Comparison of metabolic effects of mitochondrial dysfunctions in the context of vulnerability to fatigue: computer simulation study

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Appendix

Description of the mathematical model used in this work. Based on the skeletal muscle model description from http://awe.mol.uj.edu.pl/~benio/models.html [accessed 9 July 2022]

Abbreviations and subscripts

DH - NADH supply, LK - proton leak, CK - creatine kinase; AK - adenylate kinase; GL - glycolysis; EF - proton efflux/influx to/from blood; e - external (cytosolic); i - internal (mitochondrial); t - total; f - free; m - magnesium complex; j - monovalent.

Constants

Total concentrations constants:

O_2 = 30 μM
c_t = 270 μM ($c^{2+} + c^{3+}$, total concentration of cytochrome c)
a_t = 135 μM ($a^{2+} + a^{3+}$, total concentration of cytochrome a)
U_t = 1350 μM (UQH2 + UQ, total concentration of ubiquinone)
N_t = 2970 μM (NADH + NAD+, total concentration of NAD)
Mg_{fe} = 4000 μM (free external magnesium concentration)
Mg_{fi} = 380 μM (free internal magnesium concentration)
A_{iSUM} = 16260 μM (ATPti + ADPti, total internal adenine nucleotide concentration)
A_{eSUM} = 6700 μM (ATPte + ADPte + AMPe, total external adenine nucleotide concentration)
C_{SUM} = 35000 μM (Cr + PCr, total creatine concentration)

Starting metabolite concentrations: (Independent variables)

NADH = 1757.9 μM
UQH_2 = 1242.7 μM
c^{2+} = 81.16 μM
ATP_{ti} = 12939 μM
Pi_{ti} = 17330 μM
H_i = 0.03624 μM
$ATPt_e$ = 6693.0 μM
$ADPt_e$ = 7.182 μM
AMP_e = 0.0216 μM
Pi_{te} = 3215.6 μM
PCr = 28293 μM
H_e = 0.1004 μM

Respiration rate (vC4) at rest

vC4 = 264 μM *min^{-1}

Enzymatic/transporter activity rate constants and other constants

k_{DH}= 28074 μM min^{-1}
K_{mN} = 100
p_D=0.8

k_{C1}= 238.95 μM mV^{-1} min^{-1}

k_{C3}= 136.41 μM mV^{-1} min^{-1}

k_{C4}= 3.600 μM^{-1} min^{-1}
K_{mO} = 120 μM (mechanistic K_m for O_2)

k_{SN}= 34316 μM min^{-1}
n_A = 2.5 (phenomenological H^+/ATP stoichiometry of ATP synthase)

k_{EX}= 54572 μM min^{-1}
K_{mADP} =3.5 μM

k_{PI}= 69.421 μM^{-1} min^{-1}

k_{UT}= 781.97 μM min^{-1} (state of rest; A_{UT} = 1)
K_{mA}= 150 μM

k_{LK1}= 2.500 μM min^{-1}
k_{LK2} = 0.038 mV^{-1}

k_{fAK}= 862.10 μM^{-1} min^{-1}
k_{bAK}= 22.747 μM^{-1} min^{-1}

k_{fCK} = 1.9258 μM^{-2} min^{-1}
k_{bCK} = 0.00087538 μM^{-1} min^{-1}

k_{EF} = 10000 μM min^{-1}
pH_0 = 7.0

k_{GL} = 17.2 min^{-1}
H^{+rest} = 0.1 μM

Rc_{m} = 15 (cell volume/mitochondria volume ratio)
B_N = 5 (buffering capacity coefficient for NAD)

T = 298 K

R = 0.0083 kJ*mol^{-1}K^{-1}
F = 0.0965 kJ*mol^{-1}mV^{-1}
S = 2.303*R*T
Z = 2.303*R*T/F
u = 0.861 (= $\Delta\Psi/\Delta p$)
c_{buffi} = 0.022 M H+/pH unit (buffering capacity for H+ in matrix)
c_{buffe} = 0.025 M H+/pH unit (buffering capacity for H+ in cytosol)
pK_a = 6.8
ΔG_{P0} = 31.9 kJ mol^{-1}
E_{mN0} = − 320 mV
E_{mU0} = 85 mV
E_{mc0} = 250 mV
E_{ma0} = 540 mV
k_{DTe} = 24 μM (magnesium dissociation constant for external ATP)
k_{DDe} = 347 μM (magnesium dissociation constant for external ADP)
k_{DTi} = 17 μM (magnesium dissociation constant for internal ATP)
k_{DDi} = 282 μM (magnesium dissociation constant for internal ADP)

Kinetic equations

Substrate dehydrogenation: $v_{DH} = k_{DH} \frac{1}{\left(1+\frac{K_{mN}}{NAD^{+}/NADH}\right)^{p_D}}$

Complex I: $v_{C1} = k_{C1} \cdot \Delta G_{C1}$

Complex III: $v_{C3} = k_{C3} \cdot \Delta G_{C3}$

Complex IV: $v_{C4} = k_{C4} \cdot a^{2+} \cdot c^{2+} \frac{1}{1+\frac{K_{mO}}{O_2}}$

ATP synthase: $v_{SN} = k_{SN} \frac{\gamma-1}{\gamma+1}, \gamma = 10^{\Delta G_{SN}/Z}$

ATP/ADP carrier. $v_{EX} = k_{EX} \cdot \left(\frac{ADP_{fe}}{ADP_{fe}+ATP_{fe} \cdot 10^{-\Psi_e/Z}} - \frac{ADP_{fi}}{ADP_{fi}+ATP_{fi} \cdot 10^{-\Psi_i/Z}}\right) \cdot \left(\frac{1}{1+K_{mADP}/ADP_{fe}}\right)$

Phosphate carrier: $v_{PI} = k_{PI} \cdot (Pi_{je} \cdot H_e - Pi_{ji} \cdot H_i)$

ATP usage: $v_{UT} = k_{UT} \frac{1}{1+\frac{K_{mA}}{ATP_{te}}}$

Proton leak: $v_{LK} = k_{LK1} \cdot (e^{k_{LK2} \cdot \Delta p} - 1)$

Adenylate kinase: $v_{AK} = k_{fAK} \cdot ADP_{fe} \cdot ADP_{me} - k_{bAK} \cdot ATP_{me} \cdot AMP_e$

Creatine kinase: $v_{CK} = k_{fCK} \cdot ADP_{te} \cdot PCr \cdot H_e^{+} - k_{bCK} \cdot ATP_{te} \cdot Cr$

Proton efflux: $v_{EF} = k_{EF} \cdot (pH_0 - pH_e)$

Glycolysis: $v_{GL} = k_{GL} \cdot (ADP_{te} + AMP_e)(H_{rest}^{+}/H^{+})$ (anaerobic glycolysis present)

Set of differential equations

$\dot{NADH} = (v_{DH} - v_{C1}) \cdot R_{cm}/B_N$

$\dot{UQH}_2 = (v_{C1} - v_{C3}) \cdot R_{cm}$

$\dot{c}^{2+} = (v_{C3} - 2 \cdot v_{C4}) \cdot 2 \cdot R_{cm}$

$\dot{O}_2 = 0$ (constant saturated oxygen concentration)

$\dot{ATP}_{t\imath} = (v_{SN} - v_{EX}) \cdot R_{cm}$

$\dot{Pi}_{t\imath} = (v_{PI} - v_{SN}) \cdot R_{cm}$

$\dot{ATP}_{te} = (v_{EX} - v_{UT} + v_{AK} + v_{CK} + 1.5 \cdot v_{GL}) \cdot R_{cm}/(R_{cm} - 1)$

$\dot{ADP}_{te} = (v_{UT} - v_{EX} - 2 \cdot v_{AK} - v_{CK} - 1.5 \cdot v_{GL}) \cdot R_{cm}/(R_{cm} - 1)$

$\dot{Pi}_{te} = (v_{UT} - v_{PI} - 1.5 \cdot v_{GL}) \cdot R_{cm}/(R_{cm} - 1)$

$\dot{PCr} = -v_{CK} \cdot R_{cm}/(R_{cm} - 1)$

$$\dot{H}_e^{+} = (2 \cdot (2 + 2 \cdot u) \cdot v_{C4} + (4 - 2 \cdot u) \cdot v_{C3} + 4 \cdot v_{C1} - n_A \cdot v_{SN} - u \cdot v_{EX} - (1 - u) \cdot v_{PI} - v_{LK} - s \cdot v_{CK} - v_{EF} + v_{GL} - 0.2 \cdot v_{DH})/r_{buffe} \cdot R_{cm}/(R_{cm} - 1)$$

Other calculations

$c^{3+} = c_t - c^{2+}$

$UQ = U_t - UQH_2$

$NAD^+ = N_t$- NADH

Cr = C_{SUM} − PCr

$AMP_e = A_{eSUM} - ATP_{te} - ADP_{te}$

$ADP_{ti} = A_{iSUM} - ATP_{ti}$

$ATP_{fe} = ATP_{te}/(1 + Mg_{fe}/k_{DTe})$

$ATP_{me} = ATP_{te} - ATP_{fe}$

$ADP_{fe} = ADP_{te}/(1 + Mg_{fe}/k_{DDe})$

$ADP_{me} = ADP_{te} - ADP_{fe}$

$ATP_{fi} = ATP_{ti}/(1 + Mg_{fi}/k_{DTi})$

$ATP_{mi} = ATP_{ti} - ATP_{fi}$

$ADP_{fi} = ADP_{ti}/(1 + Mg_{fi}/k_{DDi})$

$ADP_{mi} = ADP_{ti} - ADP_{fi}$

$pH_i = -\log(H_i/10^6)$ (H_i expressed in μM)

$pH_e = -\log(H_e/10^6)$ (H_e expressed in μM)

$\Delta pH(mV) = Z(pH_i\text{-}pH_e)$

$\Delta p(mV) = 1/(1\text{-}u)\Delta pH$

$\Delta\Psi(mV) = -(\Delta p - \Delta pH)$

$\Psi i(mV) = 0.65 * \Delta\Psi$

$\Psi e(mV) = -0.35 \cdot \Delta\Psi$

$Pi_{je} = Pi_{te}/(1 + 10^{pHe\text{-}pKa})$

$Pi_{ji} = Pi_{ti}/(1 + 10^{pHi\text{-}pKa})$

$c0i = \left(10^{-pHi} - 10^{-pHi\text{-}dpH}\right)/dpH$ (‘natural’ buffering capacity for H^+ in matrix; $dpH = 0.001$)

$r_{buffi} = c_{buffi}/c_{0i}$ (buffering capacity coefficient for H+ in matrix)

$c_{0e} = \left(10^{-pHe} - 10^{-pHe\text{-}dpH}\right)/dpH$ (‘natural’ buffering capacity for H^+ in cytosol; $dpH = 0.001$)

$r_{buffe} = c_{buffe}/c_{0e}$ (buffering capacity coefficient for H^+ in cytosol)

$\Delta G_{SN} = n_A \cdot \Delta p - \Delta G_P$ (thermodynamic span of ATP synthase)

$\Delta G_P = \Delta G_{P0}/F + Z \cdot \log\left(10^6 \cdot ATP_{ti}/(ADP_{ti} \cdot Pi_{ti})\right)$ (concentrations expressed in μM)

$E_{mN} = E_{mN0} + Z/2 \star \log(NAD^+/NADH)$ (NAD redox potential)

$E_{mU} = E_{mU0} + Z/2 \star \log(UQ/UQH_2)$(ubiquinone redox potential)

$E_{mc} = E_{mc0} + Z \star \log\left(c/c^{2+}\right)$ (cytochrome c redox potential)

$E_{ma} = E_{mc} + \Delta p \cdot (2 + 2u)/2$ (cytochrome a_3 redox potential)

$A_{3/2} = 10^{(Ema\text{-}Ema0)/Z}$ (a^{3+}/a^{2+} ratio)

$a^{2+} = a_t/\left(1 + A_{3/2}\right)$ (concentration of reduced cytochrome a_3)

$\Delta G_{C1} = E_{mU}\text{-}E_{mN}\text{-}\Delta p * 4/2$ (thermodynamic span of complex I)

$\Delta G_{C3} = E_{mc} - E_{mU}\text{-}\Delta p * (4\text{-}2u)/2$ (thermodynamic span of complex III)

$s = 0.7\text{-}(pH - 6.0)^{*}0.5$ (net stoichiometry of proton consumption/production by creatine kinase when coupled with ATP consumption/production, respectively; Lohman reaction)