Mecanismos sensores agudos do oxigênio

Acute Oxygen-Sensing Mechanisms

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Article

To the Editor:

The review article by Weir et al. (Nov. 10 issue)[1] on acute oxygen-sensing mechanisms omits one of the most important of the mechanisms: the angiotensin-converting–enzyme (ACE) molecule. ACE is enriched in the pulmonary circulation, where it appears to function not only as a mechanosensor[2] but also as a reduction–oxidation (redox) sensor.[3] A central role for ACE in ventilation–perfusion matching would explain its involvement in lung pathology.[4,5] ACE inhibition or angiotensin II blockade may be effective for treating acute and chronic lung diseases, including the acute respiratory distress syndrome, high-altitude pulmonary edema, viral pneumonia, bronchiolitis obliterans, pulmonary fibrosis, lung cancer, and chronic obstructive pulmonary disease.

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Dr. Moskowitz is the founder, chief executive officer, and chief medical officer of GenoMed, which owns pending patents on the use of ACE inhibitors and angiotensin-receptor blockers for pulmonary disease.

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To the Editor:

Weir et al. might have mentioned that prolonged and chronic hypoxia modulates ion-channel excitability and has a role in neurodegeneration. Hypoxia leads to the formation of beta-amyloid peptides through amyloidogenic processing of amyloid precursor protein. By up-regulating L-type calcium channels, hypoxia disrupts calcium homeostasis, which may be the basis of the neurotoxicity of beta-amyloid peptides and the development of Alzheimer's disease.[1,2] In vitro studies of rat neurons suggest that cholinergic neurons are especially vulnerable to toxicity from beta-amyloid peptides.[3] The role of hypoxia in the predisposition to Alzheimer's disease is largely underrecognized.

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To the Editor:

With regard to the article by Weir et al., we would like to point out that oxygen sensing is also involved in inflammatory and infectious diseases.[1,2] Recent evidence suggests a critical role of cellular oxygen-sensing mechanisms during acute immune responses. For example, animals with a conditional knockout of the transcription factor hypoxia-inducible factor 1 (HIF-1) in their myeloid cells show impaired phagocytosis and impaired killing capacity of neutrophils.[3] In addition, hypoxia and cellular oxygen-sensing mechanisms are critical to tissue protection during acute colitis.[4] Studies of acute bacterial infection have demonstrated a central role of HIF-1 activation leading to increases in hypoxia-induced gene transcription and expression regulated by this oxygen-sensing transcription factor.[5] Taken together, such studies suggest a central role for cellular oxygen sensing in the pathogenesis and outcome of inflammatory and infectious diseases.

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To the Editor:

In the article by Weir et al., Figure 4 depicts an NADPH oxidase in the plasma membrane as a source of intracellular reactive oxygen species. The authors acknowledge uncertainties as to the presence or biochemical composition of the presumed NADPH oxidase in such tissues, but the figure poses a serious conceptual problem. If the topology of the oxidase complex has the NADPH-binding domain on the cytoplasmic side of the plasma membrane, thereby facing the source of NADPH (as is the case in the prototypic phagocyte NADPH oxidase1), electrons must be released extracellularly and there reduce molecular oxygen to superoxide ion and its derivatives. For the figure to be accurate, reactive oxygen species must reenter the cell, either through channels or as membrane-soluble agents, such as hydrogen peroxide. Alternatively, the responsible oxidase might be a previously uncharacterized enzyme unrelated to the family of NADPH oxidase proteins and with a novel organization in the membrane. Given this shortcoming in the figure, what is an alternative model that would more accurately depict the mechanism and reflect the underlying biochemistry?

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Author/Editor Response

Dr. Nauseef points out that the phagocytic NADPH oxidase in the plasma membrane releases reactive oxygen species on the outside of the cell. NADPH oxidase and its homologues may also release reactive oxygen species from intracellular granules, from the endoplasmic reticulum, and into intracellular phagocytic vacuoles.[1,2] In the setting of hypoxic pulmonary vasoconstriction, these mechanisms are speculative, and if NADPH oxidase is involved, it seems more likely that hydrogen peroxide would diffuse back into the smooth-muscle cell across the plasma membrane. We have previously shown that NADPH oxidase, containing the $gp91^{phox}$ subunit, is involved in normoxic generation of reactive oxygen species in mouse lungs.[3] However, hypoxic pulmonary vasoconstriction persists when this source of reactive oxygen species is removed, suggesting that it is not essential for initiating that condition. Our work and that of others would favor the mitochondria as a source of signaling reactive oxygen species, at least in the pulmonary arteries.

The oxygen-sensitive factor HIF-1 may play a role in the body's response to inflammation and infection, as suggested by Dr. Eltzschig and colleagues. Although the many actions of HIF-1 are fascinating, they fall outside the scope of our review, which was limited to acute oxygen sensing. It is clear that the chronic response of the pulmonary vasculature to hypoxia does involve HIF activation. Rats that are heterozygous for HIF-1 manifest less chronic hypoxic pulmonary hypertension and have less right ventricular hypertrophy.[4]

Repeated periods of hypoxia have been associated with an increased incidence of dementia. Chronic hypoxia increases the formation of beta-amyloid peptides, and these in turn increase the expression of L-type calcium channels.[5] As stated by Dr. Khan, the loss of calcium homeostasis may cause neurotoxicity and be involved in the pathophysiology of Alzheimer's disease.

Dr. Moskowitz asks whether ACE may play a part in oxygen sensing. Although ACE is active in the pulmonary circulation, we are unaware of rigorous data indicating that it is involved in

hypoxic pulmonary vasoconstriction or in oxygen sensing in general. Angiotensin II, in common with many other vasoconstrictors, will enhance hypoxic pulmonary vasoconstriction, but this action is probably distinct from the mechanism of sensing. To date, few data in animals or humans have suggested that ACE inhibitors are beneficial in pulmonary hypertension. Any effect on the pulmonary circulation may be offset by the tendency to cause systemic vasodilation, which can cause hypotension and syncope in patients with pulmonary hypertension.

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