



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

ARCHIVIO ISTITUZIONALE
DELLA RICERCA

Alma Mater Studiorum Università di Bologna Archivio istituzionale della ricerca

Oxygen Deprivation and Brain Inflammation: The Mitochondrial Link to Alzheimer's Progression

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version:

Nesci, S. (2025). Oxygen Deprivation and Brain Inflammation: The Mitochondrial Link to Alzheimer's Progression. JOURNAL OF BIOCHEMICAL AND MOLECULAR TOXICOLOGY, 39(9), 1-2 [10.1002/jbt.70527].

Availability:

This version is available at: <https://hdl.handle.net/11585/1040918> since: 2026-02-01

Published:

DOI: <http://doi.org/10.1002/jbt.70527>

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>).
When citing, please refer to the published version.

(Article begins on next page)

This is the final peer-reviewed accepted manuscript of:

Oxygen Deprivation and Brain Inflammation: The Mitochondrial Link to Alzheimer's Progression.

Salvatore Nesci

J Biochem Mol Toxicol. 2025 Sep;39(9):e70527..

The final published version is available online at: **<https://doi.org/10.1002/jbt.70527>**

Rights / License:

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

Oxygen deprivation and brain inflammation: the mitochondrial link to Alzheimer's progression

Salvatore Nesci

Department of Veterinary Medical Sciences, University of Bologna, Ozzano Emilia, 40064, BO, Italy.
Correspondence: salvatore.nesci@unibo.it

Abstract

Hypoxia is an emerging contributor to Alzheimer's disease (AD) pathogenesis, promoting microglial transition from anti-inflammatory to pro-inflammatory states and sustaining neuroinflammation. Oxygen deprivation impairs oxidative phosphorylation, reduces ATP synthesis, and triggers metabolic rewiring toward glycolysis, linking bioenergetic failure to neurodegeneration. Sirtuins, particularly SIRT1 and SIRT3, regulate microglial activation and mitochondrial homeostasis, representing promising therapeutic targets. Natural compounds such as melatonin and naringenin show potential in preserving mitochondrial integrity, preventing permeability transition pore opening, and mitigating oxidative stress. Targeting hypoxia-driven metabolic and inflammatory pathways and the adjunctive use of natural compounds may offer novel strategies to slow AD progression.

Keywords: Alzheimer's disease; hypoxia, neuroinflammation, mitochondrial dysfunction, sirtuins, natural compounds.

Insufficient cerebral oxygen supply, or hypoxia, is an emerging risk factor in the pathogenesis of Alzheimer's disease (AD). This condition not only compromises neuronal viability but is also implicated in altering the functional phenotype of microglia. Specifically, hypoxia can induce a shift in these resident immune cells from a protective, anti-inflammatory state to a chronic, pro-inflammatory phenotype. This transition exacerbates sustained neuroinflammation, a critical component of AD neuropathology ¹. Hypoxic events occurring during the early AD asymptomatic stages may act as critical modulators of disease progression. The high dependence of brain on oxidative metabolism renders it particularly susceptible to oxygen deprivation. Indeed, disruption of cellular homeostasis during hypoxia affects microglial function and mitochondrial bioenergetics. In this scenario, hypoxia insults might prompt an early change of microglia from an anti-inflammatory to a pro-inflammatory phenotype, thus contributing to a prolonged neuroinflammatory milieu that aids neurodegeneration ².

Mitochondria play a central role in sustaining neuronal function through oxidative phosphorylation (OXPHOS), the primary pathway for ATP production in the brain. Given the brain's high energy demands and its reliance on oxygen-dependent mitochondrial respiration, even mild reductions in oxygen availability can have profound effects on cellular metabolism. In the context of AD, mitochondrial dysfunction is a well-established feature, and hypoxia may act as a precipitating factor that accelerates this decline. When oxygen flux is reduced, OXPHOS is impaired, leading to a significant decrease in ATP synthesis. To compensate for this energy deficit, neurons and microglia undergo a process of metabolic rewiring, shifting their primary energy production pathway from OXPHOS to glycolysis. While glycolysis provides a rapid but limited amount of ATP, this switch has significant implications. Indeed, metabolic rewiring is a critical process of the plastic transition of anti-inflammatory/pro-inflammatory state. The reduction in oxygen by hypoxia serves as a critical driver of metabolic exchange in AD, linking impaired OXPHOS to chronic inflammation and neurodegeneration ^{2,3}.

In the context of neuroinflammation and neurodegeneration, nuclear sirtuin 1 (SIRT1) has a role as a promising molecular target implicated in the regulation of microglial activation states. Particularly, in delaying the transition from an anti-inflammatory to a pro-inflammatory phenotype. The latter, critical event in the progression of AD contributes to sustained neuroinflammation and neuronal damage. Pharmacological activation of SIRT1 has been proposed as a therapeutic method for maintaining microglial homeostasis and reducing inflammatory responses. Melatonin and naringin have been shown to be possible endogenous or dietary, respectively, SIRT1 activators ³. Melatonin has been investigated as a potential molecular therapy to counteract mitochondrial dysfunction induced by hypoxia/reoxygenation injury. Consistently, melatonin decreases oxidative stress and improves bioenergetic parameters of cell metabolism by direct action on mitochondrial F_1F_0 -ATPase, considered a possible target enzyme of melatonin ⁴. Likewise, naringenin has shown specific inhibitory activity against the hydrophilic F_1 domain of the enzyme, especially when Ca^{2+} is employed as a cofactor and linked to the opening of the mitochondrial permeability transition pore (mPTP), a crucial event in mitochondrial dysfunction and regulated forms of cell death ⁵. Naringenin inhibits the ATP hydrolysis-driven energy transmission process, hence altering mitochondrial

activity under stress circumstances. The benefit of mitochondrial function of naringenin involves the prevention of oxidative stress and bioenergetic failure ⁶.

However, SIRT3 emerges as the most common isoform found in the mitochondrial matrix, where it plays an important role in maintaining cellular energy balance. In the context of AD, where mitochondrial dysfunction and bioenergetic failure are prominent features, mitochondrial SIRT3 assumes a particularly important role ⁷. SIRT3 promotes efficient energy metabolism and reduces the negative effects of hypoxia and inflammation by regulating the acetylation state of mitochondrial proteins. Moreover, melatonin and naringenin have been recognized for their potential to counteract mitochondrial dysfunction in AD. Both natural compounds exhibit antioxidant and anti-inflammatory properties, but have the mitochondrial ability to rescue compromised mitochondrial bioenergetics ^{4,6}.

mPTP opening alters mitochondrial membrane integrity and allows the production of pro-inflammatory mitochondrial damage-associated molecular patterns (mtDAMPs) ⁸. The release of mtDAMPs following mPTP opening contributes to the activation of microglia and the perpetuation of a chronic inflammatory state, which is a hallmark of AD pathology ^{9,10}. This process not only exacerbates neuronal injury but also reinforces the metabolic and oxidative stress that further destabilizes mitochondrial function. Preventing mPTP activation by melatonin and or naringenin in hypoxia context of pathological situation of AD, is therefore considered a major approach in protecting mitochondrial function and slowing neurodegeneration.

On balance, hypoxia highlights a pivotal driver in AD pathogenesis, initiating microglial polarization toward a pro-inflammatory phenotype and amplifying mitochondrial dysfunction. As a consequence, oxygen deprivation disrupts OXPHOS, enforces metabolic rewiring, and perpetuates chronic neuroinflammation, thereby accelerating neurodegenerative processes. Sirtuins can have critical regulatory roles in microglial activation and mitochondrial homeostasis, highlighting their therapeutic relevance. Furthermore, melatonin and naringenin demonstrate significant potential in preserving bioenergetic dysfunction and mitigating oxidative stress of mitochondria, and preventing mPTP opening. These findings strongly support targeting hypoxia-induced metabolic and inflammatory pathways as a strategic approach to delay or attenuate AD progression.

Competing interests

The author declares that has no competing interests

Data Sharing and Data Availability

Data sharing not applicable to this article as no datasets were generated or analysed during the current study

Funding

None

Author contributions

Salvatore Nesci contributed to the conception, design, and drafting of the manuscript.

Acknowledgements

Not applicable

References

- [1] Chung S, Jeong JH, Park JC, Han JW, Lee Y, Kim JI, et al. Blockade of STING activation alleviates microglial dysfunction and a broad spectrum of Alzheimer's disease pathologies. *Exp Mol Med*. 2024;56(9):1936-1951. doi:10.1038/s12276-024-01295-y
- [2] Luo Z, Tian M, Yang G, Tan Q, Chen Y, Li G, et al. Hypoxia signaling in human health and diseases: implications and prospects for therapeutics. *Signal Transduct Target Ther*. 2022;7(1):218. doi:10.1038/s41392-022-01080-1
- [3] Lipari C, Patti A, Conti Nibali S, Messina A, Magri A, Sortino M, et al. Hypoxia reverses the early anti-inflammatory microglial response to the β -amyloid peptide: mitochondrial involvement and beneficial roles of melatonin and naringenin. *J Transl Med*. Published online In press.
- [4] Algieri C, Bernardini C, Cugliari A, Granata S, Trombetti F, Glogowski PA, et al. Melatonin rescues cell respiration impaired by hypoxia/reoxygenation in aortic endothelial cells and affects the mitochondrial bioenergetics targeting the F1FO-ATPase. *Redox Biol*. 2025;82:103605. doi:10.1016/j.redox.2025.103605
- [5] Nesci S. ATP synthase as a negative regulator versus a functional-structural component of the high conductance state of mitochondrial permeability transition pore. *J Biochem Mol Toxicol*. 2024;38(9):e23821. doi:10.1002/jbt.23821

- [6] Nesci S, Algieri C, Tallarida MA, Stanzione R, Marchi S, Pietrangelo D, et al. Molecular mechanisms of naringenin modulation of mitochondrial permeability transition acting on F1FO-ATPase and counteracting saline load-induced injury in SHRSP cerebral endothelial cells. *Eur J Cell Biol.* 2024;103(2):151398. doi:10.1016/j.ejcb.2024.151398
- [7] Oppedisano F, Nesci S, Spagnoletta A. Mitochondrial sirtuin 3 and role of natural compounds: the effect of post-translational modifications on cellular metabolism. *Crit Rev Biochem Mol Biol.* 2024;59(3-4):199-220. doi:10.1080/10409238.2024.2377094
- [8] Xian H, Watari K, Sanchez-Lopez E, Offenberger J, Onyuru J, Sampath H, et al. Oxidized DNA fragments exit mitochondria via mPTP- and VDAC-dependent channels to activate NLRP3 inflammasome and interferon signaling. *Immunity.* 2022;55(8):1370-1385.e8. doi:10.1016/j.immuni.2022.06.007
- [9] Cox DJ, Field RH, Williams DG, Baran M, Bowie AG, Cunningham C, et al. DNA sensors are expressed in astrocytes and microglia in vitro and are upregulated during gliosis in neurodegenerative disease. *Glia.* 2015;63(5):812-825. doi:10.1002/glia.22786
- [10] Hu MM, Shu HB. Mitochondrial DNA-triggered innate immune response: mechanisms and diseases. *Cell Mol Immunol.* 2023;20(12):1403-1412. doi:10.1038/s41423-023-01086-x