Diffusion and Perfusion Changes during Long-Term Recovery after Prolonged Hypoxia

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Introduction Tissue oxygenation deficiency due to hypoxia occurs under many clinical conditions, such as asthma, altitude sickness, carbon monoxide poisoning, and stroke. It has been postulated that hypoxia alone will not cause neuronal death, as long as cerebral blood flow and pressure are maintained. Hypoxic preconditioning, with exposure to 8% O_2 for 3 hours, has been tested in animals to study mechanisms of protection against neuronal death following brain ischemia (Ran et al. *Developmental Neuroscience* 2005;27:87-92). The effects on the brain of more extreme hypoxic conditions, and the recovery after prolonged hypoxia, have not been studied to date. We report here an MRI investigation of the physiological responses to a 30-min episode of respiratory hypoxia with 5% O_2 in mice, with the ultimate goal of understanding the mechanisms of brain injury and recovery after hypoxia.

Method The animal protocol was approved by our Institute Animal Care and Use Committee. Male CD1 mice, weighing 20-30 g, were anesthetized with pentobarbital. Animals were transorally intubated and mechanically ventilated. The hypoxic condition was administered for 30 min by adjusting pO_2 to 38 mmHg while the animals were paralyzed with pancuronium to prevent spontaneous gasping. Body temperature was held constant at 36.8 ± 0.4°C. After the hypoxia, ventilation with room air (pO_2 = 148 mmHg) was continued until spontaneous breathing was restored. The heart rate, femoral artery pulse distention, blood O_2 saturation (spO_2), breath distention, and rectal temperature were recorded continuously before, during, and after the hypoxia.

MRI scans, including T_2-weighted, diffusion-weighted, and perfusion images, as well as ADC maps, were acquired at 14.1 T to follow the damage pattern up to 12 days after the hypoxia. Control images were taken one day before the hypoxia.

Results and Discussion Normal spO_2 with room air ventilation is 96 ± 3%. During the 30-min hypoxia, spO_2 steadily decreased from 82 ± 6% (averaged the first 5 min) to 65 ± 7 % (averaged for the last 5 min). The figure below depicts the representative ADC and perfusion maps before and 1-12 days after the hypoxia. From ADC maps, it can be seen that the effects of the hypoxia damage do not manifest fully until 3-5 days after the event. While the region-averaged ADC values do not change significantly (except for hippocampus where p = 0.014 by ANOVA), some substructures of the hippocampus, hypothalamus, lateral cortex, and amygdala show the trend of transient decreases in ADC one day after hypoxia, indicating cytosolic edema, and subsequent increases lasting for a few days beyond the normal ADC level. Previous studies (Kaur, et al. *Glia* 2006;54:826-39) suggested that hypoxia can cause over-expression of VEGF, which in turn leads to higher water permeation across the blood-brain barrier. Thus, the elevated ADC might indicate a prolonged increase in the volume of interstitial fluids. The perfusion images show protracted hypoperfusion after the hypoxia. The initial severity of the hypoperfusion is almost the same as what is typically found after a brief period of global ischemia, but the duration is significantly longer. These results suggest that the cellular mechanism of neuronal injury after prolonged hypoxia might be different from that of global ischemia, calling for a different approach to treatment strategies. (This work was funded by NINDS R01NS/HL036124.)

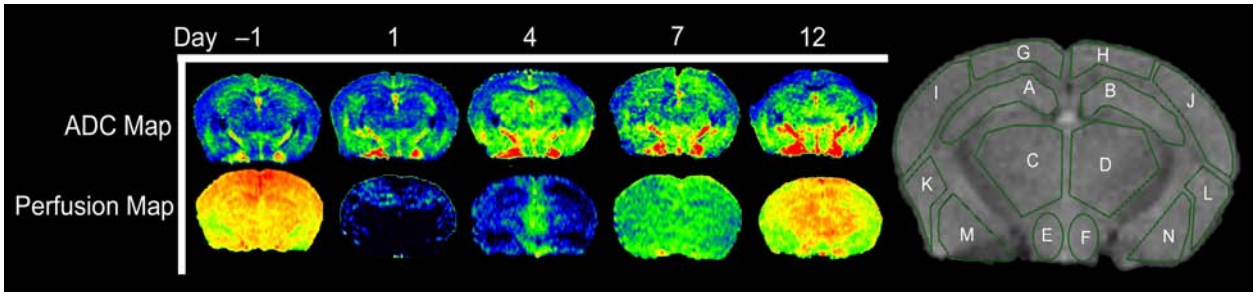

Figure Images in the upper and lower rows are a series of ADC and perfusion maps, respectively. Images were acquired from a single animal one day prior to hypoxia (far left), and 1 to 12 days after hypoxia. Colors in the ADC and perfusion images are scaled with increasing intensity from blue to green to yellow to red. On the far right is a T_2-weighted image overlaid with areas used to determine region-averaged ADC values. Left and right hippocampus (A, B), thalamus (C, D), hypothalamus (E, F), dorsal cortex (G, H), lateral cortex (I, J), piriform cortex (K, L), and the amygdala (M, N).