Acetazolamide improves tissue oxygenation during hypoxia in the human brain

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Target Audience: People interested in the physiology of cerebral hypoxia

Purpose: We have previously found that CBF and CMRO₂ 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 (& SaO₂), in addition to normalizing CBF & CMRO₂. We investigated if a common endpoint of these effects of Acetazolamide may be improvement in the PO₂ 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 (PiO₂ = 90 Torr) +/- 250 mg oral Acetazolamide. CBF was measured using a PICORE QUIPSS2 ASL technique (TE=9.1ms, TR=2.5s, T₁=700ms, T₂=1500ms, 6 mm slices, 3.5 mins) (and corrected for physiological noise and the effect of O₂ desaturation on T₁ of blood). Venous T₂ was measured using a TRUST (T₂ 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). T₂ measured with TRUST were calibrated against a prior control group [2]. SvO₂ from venous T₂, [Hb] from a blood sample, and SaO₂ from a pulseoximeter allowed for calculation of whole brain CMRO₂. Combining the CMRO₂ and CBF measurements allowed us to determine the changes in PtO₂ in cerebral tissues [5].

Results: During normoxia, SaO₂, SvO₂, CBF, CMRO₂ or PtO₂ did not change with Acetazolamide. Following hypoxia, there was an increase in CBF and CMRO₂, and a dramatic decrease in cerebral PtO₂ (P<0.01). Treatment with Acetazolamide prevented the rise in CBF and in CMRO₂, and increased SvO₂. This resulted in a smaller decline in cerebral PtO₂ during hypoxia (P<0.05).

Discussion: CO₂ 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 PaCO₂. This lowered CO₂ negatively impacts oxygenation via 2 mechanisms: 1) It limits the magnitude of the CBF increase, and hence limits cerebral O₂ delivery. 2) The reduced PaCO₂ also contributes to an increase in CMRO₂ [3]. Combined, the 2 effects result in a dramatic reduction in oxygenation of the cerebral tissues, PtO₂.

Previous studies have demonstrated decreased CO₂ clearance from cerebral tissues with Acetazolamide [6] (with an increased gradient between tissue and venous CO₂). We hypothesize that this increased PtCO₂ from Acetazolamide helps mitigate some of the physiological disturbances during hypoxia. Ventilatory drive is increased. CMRO₂ remains near normal, which results in an improved PtO₂ in hypoxia. CBF also remains almost unchanged from normoxic levels. Although this limits any potential to improve PtO₂ from increasing O₂ delivery, this is overshadowed by the greater impact of maintaining near-normal CMRO₂.

Figure 1: SaO₂/SvO₂, CMRO₂, CBF, and PtO₂ with and without acetazolamide (AZ) for normoxia and hypoxia (error bar = 1 SE).