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Immediate Energy Sources in Muscle Contraction

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Heat and Work

Muscle contraction obviously produces mechanical work. But it also produces a quite large amount of heat: this can be well appreciated by the progressive warming of a ballroom full of swinging dancers.

In the middle of the last century, *Joule* showed that any mechanical work can be converted into heat, and he derived a way to express this correlation very accurately. This finding was a momentous event in the development of the physical sciences, because it showed that heat and mechanical work are but two facets of the same underlying fundamental thing. That thing, which never changes its substance (so to speak) but shows itself under various appearances, was called 'energy'. If heat and mechanical work are fundamental manifestations of the same 'thing', they can be measured with the same yardstick, the same 'unit'. We no longer use the old physical units employed by *Joule* but, in his honor, we use a unit of energy named after him. Technically, *1 J* is the amount of mechanical work produced when a force of 1 N displaces itself by I m. It is difficult to figure out the size of this unit: in a very rough way, 1 *J* is about equal to the work needed to pick up a small-sized apple from the ground into one's pocket. On the other hand, if 1 *J* of energy were used to heat a spoonful] of water (i. e. about 5 g), the temperature of the water would rise by about 1/20°C.

If heat and work can be interconverted, it is natural to hypothesize that the work produced by our muscles could be explained by some transformation of the 'animal heat'. However, it was soon evident that this theory would not do. It is indeed clear that if our body produced work from heat, it

should cool when it works; the most casual observations show that the reverse situation is true: our body warms when it works. More detailed studies have disclosed the fact that most of the heat produced in our working body is produced in the muscles themselves. These studies showed also a second fact, perhaps surprising: a contracting muscle produces far more energy under the form of heat than under the form of mechanical work. Thus, when we consider the energy produced by a muscle, we must add to the work the superimposed heat. The ratio of the work over the total energy (heat + work) used by the muscle is called the efficiency. In the most favourable situation, the efficiency may be as high as 0.4, but it is usually much lower, between 0.2 and 0.3.

If the mechanical work produced by our muscles cannot come from transformation of our body heat, where does it come from?

Chemical Energy

The answer to this question is quite subtle. For a long time, it was thought that our body created that work from its own vitality. A living being moves. Its movement is so natural, so inherent to its state of being alive, that absence of motion is one of the best signs of death for higher animals and man. It seemed, for a long time, that no explanation was needed: a man moves about because he lives. That seemed sufficient as an explanation, until *Mayer, Helmholtz and Joule* (around 1840) set forth their bold hypothesis that energy can be neither created nor destroyed and, therefore, that our muscles can create neither mechanical work nor heat.

We know that many chemical reactions proceed in our body, and it is natural to postulate that muscular energy is brought about from chemical transformations. However, we need a method that enables us to evaluate the size of the energy set free during a chemical transformation. This can be done quite easily if the reaction occurs freely in water, because then all of the chemical energy liberated will be captured by the surrounding water molecules. Those molecules will move about more rapidly, i.e. the water will warm. Suppose that a reactant A is transformed into a reactant B: the amount of heat that is set free when 1 mol of A has been transformed into 1 mol of B is called the 'molar enthalpy change' of the reaction and it is symbolized —AHA (the minus sign is conventional). If this energy can be harnessed by a suitable structure, a fraction of it (which can be greater than unity) may be transformed into mechanical work. In muscle, reactions do not occur freely in

water; therefore, the enthalpy set free by chemical reactions is handled by complex structures which change their shape and produce the contraction, releasing thus mechanical work. This deformation requires only a fraction of the energy set free, the remaining energy being turned into heat.

The respective size of the mechanical versus the heat fraction need not be fixed (it is indeed variable), but their sum must add up to the chemical energy set free. There is every reason to think that there are several chemical reactions which occur simultaneously in muscle during (and after) the contraction. The concept can be easily extended to this case. Eventually, we may set the problem in accurate terms in this way. Suppose that i reactions occur in muscle, then [*Wilkie,* 1960]:

$$W + Q = - n_1 AHi - n2AH2 \quad - n10Hi. \tag{1}$$

This fundamental equation describes the energy balance in muscle. On the left-hand side, it gives the energy which *leaves* the muscle under the form of work (W) or heat (Q). On the right-hand side, it gives the energy that is *mobilized from* the chemical reactions. The term ni equals the amount (in moles) of substance i that has been used in reaction i, and —LH_1 is the molar enthalpy change of reaction i.

Energy Balance Sheet

Equation 1 is a powerful tool which enables us to analyse accurately the energy flow in muscular contraction by asking the relevant questions and giving us the hints for performing the most informative experiments.

It shows clearly the main steps to be taken. First the reactions which occur in the muscle must be identified. Second, the amounts of each substrate produced during (or after) the contraction must be measured. The enthalpy changes (-6,Hi) for each reaction can be measured separately in vitro. The mechanical work (W) and the heat (Q) produced by the muscle must be accurately determined. When all these data are at hand, they can be inserted into equation 1 and, if everything is correct, the equation must be balanced.

This programme of research looks large, and it is indeed. Although the first steps were taken by *Lavoisier,* the final one is not yet with us. However, our present knowledge, built on the works of several generations of scientists, has most probably reached its final stage, only details are seemingly lacking (although, as we shall briefly discuss it later, a major change in our ideas is not excluded).

Chemical Reactions in a Contracting Muscle

The number of *identified* chemical reactions which occur during a muscle contraction is very large; the number of *unidentified* chemical reactions is perhaps still larger. It seems hopeless to obtain a complete energy balance sheet. Such a situation is common in science. The usual way around that difficulty, here as elsewhere, is to neglect the things that although relevant are quantitatively unimportant. Being concerned with the energy flow in muscle, we need to be concerned only by reactions which mobilize sizeable amounts of energy. This means that the chemical energy set free by reaction i (i. e. = niAHi) must be of the same order of magnitude as the energy (heat + work) produced by the muscle.

Although this proviso lowers considerably the number of the relevant chemical reactions, we are still left with a bewildering variety of them. The analytical process has been to try to stop as many reactions as possible, either by suppressing substrates or by poisoning enzymes without impairing the contraction itself.

A third important consideration refers to cyclic reactions. If a compound A gives off AH J/mol when it is transformed into compound B, inversely, the transformation of 1 mol of B back into 1 mol of A absorbs AH J/mol. Thus, the overall transformation of A into B followed by B into A involves no net exchange of energy. Therefore, cyclic reactions do not appear in the energy balance sheet. This is a happy property, since it means that the cyclic changes which are brought about in the contractile proteins can be left aside. It is known nowadays that the exchange of energy during the cycling of the contractile proteins is far from being small. Some steps produce a large amount of energy *[Curtin and Woledge,* 1978], but other subsequent steps absorb an equally large amount. Although cyclical transformation of the contractile proteins during a muscular contraction may be neglected in an energy balance sheet, their turnover must be kept going by a constant influx of energy. It has been shown definitely that one single chemical reaction is responsible for it.

Immediate Source of Energy in Muscular Contraction

Adenosine triphosphate (ATP) was discovered in 1928 by *Lohmann* in investigations designed to uncover the chemical reactions which set free the energy needed for contraction. This compound can split into two smaller

molecules, namely adenosine diphosphate (ADP) and phosphate (P1). The splitting of I mol (about 625 g) of ATP liberates a quite large amount of energy, i.e. about 48,000 J. Chemical energy appears thus to be quite 'concentrated energy'; this means that the splitting of a small amount of ATP allows the production of a rather large amount of mechanical work. Returning to the example mentioned here above, if 1 J is needed to pick up one apple, then the splitting of 625/48,000, i.e. 13 mg, of ATP is sufficient to account for the mechanical work. It is no wonder then that it has been very difficult to measure accurately the amount of ATP split during a muscular contraction. The following energy balance sheet equation can be written:

$$W + Q = n_{ATP} A_{HATP} \bullet \qquad (2)$$

Equation 2 means that the mechanical work (W) and the heat (Q) produced by a contracting muscle must be quantitatively equal to the energy set free by the splitting of n_{ATp} mol of ATP.

Verification of equation 2 by practical experiments has not been possible for a variety of reasons. The main one is that the splitting of ATP is not the only reaction which occurs in a contracting muscle. Other reactions should be taken into account, and they will therefore be described in the next section.

The mechanism of the energy transfer between the ATP molecules and the contractile proteins is still unknown. It is known that ATP binds to myosin (one of the contractile proteins). ATP is then split, but the products (ADP and Pi) remain bound. Then the complex combines with actin (the second important contractile protein). The available energy is transformed into mechanical energy. ADP and Pi are then released. In the final step, actin detaches from myosin, while at the same time myosin binds another molecule of ATP. Thus, the actomyosin system functions as an enzyme able to capture the energy set free by the ATP splitting, and turns it into mechanical work [for reviews see *Curtin and Woledge,* 1978; *Homsher and Kean, 1978].*

Recovery Reactions

It may well be asked why there are so many other reactions occurring normally in muscle during the contraction. Why is it that the above-depicted scheme is not sufficient?

The answer is quite simple. It is found in the fact that the muscle is a very powerful machine with a limited supply of ATP. Its peak power is over 50

W/kg body weight. This can be well appreciated by a comparison. A powerful car develops 100-200 kW, but it weighs 1,000-2,000 kg. Its power per kg is thus about the same as that of a man. However, muscle is a far more complicated machinery than a car. For various reasons, the amount of ATP stored in a muscle must be kept small. In fact, there is so little of it that the muscle would split all of it within 1-2 s when contracting at peak power!

There is thus an absolute need for chemical reactions that furnish fresh ATP to the contracting muscle. These reactions play an important role not only because they supply muscle with the needed ATP, but also for a second reason, which is often very poorly appreciated. The point is that these recovery reactions do not run at an infinite velocity. Therefore, the rate at which they are able to make ATP will limit the rate at which the contractile proteins can split it. Therefore, the peak power of a muscle depends on the type of the recovery reaction which is recruited.

Three main recovery systems are at work in contracting muscle:

1. The Phosphorylcreatine System. Phosphorylcreatine (PCr) can exchaneg a P_i group with ADP. ATP is thus formed and creatine appears:

$$PC_r + ADP \rightarrow ATP + creatine. \quad (3)$$

This reaction is catalysed by a very active enzyme, creatine phosphokinase (CPK) and is thus very rapid. Thus, any ADP which appears in the muscle cytoplasm as a result of the ATP splitting activity of the contractile proteins has a very short life: it is very rapidly phosphorylated back to ATP. Therefore, it allows a sizeable prolongation of muscle activity at peak power (50 W/kg body weight) from 2 to about 10 s.

2. The Glycolytic System. This system consists of a series of several reactions in which glycogen (a normal constituent of muscle cytoplasm) is degraded to lactate. The formation of one molecule of lactate is coupled with the phosphorylation of 1.5 molecule of ADP into ATP. In this system as in the preceding one, the molecules of ADP which result from the contractile activity are rephosphorylated back into ATP as soon as they appear. However, the maximal rate at which this phosphorylation can be done is rather low. If the muscle contracted at its peak power it would soon run out of ATP, because it splits ATP at a rate which is about twice that at which the glycolytic system can supply it. The power output of the muscle must therefore be reduced by half (to about 25 W/kg body weight) if the rate of supply of ATP by glycolysis is to keep pace with the rate of its splitting by actomyosin.

It should be observed that in these two cases no oxygen is needed for the contraction. The muscular power produced in this condition is called anaerobic, the adjective lactacid' being added if lactate is produced and found in peripheral blood. The term `alactacid' is used if no lactate is produced.

3. The Oxidative System. In this system glucose or fatty acids are oxidized to water and carbon dioxide. These reactions are coupled with the phosphorylation of ADP in ATP. The maximal rate of this phosphorylation is quite low, as this system is able to phosphorylate ADP at a rate which is lower than $^1/_3$ of the rate at which ATP is hydrolysed by muscle working at peak power. This means that if the muscles are to contract using the energy (= ATP) produced by the oxidative system, they should contract at a mean power level not exceeding 15 W/kg body weight. This level corresponds to the so called $V0_0$-flax. The two concepts are linked by the fact that utilization of 1 litre of oxygen by the oxidative system is coupled with the resynthesis of 0.268 mol (or 167.4 g) of ATP.

Energy Balance in a Normal Contraction

Oxidative reactions can be easily suppressed by removing oxygen. Glycolytic reactions can be inhibited in part by poisoning the muscle with iodoacetate. In this case, the only significant reactions that provide the energy needed for the contraction are the splitting of ATP and the phosphorylation of ADP by phosphocreatine (equation 3).

It is possible to stimulate a muscle isolated from an animal, to measure accurately the mechanical work W and the heat Q that appear during the contraction, and to evaluate the amounts of ATP (nAlT) and phosphocreatine (n pc) that have been used.

The energy balance sheet is then:

$$W \quad Q = nATPAHATP\ nPCJAHIPC- \tag{4}$$

In equation 4, £HATP and Alipc are the enthalpy changes measured in vitro of the hydrolysis of ATP and of the recovery reaction of equation 3; they are respectively —48 and + 14 kJ/mol *[Curtin and Woledge,* 1978].

The energy balance holds true for all mechanical conditions whether the muscle produces mechanical work (isotonic contraction) or not (isometric contraction) *[Wilkie,* 1968]. It holds true even if the muscle is forcibly stretched during its activity; in this situation, the outside world produces

work *on* the muscle and the sign of W is reversed in equation 3 *[Marechal,* 1972].

These results are very satisfactory in that they provide a quantitative test to the question of the source of the work performed by the muscle. The problem is seemingly solved. However, it is solved only when the muscle mobilizes an amount of energy that is neither too small nor too large. For example, experiments on frog sartorius show that if the energy (heat + work) liberated by the muscle is less than 100 mJ/g muscle (for instance in a 2-s isometric contraction at 0 °C), about 40 mJ/g of energy is left unaccounted for by the chemical reactions that occur during the contraction. Thus, an unidentified process must provide the energy liberated in this case *[Gilbert* et al., 1971]. It seems that this excess heat is produced by side reactions which trigger the muscle contraction.

On the other hand, if the muscle dissipates more than 0.5 J/g during its contraction (as for example during a 10-s isometric tetanus at 20°C) then a sizeable fraction of the energy set free is obtained from unidentified reactions. This fraction may be as large as one third of the total energy liberated by the muscle *[Canfield* et al., 1973]. No chemical reactions are known in muscle that might account for this large excess heat.

Finally there is a further difficulty in that even in contractions where a moderate amount of energy is liberated, there are situations in which there is a temporary dissociation between energy expenditures and energy-yielding reactions. This implies that there is at least one intermediary reaction so far unidentified.

Conclusions

The experiments reported in this paper were performed on frog muscles. The energy balance of man has never been made up to now. It is fair to assume that the muscular power of man is obtained from a chemo-mechanical transduction operated by actomyosin that taps the energy stored in ATP. The usage of ATP and its resynthesis by the three recovery reactions have been ascertained in man. However, it has been impossible until now to measure exactly either the glycolytic power (i. e. the rate of production of lactic acid) or the instantaneous heat production in man. It is thus still possible that a fraction of the energy mobilized at peak muscular power originates from a yet unknown source.

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