Letters to the Editor

Acute Mountain Sickness, Vitamin C, Free Radicals, and HIF-1α

To the Editor:

We were interested to read Bailey’s reply1 to the recent publication examining the effects of oral medroxyprogesterone as chemoprophylaxis against acute mountain sickness.2 In his letter entitled “Ascorbate, Blood-Brain Barrier Function and Acute Mountain Sickness: A Radical Hypothesis,” he suggests that a possible confounding factor in that study was the choice of vitamin C (ascorbate) as a placebo. He hypothesized that the free radical scavenging effects of vitamin C may have significant effects in protecting against acute mountain sickness. A small field study supports his theory.3 We believe that Bailey’s “radical hypothesis” may only partially explain the theoretical benefits of vitamin C at high altitude.

Recently, vitamin C has been implicated in the process of oxygen sensing. A universal system for oxygen sensing is now recognized within all mammalian species that involves the action of prolyl hydroxylase enzymes on hypoxia-inducible factor 1α (HIF-1α). HIF-1α is a transcriptional activator that regulates the expression of a number of hypoxia-responsive genes such as erythropoietin, heme oxygenase, and vascular endothelial growth factor.4

HIF-1α is constitutively expressed in all cells but is almost immediately broken down in the presence of oxygen. However, under conditions of hypoxia, it accumulates within cells and induces transcription of its target genes. Recently, vitamin C has been found to be an essential cofactor in the HIF-1α degradation pathway,4 where it may act by maintaining the cofactor iron in the reduced state (Fe2+), which is required for the action of prolyl hydroxylases.

Knockout mice with deficient HIF-1α expression (HIF-1α−/−) show a significantly decreased acute hypoxic ventilatory response after exposure to chronic hypoxia. Furthermore, they are protected against the development of hypoxia-induced pulmonary hypertension when compared with wild-type mice with normal HIF-1α expression.5 Conversely, desferrioxamine, an iron chelator that induces HIF-1α activity, has been shown to induce a rise in pulmonary artery pressure in healthy humans similar in time course to that of hypoxia.6 This suggests that by enhancing or inhibiting HIF-1α, it may be possible to affect human physiological responses to hypoxia. Vitamin C may be capable of such manipulation of the HIF-1α pathway in humans, as experiments in cell culture have shown that ascorbate supplementation potentiates HIF degradation.7 This raises the possibility that vitamin C supplementation, by facilitating prolyl hydroxylase-mediated breakdown of HIF-1α, may affect physiological responses to hypoxia and therefore be beneficial at altitude.

Further evidence suggesting that vitamin C may play a critical role in oxygen sensing and augmenting the responses to hypoxia has been shown in a recent study of ascorbyl palmitate in hypoxic cats.8 Ascorbyl palmitate is a lipid-soluble derivative of vitamin C; its lipid solubility increases its availability to chemoreceptors in the carotid body. The study showed modification of the ventilatory response to hypoxia and concluded that ascorbyl palmitate may have therapeutic effects in hypoxia. The authors suggest a number of hypotheses for its action, including a possible role in prolyl hydroxylase oxygen sensing and HIF-1α.

These studies suggest that the theoretical benefits of vitamin C on acute mountain sickness may be through a HIF-1α–related oxygen-sensing mechanism instead of or in addition to its radical scavenging effect on the blood-brain barrier as proposed by Bailey. Although the role of vitamin C in HIF-1α regulation and oxygen sensing is not yet fully understood, we cannot ignore its role in this system or attribute all its potential beneficial effects to Bailey’s radical hypothesis.

Kyle T. S. Pattinson, BM, FRCA
Nuffield Department of Anaesthesia
University of Oxford
Oxford, UK

Andrew I. Sutherland, MB, BCh, BSc(Hons), MRCS
Nuffield Department of Surgery
University of Oxford
Oxford, UK

Thomas G. Smith, MB, BS;
Keith L. Dorrington, DPhil, DM, FRCA
University Laboratory of Physiology
University of Oxford
Oxford, UK