Hydrogen Peroxide Diffusion in the Extracellular Space: Redox Volume Signaling in the Brain

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A. Ledo[I,II], E. Fernandes[I,II], A. Salvador[II,III,IV], J. Laranjinha[I,II], R.M. Barbosa[I,II]

[I]University of Coimbra Faculty of Pharmacy, Coimbra, Portugal, [II]Center for Neurosciences and Cell Biology, University of Coimbra, Coimbra, Portugal, [III]Coimbra Chemistry Centre - Institute of Molecular Sciences (CQC-IMS), University of Coimbra, Coimbra, Portugal, [IV]IIIUC - Institute for Interdisciplinary Research, University of Coimbra, Portugal, Coimbra, Portugal

Hydrogen peroxide (H_2O_2) is a major redox signaling molecule underlying a novel paradigm of cell function and communication. A role for H_2O_2 as an intercellular signaling molecule and neuromodulator in the brain has become apparent from studies showing that it can to regulate neuronal polarity, connectivity, synaptic transmission and tuning of neuronal networks. Furthermore, H_2O_2 can travel in the extracellular space, from source of production to target, suggesting it may act as a volume signaling molecule.

This activity requires H_2O_2 to have the ability to diffuse in the extracellular space, from source of production to target. Using a novel electrochemical microsensor, we have investigated H_2O_2 concentration dynamics in the living brain and the factors which shape its diffusion pattern and half-life in the brain extracellular matrix both in an ex vivo model using rodent brain slices and in vivo. We found that exogenously applied H_2O_2 is rapidly removed, with an average half-life in the extracellular space of $t_{1/2}$ = 2.2 s *in vivo*. We determined the *in vivo* effective diffusion coefficient of H_2O_2 to be $D^* = 2.5 \times 10^{-5}$ cm^2 s^{-1}, which allows it to diffuse over 100 µm in the extracellular space within its half-life. These quantitative details allow us to interpret the physiology of the redox signal, tentatively placing H_2O_2 within the class of volume transmitters connecting all cell types with the complex network of brain tissue, regardless of whether the cells are physically connected.