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Mechanisms of action of acetazolamide in the prophylaxis and treatment of acute mountain sickness

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Leaf DE, Goldfarb DS. Mechanisms of action of acetazolamide in the prophylaxis and treatment of acute mountain sickness. *J Appl Physiol* 102: 1313–1322, 2007. First published October 5, 2006; doi:10.1152/japplphysiol.01572.2005.— Acetazolamide, a potent carbonic anhydrase (CA) inhibitor, is the most commonly used and best-studied agent for the amelioration of acute mountain sickness (AMS). The actual mechanisms by which acetazolamide reduces symptoms of AMS, however, remain unclear. Traditionally, acetazolamide's efficacy has been attributed to inhibition of CA in the kidneys, resulting in bicarbonaturia and metabolic acidosis. The result is offsetting hyperventilation-induced respiratory alkalosis and allowance of chemoreceptors to respond more fully to hypoxic stimuli at altitude. Studies performed on both animals and humans, however, have shown that this explanation is unsatisfactory and that the efficacy of acetazolamide in the context of AMS is likely due to a multitude of effects. This review summarizes the known systemic effects of acetazolamide and incorporates them into a model encompassing several factors that are likely to play a key role in the drug's efficacy. Such factors include not only metabolic acidosis resulting from renal CA inhibition but also improvements in ventilation from tissue respiratory acidosis, improvements in sleep quality from carotid body CA inhibition, and effects of diuresis.

carbonic anhydrase; altitude sickness; metabolic acidosis; hypercapnic ventilatory response; periodic breathing

AS RAPID ASCENT TO HIGH ALTITUDES has become an increasingly common phenomenon for both occupational and travel-related purposes, so too have altitude-related disorders reemerged as a significant medical issue. Three major classes of high-altitude diseases have been identified: high-altitude pulmonary edema, high-altitude cerebral edema, and acute mountain sickness (AMS), the latter being by far the most common. The incidence of reported AMS has varied widely: as low as 10% at 3,500 m in some studies (106) and as high as 75% at 4,500 m in other studies (32).

Acetazolamide, a potent carbonic anhydrase (CA) inhibitor (CAI), is the most common and best-studied agent for the amelioration of AMS (16, 95). While there is some debate regarding optimal dose, with recent studies finding that doses of as little as 250 mg/day may be equally effective compared with more conventional doses of 500–750 mg/day (8), the efficacy of acetazolamide in preventing and treating AMS has been well established (78).

The actual mechanisms by which acetazolamide reduces symptoms of AMS, however, remain unclear. This knowledge gap is likely due, in large part, to disagreement about the etiology of AMS itself. While one hypothesis has been that AMS is caused by hypoxia-mediated mild cerebral edema and increased intracranial pressure (81), a recent MRI study has challenged this hypothesis by showing that brain morphological changes do not correlate well with symptoms of AMS (24).

The contrasting "vasogenic edema" hypothesis states that disruption of the blood-brain barrier (BBB) is primarily responsible for high-altitude illness (34). However, studies of free radical-mediated damage to barrier function under conditions of hypoxia have not supported such a pathophysiology in AMS (5). Despite ambiguity regarding the etiology of AMS, there is relative agreement that symptoms are caused predominantly by hypoxia and not hypobaria (115). Consistent with this notion are the findings that oxygen therapy is an effective treatment for AMS (31).

Acetazolamide has been shown to significantly increase minute ventilation by as much as 50% relative to controls at 4,392 m (15, 58, 90). Therefore, it improves arterial Po_2 (Pa_{O_2}) (29) and oxyhemoglobin saturation so that average arterial O_2 saturation (Sa_{O_2}) during sleep increased from 72 to 79% (90). There is some evidence that the increase in minute ventilation is due predominantly to an increase in tidal volume and not due to an increase in respiratory frequency (101).

While it is known that acetazolamide increases minute ventilation and leads to improvements in arterial blood gases, the mechanism by which this effect occurs is poorly understood. The most commonly cited explanation for the drug's enhancement of ventilation is that renal bicarbonate excretion leads to metabolic acidosis (116). Metabolic acidosis, in turn, attenuates the inhibitory effects of hypoxia-induced respiratory alkalosis (Fig. 1). While metabolic acidosis is indeed likely to be integral to acetazolamide's efficacy, such an explanation fails to address the multitude of systemic effects secondary to carbonic anhydrase inhibition, as several past reviewers of the subject have indeed noted (91).
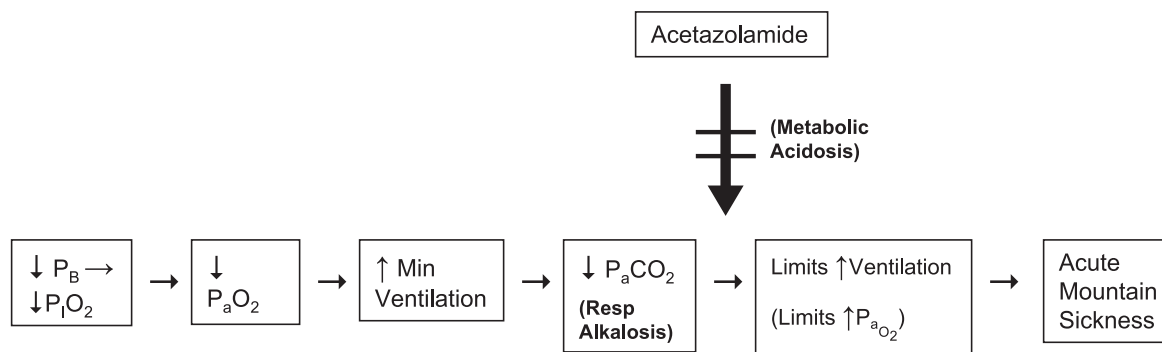
Fig. 1. Commonly cited but oversimplified explanation for acetazolamide's efficacy in the reduction of acute mountain sickness (AMS). At high altitude, reduced barometric pressure (P_B) and reduced partial pressure of inspired oxygen ($P_{I_{O_2}}$) result in hypoxemia, which drives minute ventilation. Hyperventilation causes a respiratory (Resp) alkalosis that limits the rise in ventilation and leads to symptoms of AMS. By generating metabolic acidosis, acetazolamide is able to attenuate the effects of respiratory alkalosis and improve AMS. Pa_{O_2} and Pa_{CO_2}, arterial P_{O_2} and P_{CO_2}, respectively.

This review will discuss possible mechanisms by which acetazolamide improves symptoms of AMS. While an increase in ventilation and Sa_{O_2} is likely to be paramount to acetazolamide's efficacy, other mechanisms, including reduction of sleep periodic breathing, and increased fluid diuresis, will also be explored. A model relating all of these effects to reduced AMS will be provided.

HYPERCAPNIC VENTILATORY RESPONSE

Hypercapnic ventilatory response position. The increase in ventilation following acetazolamide administration has been well documented as a leftward shift in the ventilation-CO_2 response curve (51, 95, 99). This leftward shift has also been demonstrated with administration of the CAI benzolamide (53). Figure 2 shows a model of such curves, also commonly referred to as the hypercapnic ventilatory response (HCVR) (95). For any given level of end-tidal P_{CO_2} ($P_{ET_{CO_2}}$), there is an increase in minute ventilation following treatment with acetazolamide. Possible mechanisms for this increase are discussed later in the section on central chemoreceptors (CCRs). While the curves in Fig. 2 are derived under conditions of mild

Fig. 2. Hypercapnic ventilatory response (HCVR) in control vs. acetazolamide-treated humans under conditions of mild hypoxia. CAI, carbonic anhydrase inhibitor; $P_{ET_{CO_2}}$, end-tidal P_{CO_2}; $\dot{V}_E$, minute ventilation. Reproduced with permission from the American Physiological Society (95).

hypercapnia, CAIs produce similar leftward shifts of the HCVR under conditions of hypocapnia seen at altitude as well (53).

HCVR slope. While the position of the HCVR curve reflects the magnitude of ventilation at any given level of $P_{ET_{CO_2}}$, the slope of the HCVR curve reflects chemosensitivity to changes in $P_{ET_{CO_2}}$. Investigators have found conflicting evidence of a slope change in the HCVR following treatment with acetazolamide. Some investigators have found an increased chemosensitivity (increased HCVR slope) following acetazolamide treatment (101, 109, 110), while others have found no change (62, 86) and still others have found a decrease in slope (51, 111). Swenson and Hughes (95) found an increased HCVR slope during chronic acetazolamide treatment (500 mg po every 6 h for 18 h) (Fig. 2) but a decreased HCVR slope during acute treatment (1 h after 500 mg iv) when the latter was combined with mild hypoxia.

These conflicting data might be attributed to differences in species, methodology, dosage, and route of administration. When Bashir and colleagues (7) studied the effect of a clinically relevant dose (500 mg po bid) of acetazolamide in humans, no significant change in the HCVR slope was found (7). More recently, Teppema and Dahan (99) substantiated these findings in humans using similar doses (250 mg po tid). Using a two-compartment model comprising a fast and slow component, Teppema and Dahan were further able to show that CO_2 sensitivity was unchanged in both the peripheral and central chemoreflex loops following acetazolamide.

In summary, the exact role of acetazolamide in mediating CO_2 chemosensitivity remains unclear. This ambiguity is partly attributable to imprecision in determining true P_{O_2} and P_{CO_2} at sites of chemoreception, particularly in the setting of CA inhibition and potential disequilibrium between CO_2, HCO_3^-, and H^+ (97).

PERIPHERAL CHEMORECEPTORS

Acetazolamide inhibits peripheral chemoreceptors. Understanding the mechanisms responsible for the leftward shift of the HCVR curve following acetazolamide has been the focus of much research on peripheral chemoreceptors (PCRs). Given that acetazolamide produces a metabolic acidosis resulting from renal bicarbonate diuresis (66) and that PCRs are known to increase ventilatory drive in response to low pH, some
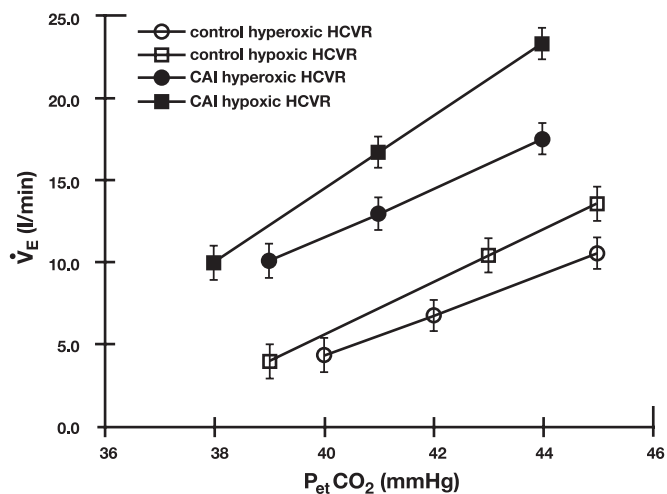
investigators have reasonably proposed that the metabolic acidosis produced by acetazolamide counteracts high-altitude respiratory alkalosis and allows PCRs to respond more fully to low Pa_{O_2} (11, 53). Research into the PCR response to acetazolamide, however, suggests that PCRs are actually inhibited by acetazolamide. Most of this research on PCRs has focused on the carotid body chemoreceptors, since it has been shown that the contribution of the aortic body chemoreceptors to CO_2-induced ventilatory responses is of minor importance (37, 56).

Teppema and colleagues (100) studied the effects of acetazolamide on ventilation in control vs. PCR-denervated cats. While acetazolamide caused ventilation to increase significantly in both groups, ventilation increased almost twice as much in those cats whose PCRs had been removed. Additionally, the effect of acetazolamide on the hypoxic ventilatory response (HVR) (minute ventilation vs. $\%Sa_{O_2}$) was examined in PCR-intact cats, and it was discovered that the hypoxic sensitivity that existed before infusion of the drug was abolished with acetazolamide.

Teppema's findings (100), suggestive of an inhibitory influence of acetazolamide on PCRs, are supported by studies that have examined the response of the carotid body to CO_2 in the absence and presence of the drug. These studies have established that acetazolamide substantially reduces carotid sinus nerve activity in response to CO_2 in vivo (36, 39, 69, 103) and also reduces dopamine release by carotid body chemoreceptor cells in vitro (80). More recently, it has been established that even low doses of acetazolamide (4 mg/kg) are capable of reducing the CO_2 sensitivity of PCRs (111).

Finally, indirect support for acetazolamide's inhibition of PCRs comes from studies of ammonium chloride (NH_4Cl). Metabolic acidosis from NH_4Cl administration has been shown to augment the HVR (43) due to direct stimulation of PCRs by H^+ (12, 101). Acetazolamide, however, fails to augment HVR despite a fall in extracellular pH, consistent with an inhibitory effect on PCRs (7, 95, 101). Thus a substantial volume of literature suggests that acetazolamide impedes the ability of PCRs to respond to a variety of stimuli, most notably CO_2 and hypoxia. Consequently, acetazolamide's stimulatory effects on ventilation are unlikely to be mediated by PCRs.

Proposed mechanism. The inhibitory influence of acetazolamide on PCRs is likely related to local inhibition of CA. The notion that CA may be involved in regulation of pH within the carotid body has long been proposed (61) and has been supported more recently by the intracellular histochemical localization of CA in type I cells of the cat carotid body (77, 79). Several authors have proposed that acetazolamide directly inhibits CA within the carotid body, thereby altering the pattern of H^+ genesis via the CO_2 hydration reaction (36, 57, 102, 110). Inhibition of the CO_2 hydration reaction within the carotid body would limit the rise in $[H^+]$ following a hypercapnic stimulus, and given strong evidence that the effective acidic stimulus at the carotid body chemoreceptors is indeed an increase in intracellular $[H^+]$, acetazolamide would be expected (and has been found) to delay chemosensory nerve activity (80).

Consistent with the above proposal are the findings by Travis (104) in anesthetized dogs. It was demonstrated that acetazolamide administration (20 mg/kg iv) eliminated the increased respiratory response to intracarotid injections of pure CO_2 that was seen before the drug was given. However,

prompt ventilatory responses to intracarotid lactic acid injections (0.15 M) were preserved after acetazolamide treatment. Therefore, acetazolamide prevented PCRs from responding to highly concentrated doses of CO_2 but did not affect their ability to respond to a non-CO_2 acidic stimulus, consistent with inhibition of CA within the carotid body.

In addition to the above inhibitory effects mediated by acid-base changes within the carotid body, acetazolamide may also have important inhibitory effects on O_2 sensing. Interestingly, the latter effects appear to be independent of CA inhibition. Expanding on prior in vitro studies (44), Teppema and colleagues (98) recently demonstrated that anesthetized cats responded to low-dose acetazolamide (3 mg/kg) with a 44% decrease in hypoxic sensitivity, while a much higher dose (33 mg/kg) of a more potent CAI, methazolamide, failed to produce any significant change in the HVR, implying a pharmacological action of acetazolamide other than CA inhibition. Although such an alternative mechanism has not been fully elucidated, inhibition of PCRs, the primary sensors of hypoxemia, may not necessarily be involved, as recent evidence points to a role of acetazolamide in blocking hypoxic pulmonary vasoconstriction independent of CA inhibition (92).

CENTRAL CHEMORECEPTORS

The inability of PCRs to account for increased ventilation following treatment with acetazolamide suggests that this effect is mediated principally by central chemoreceptors (7, 53, 101, 110). Mechanisms responsible for such an effect are considered below.

Direct effect of acetazolamide on CCRs. Several investigators have examined the possibility that acetazolamide's effects on CCRs are mediated via direct intracellular inhibition of CA within the central nervous system (CNS). The logic behind such studies is based largely on the importance of the CO_2 hydration reaction within the CNS in regulating cerebrospinal fluid HCO_3^- concentration ($[HCO_3^-]_{CSF}$) (38, 67, 107) It has been shown that cerebral intraventricular administration of acetazolamide diminishes the rise in $[HCO_3^-]_{CSF}$ and impairs CSF pH regulation during respiratory acidosis in both dogs (49) and rats (50). However, studies in which acetazolamide was administered intravenously did not substantiate such findings (4, 70). Thus, while acetazolamide is theoretically capable of crossing the BBB (82), when administered intravenously in doses that simulate those taken orally by humans it is likely that only negligible concentrations accumulate in brain tissue (1, 18).

Metabolic acidosis. Given that acetazolamide's therapeutic effects are unlikely due to direct manipulation of CA within CCRs or within the CNS, the most plausible mechanism for acetazolamide's effects on central chemoreceptors is the metabolic acidosis produced by renal bicarbonate diuresis (66, 110). Bicarbonaturia results from inhibition of intracellular CA isozymes present in the kidney and serves to establish a diffusion gradient between $[HCO_3^-]_{CSF}$ and plasma HCO_3^- concentration ($[HCO_3^-]_{plasma}$), ultimately lowering $[HCO_3^-]_{CSF}$ (53), lowering CSF pH (59), and thereby affecting CCRs. The importance of CSF pH in mediating CCR output has been well established, with lower CSF pH stimulating ventilation and higher CSF pH inhibiting ventilation (71, 84). Therefore, while the metabolic acidosis produced by acetazolamide is incapable

of stimulating PCRs due to simultaneous inhibition of carotid body CA, it is likely that such acidosis augments the output of CCRs.

Consistent with this notion are the findings that metabolic acidosis produced by other agents generates similar ventilatory effects. Studies using benzolamide, a CAI similar to acetazolamide but with greater avidity for CA, have shown that the drug causes a leftward shift in the HCVR curve and reduces symptoms of AMS (53, 96).

Other studies have evaluated the effects of direct acid infusion on ventilation. Tojima and colleagues (101) found that the metabolic acidosis produced by NH_4Cl (8 g) increases resting ventilation by the same magnitude as acetazolamide (500 mg). Still others have found that NH_4Cl increases the slope of the HCVR (9, 63). While these findings are supportive, a direct comparison between the metabolic acidoses produced by NH_4Cl vs. acetazolamide is somewhat misleading, given that the former acts principally through PCRs (12, 101) while the latter, as we have discussed, most likely acts through CCRs (7, 110). Furthermore, NH_4Cl is known to cause gastrointestinal upset and nausea, factors that might themselves produce ventilatory changes. Nonetheless, the link between metabolic acidosis and increased ventilatory drive is further supported by studies that have examined the effects of acute HCl infusion in rabbits (72). Such studies, despite their limitations, help strengthen the well-established relationship between metabolic acidosis and increased ventilation.

It should be noted that at high altitude, the metabolic acidosis produced by CAIs does not necessarily produce acidemia but rather seems to prevent respiratory-induced alkalemia, thereby maintaining plasma pH at relatively neutral levels. That is, it was found that the pH of subjects taking benzolamide for 72 h at a simulated altitude of 14,000 ft was 7.445 compared with pH 7.501 in those subjects taking a placebo (53).

Tissue respiratory acidosis. An alternative explanation for the increased ventilatory drive associated with acetazolamide, again most likely mediated through CCRs, is global tissue respiratory acidosis. That is, inhibition of red blood cell (RBC) and vascular endothelial cell CA has been shown to cause an almost immediate retention of CO_2 in all tissues as the normal mechanisms for exchange and transport are attenuated (97). The resulting tissue respiratory acidosis has been postulated by some (100, 110) to be the primary stimulus and by others to be merely an additional stimulus to the hyperventilation associated with CA inhibition (91).

Support for this notion comes from studies in which the metabolic acidosis effect of acetazolamide is eliminated. Swenson and Hughes (95) examined the effects of acute administration of the drug, 1 h after intravenous injection, that is, before any significant renal bicarbonate loss but sufficiently long to cause tissue and vascular endothelial cell CA inhibition and therefore tissue respiratory acidosis. They found that acute administration of acetazolamide produced a significant increase in resting normoxic ventilation. Moreover, when metabolic acidosis was superimposed by chronic administration of acetazolamide, no additional hyperventilation was found to that seen with an acute dose, suggesting that the entire increase in ventilation could be accounted for by mechanisms other than metabolic acidosis.

Further support for the role of tissue respiratory acidosis in modulating ventilation following CA inhibition comes from studies in nephrectomized dogs. Following an acute respiratory acidosis induced by ventilating the animals with CO_2, Javaheri and colleagues (46) found that treatment with acetazolamide resulted in higher CSF P_{CO_2} values and lower CSF pH. While the authors did not specifically investigate ventilation rate, their results provide strong support for the notion that acetazolamide, even in the absence of metabolic acidosis, affects the environment surrounding CCRs (i.e., CSF) in a manner consistent with increased ventilatory drive.

Finally, the discovery of membrane-bound CA isozymes (CA IV, XII, and XIV) has shed light on the potential role of tissue respiratory acidosis in mediating ventilation. Because of its location on the luminal side of nearly all capillary beds, including the brain (27), CA IV is completely inhibited by even low doses of acetazolamide (91). Studies in which CA IV was selectively inhibited showed mildly impaired blood CO_2 uptake and release and led to a local tissue retention of CO_2 on the order of 1–2 mmHg (17, 52, 91). Such an effect in the brain could potentially lead to profound changes in ventilation, given the high CO_2 ventilatory responsiveness (1–3 $l \cdot min^{-1} \cdot mmHg^{-1}$) of central chemoreceptors (91).

The notion that CA inhibition could induce a mild CO_2 retention within CCRs is consistent with the findings of a study in which the effects of CA inhibition were studied in humans at high altitude (19). In this study, the increase in ventilation and decrease in Pa_{CO_2} following inhibition of CA were greater than could be accounted for by the stimuli of arterial hypoxemia and pH alone (91). Similarly, Tojima et al. (101) found that acetazolamide produces a larger shift in HCVR for a given degree of metabolic acidosis than ammonium chloride (Fig. 3), also consistent with a central CA effect of the drug. Given that the drug does not cross the BBB in appreciable quantities when given in clinically relevant doses (see above), such an effect on CCRs would be attributable to inhibition of RBC and vascular endothelial cell CA within the brain, rather than accumulation of acetazolamide within the brain parenchyma.
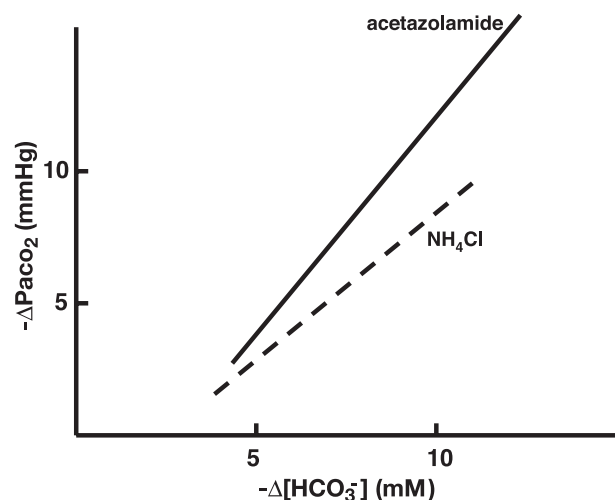

Fig. 3. Comparison of acetazolamide to NH_4Cl in the response of Pa_{CO_2} to changes in plasma HCO_3^- concentration. For a given degree of metabolic acidosis, acetazolamide produces a larger change in ventilation, reflected here by ΔPa_{CO_2}. Data are from Tojima et al. (101).

CEREBRAL BLOOD FLOW

In addition to improvements in Pa_{O_2}, presumably mediated by stimulation of CCRs, some authors have suggested that acetazolamide also ameliorates AMS by increasing cerebral blood flow (CBF) (10). That acetazolamide has the potential to increase CBF has indeed been long established (22). Given that the drug does not increase cerebral O_2 consumption (108), augmentation of CBF might logically be expected to improve cerebral oxygenation (10) and therefore ameliorate AMS.

Despite studies that have shown an increase in CBF following acetazolamide, most investigators have found that this effect is limited in time (60) and can only be produced by large doses of the drug given acutely. Friberg and colleagues (25) documented an acute 30% elevation of CBF following ingestion of 1,000 mg of acetazolamide but noted that this effect was only found 3–5 h after the initial administration (25). Others have found that when acetazolamide is given in clinically relevant doses (250 mg po tid or 5 mg/kg iv) it fails to produce any significant rise in CBF (30, 42). Thus, while acetazolamide is theoretically capable of producing cerebrovascular effects consistent with improved cerebral oxygenation, in practice such a mechanism is unlikely to contribute to the drug's efficacy in AMS.

SLEEP PERIODIC BREATHING

Periodic breathing, quality of sleep, and AMS. Periodic breathing, defined as oscillations in respiratory frequency and/or tidal volume, is a well-documented phenomenon that occurs in stages 1 and 2 of non-rapid eye movement sleep in normal healthy adults (75). Following ascent to high altitude, periodic breathing during sleep is almost universal (48, 112) and is more highly pronounced (2, 83, 118). Acetazolamide leads to significant reductions in periodic breathing during sleep at high altitude (90, 112). This reduction in sleep periodic breathing may, in turn, ameliorate symptoms of AMS by at least two mechanisms: diminution of apnea-associated hypoxemia and improvement in subjective quality of sleep.

Various studies have evaluated the relationship between sleep periodic breathing at altitude and Sa_{O_2}. The results of such studies have been inconsistent, with some investigators finding a positive correlation between sleep periodic breathing and mean $Sa_{O_2}\%$ (68, 117), others finding no correlation (35, 73), and still others finding a negative correlation (55). Despite equivocal findings when using mean $Sa_{O_2}\%$ as a measure of oxygenation, there is a well-established connection between sleep periodic breathing and greater amounts of time spent at severely desaturated levels ($Sa_{O_2} < 70\%$) (35). Accordingly, reduction of sleep periodic breathing reduces the frequency and severity of such episodes of hypoxemia and therefore might be expected to have a positive therapeutic influence in AMS.

An alternative connection between acetazolamide's reduction of sleep periodic breathing and its efficacy in treating AMS may relate to improvements in subjective quality of sleep. Sleep at high altitude is characterized by poor subjective quality, frequent arousals, decreased sleep efficiency, and decreased total sleep time (117). Subjects who report poor sleep at altitude almost invariably awake with a morning headache (89). There is evidence of a close association between this poor sleep quality, linked primarily to increased frequency of arousals, and periodic breathing (2, 76, 113). Given this association and given that acetazolamide has been shown to both reduce the number of arousals as well as improve the subjective quality of sleep at high altitude (90, 112), it is plausible that such improvements in sleep quality are mediated by profound reductions in periodic breathing. Indeed periodic breathing, in conjunction with hypoxia, has been postulated to be the principal cause of sleep disruption at altitude (117).

It should be noted that acetazolamide improves symptoms of AMS in people with acute ascent who have not yet been to sleep, and therefore the nature of any potential role of the drug in mediating AMS through sleep is more likely to be contributory than primary. Nonetheless, it is unlikely that sleep disruption plays no pathogenic role in altitude sickness, given that sleep fragmentation in other disease states (such as congestive heart failure) is associated with symptoms such as headache and daytime fatigue irrespective of altitude (45, 47). Thus, even if the headache produced by sleep apnea represents a separate entity from the "AMS headache," the two would be difficult to distinguish clinically.

Mechanism. The mechanism by which acetazolamide affects sleep periodic breathing at altitude has been studied extensively. This oscillating pattern of breathing reflects alternating respiratory stimulation by hypoxia and subsequent inhibition by hyperventilation-induced hypocapnia (114). A self-sustaining cycle is thus generated (Fig. 4). Further contributing to this cycle are the findings that the carotid body produces transient overshoots in the ventilatory response to both hypoxia, re-
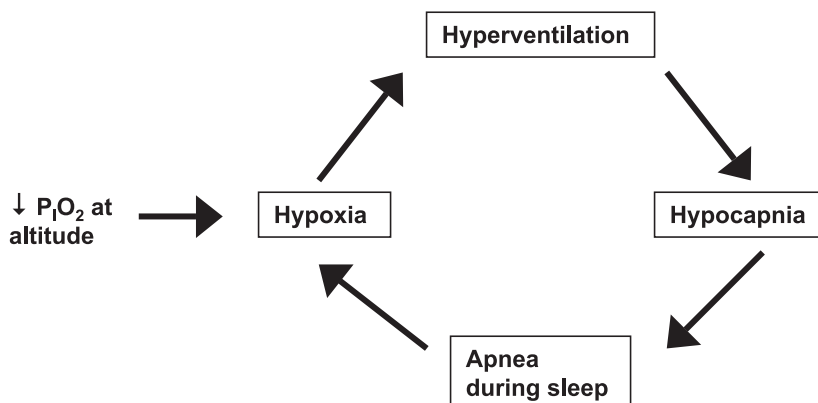
Fig. 4. Pathophysiology of periodic breathing at altitude. The hypoxia of altitude, amplified by increased hypoxic ventilatory response, stimulates ventilation. The resulting hypocapnic alkalosis and reduction of hypoxia lead to apnea during sleep. Apnea, in turn, augments hypoxia and raises P_{CO_2}, triggering hyperpnea. Adapted from Weil (114).

flected by an increased HVR at altitude (114), and to hyper-capnia (57).

Acetazolamide's effects on periodic breathing are most likely mediated through its inhibition of PCRs. The mere fact that periodic breathing reflects responses to rapidly changing stimuli suggests a critical role for fast-responding PCRs (114). Denervation of the carotid body has been shown to prevent development of sleep periodic breathing in dogs (87), and treatment with the PCR-stimulant almitrine has been shown to exacerbate periodic breathing in humans (35). Acetazolamide, on the other hand, has been shown to eliminate the carotid body's transient overshoots and undershoots to sudden changes in $P_{ET_{CO_2}}$ (57).

As stated by Swenson and Hughes (95), acetazolamide's inhibition of carotid body CA will blunt large changes in chemoreceptor $[H^+]$ that would otherwise occur with the large Pa_{CO_2} oscillations of periodic breathing. The reduced rate of uncatalyzed CO_2 hydration at PCRs, therefore, would be the principal mechanism by which acetazolamide minimizes large fluctuations in PCR output and thereby reduces periodic breathing.

Reduction of periodic breathing via inhibition of PCRs is also consistent with the hyper/hyposensitive nature in which PCRs respond to hypoxemia. That is, the PCR response to mild hypoxemia (Pa_{O_2} 50–100 mmHg) is virtually nonexistent (65), while the PCR response to more severe levels of hypoxemia (Pa_{O_2} below 50 mmHg) is steep and often exaggerated (57, 114). Therefore, the PCR response to hypoxemia is likely to contribute to the oscillations in breathing pattern seen at high altitude, as Pa_{O_2} fluctuates above and below 50 mmHg. Given the nature of PCRs to overstimulate or understimulate hyperventilation at varying levels of hypoxemia, inhibition of PCRs by acetazolamide is consistent with the finding of reduced periodic breathing. Furthermore, acetazolamide's reduction of the transient overshoots/undershoots in PCR activity is particularly relevant in the setting of high altitude and hypoxia, in which PCRs play a greater role in the HCVR and the HCVR itself has a steeper slope (65).

In addition to its effects on PCRs, acetazolamide's inhibition of periodic breathing is also likely to be related to inhibition of RBC CA. Inhibition of CA within RBCs results in delayed pulmonary washout of blood CO_2 during the first few deep and rapid breaths of a hypoxia-induced cycle. Consequently, P_{CO_2} at PCRs and CCRs falls less rapidly and produces less hypocapnic-induced hypoventilation.

DIURESIS

It has long been appreciated that humans exposed to acute hypoxia will undergo diuresis and natriuresis (88). Although not yet fully elucidated, the mechanism of such water and salt losses is likely to be mediated by activation of PCRs rather than by hypocapnia secondary to hyperventilation. Evidence supporting PCR-mediated diuresis includes animal studies in which stimulation of PCRs with almitrine produces natriuresis even in the absence of hyperventilation or hypocapnia, while carotid body denervation results in antagonism of natriuresis under conditions of hypoxia (41). Evidence in humans includes the finding that isocapnic hypoxic ventilatory response (used as a measure of PCR O_2 sensitivity) correlates positively with diuresis and natriuresis after 6 h of hypoxic exposure (94).

While the efferent limb of any pathway involving the PCRs and kidneys remains unknown, it is unlikely to be mediated by a direct neural connection given the finding that renal denervation results in greater diuresis (41).

While the phenomenon of high-altitude diuresis has been well established, its connection to AMS is less clear. Some authors have found that differences in sodium and water excretion do not predict future development of AMS (6) while a recent study by Loeppky and colleagues (64) demonstrated a significant protective role for diuresis. Regardless of discordance among such studies, differences in sodium and water balance have been consistently found when comparing subjects who have already developed symptoms of AMS with subjects who are well-acclimatized, the former exhibiting sodium and water retention and the latter exhibiting diuresis and natriuresis (6, 21). Accordingly, at the very least an exacerbating or perpetuating role of antidiuresis in the pathogenesis of AMS cannot be excluded. Consistent with such a role, more severe forms of altitude illness such as pulmonary or cerebral edema are very often associated with antidiuresis (33), and some authors have suggested that the diuretic effect of drugs such as acetazolamide is likely to contribute to its efficacy in the prevention and treatment of AMS (95). Given acetazolamide's inhibitory effects on PCRs (see above), the drug is unlikely to produce diuresis and natriuresis by enhancement of homeostatic pathways involving the carotid body chemoreceptors but rather by inducing water and salt losses by inhibition of renal CA.

Consistent with the notion that diuresis plays a role in the reduction of AMS are reports that spironolactone, a competitive inhibitor of aldosterone, also reduces symptoms of AMS (13, 14, 21). Other diuretics have also been evaluated in the context of AMS. However, unlike acetazolamide and spironolactone, most diuretics (e.g., furosemide, thiazides) cause metabolic alkalosis, not acidosis, accompanying natriuresis (74) and are therefore less likely to be helpful in the reduction of AMS. In keeping with this notion, studies of furosemide have been mixed, with some showing the drug to be ineffective in the prophylaxis and treatment of AMS, both in animals (54) and in humans (3), while Singh and colleagues (85) demonstrated the effectiveness of the drug in the prevention and treatment of AMS by using large-scale controlled trials of men airlifted to high altitude.

While the exact mechanism by which diuretics may affect AMS remains unclear, Currie (20) suggested that diuretics counteract the effect of the increased release of aldosterone at high altitude, the latter being a product of both adaptive plasma volume depletion as well as water losses from prolonged hyperventilation. Antidiuresis caused by aldosterone is an inappropriate homeostatic mechanism in the presence of overloaded pulmonary and cerebral circulations, and therefore diuretics would be expected to have therapeutic value in the context of AMS. Another possible advantage of diuresis is an increase in hematocrit and O_2-carrying capacity that is seen with reduction in extracellular fluid volume (93).

DISCUSSION

It is clear that the mechanisms of action of acetazolamide in reducing AMS are complex, often conflicting, and not fully understood. Nonetheless, here we have provided a framework

that attempts to summarize some of the drug's effects. Our main conclusions are as follows: *1*) the increase in minute ventilation seen with acetazolamide is the result of increased CCR, but not PCR, output; *2*) this increase in CCR output is the consequence of both metabolic and tissue respiratory acidoses, the former caused by bicarbonate diuresis (inhibition of CA within the kidney) and the latter caused by inhibition of tissue (intracellular and erythrocytic) CA; *3*) inhibition of PCRs by acetazolamide reduces sleep periodic breathing, and this effect may have therapeutic value in AMS by enhancing quality of sleep and by reducing episodes of hypoxemia; and *4*) diuresis produced by acetazolamide may contribute to amelioration of AMS.

While researchers are in general agreement that acetazolamide produces a leftward shift of the HCVR curve, reports on the slope of the HCVR curve following administration of a CAI are conflicting. Enhancement of CCR chemosensitivity, reflected by an increased HCVR slope, would be expected given lower levels of $[HCO_3^-]_{CSF}$ and therefore a larger change in CSF pH for any given change in CSF P_{CO_2} (Henderson-Hasselbalch equation) (40). Because most studies that have examined HCVR slope did not isolate central from peripheral chemoreceptor effects, it is possible that differential inhibition of PCRs (via different doses, routes of administration, etc.) might account for the discrepant findings.

Following CA inhibition, the relative contribution of respiratory vs. metabolic acidosis in stimulating ventilation remains unclear. Swenson and Hughes (95) found evidence that, under normoxic conditions, tissue respiratory acidosis alone (absence of metabolic acidosis) resulting from acute acetazolamide treatment was sufficient to stimulate ventilation to similar levels seen with chronic acetazolamide (95). Interestingly, this effect was not found under hypoxic conditions, which are likely to be more representative of high altitude. These findings can be reconciled by postulating that the effects of tissue respiratory acidosis during hypoxia are blunted by the respiratory alkalosis resulting from low Pa_{O_2} and hyperventilation. On the other hand, the metabolic acidosis that occurs with chronic acetazolamide would provide a stronger stimulus to increase ventilation. Teppema et al. (100) suggested that the effects of metabolic vs. respiratory acidosis are dose related. That is, under conditions in which RBC CA is completely inhibited (>99.99%), observed hyperventilation might be predominantly due to tissue CO_2 retention, whereas with lower (more clinically relevant) doses, hyperventilation might be primarily due to metabolic acidosis. Given the findings outlined in this review, however, it is likely that tissue respiratory acidosis acts in conjunction with metabolic acidosis to enhance ventilation, even when acetazolamide is administered in low doses that do not completely inhibit tissue and RBC CA.

The metabolic acidosis produced by acetazolamide is likely to have less therapeutic value in treating AMS after several days at altitude. Metabolic acidosis is a normal compensatory response to respiratory alkalosis, and therefore individuals who have began to acclimatize will already have decreased levels of $[HCO_3^-]_{plasma}$. Accordingly, the ability of a CAI such as acetazolamide to further lower HCO_3^- levels would be reduced. Thus some researchers have attributed the efficacy of prophy-

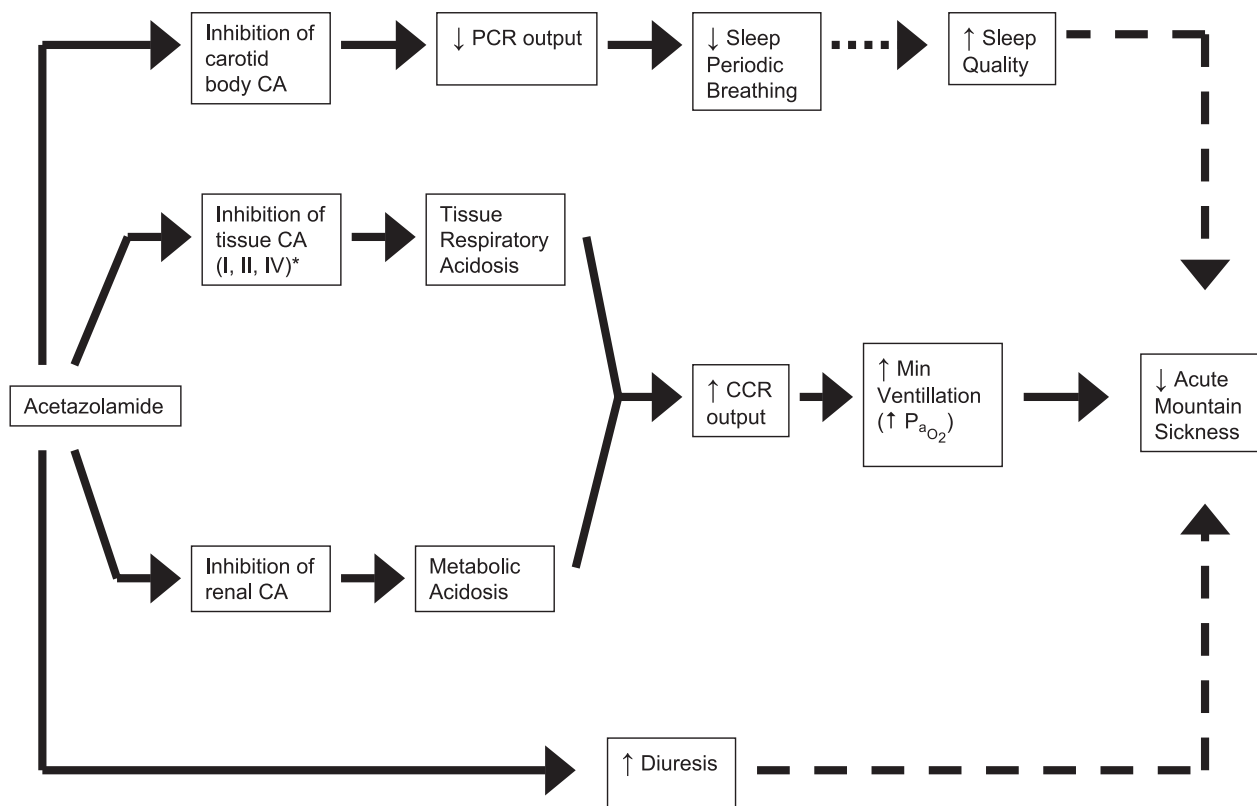

Fig. 5. Proposed model for acetazolamide's reduction of AMS. Solid lines represent well-established connections; dashed lines represent less-well established connections. *Carbonic anhydrase (CA) I and CA II are located intracellularly in red blood cells and tissues; CA IV is located on the luminal aspect of nearly all capillary beds. PCR, peripheral chemoreceptor; CCR, central chemoreceptor.

lactic acetazolamide to an acceleration or "jump-starting" of the normal acclimation process, most notably compensatory metabolic acidosis (53).

In addition to stimulating ventilation, acetazolamide-induced metabolic acidosis may have other global effects contributing to its efficacy in AMS. The Bohr effect, for example, predicts a rightward shift of the oxygen-hemoglobin dissociation curve with decreasing pH. Such a shift allows greater O_2 delivery to tissues but also impedes O_2 uptake in the pulmonary circuit. At sea level, the Bohr effect is a useful homeostatic mechanism, since Sa_{O_2} is near maximum even during exercise. At altitude, however, metabolic acidosis will have more profound effects on the oxygen-hemoglobin dissociation curve due to its sigmoidal shape, which causes a rapid drop in Sa_{O_2} as one approaches lower levels of Pa_{O_2}. More specifically, at mild to moderate hypoxemia (Pa_{O_2} as low as 50 mmHg, or an altitude as high as 14,000 ft), the Bohr effect appears to improve the efficiency of O_2 transport and delivery and therefore continues to be beneficial. With increasing levels of hypoxemia, such a rightward shift becomes counterproductive (105).

The relationship between acetazolamide's reduction of sleep periodic breathing and its improvement in subjective quality of sleep (and, ultimately, improvement in AMS) also remains unclear. Several studies that have examined this issue have failed to find a correlation between periodic breathing and AMS (23, 26, 28). Weil suggested that this dissociation might be explained by a linkage of periodic breathing with increased HVR (114). Accordingly, those individuals with a greater HVR would be more susceptible to periodic breathing but would also have higher average ventilation and oxygenation, and therefore any correlation between periodic breathing and AMS would be washed out (114). While future studies are clearly needed, we believe that sleep periodic breathing is likely to contribute to AMS (or at least produce symptoms that mimic AMS) given that sleep fragmentation in other settings is known to produce morning headache and given that daytime fatigue is one of the most commonly reported symptoms of AMS. Accordingly, acetazolamide's reduction of periodic breathing and subsequent improvements in sleep quality might contribute to the drug's therapeutic value in treating AMS.

Finally, a contributory role for acetazolamide-mediated diuresis is at present controversial, although some beneficial role is indeed suggested by the finding of antidiuresis in nearly all forms of altitude illness, including AMS. Furthermore, other diuretics, most notably spironolactone, have also been found to be efficacious in the management of AMS. A serious limitation, however, in using spironolactone to establish a therapeutic role for acetazolamide-mediated diuresis is that both drugs produce metabolic acidosis. To better elucidate the role of pharmacologically induced diuresis in AMS, studies are needed in which the effect of diuresis is isolated, either by manipulation of acid-base changes or by controlled studies in which salt and water losses are replaced in one diuretic-treated group but not the other.

Given the findings evaluated in this review, we conclude that Fig. 1, which represents a conventional explanation for acetazolamide's mechanism of action in reducing AMS, is insufficient and inaccurate. We propose an alternative model in Fig. 5, which more completely describes the complex relationship between CA inhibition and reduction of AMS.

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