Reduction of oxygen by cytochrome c oxidase

Figure 1. A schematic of the kinetically important reactions involved in the reduction of oxygen by cytochrome c oxidase. The individual reaction intermediates are designated by the Roman Numbers I through V and these numerals are used for setting up the differential equations describing the rates of formation and removal of these intermediates. The steady state rate expression is then derived assuming the rates are equal and there is no change in the concentrations of the intermediates. Only the reactions of oxidative phosphorylation from cytochrome c to oxygen are presented. All of the electron transfer reactions are assumed to occur across the same difference in redox potential (energy coupled) for which ΔG = -46.183 kcal/volt (193.23 kJ/volt).

Steady state rate expression for oxygen reduction by cytochrome c oxidase *in vivo.*

Assumptions: 1. Only the reaction for reduction of the bound peroxide intermediates (III and IV) are irreversible. 2. The overall reaction is in a steady state, i.e. the concentrations of the intermediates are not changing.

$$-\frac{dI}{dt} = k1*cr*I - k1r*co*II + k4a*cr*III - k4b*cr*IV \tag{1}$$

$$-\frac{dII}{dt} = k2*O*II - k2r*III - k1*cr*I + k1r*co*II \tag{2}$$

$$-\frac{dIII}{dt} = k2r*III - k2*O*II - (k4a*cr*III + k4b*cr*IV) \tag{3}$$

-dV/dt = k1*cr*I - k1r*co*II- k4a*cr*III-k4b*cr*IV (4)

$$K3 = \frac{IV}{III*H} \tag{5}$$

IV = K3*H*III (6)

$$K5 = \{(I*Q)/(V*H^2)\}*(co/cr)^2 \tag{7}$$

From eq 2:

k2*O*II = k2r*III + k4a*cr*III + k4b*cr*IV (8)

II = {(k2r + k4a*cr* + k4b*cr*K3*H)/k2*O}*III   II = A*III (9)

From eq 1:

$$k1*cr*I = k2*O*A*III-k2r*III + k1r*co*A*III \tag{10}$$

$$I = \{(k2*O*A - k2r + k1r*co*A)/k1*cr\}*III \qquad\qquad I = B*III \tag{11}$$

$$V = \{(Q)/(H^2)\} * (co/cr)^2 * B * III \qquad\qquad V = C*III \tag{12}$$

$$V = \langle\{(B * Q)/(K5 * H^2)\} * (co/cr)^2\rangle * II \tag{13}$$

The total cytochrome a_3 is the sum of the individual intermediates i.e.

$$a3t = I + II + III + IV + V \tag{14}$$

or

$$a3t = (1 + A + B + C + K3 * H) * III \tag{15}$$

The rate of oxygen consumption is determined by the irreversible step (reduction of III and IV)

$$v = (k4a * cr + k4b * cr * K3 * H) * 4/ct \qquad \text{(cytochrome c turnover number)} \tag{16}$$

Since the mitochondria are a particulate enzyme system, all simulations are carried out for a single cytochrome concentration (cytochrome a, 1 µM; cytochrome c, 2 µM). For other cytochrome concentrations the obtained rates are linearly extrapolated to the new cytochrome concentrations (mitochondrial content). The energy coupling is mathematically expressed as the equivalent redox voltage difference Q. This acts as an effective resistance to electron transfer and the forward rate constant decreases and the back rate constant increases with increasing energy state by Q/0.0595 (1 electron transfer) or Q/0.0296 (2 electron transfer). The rate constants put into the model are those for no energy coupling, so energy coupling is included for k1, k1r, and for the equilibrium constant K5. It is not applied to k4a and k4b. These reactions are irreversible and there is no significant back reaction under any relevant conditions.

Abbreviations:

The concentrations of reduced cytochrome c, cr; Hydrogen ion, H; Oxygen, O; Oxidized cytochrome c, co; Total cytochrome a3, a3t; Forward reaction rate constants, k1, k2, k3, k4a, k4b; Reverse rate constants, k1r, k2r; Equilibrium constants, K3 and K5;

Energy state in volts, Q to convert to kcal/2 eq, multiply by 46.18 kcal/volt or 103.23 kJ/volt.

Published in:

Wilson DF, Vinogradov SA. Mitochondrial cytochrome c oxidase: mechanism of action and role in regulating oxidative phosphorylation. *J Appl Physiol* 117: 1431-1439, 2014 as modified by Wilson DF, Vinogradov SA. in reply to Letter to the Editor by Pannala, Beard, and Dash. *J Appl Physiol 119(2):158,* 2015.

Addition of the first two sites of oxidative phosphorylation

Addition of the first two sites of oxidative phosphorylation to the cytochrome c oxidase in order to obtain a steady state rate expression for all of oxidative phosphorylation (NADH to oxygen);

The first two sites are near equilibrium so they can be approximated by the expression for the reaction:

NADH + 2 c^{3+} + 2ADP + 2 Pi ←------→ NAD$^+$ + 2 c^{3+} + 2 ATP

for use in the model the energy state is replaced by the thermodynamically equivalent redox potential difference:

$$\text{NADH} + 2\,c^{2+} \xleftrightarrow{\quad 2Q \quad} \text{NAD}^+ + 2c^{2+} + \text{H}^+$$

$$K_e = [\text{NAD}^+]\,[c^{2+}]^2\,[\text{H}^+]/[\text{NADH}]\,[c^{3+}]^2$$

The equilibrium constant calculated from the half reduction potentials for the NAD and cytochrome c couples (-0.32V and 0.235V, respectively) at pH 7.0 is 6.4 x 10^{11} M. This equilibrium expression is used to approximate the concentrations (near equilibrium) of the reduced and oxidized forms of cytochrome c for any value of intramitochondrial [NAD$^+$]/[NADH] and Q. The intramitochondrial pH is higher than the cytosolic pH by 0.3 to 0.5 pH units but it is the potential which is used in the calculations and this does not affect the calculations. It does affect the [NAD$^+$]/[NADH] calculated from the potential. A redox potential of -0.35V, for example, would be an [NAD$^+$]/[NADH] of 0.1 at pH 7.0 and about 0.3 at pH 7.5.

Published in:

Wilson DF. Regulation of metabolism: the rest-to-work transition in skeletal muscle. *Am J Physiol, Endocrinol Metab* 309: E793-E801, 2015.