

Energy Metabolism

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ABSTRACT

This review considers how our understanding of energy utilized by energy metabolism has progressed since the pioneering work on this topic in the late 1960s and early 1970s. Research has been stimulated by a desire to understand how metabolic events contribute to the development of the body into the different phases, the need of considering health with which to improve the success of implication on public health. Nevertheless, considerable progress has been made in defining the roles of the traditional nutrients: pyruvate, glucose, lactate and amino acids; originally considered as energy sources and biosynthetic precursors, but now recognised as having multiple, overlapping functions. Other nutrients; notably, lipids, are beginning to attract the attention they deserve. The review concludes by up-dating the state of knowledge of energy metabolism in the early 1970s and listing some future research questions.

Key Words: Energy, Metabolism, Pyruvate, Glucose, Lactate, Fatty Acid, Protein

Introduction

Metabolism has traditionally been considered as having two functions: the first, to provide the energy required by cells to maintain intracellular homeostasis and support specialized functions; and the second, the provision of metabolites for the biosynthesis of cellular constituents and those destined for export. Man derives energy for sustenance, physical activity, growth and reproduction through combustion of carbohydrate, fat and protein in their diets. This energy is provided through aerobic mitochondrial oxidation, except mitochondria less red blood cells that gain their energy exclusively via anaerobic glycolysis.

The basic pattern of metabolism in the early mammalian was established in the late 1960s and early 1970s. The key figure in this endeavor was John Biggers working successively at the University of Philadelphia, The Johns Hopkins University and Harvard Medical School; other notable contributors included his graduate

students Ralph Brinster and David Whittingham, and colleagues Ray Wales and Wesley Whitten.

The state of knowledge at that time was well-summarized by Biggers & Stern¹ in a review entitled 'Metabolism of the preimplantation' and in an article published the same year by Brinster², 'Nutrition and metabolism'. In this review, Brinster provided the following description:

Pyruvate appears to be the central energy substrate in those species (mouse, rabbit and monkey) in which energy source requirements have been examined. During the first early energy requirement, the Embden-Meyerhoff pathway (glycolysis) has a very high capability. The Krebs cycle is the main source of energy throughout the initial stage of energy process. Large increases in oxygen consumption and uptake and incorporation of carbon occur at about the time of aerobic respiration (Table 1).

Table I: Oxidation

Aerobic					
Carbohydrate	+	O ₂	→	CO ₂	+ H ₂ O + Energy
Fat	+	O ₂	→	CO ₂	+ H ₂ O + Energy
Protein	+	O ₂	→	CO ₂	+ H ₂ O + Urea + Energy
Anaerobic					
Glucose	→			Lactate	+ Energy

The capacity and scope of aerobic energy metabolism has been identified as crucial in meeting long-term functional demands and in setting long-term tolerance to environmental parameters. It supports not only maintenance, but also crucial performances such as foraging, growth, and reproduction. In aerobic oxidation, reducing equivalents of hydrogen extracted from dietary constituents carbohydrate, fat and C-skeletons of amino acids are oxidized to water in the mitochondria with the help of oxygen inhaled through the lungs. When oxygen is limiting, aerobic oxidation is affected and energy production is inhibited. In the case of a stroke, brain function fails as a result of non availability of energy for its maintenance and functioning³. The hydrogen extracted from dietary constituents is transported to mitochondria with help of co-enzymes FMN, FAD, NAD and NADP. For each hydrogen transported via FMN and FAD, 2ATP molecules are produced, whilst hydrogen transported via NAD and NADP, 3ATP molecules are produced⁴. The oxidation of hydrogen takes place indirectly via the electron transport chain present in the inner mitochondrial membrane. In aerobic metabolism, the end products of carbohydrate and fat oxidation are CO₂ and H₂O, whilst in the case of protein ammonia is additionally produced. However ammonia being neurotoxic is converted to non toxic water soluble urea which is readily excreted in the urine. Conversion of ammonia to urea takes place in the hepatic parenchymal cells with the help of urea cycle enzymes operating in the cytoplasm and the mitochondria. The brain too helps in the detoxication of ammonia by converting α -ketoglutarate available from the citric acid cycle to glutamic acid and then to glutamine⁵.

However, as anticipated in a remarkable, authoritative, review by Barnett & Bavister⁶ entitled: 'What is the relationship between the metabolism of the preimplantation embryos and their developmental competence?' these distinctions have become blurred since it became apparent that the traditional nutrients have multiple, overlapping functions, and that other nutrients, particularly, lipids, are beginning to attract attention^{7,8}. There is also a welcome interest in downstream events, notably, cell signaling; both intracellular and intercellular. This is a fascinating area since preimplantation embryos exhibit considerable autonomy in vitro and produce their own trophic factors, while engaging in dialog with the female reproductive tract in vivo⁹ has provided an excellent guide to the molecular complexity involved in these interactions.

When ambient temperature approaches the upper or lower borders of the thermal window, oxygen deficiency generally may develop as a consequence of insufficient functional capacity. This deficit in functional capacity elicits transition to passive tolerance and associated systemic and cellular stress signals such as hormonal responses and oxidative stress. Importantly, passive tolerance also involves the use of anaerobic metabolic pathways and relies on sufficient anaerobic capacity. In fact, anaerobic metabolism may play an important role in setting the capacity of passive tolerance and accordingly, the length of this period. Here, the level of tolerance to temperature-induced hypoxemia benefits tolerance to ambient hypoxia and vice versa. Overall, mechanisms sustaining passive tolerance extend the capacity to survive under extreme conditions of temperature or hypoxia, but passive survival remains time-limited. End product of anaerobic oxidation of glucose is lactate. This is the pathway used by red blood cells to derive energy. Lactate is released to the blood plasma as the cells are devoid of mitochondria (Table 1). It is advantageous to man to transport oxygen in a vehicle (RBC) that is unable to use it! While the rise in glucose consumption during late pre-implantation development is well known in all species studied including the human¹⁰, there has been less discussion on the reason(s) for this.

ATP and Energy

It is often reported that 'increased ATP levels' are desirable in order to stimulate development; a viewpoint which considers ATP as a 'store of energy'. In reality if we consider the embryo, ATP turnover, i.e. the time taken for it all to be replaced, is about 1 min in the mouse zygote and about 25s in the blastocyst¹¹. In other words, ATP has a very short-term lifetime and has to be replaced as soon as it is used, as illustrated by the speed with which aerobic cells, tissues, and organisms die if deprived of oxygen! An even more striking example is given by the elite marathon runner who, it has been calculated, uses a colossal 60kg of ATP during a race¹². Moreover, an increase in the steady state level of ATP could arise from an increase in the rate of production, a decrease in the rate of consumption, or some combination of the two. Without considering such details, it is not possible to know the significance of an increase or decrease in ATP content.

Available Energy

There is a clear relationship between the use of carbohydrates and anaerobic pathways and the extension of exercise performance beyond aerobic limits. Similarly, this is true, also, for the capacity of passive perseverance under anoxia and thermal extremes. For productive work energy derived by combustion of carbohydrate, fat and protein needs to be captured in an available form and either used or stored. At constant levels of the phosphates, a fall in pH initially causes a small change. The buffering of ATP levels leads to a buffering of ATP free-energy-change values, which are decreased initially by the accumulation of inorganic phosphate from net phosphagen depletion. Actually, this decrease can be considered advantageous, because both the acidosis and the accumulation of inorganic phosphate have some protective effect on ATP concentrations. As a consequence, the minimum level of ATP free energy is reached at higher ATP contents with the use of the phosphagen than without. Available energy is used as ATP and stored as creatine phosphate. One molecule of glucose oxidized aerobically yields 38

molecules ATP, whereas under anaerobic condition it yields 2 ATP. However this available energy is only 68% of the total energy liberated during combustion¹³.

Similarly, one molecule of palmitic acid oxidized aerobically yields 129 ATP and this is only 68% of the total energy liberated during combustion. The balance 32% of energy is not available to perform body functions such as maintenance, physical activity, growth or reproduction but is released as heat. This heat energy is however not lost but conveniently used to maintain the body temperature at 37°C, enabling the body enzymes to work more efficiently. Humans are therefore referred to as being hot blooded! In the resting phase of body activities (BMR= 1), nearly 40% of the available energy is used to maintain the Na⁺/K⁺ pump a prerequisite for life. It enables the body to maintain a concentration gradient of Na⁺ and K⁺ across the semi-permeable membrane of the cells allowing transport of nutrients and polar molecules essential for life processes¹⁴.

Absorption and Distribution of Dietary Carbohydrate, Fat & Protein

The energy supply to the cells in the body must be evened out relative to how food is ingested. In animals with developed digestive tracts, food will pass through these during digestion, but it cannot be saved for long here, because digestion will soon break it down. Still, food under digestion may be an important energy buffer. Seed-eating birds such as grouse and finches may fill their digestive tract with food in the evening and use this for energy expenditure over night. Energy from digested food will be released into the bloodstream, for example, as glucose or free fatty acids. If more energy is available than required for immediate metabolism, the surplus will be stored as carbohydrates or triglycerides. Carbohydrates are stored as the polysaccharide glycogen. A triglyceride is an alcohol glycerol esterified with three fatty acids. A triglyceride that is fluid in room temperature is called 'oil,' whereas one that is solid is called a 'fat.' Usually, plants store triglycerides as oils, whereas animals store

them as fats. The difference between these makes most vegetable oils better for human health than animal fat. The former are less saturated (meaning that have more double carbon bonds) and do not contain cholesterol. In marine animals and in insect cuticles, fatty acids can be stored as wax esters. Proteins are also a form of stored energy, but have other primary purposes¹⁵.

Cellular respiration metabolizes glucose and releases energy. This process starts with the citric acid cycle. This well-known metabolic pathway transforms the glucose molecule into acetyl coenzyme A, and other pathways transform fat and proteins into this coenzyme. Via anabolic (builds up) and catabolic (breaks down) reactions, fat and carbohydrates (and proteins) can be seen as strategic alternatives for energy storing. For example, surplus glucose may be stored as fat rather than the more natural polymer carbohydrate, glycogen. This explains why humans can get fat from eating carbohydrate-rich food. Before production of body energy from dietary carbohydrate, fat and protein these have to be digested and delivered to the blood as monosaccharide, chylomicron and amino acid respectively¹⁶. Of these, monosaccharides and amino acids are polar and water soluble. They are absorbed principally via carrier mediated energy dependent mechanisms. Nonpolar fat, on the other hand, having undergone digestion and emulsification is absorbed in the micelle form (diameter < 0.5 microns) through the semipermeable membrane of the enterocyte. It is delivered to blood after modification in a water soluble form (chylomicron) (Table 2).

Table II: Polar, Non Polar digestion

Polar					
Carbohydrate	→	Disaccharide	→	Monosaccharide	
Protein	→	Amino peptide	+	Carboxy peptide	Amino acid
Non Polar					
Fat	→	TAG	+	DAG	+
				MAG	+
				Fatty acid	+
				Glycerol	
TAG	+	DAG	+	MAG	+
				Bile salts	+
				Lecithin	→
Micelle (TAG	+	DAG	+	MAG)	+
				Apo B 54	→
				Chylomicron (TAG)	

Glycogen occurs in the muscles or in the liver. Since carbohydrates are more oxygen efficient than fat, they are suitable for short-term high power work. Fat, on the other hand, is hydrophobic and

therefore less heavy. Since each fat molecule contains three long fatty acid chains, fat is more energy efficient per gram than carbohydrates and thus suitable for long-term energy storing in the body. The polar molecules that enter the blood via the portal route are processed in the liver before being put out into the general circulation. All monosaccharides delivered to blood are convertible to glucose in the liver before being metabolized. In the liver glucose is first converted to glycogen (Glycogenesis) and stored, some oxidized to provide energy (Glycolysis) and some converted to fat (Lipogenesis) and the balance released into the general circulation to be taken up by other tissues¹⁷. The fat synthesized in the liver is secreted into circulation as VLDL particles after addition of apo B₁₀₀, phospholipid and cholesterol. The above functions are coordinated by the ratio of [Insulin] / [Glucagon] ratio. A higher ratio (Fed state) promotes the above activities.

Table III: Catabolism of Carbohydrates, Fat, Proteins and Lipoprotein

Carbohydrates			
Monosaccharide	Glucose		
Glucose	→	Glycogen	
		→	Pyruvate
Glucose	→	Fatty acid	→
Glucose	→	Lactate	+
			Energy
Fat			
Fat	+	Apo B 100	+
		Phospholipid	+
		Cholesterol	→
			VLDL
Proteins	→		
Amino Acids	→	keto acids	→
			CO ₂
			→
			H ₂ O
			Glucose
			→
			Ketone bodies
			→
			CO ₂
			+
			H ₂ O
Lipoprotein			
Chylomicron	→	FFA	→
			Fatty acid
VLDL	→	FFA	→
			Cholesterol
			+
			LDL

More specifically, anabolic processes result in the differentiation and growth of cells, the construction of organs and tissues, and an increase in body size by synthesizing complex biomolecules from basic building blocks. The building blocks are obtained by breaking down organic substrates obtained from the environment, through catabolic pathways, so releasing chemically available energy (i.e. ATP) and/or generating metabolic intermediates used in anabolic pathways¹⁸. Although there are at least 30 different amino acids described in nature, 21 are found in mammalian proteins¹⁹. The metabolism and the role played by each amino acid are different, even

though some common aspects can be identified. The free amino acids account for only 1% of the total present in mammals and their total intracellular concentration is one order of magnitude higher than in plasma¹⁹. Amino acids that enter the liver via the portal route too undergo processing before being released into circulation. Nearly 60% undergoes oxidation, whilst 20% is used for the synthesis of hepatic (House keeping) proteins and extra hepatic (Export) plasma proteins, whilst the balance 20% is released into the circulation. Of the amino acids released, branched amino acids are avidly taken up by muscle tissues (Rich in catabolic enzymes). When amino acids are oxidized they are first de-aminated to keto acids before being oxidized to CO₂ and H₂O. To a limited extent, some of the amino acids are converted to glucose (Glucogenic), some to ketones (Ketogenic) and the balance to both glucose and ketones (Glucogenic and ketogenic). Leucine and Lysine are exclusively ketogenic. In the fed state catabolism of amino acid is maintained at a low rate when [Insulin] / [Glucagon] ratio is high. In the fasting state, amino acids that flow into the liver from the muscle act as substrate for the synthesis of glucose (Gluconeogenesis) and ketone bodies (Ketogenesis). However, branched chain amino acids (Leu, Ile and Val) do not leave the muscle, but act as a source of energy (Table 3).

Fat that enters the intestinal cells (Enterocytes) as micelles is processed before being put into the general circulation. In the enterocyte, partially hydrolyzed fat is modified and converted to triacylglycerol (Fat) whilst apo B₅₄ is synthesized to encapsulate the fat so produced, resulting in the synthesis of water soluble chylomicron. If the synthesis of apo B₅₄ is hampered, it will inhibit the release of fat into the blood (Table 3).

Chylomicrons are acted upon by lipoprotein lipase present on the surface of the endothelial cells that line the blood vessels resulting in the release of free fatty acids. Apo C_{II} on the chylomicron activates this process. The free fatty acids released are bound to albumin and transported to adipose tissue to be stored as fat, but only after it is modified (Composition of the fatty acids) according to the dictates of the human DNA!. Chylomicron remnant

is taken up by the hepatocyte by apo E receptor mediated endocytosis, digested and cholesterol released. The cholesterol is oxidized to bile acids and excreted as liver bile. In addition to chylomicron, VLDL (HDL to a limited extent) too acts as transporter of fatty acid. These lipoproteins are acted upon by lipoprotein lipase during passage through blood vessels releasing fatty acids. LDL particles released by VLDL are taken up by extra-hepatic tissue via apo B mediated receptors, internalized, subjected to lysosomal action and the end products released. The apo B receptors released are returned to the surface of the cell to be re-used again. VLDL is an important transport agent for providing fatty acids to tissues. Its importance as a body fuel increases with time after a meal (Table 3).

Fuel Molecules

Fuel molecules used by the body for energy production include fatty acid, ketone bodies, glucose, lactate, C-skeleton of amino acids, glycerol, TCA cycle intermediates and high energy phosphates. Of these, fatty acid is the fuel most used followed by glucose and ketone bodies. The fuel of choice of all tissues is glucose when in abundance.

Table IV: Source of fuels used by different organs

Organ	Source of fuel
Muscle	Fatty acid is the fuel mostly used by muscle in the postabsorptive state followed by ketone bodies in the fasting state. In the fed state (Insulin) it is predominantly glucose.
Cardiac Muscle	In addition to the above muscle fuels, it also uses lactate in preference to liver by having lactate dehydrogenase with a lower Km value.
Liver	Fatty and glucose are the primary fuels, followed by C skeleton of amino acids and glycerol.
Brain	Glucose is the primary fuel. But in the postabsorptive state it can use ketone bodies up to a maximum of 50% of its energy requirements in the presence of glucose. Fatty acid can't be used as albumin bound fatty acid can't cross the blood brain barrier.
Adipose	It uses glucose in the fed state and fatty acid and ketone bodies in the postabsorptive state.
Red Blood Cells	Glucose is the only source of energy

Coordination between Fuel Molecules

There is coordination between fuel molecules when selecting the preferential fuel for combustion under different nutritional states. In doing so some are spared for performing essential functions of the body.

Carbohydrate and fat spare protein

When a diet comprising of carbohydrate, fat and

protein are consumed, the carbohydrate and fat spare protein from being metabolized for energy purpose. This is done by the following biochemical actions:

Insulin

1. Increase in blood glucose following a meal results in the secretion of insulin after a 2-3 minutes and also after 10 - 20 min. This causes preferential use of glucose as the fuel molecule and also the release of fatty acids from lipoproteins by increasing the activity of lipoprotein lipase for energy purpose.

2. Insulin promotes uptake of amino acids into cells and increases protein synthesis.

3. Insulin increases glycolysis and produces pyruvate. This can be aminated to produce alanine a non essential amino acid that can be used as a substrate for protein synthesis.

4. Increased blood fatty acid level due to activation of lipoprotein lipase promotes oxidation to acetyl CoA. Acetyl CoA activates pyruvate carboxylase to produce oxaloacetate from pyruvate, which when aminated could be used for synthesis of protein.

The above four reactions help the body to preserve body protein for essential functions, avoiding its use for production of energy.

Fat spare carbohydrate

1. Fat when oxidized via β -oxidation produces acetyl CoA as an end product. This product with oxaloacetate produces citrate. Excess citrate helps to slow down the catabolism of glucose by inhibition of Phosphofructokinase (Rate limiting step in glycolysis) through an Allosteric type inhibition.

2. Excess acetyl CoA produced by oxidation of fat enables activation of pyruvate carboxylase, resulting in production of oxaloacetate from pyruvate. It is an intermediate of the gluconeogenesis pathway and can be converted to glucose.

The two reactions above enable oxidation of glucose to be minimized. In fact this is the mechanism available to the body to spare glucose during periods of starvation for provision of glucose to red blood cells and the brain.

Markers of Energy Control at Clinically Important Land Marks in the Day

Fasting State is considered as usually achieved early in the morning 8 h after the night meal. Blood samples collected at this time provide useful information regarding the immediate glycaemic status. Postprandial state means it was achieved 2 h after a normal diet. Random state is considered as blood collected at any time of the day. Here the limits are set so that it takes care of the highest blood glucose reached.

Table V: Limitations of fasting to random blood glucose level

Classification	Blood Glucose Level (mg/dl)
Fasting state	
Normoglycaemic	< 100*
Glucose intolerant	125 - 100
Diabetic	> 125
* (Originally the cut off was fixed at 110, but later changed to 100 for better protection)	
Postprandial state	
Normoglycaemic	> 120- 140 <
Glucose intolerant	140 - 199
Diabetic	> 199
Random state	
Normoglycaemic	< 140
Glucose intolerant	140 - 199
Diabetic	> 199

Energy Metabolism in Diabetics

Diabetics is becoming an epidemic in the whole world, and is increasingly prevalent in developing countries, due to changes in diet, increased sedentary lifestyles, escalating obesity and an ageing population²⁰. It is a consequence of an imbalance between insulin responsiveness and insulin production. One of the first clinical signs is glucose intolerance, due to insulin resistance of peripheral organs, including liver, fat and muscle, and is initially compensated by increased pancreatic β -cell insulin secretion. Depending on the plasticity of the β -cells, the hyperinsulinemic drive may be sustained indefinitely, or β -cell dysfunction may develop leading to hypoinsulinemia, hyperglycemia and insulin-dependent diabetes²¹. As a consequence, diabetes is a highly heterogenous disease with many systemic effects. There is derangement in the metabolism of carbohydrate, fat and protein in these patients. This is brought about by a deficiency of insulin or receptors on which they act upon. The principal tissues which are affected are the muscle and adipose tissues. Insulin is necessary for the uptake

of glucose into these two tissues. In diabetics, due to reduced uptake of glucose by insulin dependent tissues, there is accumulation of glucose in the blood. Due to relative insulin deficiency, liver produces additional glucose via gluconeogenesis increasing the blood glucose further. Muscle and adipose tissues which are starved of energy via glucose metabolism have to seek the assistance of fuels whose uptake is insulin independent. Fatty acid transport to mitochondria for oxidation is primarily dependent on carnitine fatty acyl transferase. That too is for long chain fatty acids and not for short chain and medium chain fatty acids. Patients with such enzyme deficiency are unable to use fats containing long chain fatty acids, but are able to use fats containing short chain and medium chain fatty acids. For such patients coconut fat is a good source of energy. The diabetic person uses dietary triglycerides in chylomicrons or as endogenously-synthesised triglycerides in very low density lipoproteins (VLDL)²². Exogenous and endogenous triglycerides must initially be hydrolysed by endothelium-bound lipoprotein lipase to release free fatty acids for utilisation. Fatty acid is released by adipose tissue as a result of activation of triacylglycerol lipase, in the absence of insulin activity. Its entry into muscle and adipose tissues is not dependent on insulin. Hence it is used as a source of energy. The balance fatty acid is taken up by the liver and converted to ketone bodies, a readily useable fuel source by all tissues except red blood cells. Production of energy from fatty acid and ketone bodies is dependent on the availability of oxaloacetate. Glucose is the main supplier of oxaloacetate. It is produced by carboxylation of the end product of glycolysis, pyruvate. Acetyl CoA is produced as an intermediate product of fatty acid and ketone body oxidation. Its complete oxidation to CO₂ and H₂O depends on its entry into the TCA cycle. Entry of acetyl CoA into the TCA cycle is made possible by its reaction with oxaloacetate, when citrate is formed. Therefore in the case of diabetics fatty acid and ketone bodies are main sources of energy. Glucose plays a small role in supplying energy to red blood cells and part of the energy to the brain and acting as a source of oxaloacetate for oxidation of acetyl CoA, the main intermediate product of oxidations²³.

Energy Metabolism in the Fasting State Postabsorptive State

Fasting refers to person who has missed one or more major meals. If the person continues to deprive him of food for longer periods of time, then the condition is referred to as starvation and could be considered a chronic condition. In the fasting state, [Insulin] / [Glucagon] ratio is reduced and cortisol level is increased. The postabsorptive state commences when the last nutrient is absorbed from the previous meal and continues until the next meal or for approximately 12 h during a normal overnight fast. Metabolically, it is the period when there is a transition from exogenous energy consumption to reliance on endogenous energy sources. The release from the liver of approximately 200-250 g of glucose per day or 8-10 g per hour balances the rate of glucose utilization of the brain and other tissues. During an overnight fast, a significant proportion of the glucose requirements are met by the breakdown of liver glycogen. The remaining glucose is formed from noncarbohydrate sources: glycerol (from triacylglycerols), pyruvate, and lactate (from muscle). This results in the increase in the following biochemical activities:

1. Gluconeogenesis in the liver is increased
2. Hydrolysis of triacylglycerol in the adipose tissues is increased
3. Ketogenesis in the liver is increased
4. Protein catabolism in the muscle is increased

Gluconeogenesis

In the fasting state blood glucose reaches a minimal level as food eaten earlier has been completely digested, absorbed and mobilized. Therefore in order to satisfy the minimum requirement necessary to maintain body functions a blood glucose level of 80 - 100 mg/dl is established. Gluconeogenesis is the only pathway available to achieve this goal and the organs involved in order of importance are liver and kidney. The major substrates for gluconeogenesis are amino acids, glycerol and lactate in addition to TCA cycle intermediates. Muscle provides most of the amino acids by catabolism of labile proteins, adipose tissues provide glycerol by hydrolysis of stored fat and red blood cells provide lactate by anaerobic oxidation of glucose. Cortisol

and glucagon increase the activity of the three irreversible, regulatory steps of the gluconeogenesis pathway and increase the propensity of glucose production. At times the glucose production may shoot off the mark and in this case insulin will be secreted, glycogenesis activated and blood glucose brought within normal limits²⁴.

Ketogenesis

They are synthesized during fatty acid oxidation in the liver. An intermediate product of fatty acid oxidation is acetyl CoA. When acetyl CoA is in excess it is converted to ketone bodies. The principal pathway of its synthesis is via HMG CoA, an important intermediate in cholesterol metabolism. Ketone bodies provide energy to most tissues, except the red blood cells. The rapidity with which it is oxidized is so great that it is not able to reach high blood levels that glucose attains. This is due to the fact that there are only few bottle necks in the pathway to its complete oxidations. Blood ketone body level is increased when excessive amount of fatty acid is oxidized, especially when glucose is limiting²⁵.

Energy Metabolism in Starvation

In a normal adult, resting energy expenditure is proportional to lean body mass. Prolonged fasting is associated with a loss of lean body mass and in a reduction in resting energy expenditure. Fourteen to 21 days after commencing a starvation diet there is a 15% reduction in resting energy expenditure. However, at this time there is only a 5% reduction in lean body mass. Clearly, another mechanism contributes to the decreased resting energy expenditure observed in early starvation²⁶.

A number of hormonal changes occur as a response to starvation that may alter resting energy expenditure. Decreased activity of 50-monodeiodinase in the liver and peripheral tissues resulting in a reduction in the conversion of thyroxine (T₄) to the metabolically active form, triiodothyronine (T₃), has been observed within hours to days in patients on a starvation diet. This effect is modified by both the carbohydrate intake and the total energy content of the diet. However, the mechanism linking

low circulating T₃ levels to decreased resting energy expenditure in starvation is not well understood. Catecholamine secretion and turnover is decreased in uncomplicated starvation. This is clinically recognized as a reduction of core temperature, heart rate, and blood pressure in patients during starvation. Another factor contributing to the reduced resting energy expenditure observed in patients during starvation may be a reduction in the activity of the sodium-potassium pump. The activity of this pump is influenced by circulating T₃, catecholamines, and insulin all known to be altered in starvation. There is evidence that in prolonged starvation increased intracellular sodium and decreased intracellular potassium are linked to decreased pumping of sodium from cells²⁷.

It is an extension of the fasting state. The pathways which provide energy to the body in the fasting state are continued here to provide energy under life threatening conditions, such as hypoglycemia and ketosis. When the blood glucose level falls below 40 mg/dl a state of unconsciousness is likely to appear. In this state blood fatty acid level and ketone body levels are increased. The blood glucose level falls below the normal range making it difficult for normal functions to be performed at the normal rate. This makes the body to keep away from normal activities and induces it to rest preserving the energy status, a feature seen in children with PED. At this point of life muscle is wasted and the body depends on glycerol released by hydrolysis of fat remaining in the body to provide the vital substrate necessary to produce glucose in the liver. The toxicity due to accumulation of excess ketone bodies in the blood is partially overcome by increased exhalation of acetone and CO₂ and urinary excretion of ketone bodies. If an infusion of glucose is given to a starving person most of the biochemical derangements slowly disappear, resulting in a change towards normalcy in the fuel energy status²⁸.

Death will occur when there is a failure to replenish fuel stores and insufficient available energy to maintain essential bodily functions. Because fat is the predominant source of energy, the time until death in uncomplicated fasting will depend on the size of the prefasting fat stores. In a normal adult, fat stores will be sufficient to sustain life for

approximately 60-70 days. The extent of protein loss is also linked to survival. A loss of more than half of the lean body mass compartment (approximately half of total body protein) is predictive of death²⁹.

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