Humans store the vast majority of their energy as adipose tissue triacylglycerols. By contrast, very little energy is stored as the carbohydrate glycogen in liver and muscle. Energy storage as triacylglycerols is about nine times more efficient than energy storage as glycogen. This is partly because the oxidation of 1 g fat gives about twice the energy as the oxidation of 1 g carbohydrate due to its more reduced nature and partly because storage of energy as glycogen requires the storage of associated water, whereas storage of energy as triacylglycerols does not.

The principal metabolic fuels used by tissues are glucose, fatty acids, and ketone bodies. When human metabolism is subject to stresses such as starvation or sustained exercise, stores of glucose as glycogen are quickly exhausted and the body turns to its very much larger stores of triacylglycerols to provide the energy needed. Accordingly, human metabolism in starvation or sustained exercise is characterized by a shift away

**References**

from the use of glucose as a fuel and towards the use of the triacylglycerol-derived fuels, namely fatty acids and ketone bodies.

It is the purpose of this article to describe the metabolic adaptations that occur in response to starvation and sustained exercise. An increased production and utilization of triacylglycerol-derived fuels is central to this process.

**Lipolysis in adipose tissue**

Fatty acids and ketone bodies are ultimately derived from adipose tissue triacylglycerols. A key metabolic event in this process is the intracellular hydrolysis of adipose tissue triacylglycerols, a process referred to as lipolysis. Two lipases are involved. Hormone-sensitive lipase (1) catalyses the removal of fatty acids esterified to positions 1 and 3 of glycerol and the process is then completed by monoacylglycerol lipase which catalyses the removal of fatty acids esterified to position 2. The fatty acids released in lipolysis are then transported in the circulation bound to the protein albumin to tissues such as muscle and liver. The whole process of converting intracellular triacylglycerols into circulating fatty acids is often referred to as fatty acid mobilization.

Activation of lipolysis is essential in starvation and sustained exercise and this is accomplished by activation of hormone-sensitive lipase. The principal restraining influence on the activity of hormone-sensitive lipase is the hormone insulin which is accordingly an anti-lipolytic hormone. When circulating concentrations of insulin are high, as they are in the fed state and at rest, then hormone-sensitive lipase and hence lipolysis are inactive. However, in starvation or sustained exercise circulating concentrations of insulin drop and hormone-sensitive lipase is released from inhibition. This mechanism is reinforced by a rise in the circulating concentrations of a group of lipolytic hormones which stimulate the activity of hormone-sensitive lipase. Prominent among these lipolytic hormones is adrenaline.

**Fatty acid oxidation in muscle**

Skeletal muscle is one of the major users of glucose in the human body. Consequently, inhibition of the use of glucose by skeletal muscle in starvation and sustained exercise makes a major contribution to the conservation of glucose which is in short supply in these two conditions. This is achieved by replacing glucose with fatty acids.

The ability of skeletal muscle to use fatty acids as a fuel is permanently present and waiting to be used. Mobilization of fatty acids from adipose tissue provides that opportunity. The oxidation of fatty acids by skeletal muscle is proportional to their concentration in the circulation. Consequently, the higher the rate of mobilization of fatty acids from adipose tissue, the greater their rate of oxidation in skeletal muscle.

However, the mobilization of fatty acids from adipose tissue has a second and crucial metabolic effect. Some of the products of fatty acid oxidation are also inhibitors of key enzymes of glucose utilization. For example, acetyl-CoA is an inhibitor of pyruvate dehydrogenase, a key enzyme of glucose oxidation, and citric acid and glucose 6 phosphate are inhibitors of the key glycolytic enzymes phosphofructokinase and hexokinase respectively (2). As fatty acid oxidation proceeds so these inhibitors accumulate and the rate of glucose utilization is inhibited. This biochemical mechanism ensures that fatty acids replace glucose as a fuel for skeletal muscle during starvation or sustained exercise.

Hence there is a reciprocal relationship between rates of fatty acid and glucose use in skeletal muscle. This relationship is referred to as the glucose fatty acid cycle (3).

**Ketone body synthesis in liver and oxidation in brain**

Like muscle, many other tissues are able to switch from using glucose as a fuel to using fatty acids. However, brain is an exception to this rule as the blood brain barrier is impermeable to fatty acids. Since brain is also a heavy user of glucose, inhibition of glucose use by this tissue would also make a major contribution to glucose conservation in starvation and sustained exercise. The problem posed by the impermeability of the blood brain barrier to fatty acids is effectively solved by the liver which is able to convert fatty acids into ketone bodies (4).

The so-called ketone bodies, namely acetoacetic acid and 3-hydroxybutyric acid, were originally discovered in the urine of diabetic patients. As a result they were for a long time believed to be the products of a disordered metabolism and of no physiological importance. While it is true that the ketone bodies are over-produced in diabetes we now know that they are of considerable physiological importance as metabolic fuels. Ketone bodies can be considered as short-chain (four carbon) water-soluble alternatives to fatty acids which can be taken up rapidly by tissues such as the brain and oxidized for energy.

The rate of oxidation of ketone bodies, like the rate of oxidation of fatty acids, is proportional to their circulating concentration. In the brain they are the only alternative fuel to glucose and their oxidation results in the accumulation of the same inhibitors of key enzymes of glucose utilization as accumulate in response to the oxidation of fatty acids. Consequently ketone bodies replace glucose as fuel for the brain. An
important difference between the two triacylglycerol-derived fuels is that while fatty acids completely replace glucose as a fuel in muscle, ketone bodies only partially replace glucose as a fuel for brain.

**Ketone bodies and the Atkins diet**

Mobilization of fatty acids from adipose tissue and ketone body synthesis by the liver are generally associated with conditions such as starvation and sustained exercise. Both conditions are characterized by low circulating insulin concentrations which release lipolysis from inhibition. However, the consumption of diets having zero or very low carbohydrate content is also associated with low circulating insulin concentrations because glucose is the major stimulus for insulin secretion. These diets used to be called ketogenic diets and the most famous recent example is the Atkins diet.

The idea behind the consumption of a low-carbohydrate diet such as the Atkins diet is to stimulate the mobilization of fatty acids from adipose tissue. This will allow the loss of body fat providing these fatty acids are subsequently oxidized by tissues such as skeletal muscle. One indication that the Atkins diet is working is that the liver converts fatty acids into ketone bodies which can be smelt on the breath of people following low-carbohydrate diets in much the same way as they can be smelt on the breath of diabetics.

However, there is a major difficulty with the metabolic logic behind the Atkins diet. While it is true that glucose is the major stimulus for insulin secretion it is not the only stimulus. The Atkins diet has a low, or even zero, carbohydrate content. However, such diets are inevitably high-fat, high-protein diets. Since certain amino acids also stimulate insulin secretion then high-protein diets also stimulate insulin secretion. It is accordingly unclear why the Atkins diet should stimulate the mobilization of fatty acids from adipose tissue and the production of ketone bodies by the liver if it has only minimal effects on insulin secretion.

**Conclusions**

The human body’s stores of carbohydrate as glycogen are limited whereas its stores of fat as triacylglycerols are huge. Consequently when human metabolism is subjected to stresses such as starvation or sustained exercise tissues switch from using glucose as a fuel to using the triacylglycerol-derived fuels, namely fatty acids and ketone bodies. This adaptation allows the conservation of glucose which is in short supply. The signal for this switch towards the use of fatty acids and ketone bodies as fuels is the fall in the circulating insulin concentration.

Low-carbohydrate diets such as the Atkins diet attempt to use these features of human metabolism for the purpose of losing body fat. It is proposed that since glucose is the major stimulus for insulin secretion then consumption of low carbohydrate diets will be accompanied by low concentrations of circulating insulin. However, this attempt is flawed because low-carbohydrate diets are inevitably high-protein, high-fat diets and the amino acids derived from dietary protein, like glucose, can stimulate insulin release. Hence it is unclear why the Atkins diet should result in any permanent loss of body fat.

**References**


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**7th Congress of ISSFAL to be held in Australia**

On 23–28 July 2006 in Cairns, Queensland, Australia, a combined meeting will take place of three groups run under the auspices of The International Society for the Study of Fatty Acids and Lipids (ISSFAL). The groups are ISSFAL, the ‘Essential Fatty Acids & Eicosanoids Congress’, and the regular meeting of the ‘PUFA in Maternal & Child Health’ interest group.

The meetings will focus on: fatty acids and brain plasticity across the life cycle; fatty acid and carbohydrate interactions; fatty acid biosynthesis, metabolism and catabolism; eicosanoids and docosanoids — the old and the new; maternal and infant PUFAs; fatty acids and obesity; inflammation and immunity; genes and dietary fats; and drug-nutrient interactions.

For further details, contact: 2006 ISSFAL Conference, Festival City Conventions Pty Ltd, PO Box 949, Kent Town, SA 5071, Australia; tel: +61-8-8363-1307; fax: +61-8-8363-1604