Letters to the Editor

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Impaired Cerebral Autoregulation in Acute Mountain Sickness: Incidental Yet Adaptive?

To the Editor:

Subudhi et al\(^1\) recently demonstrated that dynamic cerebral autoregulation (CA) became progressively impaired when volunteers were exposed to the hypoxia of simulated high-altitude, although this was unrelated to the onset of neurological symptoms ascribed to acute mountain sickness (AMS). Although their study describes some important findings, the authors’ interpretation of similar studies conducted by our groups\(^2,3\) warrants clarification and provides an opportunity to offer complementary insight into alternative mechanisms.

The authors discuss deficiencies with the design and interpretation of our findings, thus “…making it difficult to draw conclusions regarding the role of impaired CA in the development of AMS.”\(^1\) Likewise, the inclusion of altitude-adapted natives (with the knowledge that acclimatization impairs CA\(^4\)), superimposition of physical exercise as a “primer” (exercise also impairs CA\(^5\)), comparatively milder symptoms attributable to the combined effects of a lower altitude differential, and more conservative clinical diagnosis (which may explain why arterial hypoxemia was not more marked in AMS compared to healthy controls) are also limitations that can be met with equal criticism and ultimately make for poor comparison. However, rather than dwell on the minutiae of design limitations, the basic conclusion common to all studies was precisely the same: impaired CA is not a risk factor for AMS.

These findings fit well with neuroimaging evidence for mild vasogenic brain swelling of the corpus callosum in hypoxia.\(^6\) Thus, impaired CA has the potential to disrupt the blood–brain barrier so subtly that it remains beyond the limits of molecular detection.\(^7\) However, attempts to detect any additional vasogenic brain swelling in AMS have consistently failed. Mild astrocytic swelling caused by a net redistribution of fluid from the hypoxia-primed extracellular space to the intracellular space without any evidence for further barrier disruption, brain edema, swelling, or pressure remains the only morphological feature known to differentiate the AMS brain from its healthy counterpart. However, it is unlikely that this minor shift of water into the corpus callosum accounts for symptoms and thus must be considered an incidental finding.

If impaired CA does translate into mild vasogenic edema in hypoxia, then what is its physiological significance? Because CA is impaired in high-altitude natives,\(^4\) priming of the extracellular space may represent an adaptive response\(^8\) that serves to buffer increases in the interstitial concentration of neurotransmitters, thereby reducing tonic activation of N-methyl-D-aspartate (NMDA) receptors and tempering extracellular K\(^+\) that could threaten to depolarize the brain.\(^9\) Neonates, who are far more hypoxia-tolerant than adults, exhibit an enlarged extracellular space.\(^10\) Whatever vasogenic brain swelling in hypoxia represents, it is clear that it does not account for the symptoms of AMS and suggests that we need to look beyond the blood–brain barrier to alternative mechanisms. Free radical-mediated activation of the trigeminovascular system may prove a worthy candidate.\(^11\)

Disclosure

None.

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