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Targeting hypoxic signals as a therapeutic approach to Alzheimer's disease

Mario Durán-Prado[1], Javier Frontiñán-Rubio[1], Francisco Javier Sancho-Bielsa[1], Cristina Pedrero-Prieto[1], Juan Ramón Peinado[1], Lidia Giménez-Llort[2] and **Francisco Javier Alcaín[1]**
[1]University of Castilla-La Mancha, Spain
[2]Autonomous University of Barcelona, Spain

Hypoxia, "hypoxic signals" as increased mitochondrial radical oxygen species levels and hypoperfusion occurs early in Alzheimer`s disease, inducing white matter lesions and correlating with dementia. Indeed, these abnormalities turn towards a cerebral microvascular pathology which accompanies age-related cognitive dysfunction and neurodegeneration. Therefore, alleviating cerebral microvascular pathology through the blockade of early hypoxic signals becomes a promising strategy to slow down Alzheimer`s progression. We have described that hypoxic signals (as oxidative stress) in early stages preceding vascular damage, beta amyloid deposition and appearance of brain parenchymal hypoxia, are premorbid and prodromal indicators of Alzheimer`s in the 3xTg-AD murine model of the disease. Moreover, circulating beta amyloid peptide damages the cerebral microvasculature through mechanisms that involve an increase in hypoxic signals, specifically in the mitochondrial compartment of endothelial cells, as it is an increase in superoxide ion, driving to endothelial cell death and therefore, to a compromise of cerebral microvessels function. Our results obtained with endothelial cells cultures, exposed to beta amyloid peptide, in vitro, clearly indicate that hypoxic cell responses can be blocked using a mitochondrial protector as coenzyme Q10, a lipophilic antioxidant involved in electrons transport from the mitochondrial complex I to complexes II and III, which results in a protective effect against beta amyloid cell toxicity through raising the whole cell metabolic status. We have recently assayed the effect of targeting mitochondrial hypoxic signals, in vivo, in 3xTg-AD mice. Animals were fed from prodromal stages of the disease with ubiquinol (the reduced form of coenzyme Q10) diet, compared to vehicle diet and wild type mice. Firstly, hippocampal chronic inflammation and peripheral leukocytes-oxidative stress found in 3xTg-AD mice were reversed by ubiquinol, which was mirrored by a reversion of the mice neuropathological status. Brain parenchyma hypoxia, exacerbated in vehicle-fed 3xTg-AD mice also in colocalization with large and abundant beta amyloid plaques, disappeared upon intervention with ubiquinol as well as the amount and size of beta amyloid plaques. This is correlated with a reduction in collagen deposition in the basal lamina of brain microvessels, a clear indicator of an improved brain microvessels function. Altogether, our results indicate that combating hypoxic signals from early prodromal Alzheimer´s stages could be a successful strategy to improve microvessels function, reducing parenchymal hypoxia, accumulation of beta amyloid plaques and, maybe, improving the delivery of memantine.

Recent Publications

1. Frontiñán-Rubio, Javier, Sancho-Bielsa, Francisco Javier, Peinado, Juan Ramón, LaFerla, Frank, Giménez-Llort, Lidia, Durán-Prado, Mario and Alcain, Francisco Javier () Sex-dependent colocalization of hipoxia and beta-amyloid plaques in hippocampus and enthorhinal cortex in 3xTg-AD mice is reversed by long-term treatment with ubiquinol and vitamin C. In review (second) in Mol. Cell. Neurosci.
2. Durán-Prado Mario, Javier Frontiñán, Raquel Santiago-Mora, Juan Ramón Peinado, Cristina Parrado-Fernández, et al. (2014) Coenzyme q10 protects human endothelial cells from β-amyloid uptake and oxidative stress-induced injury. PLoS One 9(10): e109223.
3. Torres-Lista Virginia, Cristina Parrado-Fernández, Ismael Alvarez-Montón, Javier Frontiñán-Rubio, Mario Durán-Prado, et al. (2014) Neophobia, NQO1 and SIRT1 as premorbid and prodromal indicators of AD in 3xTg-AD mice. Behav. Brain Res. 271:140-6.

Biograpy

Mario Durán-Prado has a Degree in Biochemistry (with Honors, 2000, University of Córdoba), Master's Degree in Biochemistry and Molecular Biology (Magna Cum Laude, 2002, University of Córdoba) and PhD in Sciences (Magna Cum Laude, 2007, University of Córdoba). After a Post-doctoral training at the Group of Neuroimmunology of Inflammatory and Autoimmune Diseases, IPBLN-CSIC (2008-2010), he joined the newly-created Faculty of Medicine of Ciudad Real (University of Castilla-La Mancha, Spain) as Associate Professor in Cell Biology, being member of the Group of Oxidative Stress and Neurodegeneration (GEON). He works on neuropeptides/GPCRs and their involvement in neuroendocrine, oncological and cardiovascular pathologies. Since 2010, his research focuses towards the role of oxidative stress in the initiation and progression of neuropathologies as brain tumors and Alzheimer`s disease, focusing in the development of novel therapeutic approaches using diverse translational and multidisciplinary research models. He holds four national and international projects as Principal Investigator, also as a collaborator in two active projects funded by the H2020. He has more than 40 publications (h-index=20), some of them in high impact factor journals (>7).

mario.duran@uclm.es

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