The Journal of Experimental Biology 204, 3161–3170 (2001)
Printed in Great Britain © The Company of Biologists Limited 2001
JEB3294

Frontiers of hypoxia research: acute mountain sickness

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Accepted 11 July 2001

Summary

Traditionally, scientists and clinicians have explored peripheral physiological responses to acute hypoxia to explain the pathophysiological processes that lead to acute mountain sickness (AMS) and high-altitude cerebral edema (HACE). After more than 100 years of investigation, little is yet known about the fundamental causes of the headache and nausea that are the main symptoms of AMS. Thus, we review the evidence supporting a change in focus to the role of the central nervous system in AMS. Our justification is (i) that the symptoms of AMS and HACE are largely neurological, (ii) that HACE is considered to be the end-stage of severe AMS and was recently identified as a vasogenic edema, opening the door for a role for blood–brain barrier permeability in AMS, (iii) that new, non-invasive techniques make measurement of brain water levels and cerebral blood volume possible and (iv) that the available experimental evidence and theoretical arguments support a significant role for brain swelling in the pathophysiology of AMS. We believe that an examination of the responses of the central nervous system to acute hypoxia will reveal important new pathophysiological processes that may help explain AMS and HACE.

Key words: exercise, hypoxia, brain swelling, cerebral oedema, vasogenic oedema.

Introduction

At the dawn of the 21st century, we are poised to make great new discoveries about how humans respond to hypoxia. These discoveries will probably include fundamentally new information about the molecular mechanisms of our physiological responses to short- and long-term hypoxia and about the functional consequences of these responses. In this review, we explore acute mountain sickness (AMS) in detail to illustrate the exciting near future in this field.

Acute mountain sickness

Many hundreds of studies of AMS over the past two centuries have examined the contributions of ventilation, pulmonary gas exchange and fluid balance to the pathophysiology of AMS. Unfortunately, the traditional paradigm that invoked these peripheral responses to acute hypobaric hypoxia to explain AMS failed to substantially advance our understanding. Therefore, this review departs from the traditional paradigm and instead focuses on the responses of the central nervous system (CNS) to reveal new and perhaps fundamental information about the pathophysiology of AMS. Our justification for focusing on the CNS is (i) that the symptoms of AMS are largely neurological (Hackett, 1980), (ii) that high-altitude cerebral edema (HACE), considered to be the end-stage of severe AMS, has recently been identified as a vasogenic edema (Hackett et al., 1998), opening the door for a role for blood–brain barrier (BBB) permeability in AMS, (iii) that new, non-invasive techniques make measurement of brain water levels and cerebral blood volume (CBV) possible and (iv) that the available experimental evidence and theoretical arguments support a significant role for brain swelling in the pathophysiology of AMS. This review expands on concepts first explored in the literature by Krasney (Krasney, 1994), Hackett (Hackett, 1999) and Hackett and Roach (Hackett and Roach, 2001) (Fig. 1).

AMS occurs in those that go too high, too fast. The most common symptoms are headache, nausea, anorexia, insomnia, fatigue/lassitude, vomiting and dizziness (Singh et al., 1969; Hackett et al., 1976; Hackett and Roach, 2000). Today's ability to travel rapidly to high altitudes results annually in millions of people being exposed to the risk of AMS worldwide. The medical risks and costs are significant since as many as 5 % of cases can develop life-threatening high-altitude cerebral edema (HACE) (Hackett and Roach, 2000). Further understanding of the pathophysiology of the high-altitude illnesses could enhance our understanding of other illnesses involving oxygen deprivation. For example, increased knowledge of the mechanisms of high-altitude headache or BBB opening induced by hypoxia could contribute insight into similar pathophysiological processes occurring in patients at sea level. In addition, identification of the mechanisms of, and a role for, brain swelling in the pathophysiology of AMS could also affect the clinical care and management of acute high-altitude illness by providing

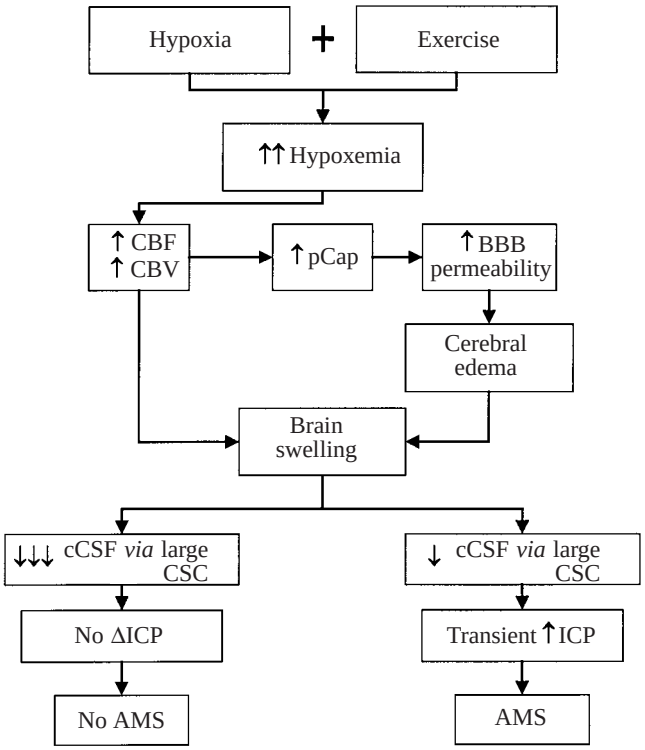

Fig. 1. Pathophysiology of acute mountain sickness (AMS). This schema emphasizes a role for blood–brain barrier opening (BBB), brain swelling and cerebrospinal compliance (CSC). Although highly speculative at present, new non-invasive and sensitive techniques will allow measurement of the variables necessary to evaluate this hypothesis (see text for more detail). pCap, cerebral capillary perfusion pressure; cCSF, cranial cerebrospinal fluid; ICP, intracranial pressure; CBV, cerebral blood volume; CBF, cerebral blood flow.

new avenues for intervention and prevention for the millions who suffer from AMS every year.

Although the numbers of visitors worldwide to altitudes above 3000 m is relatively small, in the American West at least 30 million people annually visit moderate altitudes (1500–2500 m) (Moore, 1986). With an incidence of AMS of 15–25 % (Honigman et al., 1993), 4–8 million people are therefore affected by AMS in the American West alone. Medical costs can only be estimated. In one small clinic in Summit County, Colorado, more than 400 clinic visits per year are logged for treatment of mild to severe AMS. At an average cost of $250 per clinic visit, the annual cost of AMS is approximately $100 000 in this one clinic (B. Honigman, personal communication). In addition, lost revenue due to a drop in tourists' expenditures is estimated at $80 million dollars per year (based on approximately 8 million ill with AMS spending $10 less due to headache, nausea or vomiting for 1 or 2 days). Thus, AMS presents a considerable public health problem with serious economic ramifications. As mentioned above, AMS also provides a relatively benign pathology involving responses in many cellular, molecular and organ systems that are otherwise difficult to approach in intact humans.

Pathophysiology of established AMS

This review will focus on pathophysiological events occurring during the onset of AMS. For purposes of definition, the time frame will be limited to the first 12 h of exposure to hypobaric hypoxia. To set the stage for discussion of the literature regarding acute (within 12 h) human responses to hypobaric hypoxia and the relationship between those responses and AMS, we first present a brief overview of the known pathophysiology of established AMS. Much of the literature comes from studies carried out after 24–36 h of exposure to hypobaric hypoxia. Because such studies do not usually follow the time course of pathophysiological changes, but rather examine the pathophysiology once symptoms of AMS are present, cause and effect have been difficult or impossible to establish.

Many physiological events associated with the pathophysiology of established AMS have been documented (Johnson and Rock, 1988; Hackett and Roach, 2000). The findings documented in mild to moderate AMS that relate to pathophysiology include relative hypoventilation (Moore et al., 1986), impaired gas exchange (interstitial pulmonary edema) (Larson et al., 1982; Grissom et al., 1992; Ge et al., 1997), fluid retention and redistribution (Bärtsch et al., 1992; Swenson, 1997) and increased sympathetic drive (Bärtsch et al., 1988; Bärtsch et al., 1991). In mild to moderate AMS, limited data suggest that intracranial pressure is not elevated (Hartig and Hackett, 1992; Wright et al., 1995). In contrast, increased intracranial pressure and cerebral edema are documented in moderate to severe AMS, reflecting the continuum from AMS to HACE (Singh et al., 1969; Kronenberg et al., 1971; Wilson, 1973; Houston and Dickinson, 1975; Matsuzawa et al., 1992). We recently showed that AMS was exacerbated by exercise in the early hours of altitude exposure. Most revealing in this study was the absence of any signs of pulmonary gas exchange abnormalities and only small differences in fluid balance (Fig. 2; Roach et al., 2000). These findings led us to rethink the pathophysiology of AMS and ultimately to consider a role for vasogenic cerebral edema, elevated CBV, brain swelling, fluid retention/redistribution and intracranial hypertension in AMS and HACE.

AMS and the central nervous system

We propose a CNS-based model to explain the pathophysiology of AMS (see Fig. 1). In this model, the initial insult is hypoxemia. Hypoxemia is translated through a series of cellular, molecular and physiological signals ultimately to cause brain swelling due to cerebral edema and elevated CBV. Hypoxemia stimulates cellular and molecular responses that may alter endothelial permeability (vascular endothelial growth factor) or provide cellular protection against oxygen-derived free radical damage to the endothelium. Hypoxemia is also implicated in upregulation of inducible nitric oxide synthase, and nitric oxide (NO) has been implicated in the pathophysiology of headache and BBB permeability. Through peripheral chemoreceptor activation, hypoxemia can elevate

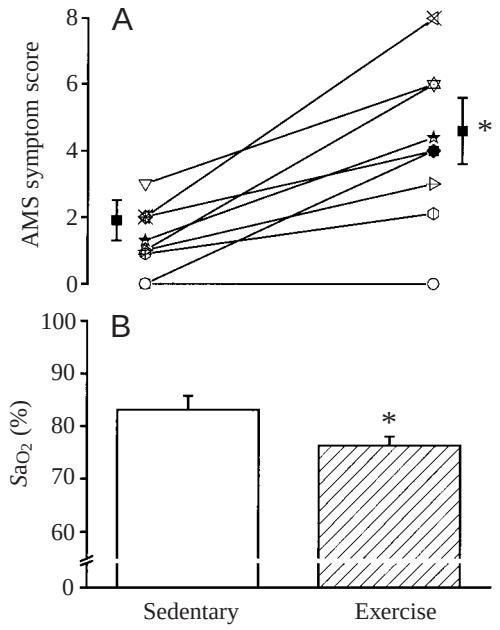

Fig. 2. (A) Symptom scores for acute mountain sickness (AMS) severity and (B) arterial oxygen saturation measured by pulse oximetry (Sa_{O_2}; %) during exercise in hypoxia. The different symbols in A represent the individual subjects in the two different trials. The solid squares in A represent the mean values ± S.E.M. for each trial. A drop in percentage Sa_{O_2} while exercising (*P<0.05 compared with the sedentary value) and a slight fluid retention (not shown) distinguished exercise (resulting in AMS) from rest (no AMS). Values are means + S.E.M. Adapted from Roach et al. (Roach et al., 2000).

circulating arginine vasopressin levels which, in turn, causes anti-diuresis and increased extracellular water levels. The sum of these peripheral responses to hypoxia arrives at the brain (and in our model they are exaggerated by exercise) and influences BBB permeability, cerebral edema and CBV. These changes cause elevated intracranial pressure in those with a cerebrospinal capacitance that cannot buffer the swelling brain. Intracranial pressure causes the symptoms of AMS *via* compression of the brain. We propose that the interplay between brain water content, brain blood volume and intracranial dynamics ultimately determines who develops AMS.

High-altitude headache

High-altitude headache (HAH) is the most prominent symptom in AMS (Honigman et al., 1993). For example, in our recent descriptive study of men and women exposed for 12 h at rest to 4800 m simulated high altitude, 48 % reported moderate to severe headache, compared with only 24 % reporting moderate to severe gastrointestinal symptoms and 20 % reporting a similar severity of dizziness. The pathophysiology of HAH, like that of migraine or tension headache, is not fully understood.

In general, the literature suggests that HAH can be prevented by the use of many different agents, including non-steroidal anti-inflammatory drugs (Broome et al., 1994; Burtscher et al., 1999) 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 non-specific nature of analgesics in some studies. As Sanchez del Rio and Moskowitz (1999) point out, different inciting factors for headache 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 (Sanchez del Rio and Moskowitz, 1999). They recently provided a useful multi-factorial concept of the pathogenesis of HAH based on current understanding of headache in general (Sanchez del Rio and Moskowitz, 1999). They suggest that the trigeminovascular system is activated at high altitude by both chemical and mechanical stimuli (e.g. NO and vasodilatation). 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 (Sanchez del Rio and Moskowitz, 1999). 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 (Ashina et al., 1999). However, confirmation of a role for NO in HAH awaits further study.

Brain oxygenation during exercise

Are brain oxygen delivery and/or global utilization impaired during acute hypoxia? If so, this could perhaps account for the effects of acute hypoxia in HAH and AMS. The global cerebral metabolic rate for oxygen ($CMRO_2$) and brain oxygen delivery seem to be maintained during acute hypoxia in subjects without AMS (Kety and Schmidt, 1948; Shimojyo et al., 1968), but no data are available on $CMRO_2$ in humans ill with AMS. However, in the hypoxic sheep model of AMS/HACE, Krasney and colleagues observed no decrement in $CMRO_2$ or in oxygen extraction (Curran-Everett et al., 1991; Iwamoto et al., 1991). Thus, through compensatory mechanisms, including elevated cerebral blood flow (CBF) and hemoglobin concentration, cerebral oxygen delivery and utilization seem to be maintained in resting subjects with acute hypoxia and in sheep ill with AMS/HACE. In contrast, recent evidence suggests that when hypoxic subjects exercise brain O_2 saturation may fall dramatically.

Two recent studies examined cerebral oxygenation by near-infrared spectroscopy (NIRS) during exercise in hypobaric hypoxia. Bradwell et al. (1999) reported that cerebral oxygenation fell in six men during maximal exercise conducted after 4 days at 3450 m. No details of degree of cerebral deoxygenation were provided (Bradwell et al., 1999). Ten trekkers (six male and four female) were studied by Saito et al. (1999) at 3700 m for evidence of cerebral desaturation during exercise (Saito et al., 1999). Because of technical limitations, they made measurements 2–3 min after cessation of moderate-intensity stepping exercise. They reported a 48 % drop from resting values in regional cerebral oxygen saturation. We predict that when humans exercise during acute

hypoxia they will experience substantial systemic and cerebral oxygen desaturation, and that those with the most severe cerebral desaturation will develop the largest brain swelling and the most severe HAH and AMS.

Vasogenic edema and high-altitude cerebral edema

Scientists and clinicians have long speculated that cerebral edema played a role in causing the symptoms of AMS (Singh et al., 1969; Sutton and Lassen, 1979; Hackett, 1999; Hackett and Roach, 2000) on the basis of the findings of increased intracranial pressure, edema on autopsy and responsiveness of AMS/HACE to steroids. Only recently has evidence been available to examine the role of cerebral edema in AMS and HACE. Magnetic resonance imaging (MRI) in seven of nine men with HACE, eight of whom also had high-altitude pulmonary edema (HAPE), showed evidence for increased water content (enhanced T2 signal intensity) only in the white matter, particularly in the corpus callosum (Hackett et al., 1998). This pattern of reversible white matter edema without gray matter involvement indicates a vasogenic rather than cytotoxic mechanism, at least in the clinical stage when these scans were obtained. The clinical course of HACE supports a vasogenic mechanism, since all subjects completely recovered and the follow-up MRI scans were normal (Hackett et al., 1998). Other evidence supporting a predominantly vasogenic mechanism includes the time course of both onset and resolution (Klatzo, 1987; Ostergaard et al., 1999), the sheep model of Krasney (Krasney, 1997), the positive response to steroids (vasogenic edema is the only steroid-responsive brain edema; Fishman, 1975) and tissue and cell experiments showing increased permeability of cerebral endothelium exposed to hypoxia (Schilling and Wahl, 1999).

Neuroimaging in humans has also provided some evidence of brain edema in established AMS, but inconsistently, in part because of inconsistent definition of AMS and HACE. Kobayashi et al. (1987) performed head computerized tomography (CT) on nine climbers with HAPE and ‘neurologic signs’ (Kobayashi et al., 1987). Four were in coma, four had drowsiness and one had only a headache. Other signs such as ataxia were not reported. Eight of the nine displayed clear cerebral edema. Without more details, whether some of these patients met the criteria for AMS or whether all had clinical HACE is unknown. Levine et al. (Levine et al., 1989) reported diffuse low density on brain CT in the sickest of five subjects ill with AMS after a 48 h altitude exposure, but did not mention specific signs and symptoms, and whether that subject had AMS or HACE is not clear. The report of Matsuzawa et al. (Matsuzawa et al., 1992) provides the most convincing evidence for brain edema in moderate to severe AMS. After a 24 h simulated altitude exposure, the T2 signal in the white matter was increased in the sickest four of seven subjects with AMS, indicating vasogenic edema. These subjects met the criteria for AMS and they did not have clinical HACE (no ataxia or altered mental status). This study supports the concept that moderate to severe AMS is associated with vasogenic edema and is an early stage of HACE.

Brain swelling/edema in early AMS

First, a definition of brain swelling and brain edema may be helpful. Brain edema is an abnormal accumulation of water within the brain parenchyma producing a volumetric enlargement of tissue. Brain swelling, in contrast, refers to enlargement of the brain from any cause, including elevated CBV and CSF and brain water levels (Klatzo, 1987; Hackett, 1999; Hackett and Roach, 2000). Is there evidence for brain swelling/edema in early AMS? Several recent MRI studies attempted to answer this question (Zavasky and Hackett, 1995; Icenogle et al., 1999; Kilgore et al., 1999; Muza et al., 1999). Muza et al. (1999) demonstrated increased brain volume in men with and without AMS after a 32 h exposure to a simulated altitude of 4400 m (Muza et al., 1999). Post-exposure MRI was performed with the subjects breathing hypoxic gas. Therefore, CBF and CBV were presumably still elevated. They could not differentiate blood from tissue volume. All seven subjects had increased brain volume, unrelated to the presence or severity of AMS, suggesting that the brain swells on ascent to altitude irrespective of AMS. Another study also found brain swelling in early AMS. Zavasky and Hackett (1995) reported that three subjects at simulated altitude (5000 m) for 8–10 h had increased brain volume measured by MRI, without a relationship between volume change and AMS scores (Zavasky and Hackett, 1995). Neither of the above studies measured CBV. As discussed in detail below, with the known elevation of CBF in humans during acute hypoxia, it is a reasonable assumption that CBV was elevated and contributed to the observed increase in brain volume.

Brain swelling in early AMS

We recently completed preliminary studies on the role of brain swelling and cerebral edema measured by MRI in early AMS. In the first study, we examined changes from baseline in cranial CSF volume in 15 subjects after they had spent 12 h at simulated high altitude (51 kPa; 426 mmHg; 4800 m). Prior studies have demonstrated the accuracy of T2 magnetic resonance imaging (MRI) in quantifying intracranial CSF (cCSF) (Kohn et al., 1991; Clarke et al., 1995). Subjects (eight male, seven female) were resting at altitude, and diet was controlled with fluid *ad libitum* on both days. AMS+ subjects developed clinically significant AMS on the basis of two independent scoring systems (Sampson et al., 1983; Roach et al., 1993). We hypothesized that, as AMS developed, a swollen brain would push cCSF out of the cranial space. However, the results showed lower cCSF volumes in both AMS+ and AMS− subjects, with a slightly greater drop in cCSF volume in AMS− subjects. This finding led to our current hypothesis that craniospinal capacitance plays an important role in determining AMS such that an inability to buffer brain swelling by moving cCSF to extracranial compartments will lead to AMS (see Fig. 1). That we did not observe a larger difference between AMS+ and AMS− subjects is not surprising because of the gender and age heterogeneity of the subjects studied. Brain and spinal volumes, including ventricular volume and subarachnoid space, vary markedly

between men and women and with age (Gur et al., 1991; Matsumae et al., 1996).

The experimental problem of individual variation in the response to hypoxia highlights one of the major advantages of using exercise as a tool to exacerbate AMS within the same subjects. For example, to expand our studies of changes in cCSF volume in AMS, we plan to study subjects during exercise at simulated altitude on several different occasions with active interventions to prevent AMS (such as acetazolamide and dexamethasone). Thus, statistical comparisons between AMS+/AMS− subjects will be made within the same brain, thereby avoiding the variability due to between-subjects factors, such as baseline brain and ventricle size, genetic predisposition to AMS and individual responses to hypoxia and exercise.

In summary, brain volume increases with acute altitude exposure, with no direct link to AMS. However, several important factors that determine how a swollen brain may impinge on well-being have not been previously measured. Such factors include the relative contributions of brain edema and increased CBV to increased brain volume in hypoxia. Future studies need to examine the role of brain volume, CBV and cerebral edema to determine the interplay between these factors and the pathophysiology of AMS.

Evidence for cerebral edema in early AMS

As mentioned above, vasogenic cerebral edema is present in moderate to severe AMS and HACE. Specifically, patients with clinical HACE demonstrated T2 MRI signal enhancement consistent with edema in the corpus callosum (Hackett et al., 1998). Using the same subjects and altitude exposure as in our cCSF study described above, the T2 MRI values in the splenium and the genu of the corpus callosum were measured from MRI scans started 20 min following altitude exposure and compared with images taken on the preceding control day. The T2 MRI from the corpus callosum increased overall in AMS+ and AMS− subjects. Although the average difference (altitude exposure minus control) in T2 MRI from the two regions was greater in AMS+ than AMS− subjects, the difference was not significant (*t*-test, P=0.06). These preliminary results show that acute exposure to altitude was associated with a very small, but statistically significant, increase in T2 MRI in the genu of the corpus callosum, with a tendency for a larger increase in AMS+ subjects.

CBF, CBV and brain swelling in AMS

In humans, CBF is elevated in response to acute hypoxia (Kety and Schmidt, 1948; Severinghaus et al., 1966; Shapiro et al., 1970; Huang et al., 1990; Buck et al., 1998). During dynamic exercise, CBF is elevated when measured by transcranial Doppler (Jorgensen et al., 1992; Madsen et al., 1993; Moraine et al., 1993; Hellstrom et al., 1996) or by the Kety–Schmidt technique using the radioactive isotope ^{133}xenon (Thomas et al., 1989), although discrepant results have been reported using ^{133}xenon (Madsen et al., 1993). Several authors have suggested that an elevation in CBF would directly cause AMS (Singh et al., 1969; Hansen and Evans, 1970; Sutton and Lassen, 1979; Lassen, 1992). In numerous field and chamber studies, this idea has not been borne out (Fukushima et al., 1988; Otis et al., 1989; Jensen et al., 1990; Baumgartner et al., 1992). A recent, careful chamber study further delineated the role of CBF alterations in the onset of AMS (Baumgartner et al., 1999). A study of 10 subjects during a 6 h exposure to 4559 m revealed no direct relationship between CBF and the incidence or severity of AMS symptoms. In summary, studies show a rise in CBF in humans with acute hypoxia and exercise, with notable individual variation, but no direct relationship between the changes in CBF and AMS. Thus, alterations in CBF alone cannot explain the onset of AMS. But elevated CBF could play a role in the onset of AMS in an edematous brain. In an edematous brain, elevated CBF and CBV will cause an elevation of intracranial pressure. In turn, intracranial hypertension can generate headache, a principal symptom of AMS, through compression or distension of pain-sensitive regions in the meninges and large intracranial blood vessels (Ray and Wolff, 1940; Wolff, 1972; Sanchez del Rio and Moskowitz, 1999).

What evidence is there that CBV is elevated in acute hypoxia and, thus, that elevated CBV could explain part of the observed brain swelling in acute AMS? In contrast to the numerous measurements of CBF during acute hypoxia, measurements of CBV are nonexistent. In non-human primates, a 50 % increase in CBF caused CBV to increase by approximately 15 %; CBF increased by twice that much for a flow increase of 100 % (Grubb et al., 1974). An equivalent volume increase (15 %) in a 1500 g human brain would be 6–8 ml. An increase in CBV of 6–8 ml would be sufficient to displace some CSF and, therefore, could be detected by neuroimaging as smaller ventricles and less extracerebral CSF. In this case, such an increase in volume is probably easily buffered by CSF dynamics and is insufficient to raise intracranial pressure and cause symptoms. However, in the presence of brain edema, the slope of the intracranial pressure/volume curve increases, and a small increase in CBV will cause a large increase in intracranial pressure. Reflecting this fact, reducing CBV by hyperventilation is a common practice in the treatment of cerebral edema (Shenkin and Bouzarth, 1970). Thus, while an elevated CBV may cause brain swelling, it would contribute to an increased intracranial pressure only in the setting of elevated brain water content (or an inability to accommodate the swelling by CSF dynamics).

What causes vasogenic edema at high altitude?

An explanation for the cause of vasogenic edema in AMS/HACE should consider both mechanical factors (BBB failure equivalent to capillary failure in high-altitude pulmonary edema; West et al., 1995) and biochemical mediators. Mayhan and Heistad (Mayhan and Heistad, 1986) showed that acute, severe elevations of cerebral capillary pressure resulted in a mechanical vascular leak *via* disruption of cerebral veins. Abbott has demonstrated that stretching of brain endothelium induces increased BBB opening (Abbott

and Revest, 1991). A number of authors have suggested that, in the setting of hypoxic cerebral vasodilatation, autoregulation might be impaired (Sutton and Lassen, 1979; Lassen, 1992; Levine et al., 1999), resulting in high cerebral capillary pressure and vasogenic edema (Lassen, 1974; Sutton and Lassen, 1979). Krasney and associates addressed this issue of cerebral vasodilatation, cerebral capillary pressure and brain edema in a series of sheep experiments. They first showed that cerebral capillary pressure rose from 2.4 to 6 kPa (from 20 to 50 mmHg) and remained elevated during 96 h of hypoxia (Curran-Everett et al., 1991; Iwamoto et al., 1991; Yang and Krasney, 1995). This was accompanied by an increase in epidural pressure and increased filtration of plasma across the brain microcirculation, i.e. increased brain water content, along with symptoms of AMS/HACE. To test whether the edema was due to the increased CBF and cerebral capillary pressure, they then subjected animals to CO_2 breathing and also to nitroglycerine infusion, both of which elevated CBF and cerebral capillary pressure to even greater levels than hypoxia, but neither of which produced as much brain edema as hypoxia. They concluded that cerebral vasodilatation and elevated cerebral capillary pressure *per se* did not explain the edema (Yang and Krasney, 1995; Krasney, 1997). It is important to note that there was no systemic hypertension or elevation of central venous pressure in these animal experiments, as there would be in humans at altitude during exercise. Nonetheless, these experiments indicate that another factor besides vasodilatation is necessary to disrupt the BBB and cause AMS/HACE. This is consistent with the earlier observation that CBF is elevated during acute hypoxia and exercise but is not the sole determinant of AMS. Of course, in the setting of elevated cerebral capillary pressure, only a small perturbation in BBB opening is necessary to produce brain edema (Krasney, 1997). Could chemical mediators or cellular processes induced by hypoxia or its consequences cause vasogenic edema? Mediators identified to date include free radicals (e.g. oxygen and hydroxyl radicals), bradykinin, histamine, arachidonic acid and NO (Schilling and Wahl, 1999). Interventions to block some of these mediators will be a logical next step if elevated BBB permeability is shown to play a role in AMS. Steroids and non-steroidal anti-inflammatory drugs block some of these mediators and are successful in the treatment and prevention of AMS.

Intracranial pressure

If all brains swell on ascent to altitude, could it be an incidental finding and have nothing to do with AMS? This might be true if the swelling were due merely to increased CBV, but not if it were due to increased brain water content. The sheep model clearly showed that increased brain water content was associated with illness (Krasney, 1994). If, as Hansen and Evans hypothesized (Hansen and Evans, 1970), brain cell compression causes AMS, then we cannot answer the question of whether swelling is causing symptoms without estimates of intracranial pressure. Non-invasive measurements of intracranial pressure based on the cerebral hemodynamics model of Aaslid and Newell (Aaslid and Newell, 1999) that use transcranial Doppler and non-invasive arterial blood pressure recordings may provide important new insights into the role of intracranial pressure in AMS. Because of differences among individuals in volumetric buffering of brain swelling, the magnitude of the volume change due to swelling does not predict the increase in intracranial pressure. The brain scans showing edema in AMS (Levine et al., 1989; Matsuzawa et al., 1992) did not display compression of gyri or effacement of sulci suggestive of a severe elevation of intracranial pressure, but such gross changes would not be expected in early AMS. Symptoms could result, however, from a moderate elevation in intracranial pressure or perhaps from transient episodes of raised intracranial pressure, such as might occur during exercise.

Direct measurements of intracranial pressure or CSF pressures in subjects exposed to acute hypoxia or with mild AMS are scarce. In a classic series, Schaltenbrand (1933) exposed several human subjects to simulated high altitudes and found that cerebrospinal fluid pressure began to increase at 3000 m and reached 1.5 kPa (12 mmHg) at 5200 m (Schaltenbrand, 1933). Hartig and Hackett performed a pilot study with three subjects during simulated exposure to 5000 m altitude (Hartig and Hackett, 1992). CSF pressure measured by lumbar catheter while supine and at rest showed only a slight increase in intracranial pressure, without a relationship to headache score. However, they also noted that CSF pressure became markedly elevated during exertion and during periodic breathing. One of their subjects with periodic breathing demonstrated a remarkable threefold increase in intracranial pressure, from 1.2 to 4 kPa (from 10 to 30 mmHg), in phase with the nadir of the oscillating arterial oxygen saturation (P. H. Hackett, personal communication). This suggested that brain compliance was altered, such that small changes in intracranial volume (blood) markedly elevated intracranial pressure. Measurements confirmed this: the change in CSF pressure for a given change in CBF (induced by hypoxic gas breathing) was 43 % higher at altitude than at sea level. Further, measures that objectively reduced intracranial pressure (breathing oxygen and hyperventilation) improved symptoms, while increasing intracranial pressure by breathing hypoxic gas or 7 % CO_2 (the latter also raised arterial oxygen saturation) made subjects considerably worse (Hartig and Hackett, 1992). These data are consistent with altered brain compliance due either to increased brain water content or to a large increase in CBV coupled with small cerebrospinal capacitance. One study used an indirect measurement of intracranial pressure *via* tympanic membrane displacement and showed no increase in intracranial pressure in those with AMS (Wright et al., 1995). These findings are difficult to evaluate because of the questionable reliability of the technique (Samuel et al., 1998).

A fair summary is that intracranial pressure may be elevated by hypoxia alone, but limited data to date have not confirmed the presence of consistently elevated intracranial pressure in AMS. The data further support the possibility that transient elevations in intracranial pressure occur upon slight physical

exertion or as a result of interventions that change intracranial pressure (or CBV). Moreover, these changes in intracranial pressure (and/or CBV) seem to be reproducibly related to symptoms of AMS.

Individual susceptibility and intracranial dynamics

What might explain the individual susceptibility to AMS? Correlation of AMS with hypoxic ventilatory response (HVR), ventilation, fluid status, lung function and physical fitness has been weak at best. Ross (1985) hypothesized that the apparently random nature of susceptibility might be explained by random anatomical differences (Ross, 1985). Specifically, he suggested that people with a smaller intracranial and intraspinal CSF capacity would be disposed to develop AMS, since they would not tolerate brain swelling as well as those with more 'room' in the craniospinal axis. It is the displacement of CSF through the foramen magnum into the spinal canal that is the first compensatory response to increased brain volume, followed by increased CSF absorption and decreased CSF formation. Studies have shown that the increase in intracranial pressure for a given increase in brain volume is directly related to the ratio of brain volume to intracranial volume and to the volume of the spinal canal (Shapiro et al., 1980). Thus, the greater the initial CSF volume, the more accommodation that can take place in response to brain swelling. Increases in brain volume are thus 'buffered' by CSF dynamics. In the light of our present understanding of increased brain volume on ascent to altitude, this hypothesis is attractive. Ross (Ross, 1985) goes on to suggest that, if his hypothesis is true, then the elderly should have a lower incidence of AMS as a result of their enlarged ratio of brain to cranial vault volume because brain size decreases with increasing age. This is supported indirectly by the findings of a lower AMS incidence in elderly groups studied at moderate (Roach et al., 1995) and high (>5000 m) altitudes (B. Kayser, personal communication).

Other factors that influence CNS function in AMS

The use of clonidine to prevent AMS

A recent preliminary field study demonstrated the marked effectiveness of clonidine (0.2 mg day^{-1}) for AMS prophylaxis (Wedmore et al., 1999). In 37 climbers ascending Mount Rainier (4392 m), clonidine reduced the incidence of AMS from 89 % (17/19) in placebo-treated climbers to 50 % in clonidine-treated climbers (P<0.02). Further evidence that sympathetic activation may play a role in the onset of AMS comes from a study of propranolol that showed that AMS symptom severity was reduced in six subjects after acute ascent to 4300 m (Fulco et al., 1989). Some studies have shown elevated peripheral plasma norepinephrine levels in AMS (Krasney et al., 1985; Bärtsch et al., 1988) while, in our recent descriptive study of the responses of women to acute altitude exposure, we found no relationship between peripheral norepinephrine levels and AMS (R. C. Roach, unpublished data). However, there is no doubt, from direct measurement of peroneal sympathetic nerve activity, that sympathetic activation with acute hypoxia reaches 50–100 % above control values (Roach et al., 1996; Duplain et al., 1999). The elevation is maintained for at least 24 h (Roach et al., 1996) and is 2–3 times greater in subjects prone to HAPE (Duplain et al., 1999). The absence of a relationship between direct nerve recordings and peripheral blood levels of norepinephrine is probably due to enhanced norepinephrine re-uptake and clearance during acute hypoxia (Leuenberger et al., 1991). No studies have examined norepinephrine re-uptake and/or clearance in the setting of AMS and acute altitude exposure.

How could elevated peripheral sympathetic activity influence AMS? Elevated peripheral sympathetic activity would serve to elevate mean arterial pressure and thus to elevate cerebral perfusion pressure, one factor hypothesized to contribute to cerebral edema in the face of a leaky BBB. Elevated peripheral sympathetic tone would also contribute to an increase in renal sympathetic tone, a result likely to cause neurogenic antinatriuresis (DiBona, 1982). An additional role for sympathetic activation in AMS/HACE comes from an interesting study in monkeys that demonstrated a central noradrenergic mechanism that effected an increase in BBB opening *via* innervation of the cerebral arterioles. Stimulation of the locus coeruleus prompted an immediate leak in the BBB (Raichle et al., 1978). Also, Burtscher et al. (1998) recently speculated that the marked effectiveness of aspirin in preventing high-altitude headache may result from its effects in diminishing central sympathetic outflow (Burtscher et al., 1998). Thus, it is conceivable that clonidine prevented AMS as a result of a drop in mean arterial pressure, cerebral perfusion pressure and CBV, and that BBB opening did not increase in clonidine-treated subjects, thus avoiding elevated CBV, cerebral edema and the symptoms of AMS.

The use of Egb761 to prevent AMS

A recent field study demonstrated the marked effectiveness of Egb761 (ginko biloba; 160 mg twice a day) in preventing AMS. In a study of 44 trekkers in Nepal at altitudes up to 5400 m, Roncin et al. (1996) reported that none of the Egb761-treated subjects developed AMS, compared with 41 % in the placebo-treated group (P<0.001) (Roncin et al., 1996). If these findings are confirmed, Egb761 will easily be the most potent known prophylaxis for AMS.

Unfortunately, the mechanism of action of Egb761 for AMS prevention is unknown. The well-documented oxygen-derived free-radical-quenching properties of Egb761 (Droy-Lefaix et al., 1991; Szabo et al., 1991; Rong et al., 1996; Pietri et al., 1997; Bekerecioglu et al., 1998) offer a possible role for Egb761 in preventing oxygen-derived free-radical-induced endothelial damage that could cause BBB opening in AMS. Free radical generation plays a role in experimental BBB opening. Schilling et al. (Schilling and Wahl, 1997; Schilling and Wahl, 1999) point out that application of a free-radical-generating compound has BBB-opening effects *in vitro* (Imaizumi et al., 1996) and *in vivo* (Olesen and Crone, 1986). Moreover, intraparenchymal infusion of a mixture containing hypoxanthine and xanthine oxidase to generate oxygen-derived

free radicals induced cerebral edema in rats (Chan et al., 1984). If Egb761 is confirmed as a potent prophylaxis for AMS, future studies should target the role of changes in BBB opening, changes in CBV and cerebral edema in the onset of the symptoms of AMS.

Concluding remarks

We have reviewed the evidence for a link between AMS and HACE based on brain water levels and brain swelling. At the present limits of technology, it seems clear that human brains swell during exposure to acute hypoxia, but that process alone does not account for the early symptoms of AMS. A logical next step is to explore fully whether different strategies for anatomical or physiological accommodation of brain swelling can account for individual differences in susceptibility to AMS. For example, the hypothesis of Ross (Ross, 1985) has not been experimentally evaluated. Current and emerging magnetic resonance imaging techniques will make possible quantification of the ratio of brain volume to intracranial volume and to the volume of the spinal canal. Also, CSF production and/or flow may be susceptible to measurement. Perhaps equally important is a quantification of the components of brain swelling. Currently, we only know that brains swell during acute hypoxia. Is the swelling due to both increased brain water levels and cerebral blood volume, or are there differences that relate to who gets sick and who remains immune to AMS? And finally, magnetic resonance imaging techniques allow quantification of BBB leak in intact humans. Does the BBB leak in early AMS? Can the leak be reversed by compounds effective in the treatment of AMS? In summary, scientists exploring this new paradigm centered on central nervous system responses to acute hypoxia are poised to make great headway in understanding the basic pathophysiology of AMS.

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