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Acute Mountain Sickness: Pathophysiology, Prevention, and Treatment

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Abstract Barometric pressure falls with increasing altitude and consequently there is a reduction in the partial pressure of oxygen resulting in a hypoxic challenge to any individual ascending to altitude. A spectrum of high altitude illnesses can occur when the hypoxic stress outstrips the subject's ability to acclimatize. Acute altitude-related problems consist of the common syndrome of acute mountain sickness, which is relatively benign and usually self-limiting, and the rarer, more serious syndromes of high-altitude cerebral edema and high-altitude pulmonary edema. A common feature of acute altitude illness is rapid ascent by otherwise fit individuals to altitudes above 3000 m without sufficient time to acclimatize. The susceptibility of an individual to high-altitude syndromes is variable but generally reproducible. Prevention of altitude-related illness by slow ascent is the best approach, but this is not always practical. The immediate management of serious illness requires oxygen (if available) and descent of more than 300 m as soon as possible. In this article, we describe the setting and clinical features of acute mountain sickness and high-altitude cerebral edema, including an overview of the known pathophysiology, and explain contemporary practices for both prevention and treatment exploring the comprehensive evidence base for the various interventions. (Prog Cardiovasc Dis 2010;52:467-484)

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Acute mountain sickness (AMS) and high-altitude cerebral edema (HACE) strike people who travel too fast to high altitudes that lie beyond their current level of acclimatization. In this paper, we describe the setting and clinical features of AMS and HACE, including an overview of the known pathophysiology, and then explain contemporary practices for prevention and treatment. Understanding AMS and HACE is important because AMS can sharply limit recreation and work at high altitude, especially in the first few days following arrival at a new, higher altitude, and if AMS worsens and HACE develops, the risk of fatality is significant.[1] Fortunately, most cases of AMS and HACE can be prevented or managed effectively with appropriate planning. The syndromes can be identified early and reliably without sophisticated instruments, and when AMS and HACE are recognized early, most cases respond rapidly with complete recovery in a few hours (AMS) to days (HACE).[2,3]

Symptoms and signs

High-altitude headache (HAH) is the primary symptom of AMS.[4] High-altitude headache in AMS usually occurs with some combination of other symptoms

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Abbreviations and Acronyms

AMS = Acute mountain sickness

CA = Carbonic anhydrase

CBF = Cerebral blood flow

HACE = High-altitude cerebral edema

GI = Gastrointestinal

HAH = High-altitude headache

HAPE = High-altitude pulmonary edema

ICP = Intracranial pressure

MRI = Magnetic resonance imaging

NO = Nitric oxide

PDE = Phospodiesterase inhibitors

SR = Systematic review

TCD = Transcranial Doppler

RCT = Randomized controlled trial

VEGF = Vascular endothelial growth factor

including insomnia, fatigue (beyond that expected from the day's activities), dizziness, anorexia, and nausea. The headache often worsens during the night and with exertion.[4,5] Insomnia is the next most frequent complaint. Poor sleep can occur secondary to periodic breathing, severe headache, dizziness, and shortness of breath, among other causes. Anorexia and nausea are common, with vomiting reported less frequently in trekkers to 4243 m.[6] Many sea-level residents are surprised on their first encounter with AMS by the debilitating lassitude that strikes. Decreased urinary output, independent of fluid intake, is common. Diagnostic physical findings in AMS only become apparent when the syndrome progresses to HACE. Prior to such progression, AMS is distinguished only by symptoms. The progression of AMS to HACE is marked by altered mental status, including impaired mental capacity, drowsiness, stupor, and ataxia. Coma may develop as soon as 24 hours after the onset of ataxia or change in mental status. The severity of AMS can be scored using the Lake Louise Questionnaire,[7] or the more detailed Environmental Symptoms Questionnaire (see Table 1),[8] or by the use of a simple analogue scale.[9] Today, more than 100 years after the first clear clinical descriptions of AMS and HACE,[2,3] we have advanced our understanding of the physiology of acclimatization to high altitude, and the pathophysiology of AMS and HACE, yet many important questions remain.

The setting

As altitude increases, barometric pressure falls (see Fig 1). This fall in barometric pressure causes a corresponding drop in the partial pressure of oxygen (21% of barometric pressure) resulting in hypobaric hypoxia. Hypoxia is the major challenge humans face at high altitude, and the primary cause of AMS and HACE. It follows that oxygen partial pressure is more important than geographic altitude, as exemplified near the poles where the atmosphere is thinner and, thus, barometric pressure is lower. Lower barometric pressure at the poles can result in oxygen partial pressures that are physiologically equivalent to altitudes 100 to 200 m higher at more moderate latitudes.[10] We define altitude regions as high altitude (1500-3500 m), very high altitude (3500-5500 m), and extreme altitude (>5500 m).[11]

Table 1
An individual has AMS as assessed by the Lake Louise self-assessment scoring system[7] when they fulfill the following criteria (a) recent ascent in altitude, (b) have a headache, and (c) have a total symptom score above 3

Symptoms:	
1. Headache:	
No headache	0
Mild headache	1
Moderate headache	2
Severe, incapacitating	3
2. GI symptoms:	
No GI symptoms	0
Poor appetite or nausea	1
Moderate nausea or vomiting	2
Severe nausea and vomiting incapacitating	3
3. Fatigue/weak:	
Not tired or weak	0
Mild fatigue/weakness	1
Moderate fatigue/weakness	2
Severe fatigue/weakness, incapacitating	3
4. Dizzy/lightheadedness:	
Not dizzy	0
Mild dizziness	1
Moderate dizziness	2
Severe, incapacitating	3
5. Difficulty sleeping:	
Slept well as usual	0
Did not sleep as well as usual	1
Woke many times, poor night's sleep	2
Could not sleep at all	3
Total symptom score:	
Clinical assessment:	
6. Change in mental status:	
No change	0
Lethargy/lassitude	1
Disoriented/confused	2
Stupor/semiconsciousness	3
7. Ataxia(heel to toe walking):	
No ataxia	0
Maneuvers to maintain balance	1
Steps off line	2
Falls down	3
Can't stand	4
8. Peripheral edema:	
No edema	0
One location	1
Two or more locations	2
Clinical assessment score:	
Total score:	

An additional clinical assessment scoring is sometimes used.
GI indicates gastrointestinal.

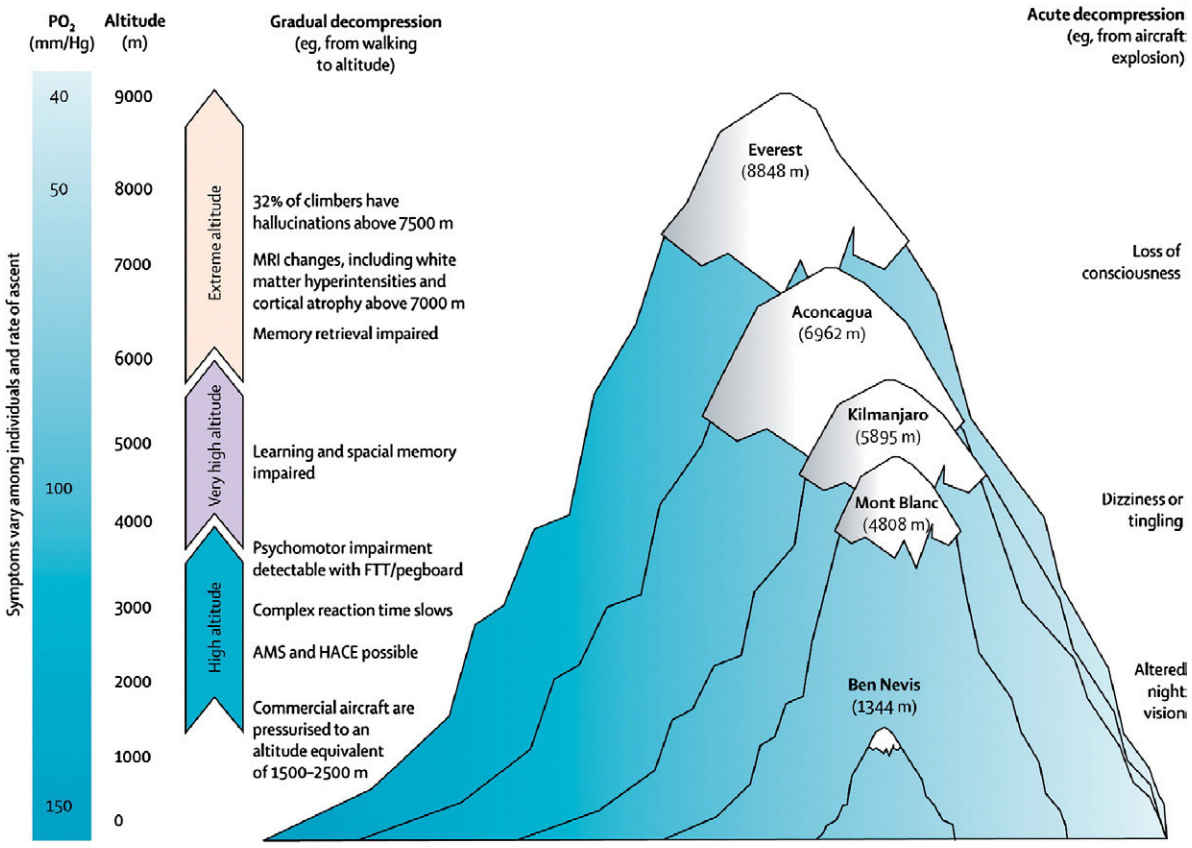

Fig 1. Neurological consequences of increasing altitude: The relation among altitude (classified as high [1500–3500 m], very high [3500-5500 m] and extreme [>5500 m]), the partial pressure of oxygen, and the neurological consequences of acute and gradual exposure to these pressure changes. Neurological consequences will vary greatly from person to person and with rate of ascent. HACE is far more common at higher altitudes, although there are case reports of HACE at 2500 m. Abbreviations: PO_2, partial pressure of oxygen. AMS, acute mountain sickness. HACE, high altitude cerebral oedema. FTT, finger-tapping test.

Acclimatization

It is important for any discussion of AMS and HACE to have as a starting point an understanding of acclimatization. The process of acclimatization involves a series of adjustments by the body to meet the challenge of hypoxemia. While we have a general understanding of systemic changes associated with acclimatization, the underlying molecular and cellular processes are not yet fully described. Recent findings suggest that the process may be initiated by widespread molecular up-regulation of hypoxia inducible factor-1.[12] Downstream processes ultimately act to offset hypoxemia, including elevated ventilation leading to a rise in arterial oxygen saturation (SaO_2), a mild diuresis and contraction of plasma volume such that more oxygen is carried per unit of blood, elevated blood flow and oxygen delivery, and eventually a greater circulating hemoglobin mass. Acclimatization can be viewed as the end-stage process of how humans can best adjust to hypoxia. But optimal acclimatization takes from days to weeks, or perhaps even months. It is the phase between initial hypoxic exposure and the onset of acclimatization where AMS and HACE occur. The degree of hypoxemia plus the rate of change from normoxia directly predict the severity of AMS and possibility of developing HACE.

It is striking how much individuals vary in their ability to acclimatize, with a few adjusting quickly, without discomfort, and some developing such severe AMS that they must descend and appear unable to ever acclimatize; however the majority of people fall somewhere in between. The natural acclimatization process over the first few days at high altitude protects against AMS and HACE, while further acclimatization over weeks or months is needed to see significant improvements in aerobic exercise and work performance. To briefly review the physiology of acclimatization we examine the effects of prolonged hypoxia on ventilation, circulation, and blood during the first few days of exposure to high altitude (more in-depth view of acclimatization is available in our recent review[11]). We exclude responses that occur at extreme altitude as acclimatization does not seem to occur above about 5000 m.

Ventilation, circulation, and the blood in acclimatization to high altitude

The initial and immediate strategy to protect the body from hypoxia is to increase ventilation. This compensatory mechanism is triggered by stimulation of the carotid bodies, which sense hypoxemia (low arterial P_{O_2}), and increase central respiratory drive. This is a fast response, occurring within minutes of exposure to hypoxia persisting throughout high altitude exposure. This is why one cautions against the use of respiratory depressants such as alcohol and some sleeping medications, which can depress the hypoxic drive to breathe and may thus worsen hypoxemia. The hypoxic drive to breathe was proposed as the key to acclimatization and an indicator of one's susceptibility to altitude illness, but further study by independent groups revealed that while it is better to breathe more at high altitude, that response is highly variable and is not a sole predictor of either acclimatization or of risk of altitude illness.[13,14] Pharmacological simulation of this natural process by acetazolamide, a respiratory stimulant and mild diuretic, largely protects from AMS and HACE by stimulating acclimatization[15] (see below for more details about acetazolamide in AMS prevention and treatment). Circulatory responses are key to improving oxygen delivery, and are likely regulated by marked elevations in sympathetic activity.[16,17] Field experience suggests that a marked elevation in early morning resting heart rate is a sign of challenges to acclimatization, perhaps secondary to increased hypoxemia, or dehydration. For the pathophysiology of AMS and HACE responses of the cerebral circulation are especially important. Maintenance of cerebral oxygen delivery is a critical factor for survival at high altitude. The balance between hypoxic vasodilation and hypocapnia-induced vasoconstriction determines overall cerebral blood flow (CBF). In a classic study, CBF increased 24% on abrupt ascent to 3810 m, and then returned to normal over 3 to 5 days.[18] Recent studies, largely using regional transcranial Doppler measures of CBF velocity as a proxy for CBF, report discernible individual variation in the CBF response to hypoxia, with some studies showing no elevation in CBF with hypoxia, a finding that may be as much due to technique as to physiology. So while large individual variation is seen, all advanced brain imaging studies to date have shown both elevations in CBF in hypoxic humans and striking heterogeneity of CBF distribution in the hypoxic brain, with CBF rising up to 33% in the hypothalamus, and 20% in the thalamus with no other significant changes.[19] Also, it is becoming clear that cerebral autoregulation, the process by which cerebral perfusion is maintained as blood pressure varies, is impaired in hypoxia. Interestingly, this occurs in both newcomers, with acute[20] and prolonged hypoxia,[21] and in natives to high altitude.[22] This observation suggests a previously unknown role for hypoxia to modulate cerebral autoregulation and raises interesting questions about the importance of this process in AMS and acclimatization, since it appears to be a uniform response in all humans made hypoxemic. Further study is necessary to understand the response of whole brain CBF and cerebral autoregulation to acclimatization to hypoxia. And finally, hematocrit and hemoglobin concentration are elevated after 12 to 24 hours of hypoxic exposure due to a fall in plasma volume.[23] After several weeks of acclimatization, plasma volume returns to near sea level values. Normalization of plasma volume coupled with an increase in red cell mass secondary to the hypoxia-stimulated erythropoiesis leads to an increase in total blood volume after several weeks of acclimatization. The time course of these changes in hemoglobin concentration and total blood volume dictate that they play little role in susceptibility to high-altitude illness on initial ascent, but a major role in the process of acclimatization. Whether the initial drop in plasma volume is pathogenic is an open question. Adequate iron stores are required for adequate hematologic acclimatization to high altitude,[24] and iron may play a role in susceptibility to high-altitude pulmonary edema (HAPE), but a role of iron stores in susceptibility to AMS and HACE has not been studied.[25,26]

Acclimatization, then, is a series of physiological responses to hypoxia that serve to offset hypoxemia, improve systemic oxygen delivery, and avoid AMS and HACE. When acclimatization fails, or the challenge of hypoxia is too great, AMS and HACE can develop. We now explore the epidemiology and risk factors for AMS and HACE, before embarking on an examination of the relevant features of pathophysiology.

Epidemiology and risk factors

AMS occurs in susceptible individuals when ascent to high altitude outpaces the ability to acclimatize. For example, most people ascending very rapidly to high altitude will get AMS. The symptoms, although often initially incapacitating, usually resolve in 24 to 48 hrs. The incidence and severity of AMS depend on the rate of ascent and the altitude attained, the length of time at altitude, the degree of physical exertion, and the individual's physiological susceptibility.[27] The chief significance of AMS is that planned activities may be impossible to complete during the first few days at a new altitude due to symptoms. In addition, in a few individuals, AMS may progress to life-threatening HACE or HAPE,[28] the subject of a review in this issue (see Scherrer et al, p. 485). A survey of 3158 travelers visiting resorts in the Rocky Mountains of Colorado revealed that 25% developed AMS, and most decreased their daily activity because of their symptoms.[29] Women, obese persons, and

those with underlying lung disease also had a slightly higher occurrence of AMS. At 4000 m and above, the incidence of AMS ranges from 50% to 65% depending on the rate and mode of ascent, altitude reached, and sleeping altitude.[30,31] Older age does not preclude travel to moderate high altitude. In one study of 97 elderly (average age = 69.8 years) visitors to 2500 m, only 16% reported AMS, compared with 20% to 25% persons aged about 44 years at a similar altitude.[32]

Newcomers to high altitude are often surprised that sea level aerobic fitness is not protective for altitude illness. Acclimatization is thus the only known way to avoid AMS and HACE, thus prior altitude exposure is the best prophylaxis. Protective effects of previous periods of hypoxia have been reported by Schneider et al[30]; in their report AMS incidence fell from 58% to 29% when there was an altitude exposure above 3000 m during the previous 8 weeks. Other studies have shown a persistence of ventilatory adaptation and a maintenance of exercise capacity after acclimatization,[31] but Schneider et al were the first to recognize the possibility that an initial hypoxic exposure will protect an individual from AMS on subsequent trips. Support for this idea comes from a recent study from Tibet where repeat exposures to high altitude was shown to confer protection from subsequent AMS, even when high altitude sojourns were interspersed with up to 5 months at low altitude.[33] The physiological basis for this effect is unknown and worthy of future study.

High-altitude cerebral edema is rare and largely confined to altitudes over 4000 m, but recent magnetic resonance imaging (MRI) studies suggest that HACE can occur at lower altitudes (3000-3500 m). In 1925 soldiers studied at altitudes ranging from 3350 to 5000 m, only 23 men (1.2%) developed the HACE;[34] similarly, only 5 (1.8%) of 278 trekkers were diagnosed with HACE at 4243 m.[6]

Differential diagnosis

Symptoms suggestive of AMS in a setting of recent ascent to a new altitude are probably due to altitude sickness and should be treated as such until proven otherwise.[31] It is common to misdiagnose AMS as a viral flulike illness, but alcohol hangover, exhaustion, and dehydration are also commonly suspected. All misdiagnoses must be eliminated by physical exam, history, or treatment. As noted previously, fever is usually absent in AMS, and alcohol or other drug use can be excluded by the history. Rest and rehydration can eliminate fatigue and dehydration from the differential diagnosis of AMS. Mental confusion and ataxia, the hallmarks of HACE, are also present with hypothermia; thus, care must be taken to rule out alternative explanations.

Pathophysiology of AMS and HACE

Despite dozens of investigations, the basic pathogenic mechanisms of AMS (and HACE) remain elusive. The extremely low incidence of HACE limits research into its pathophysiology largely to conclusions drawn from the similarity of the clinical presentation of severe AMS and early HACE. To be clear, it is not certain that AMS and HACE have the same underlying pathophysiology, but the idea of a continuum of severity between AMS and HACE serves as a useful construct for researchers exploring the basic pathophysiology.

The pathophysiology of AMS and HACE includes many common features, some well-understood and others that remain obscure despite intense scientific scrutiny. Singh et al[33] proposed that the high-altitude syndromes are secondary to the body's responses to hypobaric hypoxia, not due simply to hypoxemia. They based this conclusion on 2 observations: (1) there is a delay between the onset of hypoxia and the onset of symptoms after ascent (from hours to days), and (2) not all symptoms are immediately reversed with oxygen. On the other hand, scientists have long assumed that AMS and HACE are due solely to hypoxia, based largely on 2 reports: the pioneering experiments of Paul Bert[34] and the Glass House experiment of Barcroft.[35] When these assumptions were tested in a laboratory setting to study symptom responses to hypobaric hypoxia (simulated high altitude), hypoxia alone, and hypobaric normoxia, AMS occurred soonest and with greater severity with simulated altitude, compared with either normobaric hypoxia or normoxic hypobaria.[38-41] However, AMS also occurred in normobaric hypoxia, it just took longer and was less severe. For the overall incidence and severity of AMS, given sufficient time for AMS to develop, normobaric and hypobaric studies are likely to be largely comparable. But for answers about the pathophysiology of AMS, a quest that has remained largely unsolved for decades, it is important to examine rigorously assumptions and experimental conditions. For example, recent studies have been completed using normobaric hypoxia and brain imaging techniques, without first establishing a comparability of results from brain imaging in normobaric hypoxia to those obtained in hypobaric hypoxia. In 2 such studies, one in normobaric hypoxia found no MRI signs of vasogenic edema but suggested that AMS was associated with "cytotoxic edema",[42] whereas a comparable study in hypobaric hypoxia found combined vasogenic and intracellular edema.[43] The conclusions from the 2 studies have very different implications for refining a theory of the pathophysiology of AMS. Although the studies were not designed for a direct comparison between hypobaria and hypoxia, the discrepancy points out an assumption about normobaric hypoxia and the pathophysiology of AMS that may warrant further investigation.

Physiological responses central to pathophysiology of established mild to moderate AMS include relative hypoventilation,[13,14] impaired gas exchange,[44-46] fluid retention and redistribution,[6,32,43-45] and increased sympathetic drive.[16,17] Increased intracranial pressure (ICP) and cerebral edema are documented only in moderate to severe AMS, supporting the concept of a continuum from AMS to HACE.[47-49]

Our central hypothesis regarding the pathophysiology of AMS, and by extension of HACE, is that it is centered on dysfunction within the brain. This is not a new idea, but it is one of current intense interest thanks to advances in brain imaging and neuroscience techniques. Barcroft,[37] writing in 1924, argued that the brain's response to hypoxia was central to understanding the pathophysiology of mountain sickness. He wrote:

> Taking it, therefore, as settled that mountain sickness is due to oxygen want, the question arises, "oxygen want of what?" And the answer is, "of the brain." Such evidence as is at our disposal goes to show that the brain wants but little oxygen; that little, however, it wants very badly indeed.[37] (p 91)

We will return to consideration of the central role the brain plays in the pathophysiology of AMS and HACE after a brief consideration of the systemic changes in ventilation and fluid balance that characterize AMS versus healthy individuals.

Ventilation

A low ventilatory response to hypoxia coupled with increased symptoms of AMS led to intensive investigation of a link between the chemical control of ventilation and the pathogenesis of AMS.[13,14] As stated previously, the results of these investigations suggest that for most people, the ventilatory response to hypoxia has little predictive value for AMS risk.[13,14] Only if the extremes of ventilatory responsiveness are contrasted can accurate predictions be made, where those with extremely low ventilatory drives being more likely to suffer AMS. In the classic study by Moore et al,[14] ventilatory responses of 8 men with history of AMS and of 4 men with no history of AMS, illustrate the conundrum. The "sick" subjects had a low hypoxic ventilatory response at sea level and breathed less and had disproportionately lower Sa_{O_2} values at altitude, although the difference in Sa_{O_2} between the "sick" and "well" groups was small. Yet, in larger studies, the hypoxic ventilatory response has shown no predictive value.[10,49-53] At the extreme end of the distribution (i.e., for very high responses), the protective role of a brisk hypoxic ventilatory response may be due to increased arterial oxygen content and cerebral oxygen delivery despite mild hypocapnic cerebral vasoconstriction.

Fluid homeostasis

As persons become ill with AMS, the renal processing of water switches from net loss or no change to net gain of water. Singh et al[35] noted less of a diuresis (urinary output minus fluid intake: ¯1100 to +437 mL) in 118 soldiers with known susceptibility to AMS, compared with that seen in 46 "absolutely immune" (+930 to +4700 mL) soldiers. They also noted that clinical improvement was preceded by diuresis. Subsequent investigations have failed to elucidate the exact mechanism of the fluid retention, nor is fluid retention a universal finding in AMS.[50] The mechanisms of fluid retention when present are likely to be multifactorial and capable of dynamically adjusting to oxygenation, neural input, and hormonal action.

Adrenergic activation is a relatively unexplored topic with strong evidence for a role in the pathophysiology of AMS, and a possibility that may link the observed changes in fluid balance in AMS to a central mechanism. Krasney[51] postulated that cerebral edema causes brain compression, and that this will lead to an increase in peripheral sympathetic nervous system activity (see more about brain volume below). Increased sympathetic stimulation causes vasoconstriction of the renal circulation and subsequent renal hypoperfusion and increased aldosterone and arginine vasopressin levels and reduces glomerular filtration rate and urinary output. Increased sympathetic activity is consistent with the increased epinephrine levels in AMS noted in recent studies.[17] For example, during 8 hours of normobaric hypoxia, Kamimori et al[17] noted that epinephrine was increased in all subjects with AMS, but arterial norepinephrine was not, suggesting that adrenal medullary responses may play an important role in the pathophysiology of AMS. In addition, support for a role of sympathetic activation in the pathogenesis of AMS comes from the work by Fulco et al,[52] showing that subjects with β-adrenergic blockade had less severe AMS than subjects taking placebo. More complete adrenergic blockade may result in even greater decrease in AMS severity if the hypothesis that sympathetic activation plays a central role in the pathogenesis of AMS is correct. Taken together, the evidence points to the possibility that the sympathetic nervous system has a role in the early development of AMS and HACE. Whether differences in the intensity of this response may be related to who gets sick and who remains free of AMS remains to be determined.

In general, an individual on exposure to hypoxia who breathes more and develops marked diuresis seems less likely to develop AMS.[53] But large interindividual variations in response to hypoxia and control of fluid balance preclude a universal understanding of development of AMS. These findings and important technological advances in noninvasive measurements have led scientists

to increasingly focus in recent years on the role of the brain in AMS and HACE pathophysiology.

Hansen and Evans[54] were the first to publish a comprehensive hypothesis of the pathophysiology of AMS centered on the brain. Their theory posited that compression of the brain, either by increased cerebral venous volume, reduced absorption of cerebral spinal fluid, or increased brain-tissue hydration (edema), initiates the development of the symptoms and signs of AMS and HACE. Ross[55] built on these ideas with his "tight fit hypothesis," published in 1985, and others have developed these ideas into a series of testable hypotheses congruent with today's knowledge of AMS and HACE.[56,57] The tight fit hypothesis states that expanded intracranial volume (due to the reasons put forth by Hansen and Evans,[54] or other causes) plus the volume available for intracranial buffering of that expanded volume would predict who would get AMS. Greater buffering capacity leads to AMS resistance, lower buffering capacity, or a 'tight fit' of the brain in the cranial vault, would lead to greater AMS susceptibility. Ross was careful to describe his ideas on how intracranial volume could be buffered, with a focus on compressible dura in the thoracic and cervical spinal column as a hypothesized sight of largest buffering capacity.[55] The end stage of both the hypotheses of Hansen and Evans, and of Ross, and their scientific descendants, is hinged on the assumption that brain swelling leads to exhaustion of intracranial buffering capacity, and that in turn leads to elevated ICP which causes the headache of AMS. Unfortunately this hypothesis remains today largely untested by direct measurements. No studies have yet compared radiographic volume buffering capacity compared to AMS to evaluate Ross' ideas; neither venous blood volume nor reduced absorption of cerebral spinal fluid has been studied, and no studies have measured ICP before, during the onset of AMS, or after treatment to reverse the symptoms. These studies need to be done, and are not prohibitively expensive nor too invasive to be considered in a laboratory setting. This final section on pathophysiology will step through what is known in AMS and HACE about brain volume, brain edema, ICP, and cerebral blood flow.

Brain volume

All studies to date generally support the idea that hypoxia causes elevated brain volume, but a direct relationship of greater brain volume to AMS is not apparent, or is at least beyond current measurement capabilities. However, Ross argued that only when buffering capacity is exhausted will elevated brain volume result in AMS. No study has yet linked brain volume to intracranial compliance measurements (a quantifiable measurement of intracranial volume buffering); thus, this core tenet of the hypothesis remains untested.

How accurate is MRI estimation of brain volume? Modern techniques can reliably identify changes in brain volume as small as 0.2%, but they require careful adherence to sophisticated analysis protocols as these are very small, but perhaps meaningful changes in volume, especially in a brain with no remaining volume buffering capacity. Hypoxia and brain volume studies published to date have not reported details of software-based protocols designed to optimize brain extraction from the skull in MRI images, nor have they reported scan-rescan reliability measurements. Moreover, none have utilized a cross-over design where subjects are allowed to develop AMS once, and are pharmacologically protected from AMS in a second experiment to control for the known large intra-individual differences in responses to hypoxia. All of these experimental approaches would optimize the chance of finding a real difference if it exists. Overall, it is clear that brain volume increases in humans on exposure to hypoxia. It is less certain whether this elevation in brain volume plays a role in AMS.

Brain edema

Hackett's pioneering MRI study in HACE, with marked white matter edema suggestive of a vasogenic origin, has led to a decade of studies looking for a similar finding in AMS. In moderate to severe AMS, all imaging studies have shown some degree of cerebral edema. But in mild to moderate AMS, admittedly an arbitrary and subjective distinction, brain edema is present in some MRI studies of AMS subjects, but not in all. It seems reasonable to conclude from the available data that the increase in brain volume observed is at least partially due to brain edema, and that earlier studies missed the edema more for technical than physiological reasons. It is less clear whether the brain edema is largely of intracellular or vasogenic origin, and what role if any it plays in the pathophysiology of AMS. One study in normobaric hypoxia found no MRI signs of vasogenic edema but claimed that AMS was associated with "cytotoxic edema,"[42] while a comparable study in hypobaric hypoxia found combined vasogenic and intracellular edema.[43] Future studies may unravel these differences with advanced diffusion tensor imaging, or it remains possible that these 2 studies revealed a difference between AMS pathophysiology in normobaric versus hypobaric hypoxia.[39,41] Because no brain MRI studies have been conducted during the onset of AMS, it is impossible to know if either intracellular or vasogenic edema precedes the other, or if they both occur simultaneously with the onset of AMS.

Intracranial pressure

From Singh's initial report in 1969, all subsequent studies in HACE and severe AMS have revealed elevated ICP. The recent publication of the fascinating case history of Brian Cummings tantalized all high altitude researchers with the possibilities of field studies. This article was long lost and only recently discovered and published.[58] In it is recounted the story of a neurosurgeon who has an ICP monitoring bolt implanted in his own skull prior to going on an expedition in the Himalayas. From this limited but remarkable study came the observation that when he had a headache, ICP was elevated, and when he did any physical activity thought to elevate ICP, the increases were substantial, as if compliance was reduced in his hypoxic brain. The important premise that changes in brain hemodynamics may be occurring only when the brain compliance is challenged needs to be examined in further studies of humans or animals. Additionally, the role of changes in brain hemodynamics and ICP during the onset of AMS and later after treatment has led to symptoms resolution are necessary steps to address the role of such changes in the pathophysiology of AMS.

Cerebral blood flow

As mentioned previously, cerebral blood flow is initially elevated with hypoxia, and with acclimatization it returns to pre-ascent values. We also briefly mentioned above that while all brain imaging studies have shown elevation in CBF with acute hypoxia, some noninvasive transcranial Doppler (TCD) studies have not show such elevation. We propose that whole brain imaging studies more reliably represent the underlying physiology of the hypoxic brain during acute hypoxia. Whether CBF plays a role in AMS onset is unknown. In a study by Baumgartner et al, CBF velocity was measured and found to be higher in subjects with AMS than in healthy climbers, with a direct correlation between CBF and symptom severity.[59] A follow-up study[60] and a similar study by Otis et al did not support these early results.[61] Although we support TCD for many investigations in integrative physiology, the complex interplay of hypoxia and hypocapnia that is present in acutely hypoxic humans may present a situation where whole brain imaging is a more reliable and accurate tool to discern the role of CBF in the onset of AMS. To date, no brain imaging studies have addressed global cerebral perfusion in AMS.

Alternative explanations for the onset of AMS

If studies reveal that intracranial volume buffering, pressure, and hemodynamics do not play a role in AMS, then where can we turn for an explanation of the headache of high altitude which marks the onset of AMS, and is its cardinal symptom—HAH? High-altitude headache is the most prominent symptom in AMS[29,35,62] The pathophysiology of HAH, such as that of migraine or tension headache, is not fully understood. Recent clinical surveys of HAH have advanced its clinical characterization,[4,5,63] but whether HAH shares a common pathophysiology with migraine or other headaches is not known. In general, the literature suggests that HAH can be prevented by the use of many different agents, including nonsteroidal anti-inflammatory drugs[64-66] and the drugs commonly used for prophylaxis of AMS, acetazolamide and dexamethasone. The response to many different agents might reflect multiple components of the pathophysiology or merely the nonspecific nature of analgesics. As Sanchez del Rio and Moskowitz[67] point out, different inciting factors may act to cause headache through a final common pathway, such that the response to different therapies is not necessarily related to the initial cause of the headache. They recently provided a useful multifactorial concept of the pathogenesis of HAH based on current understanding of headache in general.[67] They suggest that the trigeminovascular system is activated at high altitude by both chemical and mechanical stimuli (eg, nitric oxide [NO] and vasodilation). For example, NO release is stimulated by hypoxia, and NO is thought to sensitize small ummyelinated fibers conveying pain and may accumulate in proximity to trigeminovascular fibers to cause HAH.[67] In support of a role for NO in the genesis of headache is a recent report showing that inhibition of NO synthase improved tension-type headache.[68] An early study using methylene blue, a blocker of NO metabolism, was notably effective for AMS prevention.[69] However, confirmation of a role for NO in HAH awaits further study.

Table 2
Methodology for assessing the evidence base

Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)[76]	
1	SR (with homogeneity) of RCTs or individual RCT (with narrow Confidence Interval)
2	SR (with homogeneity) of cohort studies or individual cohort study (including low quality RCT, eg, <80% follow-up)
3	SR (with homogeneity) of case-control studies or individual case-control study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
Grades of recommendation	
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence *or* troublingly inconsistent or inconclusive studies of any level

SR indicates systematic review; RCT, randomized controlled trial.

Table 3
Evidence based recommendations for the prevention of acute mountain sickness and HACE

Intervention	Dose	Level of Evidence	Recommendation	Reference
Slow ascent	<300 m d^{-1} >3000 m	1-2	A	[31,77]
Avoid exercise		2	B	[78]
Hydrate adequately	N/A	2-3	C	[79,80]
Hypoxicator	Unknown	4	C	[81-84]
Oxygen supplementation	2 L min^{-1}	2	A	[31,36,85]
PEEP (Positive end-expiratory pressure)	5 cm H_2O	3	B	[86,87]
Carbohydrate rich diet		3	C	[88]
Acetazolamide	250 mg-1 g daily	1	A	[89-93]
Methazolamide	150 mg/d	2	B	[94]
Dexamethasone				
AMS	8 mg/d	1	A	[95,96]
Medroxyprogesterone	60 mg/d	2	B	[97]
Theophylline	375 mg BD	1	B	[98,99]
Ginko biloba				
Effective	240 mg/d	3	C	[100-104]
Not effective	240 mg/d	1	B	[101,105,106]
Sumatriptan	50 mg once	2	B	[105]

Animal model of AMS and HACE

A final consideration for readers curious about how to advance the field of AMS and HACE pathophysiology is the absence of a validated animal model. Great advances could be made in studying the hypoxic brain if an animal model were available. The elegant early work of Krasney[51,70-73] on sheep was promising, but never widely adapted. To those who argue that it is difficult to know when a guinea pig has a headache, a page can be taken from the remarkable recent progress in migraine pathophysiology by using animal models of parts of the known pathophysiology of migraine.[74] Exciting recent work on hypoxic rodents[75] suggest that even in these hypoxia-resistant animals there is hope of new breakthroughs in how animals respond to hypoxia that could eventually reveal the still elusive mechanisms responsible for AMS and HACE in humans. We now turn to strategies to prevent and treat AMS and HACE.

Prevention and treatment of acute mountain sickness

The levels of evidence have been assessed according to the methods described by the Oxford Centre for Evidence-based Medicine,[76] which are summarized in Table 2. The evidence based recommendations for the prevention of AMS and HACE are found in Table 3, and the recommendations for the treatment of AMS and HACE are found in Table 4. A summary of the field treatment of AMS and HACE is found in Table 5.

A slow ascent with sufficient time for acclimatization is the best way of preventing AMS and HACE.[31] When traveling above 3000 m the recommended ascent rate is less than 300 m daily with a rest day for every 1000 m climbed. Mild high altitude headache is common and usually can be treated with simple analgesia. However, further ascent should be avoided if symptoms of AMS have not settled and descent should be arranged if moderate symptoms of AMS persist or if symptoms worsen.[77]

The immediate management of serious illness requires oxygen (if available), and descent of more than 300 m as soon as possible. Pharmacotherapy should be considered for both prophylaxis and treatment of AMS. Acetazolamide remains the most useful drug for prophylaxis, although protection is not complete. Glucocorticoids, such as dexamethasone, can also prevent AMS but are largely reserved for the treatment of the more severe forms of AMS and for HACE. Calcium-channel blockers are

Table 4
Evidence-based recommendations for the treatment of acute mountain sickness and HACE

Treatment	Dose	Level of Evidence	Recommendation	Reference
Descent	>300 m	1	A	[31,77]
Oxygen supplementation	35% at 4300 m	2	A	[85]
Portable hyperbaric chamber	193 mBar 1 h	1	A	[108]
Acetazolamide	125-500 mg BD	1	A	[45]
Dexamethasone				
AMS	8 mg stat		A	[95]
HACE	8 mg/d	1	A	[1]

Table 5
Field treatment of acute mountain sickness and HACE

Condition	Drug/Intervention	Dose
High altitude headache		
	Stop ascent/rest	
	Paracetamol	1g QDS
	Ibuprofen	400 mg TDS
AMS		
Mild (Lake Louise Score <4)		
	Stop ascent / rest	24 hours
	Paracetamol	1g QDS
	Ibuprofen	400 mg TD
	Acetazolamide	125-500 mg BD
	Descend	300-500 m
Moderate/severe (Lake Louise Score <4)		
	Descend	300-500 m
	Paracetamol	1g QDS
	Ibuprofen	400 mg TD
	Acetazolamide	125-500 mg BD
	Dexamethsone	4 mg QDS PO, IM, IV
	Oxygen	1-2 l min^{-1}
	1 h hyperbaric chamber	193 mBar
HACE		
	Immediate descent	>300-500 m
	Oxygen	2-4 l min^{-1}
	Dexamethsone	4 mg QDS PO, IM, IV
	Hyperbaric chamber (if able to protect airway)	193 mBar

established for the management of HAPE, but the reduction in pulmonary artery pressure with phospodiesterase inhibitors (PDE) inhibitors has provided an alternative for both the prevention and management of this serious problem. Other suggested approaches to the pharmacotherapy of altitude-related syndromes include antioxidant supplementation, although this hypothesis has yet to be rigorously tested.

The severity of AMS is the end point of many therapeutic trials at altitude, but assessment of AMS itself remains difficult because it is relatively subjective and highly dependent on self-reporting. All investigators and those responsible for people visiting high altitudes would welcome a diagnostic test for AMS that is both sensitive and specific and a diagnostic procedure that might identify susceptible individuals before ascent.

Predisposing factors

Individual susceptibility, rate of ascent, and previous recent exposure are major, independent determinants for AMS. There is generally no relationship between AMS and either age, gender, training, alcohol intake, or cigarette smoking.[30,109] Acute mountain sickness is associated with obesity,[110] and with sleep desaturation at high altitude in one study.[111]

Physical exertion at altitude increases the incidence and severity of AMS, likely because of further reductions in arterial oxygen saturation.[78] A resting individual at a higher altitude may have the same arterial saturation as an exercising individual at a lower altitude,[112] therefore ascending slowly or avoiding strenuous activity on arrival at a new altitude to protect arterial oxygenation is recommended. Increased ventilation during exercise also exacerbates insensible water loss from the pulmonary tract, therefore attention should be given to maintaining adequate hydration.[79,80]

Ascent profiles

In an interesting field study in climbers ascending to very high altitudes, differences of a few days in acclimatization had a significant impact on symptom severity, the prevalence of AMS and subsequent mountaineering success.[27,113] Different ascent profiles have been assessed, and acclimatization benefits after 5 days at 4200 m are lost within a few days.[114] More recently, it has been reported that repetitive 7-month high altitude exposures increasingly protect lowlanders against AMS, even when interspaced with 5-month periods spent at low altitude.[34]

Since the 1990s, the live high-train low altitude training model has been used to stimulate physiological acclimatization (primarily increased red cell mass) and enhance performance in at sea level. More recently low cost, hypoxic-air generators (eg, AltiPower, CAT, and GO2Altitude) have been manufactured to bring an hypoxic environment to low altitude residents.[81-84] Preconditioning with normobaric hypoxia may be an effective strategy for reducing symptoms of AMS. Pre-acclimatization to 4300 m for 3 weeks attenuated subsequent AMS symptoms when individuals were re-exposed 8 days later to 4300 m.[115,116] They also found intermittent altitude exposures improved muscular performance at 4300 m.[117] More recently, the same group found increased exercise tolerance at 4300 m following 6 days staging at 2200 m[118] and a reduced the incidence and severity of AMS during rapid ascent to 4300 m.[115] Interestingly, they found intermittent altitude exposures for 4 h d^{-1}, 5 d wk^{-1} at the equivalent of 4300 m (446 mm Hg) improved time-trial cycle exercise performance and induced physiological adaptations consistent with chronic altitude adaptation to 4300 m.[119]

Oxygen

Low arterial oxygen saturations are related to subsequent development of AMS[120] and supplementary oxygen has been used to prevent AMS, and is one of the mainstays

for the treatment of AMS and HACE,[6,35,85] but short-term oxygen supplementation does not reverse all signs of AMS.[121] However, any strategy to improve SaO_2 will help prevent or treat AMS and HACE. Strategies shown to boost SaO_2 in humans suffering from environmentally induced hypoxemia include CO_2 breathing which stimulates ventilation thus raising SaO_2,[122,123] hyperbaric therapy which elevates relative inspired pressure of oxygen,[108,124,125] and positive pressure breathing which improves gas exchange.[126-128] A novel recent approach addresses oxygenating train cars on the Qinghai-Tibet Railway (maximum altitude 5072 m) in an attempt to protect against AMS.[129] And for workers at high altitude, 6% oxygen enrichment of room air at simulated 5000-m altitude improved neuropsychological function.[130,131]

Diet

A high-carbohydrate diet was reported to reduce symptoms of AMS and increase endurance for heavy work.[88] Although a high carbohydrate diet for 4 days did not reduce the symptoms of AMS after 8 hours of 10% normobaric oxygen,[126] there are 2 reports that ingestion of carbohydrates can improve arterial oxygenation during acute hypoxic exposure.[127,128]

Drugs

The main approaches to therapy of AMS and HACE are to improve oxygenation by the use of such drugs as carbonic anhydrase (CA) inhibitors or medroxyprogesterone, or by attenuating the cytokine and inflammatory responses with for example glucocorticoids or antioxidants.

Carbonic anhydrase inhibitors

Carbonic anhydrase enzymes catalyze the hydration of carbon dioxide to bicarbonate and protons and consequently play a vital role in acid-base balance. In mammals, 16 isoenzymes with different distributions have been described.[132] Inhibitors of CA act by binding to the zinc ion of the enzyme.[133] Sulfonamides are organic inhibitors of CA and 2 derivatives, acetazolamide and methazolamide, have been used in the management of altitude-related illnesses.

Acetazolamide: prophylaxis

Acetazolamide blocks CA in red blood cells, renal tubules, chemoreceptors, the brain, and pulmonary and systemic blood vessels. The conventional view of the mechanism of action of acetazolamide in the treatment of AMS is that inhibition of renal CA leads to a bicarbonate diuresis with a metabolic acidosis. Acetazolamide increases the poikilocapnic hypoxic ventilatory response and results in a higher arterial partial pressure of oxygen.[15,134-137] Cerebrospinal fluid production is also reduced, which may contribute to its beneficial effect. However, CA inhibition in other tissues, particularly the vasculature and the chemoreceptors, may also be important. The mechanism of acetazolamide is unlikely to be purely as a result of increased ventilation, since almitrine, another respiratory stimulant, has been shown to be less effective than acetazolamide in a small number of subjects.[134]

Prophylactic acetazolamide has been shown to reduce symptoms of AMS[89] although this meta-analysis included several different doses, ranging between 250 mg and 1 g daily. It is usually recommended that acetazolamide is started at least one day before ascent and continued until descent has begun at a dose of 500 mg/d.

Determining the optimal dose of acetazolamide from the large number of studies is not straightforward. Many studies have involved small numbers of subjects with a variety of altitudes and ascent rates. Another meta-analysis concluded that 750 mg/d prevented AMS, but lower doses did not.[90] However, this has not been generally accepted because different ascent rates were analyzed together. On the other hand, an effective trial of 250 mg compared with 750 mg/d may have had a selection bias towards non-susceptible individuals.[91] However, more recently, low-dose acetazolamide (125 mg BD) was also shown to reduce the incidence and severity of AMS,[92] contradicting another report which found that 500 mg/d was effective, but 250 mg was not.[93]

Contrary to widespread perception, Sherpas may be susceptible to AMS when exposed to altitudes significantly higher than their residing altitude,[138] and acetazolamide prevented AMS in Nepali lowland porters.[139]

It should be noted that acetazolamide will not prevent AMS when excessively fast ascent profiles are used. 500 mg/d did not prevent AMS in some individuals climbing at the typical commercial ascent rate on Kilimanjiro.[140] Side effects of acetazolamide are usually well tolerated and include parasthesiae, a short-lived diuresis and an unpleasant metallic taste to carbonated drinks. Allergic reactions are rare.

Another concern that trekkers and climbers have about the use of acetazolamide is the possible effect on exercise capacity. Hackett et al[141] showed at a high altitude (6300 m) that 3 doses of acetazolamide 250 mg every 8 hours reduced maximum work rate in 2 of 4 subjects. In another study of acetazolamide under hypoxic conditions at sea level, exercise capacity was reduced.[142] In addition, muscle mass and exercise performance fell at 4846 m in those on acetazolamide.[143] However, there are several findings of exercise being unchanged or even improved by

acetazolamide.[144,145] Improvement in general well being and oxygen saturation may be more important than any adverse effect of metabolic acidosis on gas exchange in the muscle.

Acetazolamide: treatment

Acetazolamide should also be considered for acute therapy of AMS with moderate or severe persistent symptoms, providing the subject has not been taking the drug prophylactically. A limited number of studies have shown improvement in overall AMS scores,[45,146] although relief of symptoms may take 24 hours and headache may worsen. For the treatment of AMS, a dosage of 250 mg every 12 hours is recommended. The medication can be discontinued once symptoms resolve. Children may take 2.5 mg/kg body weight every 12 hours.

Methazolamide

Methazolamide is a CA inhibitor that has a lower affinity for plasma proteins, diffuses more rapidly into tissues.[147] and is associated with fewer side effects.[148] In a comparative study, methazolamide 150 mg/d was equally effective in preventing AMS with slightly less parasthesiae.[94]

Steroids

Glucocorticoids: prophylaxis

The exact mechanism of action of glucocorticoids, such as dexamethasone, is largely speculative, but is likely to be mediated through changes in capillary permeability and cytokine release. Dexamethasone 8 mg/d in divided doses has been used in the prevention of AMS[95,96,149] with lower doses being relatively ineffective.[150] Most consider that the potential side effects of glucocorticoids outweigh the benefits thus they are not normally justified for prophylaxis. Exceptions are if acetazolamide is contraindicated or when a very rapid effect is required, as for example when rescue workers are called to ascend very fast. In a comparison of prednisolone 10 to 40 mg/d with dexamethasone 0.5 mg/d, reduction in symptoms of AMS occurred in all groups and interestingly the best results were obtained with prednisolone 20 mg/d.[151] When dexamethasone is given alone, it should not be discontinued if the risk of AMS or HACE remains, as symptoms may recur. Although acetazolamide is probably more effective than dexamethasone in the prophylaxis of AMS,[89] more direct comparisons are needed. The combination of acetazolamide 500 mg with dexamethasone 4 mg BD in a small number of subjects was more effective than acetazolamide alone.[152] When comparing simulated descent in a portable hyperbaric chamber to dexamethasone for the treatment of AMS, dexamethasone resulted in a longer-term clinical improvement.[153]

The main use of dexamethasone is in the acute management of severe AMS and of HACE when the serious nature of the illnesses justifies high-dose steroids.[1] Dexamethasone 8 mg initially and 4 mg every 6 h orally or parenterally will improve the clinical situation sufficiently to make evacuation easier,[154] but how long the treatment should be continued for after the subject has descended is not known.

Medroxyprogesterone

Progesterone is a respiratory stimulant and assessed in one clinical trial using medroxyprogesterone 60 mg/d prophylactically. Although oxygenation improved, AMS symptoms were not significantly reduced in the relatively small number of subjects studied.[97]

Phosphodiesterase inhibitors

The effects of PDE inhibitors on AMS and HACE have been less studied than in HAPE, but it seems promising that sildenafil increases cerebral oxygentation[155] and therefore, such treatment might be helpful for AMS and HACE. However, in the study of tadalafil and dexamethasone, tadalafil was no better than placebo in preventing AMS and 2 of the 10 subjects on tadalafil withdrew from the study because of severe AMS.[156]

Theophyllines

Theoretically theophylline should be of value in AMS and HACE as it reduces periodic breathing, cerebral and pulmonary microvascular permeability and also pulmonary artery pressure. A trial of slow-release theophylline 375 mg BID PO at 3454 m showed increased oxygenation and lower AMS scores on arrival and after 18 hours.[157] A direct comparison of acetazolamide and theophylline showed that both helped to normalize sleep-disordered breathing, but only acetazolamide improved oxygen saturations.[98] Low-dose theophylline (300 mg OD) has recently been shown to reduce symptoms of AMS.[99]

Magnesium

Magnesium is a physiological *N*-methyl-D-aspartate antagonist (NMDA) and may protect the hypoxic brain. The NMDA receptor is involved in the pathophysiology of hypoxic convulsions.[158] and blockage of NMDA receptors has been shown to be beneficial.[159] There is, however, no human data to link the NMDA receptor to the pathogenesis of AMS and oral magnesium in a randomized, controlled trial at 4559 m did not prevent AMS.[160] In the treatment of AMS, intravenous magnesium reduced symptoms compared with placebo, but was not clinically important.[161]

Antioxidants

Ginko biloba is a traditional Chinese medicine containing flavonol glycosides and terpene lactones, which, among many effects, scavenge excess free radicals.[162] There is conflicting evidence of its effectiveness in the prevention of AMS with some studies showing a benefit.[100-104] More recent randomized trials showed that Ginko biloba was not effective in comparison with acetazolamide and placebo.[101,105,106] The lack of a standardized chemical preparation for Gingko biloba may be part of the explanation for the wide variation in results from AMS trials with Gingko. Antioxidant supplementation did not diminish AMS incidence, but showed a trend toward lower severity in one study,[163] and no effect in another.[164] There is concern that antioxidants may interfere with the action of acetazolamide on the normocapnic hypoxic ventilatory response.[165]

Diuretics

Diuresis is a general physiological response to hypoxia. Subjects with AMS report less diuresis and have been shown to lose less weight than subjects who are free of AMS. In the only large trial in acute altitude-related illnesses, furosemide was reported to be successful in the prevention and management of AMS and in the prevention of HAPE.[35] In smaller, chamber studies at 4270 m[166] and in field studies at 5340 m,[167] no benefit from diuretics lacking ventilatory stimulating action, such as acetazolamide, was demonstrated.

Furosemide is potentially dangerous at high altitude as serious reductions in blood volume may occur. Although plasma aldosterone concentrations are reduced at altitude, spironolactone is of interest, not because of any diuretic effect, but since the mild acidosis and reduction in cerebrospinal fluid production it causes may be beneficial. There have been conflicting reports on the use of spironolactone at altitude with one showing benefit[168] and another showing little value in preventing AMS.[169]

Sedatives and other drugs

Sleep disorders are commonly experienced at altitude and acetazolamide reduces the time spent in periodic breathing.[170] Similar findings have been reported with theophylline. Improved sleep quality has also been shown using temazepam[171-173] without any significant adverse effects.[174]

Gabapentin has been used to treat high altitude headache[175] and the same group have shown that sumatriptan can prevent AMS.[107] A leukotriene receptor blocker did not prevent AMS induced by normobaric hypoxia.[176]

Drug metabolism at altitude

The metabolism of drugs may be altered by hypoxia[177] if the rate of clearance of drugs by cytochrome P450 is decreased.[178] Although there is little data on drug metabolism at altitude, it is reassuring that only a small decrease in the activity of CYP2D6 and CYP3A4, both members of the cytochrome P450 mixed-function oxidase system, at 4559 m and only small changes in the metabolism of cortisol, mephenytoin and antipyrine have been shown.[179] Similarly at 4500 m the metabolism of theophylline and verapamil was not impaired.[180]

Summary and future directions

The management of AMS and HACE is based on our current understanding of the physiological and pathophysiological responses to hypoxia. Hypoxia itself, however, does not immediately lead to AMS as there is a delay of several hours after arrival at high altitude before symptoms develop. Increased knowledge of hypoxic inducible factor and cytokines that alter capillary permeability may lead to the discovery of new drugs for the prevention and alleviation of AMS and HACE.

Much work has focused on the role of vascular endothelial growth factor (VEGF), a potent permeability factor up-regulated by hypoxia.[181] Some studies have found no evidence of an association of changes in plasma concentrations of VEGF and AMS,[182,183] whereas others support the hypothesis that VEGF contributes to the pathogensis of AMS.[184,185] Clearly a better understanding of the mechanisms of increased capillary permeability of cerebral capillaries will greatly enhance the management of AMS and HACE.

Acute mountain sickness is a relatively common condition that can affect any individual who ascends to altitude too quickly. The usual clinical course is self limiting and benign and normally responds to simple measures. However failure to descend or worse still, further ascent is likely to exacerbate the condition and can precipitate the much more serious and potentially fatal high altitude cerebral edema and high altitude pulmonary edema. Taken together, ascending gradually, or using acetazolamide to aid in acclimatization when time is short, should lead to healthy travel at high altitude.

Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

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