The pH-dependence of post-exercise PCr and ADP recovery: a simple modelling approach reproduces important features of 31P MRS data from skeletal muscle

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Introduction. Noninvasive 31P MRS measurements of the post-exercise recovery kinetics of pH, [PCr] and [ADP] contain much information about muscle mitochondrial function and cellular acid-base balance in vivo, but quantitative interpretation depends on understanding the physiology (1-4). Both analytical and simulation approaches may be useful, particularly given the interactions between these variables imposed by the creatine kinase equilibrium. The dependence of the phosphocreatine recovery time constant (τPCr) on end-exercise pH (pH E) is important in inferences about mitochondrial function, and the pH E-dependence of the end-exercise/initial-recovery rate of acid efflux (EE, which can be estimated from pH and PCr recovery data (5)) likely reflects a fundamental cellular physiological setting (e.g. higher in glycolytic fibres). It has recently been noted (1) that the slopes of these two relationships, λ = -(dEE/dpH E)mean and (dτPCr/dpH E)mean, correlate across individuals, suggesting that intersubject differences in the pH-dependence of τPCr, are related to differences in cellular pH control (1). It was noted (1) that a simple model reproduces the pH E-dependence of τPCr (2). Here we show that, further, it directly predicts the λ-dependence of (dτPCr/dpH E)mean as well as individual values of τPCr and λ, and further, that these depend also on the relationship between pH E and [PCr] E, which is not under direct experimental control.

Methods. Experimental data methods and results are as previously published (1). The basis of the model is that under the feedback influence (3) of [ADP] (which is in creatine kinase equilibrium with pH and [PCr]), oxidative ATP synthesis drives PCr recovery, this being accompanied by net H+ generation (4) which is opposed by linearly pH-dependent H+ efflux (1, 5). Values of mitochondrial capacity QMAX and λ are obtained from each subject’s data, and assumptions about mitochondrial control and cellular buffering are described elsewhere (4-8).

Results and Discussion. Figure A shows relationships between [PCr] E and pH E in the present simulations (solid lines: [PCr] E is varied incrementally and pH E is obtained for various values of d[PCr]/d(pH E), increasing as the arrow indicates) and in the data points from each of the 5 subjects (1), sorted for clarity into means for each individual of studies where pH E was ‘near-resting’, ‘intermediate’, and ‘acid’ (a mean data d[PCr]/d(pH E) line is also shown: see legend for key). The more steeply [PCr] E decreases with pH E, the more steeply [ADP] E increases (not shown). Figure B shows simulated τPCr (solid lines) and τADP (dashed lines) as a function of λ for various values of pH E, which here is varied holding [ADP] E constant: τPCr decreases markedly with increasing λ while τADP changes little. Figure C shows the same thing (with the same key) in a different way, the lines showing τPCr and τADP as a function of pH E for various values of λ: the increase in τPCr with decreasing pH E is more marked at high efflux settings (high λ). The data points in Figures B & C (key as in Figure A) show that the experimental results (1) exhibit the same behaviour as the theoretical lines. The increase in τPCr/τADP as pH E decreases (Figure C) was recently reported in a patient group (9).

In Figures B & C d[PCr]/d(pH E) was chosen to keep [ADP] E constant as pH E is varied, but different assumptions are possible, and better match the experimental initial conditions in Figure A, where [ADP] E (not shown) rises modestly with decreasing pH E. In the summary Figure D (which has a similar format to Fig 4B in the experimental paper (1)) each pair of lines (solid = τPCr, dashed = τADP) makes a different assumption about d[PCr]/d(pH E) (as in Figure A). Figure D shows that the pH E-dependence of τPCr decreases with increasing λ, while τADP is insensitive to λ except in the extreme case where d[PCr]/d(pH E) is so shallow that [ADP] E falls with decreasing pH E.

Thus a simple model of mitochondrial control and acid efflux explains much of post-exercise PCr and ADP recovery in relation to pH E. More generally, simple modelling can avoid some ambiguities of purely verbal argument about a multiply-interacting physiological system, and provide a bridge to more detailed mechanistic treatments of mitochondrial control (8) and acid handling by the myocyte.

1. NM van den Broek et al., Am J Physiol 293, C228 (2007).