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Review

Control of oxidative phosphorylation in skeletal muscle

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Abstract

The classical concept of ATP-demand control of energy metabolism in skeletal muscle has to be modified on the basis of studies showing the influence of additional controlling parameters (reducing equivalent supply, oxygen availability, proton leak, diffusion restrictions and the creatine kinase system) and on the basis of applications of metabolic control analysis showing very clearly multistep control. This concept of multistep control allows to quantify the individual influence of any parameter on mitochondrial oxidative phosphorylation and is extremely helpful to analyze the metabolic consequences of enzyme deficiencies in skeletal muscle occurring in mitochondrial myopathies. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Mitochondrial oxidative phosphorylation; Skeletal muscle; Flux control; Metabolic control analysis; Metabolic threshold

1. Introduction

Skeletal muscle is known to be a tissue of high energy demand. It consists mainly of slow twitch ('type 1') and fast twitch ('type 2a and 2b') fibers. The type 1 and type 2a fibers are mitochondria-rich and rely in their ATP supply mainly on oxidative phosphorylation, while type 2b fibers are mitochondria-poor and have a very effective glycolytic ATP production. The fiber type composition of individual muscles is muscle specific and highly variable upon electrical stimulation [1]. Therefore, skeletal muscle has to be considered as a heterogeneous tissue and the large differences in enzyme composition of the individual myofibers may create problems in the detailed description of the metabolism in the tissue in its entirety. Nevertheless, the high ATP turnover which is to about 50–70% utilized by actomyosin ATPase, the big cell size and the rather simple metabolism offer advantages for the study of basic principles of control of oxidative phosphorylation. Moreover, the interest to the control of mitochondrial oxidative phosphorylation in skeletal muscle has been considerably increased since the discovery of a group of heterogeneous myopathies which are caused by mutations of the mitochondrial DNA (for review see [2]). However, control in its biochemical context is a vague term and needs a precise definition. This definition is given in a neutral sense by Kacser and Burns [3] who defined that control implies a quantitative relationship between components of a system. Since control of oxidative phosphorylation is discussed in this review, the system has to be defined. A simplified scheme which illustrates the main components of the system and the corresponding fluxes of reducing equivalents (in three boxes from left), of protons (fourth box from left) and phosphate (fifth box from left) is outlined in Fig. 1.

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2. Classical view of control of oxidative phosphorylation

In earlier work with isolated mitochondria it was demonstrated that the rate of oxygen consumption was greatly increased by the addition of an external ADP-regenerating system (hexokinase/glucose, [4]). The rate of oxidative phosphorylation was therefore postulated to be controlled by ADP [5] or by the extramitochondrial phosphorylation potential [6]. In later work the adenine nucleotide carrier which connects the matrix and extramitochondrial adenine nucleotide pools was suggested as the rate limiting step in respiration [7]. Since this carrier catalyzes the exchange of ATP^{4-} for ADP^{3-} [8], the respiration of isolated mitochondria was considered to be controlled by the extramitochondrial ATP/ADP ratio [9,10]. In line with these results obtained with isolated mitochondria reconstituted with external ATP consumers, calculations on the basis of in vivo ^{31}P nuclear magnetic resonance (NMR) measurements revealed that the ATP turnover rate in contracting skeletal muscle increases about 30-fold while the ATP/ADP ratio decreases about five times [11]. This was interpreted in terms of nearly exclusive control of ATP flux by energy demand, e.g. actomyosin ATPase [12]. Variations of the phosphate concentration in the physiological range (1–10 mM) have been shown to have only little influence on control of oxidative phosphorylation in skeletal muscle [13].

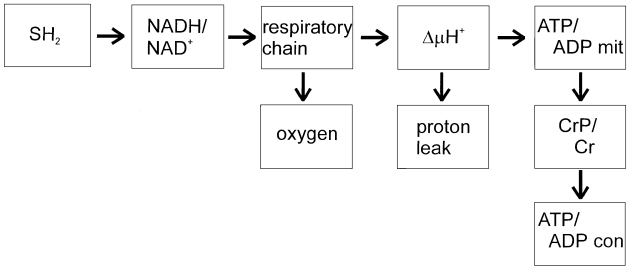

Fig. 1. Schematic representation of the pathway structure of oxidative phosphorylation in skeletal muscle. The arrows indicate fluxes of reducing equivalents, protons or phosphate which are coupled (with the exception of the proton leak flux). SH_2 – mitochondrial substrates; $\Delta\mu H^+$ – electrochemical proton gradient; ATP/ADP_{mit} – ATP/ADP ratio in the mitochondrial intermembrane space; ATP/ADP_{con} – ATP/ADP ratio at the site of ATP consumers (mainly actomyosin ATPase).

3. Reinterpretation of OXPHOS control in broader context

That this rather simplified description of control of oxidative phosphorylation in skeletal muscle is incomplete has been noted by many investigators. It is visible from Fig. 1 that additional factors in addition to the ATP utilization by actomyosin ATPase have to be considered for a more detailed description of control of oxidative phosphorylation in skeletal muscle. At least the following five additional processes have to be taken into consideration: supply of reducing equivalents, (ii) oxygen availability, (iii) the proton leak, (iv) diffusion restrictions and (v) the creatine kinase system.

(i) A main factor which is assumed to modulate the supply of reducing equivalent is the free Ca^{2+} concentration which was observed to influence the activities of dehydrogenases [14]. This mechanism was used to explain the discrepancies of tissue high energy phosphate concentrations determined by ^{31}P NMR spectroscopy, NADH/NAD^+ ratios and metabolic flux rates observed in perfused heart muscle preparations [15,16]. Really, also in skeletal muscle in some experiments during transition from resting to working state, an increase in NADH/NAD^+ was observed [17,18]. However, in contrast to the extensive evidence reported for the heart muscle [15,16], these results were not confirmed by other groups either in intact skeletal muscle [19,20] nor in isolated preparations like saponin-permeabilized skeletal muscle fibers [21,22].

(ii) For most tissues it has been suggested that the control of electron flux by oxygen concentration appears to be minimal since the K_m of respiration for oxygen in cells and isolated mitochondria seems to be less than 1 μM [23,24] and the diffusion of oxygen in most tissues is rapid enough to prevent the formation of steep oxygen gradients [25]. However, in skeletal muscle there are well known aerobic/anaerobic transitions during exercise which in turn should influence the control of oxidative phosphorylation. The maximal oxygen consumption of skeletal muscle in vivo was reported to be proportional to oxygen supply without attainable saturation [26] and maximal aero-

bic muscle activity was postulated to be limited by cardiac output and oxygen supply to the muscle [27]. This concept was further improved by Hogan et al. [28] who demonstrated that the regulation of energy metabolism in oxidative skeletal muscle was dependent on oxygen tension (cf. also [29]). Due to the large size of individual fibers in skeletal muscle, rather steep oxygen gradients can be formed [30]. The controlling influence of low oxygen tension, which is realized in the cytochrome *c* oxidase reaction, is also shown in experiments with saponin-permeabilized muscle fibers [31].

(iii) In experiments with isolated perfused rat hindquarter, the proton leak accounts for approximately one-half of the oxygen consumption of the resting muscle [32]. This result points to a considerable thermogenesis of the resting skeletal muscle. Upon stimulation of muscle this controlling effect of the proton leak decreases but was estimated to contribute at doubled oxygen consumption of the perfused rat hindquarter preparation still to about 34% of respiration rate [33]. These results were obtained by direct measurements of rates of oxygen consumption and mitochondrial membrane potential in perfused rat hindquarter preparations in which approximately 15% of the containing muscle tissue is stimulated. However, upon maximal stimulation the oxygen consumption of the working muscle increases more than 10-fold [34], and under these circumstances the contribution of proton leak is very likely to be much lower (cf. [35]).

(iv) In many ^{31}P NMR studies describing the control of oxidative phosphorylation in muscle, cellular compartmentation and related diffusion control of an important reaction has not been taken into consideration so far. In these experiments, the ADP concentration is calculated assuming equilibrium of the creatine kinase reaction which is however very unlikely to be valid at high flux rates [36]. The influence of diffusion limitations for ADP through the porin pore of the mitochondrial outer membrane is demonstrated in competition experiments with reconstituted systems consisting of isolated mitochondria an different external ATP consumers [37]. Under in vivo conditions, the tight interaction of mitochondria with the cytoskeleton [38,39] and the mitochondrial heterogeneity within individual muscle fibers [40] affecting the ADP diffusion could also be important. The high complexity of skeletal muscle, already present at the level of a single muscle fiber, can be visualized if the distribution of mitochondria is studied by confocal microscopy of flavoprotein autofluorescence [40]. This fluorescence originates almost exclusive from the mitochondrial flavoprotein α-lipoamide dehydrogenase [41]. One confocal plane across a saponin-permeabilized single human muscle fiber (and its reconstructed cross section) in its endogenous oxidized state is shown in Fig. 2 (left two images). It

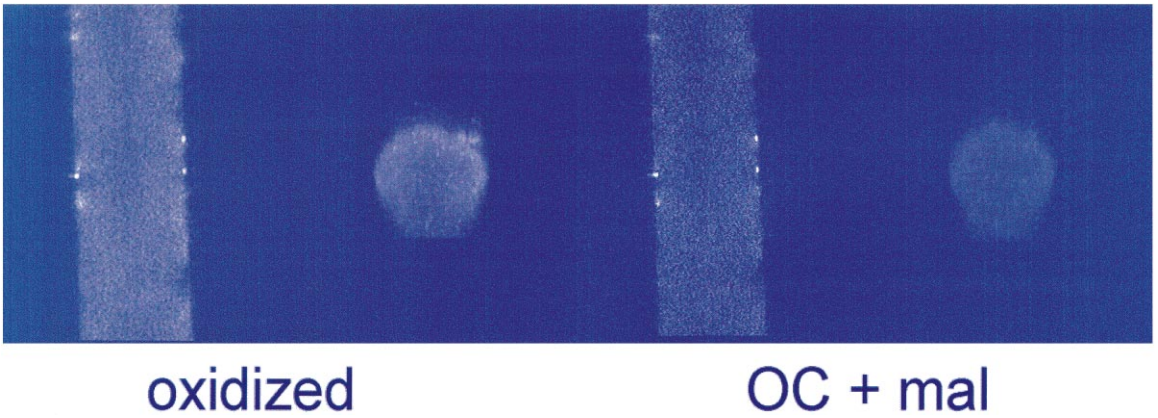

Fig. 2. Confocal planes and reconstructed cross sections of flavoprotein autofluorescence of a single human skeletal muscle fiber. Experimental conditions as described in [40]. To the substrate free incubation (left two images) 1 mM octanoylcarnitine and 5 mM malate were added (right two images). Fiber diameter −75 μm.

can be seen that the autofluorescence signal is in the subsarcolemmal region substantially brighter. That led in the reconstituted cross section to the higher fluorescence in the border region of the fiber. The addition of mitochondrial substrates (octanoylcarnitine+malate) to the fiber quenched partially the flavoprotein fluorescence due to the reduction of the flavin moiety of α-lipoamide dehydrogenase and affected the subsarcolemmal fraction of mitochondria to a greater extent (the fluorescence is in both images now nearly even distributed, Fig. 2 right two images), indicating metabolic heterogeneity (cf. discussion in [40]).

(v) In skeletal muscle tissue, the creatine kinase system seems to be an essential constituent of the energy metabolism, partly to overcome the in (iv) mentioned diffusion restrictions for ADP across the mitochondrial outer membrane [37,42]. The presence of this shuttle system leads in the presence of this diffusion barrier to a dramatic decrease of the K_m of oxidative phosphorylation for ADP and at high flux rates to a displacement of the creatine kinase equilibrium [43]. This can cause very flat plots when [ADP] or [ATP]/[ADP] is plotted against the respiration rate (cf. discussion by Wyss et al. in [36]). In contrast to heart muscle, in skeletal muscle, mainly due to the high activity of myofibrillar creatine kinase and the lower mitochondrial content, several experimental data and theoretical estimations testify however against any significant displacement of creatine kinase from equilibrium under in vivo conditions [44–46]. Therefore, the large changes in ATP turnover (30-fold) at only about 4-fold changes in [ATP]/[ADP] determined by ^{31}P NMR in intact skeletal muscle [11] which seem to be in apparent contradiction to findings with isolated mitochondria, can be explained by a parallel activation of ATP demand and ATP production (cf. discussion in [11,47]).

4. Application of metabolic control analysis

A completely new view on control of oxidative phosphorylation emerged from the application of metabolic control analysis developed independently by Kacser and Burns [48] and Heinrich and Rapoport [49]. So called flux control coefficients (initially named 'control strength') were defined which allowed a quantification of control of each individual enzyme. The first applications of this theory to an oxidative phosphorylation system consisting of isolated rat liver mitochondria reconstituted with a glucose/hexokinase ATP consumer were performed by Groen et al. [50] and Gellerich et al. [51]. As main result, both groups reported that the control of flux is shared among the individual components of the OXPHOS system and the values of flux control coefficients depend as well on flux rates of oxidative phosphorylation as on the detailed composition of the reconstituted system.

4.1. Enzyme-based approach ('bottom up' approach)

The basic principle of this method for experimental determination of flux control coefficients consists in inhibitor titration experiments performed with specific, either irreversible or reversible non-competitive, inhibitors. If these inhibitors are available it is possible to perform an analysis of a metabolic system starting from individual enzymes ('bottom up' approach).

As shown by Groen et al. [50] for irreversible inhibitors, the following equation for the flux control coefficient C_i of the enzyme i can be applied:

$$C_i = -(dJ/J)/(dI/I_{max}) \quad (1)$$

where J is the respiration flux, dJ is the decrement of respiration flux caused by the increment of inhibitor addition dI and I_{max} is the maximal amount of inhibitor. For reversible non-competitive inhibitors this equation has to be modified to

$$C_i = -(dJ/J)/(dI/K_d) \quad (2)$$

where K_d is the dissociation constant of the inhibitor.

Using these equations, flux control coefficients of individual enzymes of respiratory chain can be determined experimentally. Applying this concept to isolated muscle mitochondria in comparison to liver mitochondria, important differences were detected. In the active state of glutamate oxidizing rat skeletal muscle mitochondria control is shared more or less uniformly between many steps [52,53], while in rat liver mitochondria most of the control is localized at the ATP/ADP carrier [50,51]. This phenomenon is

most probably related to differences in the detailed protein composition of the mitochondria from the different tissues [52]. The tissue specificity of distribution of flux control of oxidative phosphorylation is extensively discussed recently by Mazat and coworkers [54]. They noted that the active state respiration of skeletal muscle and heart mitochondria is controlled essentially at the level of respiratory chain while liver, kidney and brain mitochondria were observed to be controlled mainly on the phosphorylation level [54].

One problem of the 'bottom up' approach is the relatively large experimental error of the graphical method for determination of flux control coefficients [50]. To overcome this difficulty a curve fitting procedure which analyzes the entire titration curve has been emphasized [55]. This approach has also been applied to describe the control of oxidative phosphorylation in the more complex system of calcium-activated saponin-permeabilized rat soleus fibers [13]. By the addition of 2 μM free calcium, the oxygen consumption rate of fibers could be stimulated approximately 4-fold reaching approximately 80% of active state respiration. In this in vitro system, the control of oxidative phosphorylation was observed to be split almost equally between mitochondrial enzymes and the ATP consumers (mainly the actomyosin ATPase).

4.2. Subsystem-based approach ('top down' approach)

The main disadvantage of the enzyme-based method for the description of a complex metabolic system is the difficulty of experimental determination of flux control coefficients for all enzymes of the pathway since specific inhibitors with well known kinetic properties are often missing. Therefore, it is often advantageous to dissect the complex metabolic pathway structure into subsystems for which the metabolic control analysis can be performed. This subsystem approach was suggested theoretically by Bohnensack [56] and applied for control analysis of oxidative phosphorylation in bull spermatozoa [57] and of the β-oxidation pathway in rat liver mitochondria [58]. The theoretical basis of this approach is the connectivity theorem [48,49] which connects the flux control coefficients of two enzymes C_a and C_b (or two complex enzyme systems) having a common intermediate i with their elasticity coefficients in respect to this common intermediate ε_i^a and ε_i^b.

$$C_a * \varepsilon_i^a + C_b * \varepsilon_i^b = 0 \quad (3)$$

and the summation property of flux control coefficients:

$$C_a + C_b = 1 \quad (4)$$

The elasticity coefficients can be assessed experimentally and for the determination of flux control coefficients the system of the two equations has to be solved yielding:

$$C_a = -\varepsilon_i^b/(\varepsilon_i^a - \varepsilon_i^b) \quad (5)$$

and

$$C_b = \varepsilon_i^a/(\varepsilon_i^a - \varepsilon_i^b) \quad (6)$$

The detailed application and development of this approach to study complex metabolic networks, named later 'top down' approach, was performed by Brand and coworkers [35,59,60]. It was applied to perform a metabolic control analysis of a large number of metabolic systems [32,61–63]. Applying this method, the considerable contribution of the proton leak (having a flux control coefficient of 0.38) to the control of respiration of resting skeletal muscle was shown [32,33]. This finding indicates that the mitochondrial proton leak significantly contributes to the basic metabolic rate and has to be considered as an important thermoregulatory mechanism. Problems with the application of the top down approach may arise if the precise structure of the metabolic pathway is not known or the common intermediate metabolite cannot be assessed. However, the general agreement of results obtained with the classical enzyme-based 'bottom up' approach and the 'top down' approach for the very simple pathway of oxidative phosphorylation in submitochondrial particles was experimentally shown by Moreno-Sanchez et al. [64].

5. Implications to mitochondrial myopathies and threshold concept

Based on the interpretation of the sigmoidal shaped inhibitor titration curves of enzymes of mitochondrial respiratory chain having low flux control

coefficients, a threshold concept describing the metabolic effect of enzyme deficiencies has been developed [65,66]. This concept predicts from the sigmoidal shaped inhibitor titration curves of respiratory chain complexes with specific inhibitors the occurrence of thresholds if the activity or the expression of these enzyme is affected by mutations of the mitochondrial DNA observed in mitochondrial myopathies. In general the flux control coefficients of these enzyme complexes are rather low, causing therefore high threshold values [66]. As an example, for cytochrome *c* oxidase in rat skeletal muscle mitochondria oxidizing pyruvate and malate, threshold values of about 80% have been determined [53,66]. However, these results are specific to the respiratory substrates used (cf. also detailed discussion in [67]). To illustrate this problem of dependency of metabolic thresholds on the detailed experimental system, a typical cyanide titration

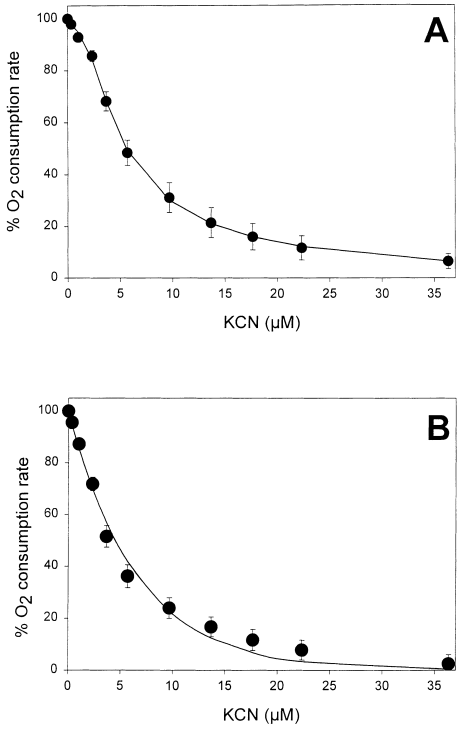

Fig. 3. Cyanide titrations of maximal oxygen consumption of isolated rat skeletal muscle mitochondria oxidizing succinate+glutamate+malate (A) or TMPD+ascorbate (B). The data points are averages of 10 independent experiments. Experimental conditions as described in [52,73]. A: 10 mM succinate, 10 mM glutamate, 5 mM malate and 2 mM ADP present. The 100% value corresponds to 248 ± 84 nmol O_2/min/mg protein at 30°C. B: 500 μM TMPD, 1 mM ascorbate, 2 mM ADP and 0.2 μM antimycin present. The 100% value corresponds to 336 ± 94 nmol O_2/min/mg protein at 30°C.

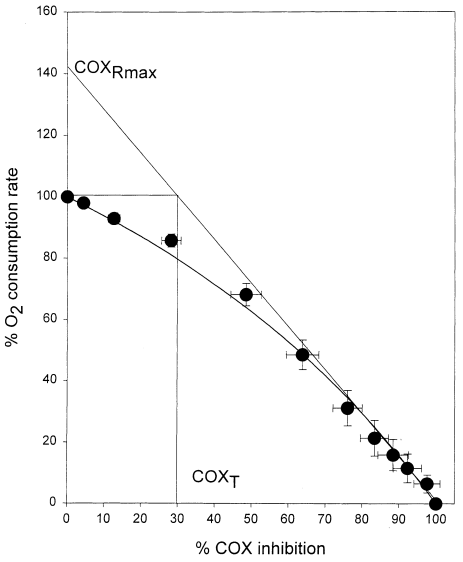

Fig. 4. Threshold plot of cytochrome *c* oxidase in succinate+glutamate+malate oxidizing skeletal muscle mitochondria. The experimental data shown in Fig. 3A,B are re-plotted according to [66,68,73]. COX_T – threshold of cytochrome *c* oxidase. COX_{Rmax} – reserve capacity of cytochrome *c* oxidase.

curve of ADP-stimulated respiration of succinate+glutamate+malate oxidizing rat skeletal muscle mitochondria is shown in Fig. 3A. In analogy to titrations with the substrates pyruvate+malate (cf. [66]), this titration curve is also sigmoidal shaped. If under identical conditions the cytochrome *c* oxidase reaction rate, using the substrates TMPD+ascorbate, is titrated with cyanide then the hyperbolic curve shown in Fig. 3B is obtained. As introduced by Letellier et al. [66] from the combination of both titration curves, a so called threshold plot shown in Fig. 4 can be constructed. Surprisingly, in this plot a clear metabolic threshold is nearly missing. In line with earlier data with mice skeletal muscle fibers [70,69], a low threshold value of approximately 30% and a low excess capacity (1.4-fold) of cytochrome *c* oxidase can be calculated (according to [68,69]) for rat skeletal muscle mitochondria. This seems to be in clear contrast to the mentioned very similar experiments in [66,67] with the substrate combination pyruvate+malate which reported a metabolic threshold of cytochrome *c* oxidase of about 70–80%. This apparent discrepancy is most likely related to the large differences in maximal oxygen consumption rates with the individual substrate combinations used since the following rates can be determined for rat skeletal muscle mitochondria: pyruvate+malate, 188 ± 61

nmol O_2/min/mg protein; glutamate+malate+succinate, 248 ± 84 nmol O_2/min/mg protein (at 30°C, 10 independent preparations). Similar observations were made for the threshold plot of the adenine nucleotide translocator in rat liver mitochondria [67]. With the substrates pyruvate+malate, a high threshold was determined while in the presence of succinate the curve changed, indicating a much lower threshold (cf. figure 3F in [67]).

These are clear examples that metabolic thresholds similar to flux control coefficients are extremely dependent on the detailed experimental condition and cannot simply be generalized. Nevertheless, the results with cytochrome *c* oxidase could explain why deficiencies of this enzyme have a preferential expression in skeletal muscle [54,70] but not in brain [71]. Moreover, the low thresholds of cytochrome *c* oxidase under conditions of maximal electron flow through respiratory chain are in line with findings that mitochondrial DNA mutations at a low degree of heteroplasmy affect muscle energy metabolism and cause a pathological phenotype [72,73]. Despite the fact that flux coefficients and also metabolic threshold values depend largely on the flux rate and the detailed metabolic system studied, they can be used for quantitative estimation of the metabolic influence of enzyme deficiencies. This approach has been applied for the description of metabolic consequences of respiratory chain enzyme deficiencies in mitochondrial myopathies [74].

6. Concluding remarks

The classical concept of ATP-demand control of energy metabolism in skeletal muscle has to be modified on the basis of applications of metabolic control analysis showing very clearly multistep control. However, the amount of control of the individual steps is to a large extent dependent on the individual conditions, which include the flux rate, the availability of metabolites, possible diffusion limitations and the enzyme composition (which can be altered by genetic defects). Nevertheless, the concept of multistep control within the framework of metabolic control analysis allows to quantify the individual influence of any parameter of a well defined complex system and is therefore extremely helpful to analyze the metabolic consequences of enzyme deficiencies in skeletal muscle.

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References

[1] D. Pette, G. Vrbova, Muscle Nerve 22 (1999) 666–677.
[2] D.C. Wallace, Ann. Rev. Biochem. 61 (1992) 1175–1212.
[3] H. Kacser, J.A. Burns, Biochem. Soc. Trans. 7 (1979) 1149–1160.
[4] H.A. Lardy, H. Wellman, J. Biol. Chem. 195 (1952) 215–224.
[5] B. Chance, G.R. Williams, J. Biol. Chem. 217 (1955) 383–393.
[6] M. Klingenberg, Angew. Chem. 3 (1964) 54–61.
[7] H.W. Heldt, M. Klingenberg, Eur. J. Biochem. 4 (1968) 1–8.
[8] P.V. Vignais, Biochim. Biophys. Acta 456 (1976) 1–38.
[9] E.J. Davis, L. Lumeng, J. Biol. Chem. 250 (1975) 2275–2282.
[10] W. Kunz, R. Bohnensack, G. Böhme, U. Küster, G. Letko, P. Schönfeld, Arch. Biochem. Biophys. 209 (1981) 219–229.
[11] J.A.L. Jeneson, R.W. Wiseman, H.V. Westerhoff, M.J. Kushmerick, J. Biol. Chem. 271 (1996) 27995–27998.
[12] R.W. Wiseman, J.A.L. Jeneson, in: C. Larson, I. Pahlman, L. Gustafsson (Eds.), BioThermoKinetics in the Post Genomic Era, Chalmers Reproservice Göteburg, 1998, pp. 183–185.
[13] E. Wisniewski, F.N. Gellerich, W.S. Kunz, Eur. J. Biochem. 230 (1995) 549–554.
[14] R.M. Denton, J.G. McCormack, Am. J. Physiol. 249 (1985) E543–E554.
[15] L.A. Katz, A.P. Koretsky, R.S. Balaban, FEBS Lett. 221 (1987) 270–276.
[16] A.H.L. From, M.A. Petein, S.P. Michurski, S.D. Zimmer, K. Ugurbil, FEBS Lett. 206 (1986) 257–261.
[17] K. Sahlin, Pflüg. Arch. 403 (1985) 193–196.
[18] D. Duboc, M. Muffat-Joly, G. Renault, M. Degeorges, M. Toussaint, J.J. Pocidalo, J. Appl. Physiol. 64 (1988) 2692–2695.
[19] F.F. Jöbsis, W.N. Stainsby, Respir. Physiol. 4 (1968) 292–300.
[20] I.R. Wendt, J.B. Chapman, Am. J. Physiol. 230 (1976) 1644–1649.
[21] W.S. Kunz, A.V. Kuznetsov, F.N. Gellerich, FEBS Lett. 323 (1993) 188–190.
[22] Z. Khuchua, Y. Belikova, A.V. Kuznetsov, F.N. Gellerich,

L. Schild, H.W. Neumann, W.S. Kunz, Biochim. Biophys. Acta 1188 (1994) 373–379.
[23] H. Degn, H. Wohlrab, Biochim. Biophys. Acta 245 (1971) 347–355.
[24] D.F. Wilson, C.S. Owen, Arch. Biochem. Biophys. 195 (1979) 494–504.
[25] B.A. Wittenberg, J.B. Wittenberg, Annu. Rev. Physiol. 51 (1989) 857–878.
[26] W.J. Whalen, D. Buerk, C.A. Thuning, Am. J. Physiol. 224 (1973) 763–768.
[27] P.O. Astrand, in: W. Wieser, E. Gnaiger (Eds.), Energy Transformation in Cells and Organisms, Thieme, Stuttgart, 1989, pp. 254–261.
[28] M.C. Hogan, P.G. Arthur, D.E. Bebout, P.W. Hochachka, P.D. Wagner, J. Appl. Physiol. 73 (1992) 728–736.
[29] P.G. Arthur, M.C. Hogan, P.D. Wagner, P.W. Hochachka, J. Appl. Physiol. 73 (1992) 737–743.
[30] D.P. Jones, F.G. Kennedy, Am. J. Physiol. 250 (1986) C384–C390.
[31] F.R. Wiedemann, W.S. Kunz, FEBS Lett. 422 (1998) 33–35.
[32] D.F.S. Rolfe, M.D. Brand, Biochim. Biophys. Acta 1276 (1996) 45–50.
[33] D.F.S. Rolfe, J.M.B. Newman, J.A. Buckingham, M.G. Clark, M.D. Brand, Am. J. Physiol. 276 (1999) C692–C699.
[34] P.W. Hochachka, Muscles as Molecular and Metabolic Machines, CRC Press, Boca Raton, FL, 1994.
[35] E.K. Ainscow, M.D. Brand, Eur. J. Biochem. 231 (1995) 579–586.
[36] M. Wyss, J. Smeitink, R.A. Wevers, T. Wallimann, Biochim. Biophys. Acta 1102 (1992) 119–166.
[37] F.N. Gellerich, M. Schlame, R. Bohnensack, W. Kunz, Biochim. Biophys. Acta 890 (1987) 117–126.
[38] L. Kay, Z. Li, M. Mericskay, J. Olivares, L. Tranqui, E. Fontaine, T. Tiivel, P. Sikk, T. Kaambre, J.-L. Samuel, L. Rappaport, Y. Usson, X. Leverve, D. Paulin, V.A. Saks, Biochim. Biophys. Acta 1322 (1997) 41–59.
[39] S. Reipert, F. Steinböck, I. Fischer, R.E. Bittner, A. Zeöld, G. Wiche, Exp. Cell Res. 252 (1999) 479–491.
[40] A.V. Kuznetsov, O. Mayboroda, D. Kunz, K. Winkler, W. Schubert, W.S. Kunz, J. Cell Biol. 140 (1998) 1091–1099.
[41] I. Hassinen, B. Chance, Biochem. Biophys. Res. Commun. 31 (1968) 895–900.
[42] R. Benz, L. Wojtczak, W. Bosch, D. Brdiczka, FEBS Lett. 231 (1988) 75–80.
[43] V.A. Saks, R. Ventura-Clapier, M.K. Aliev, Biochim. Biophys. Acta 1274 (1996) 81–88.
[44] E.W. McFarland, M.J. Kushmerick, T.S. Moerland, Biophys. J. 67 (1994) 1912–1924.
[45] R.W. Wiseman, M.J. Kushmerick, J. Biol. Chem. 270 (1995) 12428–12438.
[46] C.I. Funk, A. Clark Jr., R.J. Connett, Am. J. Physiol. 258 (1990) C995–C1005.
[47] B. Korzeniewski, Biophys. Chem. 83 (2000) 19–34.
[48] H. Kacser, J.A. Burns, in: D.D. Davies (Ed.), Rate Control of Biological Processes, Cambridge University Press, London, 1973, pp. 65–104.
[49] R. Heinrich, T.A. Rapoport, Eur. J. Biochem. 42 (1974) 97–105.
[50] A.K. Groen, R.J.A. Wanders, H.V. Westerhoff, R. van der Meer, J.M. Tager, J. Biol. Chem. 275 (1982) 2754–2757.
[51] F.N. Gellerich, R. Bohnensack, W. Kunz, Biochim. Biophys. Acta 722 (1983) 381–391.
[52] E. Wisniewski, W.S. Kunz, F.N. Gellerich, J. Biol. Chem. 268 (1993) 9343–9346.
[53] B. Korzeniewski, J.-P. Mazat, Biochem. J. 319 (1996) 143–148.
[54] R. Rossignol, T. Letellier, M. Malgat, C. Rocher, J.-P. Mazat, Biochem. J. 347 (2000) 45–53.
[55] F.N. Gellerich, W.S. Kunz, R. Bohnensack, FEBS Lett. 274 (1991) 167–170.
[56] R. Bohnensack, Biomed. Biochim. Acta 44 (1985) 1567–1578.
[57] R. Bohnensack, W. Halangk, Biochim. Biophys. Acta 850 (1986) 72–79.
[58] W.S. Kunz, Biomed. Biochim. Acta 50 (1991) 1143–1157.
[59] M.D. Brand, R.P. Hafner, G.C. Brown, Biochem. J. 255 (1988) 535–539.
[60] G.C. Brown, R.P. Hafner, M.D. Brand, Eur. J. Biochem. 188 (1990) 321–325.
[61] R.P. Hafner, G.C. Brown, M.D. Brand, Eur. J. Biochem. 188 (1990) 313–319.
[62] A. Kesseler, P. Diolez, K. Brinkmann, M.D. Brand, Eur. J. Biochem. 210 (1992) 775–784.
[63] P.A. Quant, D. Robin, P. Robin, J. Girard, M.D. Brand, Biochim. Biophys. Acta 1156 (1993) 135–143.
[64] R. Moreno-Sanchez, C. Bravo, H.V. Westerhoff, Eur. J. Biochem. 264 (1999) 427–433.
[65] T. Letellier, M. Malgat, J.P. Mazat, Biochim. Biophys. Acta 1141 (1993) 58–64.
[66] T. Letellier, R. Heinrich, M. Malgat, J.P. Mazat, Biochem. J. 302 (1994) 171–174.
[67] R. Rossignol, M. Malgat, J.P. Mazat, T. Letellier, J. Biol. Chem. 274 (1999) 33426–33432.
[68] G. Villani, G. Attardi, Proc. Natl. Acad. Sci. USA 94 (1997) 1166–1171.
[69] G. Villani, M. Greco, S. Papa, G. Attardi, J. Biol. Chem. 273 (1998) 31829–31836.
[70] A.V. Kuznetsov, J.F. Clark, K. Winkler, W.S. Kunz, Increase of flux control of cytochrome *c* oxidase in copper-deficient mottled brindled mice, J. Biol. Chem. 271 (1996) 283–288.
[71] W.S. Kunz, A.V. Kuznetsov, J.F. Clark, I. Tracey, C.E. Elger, J. Neurochem. 72 (1999) 1580–1585.
[72] R. Schröder, S. Vielhaber, F.R. Wiedemann, C. Kornblum, A. Papassotiropoulos, P. Broich, S. Zierz, C.E. Elger, H. Reichmann, P. Seibel, T. Klockgether, W.S. Kunz, J. Neuropathol. Exp. Neurol. 59 (2000) 353–360.
[73] W.S. Kunz, A. Kudin, S. Vielhaber, C.E. Elger, G. Attardi, G. Villani, J. Biol. Chem. 275 (2000) 27741–27745.
[74] A.V. Kuznetsov, K. Winkler, E. Kirches, H. Lins, H. Feistner, W.S. Kunz, Biochim. Biophys. Acta 1360 (1997) 142–150.