Metabolic functions of skeletal muscles of man, mammals, birds and fishes: a review[1]

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Concept of the storage function of muscle

The skeletal muscles are always thought of as relatively small individual units and we forget that, taken together, these units, which are composed of an almost identical tissue, constitute a huge organ, which represents a large proportion of the body mass. While the obvious function of the skeletal muscles, the production of movement both for locomotion and for the maintenance of posture, has been studied in great detail, little attention has been paid to another function of this great mass of homogeneous tissue. The second function is the provision of a large reservoir of protein, which enables the muscles, working in concert with the liver, to regulate the levels of glucose and of amino acids in the circulating blood in the various conditions which lead to alterations in these levels.

In a normal 70 kg man it is customary to think of the liver, weighing some 1.5 kg, as the largest organ in the body; but the skeletal muscles, weighing about 32 kg and making up roughly 45% of the total body mass, are some 20 times the weight of the liver. The major constituent of both liver and muscles, apart from water, is protein and much of this protein is labile: it is continually being broken down and resynthesized. The rate of breakdown and resynthesis differs considerably in the various tissues of the body. For instance, Millward (1970) has shown that the daily turnover rate of liver protein is of the order of 48% whilst the turnover rate of the protein of skeletal muscle is 12%. However, when one takes into account the relative sizes of these two masses of tissue, the actual amount of protein that is broken down and resynthesized in the muscles is twice as large as that in the liver. It is the labile nature of muscle protein which enables the skeletal muscles to act as a storage organ and thus to play an important part in maintaining the levels of glucose and of amino acids in the circulation. The advantages of a rapid protein turnover in muscle and liver, as a means of adapting to a changing environment, have been emphasized by Swick & Song (1974).

Maintenance of relatively normal levels of blood glucose by the muscles during fasting

There are various conditions which lead to a diminution in the concentration of glucose in the blood, but we will examine here one state which illustrates admirably our new concept of the second, metabolic, function of the skeletal muscles (Daniel *et al.* 1977*a*). This is the state of fasting. When an animal fasts, the glycogen in the liver (and to a lesser extent the glycogen in the muscle) which represents the body's store of carbohydrate, is used up within a day (Hultman & Nilsonn 1971), while in small children it is used up within a few hours. The level of glucose in the blood thus begins to fall. However, it does not fall far since the circulating glucose is maintained, although at a lower level, by the synthesis of glucose in the liver from amino acids: a process known as gluconeogenesis. This process causes a reduction in the levels

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in the blood of those amino acids which are used by the liver to make glucose, i.e. the gluconeogenic amino acids. In response to these reductions in levels, the skeletal muscles start to release amino acids into the circulation, and thus partially restore the amino acid levels or at least limit the extent of their fall in the blood. The muscles thus act as a potential source of protein from which amino acids can be released at need, and following this line of thought, we have regarded the muscles as a great reservoir of protein which can be used to store or release at need gluconeogenic amino acids (Baños *et al.* 1973*a*, Daniel *et al.* 1975, 1977*a, b, d*). Subsequently we have made a number of studies of the way in which the release of amino acids from this store is regulated by changes in the balance of various hormones and of alanine in the circulation (Daniel *et al.* 1977*b, c, d*, 1978*b, d*, 1979*b*). The results of our work are summarized in Table 1.

Table 1. The effect of fasting and of other procedures upon the synthesis of glucose from gluconeogenic amino acids by the liver and upon their release of these amino acids from the skeletal muscles of rats and rabbits.

State of animal	Synthesis of glucose from amino acids (gluconeogenesis)	Circulating gluconeogenic amino acids (% of control)	Release of amino acids from muscle (% of control)
Fed (controls)	Normal	100	100
Fasted (*a, b*)	Raised	75	163
On protein-free diet (*b*)	Normal	105	111
Given glucagon (*a*)	Maximal	60	200
Given glucagon + substances for gluconeogenesis (*a*)	Maximal	100	zero (or reversed)
Isolation of 25% of muscle mass (*c*)	Normal	75	75

(*a*) (*b*) (*c*): Daniel *et al.* 1977 *a, b, c*

Way in which muscles maintain levels of amino acids in the blood

The proteins of the muscles are in a constant state of flux, being broken down into amino acids and resynthesized continuously, and at a surprisingly rapid rate. There is a ceaseless exchange of the free amino acids in the pool in the muscle cells, some being reincorporated into the protein of the muscles; some passing out into the circulating blood, whilst some of those in the blood enter the pool. During fasting, when the levels of the gluconeogenic amino acids in the circulation fall, a greater proportion than normal of free amino acids from the pool in the muscle cells enter the blood stream and are therefore no longer available for the resynthesis of muscle protein. Since, when protein is synthesized, it is essential that a mixture of amino acids is present in the correct proportion, the loss of the glucogenic amino acids from the pool prevents the remaining amino acids from being used for resynthesis of muscle protein. Thus the excess of those amino acids which are not gluconeogenic leaves the free pool and enters the circulation. The unavailability of some of those amino acids in the pool which are needed for the synthesis of muscle protein causes a slowing down of the rate of synthesis of this protein and therefore leads to wasting of the muscles. A short fast will lead to minimal, virtually undetectable wasting of the muscles. However, in prolonged starvation in man by far the most prominent visible evidence of lack of food is the wasting of the muscles. In the concentration camps of Nazi Germany or in famines (Figure 1), people might lose half their body weight (Helweg-Larson *et al.* 1952). Since the skeletal muscles make up 45% of a man's total weight (Widdowson & Dickerson 1960) this means that over half their muscle mass had been lost. Yet, in spite of this severe loss of muscle, the unfortunate men in the camps could still be forced to run and to work, albeit inefficiently. Thus, one is compelled to conclude that the normal, well-nourished human being has a mass of muscle which is well in excess of his normal needs for movement.

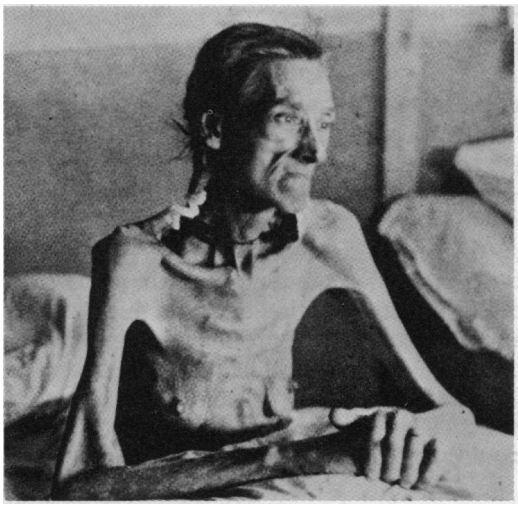

Figure 1. Loss of muscle in a survivor of the Dutch famine, 1944–45. (Reproduced by kind permission from: Malnutrition and Starvation in Western Netherlands (Part 1, p 85, Fig. 30). Ed. G C E Burger, J C Drummond and H R Standstead. General State Printing Office, The Hague, 1948)

In addition the metabolic functions of the muscles may be of considerable importance in various pathological conditions, e.g. haemorrhage (Daniel *et al.* 1977*d*) and the muscular dystrophies (Daniel *et al.* 1978*c*, 1979*a*; Spargo *et al.* 1979).

Evidence from experiments in man that the muscles act as a store of protein

Can the experimental results shown in Table 1 be applied to man? It has been found that there is, at rest, a release of gluconeogenic amino acids, especially alanine, from the muscles in man and that the release is increased by fasting (Pozefsky *et al.* 1969, Marliss *et al.* 1971). However, the majority of these studies have been carried out on obese subjects who 'have ample calories on board' (Cahill & Aoki 1971).

In the Minnesota study, Keys *et al.* (1950) maintained healthy young men on a reduced food intake for approximately six months. The authors estimated the quantity of 'active tissue' (i.e. body mass minus bone, fat and extracellular fluid) before and at intervals during the period of semi-starvation and during refeeding, and found that at the end of 24 weeks of semi-starvation there had been a reduction of 'active tissue' of some 26%. From the figures of Widdowson & Dickerson (1960) we find that the major viscera account for some 14.5–16% of the body mass and we can calculate that the changes in 'active tissue' are reflected in similar changes in muscle mass; we calculate from these figures that the 26% reduction in 'active tissue' found by Keys *et al.* (1950) represents approximately a 29% reduction in muscle mass. During this period of semi-starvation the total body weight had fallen by some 23%. Subsequent refeeding restored the body weight and mass of muscle and active tissue, although the repletion process was very slow, 2½ times longer than the depletion period.

Storage function of muscles in birds

There is an interesting parallel to our work (which was done on small mammals and on a few cases of muscle wasting in man) in the way non-mammalian species, such as birds and fishes, make use of their skeletal muscles as a store of protein, from which amino acids can be released not only during food deprivation but also during other special periods such as migration or breeding. There is now evidence that the pectoral muscles of certain birds provide a means of storing protein, especially during the migratory period. In the premigratory

fattening period a small but significant increase in muscle protein content has been recorded in the lesser redpoll (*Carduelis flammes*), Swainson's thrush (*Hylocichia ustulata*) and in the yellow wagtail (*Motacilla flavia*) (Evans 1969, Child 1969, Fry *et al.* 1972). Ward & Jones (1976) have shown that hypertrophy of the flight muscles also occurs in one of the weaver birds, the red-billed quelea (*Quelea quelea*), in the premigratory fattening period. These authors calculate that 0.03 g of protein is stored in the flight muscles for each gram of fat laid down. These small birds (weighing only some 20 g) eat voraciously for about 10 days preceding migration and lay down about 2.0–2.5 g of fat according to the distance they migrate and there is a corresponding 10% increase in the weight of flight muscle protein. Jones & Ward (1976) have also shown that the quelea accumulate protein in the flight muscles immediately before the breeding season. They found that at the start of the breeding period the flight muscles were heavier than at any other time in the year and calculated that the pre-breeding increase of muscle protein was some 80% in the female but only 14% in the male. Thus the store of protein in the muscles may be drawn upon in times of deprivation and replenished in times of plenty. In the quelea and other birds the process is particularly highly developed, since protein is stored in the muscles in anticipation of future requirements.

Storage function of muscles of fishes

Perhaps the most spectacular examples of the storage function of the muscles are seen among the fish. Love (1970) has shown that when cod (*Gadus morhua*) are starved there is an increase in the water content of muscle and a corresponding loss of protein nitrogen. Increase of the water content of muscles is a characteristic feature of starvation which is seen in all animals, but the record appears to be held by a fish. Templeman & Andrews (1956) reported finding naturally depleted specimens of *Hippoglossoides platessoides* off the Newfoundland Grand Banks. The fish were so depleted of protein that their muscles had a jelly-like consistency. The most jellied specimen they investigated was found to consist of 2.83% protein and 96.18% water (representing a loss of protein of the order of 80%). Love (1970) has also shown that such increases in the water content of the muscles are reversible on refeeding and Love & Laverty (1977) have made an interesting study of jelly muscles. As in other animals the muscle protein of fish appears to be broken down in response to falling levels of the gluconeogenic amino acids, and Creach & Serfaty (1965) have shown that starvation in the carp seriously reduces the blood levels of the gluconeogenic amino acids, particularly glycine and alanine.

Necessity for a store of protein

Of all the organs in the body the needs of the brain for glucose and amino acids are the most imperative. It has long been known that a lowering of the blood glucose leads to clouding of consciousness, convulsions and finally death. It is less well known that alterations in the levels of amino acids in the blood also cause abnormalities in the brain, although the mental changes seen in phenylketonuria have long been appreciated. We have suggested that these changes may be due not only to the ill effect of raised levels of phenylalanine in the blood, but also to a diminution in the supply of other amino acids which are excluded from entering the brain by these high levels of phenylalanine (Baños *et al.* 1974*a, b*). We have shown elsewhere the continuous needs of the brain for glucose and amino acids in the adult animal and at various ages (Bachelard *et al.* 1973, Baños *et al.* 1973*b*, 1975, 1978, Daniel *et al.* 1978*a*), and we now see that the skeletal muscles of mammals, birds and fishes can and do act as a huge metabolic and storage organ which functions to maintain glucose and amino acid levels in the blood to meet the brain's continuous demands for these substances.

Conclusions

The protein of the skeletal muscles acts as a major store from which amino acids can be drawn when circumstances lead to a fall in the levels of blood glucose and of amino acids in the circulation.

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