Altered creatine dependence of muscle mitochondrial respiration in vitro: what are the likely effects in vivo?

To the Editor: Muscle mitochondria show greater creatine (Cr)-stimulated respiration in rats bred for high running capacity (HCR) than low (LCR), despite similar mitochondrial density, suggesting increased coupling between mitochondrial creatine kinase (CK) and adenine nucleotide translocase (4). How important is this effect in vivo, embedded in the cytosolic CK equilibrium?

On the simplest model, respiration rate (V) is a hyperbolic (Michaelis-Menten) function of ADP concentration ([ADP]) (call this A; Ref. 1; Fig. 1A, control case). If mitochondrial capacity increases, e.g., with training (5), then the slope dV/dA increases throughout, and [ADP] for given V is less, so relative ADP sensitivity (S = dlnV/dlnA, formally an elasticity) increases (Fig. 1C); if training also increases K_m (5) then V/A and dV/dA could increase or decrease. The V-A relationship in vivo is better described by cooperative (sigmoid) kinetics (Hill coefficient n > 1; Ref. 2), which permits higher ADP sensitivity S (Fig. 1C, see legend). Somewhat similar kinetics result if K_m for ADP decreases with respiration rate (3). This could arise from Cr-stimulated respiration (4; Fig. 2, A and B), but as phosphocreatine (PCr) has an opposite effect, the relevant variable in vivo is Cr/PCr (6), which at constant pH is linear with [ADP]. If K_m for ADP decreases with Cr/PCr (6; Fig. 2C), in vivo it must decrease with [ADP] (Fig. 1B). This yields a sigmoid V-A curve (3), especially in HCR (Fig. 1A), substantially decreasing [ADP] and increasing ADP sensitivity, usefully characterized by the apparent Hill coefficient (Fig. 1C). However, only with greater Cr sensitivity than observed in vitro (4, 6) does this approach values observed in vivo (2; Fig. 1C, see legend). Lastly, whether increased Cr sensitivity in HCR represents a physiological shift toward creatine shuttling from simple ADP signaling (4), this can be quantified as the fraction of total respiration change due to Michaelis-Menten ADP-dependence; this is lower in HCR (Fig. 1C, see legend) because of the steeper relation of K_m to [ADP].

Thus the effects in vivo of these interesting differences in Cr sensitivity (4) are constrained by the CK equilibrium, and Cr sensitivity cannot account fully for the ADP sensitivity of respiration in vivo. These points do not depend critically on my crude parameterization (Fig. 2) of the in vitro data (4, 6) or on a particular view of, for example, mitochondrial CK and spatial compartmentation.

Fig. 1. The ADP dependence of respiration modeled in vivo. A: respiration relative to maximal: v = 1/(1 + KA/4) with variable K for low- and high-capacity running (LCR and HCR, respectively; Ref. 4) and extreme Cr sensitivity (see Fig. 2C) and constant K for control (= hyperbolic kinetics, no Cr stimulation). Straight dashed lines, half-maximal respiration. B: formal ADP dependence of K_m for ADP follows from causal dependence on Cr/PCr (Ref. 5; in human muscle at pH 7, [ADP] = 50 * Cr/PCr). Assume K = K_m/(1 + KA/4), where K_m is a maximum at zero Cr/PCr and A = ADP at half-maximal K (see Fig. 2C). The [ADP] at half-maximal respiration (Am) is the intersection with the line of identity, here Am = (ω/2)(β − 1) where β = 1 + 4K_m/ω. For LCR, based on Ref. 5, K_m = 300 μM and ω = 160 μM (corresponding to Cr/PCr = 3) so β = 3; to model 3-fold greater Cr sensitivity in HCR (Fig. 2C), ω = 50 μM (Cr/PCr = 1) so β = 5; for hypothetical extreme Cr sensitivity ω = 5 μM (Cr/PCr = 0.1) so β = 16. The fraction of respiration change due to Michaelis-Menten ADP dependence, rather than creatine sensitivity, is F = 1/(1 − dlnK/dlnA) = (A+ω)/(2A+ω); at half-maximal respiration F = (1/2)(1+1/β), which is 0.7, 0.6, and 0.5 for LCR, HCR, and extreme cases, respectively. C: relative ADP sensitivity. For hyperbolic kinetics S = 1/(1 + KA/4) = 1 − v. For classical cooperative kinetics v = 1/(1 + (KA)γ) and S = n/(1 + (KA)γ); at given v, S is n times the “hyperbolic” control value. With Cr sensitivity, S = 1/(1 + dlnK/dlnA), higher than control by a factor (>= 1/F, above) here equal to 2γ/γ + 1, where γ = 1 + 4v/(1 − v)K_m/ω. For example, S at half-maximal respiration is S_m = β/(β + 1), compared to 1/2 for the hyperbolic case. [Thus both reported effects of aerobic training (5), increased K_m and decreased ω, tend to increase S]. Define an apparent Hill coefficient n_app = 2S_m, which is 1.5, 1.7, and 1.9 for LCR, HCR, and the extreme case, respectively; for comparison, observed n ∼ 2 in vivo (2). Abbreviations: Cr, creatine; PCr, phosphocreatine; [ADP], ADP concentration. 
REFERENCES


Graham Kemp
Division of Metabolic and Cellular Medicine
Faculty of Medicine
University of Liverpool
Liverpool, United Kingdom
e-mail: gkemp@liv.ac.uk