Acetazolamide improves tissue oxygenation during hypoxia in the human brain

Kang Wang[1], Zachary M Smith[1], and David J Dubowitz[1]
[1]*University of California San Diego, La Jolla, CA, United States*

Target Audience: People interested in the physiology of cerebral hypoxia

Purpose: We have previously found that CBF and $CMRO_2$ increase in acute and sustained hypoxia in human subjects [1, 2, 3] – which we hypothesize occurs via adenosine-mediated modulation in neural excitability [4]. Acetazolamide (AZ), a carbonic anhydrase inhibitor, provides symptomatic relief from high altitude hypoxia. The exact mechanism of action remains unclear as Acetazolamide increases ventilation (& SaO_2), in addition to normalizing CBF & $CMRO_2$. We investigated if a common endpoint of these effects of Acetazolamide may be improvement in the PO_2 of cerebral tissues during hypoxia.

Methods: Five healthy human subjects participated (1F, 4M age 34 ±10 yrs). 3T MRI measurements were made under 4 conditions; Normoxia +/- 250mg oral Acetazolamide, and 6-hrs hypoxia (PiO_2 = 90 Torr) +/- 250 mg oral Acetazolamide.

CBF was measured using a PICORE QUIPSS2 ASL technique (TE=9.1ms, TR=2.5s, TI_1=700ms, TI_2=1500ms, 6 mm slices, 3.5 mins) (and corrected for physiological noise and the effect of O_2 desaturation on T_1 of blood). Venous T_2 was measured using a TRUST (T_2 relaxation under spin tagging) MRI technique with a single shot spiral readout (TE=2.8ms, TR=8s, TI=1.2s, 4 echoes, 10 mm slice, 80 mm tag, 4.5 mins). T_2 measured with TRUST were calibrated against a prior control group [2]. SvO_2 from venous T_2, [Hb] from a blood sample, and SaO_2 from a pulseoximeter allowed for calculation of whole brain $CMRO_2$. Combining the $CMRO_2$ and CBF measurements allowed us to determine the changes in PtO_2 in cerebral tissues [5].

Results: During normoxia, SaO_2, SvO_2, CBF, $CMRO_2$ or PtO_2 did not change with Acetazolamide. Following hypoxia, there was an increase in CBF and $CMRO_2$, and a dramatic decrease in cerebral PtO_2 (P<0.01). Treatment with Acetazolamide prevented the rise in CBF and in $CMRO_2$, and increased SvO_2. This resulted in a smaller decline in cerebral PtO_2 during hypoxia (P<0.05).

Discussion: CO_2 appears to be an important modulator of oxygenation during hypoxia. Hypoxic hypoxia results in increased CBF. There is also increased hypoxic ventilatory drive, which reduces $PaCO_2$. This lowered CO_2 negatively impacts oxygenation via 2 mechanisms: 1) It limits the magnitude of the CBF increase, and hence limits cerebral O_2 delivery. 2) The reduced $PaCO_2$ also contributes to an increase in $CMRO_2$ [3]. Combined, the 2 effects result in a dramatic reduction in oxygenation of the cerebral tissues, PtO_2.

Previous studies have demonstrated decreased CO_2 clearance from cerebral tissues with Acetazolamide [6] (with an increased gradient between tissue and venous CO_2). We hypothesize that this increased $PtCO_2$ from Acetazolamide helps mitigate some of the physiological disturbances during hypoxia. Ventilatory drive is increased. $CMRO_2$ remains near normal, which results in an improved PtO_2 in hypoxia. CBF also remains almost unchanged from normoxic levels. Although this limits any potential to improve PtO_2 from increasing O_2 delivery, this is overshadowed by the greater impact of maintaining near-normal $CMRO_2$.

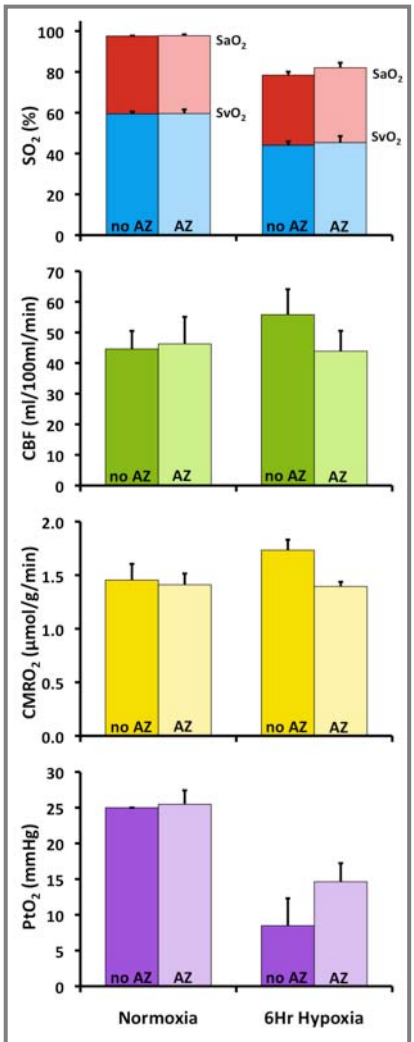

Figure 1: SaO_2 /SvO_2, $CMRO_2$, CBF, and PtO_2 with and without acetazolamide (AZ) for normoxia and hypoxia (error bar = 1 SE).

References: [1] Dyer et al. 2008 Resp Physiol Neurobiol: 160:267-276 [2] Smith et al. J Appl Physiol 2012 [epub] [3] Smith et al. 2011 ISMRM: 4456. [4] Dulla et al. 2005 Neuron: 48:1011-1023. [5] Buxton. Front Neuroenergetics. 2010 2:8 [6] Bickler et al. 1988 J Appl Phys: 65:422-427.
Supported by: NIH NS053934 (DJD) NIH NS075812 (DJD)