Estimating the time-course of brain adaptation and angiogenesis using PtO2 measurements—an in vivo EPR study

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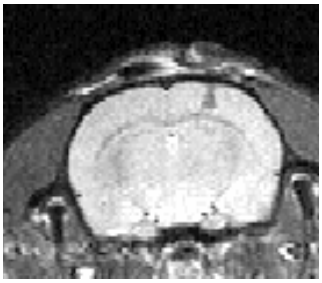
INTRODUCTION

Chronic hypoxic exposure initiates a range of adaptive processes, including angiogenesis, upregulation of glycolysis and increased hematocrit [1]. There are no major changes in $CMRO_2$. Since PtO_2 is determined by a balance between oxygen delivery and utilization, and utilization remains constant, then PtO_2 can be used to monitor adaptation. The time-course of brain PtO_2 during chronic and acute exposure to systemic hypoxia was investigated. A unique feature of this study, is that we can monitor brain PtO_2 in awake restrained animals using electron paramagnetic resonance [2].

METHODS

EPR measurements were done while animals (n=7, Wistar rats) breathed both 10% and 21% O_2. Measurements were taken over a time-course of acclimation to chronic hypoxia (1/2 atm) and recovery. EPR methods have been previously described [2], and involve implantation of lithium phthalocyanine (LiPc) into the cortex, which has an EPR linewidth that is linearly proportional to pO_2 over 0 to 713 mmHg. EPR oximetry was conducted using a low frequency (1.18GHz, L-band) spectrometer with a surface-loop resonator. Awake restrained animals had PtO_2 measured while breathing 21% and 10% O_2 before and after acclimation. During acclimation, they were exposed to 10% FiO_2. Acclimation was at a pressure of 370 mmHg, corresponding to a normobaric O_2 of 10%. Analysis of the data on the time-course of PtO_2 was accomplished using a nonlinear, exponential mixed effects model [3]. MRI for LiPc localization was done before the study began to confirm the material was within the cortex using T2w MRI, Varian console and a 7T Magnex magnet.

RESULTS



MRI confirmed that LiPc was within the cortex (Fig. 1). The mean PtO_2 before acclimation breathing 21% O_2 was 13±2 and while breathing 10% O_2 was 7±2 mmHg (mean±SD, n=7). During acclimation, the PtO_2 was measured while breathing 10% O_2 to determine the time needed for brain PtO_2 to stabilize to a new level. The time required for the PtO_2 to reach a level not significantly different from control was 5-7 days with a T1/2 for adaptation of 3.7 days. The time required for the PtO_2 to stabilize during deacclimation was 7-10 days, with a T1/2 for deacclimation of 1.8 days (Fig. 2).

Figure 1. MRI of the LiPc implant showing cortical localization

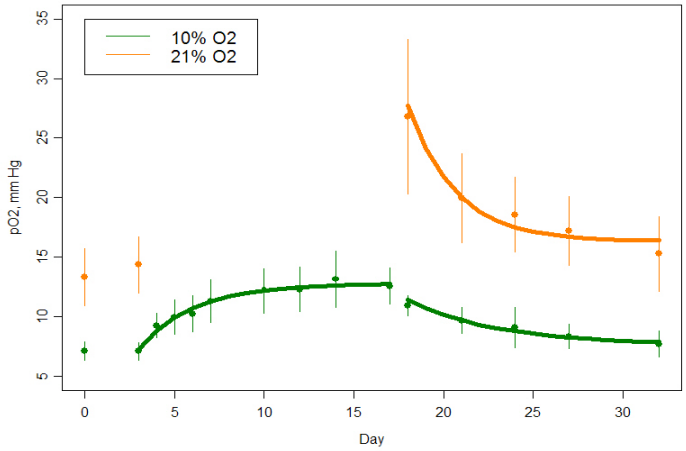


Figure 2. Cortical PtO_2 measured while breathing 21% O2 (top traces) and 10% O_2 (bottom traces) before acclimation (2 points), during acclimation (10% only) and during recovery. The curves represent the results of non-linear mixed effects statistical modeling (mean±SD, n=7)

DISCUSSION

The PtO_2 represents the sum of many complex physiological processes. However, since $CMRO_2$ remains relatively constant, then it can be used to determine the sum of all adaptive processes during exposure to hypoxia. These data indicate that 5-7 days is sufficient for most adaptive processes during exposure, and that de-acclimation is also very rapid.

REFERENCES

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