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

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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_O-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

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