The Journal of Experimental Biology 204, 3129–3132 (2001)
Printed in Great Britain © The Company of Biologists Limited 2001
JEB3295

The high-altitude brain

Thomas F. Hornbein*
Departments of Anesthesiology and Physiology and Biophysics, University of Washington, Seattle, WA 98195, USA
*e-mail: hornbnt@u.washington.edu

Accepted 28 June 2001

Summary

The highest place on our planet, Mount Everest (8850 m), appears to be close to the limit of how high an acclimatized human can go, albeit slowly. In this paper, I will explore the possibility that what limits human performance at such extreme degrees of hypoxia is the availability of oxygen to the brain. Also, one of the known costs of such extreme exposure is residual mild impairment of performance on neuropsychometric tests after return to sea level, implying injury to brain cells. That such injury could occur in the absence of any overt impairment of function, much less without loss of consciousness, is unexpected. I will speculate about physiological mechanisms that might cause or contribute to both decrements in real-time performance while at altitude and residual deficits for a time after return to low elevations; the effects of hypoxia on brain cells are an even greater puzzle at the present time.

Key words: high altitude, brain, hypoxia, neurobehavioural impairment, brain injury, limitation to exercise performance.

Introduction

I would like to speculate on how high altitude may limit the brain and how, as a consequence, the brain might limit the body it occupies at high altitude. Such limitations will be more apparent at extremely high altitudes, by which I mean above approximately 7000–8000 m. To characterize the territory we will wander, I will share a personal experience, one of those pivotal moments that can change the direction of a life in unexpected ways.

Shortly before 19:00 h on 22 May 1963, Willi Unsoeld and I departed the summit of Mount Everest (8850 m). We had ascended another way, hence, were descending what for us was unknown terrain.

> ‘We almost ran along the crest, trusting Lute and Barrel’s tracks to keep us a safe distance from the cornice edge. Have to reach the South Summit before dark, I thought, or we’ll never find the way. The sun dropped below the jagged horizon. We didn’t need goggles any more. There was a loud hiss. Damn! Something’s broken. I reached back and turned off the valve. Without oxygen, I tried to keep pace with the rope disappearing over the edge ahead. Vision dimmed, the ground began to move. I stopped till things cleared, waved my arms and shouted into the wind for Willi to hold up. The taught rope finally stopped him. I tightened the regulator, then moved the oxygen on. No hiss! To my relief it had only been jarred loose. On oxygen again I could move rapidly’.
>
> Thomas F. Hornbein, *Everest, the West Ridge* (Hornbein, 1998)

Thinking back on this moment, and recalling descriptions of similar experiences, a number of thoughts, and questions, occur.

First, although an acclimatized lowlander can survive for a time on the summit of Everest without supplemental oxygen, one is so close to the limit that even a modicum of excess exertion may impair brain function. In my case, the visual cortex seemed to be the prime target; this same dimming was experienced the evening before while digging a tent platform a bit too strenuously at 8320 m while not using supplemental oxygen. Lionel Terray, indulging in the same activity at approximately 7400 m on Annapurna in 1950, wrote: ‘At times I would force so much that a black veil began to form in front of my eyes and I fell to my knees, panting like an overdriven beast’ (Terray, 1963). Descriptions of hallucinations at these extreme heights are not uncommon in the literature. Two questions were provoked by this experience. (i) Might lack of oxygen to the brain limit maximum physical performance at these extremely high altitudes? (ii) If brain oxygenation near the summit of Everest is so close to the threshold where function is actually inhibited, could such exposure also cause residual brain injury following return to sea level?

This second question has been a matter of speculation and concern since humans first contemplated venturing to these great heights. By now, a fairly extensive literature exists that describes how a low partial pressure of oxygen affects the brain, both acutely and after varying durations of acclimatization. We also have some information on the aftereffects of hypoxia.

Consequences of hypoxia: real time

Acute exposure

Beginning with the notorious balloon flights in the latter half of the 19th century (Glaisher et al., 1981), an extensive literature describes not only such dramatic but also subtler effects of hypoxia on the central nervous system. Investigators have documented decrements in performance on a variety of neuropsychometric tests after sudden exposure to even relatively moderate hypoxia (2000–4500 m). The literature has been reviewed by Stickney and Van Liere (Stickney and Van Liere, 1953), Tune (Tune, 1964) and, more recently, by Ernsting (Ernsting, 1978). One response to acute hypoxia is slowed performance, particularly on more complex tests of cognitive and motor function. While error rates also increase, a number of investigators have suggested that slowing might be a strategy designed to minimize mistakes. Changes (in a visual-positioning test performed during light work) have been reported at an altitude as low as 1500 m (Denison et al., 1966). These changes with acute hypoxia are evidence that even modest levels of hypoxia can impair brain function.

Sustained hypoxia

The history of Mount Everest climbs is replete with anecdotal accounts of cognitive impairment of various forms, dating from the early attempts in the 1920s and 1930s. ‘Mental laziness’, i.e. a disinclination rather than an inability to perform mental work, was reported (Greene, 1957). Greene also reported hallucinations, such as Frank Smythe’s famous ‘pulsating teapots’; the feeling that another individual is present, sometimes as a benevolent protector, exists anecdotally from both old and recent climbs. A variety of tests have revealed decrements in performance manifest, as with acute hypoxia, by slowing in reaction time with a lesser impact on error rates (Kennedy et al., 1989), changes being more prominent with more complex tests demanding higher levels of cognitive function. The seminal studies by Ryn of Polish mountaineers ascending to 5300 m revealed remarkable perturbations not only of performance on neuropsychometric tests but of behavior, mood and even neurological function (Ryn, 1971).

Consequences of hypoxia: aftereffects

In this same paper Ryn also provided the first report of behavioral abnormalities persisting after returning to low altitude (Ryn, 1971). Since that time, a small but mostly consistent literature has documented neurobehavioral changes following exposure to very high altitude. I will describe two of these works briefly, that of Hornbein, Schoene and Townes (Hornbein et al., 1989) and the observations reported by Regard et al. (Regard et al., 1989). We studied mainly members of the American Medical Research Expedition to Mount Everest (AMREE) in 1981 and subjects participating in Operation Everest II, a chamber simulation performed in 1985. Comparing performance following hypoxic exposure with that prior to ascent, we found decrements in short-term memory, aphasic deficits and decreased finger-tapping speed. When AMREE members were tested a year later, memory and aphasia deficits were no longer apparent, but in 13 of 16 participants finger-tapping speed remained impaired. Regard et al. studied eight ‘world-class’ mountaineers, all of whom had climbed above 8500 m one or more times without the use of supplemental oxygen (Regard et al., 1989). Neuropsychometric tests were performed 2–10 months after return to low altitude. All eight showed some performance decrements compared with a matched group of climbers who had no such high-altitude exposure. Five individuals seemed to be particularly affected, with mild impairment of concentration, short-term memory and cognitive flexibility (the ability to shift concepts and control errors). Three of these five showed electroencephalographic (EEG) abnormalities. Garrido et al. have reported magnetic resonance imaging (MRI) abnormalities in some individuals after return from these high altitudes (Garrido et al., 1993). Other literature is summarized by Raichle and Hornbein (Raichle and Hornbein, 2001).

The conclusions from these observations are that, even without a loss of consciousness or overt evidence of impaired function while at extreme altitude, some individuals show evidence of brain injury, at least for a time, after return to sea level. Individuals seem to vary considerably in their vulnerability. One factor associated with such variability is the ventilatory response to hypoxia (HVR). Curiously, individuals with a higher HVR appeared to sustain greater impairment in spite of a higher arterial oxygen saturation and a greater capacity to perform work while at high altitude (Masuyama et al., 1986; Schoene et al., 1984). I will return to the possible significance of this observation in the next section.

A sea-level counterpart to these high-altitude mountaineers may be individuals with arterial hypoxemia consequent to chronic obstructive pulmonary disease. These individuals show similar impairment on neuropsychometric tests (Grant et al., 1982), and the progression of this impairment can be prevented, perhaps even reversed, by long-term continuous oxygen therapy to ameliorate the hypoxemia (Grant and Heaton, 1985). These findings too support the presumption that even non-life-threatening hypoxia may hurt the brain if sustained long enough.

What is going on?

High altitude slows the brain and can injure the brain, and brain hypoxia may play a role in limiting physical performance at extreme elevations. How do these changes come about? I would like to speculate on two interconnected questions. (i) Does brain hypoxia limit work capacity, at least at extremely high altitude? If so, what mechanisms might provoke sufficient hypoxia of the relevant neuronal pathways? (ii) Noting the general belief, based upon extensive laboratory investigations in non-human primates, that inspired hypoxia alone does not cause brain injury, how might we explain the residual deficits observed in apparently normally functioning high-altitude mountaineers and chronically hypoxemic sea-level dwellers?

The mechanism of injury

The transition from rest to exercise might contribute to impairment of brain function. The increase in cardiac output shortens both pulmonary and peripheral tissue capillary transit time, a perfect setup at low arterial P_{O_2} for diffusion limitation. Such exercise-induced arterial hypoxemia is well-documented (Wagner et al., 1987; West et al., 1962), and recently Wagner has proffered the possibility of diffusion limitation playing a role in oxygen flux at the tissue level (Wagner, 1996).

The additional hypoxemia may set in motion a second means of increasing brain hypoxia, particularly in those with a higher HVR. As noted above, a higher HVR seems to be associated with greater brain injury. A higher HVR will result in both a higher arterial P_{O_2} and a lower arterial P_{CO_2} than in those with a lower HVR. Both these changes could decrease cerebral blood flow and, hence, cerebral oxygen delivery, even though the small rise in arterial P_{O_2} might increase arterial oxygen content appreciably because of the steep slope of the oxygen–hemoglobin dissociation curve at these low values of P_{O_2}. The end result might be that, while muscle is receiving more oxygen, the brain is getting less, perhaps enough less when added to the already extreme arterial hypoxemia to result in neuronal injury.

Can hypoxia alone injure brain cells? The general thinking on the basis of short-term studies of severe acute hypoxia is that hypoxia alone cannot injure the brain; some ischemia is also required (Simon, 1995). We do not know whether long-term hypoxia in the awake animal might cause brain injury in the absence of ischemia.

What might cause the injury? Acute ischemia severe enough to injure brain cells is associated with a loss of consciousness, the absence of brain electrical activity and the depletion of energy stores, setting in motion release of the excitotoxic neurotransmitter, glutamate, followed by Ca^{2+}-mediated cell death. Such a mechanism seems unlikely to explain how high altitude causes injury to brain cells. Might programmed cell death, apoptosis, be set in motion, to be manifest over a longer time (Miller and Marx, 1998)? Could oxygen radicals play a role (Coyle and Puttfarcken, 1993)? Might there be a contribution from hypoxic release of hormones such as glucocorticoids? At this stage, we have no explanation, only speculation about what, at the cellular level, could cause such selective cell death (Sapolsky et al., 1985).

Limitation of performance

How might such extreme hypoxemia, arterial P_{O_2} slightly below 30 mmHg (1 mmHg=0.133 kPa) at rest and even lower with exercise, limit work capacity? The diminishing maximum rate of oxygen uptake ($\dot{V}_{O_2max}$) with increasing altitude is well documented: at the summit of Mount Everest, it is no more than 25–30 % of the sea-level value. Might brain hypoxia contribute to this performance limitation? We do know that above 8000 m, perhaps even lower, dimming of vision with but modest exertion, reports of hallucinations and accounts of impaired judgment occur; all are compatible with a brain hovering dangerously close to imbalance between oxygen supply and need. Thus, only a small additional diminution in supply or increase in need might be sufficient to tip the scales towards impaired brain function.

The same physiological mechanisms I have described above as possible inciters of hypoxic brain injury might also interfere with brain function while at altitude, at rest and particularly with exertion. Another possible mechanism might relate less to diminished supply than to an increased need. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies document activation of focal areas within the brain, e.g. the motor cortex with exercise (Raichle and Hornbein, 2001). If increased flow fails to match the increased need, focal failure of neuronal function may result. Such focal depression could occur even in the absence of signs of more global inadequacy such as visual or other changes. Studies during Operation Everest II, a chamber simulation of an Everest ascent, found that muscle energy stores are normal and that the muscle was capable of responding fully to electrical stimulation of its innervation, implying that the muscle itself is not limiting performance (Green et al., 1989).

What is happening at the cellular level to slow or impair performance in the presence of conscious hypoxia is no clearer than how injury occurs. Possible direct cellular effects of hypoxia and hypocapnia, or secondary influences of alterations in levels of neurotransmitters (e.g. dopamine, norepinephrine) and hormones (e.g. glucocorticoids), are discussed in the review by Raichle and Hornbein (Raichle and Hornbein, 2001).

Concluding remarks

We know that the human brain at extremely high altitude exists in an environment close to the limits of what is needed for it to function. Both real-time and residual impairments occur. What we do not know yet is whether brain hypoxia limits the capacity to perform work near the summit of Mount Everest. Nor do we understand how hypoxia of a degree that appears to allow fairly normal function (such as climbing Everest without oxygen) leaves in its wake a residual injury to the brain.

References

Coyle, J. T. and Puttfarcken, P. (1993). Oxidative stress, glutamate and neurodegenerative disorders. *Science* **262**, 689–695.

Denison, D. M., Ledwith, F. and Poulton, E. C. (1966). Complex reaction times at simulated cabin altitudes of 5,000 feet and 8,000 feet. *Aerospace Med.* **37**, 1010–1013.

Ernsting, J. (1978). Prevention of hypoxia – acceptable compromises. *Aviat. Space Env. Med.* **49**, 495–502.

Garrido, E., Castello, A. and Ventura, J. L. (1993). Cortical atrophy and other brain magnetic resonance imaging (MRI) changes after extremely high-altitude climbs without oxygen. *Int. J. Sport Med.* **14**, 232–234.

Glaisher, J., Flammarion, C., De Fonvielle, E. and Tissandier, G. (1981). Ascent from Wolverhampton. In *High Altitude Physiology* (ed. J. B. West), pp. 104–110. Stroudsberg, PA: Hutchinson Ross.

Grant, I. and Heaton, R. K. (1985). Neuropsychiatric abnormalities in advanced COPD. In *Chronic Obstructive Pulmonary Disease* (ed. T. L. Petty), pp. 355–373. New York: Marcel Dekker.

Grant, I., Heaton, R. K., McSweeney, A. J., Adams, K. M. and Timms, R. M. (1982). Neurophysiologic findings in hypoxemic chronic obstructive pulmonary disease. *Archs. Int. Med.* **142**, 1470–1476.

Green, H. J., Sutton, J. R., Cymerman, A., Young, P. M. and Houston, C. S. (1989). Operation Everest II: Adaptations in human skeletal muscle. *J. Appl. Physiol.* **66**, 2454–2461.

Greene, R. (1957). Mental performance in chronic anoxia. *Br. Med. J.* **1**, 1028–1031.

Hornbein, T. F. (1998). *Everest, The West Ridge*. Seattle: The Mountaineers. 181pp.

Hornbein, T. F., Townes, B. D., Schoene, R. B., Sutton, J. R. and Houston, C. S. (1989). The cost to the central nervous system of climbing to extremely high altitude. *N. Engl. J. Med.* **321**, 1714–1719.

Kennedy, R. S., Dunlap, W. P., Banderet, L. E., Smith, M. G. and Houston, C. S. (1989). Cognitive performance deficits in a simulated climb of Mount Everest: Operation Everest II. *Aviat. Space Env. Med.* **60**, 99–104.

Masuyama, S., Kimura, H., Sugita, T., Kuriyama, T., Tatsumi, K., Kunitomo, F., Okita, S., Tojima, H., Yuguchi, Y., Watanabe, S. and Honda, Y. (1986). Control of ventilation in extreme-altitude climbers. *J. Appl. Physiol.* **61**, 500–506.

Miller, L. J. and Marx, J. (1998). Apoptosis. *Science* **281**, 1301.

Raichle, M. E. and Hornbein, T. F. (2001). The high altitude brain. In *High Altitude: An Exploration of Human Adaptation* (ed. T. F. Hornbein and R. B. Schoene). New York: Marcel Dekker (in press).

Regard, M., Oelz, O., Brugger, P., Biol, D. and Landis, T. (1989). Persistent cognitive impairment in climbers after repeated exposure to extreme altitude. *Neurology* **39**, 210–213.

Ryn, Z. (1971). Psychopathology in alpinism. *Acta Med. Pol.* **12**, 453–467.

Sapolsky, R. M., Krey, L. C. and McEwen, B. S. (1985). Prolonged glucocorticoid exposure reduces hippocampal neuron number: implications for aging. *J. Neurosci*. **5**, 1222–1227.

Schoene, R. B., Lahiri, S., Hackett, P. H., Peters Jr, R. M., Milledge, J. S., Pizzo, C. J., Sarnquist, F. H., Boyer, S. J., Graber, D. J., Maret, K. H. and West, J. B. (1984). The relationship of hypoxic ventilatory response to exercise performance on Mount Everest. *J. Appl. Physiol.* **56**, 1478–1483.

Simon, R. P. (1995). CNS response to hypoxia. In *Hypoxia and the Brain. Proceedings of the Ninth International Hypoxia Symposium* (ed. J. R. Sutton, C. S. Houston and G. Coates), pp. 1–7. Burlington, VT: Queen City Printers.

Stickney, J. C. and Van Liere, E. J. (1953). Acclimatization to low oxygen tension. *Physiol. Rev.* **33**, 13–34.

Terray, L. (1963). *Conquistadors of the Useless*. London: Victor Gollancz, Ltd.

Tune, G. S. (1964). Psychological effects of hypoxia: Review of certain literature from the period 1950–1963. *Percept. Motor Skills* **19**, 551–562.

Wagner, P. D. (1996). A theoretical analysis of factors determining $\dot{V}_{O_2MAX}$ at sea level and altitude. *Respir. Physiol.* **106**, 329–343.

Wagner, P. D., Sutton, J. R., Reeves, J. T., Cymerman, A., Groves, B. M. and Malconian, M. K. (1987). Operation Everest II: Pulmonary gas exchange during a simulated ascent of Mt. Everest. *J. Appl. Physiol.* **63**, 2348–2359.

West, J. B., Lahiri, S., Gill, M. B., Milledge, J. S., Pugh, L. G. and Ward, M. P. (1962). Arterial oxygen saturation during exercise at high altitude. *J. Appl. Physiol.* **17**, 617–621.