Title: DESATURATION OF CYTOCHROME a,a_3 IN BRAIN AND FOREARM MUSCLE DURING TRANSIENT HYPOXIA IN VOLUNTEERS

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Introduction. Mitochondrial electron transport is the primary means of producing high energy phosphates for cellular function. It is known that the terminal member of the respiratory chain, cytochrome a,a_3 (**cyt a,a_3**) utilizes the large majority (>90%) of the O_2 consumed by tissues during active phosphorylation. Tissue hypoxia decreases O_2 availability to **cyt a,a_3**, causing its reduction level to increase with attendant reduction of oxidative metabolism. For this reason, monitoring the oxidation-reduction (redox) state of **cyt a,a_3** is of great importance in pathologic states characterized by impaired O_2 delivery. Sensitive optical methods are available to study **cyt a,a_3** redox level in situ. Recent advances permit changes in the near-infrared (NIR) absorption band of **cyt a,a_3** to be monitored directly through skin and bone in humans (1), during various stresses, e.g. transient hypoxemic excursions.

Method. We used NIR multiwavelength spectrophotometry to measure and compare regional hemodynamic and oxidative metabolic responses to hypoxia in undisturbed brain and forearm skeletal muscle. After Institutional Review Board approval and written consent, we studied eight normal healthy volunteers. Graded hypoxia was produced by a low-resistance rebreathing circuit that decreased arterial hemoglobin saturation (SaO_2) to 70% over 8 min. Recovery was rapidly induced by O_2 breathing. Arterial blood gases, SaO_2 (CO-oximeter) and continuous blood pressures were obtained and recorded from an indwelling arterial cannula. Finger oximetry, heart rates and end-tidal CO_2 were continuously recorded, as well as respiratory volumes. During the first protocol (**hypocapnia**), each subject was allowed to hyperventilate and reduce $PaCO_2$, while in protocol two (**normocapnia**), $PaCO_2$ was controlled at baseline levels in spite of spontaneous hyperventilation. Cerebral and forearm muscle oxygenation was assessed with noninvasive near infrared (NIR) multiwavelength spectrophotometry, a technique able to continuously monitor changes in regional blood volume, oxygenation level of hemoglobin within the tissue under observation, and the redox level of **cyt a,a_3** in the tissue. After recovery from the hypoxic protocols, 8 min of forearm **ischemia** was produced by inflating a cuff at pressure larger than systolic. This induced progressive and complete reduction of hemoglobin and of **cyt a,a_3** in forearm muscle.

Results. Forearm ischemia induced changes in redox units from 0 to -39.6 ± 4.3. Measured values at the beginning and at the end of the hypoxic excursions are indicated in the following table as mean ± SE for all 8 subjects. V_E is BTPS.

	Pre-hypoxia	Hypocap. Hyp.	Normocap. Hyp.
SaO_2 %	97.5 ± 0.2	69.8 ± 1.3	70.1 ± 1.4
$PaCO_2$ mmHg	39.0 ± 1.6	27.3 ± 1.9	38.5 ± 1.3†
pH units	7.41 ± 0.02	7.53 ± 0.03	7.41 ± 0.01†
PaO_2 mmHg	89 ± 3.5	28.9 ± 0.6	34.1 ± 0.7†
$\dot{V}_E$ l/min	9.4 ± 1.2	32.3 ± 4.4	43.5 ± 8.0†
HR, b/min	73 ± 4	111 ± 3.3	96 ± 4†
Brain a,a_3 ($x10^{-2}$) redox*	0	-18.9 ± 2.1	-13.4 ± 1.8†
Muscle a,a_3 ($x10^{-2}$) redox*	0	-1.9 ± 1.1	-3.7 ± 1.7
Δ Brain blood volume* ($x10^{-2}$)	0	-2.7 ± 2.1	8.7 ± 1.3†

* measured as changes in relative optical density: 1 unit = tenfold change in photosignal.
† $P < 0.05$; significantly different from hypocapnia.

Discussion. Alterations in **cyt a,a_3** redox state induced by the same level of hypoxia (SaO_2 = 70%) varied widely in brain and in peripheral muscle, and were modulated by CO_2 levels. In muscle the desaturation of **cyt a,a_3** with hypoxemia was of the order of only 5 to 10% of the maximal reduction oberved during ischemia. This difference could be attributable to continued oxymyoglobin availability in muscle at this SaO_2 level. Maximal reduction of brain **cyt a,a_3** obviously could not be obtained in our subjects, but interpretation of brain signals can be attempted on the basis of experimental observations in cat which have utilized similar NIR monitoring. In this anesthetized preparation (2), SaO_2 = 70% and PaO_2 values = 48 mmHg correspond to at least 50% desaturation of a brain **cyt a,a_3** from normoxic levels, when normocapnia was maintained. Therefore the value of 13.4 units in normocapnic hypoxia probably corresponds to 50% reduction of brain **cyt a,a_3**, and the redox state is proportionately even more reduced during hypocapnia, possibly due to the attendant reduction of cerebral perfusion (see Δ brain blood volume). This data indicates vulnerability of brain **cyt a,a_3** to hypoxia, particularly during hypocapnia. Muscle redox state is substantially buffered and is not affected by CO_2 levels. This study demonstrates that brain redox levels are rapidly reduced during hypoxemia in volunteers.

References:

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