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## CHAPTER 6 HUMAN ENERGY SYSTEM BACKGROUND

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*This chapter presents a background literature study of the complexities associated with the entire human energy system. The flow of energy in the system is discussed and represented schematically. Then the interactive control system is also investigated and summarised schematically. The complex system is shown to emphasise the need to simplify the processes of the energy acquisition, storage and utilisation in order to simulate glycaemic response to different influences.*

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## 6.1 Introduction

For the successful construction of a simulation model of the entire human energy system some understanding of the bodily processes is required. The model discussed in Chapter 7 is only aimed at predicting glycaemic response. However, due to the integrated nature of the processes in the entire human energy system all the pathways of energy flow need to be investigated.

This chapter is a literature study into the acquisition, storage and utilisation of the fuels used by the human body (Sections 6.2 and 6.3). Furthermore, the control system involved with glycaemic control is examined (see Sections 6.4 and 6.5).

Importantly, two schematic layouts are presented. One is for the major energy pathways involved in the human energy system and the other concerns the control system of the glucose energy system. These layouts provide a clearer understanding of the processes involved and can also be applied for future research.

## 6.2 The human energy system

All nutritious food intakes constitute energy sources for the human body [1]. Ingested food is broken down into its absorbable components through the process of digestion, after which these components are either used as, or converted into, direct energy supply for the body or placed into storage for later use. All food is composed of macronutrients, micronutrients and water [2].

- Macronutrients comprise protein, fat and carbohydrates. These macronutrients are the only food components that provide energy to sustain life.
- Micronutrients comprise vitamins, minerals and trace elements. They do not provide energy but perform a host of cellular functions, the bulk of which involve the efficient use and disposal of macronutrients, and are as such essential for life.

The rest of Section 6.2 is divided into four main headings to describe the human energy system. The headings are:

- fuel source types;
- factors affecting availability of fuel;

- energy utilisation, and;
- energy storage.

### 6.2.1 Fuel source types

There are four basic forms of usable fuel needed by the body in order to fire its internal furnaces of metabolism, movement and mental functions. These main fuel types, which can be directly burned for energy by the energy system, are glucose, keto acids, fatty acids and ketones [3]. The brain and central nervous system, for instance, are primarily dependent on a minimum constant level of blood glucose to stay healthy and able to function [4]. The heart muscle, on the other hand, prefers ketones as the principal fuel [5].

As mentioned in section 2.2, carbohydrates are converted into monosaccharide sugars, namely glucose, fructose and galactose through the process of digestion. Glucose is directly useable as energy source, but galactose and fructose are first converted into glucose before utilisation. In the presence of insulin glucose is converted into usable or stored energy [6],[7]. The storage function (process of converting glucose to glycogen) is performed in both the liver and muscle tissue [8].

After the glycogen is stored the regulatory system of the body may release regulation hormones. At this stage the glycogen is converted back into glucose for burning [9]. This will be discussed later.

Another fuel source is protein. Ingested protein is broken down into its amino acid components in the gastrointestinal tract. Then, in the liver, the amino acids are converted into fuels called keto acids and fatty acids. Almost all tissues can utilise these acids for energy. When fatty acids are burned for energy, ketones are produced as by-product, which in turn can further be utilised for energy or in the event of overproduction, excreted through the breath, urine or stool [10].

In the event of a shortage of glucose in the blood, one of the mechanisms to increase the blood glucose level is to break down protein in the muscle tissue into its amino acid components. These amino acids are then converted into keto acids and back into glucose by the liver to replenish the shortage of blood glucose [10].

The fuel with the most available energy per mass is fat. Dietary fat is conveyed from the gastrointestinal tract in the form of triglycerides to the liver and adipose (fat) tissue. Triglyceride is one of the primary forms of energy storage in the body. In the presence of sufficient blood glucose levels,

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triglycerides will be stored in adipose tissue for later use. If however the energy is again required, the triglycerides are converted to glycerol and fatty acids in the adipose tissue. Glycerol is then converted to glucose by the liver, and fatty acids can be used as fuel by most tissues [11].

### **6.2.2 Factors affecting availability of fuel**

The availability of the fuel sources as discussed above is fairly uniform, except for some occurrences that may influence absorption, oxidation or digestion. These include effects like morning effect, mixed meal effect and second meal effect [12],[13],[14].

#### **Morning effect**

Preliminary investigations in regard to glycaemic response pointed to the possibility of the existence of a morning effect (or first-meal-after-extended-fasting effect). This effect has manifested itself as lowered glycaemic response to a meal consumed after extended fasting such as a night's sleep, in comparison to the normal glycaemic response of the identical meal consumed later during the day [12].

It is not certain whether the phenomenon is attributable to preceding extended fasting, preceding sleep (resting), or a combination of both. These findings are, however, based on a relatively small sample of test subjects, and will require further research and clinical testing to verify the existence and magnitude of the effect of such a phenomenon.

Furthermore, the preliminary tests reveal that the effect may be relatively small. For this reason and the prevailing uncertainties the morning effect will therefore be negated for simulation purposes discussed later in this study.

#### **Mixed meal effect**

The mixed meal effect refers to the phenomenon encountered during blood sugar testing of a lower glycaemic response than expected to carbohydrate food intake when it is consumed together with protein and fat. Some researchers have argued that the GI values of foods do not persist in mixed meals owing to the effect of fat and protein on reducing glycaemic absorbability [15].

Others do not agree with this interpretation and state that accurate predictions of the glycaemic response of mixed meals are closely related to the weighted average GI of the individual foods [13].

They claim that the properties of foods that influence their digestibility and hence their physiological effects are preserved when the foods are consumed within the context of a meal. In Chapter 7 these effects are taken into account with the development of the simulation model.

### **Second meal effect**

Studies have shown that a low erts (or low GI) meal improves the carbohydrate tolerance of a subsequent or second meal if the second meal is taken in relative quick succession to the first [14]. This improvement in glucose tolerance is a phenomenon known as the “second meal effect”.

The hypothesis upon which Jenkins, who first discovered it, based the second meal effect is that when CHO absorption of the first meal is ineffective, there is a less rapid rise of blood glucose levels [16]. This in turn causes less undershoot of the baseline glucose levels and consequently less counter regulation hormones are secreted. According to Wolever, the less counter regulation hormones lead to improved glucose disposal after the second meal [17].

High erts foods on the other hand do not induce a second meal effect of the same magnitude. In the case of a large glycaemic response, more insulin and hence more counter regulation hormones are secreted. This causes the second meal to produce a larger response than with less counter regulation hormones present [14].

### **6.2.3 Energy utilisation**

The following topics will be discussed owing to energy utilisation:

- Basal metabolism;
- Exercise and excitement;
- Stress, and;
- Growth.

#### **Basal metabolism**

Basal metabolism, according to Miller-Keane Medical Dictionary 2000, is the minimal energy expended for the maintenance of respiration, circulation, peristalsis, muscle tonus, body

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temperature, glandular activity, and the other vegetative functions of the body [19]. It is the energy expenditure of cells of the whole body, except for the energy devoted to the movement activities [18].

In the process of maintaining itself, the body utilises available fuels of which blood glucose is the easier accessible. However, in the absence of blood glucose other sources are also utilised.

### Exercise and excitement

The expenditure of energy through exercise also has a blood glucose lowering effect, and requires additional energy above and beyond that which is needed for the basal metabolism. At high intensity exercise, blood glucose is accessed and used as the primary fuel for the body cells. Only after the blood glucose is inadequate will the body revert to other mechanisms to fulfil its energy needs [20].

As the intensity of exercise increases, carbohydrates become more important for energy production [21]. This is because as the exercise intensifies, the oxidation of fatty acids is too slow to produce enough energy for the body [22],[23]. This finding led to the postulation of the “crossover concept” by Brooks [24]. Figure 6.1 shows measurements by Brooks to illustrate the concept [24].

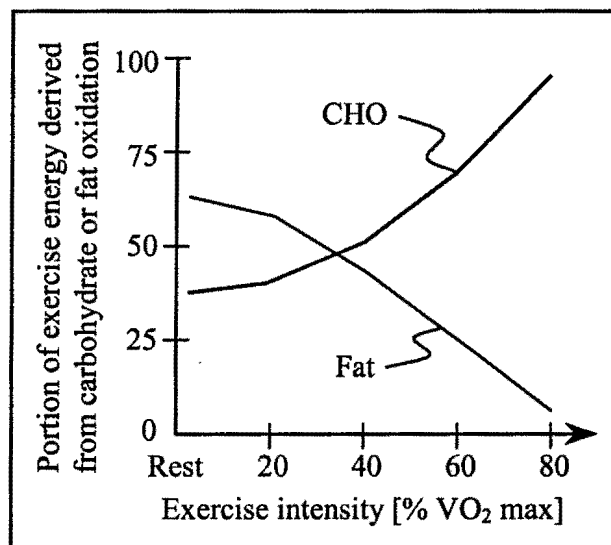


Figure 6.1 – The “crossover concept” of Brooks showing increasing importance of carbohydrate oxidation at high exercise intensities.

Excitement or “positive stress” may have a similar effect as exercise and appears to accelerate the use of energy by the body. Very little information is available on this matter and the validity of the statement on excitement is subject to further study and verification.

## **Stress**

Stress is defined as the sum of the biological reactions to any adverse stimulus, physical, mental, or emotional, internal or external, that tends to disturb the homeostasis of an organism [25]. In this sense “stress” is referred to in a negative connotation, and stands in contrast to exercise or excitement, which in essence is a positive form of stress with reversed reactionary effects.

Stress can be divided into two categories, namely physical stress and psychological stress.

### **Physical stress**

There are many kinds of physical stress, which can be subdivided into two principal subcategories, to which the body reacts in different ways [27]. In both these cases blood glucose is made available and hence energy can easily be utilised by the body.

Firstly, emergency stress (also known as “short-term” or “fight or flight” stress, see Section 4.3) is induced by a situation that poses an immediate threat, such as a near automobile accident, a wound, or an injury. Continuing stress (or “long-term” stress) on the other hand is a stress situation that is caused by changes in the body during puberty, pregnancy, menopause, acute and chronic diseases, and continuing exposure to excessive noise, vibration, fumes, chemicals, or other agents.

The body's reaction to emergency stress is set off by the adrenal medulla. The medulla of each adrenal gland is directly connected to the nervous system. When an emergency arises, it pours the hormone “epinephrine” into the bloodstream. This has the effect of speeding up the heart and raising the blood pressure, emptying sugar supplies swiftly into the bloodstream, and dilating the blood vessels in the muscles to give them immediate use of this energy. At the same time, the pupils of the eyes dilate [26].

The reaction of the body to continuing stress is even more complex. Again the principal organs are the adrenal glands, but after the first phase of alarm, the glands continue to produce a steady supply of hormones that apparently increase the body's insulin resistance. This is in addition to specific defences such as the production of antibodies to fight infection.

If the stress is overwhelming, as in the case of an extensive third-degree burn or an uncontrollable infectious disease, the third phase, exhaustion of the adrenal glands, sets in, sometimes with fatal results.

### **Psychological stress**

The same two sub-categories of stress as described above, emergency and long-term stress, are also evident in the psychological stress category [27]. The emergency response of the body comes into play when a person merely foresees or imagines danger, as in the case of real emergency situations. The thought of danger, or the vicarious experience of danger in a thrilling story, play, or film, may be enough to cause the muscles to tense and accelerate the heart rate.

One of the best-known examples of this is “stage fright”, often characterised by tensed muscles and an increased heart rate. At times the person may not even be aware of the unconscious thought that produces this dramatic reaction, but since the blood glucose levels are elevated, more energy can be utilised while in the stressful state. This was explained in more detail in Section 4.3.

Long-term psychological stress is dealt with by the body in the same manner as long-term physical stress and is also characterised by elevation of blood sugar levels.

In recent years, there have been numerous attempts to find a direct correlation between certain diseases and a stressful environment or a personality type that responds to the environment in a certain way. However, while inappropriate activity and a “hectic” lifestyle can cause illness in some persons, a busy and productive person can actually be subject to less stress than one who feels trapped in a limited position with no hope for release or a sense of accomplishment.

Advances have been made with regard to stress research, but the complex nature of the subject and varied range of individual responses in regard to stress will require many more years of intensive research to be fully understood.

### **Growth**

Growth is the progressive development of a living thing, especially the process by which the body reaches its point of complete physical development [19]. Human growth from infancy to maturity involves great changes in body size and appearance, including the development of the sexual

characteristics. The growth process is not a steady one, in other words during some periods growth occurs rapidly, while at others it happens slowly.

Individual patterns of growth vary widely because of differences in heredity and environment. Children tend to have physical properties similar to those of their parents or of earlier ancestors. However, environment may modify this tendency. Living conditions, including nutrition and hygiene, have considerable influence on growth.

The regulators of growth are the endocrine glands, which in themselves are also subject to genetic influence. The pituitary gland secretes growth hormone, which controls general body growth, particularly the growth of the skeleton. It also influences the metabolism [28].

In addition to influencing growth directly, the pituitary gland has a central role in regulating the other endocrine glands as well. These other glands in turn control many other bodily functions, and they secrete the various hormones that directly regulate the rest of the metabolism [29]. Elevated blood glucose levels are often measured if growth hormone is present in the blood [9].

Growth in height occurs as a result of maturation of the skeleton. When the long bones have reached maturity at about age 18, linear growth stops. In general, the birth weight of the average baby doubles in 5 to 6 months and triples by the end of the first year. At the end of the second year of life birth weight quadruples and then there is a steady increase of 2 to 2.75 kg each year until the child reaches puberty. At this time there is a period of rapid growth in both weight and height [28].

### **6.2.4 Energy storage**

The human body makes extensive use of its energy storage system to maintain and regenerate itself in a fluctuating food supply and intake pattern. Almost all tissue, with the exception of nervous tissue, is employed to store excess fuel for later use. The main fuel storage facilities in the human body are the liver, muscle tissue and adipose (fat) tissue [30].

#### **The liver**

The liver is a large storehouse of the following substances:

- Glycogen that has been converted from glucose;

- Triglycerides that have been derived from glucose or have been absorbed from the gastrointestinal tract;
- Amino acids, which have been absorbed from the gastro-intestinal tract.

All of these stored fuels are stored for the short-term used in preference to long-term stored fuels such as the breakdown of stored fat tissue [31].

In terms of ets the amount of blood sugar energy that is usually stored in an average sized person's liver is 30 ets [20].

### **Muscle tissue**

Muscle tissue is the largest tissue group in a healthy individual that can be used as a storage facility. The following fuels are stored in the muscles:

- Glycogen, which has been converted from glucose in the blood;
- Protein, which has been produced from amino acids released into the blood by the liver.

Glycogen is a short-term storage form of glucose and used relatively quickly during exercise. Protein is the muscle tissue itself, and is therefore only called upon when other fuels are in short supply. Although not strictly fuel, protein can be converted back to amino acids and used as fuel and is accordingly considered a long-term storage form of fuel [20].

An average person stores approximately 85 ets of usable energy in the muscle tissue [20].

### **Adipose tissue**

Adipose tissue is the storage facility for primarily long-term storage of fuel in the form of triglycerides. Fat in the body provides the reserves to be called upon in the event of longer term deprivation of fuel supply to the body [32]. Theoretically a person can survive for months without food if fat reserves are adequate.

However, during exercise or long-term fasting periods the fat stores are used to replenish the shorter-term storage facilities like the liver as well as provide a certain portion of energy directly for use [32]. This is shown in Figure 6.1 where the fat stores are used under light exercising conditions.

### 6.3 The major energy pathways

The energy system of the human body is schematically represented in Figure 6.2. The pathways for sugars, protein and fat to provide energy to fuel the processes required for life in the human body are described separately although the processes are integrated and interlinked, with some forms of fuels converted to others when needed.

It is important to note that, while there is a distinction made between the absorptive phase and fasting or burning phase in energy flow, these processes are never exclusive but always occur simultaneously with one more dominant than the other depending on the body's state. Whenever the absorptive phase is indicated, it merely refers to the dominant set of processes that are in operation at that particular instance. When both processes are indicated it means that they occur almost constantly, irrespective of the body state.

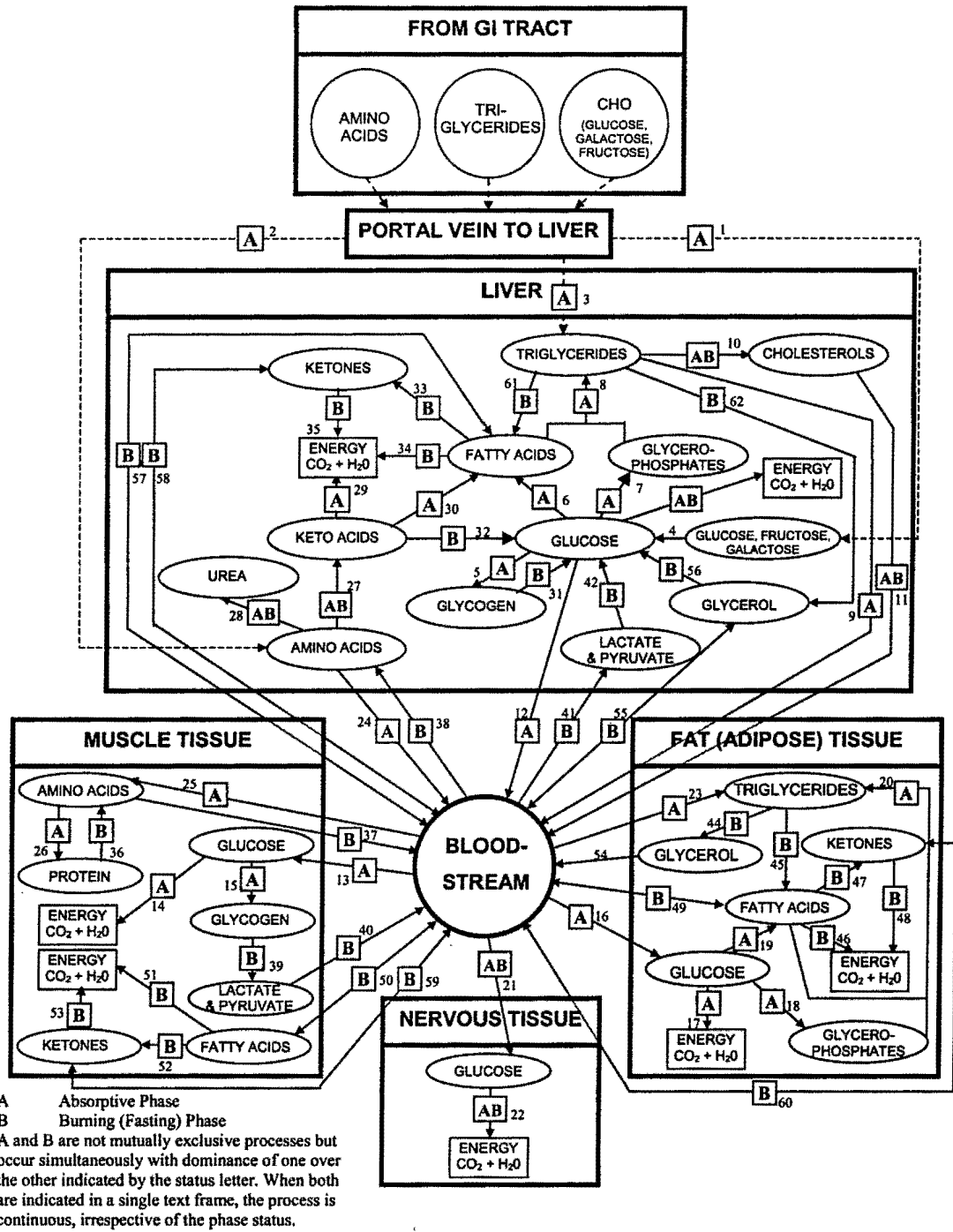


Figure 6.2 – Simplified schematic layout of the major energy pathways in the human energy system.

The description of the process of fuel consumption begins when sugars, amino acids and tri-glycerides are absorbed in the gastro-intestinal tract and transported via the portal vein directly to the liver [33]. The processes that follow are determined by the requirements of the body, and their

proportionate contributions, as percentages of the whole, are dependent on the specific state of the body at any particular time.

### **6.3.1 The carbohydrate pathway**

The carbohydrate pathway begins at the point where glucose, fructose and galactose are transported from the gastro-intestinal tract via the portal vein to the liver (1). In the liver galactose and fructose are converted to glucose (4) [7]. Some of the glucose is released into the bloodstream (12).

The four pathways for glucose utilisation then lead from the bloodstream into the liver, the muscle tissue, the adipose tissue and the nervous system. Here follows a short description of each of these pathways.

#### **In the liver**

A part of glucose is directly converted into glycogen and stored in the liver (5) while some is burnt for energy [31].

Another portion of glucose is converted into fatty acids (6) and glycerophosphates (7), which combine to form triglycerides (8). The triglycerides are then either stored in the liver, released into the bloodstream (9), or converted to cholesterol (10) and in turn released in the blood (11).

The portion of glucose that was converted into fatty acids can directly be burned for energy in the liver (34). This process produces ketones as by-product (33). Ketones can in turn also be burned for energy in the liver (35) or released into the bloodstream (58). Unused ketones are excreted through the breath, urine and stool. Similarly fatty acids can also be released into the bloodstream (57) to be used for energy elsewhere.

When required, glycogen stored in the liver can be reconverted back into glucose (31) and any of the above processes can again be performed.

#### **In the muscle tissue**

Glucose from the bloodstream can be absorbed in the muscle (13) and burned directly in the muscle tissue for movement and heat energy (14). It can however also be converted into glycogen for energy storage (15) [20].

Furthermore, the glycogen can also be converted into lactate and pyruvate (39), which is released into the bloodstream (40) and converted in the liver (41) back into glucose (42) [34]. From here the pathways for glucose utilisation in the liver are the same as described above.

### **In the adipose tissue**

Glucose absorbed from the bloodstream (16) can be burned directly for heat energy in the adipose or fat tissue (17), or, as in the case of the liver, converted into fatty acids (19) and glycerophosphates (18). These two again combine to form triglycerides (20), which are stored as energy reserves [32].

Similarly to the case of the liver, the portion of glucose that was converted into fatty acids can directly be burned for energy in the adipose tissue (46). This also produces ketones as by-product (47). The ketones can in turn be burned for energy in the adipose tissue (48).

### **In the nervous tissue**

A constant flow of glucose is required from the bloodstream (21) to supply the nervous tissue with fuel [4],[35]. The glucose is then directly burned within the nervous tissue to produce energy for sustaining life (22).

## **6.3.2 The amino acid pathway**

The amino acid pathway begins at the point where amino acids are transported from the gastrointestinal tract via the portal vein to the liver (2) [33]. Amino acids are only utilised in the liver and muscle tissue, and the pathways for utilisation are the following:

### **In the liver**

A portion of the absorbed amino acids is released by the liver into the bloodstream (24).

Another portion of amino acids is converted directly in the liver into keto acids (27), which can be directly utilised as energy (29). The remaining amino acids are directly excreted from the body as waste (28) [31].

The keto acids can furthermore be converted into fatty acids (30) from where it follows the same path as was described in the carbohydrate pathway (Section 6.3.1). In other words fatty acids can be

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burned directly for energy in the liver (34), with ketones as a by-product (33). The ketones in turn can also be burned for energy in the liver (35) [10]. The fatty acids can furthermore follow the path of formation of triglycerides as was mentioned in the carbohydrate pathway.

### **In the muscle tissue**

The muscles can absorb the free amino acids from the bloodstream (25) and convert it into protein for building muscle tissue (26) [20]. If required in low energy availability situations, protein (muscle tissue) can be converted back into amino acids (36) and released into the bloodstream (37). From here it follows the pathway back to the liver, as described above, to replenish the energy store that is low.

### **6.3.3 The fat pathway**

The triglyceride or fat pathway begins at the point where triglycerides are transported from the gastro-intestinal tract via the portal vein to the liver (3). Triglycerides or their derivatives are mainly utilised along the following pathways:

#### **In the liver**

A portion of the ingested triglycerides as well as the triglycerides produced in the liver (from the glucose pathway) can be stored in the liver or released directly into the bloodstream (9) [33].

Another portion is directly converted in the liver into cholesterol (10), which are in turn also released into the bloodstream (11).

The remaining portion may be broken down into fatty acids (61) and glycerol (62) before being released into the bloodstream (55 and 57).

#### **In the adipose tissue**

The fat or adipose tissue can absorb the triglycerides from the bloodstream (23) and can directly store it as triglyceride energy reserves [11].

When required in low energy availability situations, triglycerides can be converted into glycerol (44) as well as fatty acids (45). Glycerol is released into the bloodstream (54), conveyed back to the

liver (55) and converted back into glucose (56). From here it follows the glucose pathways in the liver as already described.

A portion of the fatty acids produced from triglycerides in the adipose tissue (45) can directly be burned for energy in the adipose tissue (46), which produces ketones as a by-product (47). The ketones can in turn also be burned for energy in the adipose tissue (48) or it can be released into the bloodstream (60) [20].

The remainder of fatty acids are then also released into the bloodstream (49) from where it is either utilised in the liver (57) along the same pathway as fatty acids produced in the liver, or used in the muscle tissue (50). The burning of the fatty acids in the liver was already describe in Section 6.3.2.

### **In the muscle tissue**

Fatty acids produced by adipose tissue (49) or by the liver (57) and released into the bloodstream can be transported to the muscle tissue (50) or any other tissue (except the nervous tissue) to be burned for energy [20].

The process of burning the fatty acids is very similar to that already described in the liver. The fatty acids can directly be burned for energy in the muscle tissue (51), which produces ketones as by-product (52). The ketones can in turn also be burned for energy in the muscle tissue (53). As in the case with all ketone production, some may be released into the blood (59) and utilised elsewhere.

## **6.4 The blood sugar control system**

In the previous section the flow of energy in the human energy system was described. The flow will however only occur due to certain interactive controls that are designed to regulate the fuels in the body. In this section the control strategies used and the system components responsible for the control are investigated.

Due to the complexity of the entire system all the controls will however not be discussed. The main purpose of the study is to simulate glycaemic response, so only the blood sugar control system is schematically presented (see Section 6.5).

Firstly, discussions on the components responsible for energy flow regulation in the glycaemic energy subsystem are briefly discussed. These include organs, glands, tissues and hormones.

## 6.4.1 Control organs and tissues

### The liver

The liver is a soft, reddish, wedge-shaped gland that is located predominantly on the right side of the body, beneath the rib cage. In average sized adults, it normally measures approximately 10 cm by 15 cm by 20 cm at its greatest dimensions [36].

The liver is responsible for regulating so many bodily functions that it has been referred to as “the custodian of the interior milieu”. Because of the wide range of bodily processes that occur in the liver, disruption of liver function has far-reaching consequences [36].

The main functions of the liver can be divided into two categories namely storage and protection.

#### Storage functions

The liver can store up to 20% of its own weight in glycogen and up to 40% of its weight in fats. The most basic fuel of the body is glucose. As described earlier, this comes to the liver as one of the products of digestion, and is converted into glycogen for storage [36]. The stored glycogen can be reconverted to glucose when necessary, to maintain a steady level of sugar in the blood [20]. This is normally a slow continuous process, but in emergencies the liver, responding to a need for epinephrine in the blood, can release large quantities of glucose into the blood for use by the muscles [37].

As the chief supplier of glucose in the body, the liver is also sometimes called on to convert other substances into blood sugar. The liver cells can produce glucose out of both protein (through amino acids) and fat (through glycerol). This process also works in reverse, i.e. the liver cells can convert excess blood glucose into fat (triglycerides) and release it for storage in other parts of the body [36],[37].

In addition to these fuel related functions, the liver furthermore stores many essential and necessary vitamins until they are needed by other organs or tissues in the body.

#### Protective function

As a filtering device the liver disposes of worn-out blood cells by breaking them down into their different elements, storing some and sending others to the kidneys for disposal in the urine. It also

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filters and destroys bacteria. In addition, one of the most important functions of the liver is the detoxification of drugs, alcohol, and environmental poisons [38].

The liver furthermore helps to maintain the balance of sex hormones in the body. A certain amount of female hormones are normally produced in males, and male hormones in females. When the level of these opposite sex hormones rise above a certain maximum acceptable value, the liver takes up the excess and disposes of it [38].

Finally, the liver screens and filters the proteins that pass through the digestive system. Some of the amino acids derived from protein metabolism cannot be used by the body, so the liver rejects and neutralises these acids and sends them to the kidneys for disposal.

Here follows a list of the essential functions of the liver.

- The liver produces bile, which is stored in the gall bladder and used to break down fats. If the excretion of bile is blocked, stools become pale and contain fat. As a result, fat-soluble vitamins (vitamins A, D, E and K) are not properly absorbed. In addition, levels of bilirubin (the main component of bile) rise in the blood. Once bilirubin levels reach 2.5 mg/dl, jaundice, or yellowing of the skin and eyes, occurs [39].
- The liver is also responsible for the synthesis of proteins, including albumin. Albumin is the predominant protein present in blood plasma and helps to retain fluid within the blood vessels. The loss of albumin results in fluid shifting from the blood vessels to the surrounding tissue. The consequence is swelling of the tissue, a condition called “edema” [40].
- The production of blood clotting factors is also one of the liver functions. These factors are responsible for the control of bleeding. Loss of clotting factors leads to increased chance of haemorrhages [40].
- The liver causes the metabolism of hormones and medications, such as estrogen and acetaminophen (tylenol). When the liver is damaged, its ability to metabolise hormones decreases. This can result in changes to estrogen and testosterone levels in the body.

Symptoms of these changes include loss of pubic hair and the development of spider angiomas (small clusters of red blood vessels on the skin of the upper body) in both males

and females. Men sometimes experience a decrease of testicular size and development of breast tissue (a condition called “gynecomastia”). A decline in the body's ability to metabolise medications means that normal doses can become toxic levels. Therefore, doses of medicines are often reduced for people who have liver disease [38].

- The liver is one of the blood glucose level regulation organs. The loss of liver cells leads to poorly controlled glucose levels. This poor regulation of blood sugar is due to less glycogen that is available in the liver store. The condition is often found with Type 1 diabetics [36].
- The liver is responsible for the conversion of ammonia, a by-product of metabolism, into a less toxic form called urea. The inability to convert ammonia to urea results in elevated ammonia levels in the bloodstream. This can result in a condition called hepatic encephalopathy, which is a neurological syndrome characterised by alterations in mental status and behaviour. Although acute episodes can be reversible, severe cases of hepatic encephalopathy can lead to coma and death [41].

### **Muscle tissue**

Muscle tissue consists largely of protein derived from amino acids, and provides the body with its capability for movement and kinetic energy expenditure. Muscles represent a large consumer of energy in the body, and increased muscle mass will necessitate a higher caloric intake to maintain [20].

Muscle tissue has both energy storage and release capability, and can utilise glucose, fatty acids and ketones as fuel for burning [20]. These processes were described in Section 6.3.

### **Adipose tissue**

Adipose or fat tissue essentially represents energy storage of the body. Fat tissue is stored in the form of triglycerides, which can be called upon by the body as energy source when required. Adipose tissue has a diminished energy burning capability, but is also able to utilise glucose, fatty acids and ketones as fuels [32]. These processes were also described in more detail in Section 6.3.

## **Nervous tissue**

Nervous tissue encompasses all neurological tissue found in the body such as the brain, spinal chord and nerves throughout the body. Nervous tissue requires a certain minimum blood glucose level to remain operational and control bodily functions. Although small amounts of other types of fuel may be utilised by nervous tissue, glucose is the primary fuel without which coma and death are quick successors [4],[35].

### **6.4.2 Endocrine control glands**

The endocrine system controls a large proportion of the body's functions. The endocrine glands secrete a range of hormones into the bloodstream and thereby relay messages to various organs, which are stimulated, to engage in specific processes. These include, among others metabolism, growth, reproduction and blood sugar control.

Hormones are chemical messengers and are circulated in the blood to other parts of the body where their effects are brought about. Hormones act slower than nerve impulses and also take longer to pan out their activity. Hormones, made by the major endocrine glands such as the pancreas or pituitary gland, have widespread effects and are as such called general hormones [42].

Local hormones, on the other hand, act much nearer to the point of origin. An example is secretin, which is produced in the duodenum in the presence of food. It travels a relatively short distance to the pancreas and stimulates it to produce its required secretions necessary for digestion [43].

Hormones can chemically be grouped into two categories. These are protein derivatives such as insulin and thyroid hormone as well as steroids including adrenalin and sex hormones [42].

Here follows a short description of the glands that produce the control hormones.

#### **Hypothalamus**

The hypothalamus is the link between the nervous system and the endocrine glands. One of its main functions is to relay impulses and stimuli between the brain and organs such as the liver and kidneys. Its mechanism is by receiving signals from the brain and in response, triggering the release of hormones by the pituitary gland, adrenal glands and thyroid [26].

## **Pituitary gland**

The pituitary gland is found in the base of the brain, next to the hypothalamus. It consists of two distinct halves, the posterior and anterior pituitary. These two have different mechanisms.

The posterior pituitary is connected to the hypothalamus via a nerve path called the pituitary stalk, and together these two form a self-contained unit. The posterior pituitary secretes mainly oxytocin (regulating labour initiation and breast milk) and ADH, which controls the body's water balance [44].

The anterior pituitary on the other hand produces hormones that activate the production of other hormones in other endocrine glands. It has no direct nervous link to the hypothalamus, but is closely linked via the pituitary portal blood system, which facilitates relatively quick transportation of messenger hormones. Hormones secreted by the anterior pituitary include TSH which stimulates the thyroid to secrete the thyroid hormone, ACTH. ACTH then triggers the adrenal glands to produce cortisone, prolactin for breast milk production, growth hormone as well as the hormones FSH and LH that control sex hormone production [44].

## **Thyroid**

The thyroid gland is situated in the neck, just below the larynx. The thyroid gland produces the thyroid hormone thyroxin, the effect of which is to increase the amount of energy the cells use as well as increasing the amount of protein produced by the cells [45].

Although the exact role of thyroid hormone is not fully understood, it is known to be essential for sustaining life. The secretion of thyroid hormone triggers a rise in blood glucose levels and as such forms part of the blood sugar control system.

## **Adrenal glands**

The adrenal glands are located immediately above the kidneys in the form of kidney caps. Each adrenal gland consists of two different parts, namely the adrenal medulla or core and the adrenal cortex or outer part.

The adrenal medulla secretes adrenalin and noradrenalin, which are known as the “fight or flight” hormones. These are required by the body to react to danger and stress. The adrenal medulla is closely connected to the central nervous system, enabling it to prime the body for almost

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instantaneous action when required. The release of these hormones increases the heart rate, raises blood pressure and turns glycogen, stored in the liver and muscles, into glucose as an extra energy source [46].

The adrenal cortex on the other hand secretes a series of steroid hormones, the most important of which are aldosterone and cortisone (or cortisol). Cortisol is responsible for raising blood sugar levels and induces the conversion of protein into glucose when the body requires it, for example in times of stress [46].

## **Pancreas**

The pancreas is the second largest organ in the body (after the liver), and comprises of two glands contained in one. On the one hand it is an exocrine gland, which secretes digestive juices not in the blood but into the gut. On the other hand it is an endocrine gland, which secretes hormones into the blood for various control functions [47].

Within the pancreas are small groups of cells called the “islets of Langerhans”. These islets contain beta cells that are primarily responsible for the production of the hormones insulin, and alpha cells that produce the hormone glucagons [47],[48].

Insulin is the only hormone that has a blood glucose lowering effect. Conversely glucagon acts in the opposite fashion and reverses the processes to provoke blood glucose level rise should the body require it [48].

### **6.4.3 Main control hormones**

The two major control hormones are insulin (the regulation hormone) and glucagon (the primary counter regulation hormone) [48],[49].

#### **Insulin**

Insulin is an anabolic hormone secreted by the beta cells of the islets of Langerhans in the pancreas. Amongst others its functions include:

- The regulation of blood glucose by suppressing blood glucose level and repressing gluconeogenesis and glycogenolysis. It also decreases substrates used in gluconeogenesis and inhibits lipolysis [47];

- Controlling the flow of carbohydrates, fatty acids and amino acids to the different body tissues. It henceforth causes enhancing of amino acid uptake and protein synthesis [50];
- Regulation of the production of cholesterol by the liver [51];
- Controlling the absorption mechanisms for storage of fat and glycogen for later use as an energy source [48].

Insulin is the body's top-end blood sugar level controller since an increase in insulin concentration has the direct effect of lowering high blood sugar. Type 1 diabetics do not have the substance produced in their bodies and therefore have to inject it at the appropriate times, usually before meals. Type 2 diabetics on the other hand do produce insulin, but it is either in inadequate quantities or they are unreceptive to the insulin.

Insulin acts by enhancing glucose uptake into the peripheral tissues and inhibiting glycogen breakdown and glucose release from the liver. Insulin is the primary “key” to “unlocking” tissues for glucose uptake. There are, however, some tissues that do not require insulin for efficient uptake of glucose such as the liver itself and some of the nervous tissue [52].

One of the interesting phenomena associated with insulin injections is the Somogyi effect [53]. Somogyi is a rebound phenomenon occurring in diabetes mellitus. Over treatment with insulin induces hypoglycaemia, which initiates the release of epinephrine, ACTH, glucagon, and growth hormone. These counter regulation hormones stimulate lipolysis, gluconeogenesis, and glycogenolysis, which in turn result in rebound hyperglycaemia and ketosis.

Indications that the Somogyi effect may be taking place include the following:

- The appearance of strongly positive tests for sugar and acetone in the urine within a few hours after a period in which the urine had been negative for both tests;
- A 2% glycosuria during the day, preceded by nocturnal sweating, headaches, and other symptoms of hypoglycaemia;
- Unresponsiveness to insulin during the period of rebound hyperglycosuria;
- Wide fluctuations in blood glucose levels, over several hours, and unrelated to meals;

- Improved control of blood sugar levels and ketonuria with gradual reduction in the amount of insulin taken.

Current treatment for the Somogyi effect consists of gradual reduction of the insulin dose until the optimum dose is reached.

## **Glucagon**

Glucagon is a catabolic hormone produced by the alpha cells in the islets of Langerhans within the pancreas. Cellular uptake of glucose (and resulting decrease in blood glucose) stimulates secretion of glucagons [54]. Glucagon acts in diametrically opposite fashion to insulin and some of its functions include [49]:

- It decreases the cellular uptake rate of glucose;
- Glucagon increases synthesis (from stored glycogen and from amino acids) and release of glucose from the liver, thereby raising blood glucose levels. It is sometimes manually injected for the treatment of severe insulin reactions;
- It increases the breakdown of fats and the formation of ketones and ketoacids. These are also potential energy sources.

In other words, glucagon opposes the actions of insulin, it stimulates lipolysis, ketogenesis, proteolysis, and gluconeogenesis [54]. Interestingly, glucagon secretion is also stimulated by stress.

The delicate balance between the antagonistic effects of insulin and glucagon results in fine-tuning of the steady-state levels of blood glucose. Glucagon results in the breakdown and use of stored glucose, fats and protein, while insulin conversely causes storage of the fuels. Insulin causes an anabolic metabolic action and glucagon a catabolic one. An insulin to glucagon ratio of 10 mg/l to 1 mg/l respectively is considered to be the switching point between the anabolic and catabolic metabolisms [54].

### **6.4.4 Additional control hormones**

The additional control hormones relative to this study are cortisol, adrenaline, and growth hormone [49]. Here follows a short description of each.

## Cortisol

A glucocorticoid, such as cortisol, cortisone, and corticosterone, is any corticoid substance that increases gluconeogenesis, thereby raising the concentration of blood sugar. The principal glucocorticoid hormone is cortisol.

The release of glucocorticoids from the adrenal cortex is initially triggered by corticotropin-releasing hormone (CRH) elaborated by the hypothalamus. The target organ for this factor is the anterior lobe of the pituitary gland, which reacts to the presence of CRH by releasing adrenocorticotrophic hormone (ACTH). ACTH, in turn, stimulates the release of the glucocorticoids from the adrenal cortex [55].

Cortisol regulates the metabolism of proteins, carbohydrates, and lipids. It specifically increases the catabolism or breakdown of protein in bone, skin, muscle, and connective tissue. Cortisol also diminishes the cellular utilisation of glucose and increases the output of glucose from the liver.

Because of their effects on glucose levels and fat metabolism, all of the glucocorticoids are referred to as “anti-insulin diabetogenic” hormones. They increase the blood sugar level and raise the concentration of plasma lipids. Many other physiological processes within the body can occur only in the presence of the glucocorticoids. For example, the secretion of digestive enzymes by gastric cells require a certain level of glucocorticoids [56].

The glucocorticoids also promote the transport of amino acids into the extra cellular compartment, making them more readily available for the production of energy. In times of stress the glucocorticoids influence the effectiveness of the catecholamines: dopamine, epinephrine, and norepinephrine. For example, the presence of cortisol is essential to norepinephrine-induced vasoconstriction and other physiologic phenomena necessary for survival under stress [56].

The time of day plays a vital role towards the cortisol appearance in the body. Normally, cortisol levels rise and fall during the day. Highest levels are usually found at about 6 to 8 a.m., while and lowest levels are often encountered at midnight.

Cortisol levels may increase after meals. Cortisol helps to increase the release of amino acids from skeletal muscle, and fatty acids from adipose tissue. The amino acids are taken up by the liver and converted into glucose, which is subsequently secreted into the bloodstream to be used for energy by certain tissues such as brain cells and red blood cells. The fatty acids released from the adipose

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tissue are used for energy by skeletal muscle, thus sparing the available glucose for use by the brain and other nervous tissue.

Another effect of cortisol is that of dampening the body's inflammatory response to invasion by foreign agents. Since the immune response can damage body cells as well as those of foreign agents, the anti-inflammatory protective mechanisms of cortisol help preserve the integrity of body cells at the site of the inflammatory response [56].

Both physical and emotional stress (see Section 6.2.3) can increase serum cortisol, because a normal response to stress involves increased secretion of ACTH by the pituitary gland. Cortisol (or any other glucocorticoid) in pharmacological doses (when given as a medication) reduces inflammation and inhibits the immune response. Even at physiological (normal body) concentrations, cortisol has an effect on the immune system and the inflammatory response, especially in people subject to chronic stress.

## **Adrenalin**

Epinephrine is a hormone produced by the medulla of the adrenal glands and is also called adrenaline. Its function is to aid in the regulation of the sympathetic branch of the autonomic nervous system. At times when a person is highly stimulated, as by fear, anger, or some challenging situation, extra amounts of epinephrine are released into the bloodstream, preparing the body for energetic action [57].

Epinephrine is a powerful vasoconstrictor that increases blood pressure as well as the heart rate and cardiac output. It also increases glycogenolysis and the release of glucose from the liver, thus aiding in raising blood glucose levels, in opposite fashion to insulin. Whenever adrenaline is secreted, the person has a suddenly increased feeling of muscular strength and aggressiveness.

Some disorders of the adrenal glands, such as Addison's disease, reduce the output of epinephrine below normal. By contrast, excessive activity of the adrenals, often seen in highly emotional people, tends to produce tenseness, palpitation, high blood pressure, sometimes diarrhoea, and over aggressiveness. Conversely, sometimes certain adrenal tumours result in the production of too much epinephrine [58].

Epinephrine is also produced synthetically and acts as a vasoconstrictor, antispasmodic, and sympathomimetic. It is used as an emergency heart stimulant and to relieve symptoms in allergic

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conditions such as asthma. It is the most effective drug for counteracting the lethal effects of anaphylactic shock.

## **Growth hormone**

Growth hormone is a protein hormone released from the anterior pituitary gland. In children, the major function of the growth hormone is to stimulate growth. Actually, the major regulator of body growth is IGF-1, which is a growth factor released from the liver after being stimulated by growth hormone [59],[60].

In adults, the growth hormone mainly stimulates protein synthesis in muscle and the release of fatty acids from adipose tissue. It inhibits uptake of glucose by the muscles while stimulating uptake of amino acids. The amino acids are then used in the synthesis of proteins, so the muscle therefore shifts from glucose to using fatty acids as a source of energy [59].

## **6.5 The blood sugar control processes**

In the context of the entire energy system of the human body, blood sugar forms a very important part of the fuel supply. The effects on blood sugar levels by a number of controlling factors are much more measurable when compared to the energy pathways for all fuels as described in the previous sections. Knowledge of the energy pathways is, however, essential for the understanding of phenomena occurring in the process of blood sugar control.

Since this study is aimed at constructing a simulation model for blood glucose prediction, only the blood sugar control is discussed. The blood sugar control system of the human body is schematically represented in Figure 6.3.

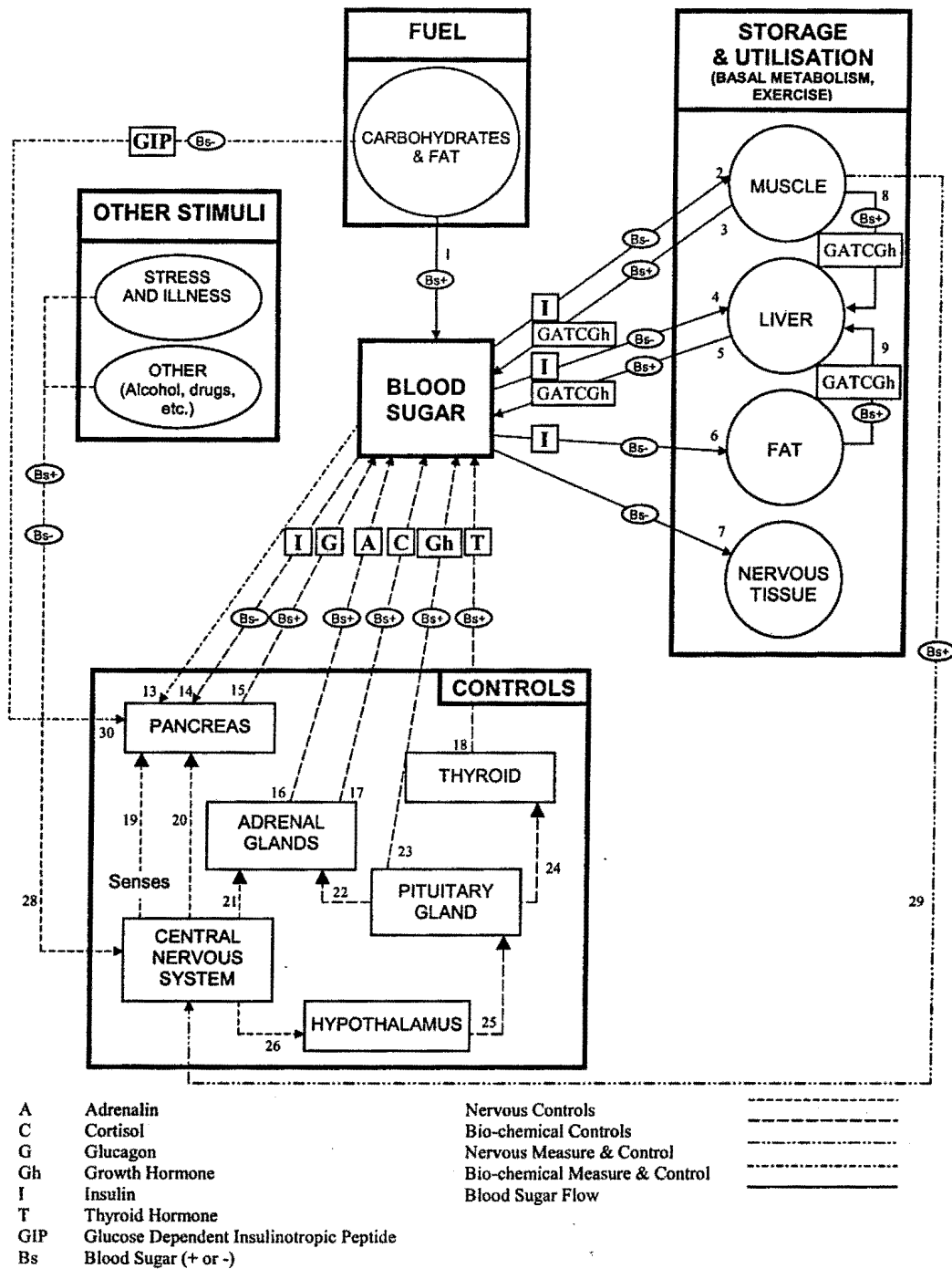


Figure 6.3 – Simplified schematic layout of the blood sugar control system in the human energy system.

It is important to note that processes described in blood sugar control always occur in an integrated manner. Processes are described individually but it must be remembered that each process forms part of a bigger control system with interdependency on the other processes.

Like with the energy pathways described in Section 6.3 the processes are described and referenced through numbers on the sketch, which are referenced in this text in parentheses. Arrowed solid hairlines indicate changes in blood glucose concentrations and direction of energy flow, while broken arrowed lines indicate control or measuring mechanisms and direction of targets. The controlling hormone for each process is indicated in abbreviated form in square text frames. Processes that increase and decrease blood sugar levels are indicated with “Bs+” and “Bs-“ respectively, enclosed in oval text frames. More details are given on the sketch.

Fuel intake in the form of carbohydrate leads to a relatively quick rise in blood glucose [48]. The maximum blood glucose response in a healthy individual is usually reached between 20 and 40 minutes after eating. The rise in blood sugar due to food consumption is determined and influenced by a number of factors including:

- The amount of carbohydrate contained in the food that is consumed (Section 2.2);
- The glycaemic index of the carbohydrate in the consumed food (Section 2.3);
- The morning or first meal effect (Section 6.2.2);
- The mixed meal effect (Section 6.2.2);
- The second meal effect (Section 6.2.2);
- The characteristics of the individual human body in question (Chapters 3 and 4).

As described previously, the process of digestion and processing by the liver releases a certain amount of glucose in the blood (1), causing the blood sugar level to rise. This rise is easily and accurately measurable through commercially available test kits [61],[62].

The blood glucose level is controlled by a range of control mechanisms. These include impulses or triggers from the central nervous system, and a series of hormones. Whereas nerve impulses are electrical in nature and quick, the effect of hormones is slower because they have to be transported through the blood vessels to their target organs upon which they act [42].

For the purposes of clarification of the blood glucose control system, the hormones are divided into two groups, namely storage hormones and retrieval hormones [48].

### 6.5.1 Storage hormones

A storage hormone has the effect of facilitating storage of blood glucose in the liver and tissues, and thus lowering the blood glucose concentration. There is only one storage hormone present in the human energy system, namely insulin [52]. From a control point of view, insulin secretion from the pancreas (14) is triggered in three different ways:

- Glucose Dependent Insulinotropic Peptide (GIP). The plasma level of GIP increases after meals containing carbohydrates or fats are consumed. GIP serves to act as a mechanism to “prepare” or “warn” the pancreas of an incoming glucose load, and early insulin is secreted in anticipation (30) [63].
- The senses, which are controlled by the central nervous system, also act as an anticipatory mechanism for insulin release (19). Upon the sight, smell or taste of food the pancreas is triggered to release a small amount of insulin to prepare for incoming glucose load.
- The primary mechanism for triggering insulin secretion (14) however is elevated blood glucose concentrations (13). Insulin is also secreted in the presence of other fuel molecules such as amino acids and fatty acids, but their effect is considerably less when compared to glucose. The glycaemic threshold for insulin is about 4.1 mmol/l, which means that below this plasma glucose concentration the secretion of insulin will be inhibited [9].

With insulin present glucose is converted into glycogen for short-term availability to the liver (4). It is also converted into tricyclerides for longer-term storage or other utilisation [63]. Glucose flow to the liver has a lowering effect on the blood glucose levels.

In the muscles tissue insulin causes glucose to be converted into glycogen for short-term storage (2). The glycogen can later be retrieved for utilisation as fuel.

In the presence of insulin glucose is converted in the adipose tissue to triglycerides for long-term storage (6).

### 6.5.2 Retrieval hormones

All the blood glucose counter regulation hormones have the effect of increasing blood glucose concentrations and can be classified as retrieval hormones. The design of these controls seem to be

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primarily geared for protection of the central nervous system above all else. The retrieval hormones include glucagon, adrenalin (epinephrine), cortisol, growth hormone and thyroid hormone.

The retrieval (counter regulation) hormones each act as follows (more detail is given in Section 6.4.3 and 6.4.4):

- The primary hormone for increasing blood glucose concentrations is glucagon. It is secreted by the pancreas to increase blood glucose levels (15) whenever blood glucose concentrations fall below a value of about 3.8 mmol/l (13) [54],[64].
- Adrenalin is also secreted by the adrenal glands to increase blood glucose levels (16) when they fall below plasma glucose concentrations of about 3.8 mmol/l. Adrenaline secretion is primarily controlled by the central nervous system (21). Large amounts of adrenalin and noradrenalin under “fight or flight” conditions can be released via direct trigger from the central nervous system (21) [57],[64].
- Growth hormone is released from the pituitary gland to increase blood glucose levels below plasma glucose concentrations of about 3.7 mmol/l (23). The control pathway is via the central nervous system (26), and hypothalamus (25) [59],[60],[64].
- Cortisol is secreted by the adrenal glands to increase blood glucose levels (17) below plasma glucose concentrations of approximately 3.2 mmol/l. Cortisol is controlled by the central nervous system (26) via the hypothalamus (25) and pituitary gland (22) [55],[64].
- Lastly thyroid hormone is secreted by the thyroid gland and it also increases blood glucose levels. The controlling pathway is via the central nervous system (26), hypothalamus (25) and pituitary gland (24) [45],[64].

	<b>Hormone</b>	<b>Upper control limit mmol/l blood glucose concentration</b>
1	Glucagon	3.8
2	Adrenaline	3.8
3	Growth hormone	3.7
4	Cortisol	3.2

*Table 6.1 – Control setpoints for counter regulation (retrieval) hormone release.*

The above table shows the control setpoints at which the various counter regulation hormones are released into the bloodstream [64]. Thyroid is not among the list in Table 6.1 because it is released continually and not only in the event of low blood sugar levels.

Energy utilising processes such as metabolism, exercise (29) and stress (28) affect blood glucose regulatory and counter regulatory control via the central nervous system (20), (21), (26) [4],[35]. There is also a nervous control pathway between the hypothalamus and posterior pituitary gland but it is not shown in the diagram. The reason is that the production of hormones oxytocin and ADH, which are regulated along this route, are not associated with blood glucose control.

The process of retrieval of stored fuels for utilisation incorporates accessing the stored reserves, converting them back into glucose and releasing the glucose into the bloodstream. This has a blood glucose increasing effect [48]. The retrieval of stored fuels and their conversion into blood glucose happens as follows:

- Glycogen is converted in the liver back into glucose and released into the bloodstream in the presence of one or a combination of the retrieval hormones (5).
- Glycogen is also converted in muscle tissue back into glucose and released in the blood in the presence of the retrieval hormones (3).
- Glycogen is furthermore converted to lactate and pyruvate in the muscle tissue. That is then transported to the liver and converted into glucose in the presence of one or more of the retrieval hormones (8).
- Triglycerides are converted into glycerol in the adipose tissue, transported to the liver and converted into glucose in the presence of the retrieval hormones (9).

### 6.5.3 Utilisation

Utilisation of blood sugar indicates the usage of glucose in the blood as energy source and therefore it will have a net effect of lowering blood glucose concentrations. Insulin is required to enable the body to burn glucose for energy [52]. In the absence of insulin fats are burned as energy source. Glucose is burned as fuel for basal metabolism in all tissues including the muscles (2), liver (4), adipose tissue (6) and nervous tissue (7), thereby reducing blood glucose levels. The same processes occur at an accelerated pace when the body performs any action such as exercising.

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An exception to the blood glucose-lowering rule of utilisation may occur in Type 1 diabetics where the absence of insulin prevents the utilisation of blood glucose, rendering it effectively unavailable [48]. The body's control system interprets this unavailability of insulin as a shortage of blood glucose (since little energy can be absorbed from the bloodstream) and therefore, control mechanisms are activated to raise blood sugar levels even further (29). This results in the reversed phenomenon of blood sugar levels increasing under these conditions, especially common during exercise.

Stress is another stimulus that effects blood sugar concentrations. Stress, both short and long term, result in increasing blood glucose levels (28). This is due to the secretion of the retrieval hormone adrenalin under stressful conditions that raise blood glucose [25].

Storage of glucose, made available in the blood from fuel intake, causes the removal of the glucose from the blood and moves it into the storage facilities. This process has a blood glucose lowering effect. As in the case of glucose utilisation for energy, insulin is also required for "unlocking" the tissues for glucose (or other fuel types) storage. It has been established that without insulin, it is difficult for a human to gain weight attributable to ineffective storage. Storage of blood glucose in the main storage facilities happens as described in 6.2.4 [48],[50].

## 6.6 Conclusion

In this chapter a description and a schematic layout of the human energy system was given. The interactive control strategies associated with the system was outlined and presented schematically.

The extent of the information provided indicates that the system is relatively complex, which offers an explanation as to why successful simulations have not been performed prior to this study. As can be seen, the flow of especially energy is very integrated and therefore not quantified in a practical manner.

With the aid of the ets concept derived in Section 2.4 the complex processes of the human energy system can now be simplify. In the following chapter a simplified model is presented for the simulation and prediction of blood glucose response according to various influences.

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