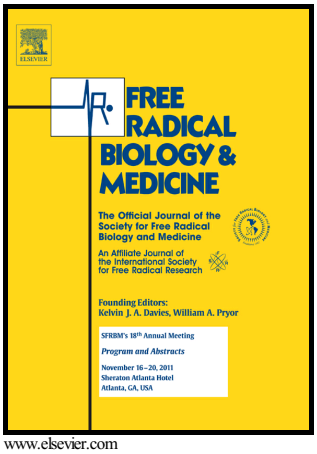
Neurovascular-neuroenergetic coupling axis in the brain: master regulation by nitric oxide and consequences in aging and neurodegeneration

Cátia F. Lourenço, Ana Ledo, Rui M. Barbosa, João Laranjinha



www.elsevier.com

PII: S0891-5849(17)30229-0
DOI: http://dx.doi.org/10.1016/j.freeradbiomed.2017.04.026
Reference: FRB13307

To appear in: *Free Radical Biology and Medicine*

Received date: 31 July 2016
Revised date: 21 February 2017
Accepted date: 18 April 2017

Cite this article as: Cátia F. Lourenço, Ana Ledo, Rui M. Barbosa and João Laranjinha, Neurovascular-neuroenergetic coupling axis in the brain: master regulation by nitric oxide and consequences in aging and neurodegeneration *Free Radical Biology and Medicine* http://dx.doi.org/10.1016/j.freeradbiomed.2017.04.026

Neurovascular-neuroenergetic coupling axis in the brain: master regulation by nitric oxide and consequences in aging and neurodegeneration

Cátia F. Lourenço[a1], Ana Ledo[a1], Rui M. Barbosa[a, b], João Laranjinha[a,b*]
[a]Center for Neuroscience and Cell Biology, University of Coimbra, Portugal

[b]Faculty of Pharmacy, University of Coimbra, Coimbra, Portugal

[*]Correspondence to: João Laranjinha, Faculty of Pharmacy, University of Coimbra, Health Sciences Campus, Azinhaga de Santa Comba, 3000-548 Coimbra, Portugal. laranjin@ci.uc.pt

Abstract

The strict energetic demands of the brain require that nutrient supply and usage be fine-tuned in accordance with the specific temporal and spatial patterns of ever-changing levels of neuronal activity. This is achieved by adjusting local cerebral blood flow (CBF) as a function of activity level – neurovascular coupling – and by changing how energy substrates are metabolized and shuttled amongst astrocytes and neurons – neuroenergetic coupling. Both activity-dependent increase of CBF and O_2 and glucose utilization by active neural cells are inextricably linked, establishing a functional metabolic axis in the brain, the neurovascular-neuroenergetic coupling axis. *This axis incorporates and links previously independent processes that need to be coordinated in the normal brain.* We here review evidence supporting the role of neuronal-derived nitric oxide ($^{\bullet}$NO) as the master regulator of this axis. Nitric oxide is produced in tight association with glutamatergic activation and, diffusing several cell diameters, may interact with different molecular targets within each cell type. Hemeproteins such as soluble guanylate cyclase, cytochrome c oxidase and hemoglobin, with which $^{\bullet}$NO reacts at relatively fast rates, are but a few of the key in determinants of the regulatory role of $^{\bullet}$NO in the neurovascular-neuroenergetic coupling axis. Accordingly, critical literature supporting this concept is discussed. Moreover, in view of the controversy regarding the regulation of catabolism of different neural cells, we further discuss key aspects of the pathways through which $^{\bullet}$NO specifically up-regulates glycolysis in astrocytes, supporting lactate shuttling to neurons for oxidative breakdown. From a biomedical viewpoint, derailment of neurovascular-neuroenergetic axis is precociously linked to aberrant brain aging, cognitive impairment and neurodegeneration. Thus, we summarize current knowledge of how both neurovascular and neuroenergetic coupling are compromised in aging, traumatic brain injury, epilepsy and age-associated neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease, suggesting that a shift in cellular redox balance may contribute to divert $^{\bullet}$NO bioactivity from regulation to dysfunction.

Keywords: Neurovascular coupling, neuroenergetic coupling, nitric oxide, aging, neurodegeneration

1. Introduction

[1] These authors contributed equally to this work