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Mitotherapy and the Possibility of Energetic Rescue in Evolving Brain Death

Ali Dabbagh [1,*], Jalal Pourahmad [2], Amir Farrokhian [3]

[1] Department of Anesthesiology, Anesthesiology Research Center, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Department of Toxicology and Pharmacology, School of Pharmacy, Shahid Beheshti University of Medical Sciences Tehran, Iran
[3] Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[*] ***Corresponding Author:*** Department of Anesthesiology, Anesthesiology Research Center, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: alidabbagh@yahoo.com

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Dear Editor,

Brain death is defined as the irreversible cessation of all brain functions; however, the biological sequence that leads to this brain death is not yet fully understood. Accumulating evidence suggests that what we currently label as “irreversibility” is largely the consequence of a profound bioenergetic collapse — an event in which mitochondrial failure, rather than structural injury alone, determines the terminal loss of neuronal viability. This perspective opens a provocative question: If the critical determinant of irreversibility is energetic failure, could mitochondrial-based interventions alter the trajectory before brain death becomes fixed (1-3)?

Ischemia is the primary trigger causing catastrophic damage to the mitochondrial architecture in the central nervous system. During acute cerebral hypoxia-ischemia, mitochondrial oxygen consumption decreases within minutes, the membrane action potential collapses, and ATP synthesis is rapidly reduced (4). Impaired electron transport accelerates the production of reactive oxygen species, causing lipid peroxidation, protein oxidation, and mitochondrial permeability transition; as cytochrome c escapes into the cytosol, the intrinsic apoptotic cascade is activated (5). But from here on, what happens is not cell death, but a rapidly expanding energetic vacuum: If mitochondria become dysfunctional, cellular ion homeostasis breaks down, membrane pumps fail, and neurons lose the ability to maintain structural and electrical integrity. In severe global ischemia, this cascade spreads across brain regions and culminates in the metabolic silence characteristic of brain death (4, 6).

Current neuroprotective strategies are inadequate because they fail to directly address this energy collapse. Hemodynamic optimization, oxygenation, osmotherapy, and hypothermia may reduce secondary damage, but none restore mitochondrial function after the respiratory chain has failed. This therapeutic gap, which is in fact a paradox between the initial injury and the treatment methods and is the source of irreversible damage, is precisely where mitotherapy may play a role as a potentially life-saving concept (7, 8).

Mitochondrial targeted therapy (mitotherapy) encompasses several approaches aimed at restoring or enhancing mitochondrial function (9). The most important of these approaches include: Direct mitochondrial transplantation, stimulation of endogenous mitochondrial biogenesis, transfer of healthy mitochondria via extracellular vesicles, mitochondrial-targeted peptides, and modulation of intercellular mitochondrial exchange. Experimental data are still preliminary and require further study; however, these initial research findings are very promising. In animal models of cerebral ischemia, exogenous mitochondria delivered to damaged brain tissue have shown rapid internalization by neurons and glia, restoration of ATP levels, increased oxygen consumption, reduced neuronal apoptosis, and improved functional outcomes (10-12).

Mitochondrial transfer from astrocytes to neurons has been observed as a natural salvage mechanism,

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suggesting an intrinsic biological background for mitochondrial replacement (13, 14). These findings lend mechanistic validity to the idea that restoration of bioenergetic capacity, even after profound injury, may revive cellular processes once thought to be permanently shut down.

Footnotes

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References

1. Olatona OA, Sterben SP, Kansakar SBS, Symes AJ, Liaudanskaya V. Mitochondria: the hidden engines of traumatic brain injury-driven neurodegeneration. *Front Cell Neurosci*. 2025;**19**:1570596. [PubMed ID: 40417416]. [PubMed Central ID: PMC12098645]. https://doi.org/10.3389/fncel.2025.1570596.
2. Clemente-Suarez VJ, Redondo-Florez L, Beltran-Velasco AI, Ramos-Campo DJ, Belinchon-deMiguel P, Martinez-Guardado I, et al. Mitochondria and Brain Disease: A Comprehensive Review of Pathological Mechanisms and Therapeutic Opportunities. *Biomedicines*. 2023;**11**(9). [PubMed ID: 37760929]. [PubMed Central ID: PMC10526226]. https://doi.org/10.3390/biomedicines11092488.
3. Valenti D, Vacca RA. Brain Mitochondrial Bioenergetics in Genetic Neurodevelopmental Disorders: Focus on Down, Rett and Fragile X Syndromes. *Int J Mol Sci*. 2023;**24**(15). [PubMed ID: 37569863]. [PubMed Central ID: PMC10419900]. https://doi.org/10.3390/ijms241512488.
4. Kaur MM, Sharma DS. Mitochondrial repair as potential pharmacological target in cerebral ischemia. *Mitochondrion*. 2022;**63**:23-31. [PubMed ID: 34999014]. https://doi.org/10.1016/j.mito.2022.01.001.
5. Doulamis IP, Tzani A, Alemany VS, Nomoto RS, Celik A, Recco DP, et al. Mitochondrial transplantation normalizes transcriptomic and proteomic shift associated with ischemia reperfusion injury in neonatal hearts donated after circulatory death. *Sci Rep*. 2024;**14**(1):31236. [PubMed ID: 39732955]. [PubMed Central ID: PMC11682362]. https://doi.org/10.1038/s41598-024-82578-2.
6. Zheng Y, Sun J, Luo Z, Li Y, Huang Y. Emerging mechanisms of lipid peroxidation in regulated cell death and its physiological implications. *Cell Death Dis*. 2024;**15**(11):859. [PubMed ID: 39587094]. [PubMed Central ID: PMC11589755]. https://doi.org/10.1038/s41419-024-07244-x.
7. Olaru G, Buga AM, Sandu RE, Padureanu V, Popa DG, Calina D. Harnessing Mitochondrial Function for Post-Stroke Rehabilitation: Unlocking Antioxidant Power. *Antioxidants (Basel)*. 2025;**14**(9). [PubMed ID: 41008986]. [PubMed Central ID: PMC12466533]. https://doi.org/10.3390/antiox14091080.
8. Choudhary RC, Shoaib M, Sohnen S, Rolston DM, Jafari D, Miyara SJ, et al. Pharmacological Approach for Neuroprotection After Cardiac Arrest-A Narrative Review of Current Therapies and Future Neuroprotective Cocktail. *Front Med (Lausanne)*. 2021;**8**:636651. [PubMed ID: 34084772]. [PubMed Central ID: PMC8167895]. https://doi.org/10.3389/fmed.2021.636651.
9. Modiri A, Hosseini L, Abolhasanpour N, Azizi H, Sadeh RN. Mitotherapy in Alzheimer's and Parkinson's diseases: A systematic review of preclinical studies. *BMC Neurol*. 2025;**25**(1):227. [PubMed ID: 40426090]. [PubMed Central ID: PMC12108016]. https://doi.org/10.1186/s12883-025-04241-1.
10. Yan C, Ma Z, Ma H, Li Q, Zhai Q, Jiang T, et al. Mitochondrial Transplantation Attenuates Brain Dysfunction in Sepsis by Driving Microglial M2 Polarization. *Mol Neurobiol*. 2020;**57**(9):3875-90. [PubMed ID: 32613465]. https://doi.org/10.1007/s12035-020-01994-3.
11. Jia X, Wang Q, Ji J, Lu W, Liu Z, Tian H, et al. Mitochondrial transplantation ameliorates hippocampal damage following status epilepticus. *Animal Model Exp Med*. 2023;**6**(1):41-50. [PubMed ID: 36734302]. [PubMed Central ID: PMC9986225]. https://doi.org/10.1002/ame2.12310.
12. Bamshad C, Habibi Roudkenar M, Abedinzade M, Yousefzadeh Chabok S, Pourmohammadi-Bejarpasi Z, Najafi-Ghalehlou N, et al. Human umbilical cord-derived mesenchymal stem cells-harvested mitochondrial transplantation improved motor function in TBI models through rescuing neuronal cells from apoptosis and alleviating astrogliosis and microglia activation. *Int Immunopharmacol*. 2023;**118**:110106. [PubMed ID: 37015158]. https://doi.org/10.1016/j.intimp.2023.110106.
13. Kubat GB, Picone P, Tuncay E, Aryan L, Girgenti A, Palumbo L, et al. Biotechnological approaches and therapeutic potential of mitochondria transfer and transplantation. *Nat Commun*. 2025;**16**(1):5709. [PubMed ID: 40593725]. [PubMed Central ID: PMC12217326]. https://doi.org/10.1038/s41467-025-61239-6.
14. Berridge MV, Schneider RT, McConnell MJ. Mitochondrial Transfer from Astrocytes to Neurons following Ischemic Insult: Guilt by Association? *Cell Metab*. 2016;**24**(3):376-8. [PubMed ID: 27626198]. https://doi.org/10.1016/j.cmet.2016.08.023.