Prevention of acute mountain sickness by acetazolamide: 
as yet an unfinished story

Since the 1970s, over 200 studies with acetazolamide have 
shown it safe and 60–80% effective in acute mountain sick-
ness (AMS). Despite much investigation, our understanding of 
its action in AMS remains incomplete and more complicated 
than generally taught. This should come as no surprise consid-
ering the presence of carbonic anhydrase (CA) in many tissues 
relevant to high-altitude adaptation or maladaptation. In this 
issue of the Journal of Applied Physiology, Leaf and Goldfarb 
(10) provide a fine state-of-the-art review that highlights this 
complexity and updates the field since last reviewed in 1998 
(12).

A brief history of CA and its inhibitors serves to give some 
perspective on acetazolamide in AMS prevention. Shortly after 
the discovery of CA in red blood cells in 1932, sulfanilamide, 
the first nontoxic oral antibiotic, was introduced and noted to 
have side effects including mild diuresis, metabolic acidosis, 
and hyperventilation. These were quickly recognized to be a 
consequence of renal CA inhibition. Following World War II, 
synthesis of stronger CA inhibitors yielded the 1,000-fold more 
potent sulfonamide, acetazolamide. Although first used as a 
diuretic and gastric acid suppressant, by the mid-1950s it found 
greater efficacy in glaucoma and hydrocephalus. Pulmonolo-
gists explored acetazolamide concurrently as a respiratory 
stimulant for hypoxic patients with chronic obstructive 
pulmonary disease in the expectation of improving arterial 
oxgenation. Albeit effective, patients could not tolerate the 
worsened dyspnea when forced to breathe more. Kronenberg 
and Cain (9), however, realized that such ventilatory stimula-
tion might have a significant impact at high altitude in healthy 
persons and indeed showed better oxygenation and ventilation 
in subjects at high altitude. Shortly thereafter, Forward et al. 
(4) demonstrated that such ventilatory stimulation by acetazo-
lamide could reduce AMS symptoms, and its use for this 
purpose was established.

How then does acetazolamide work in AMS and what 
questions remain to be investigated? Leaf and Goldfarb (10) 
posit that the conventional view by which acetazolamide works 
is too simplistic. In this model, urinary bicarbonate loss from 
renal CA inhibition and the resultant mild metabolic acidosis (a 
ventilatory stimulant) opposes and limits the braking effect of 
hypocapnia on the full ventilatory response to hypoxia. In 
essence, acetazolamide simply accelerates the normal bicar-
bonaturia that would otherwise happen over several days of 
acclimatization. Although this is clearly not the full story, the 
renal effect is nonetheless primus inter pares among other 
possible mechanisms, which include relevant CA inhibition in 
red blood cells, brain, pulmonary and systemic vasculature, 
and chemoreceptors.

Leaf and Goldfarb (10) explain how tissue enzyme concen-
trations and drug penetration into various tissues rule out any 
significant effect of clinically useful dosing of acetazolamide 
(3–5 mg/kg) on red blood cell CO2 transport, cerebral blood 
flow (CBF), and CA inhibition within the central chemorecep-
tors. The only caveat with respect to CBF is that if regional 
brain blood flow changes are heterogeneous, measurements of 
total CBF may not reflect changes in blood flow in critical 
areas such as the brain stem. Since tissue pH, P CO2, and P O2 are 
determined by the metabolic rate of the tissue, its blood flow, 
and arterial values, blood flow changes will alter ventilatory 
responsiveness. Another effect of CA inhibition in the brain 
not mentioned, but conceivably relevant to AMS, is cerebro-
spinal fluid (CSF) formation. Complete choroid plexus CA 
inhibition reduces this by 50% and in principle could reduce 
overall intracranial volume and pressure, which are slightly 
increased with hypoxia and in AMS and have been proposed as 
pathogenetic in AMS. However, effective doses of acetazo-
lamide that penetrate the blood-brain barrier, reach the choroid 
plexus, and depress CSF flow and volume are on the order of 
20 mg/kg (18).

Our present understanding of how acetazolamide works 
points to critical CA inhibition in the brain vascular endothe-
lium, kidneys, and peripheral chemoreceptors interacting with 
the primary effect of hypoxia to stimulate ventilation. Luminal 
brain vascular endothelial CA will be fully and immediately 
inhibited by even very low drug concentrations in blood, 
causing a small hindrance to normal “tissue-to-blood” transfer 
such that tissue P CO2 will be elevated by 1–2 Torr (8). A slight 
CO2 retention in the vicinity of both the central and peripheral 
chemoreceptors will be sufficient to stimulate ventilation. 
Acetazolamide (5–7 mg/kg iv) in normoxic humans induces a 
small increase in ventilation within minutes consistent with 
endothelial CA inhibition, well before any significant urinary 
bicarbonate loss or red blood cell drug uptake reaches a critical 
inhibitory level (13). Thus, in addition to the metabolic acido-
sis, slight CO2 retention from vascular CA inhibition will help 
mitigate the suppressant effect of the primary respiratory alkalo-
sis generated by hypoxic hyperventilation and so allow a 
more complete hypoxic ventilatory response.

Despite the metabolic acidosis, an expected increase in 
the acute isocapnic hypoxic ventilatory response (HVR) is lacking, 
indicating that acetazolamide abolishes the H +–O2 interaction in 
the peripheral chemoreceptors (2, 13, 17). This raises an 
interesting question as to what could be the advantage of taking 
a drug at altitude that has inhibitory effects on oxygen-sensing 
cells. The answer lies in the fact that the ventilatory response 
high-altitude hypoxia is essentially poikilocapnic (i.e., hy-
pocapnic). Consequently, any agent abolishing the H +–O2 
interaction under these circumstances will blunt the action of a 
low P CO2 on the hypoxic response and generate more ventila-
tion than would otherwise occur (17). In humans at sea level, 
acetazolamide has no influence on the peripheral chemorecep-
tor contribution to the ventilation response on stepwise changes 
in end-tidal P CO2 (14). It cannot be excluded that, in part, 
CO2–H + and O2 follow separate signal-transduction pathways 
in the carotid bodies. Future studies with acetazolamide are 
warranted to determine if, despite the absence of a O2–H + 
interaction, the carotid bodies may retain their H + sensitivity.

Predictably, acetazolamide’s inhibitory effect on the HVR 
should be due to peripheral chemoreceptor CA inhibition. 
However, in the cat, even the more lipophilic inhibitor metha-
zolamide does not reduce the HVR, suggesting that acetazo-
lamide may act by a mechanism other than CA inhibition (15).
as already established for hypoxic pulmonary vasoconstriction (6). Interestingly, antioxidants reverse the inhibitory effects of low-dose acetazolamide on HVR in humans (16). Further studies are needed to establish if antioxidants interfere with the prophylactic effects of acetazolamide and how possibly acetazolamide, either by CA inhibition or by ligation to some other receptor, alters intracellular redox status of the peripheral chemoreceptors.

The contribution of the central chemoreceptors to increased ventilation with acetazolamide is via the stimulatory effect of the metabolic acidosis in raising H+ concentration to counteract the effect of increased ventilation to washout CO2 and raise pH. If a clinically relevant dosing of acetazolamide decreases arterial Pco2 (PaCO2) by −7 Torr (14, 17) but does not alter CBF (7, 17) or impair blood CO2 transport, then the brain tissue-to-blood Pco2 gradient should not change very much, implying a considerable fall in brain tissue Pco2. However, as mentioned above, brain vascular endothelial CA inhibition will limit this fall to some extent and so lessen the braking effect of increased ventilation to return H+ in the central chemoreceptors to a less acidic state.

Acetazolamide’s actions on respiration and the vasculature suggest how it reduces periodic breathing in sleep at high altitude (5). Dempsey (3) proposed that the “CO2 reserve” (i.e., the difference in Pao2 between eupnea and the apneic threshold), when combined with “plant gain” (or the ventilatory increase required for a given reduction in PaCO2) and “controller gain” (ventilatory responsiveness to CO2 above eupnea), are the key determinants of breathing stability in sleep. In general, breathing during sleep is made more stable by increases in the CO2 reserve, and reductions in plant and controller gain. Acetazolamide alters all three favorably. First, with elevated arterial Po2 and decreased Pao2, plant gain will be reduced because larger changes in ventilation are needed to cause equivalent changes in blood gases. Second, a parallel left shift of the CO2 response curve will raise the difference between the prevailing PaCO2 and the apneic threshold (CO2 reserve) and decrease the propensity for apnea. A small rise in brain stem Pco2 with inhibition of vascular CA will have a similar tonic stabilizing influence. Third, due to the higher prevailing Po2, subjects are in a flatter region of the (hyperventilatory) hypoxic response curve, resulting in a reduced O2 controller gain. A further reason why acetazolamide reduces ventilatory controller gain in sleep is the abolishment of the CO2–O2 interaction so that responses to hypoventilation-induced combined hypoxia/hypercapnia may be reduced considerably. Finally, it cannot be ruled out that acetazolamide increases the cerebrovascular response to combined hypoxia/hypcapnia (17), leading to a dampening influence on subsequent changes in brain stem Pco2. Note that a lowered cerebrovascular CO2 sensitivity may play a role in the genesis of periodic breathing at high altitude (1). Because acetazolamide does not affect the time constant of the peripheral CO2 response (14) or the time course of the HVR (17), we do not believe slower reaction times within the carotid bodies play a significant role in reducing periodic breathing.

Many questions remain to be investigated before we have a complete understanding of acetazolamide protection in AMS. Although not an exhaustive list of experiments and methodological approaches, we believe the following are several key directions to pursue.

1) Regional brain blood flow, pH, metabolic rate, and oxygenation (such as with magnetic resonance imaging and spectroscopy) in areas of brain involved in respiratory control need to be performed in humans in conjunction with ventilation, ventilatory responses, and arterial blood gas measurements. Dose-response experiments with acetazolamide in normoxia and hypoxia, combined with plasma measurements of total and free drug levels, are needed to better calculate the degree of red blood cell and tissue CA inhibition. Although not presently available for humans, analogs of acetazolamide, lacking CA inhibiting activity, will be useful in animals to test whether and how much of the effect of acetazolamide is due to CA inhibition or to some other action on O2 and CO2 sensing and responsiveness.

2) Studies of acetazolamide in conscious and sleeping chemoreceptor-intact animals are needed, both in normoxia and hypoxia, in which central and peripheral chemoreceptor contributions can be gauged by isolating the drug and/or systemic acid-base changes to either the central or peripheral chemoreceptors. This can be done by isolating the circulation to the carotid bodies and perfusing them with appropriately conditioned blood (11).

3) The contributions of the renal metabolic acidosis and diuresis of acetazolamide to the protection with acetazolamide in AMS need to be explored by using other mild diuretics to achieve the same magnitude of diuresis as acetazolamide and/or using acetazolamide but preventing bicarbonate and sodium losses by carefully calibrated replacement.

REFERENCES


Erik R. Swenson
University of Washington
Veterans Affairs Medical Center
Pulmonary Disease Section
Seattle, Washington
e-mail: eswenson@u.washington.edu

Luc J. Teppema
Anesthesiology
Leiden University Medical Center
Leiden, The Netherlands