

## Energetics

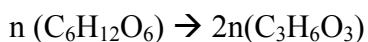
Muscle can be regarded as a machine that converts chemical energy into work. The first and second laws of thermodynamics apply to muscle the same way as they apply to other machines. The first law states that the total energy remains constant when it changes from one form to another:

$$427.263 \text{ kg.m} = 1.000 \text{ kilocalorie} = 4.184 \text{ kilojoules}$$

The ultimate source of our energy resides in the food that we eat. The energy values of the various foodstuffs are known since the beginning of the 20<sup>th</sup> century: When 1.0-g of carbohydrate was oxidized to CO<sub>2</sub> and H<sub>2</sub>O in a bomb calorimeter 4.1 kcal was released. Values for 1.0-g fat or 1.0-g protein were 9.1 or 4.1 kcal, respectively. Similarly, the calorie values of various substances in the body were determined and the next job was to find the chemical substance that directly provides the energy for muscle work.

## Historical Development of Muscle Energetics

The lactic acid theory and its disproof: Experiments at the beginning of the 20<sup>th</sup> century were directed to find the chemical substance that provides the energy for muscle contraction. The procedure was as follows: One of the two gastrocnemius muscles of a frog was stimulated until fatigue, while the other muscle was resting. Both muscles were analyzed for their chemical constituents. In the stimulated muscle the lactic acid content was increased, its formation was equivalent to the glycogen breakdown. Based on this type of experiments, it was postulated that the energy for contraction was provided by glycolysis that is the breakdown of glycogen to lactic acid:



This was called the Lactic Acid Theory. However, Lundsgaard showed in 1930 that lactic acid production is not essential for muscle contraction. He injected one of two frogs with iodoacetate (IA), stimulated one muscle of both frogs to perform a certain amount of work while the other muscle of both frogs was resting (Fig. EN1).



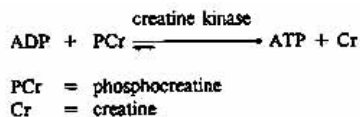
**Fig. EN1.** The Lundsgaard experiment (From Needham, 1971). Tension records; *Upper curve:* Contraction of normal muscle. *Lower curve:* IA-poisoned muscle.

In the IA-injected frog, in which glycolysis was inhibited, the lactic acid content was very small, it was the same in the working and resting muscle; importantly, the phosphocreatine was completely used up in the working muscle (Table EN2). On the other hand, in the control frog, lactic acid production increased about 3-fold in the working muscle (as compared to the resting muscle) whereas the phosphocreatine decreased only slightly. Based on these types of experiments, the Lactic Acid Theory was ruled out and it was suggested that phosphocreatine may be the immediate energy source of muscle contraction.

		Lactic acid	PCr
Normal muscle	Resting	25	61
	Working	84	46
IA-poisoned muscle	Resting	16	57
	Working	15	0

**Table EN2.** Chemical analyses of the muscles from the Lundsgaard experiment, shown on Fig. EN1. Values correspond to mg lactic acid/g muscle and mg PCr/g muscle.

The Lohmann reaction and its inhibition: In 1934, Lohmann showed that in muscle extracts, ATP and PCr were held in equilibrium by a specific enzyme now known as creatine kinase (Equation, EN3):



The equilibrium constant of this reaction is

$$K = \frac{[\text{ATP}] [\text{Cr}]}{[\text{ADP}] [\text{PCr}]} \sim 20 \text{ to } 100$$

**Equ. EN3.** The Lohmann reaction.

Since the equilibrium constant is greatly shifted toward ATP formation and not toward PCr formation, the results indicated that PCr might not be the immediate energy source for muscle contraction. This conclusion was substantiated by the lack of an enzyme in muscle that would hydrolyze PCr into Cr and P<sub>i</sub>. The results also indicated that ATP might be the immediate energy source; demonstration of this required the inhibition of creatine kinase.

Almost 30 years have passed until Cain and Davies (1962) were able to inhibit creatine kinase in frog muscle with 1-fluoro-2,4-dinitrobenzene (FDNB) and thereby measured the decrease in ATP concentration during contraction (Table, EN4). This provided the proof that ATP is the direct energy source for contraction. Without inhibiting creatine

kinase, decrease in ATP concentration could not be measured because the formed ADP was immediately rephosphorylated to ATP via the creatine kinase (Lohmann) reaction. As a matter of fact, during contraction of normal muscle, the ATP concentration remains fairly constant while the PCr concentration decreases.

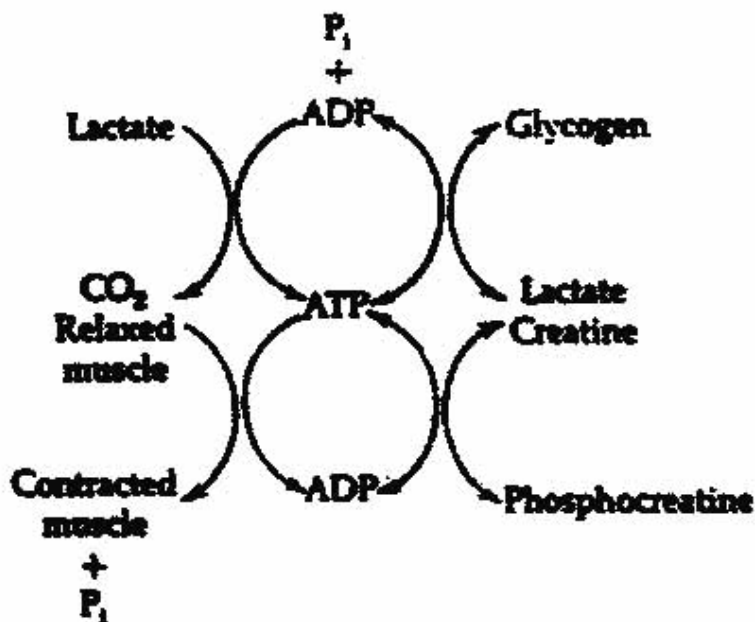
	ATP	ADP
Resting	1.25	0.64
Single contraction	0.81	0.90

**Table EN4.** ATP breakdown in FDNB-treated muscle (Cain and Davies, with permission from *Biochem. Biophys. Res. Commun.*, 1962, Academic Press). Values in micromoles/g wet weight muscle.

### ATP, Phosphocreatine and Glycogen Provide Energy for Muscle Contraction

The direct energy source for muscle contraction is ATP. The contractile protein, actomyosin, hydrolyzes ATP to ADP + P<sub>i</sub>, the used ATP is quickly restored via the Lohmann reaction during contraction (Fig. EN5a). The depleted store of PCr is restored from ATP when the muscle is returned to the resting state.

ATP is synthesized via glycolysis in the sarcoplasm and/or via oxidative phosphorylation in the mitochondria. Glycolysis may occur under anaerobic condition, the yield is 2 or 3 ATP/glucose. The lactate produced from glycogen is oxidized to yield 36 ATP/glucose. Also, dismutation of 2 ADP catalyzed by adenylate kinase yields 1 ATP + 1 AMP.



**Fig. EN5a.** The energy for muscle contraction.

It is important to realize that the ATP concentration in muscle is quite low (5-8 μmoles/g muscle), enough only for a few contractions. The used ATP is immediately

resynthesized from PCr. However, the PCr concentration is also low (20-25  $\mu\text{moles/g}$ ), enough for some additional contractions. Glycogen offers a rapid but still limited energy store (endogenous glycogen concentration about 75  $\mu\text{moles glucose units in glycogen/g muscle}$ ), whereas oxidative phosphorylation is the slowest and most efficient process for ATP production. For example, the glycogen store offers energy for a runner for about 1/2 hr and oxidative phosphorylation for an additional 2 hrs (Paul et al., 1993).

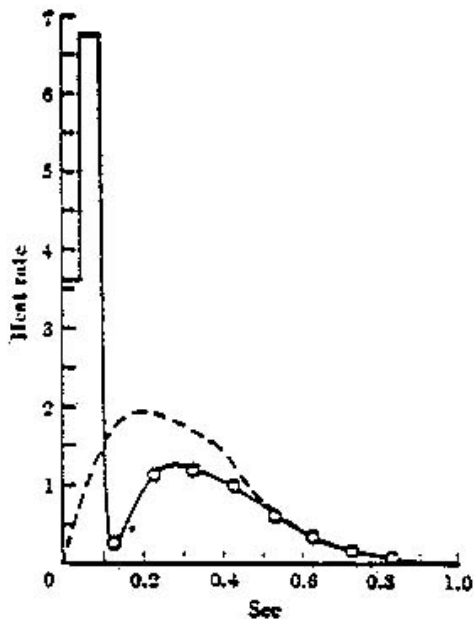
### Heat Production during Muscle Contraction

The muscle converts the free energy of ATP into work and heat. According to the second law of thermodynamics, in a system like muscle, which is *at uniform temperature*, it is impossible to convert heat into work (This is possible in a steam engine, which is not at uniform temperature, but there is a rather large temperature gradient within the engine). It follows that in muscle the heat produced is a lost free energy and the efficiency of the muscle is the ratio of the work produced to the free energy of ATP:

$$\text{Efficiency} = \frac{\text{Work produced}}{\text{Free energy of ATP}}$$

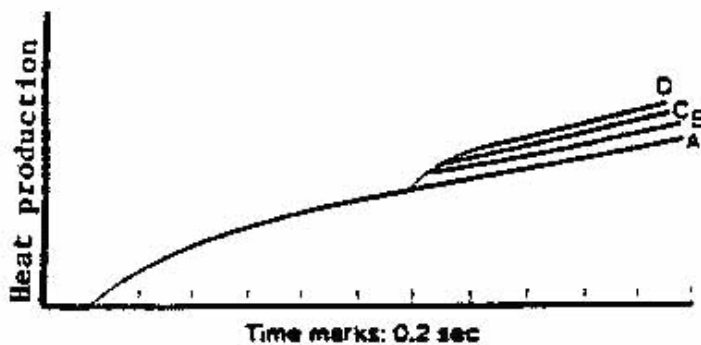
The chemical reactions occurring in muscle generate heat that is vital for maintaining body temperature. Inversely, measuring heat in various phases of muscle contraction indicate the existence of exothermic chemical reactions. A.V. Hill has initiated sensitive and fast heat measurements at the beginning of the 20<sup>th</sup> century. The book of Carlson and Wilkie (1974) describes in detail the heat studies on muscle.

Fig. EN6 illustrates the two phases of heat production during isometric muscle contraction. The activation heat appears in a burst soon after activation of muscle and declines before the full force is reached. It parallels changes in  $\text{Ca}^{2+}$  concentration in the sarcoplasm. The maintenance heat parallels the force produced. This corresponds to the steady state of ATP hydrolysis catalyzed by actomyosin.



**Fig. EN6.** Heat production during a single isometric twitch of frog sartorius at  $0^{\circ}\text{C}$  (From Needham, 1971). Full line, heat analysis; broken line, force curve. Not shown on the Figure is the recovery heat that occurs after contraction. This represents the recovery of energy sources.

During isotonic contraction more heat is liberated than during isometric contraction. Fenn called this extra heat the *shortening heat*. Fig. EN7 shows that the shortening heat is proportional to the shortening of the muscle; the larger the shortened distance, the more extra heat is produced (this is called the Fenn effect).



**Fig. EN7.** The Fenn effect (From Carlson and Wilkie, 1974). Curve A, only isometric contraction. Curves B-D, the muscle was contracting isometrically until it was released and allowed to shorten various distances.

The relationship between energy output and chemical breakdown: If a muscle is completely deprived of oxygen by keeping it in pure nitrogen, and if the formation of lactic acid is prevented by applying iodoacetate, the inhibitor of glycolysis, then it is thought that only one net reaction occurs, the hydrolysis of PCr. Experimentally, the output of heat + work is directly proportional to the breakdown of PCr under many different conditions of contraction (Fig. EN8). The energy equivalent of PCr breakdown in the intact muscle was found to be 11 kcal/mol (the slope of the curve); this is in good agreement with the heat value of PCr in the test tube. Accordingly, muscle fulfills the laws of thermodynamics: it transforms mechanical energy to heat energy (first law) and it does not convert heat into work at constant temperature (second law).

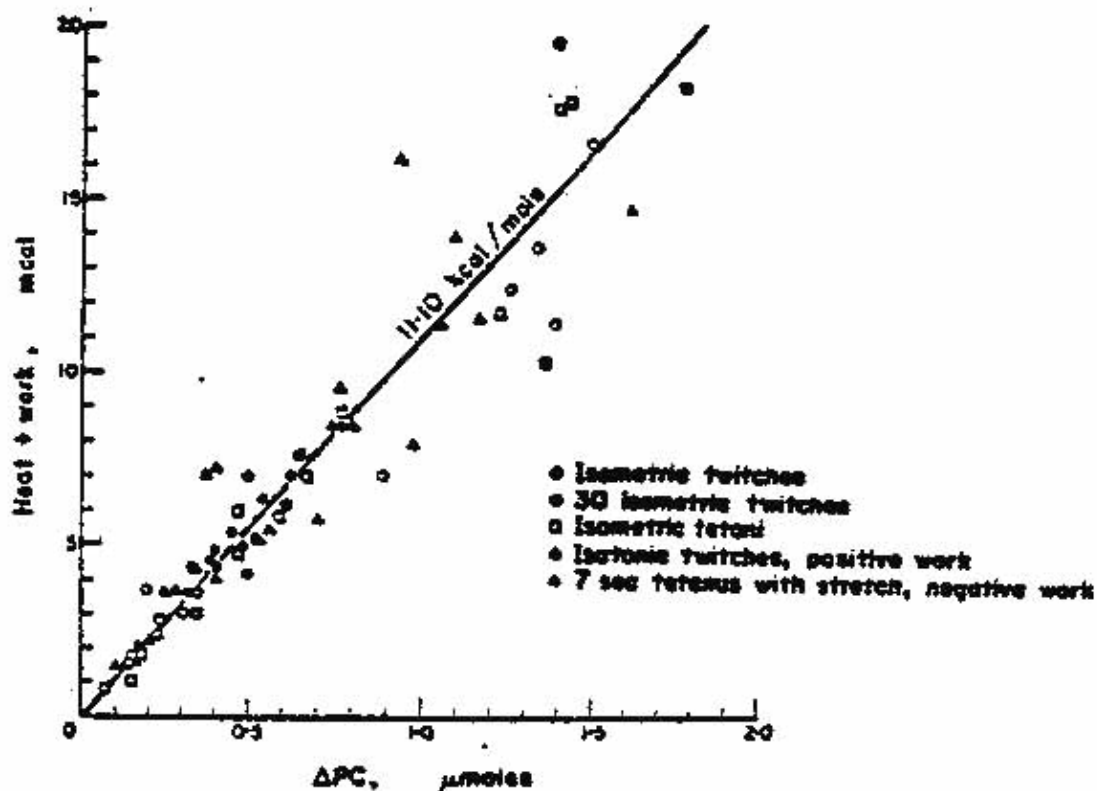


Fig. EN8. Energy output and chemical breakdown (From Carlson and Wilkie)

## Energy Cost Assessment in Humans

Heat generated by humans during rest and muscular activities can be measured by direct and indirect calorimetry.

Direct calorimetry: This is essentially an airtight, thermally insulated chamber where the subject is either resting or exercising. Humidified air providing  $O_2$  is constantly supplied while chemical absorbents remove  $CO_2$ . The heat produced by the subject is picked up by a stream of cold water flowing at constant rate through coiled tubes. The difference in the temperature of water entering and leaving the chamber reflects the subject's heat production.

Indirect calorimetry: This is based on the fact that energy metabolism in the body ultimately depends on the utilization of oxygen. Therefore, oxygen consumption is measured and energy equivalent is determined. One liter of  $O_2$  consumption corresponds to 4.8 kcal. Closed circuit or open-circuit spirometer measures  $O_2$  consumption.

Relationship between work-output and  $O_2$  consumption: If work-output can be measured, it can be converted into kcal equivalents. For example, on the bicycle ergometer with a

fly wheel of 6 m and a pedaling rate of 50 RPM (300 m total distance per min) with 1 kg resistance, 300 kg.meter work are performed per minute. Since 1 kg.meter corresponds to 0.00234 kcal, 300 kg.meter can be converted into 0.7 kcal of work-output. Assuming 25% efficiency, the total energy expenditure per minute is  $4 \times 0.7 = 2.8$  kcal. Since 4.8 kcal corresponds to 1-liter O<sub>2</sub> consumption, the 2.8 kcal is equivalent to 0.58-liter O<sub>2</sub> consumption. (Note the following terms: *work* = force x distance; *force* = mass x acceleration; *power* = work per unit of time; *energy* = the capacity of performing work).

Many studies were carried out to relate different work-outputs under various conditions with oxygen consumption, in healthy individuals and in patients. Such studies are helping physicians to design programs for individuals to lose weight, improve athletic performance, or to rehabilitate following muscle injury or heart disease.

Oxygen debt: During an intense period of exercise, PCr level has decreased and much of the glycogen may have been converted to lactic acid. Oxygen debt has been created. Namely to restore the normal cellular metabolite levels, energy is needed and the muscle utilizes oxygen to provide energy for the cellular processes. The muscle continues to consume oxygen at a high rate after it has ceased to contract. Therefore, we breathe deeply and rapidly for a period of time, immediately following an intense period of exercise, repaying the oxygen debt.

Example for calculation of oxygen debt: After exercise, a total of 5.5 liters of O<sub>2</sub> were consumed in recovery until the resting value of 0.31 liter/min was reached. The recovery time was 10 min.

Oxygen debt =  $5.5 - (0.31 \times 10) = 2.4$  liters

Adaptation to exercise: It is customary to differentiate between *high-intensity strength activities* and *low-intensity endurance* exercises. The different types of exercises elicit different patterns of neural activity to muscle resulting in specific adaptation. High intensity strength activities, such as weight lifting and bodybuilding, induce hypertrophy of the muscle with an increase in strength. Endurance exercises, such as swimming and running, increase the capacity of muscle for aerobic metabolism with an increase in endurance.

Fatigue: Muscle fatigue is defined as a loss of work-output leading to a reduced performance of a given task. Fatigue may result from deleterious alterations in the muscle itself and/or from changes in the neural input to the muscle.

During prolonged endurance exercise, e.g. marathon-running, depletion of muscle glycogen, decrease in blood glucose, dehydration, or increase in body temperature contribute to fatigue. During intense muscular activity, e.g. short-distance running, lactic acid is formed via anaerobic glycolysis. The H<sup>+</sup> ions dissociated from lactic acid decrease the pH of the muscle; this may inhibit metabolic processes, disturb excitation-contraction coupling, Ca<sup>2+</sup> fluxes, actomyosin ATPase activity, and thereby decrease work output.

## References

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