 0.5 °C lower than rectal temperature and show greater variation. There is normally a diurnal variation in core temperature, the temperature being the highest in the evening (37.3 °C) and lowest in the early morning (35.8). In females core temperature varies during the menstrual cycle, being about 0.5 °C higher in the latter half of the cycle.

Peripheral (Shell) Temperature

Skin temperature is somewhat less than core temperature and varies much more widely. The extremities have a large surface area relative to their mass. Other than active muscle their only endogenous heat source is the blood flowing from the trunk. The volume of the limb which remains close to the core temperature depends on the size of the heat load. When cold environmental conditions favour heat loss, the core is restricted to the head and trunk, and the shell includes a large proportion of the limb volume. The total body heat content is reduced and if it were evenly distributed core temperatures could fall to unacceptable levels. When total body heat content is high, increased blood flow enlarges the volume of the core.

Thermal Comfort and Thermoneutrality

Thermal comfort is a conscious experience. It is a mental phenomenon elaborated by the nervous system from a variety of inputs related to temperature. It is an awareness of the thermal state plus an emotional content. Thermoregulatory centres in the hypothalamus monitor central core temperature and receive inputs from peripheral thermal receptors. Thermal comfort provides the motivation for thermoregulatory behaviour. The temperature chosen by a subject as comfortable is the *preferred comfort zone,* which covers a very narrow span. It is that combination of air temperature, air movement, humidity and radiation intensity that leads to a skin temperature of about 33 °C. It is this skin temperature that is aimed at by varying clothing or environmental factors. For lightly clothed sedentary adults the preferred ambient temperature is about 21 °C when air movement is less than 30 cm/min and relative humidity less than 50%. The elderly and infirm who have reduced thermal responses require a higher minimal temperature.

Below a certain *critical temperature* the metabolic rate rises linearly as temperature is lowered further. This rise, reflecting the activity of skeletal muscle and other mechanisms is sufficient to maintain deep body temperature until the total body heat loss becomes too great. Then core temperature begins to fall as the *zone of hypothermia* is entered, and regulation is lost. With increasing environmental temperatures above the critical temperature, the metabolic rate remains steady and minimal until at an upper limit the rate rises again. Here the *zone of hyperthermia* is reached as body temperature rises and regulation is lost. The range of environmental temperatures in which the metabolic rate is minimal and steady defines the *thermoneutral zone.*

Thermoreception

The skin, mouth and pharynx contain thermal receptors (*peripheral thermoreceptors*), the signals of which reach consciousness. There are both warm and cold thermoreceptors. As well as the superficial receptors there is evidence for *deep body thermoreceptors* located within the oesophagus, stomach and perhaps duodenum and possibly in the intra-abdominal veins.

Thermoregulatory responses in a variety of animal species can be elicited by local thermal stimulation of various areas in the CNS - the spinal cord, medulla oblongata and mid-brain reticular formations and most importantly the *preoptic-anterior hypothalamic region.* From this latter region maximal responses to both warming and cooling can be obtained. It seems to act as a thermostat as far as core temperature is concerned, causing cooling or heat retention as necessary.

The thermal drives from various parts of the body may interact synergistically or antagonistically. For instance during heavy exercise in cold weather, skin temperature can be low at the same time as heat production is high and core temperature is above resting levels. Thus information from temperature-sensitive neurones in the hypothalamus is combined with information from other parts of the body. These combinations can alter the threshold temperature of the hypothalamus at which thermoregulatory responses occur. As well as this combined information can modify the sensitivity of the hypothalamus to the input and thus the briskness of the reflex response. However if core temperature moves significantly away from normal the hypothalamic responses increasingly dominate.

Thermoregulatory Effectors

Short-term control is initiated via efferent nervous pathways both somatic and autonomic.

Shivering Thermogenesis

This is an involuntary contraction of skeletal muscle fibres which can rise the metabolic rate three-fold and is controlled from the hypothalamus. The muscle activity produced commences in the upper half of the body as a gradual increase in contraction of muscle fibres and can extend to the whole body. As shivering becomes more intense, cyclical muscle rigors at the rate of 10-20 per s appear. Purposeful movement inhibit shivering.

Non-Shivering Thermogenesis

Under cold stress there is an increased discharge of the sympathetic nervous system. One consequence of this is lipolysis which in the case of white adipose tissue increases plasma glycerol and free fatty acids. The free fatty acids are then available as energy sources for skeletal muscle and myocardium. In the new-born there are also deposits of highly vascular brown fat situated between the scapulae and around the intra-abdominal vessels. Brown fat itself metabolizes the free fatty acids generating heat which is distributed to the rest of the body via the blood. In the new-born this, rather than shivering, is the principal means of increasing heat production and this non-shivering thermogenesis can increase metabolic rate to about two-and-a-half times resting value. As a healthy baby can produce heat only at about 0.34 kJ/kgmin, it requires help to reduce heat loss which immediately after birth, while it is still wet, can reach 0.8 kJ/kgmin.

Although cooling the preoptic region of the hypothalamus in animals has been shown to increase the rate of secretion of thyroid hormone, the effect in adult humans is uncertain. Variations in thyroid function do not seem to play a part in long-term adaptation to cold environments but pathological alterations in thyroid function certainly alter heat production.

Cutaneous Heat Transfer

For heat to be lost from the body it must be conveyed by the blood to the skin. If skin temperature is below the ambient temperature, heat can be lost by conduction, convection and radiation. If it is above ambient temperature heat can only be lost by evaporation of sweat. Blood flow to the skin is therefore important not only to provide the heat but also the water for sweat.

During exercise cutaneous vasodilatation is confined to the profusely sweating areas of head, trunk and proximal limbs, while blood flow in distal portions of limbs does not alter much. This may assist in the maintenance of blood pressure during exercise.

Cutaneous veins have a specialized function in thermoregulation. Their calibre is under noradrenergic sympathetic control and varies directly with heat load. The pathway for blood returning from the limbs can be either superficial or deep veins. In cold conditions it is predominantly in the deep veins and this permits transfer of heat directly from artery to vein thus preventing heat loss from reaching body surfaces. This is a *thermal counter-current system* for heat conservation.

Sweating

This is an active secretory process from eccrine sweat glands which are widely distributed over the surface of the body. They are innervated by sympathetic postganglionic cholinergic fibres and produce a hyposmotic secretion. Their activity is blocked by atropine, the administration of which can lead to elevated body temperature.

Sweating can result in a fluid loss of as much as 1 litre per hour. This can rapidly diminish body water and electrolyte content and if these are severely depleted the rate of sweating diminishes and body temperatures can rise to fatal levels. For effective heat loss complete evaporation is needed. Therefore sweating becomes more obvious but is less effective as environmental humidity increases.

Fever

During continuous exercise and at a time when energy balance has been achieved, the core temperature can be elevated by as much as 1°C. However, the subject has little sense of discomfort. The sensation of discomfort seems to be present when heat balance has not been achieved and actual temperature and set-point are different. The degree of discomfort is related to the size of the discrepancy. The set-point can be altered physiologically during exercise. The elevated temperature continues until recovery from the exercise is complete.

A variety of substances resulting from infections (pyrogens) can elevate the set-point. The subject, even though body temperature is still normal, feels cold. Peripheral vasoconstriction and shivering then ensures that heat balance is re-established at a higher temperature. This is called fever or *pyrexia.* Aspirin lowers the temperature and, since it also inhibits prostaglandin synthetase, prostaglandin appear to be involved in the mechanism of temperature regulation. Where the cause of the fever is removed the excess heat which has been gained is then lost through vasodilatation and sweating.

Excessive temperatures can also arise following damage to the CNS, from excessive heat production related to varieties of muscular dystrophy and from failure of the heat loss mechanism such as in dehydration.

Survival and Temperature

Body temperature above 40°C cause heat stroke, mental confusion and unconsciousness; temperatures below 34°C give rise to amnesia and also to unconsciousness. Lowering cardiac temperature below 30°C causes arrhythmia and then cardiac arrest. However, if the circulation is externally supported, the heart can survive for a period and functions well on rewarming. In fact the whole body can be cooled to 10°C with consequently no circulation and yet with a very high probability of unimpaired survival on rewarming. Cooling of individual organs and tissues is deliberately used to permit survival in the absence of circulation.