Respiration and Heat in Contracting and Non-contracting Dissipative Muscle

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Abstract. The oxygen consumption-heat relationship is analyzed using a scheme of reactions underlying muscle aerobic metabolism. The enzymatic chemical reactions of the scheme are considered near equilibrium during a contraction, and far from equilibrium during energy dissipation in a non-contracting state. Implications show that for two different metabolic rates, the proportionality between oxygen consumption and heat is a very specific case, because of restricting necessary conditions.

Key words: Muscle — Respiration — Heat — Energy dissipation — Non-equilibrium thermodynamics

Introduction

An excellent textbook on muscle energetics (Woledge et al. 1985) starts with the sentence: "The physiological function of muscle is to convert energy from chemical reactions into mechanical work and heat." At least for the purposes of this study, deletion of the word *mechanical* would be contextual. Besides the mechanical work due to a contraction, a skeletal muscle is able to increase the intensity of its metabolism in an entirely non-contracting state, producing the *chemical* work and heat.

The purpose of this study was to find the answer to the question, whether there is a fixed stoichiometric ratio between the chemical reactions underlying aerobic metabolism and the measured heat output in contracting, as well as in non-contracting dissipative muscle. The term *dissipative* is characterized by equations (4), (6) and (7) (see below).

Respiration — derived energetic scheme for a muscle (RDES)

In both cases (contracting and non-contracting muscle) the same simplified scheme can be considered involving the sequence of particular enzymes manifested as a chain of reactions with particular reactants and products. According to the central bioenergetic dogma, the electron-transfer chains (the red/ox system) of mitochondria are coupled to ATP synthesis by a proton electrochemical potential $\Delta\mu_{H^+}$. Phosphocreatine (CP) is formed by direct enzymatic transfer of a phosphate group from ATP to creatine; there is no other pathway for the formation of CP. Finally, the only known pathway for dephosphorylation of CP is the reversal of the reaction by which it has been formed. Then, the scheme can be accepted:

$$\mathrm{A} \overset{1}{\rightharpoonup} \mathrm{red/ox} \rightharpoonup \Delta\mu_{H^+} \rightharpoonup \mathrm{ATP} \overset{2}{\rightharpoonup} \mathrm{B}$$
$$\updownarrow 3$$
$$\mathrm{CP}$$

where the capital letters stand for concentrations and the numbers for the respective reaction rates.

Let us make the following definitions. RDES is isothermal, with its chemical reactions proceeding at a constant temperature, in the absence of any significant volume and pressure changes, and is not subject to external fields. RDES is open in communication with its surroundings, which are in a time-independent state. The surroundings are characterized by given values of temperature, pressure and chemical potentials. RDES is thus open to the flows of substrates (resulting in a concentration A) and oxygen from, and to the flow of products to, its surroundings. The oxygen consumption indicates the reaction rate v_1. Supposing the stoichiometric coefficient ν_{O_2} in the expression for the rate v_1

$$v_1 = \nu_{O_2}(\mathrm{d}\xi_1/\mathrm{d}t)$$

(where ξ_1 is the extent of this reaction, and t is time) being equal to -1 (because of the generally considered stoichiometry $2\mathrm{A}_{red} + \mathrm{O}_2 \rightarrow 2\,\mathrm{H}_2\mathrm{O} + 2\mathrm{A}_{ox}$), then the oxygen consumption equals the reaction rate v_1. Since RDES produces heat and does not have an infinite thermal conductivity, an incidental temperature gradient occurs even under the isothermal condition (Wilkie 1960), which implies a heat flow out of the system. The flow thus represents a component of the negative flow of entropy $J(\mathrm{S})$ for RDES. The entropy production $P(\mathrm{S})$ resulting from all reactions of the scheme is given by:

$$P(\mathrm{S}) = (1/T)\left(\sum_i A_i v_i\right) > 0 \qquad (1)$$

(where A_i is the affinity of the i-th chemical reaction and v_i is the i-th reaction rate at temperature T), because the general conclusion coming from original studies on particular reactions of the RDES scheme ".... is that there is a network of *near-equilibrium* reactions involving metabolites of energetic interest, so that changes in the ratios of products to reactants of one of the component reactions are necessarily coupled to the same changes in other component reactions" (Kushmerick 1983). Since the scheme is one of respiration-derived, the anaerobic synthesis of ATP as well as other reactions out of scheme are neglected by definition.

RDES allows to specify the introductory question. The question is, whether there is a fixed stoichiometric ratio between the chemical reactions of RDES and the released heat. In other words, whether there is a proportionality between oxygen consumption and heat, the constant of which can be called *energetic, thermic* (formerly calorigenic) *equivalent*.

RDES for a contracting muscle

As it is stated above concerning Eq. (1), generally it is considered that during a contraction RDES acts *near* equilibrium (Woledge et al. 1985; Kushmerick 1983). As a matter of fact, no reaction of this scheme can actually be in equilibrium because in such a case its appropriate affinity would be zero. There are several ways how to estimate a distance from the equilibrium. The simpliest way seems to be the value of the proton electrochemical potential (μ_{H^+}). It represents a thermodynamic measure of the extent to which the proton gradient across the mitochondrial membrane is shifted from equilibrium.

Another suitable expression of the thermodynamic potential is used in a way of the Gibbs free energy (G). The Gibbs energy is a function of the actual substrate and product concentrations, which change during a contraction. Therefore, the Gibbs energy change of each i-th reaction of RDES can be described by the integral:

$$\Delta G_i = \int (\mathrm{d}G_i/\mathrm{d}\xi_i)\, \mathrm{d}\xi_i \tag{2}$$

where ξ_i is the extent of i-th reaction

How Eq. (2) looks for the steady state? For this, the time dimension has to be involved. If A_i is the affinity of this reaction in the steady state:

$$A_i = k_B T \ln (k_1[\mathrm{R}]/k_2[\mathrm{P}] \tag{3}$$

and the differential ratio $\mathrm{d}\xi_i/\mathrm{d}t$ defines the chemical reaction rate, then the

amount of energy per unit time required to maintain the steady state is

$$d\Delta G_i/dt = (k_1[R] - k_2[P])\, k_B T \ln (k_1[R]/k_2[P])\,^* \tag{4}$$

where $[R]$, $[P]$ are substrate and product concentrations, k_1, k_2, k_B are constants, and T is temperature.

Thus Eq. (4) evaluates the entropy production rate $P(S)$ (see Eq. (1)) which is closely related, over the constant T, to energy dissipation. It might be useful to emphasize that a linear relation between the affinity and the reaction rate, implicitly involved in Eq. (4), is another expression of the near equilibrium condition.

Using the definition for the Gibbs free energy: $G = H - TS$, and $r_{p,T}$ which denotes the reaction heat associated with a change of ξ at constant T and p as a partial derivative of the enthalpy: $-(\partial H/\partial \xi) = r_{p,T}$, we obtain a direct relation between affinity and reaction heat:

$$A_i = r_{p,T} + T(\partial S/\partial \xi_i)_{p,T} \tag{5}$$

If we assume that all the heat of a chemical reaction is comprised in its affinity (i.e. that the entropy of a system under steady state is not changed), or in other words, if in Eq. (5) the entropy variation term is neglected, then the entropy production due to i-th reaction becomes proportional to the heat of reaction:

$$P(S) = A_i v_i / T \approx (r_{p,T} \cdot v_i)/T = -(1/T)(dQ/dt)_{p,T} \tag{6}$$

Since $P(S)$ is the extensive variable of RDES, for the RDES as a whole it becomes:

$$P(S) = (1/T) \sum r_{p,T} \cdot v_i = -(1/T)(dQ/dt)_{p,T} \tag{7}$$

In the approximation given in Eq. (6), the entropy production in RDES can be measured by its thermogenesis ($\Delta Q/\Delta t$). Additionally, the summation in Eq. (7) means that the presence of any coupled reaction, for which $Av < 0$, will be manifested as a diminution of the total heat which RDES gives off to the surroundings.

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* From the definition of affinity according to De Donder: $A = -\sum_i \nu_i \mu_i$ it follows: $A = -(\delta G\ \delta \xi)_{p,T}$ or $\delta G = -A\delta\xi$. Thus, the right side of Eq. (4) expresses the product of the chemical reaction rate and the affinity, if ΔG is considered positive.

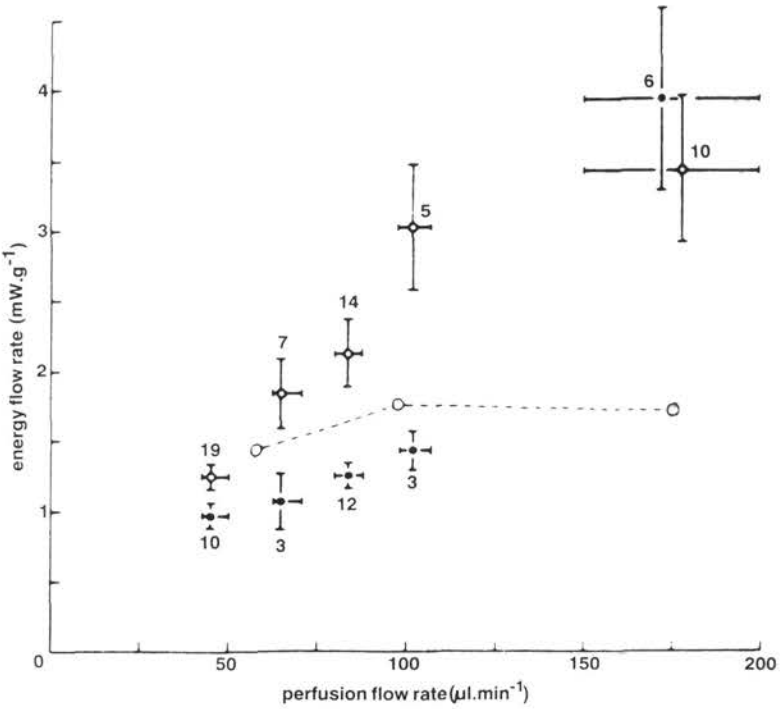

Fig. 1. Mean specific values of direct (●) and indirect (○) calorimetric fluxes measured at 28 °C on perfused and superfused gracilis muscle from 5 °C-acclimated rats, as a function of imposed perfusion flow rate. Superfusate pO_2 was 6.3 kPa; for comparison, mean values obtained under 88 kPa superfusate pO_2 are also indicated by the dashed line. The indirect flux means O_2 consumption multiplied by 450 kJ/mol O_2 of the mean energetic equivalent for oxygen. Vertical bars indicate S.E.; horizontal bars indicate the domain around mean perfusion flow rate (Chinet and Mejsnar 1989).

RDES for a non-contracting muscle

Contrary to contraction, the physiological conditions for increased metabolic rate in non-contracting state are not clear. One of the stimulating physiological factors is increased blood (medium) flow. The gracilis muscle from cold-acclimated rats, *in vitro* simultaneously perfused and superfused with a medium, raises its metabolic rate with the increasing perfusion rate. The conditions of this experiment with the organ as a whole seem to be the simpliest ones, and thus well defined to throw light upon the problem, concerning the mechanism of the stimulative effect of flow on muscle metabolism. Fig. 1 shows the characteristic

feature of this flow dependent experimental model; the indirect calorimetric flux (the product of O_2 consumption and the mean O_2 energetic equivalent) is higher than the heat production. The experimental finding illustrated in Fig. 1 shows that the oxygen consumption is related to the perfusion rate through the effect of the perfusion rate on affinity A_1 (on the corresponding rate v_1) in the RDES. It is obvious from the scheme how perfusion rate affects the overall affinity A of the overall reaction A → B.

Let us suppose an influence of phosphocreatine concentration on rate v_1. To avoid discussion of relevant voluminous literary data, this point can be accepted as a testable hypothesis. With all the following considerations restricted *only* to the case of *steady state*, the non-linear model of Prigogine (1967) is highly relevant.

The non-linear thermodynamic model considers a RDES sequence of reactions

$$\mathrm{A} \overset{1}{\leftrightarrows} \mathrm{X} \overset{2}{\leftrightarrows} \mathrm{B}$$
$$\quad\;\; \updownarrow 3$$
$$\quad\;\; \mathrm{M}$$

where the letters stand for concentrations, and the numbers represent the respective reaction rates (v_i).

The steady state conditions are $v_1 = v_2; v_3 = 0$. The above assumption of the non-linear behavior for rate v_1 is expressed by:

$$v_1 = (1 + \alpha \mathrm{M})(\mathrm{A} - \mathrm{X}) = \mathrm{X} - \mathrm{B} \qquad (8)$$

where α itself is a measure of catalytic enzymatic activity.

From Eq. (8) it follows that the steady state concentration of M increases with incerasing A, and that entropy production is enhanced (Prigogine 1967). In other words, the effect of the model is to propagate the chemical potential without degradation along the sequence of reactions, or to enhance the chemical potential of M up to potential A with the consequent larger entropy production.

The solutions contain γ as a parameter, defined by

$$\mathrm{B}/\mathrm{A} = 1 - \gamma \qquad *(9)$$

which itself is a measure of the affinity A of the overall reaction A → B (Prigogine 1967). The stimulating effect of the perfusion rate (Fig. 1) can consist, according to Eq. (9), either in an elevation of A or in a diminution of B. If A is set equal to one, then the arbitrary decrease of B from 1 to zero is proportional, according to Eq. (9), to the increase of γ from zero to 1.

* γ is related to α by: $\gamma = [(\mathrm{A} - \mathrm{M})/\mathrm{A}] . (2 + \alpha \mathrm{M})$

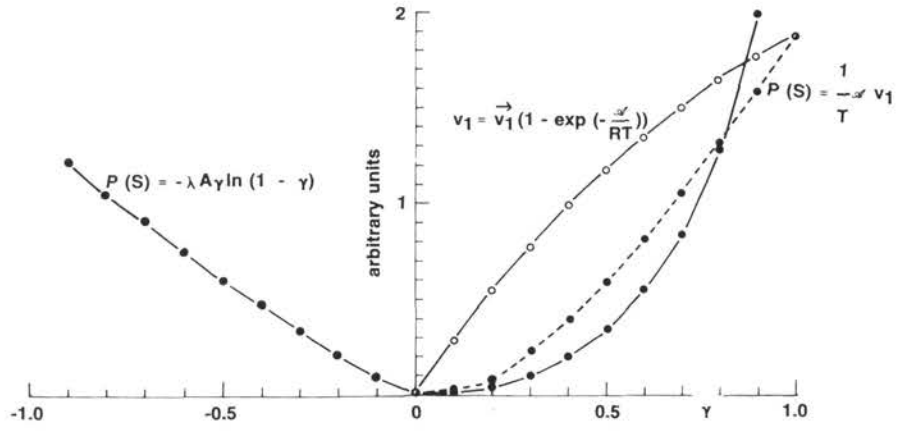

Fig. 2. The oxidative reaction rate v_1 and the entropy production $P(S)$ in the respiration-derived energetic scheme of a muscle, with respect to the overall affinity γ, changing in dependence on perfusion rate. R, T, A are set equal to 1; the partial rate $\vec{v}_1$ is 3 (see text); coefficient $\lambda = 1$ (see text). Affinity A is substituted by γ. If $P(S)$ means the total heat given off to the surroundings, rate v_1 approximates the heat flux as a product with its affinity A_1 (dashed line).

Using the general relation between reaction rate and affinity, we obtain the oxygen consumption as a saturable process with increasing γ (Fig. 2). In the figure, v_1 was arbitrarily set equal to 3, to emphasize the analogy with Fig. 1. Fig. 2 further shows the course of the entropy production in RDES with respect to γ. The calculation by Prigogine (1967) shows a shift in the entropy production with respect to coefficient α in Eq. (8), giving solutions for $\alpha \to 0$ and $\alpha \to \infty$: $-(A/2)\,\gamma \ln(1-\gamma)$, and $-A\gamma \ln(1-\gamma)$, respectively. Coefficient λ changes from 1/2 to 1 as α increases to a maximum. The typical shape of curve $P(S)$ is shown in Fig. 2.

The accordance of Fig. 2 with Fig. 1 may shed some light on the effect of non-linearity in one enzymatic reaction, which shifts the steady state concentrations of RDES *far* from the equilibrium. Consequently, the very large affinity of reaction 2 (ATP → B) is connected with an enhanced rate of entropy production due to this reaction. One fact is basically important for physiology. The total $P(S)$ of RDES, when released as heat, can be only approximated, using rate v_1. This approximation is obtained as the result of multiplication by affinity A_1. This is shown in Fig. 2 by the dashed line. However, affinity A_1 is a variable and in no way can be a constant or "equivalent".

Discussion

If the flow-dependent metabolic model functions as considered above, the shift from equilibrium implies a simultaneous increase of phosphocreatine and ATP concentrations. ^{31}P NMR spectroscopy data (Mejsnar et al. 1991) might provide support for this assumption.

Finally, it can be summarized once more, why it is questionable to evaluate thermogenesis from oxygen consumption data of changing muscle metabolism, using the so-called thermic equivalent of oxygen. Comparing v_1 as the input characteristic, and $P(S)$ as the output characteristic of the RDES, for a stoichiometry several restricting necessary conditions have to be met:

— constant physical parameters of experiment (see definitions of RDES)

— the entropy variation term in affinities of chemical reactions (Eq. (5)) can be neglected

— the ATP-ase reaction (#2 in the scheme) is not coupled with any reaction for which the product $Av < 0$ (Eq. (7), i.e. the first principle of mass-energy conservation)

— all enzymatic reactions have to be kept *near* equilibrium, i.e. with a constant proportional relationship between chemical rates and affinities and without propagations of chemical potentials.

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