PSYCHIATRIKI

Journal Pre-proof

Link between the mechanism of mitophagy and schizophrenia: A narrative review

Nikolaos Statharakos

DOI: https://doi.org/10.22365/jpsych.2025.008

To appear in: Psychiatriki Journal

Received date: 3 November 2024
Accepted date: 17 December 2024

Please cite this article as: Nikolaos Statharakos, Link between the mechanism of mitophagy and schizophrenia: A narrative review, Psychiatriki (2025), doi: https://doi.org/10.22365/jpsych.2025.008

REVIEW

Link between the mechanism of mitophagy and schizophrenia: A narrative review

Nikolaos Statharakos[1,2]

1. *Adult Psychiatry, Papanikolaou Hospital Thessaloniki, Greece*
2. *Psychiatric Hospital of Thessaloniki, Greece*

ARTICLE HISTORY: Received 3 November 2024 / Revised 12 December 2024 / Published Online 24 March 2025

ABSTRACT

Despite extensive research, the precise pathophysiology underlying schizophrenia remains unclear, but accumulating evidence suggests that mitochondrial dysfunction and oxidative stress play significant roles in its development. Mitophagy, the selective degradation of damaged or dysfunctional mitochondria, plays a critical role in maintaining cellular homeostasis and is increasingly recognized for its implications in various neuropsychiatric disorders, including schizophrenia. This review examines current knowledge regarding mitophagy and its association with schizophrenia. The literature was searched in PubMed-Medline and Scopus databases, and as a narrative review, the methodology focuses on the comprehensive coverage and synthesis of relevant studies. The hypothesis of the review claims that there is a link between mitophagy and schizophrenia. The terms used in the search query are “mitophagy”, “schizophrenia” with the Boolean variable “AND”. The relationship between mitophagy and schizophrenia is complex and multifaceted, involving mitochondrial dysfunction, neuroinflammation, and the integrity of oligodendrocytes and microglia. Schizophrenia is associated with dysfunctional mitophagy and elevated oxidative stress. These mechanisms may help to explain overlapping symptoms, particularly cognitive deficits. While the emerging data linking mitophagy and schizophrenia are promising, current research has limitations. Much of the evidence for mitophagy dysfunction in schizophrenia comes from animal models or postmortem studies, which may not fully capture the complexity of the disorder in humans. Moreover, mitophagy is challenging to study in vivo, particularly in the human brain, making it difficult to directly observe mitophagy processes in patients with schizophrenia. Mitophagy and its dysfunction may contribute to the pathophysiology of schizophrenia. Evidence suggests that impaired mitophagy can lead to energy dysregulation, oxidative stress, and neuroinflammation, all of which are implicated in schizophrenia. While more research is needed, the potential link between mitophagy and schizophrenia presents an interesting area for future studies and therapeutic development. Targeting mitophagy could offer new approaches for addressing cognitive and negative symptoms, providing hope for improved treatment outcomes.

KEYWORDS: Mitochondria, mitophagy, schizophrenia, mitochondrial dysfunction.

Corresponding Author: Nikolaos Statharakos, Adult Psychiatry, Papanikolaou Hospital, Papanikolaou blvd, Exochi, 57100, Thessaloniki, Greece, Email: nicstath@gmail.com

Introduction

Schizophrenia is a chronic and often debilitating psychiatric disorder characterized by a constellation of positive symptoms (such as hallucinations and delusions), negative symptoms (such as apathy and social withdrawal), and cognitive deficits.[1] Despite extensive research, the precise pathophysiology underlying schizophrenia remains unclear, but emerging evidence suggests that mitochondrial dysfunction and oxidative stress have a pivotal role in its development.[2] Given the critical energy demands of neurons, mitochondrial health is essential for maintaining cellular homeostasis and function in neural cells.[3]

Mitophagy, a selective autophagy process that removes damaged or dysfunctional mitochondria, is essential for mitochondrial quality control. By preventing the accumulation of damaged mitochondria, mitophagy plays a crucial role in preventing oxidative damage and sustaining cellular health. Recent research has highlighted disruptions in mitophagy as a contributing factor to neurodegenerative diseases[4] and, increasingly, neuropsychiatric disorders like schizophrenia.[5] Understanding how mitophagy functions in neurons—and how its dysregulation could contribute to the symptoms of schizophrenia—could provide new insights into disease mechanisms and potential therapeutic strategies.

This review examines current knowledge regarding mitophagy and its association with schizophrenia. It starts by examining the process of mitophagy, followed by mitochondrial abnormalities and emerging evidence that links disruptions in mitophagy with schizophrenia's pathophysiology. Finally, it discusses potential therapeutic implications and areas for further research.

Overview of mitophagy

Mitophagy is a specialized form of autophagy responsible for the targeted removal of damaged or dysfunctional mitochondria, thereby preserving cellular health.[5] Through the process of mitophagy, cells can maintain mitochondrial quality control, preventing the accumulation of malfunctioning mitochondria that might otherwise generate excessive reactive oxygen species (ROS) or trigger apoptotic pathways. [6] This mechanism is particularly critical in neurons, where stable mitochondrial function is essential to meet the high energy demands necessary for synaptic transmission and plasticity.[4]

Several well-characterized pathways regulate mitophagy, each playing a unique role in recognizing and targeting damaged mitochondria for degradation.

- **PINK1/Parkin Pathway**: PINK1 (PTEN-induced kinase 1) accumulates on the outer mitochondrial membrane once the mitochondrion becomes depolarized and loses membrane potential. Due to this accumulation, Parkin, an E3 ubiquitin ligase, is drawn to the membrane. Parkin then ubiquitinates other mitochondrial proteins, indicating the organelle for autophagic degradation. This pathway has been extensively studied in the context of neurodegenerative diseases like Parkinson's but is also pertinent in schizophrenia.[4,6]
- **BNIP3/NIX Pathway**: BNIP3 and NIX are two proteins that facilitate mitophagy in response to hypoxia. These proteins assist in the engulfment of mitochondria within autophagosomes via interaction with the autophagic protein LC3. This pathway may also be relevant in the brain, where hypoxic conditions are related to various neuropsychiatric conditions.[4,5]
- **FUNDC1 Pathway**: FUNDC1 is a mitophagic receptor, essential for hypoxia-induced mitophagy. It binds directly to LC3, indicating mitochondria for degradation. Although less studied in schizophrenia, emerging evidence suggests it may contribute to cellular responses to environmental stressors implicated in schizophrenia.[4]

Neurons are uniquely dependent on effective mitophagy. They have a highly polarized

structure and are less capable of regenerating compared to other cell types, making mitochondrial quality control essential. Neuronal health relies on continuous mitophagy to meet synaptic demands, support neuroplasticity, and maintain overall brain function. [7] Impairments in mitophagy have been linked to neurodegenerative diseases, but recent findings suggest that similar dysfunctions might also contribute to the pathogenesis of psychiatric conditions, including schizophrenia.[5]

Mitochondrial dysfunction in schizophrenia

Research has increasingly highlighted mitochondrial dysfunction as a factor in the pathophysiology of schizophrenia.[5] Mitochondria are essential for ATP production, calcium buffering, and regulation of oxidative stress, all of which are critical for neuronal function.[4] Studies have documented various mitochondrial abnormalities in patients with schizophrenia, including structural changes, impaired bioenergetics, and increased oxidative stress.

Postmortem studies have identified structural changes in the mitochondria of individuals with schizophrenia, such as alterations in mitochondrial density and morphology.[8] These changes are thought to compromise cellular energy production, leading to an energy deficit in neurons. Functional imaging studies have also shown reductions in glucose metabolism and ATP levels in specific brain regions associated with schizophrenia symptoms, including the prefrontal cortex and hippocampus.[9]

Mitochondrial dysfunction is a well-documented feature in schizophrenia, with evidence suggesting that impaired mitophagy may contribute to the observed mitochondrial abnormalities.[11] Oligodendrocytes and microglia exhibit mitochondrial dysfunction in schizophrenia, positing that increased mitophagy could be a response to mitochondrial damage, thereby influencing white matter pathology.[10] This aligns with findings by Li et al., who note that mitochondrial dysfunction is prevalent in various psychiatric disorders, including schizophrenia, indicating a broader pattern of mitochondrial involvement in mental health conditions. They argue that increased mitophagy could be a compensatory response to mitochondrial damage, which is prevalent in the prefrontal gray matter of individuals with schizophrenia.[11]

One prominent hypothesis is that the dysregulation of mitochondrial function leads to increased oxidative stress. Neurons are particularly vulnerable to oxidative damage due to their high metabolic demand, and accumulating evidence suggests that schizophrenia is associated with elevated levels of oxidative stress markers.[12] The energy deficits and oxidative stress resulting from mitochondrial dysfunction are thought to contribute to several aspects of schizophrenia pathology. For instance, impaired ATP production may impact neurotransmitter regulation, leading to disruptions in dopamine and glutamate signaling—both implicated in schizophrenia. Additionally, energy dysregulation and increased ROS can lead to cellular damage, potentially contributing to the progressive cognitive decline and negative symptoms observed in schizophrenia.[13,14]

Potential mechanisms linking mitophagy to schizophrenia

Several specific mechanisms could explain the connection between impaired mitophagy and schizophrenia. Since neurons rely heavily on mitochondrial energy production, impaired mitophagy can lead to an accumulation of dysfunctional mitochondria that fail to meet neuronal energy demands.[4] This energy deficit can impair neurotransmission and synaptic plasticity, processes essential for cognition and behavior. The resulting deficits could contribute to both the cognitive and negative symptoms of schizophrenia, such as poor working memory and diminished motivation.[12]

Mitochondria are both sources and targets of oxidative stress. When mitophagy is impaired, damaged mitochondria accumulate, leading to increased production of ROS.[14] Excessive ROS can damage cellular components, including lipids, proteins, and DNA,

potentially contributing to the cellular pathology observed in schizophrenia. Increased oxidative stress may also disrupt neuronal signaling and plasticity, further exacerbating cognitive symptoms.[13]

Mitophagy plays a key role in maintaining synaptic health. Mitochondria are essential for supplying ATP at synaptic sites and buffering calcium during neurotransmitter release. When mitophagy is impaired, dysfunctional mitochondria can lead to synaptic deficits, as they fail to support the energy-intensive processes required for proper synaptic transmission and plasticity. These disruptions may underlie some of the cognitive impairments' characteristic of schizophrenia.[5]

Recent studies suggest that impaired mitophagy may contribute to neuroinflammation, which is increasingly recognized as a factor in schizophrenia. When dysfunctional mitochondria accumulate, they can release pro-inflammatory signals, such as mitochondrial DNA and ROS, that activate the immune system. Chronic neuroinflammation can alter brain function and has been linked to various neuropsychiatric disorders, including schizophrenia.[13]

Moreover, the role of antipsychotic medications in influencing mitophagy has garnered attention. Olanzapine can induce mitochondrial damage and impair mitophagy, thereby influencing mitochondrial dynamics and autophagic processes, potentially leading to accelerated aging effects in neuronal cells.[15,16] This finding underscores the importance of considering how pharmacological interventions may impact mitochondrial function and mitophagy in patients with schizophrenia. Additionally, natural compounds that enhance mitophagy could serve as adjunctive therapies to improve mitochondrial function and reduce oxidative stress in patients with schizophrenia.[17]

Mitophagy and neurodegeneration: A mechanistic link to schizophrenia?

Both neurodegenerative disorders and schizophrenia are associated with dysfunctional mitophagy and elevated oxidative stress. These shared mechanisms may help to explain overlapping symptoms, particularly cognitive deficits.[5] Moreover, mitophagy dysfunction in neurons can result in an accumulation of damaged mitochondria, leading to impaired neuronal function and increased susceptibility to apoptosis.[4] Understanding these shared mechanisms may provide novel treatment potentials for schizophrenia, through therapies aimed at enhancing mitophagy.

Research on neurodegenerative diseases has established that mitophagy is crucial for neuronal survival and function.[4] Dysregulation of mitophagy is known to contribute to diseases like Parkinson's and Alzheimer's, and emerging studies suggest that similar mechanisms may be at play in schizophrenia.[5] Although schizophrenia is traditionally classified as a psychiatric disorder rather than a neurodegenerative one, the two categories share common pathological features, including mitochondrial dysfunction and cellular stress responses.[18]

Animal studies have shown that genetic mutations affecting mitophagy (e.g., PINK1, Parkin) can lead to neuropsychiatric symptoms, including behaviors akin to those seen in schizophrenia, such as social withdrawal and cognitive impairment.[11] Additionally, postmortem analyses of brain tissue from individuals with schizophrenia have identified alterations in mitophagy-related proteins.[8] This suggests that impairments in mitophagy may play a role in the neuronal abnormalities seen in schizophrenia.

The mechanisms underlying mitophagy are complex and involve various signaling pathways. Wang et al. provide a comprehensive overview of the mechanisms of mitophagy, emphasizing the importance of ubiquitin-dependent and receptor-mediated signals in the degradation of damaged mitochondria.[6] This is particularly relevant in the context of schizophrenia, where disrupted signaling pathways—such as those involving PINK1/Parkin, BNIP3/NIX, and FUNDC1—may impair mitophagy, leading to the accumulation of damaged mitochondria. This impairment exacerbates mitochondrial dysfunction, contributing to

neuroinflammation and oxidative stress, which are key features of schizophrenia pathology.

The role of mitochondrial dysfunction in psychiatric disorders, including schizophrenia, has been well documented. Impaired mitophagy in neurons and glial cells during aging and age-related disorders can lead to neurodegeneration, which may also be relevant to the pathophysiology of schizophrenia. The accumulation of dysfunctional mitochondria due to defective mitophagy can exacerbate neuroinflammatory processes, further complicating the clinical picture of schizophrenia.[13] Neuroinflammation is another critical factor that intersects with mitophagy in the context of schizophrenia. The activation of microglia, the brain's resident immune cells, can lead to the release of pro-inflammatory cytokines, which may further exacerbate mitochondrial dysfunction and impair mitophagy.[13] Mitochondrial dysfunction can lead to increased oxidative stress and neuroinflammation, both of which are implicated in the pathophysiology of schizophrenia.[14,19] This interplay suggests that impaired mitophagy may not only contribute to mitochondrial dysfunction but also exacerbate inflammatory processes that are characteristic of schizophrenia.

Recent research has identified specific genes associated with mitophagy that may be implicated in schizophrenia. The expression of genes associated with mitophagy, such as those identified by bioinformatic analyses, has been shown to correlate with schizophrenia, indicating a potential genetic basis for impaired mitochondrial quality control in this disorder.[20] The gene BNIP3L, which is involved in mitophagy, has been highlighted in studies linking genetic risk factors to schizophrenia.[20] This gene's expression is altered in the context of neurodevelopmental disorders, suggesting that disruptions in mitophagy could be a contributing factor to the etiology of schizophrenia. Additionally, MEF2C, a gene enriched in neuronal populations, is involved in regulating mitochondrial function and its potential implications for cognitive function in schizophrenia.[21]

The mechanisms underlying mitophagy are multifaceted and involve various signaling pathways. The involvement of the PINK1/Parkin pathway in mitophagy regulation has been implicated in both neurodegenerative diseases and schizophrenia.[6] Wang et al. provide insights into how mitochondrial biogenesis and mitophagy are regulated through various signaling pathways, including the PGC-1 family proteins and AMPK.[6] These pathways are crucial for maintaining mitochondrial health and could be targeted for therapeutic interventions in schizophrenia, as suggested by the potential of pharmacological agents to modulate these pathways.[3] BNIP3L/NIX, a mitophagy receptor, plays a significant role in recognizing damaged mitochondria and facilitating their degradation.[22] This process is crucial in neurons, which are particularly vulnerable to mitochondrial damage due to their high energy demands. Impaired mitophagy has been linked to the accumulation of dysfunctional mitochondria, leading to increased oxidative stress and neuronal death, which are observed in neurodegenerative diseases and may also be relevant to schizophrenia.[5]

Furthermore, the role of specific proteins, such as Disrupted-in-Schizophrenia-1 (DISC1), has been explored in the context of mitophagy and synaptic DISC1 acts as a mitophagy receptor, and its dysregulation may contribute to synaptic dysfunction in schizophrenia. This highlights the potential for targeting mitophagy pathways as a therapeutic strategy to restore synaptic integrity and improve clinical outcomes in schizophrenia.[23]

Current evidence and limitations in mitophagy research in schizophrenia

While the emerging data linking mitophagy and schizophrenia are promising, current research has limitations. Much of the evidence for mitophagy dysfunction in schizophrenia comes from animal models or postmortem studies[8,11], which may not fully capture the complexity of the disorder in humans. Moreover, mitophagy is challenging to study in vivo, particularly in the human brain, making it difficult to directly observe mitophagy processes in patients with schizophrenia.

Further research is needed to clarify the role of mitophagy in schizophrenia, including studies using advanced imaging techniques and biomarkers to measure mitophagy activity in vivo. Additionally, research into genetic and environmental factors that influence mitophagy in schizophrenia may shed light on individual differences in disease presentation and treatment response.

Potential therapeutic implications

Understanding the role of mitophagy in schizophrenia opens the door to potential therapeutic interventions aimed at restoring mitochondrial function. Research is exploring pharmacological agents that can enhance mitophagy, including compounds that activate the PINK1/Parkin pathway.[24] Although many of these agents are still in experimental stages, they may offer a new approach for treating schizophrenia by targeting mitochondrial function and cellular resilience. Lifestyle factors, such as regular physical exercise and caloric restriction, have been shown to stimulate mitophagy and improve mitochondrial function.[25,26] Additionally, certain nutrients (e.g., NAD+ boosters) may support mitochondrial health and could be considered as adjunctive therapies for schizophrenia.[27]

Conclusion

Mitophagy is a critical process for maintaining neuronal health, and its dysfunction may contribute to the pathophysiology of schizophrenia. Evidence suggests that impaired mitophagy can lead to energy dysregulation, oxidative stress, and neuroinflammation, all of which are implicated in schizophrenia. While more research is needed to elucidate the precise mechanisms and the potential link between mitophagy and schizophrenia, it represents a promising field for future studies and therapeutic development. Targeting mitophagy could offer new approaches and explore potential therapeutic strategies for addressing cognitive and negative symptoms, providing hope for improved treatment outcomes.

References

1. American Psychiatric Association, Dsm-5-Tr Classification, Amer Psychiatric 2022
2. Andreazza AC, Shao L, Wang JF, Young LT. Mitochondrial complex I activity and oxidative damage to mitochondrial proteins in the prefrontal cortex of patients with bipolar disorder. *Arch Gen Psychiatry* 2010, 67:360-368, doi:10.1001/archgenpsychiatry.2010.22
3. Clemente-Suárez VJ, Redondo-Flórez L, Beltrán-Velasco AI, Ramos-Campo DJ, Belinchón-deMiguel P, Martinez-Guardado I, et al. Mitochondria and Brain Disease: A Comprehensive Review of Pathological Mechanisms and Therapeutic Opportunities. *Biomedicines* 2023, 11:2488, doi:10.3390/biomedicines11092488
4. Cen X, Zhang M, Zhou M, Ye L, Xia H, Mitophagy regulates neurodegenerative diseases. *Cells* 2021, 10:1876, doi:10.3390/cells10081876
5. Doblado L, Lueck C, Rey C, Samhan-Arias AK, Prieto I, Stacchiotti A, et al. Mitophagy in human diseases. *Int J Mol Sci* 2021, 22:3903, doi:10.3390/ijms22083903
6. Wang X, Zhang Y, Dong L, Li H, Xu W, Zhao Y, et al. Mechanisms and roles of mitophagy in neurodegenerative diseases. *CNS Neurosci Ther* 2019, 25:859-875, doi:10.1111/cns.13140
7. Evans CS, Holzbaur ELF. Quality control in neurons: mitophagy and other selective autophagy mechanisms. *J Mol Biol* 2020, 432:240-260, doi:10.1016/j.jmb.2019.06.031
8. Roberts RC. Postmortem studies on mitochondria in schizophrenia. *Schizophr Res* 2017, 187:17-25, doi:10.1016/j.schres.2017.01.056
9. Howes OD, Cummings C, Chapman GE, Shatalina E. Neuroimaging in schizophrenia: an overview of findings and their implications for synaptic changes. *Neuropsychopharmacology* 2023, 48:151-167, doi:10.1038/s41386-022-01426-x

10. Uranova NA, Vikhreva OV, Rakhmanova VI, Orlovskaya DD. Dystrophy of oligodendrocytes and adjacent microglia in prefrontal gray matter in schizophrenia. *Front Psychiatry* 2020, 11, doi:10.3389/fpsyt.2020.00204
11. Li J, Yu W, Ding X, Liu Z, Liu X, Zhang Y, et al. Wuling powder prevents the depression-like behavior in learned helplessness mice model through improving the TSPO mediated-mitophagy. *J Ethnopharmacol* 2016, 186:181-188, doi:10.1016/j.jep.2016.03.065
12. Ermakov EA, Dmitrieva EM, Parshukova DA, Kazantseva DV, Vasilieva AR, Smirnova LP. Oxidative stress-related mechanisms in schizophrenia pathogenesis and new treatment perspectives. *Oxid Med Cell Longev* 2021, 2021:8881770, doi:10.1155/2021/8881770
13. Sukhorukov V, Kosyuga Y, Saveliev E, Ivanov S, Mitin A, Rukavitsyna D, et al. Impaired mitophagy in neurons and glial cells during aging and age-related disorders. *Int J Mol Sci* 2021, 22:10251, doi:10.3390/ijms221910251
14. Picca A, Calvani R, Coelho-Junior HJ, Landi F, Bernabei R, Marzetti E. Mitochondrial Dysfunction, Oxidative Stress, and Neuroinflammation: Intertwined Roads to Neurodegeneration. *Antioxidants (Basel)* 2020, 9:647, doi:10.3390/antiox9080647
15. Chen B, Liu X, Liu Y, Zhang T, Huang Z, Li M, et al. Impaired mitophagosome–lysosome fusion mediates olanzapine-induced aging. *Aging Cell* 2023, doi:10.1111/acel.14003
16. Boz Z, Akbulut KG, Karasu C. N-acetylcysteine prevents olanzapine-induced oxidative stress in mHypoA-59 hypothalamic neurons. *Sci Rep* 2020, 10:19185, doi:10.1038/s41598-020-75356-3
17. Stacchiotti A, Corsetti G. Natural compounds and autophagy: allies against neurodegeneration. *Front Cell Dev Biol* 2020, 8:555409, doi:10.3389/fcell.2020.555409
18. Stone WS, Phillips MR, Yang LH, Kegeles LS, Susser ES, Lieberman JA. Neurodegenerative model of schizophrenia: growing evidence to support a revisit. *Schizophr Res* 2022, 243:154-162, doi:10.1016/j.schres.2022.02.004
19. Morris G, Berk M. The many roads to mitochondrial dysfunction in neuroimmune and neuropsychiatric disorders. *BMC Med* 2015, 13:31, doi:10.1186/s12916-015-0310-y
20. Zhu X, Wang CL, Yu JF, Weng J, Han B, Liu Y, et al. Identification of immune-related biomarkers in peripheral blood of schizophrenia using bioinformatic methods and machine learning algorithms. *Front Cell Neurosci* 2023, 17:1256184, doi:10.3389/fncel.2023.1256184
21. Ali M, Hashemi V, Rostami S, et al. Direct targets of MEF2C are enriched for genes associated with schizophrenia and cognitive function and are involved in neurogenesis and mitochondrial function. *BioRxiv* 2023; doi:10.1101/2023.12.07.570529
22. Li Y, Zheng W, Lu Y, Zheng Y, Pan L, Wu X, et al. BNIP3L/NIX-mediated mitophagy: molecular mechanisms and implications for human disease. *Cell Death Dis* 2021, 13:14, doi:10.1038/s41419-021-04469-y
23. Wang ZT, Lu MH, Zhang Y, Ji WL, Lei L, Wang W, et al. Disrupted-in-schizophrenia-1 protects synaptic plasticity in a transgenic mouse model of Alzheimer's disease as a mitophagy receptor. *Aging Cell* 2019, 18:e12860, doi:10.1111/acel.12860
24. Asthana J, Shravage BV. Exploring therapeutic potential of mitophagy modulators using Drosophila models of Parkinson's disease. *Front Aging Neurosci* 2022, 14:986849, doi:10.3389/fnagi.2022.986849
25. Papageorgiou C, Stamatopoulos V, Samaras C, Statharakos N, Papageorgiou E, Dzhambazova E. Hormesis-like benefits of physical exercises due to increased reactive oxygen species. *Phys Educ Sport Kinesitherapy Res J* 2016, 76-84
26. Kyriazis ID, Vassi E, Alvanou M, Angelakis C, Skaperda Z, Tekos F, et al.. The impact of diet upon mitochondrial physiology. *Int J Mol Med* 2022, 50:135, doi:10.3892/ijmm.2022.5191

27. Xu X, Shao G, Zhang X, Hu Y, Huang J, Su Y, et al. The efficacy of nutritional supplements for the adjunctive treatment of schizophrenia in adults: A systematic review and network meta-analysis. *Psychiatry Res* 2022, 311:114500, doi:10.1016/j.psychres.2022.114500

Table 1. Summary of key findings on mitochondrial and mitophagy abnormalities in schizophrenia

Mitochondrial dysfunction	Structural changes in mitochondria in schizophrenia.	Postmortem studies show altered mitochondrial density and morphology, particularly in the prefrontal cortex.	Roberts (2017), Uranova et al. (2020)
	Impaired energy production and ATP synthesis.	Glucose metabolism and ATP levels are reduced in brain regions associated with cognitive functions (e.g., prefrontal cortex, hippocampus).	Howes et al. (2023), Li et al. (2021)
	Elevated oxidative stress levels.	Increased markers of oxidative damage, including lipid peroxidation and protein oxidation, observed in patients with schizophrenia.	Ermakov et al. (2021), Stone et al. (2022)
Mitophagy pathways	Dysfunctional PINK1/Parkin pathway.	Damaged mitochondria fail to recruit PINK1/Parkin for ubiquitination and degradation, leading to accumulation of defective mitochondria.	Wang et al. (2019), Cen et al. (2021)
	BNIP3/NIX pathway alterations under hypoxic conditions.	BNIP3/NIX proteins are involved in mitochondrial degradation during stress, with potential dysfunctions contributing to neuronal pathology in schizophrenia.	Cen et al. (2021), Doblado et al. (2021)
	FUNDC1 receptor-mediated mitophagy under stress.	Impairment of FUNDC1 may reduce mitophagy in neurons, exacerbating stress responses in schizophrenia.	Cen et al. (2021)
Neuroinflammation	Dysfunctional mitophagy	Damaged mitochondria release pro-inflammatory	Sukhorukov et al. (2021),

	exacerbates neuroinflammation.	signals such as mitochondrial DNA and ROS, triggering immune responses.	Picca et al. (2020)
	Microglial activation contributes to inflammation.	Persistent microglial activation releases pro-inflammatory cytokines, worsening neuronal damage and cognitive symptoms.	Uranova et al. (2020), Ermakov et al. (2021)
	Excess ROS production leads to neuronal damage.	Dysfunctional mitochondria generate excessive ROS, causing damage to proteins, lipids, and DNA, and impairing synaptic plasticity.	Morris & Berk (2015), Boz et al. (2020)
	Energy deficits contribute to oxidative stress.	Reduced mitochondrial bioenergetics impair neurotransmitter systems (e.g., glutamate and dopamine), crucial in schizophrenia pathology.	Stone et al. (2022), Li et al. (2021)
Cognitive deficits	Linked to mitochondrial and oxidative dysfunctions.	Impaired ATP synthesis and excessive oxidative stress disrupt neurotransmission and synaptic plasticity, leading to cognitive impairments in schizophrenia.	Li et al. (2021), Howes et al. (2023)
Therapeutic implications	Pharmacological agents targeting mitophagy pathways.	Activators of PINK1/Parkin pathways and antioxidants show potential in restoring mitochondrial health and reducing oxidative damage.	Wang et al. (2019), Stacchiotti et al. (2020)
	Lifestyle interventions enhance mitophagy.	Physical exercise and caloric restriction promote mitophagy, reduce oxidative stress, and improve mitochondrial function.	Kyriazis et al. (2022), Xu et al. (2022)
	Adjunctive therapies include natural compounds.	Nutritional supplements (e.g., NAD+ boosters) and antioxidants may serve as supportive therapies for cognitive and negative symptoms.	Boz et al. (2020), Stacchiotti et al. (2020)

PSYCHIATRIKI

ΑΝΑΣΚΟΠΗΣΗ

Σύνδεση του μηχανισμού της μιτοφαγίας με τη σχιζοφρένεια: Αφηγηματική ανασκόπηση

Νικόλαος Σταθαράκος[1,2]

1. *Ψυχιατρική Ενηλίκων, ΓΝΘ «Γ.Παπανικολάου», Θεσσαλονίκη, Ελλάδα*
2. *Ψυχιατρικό Νοσοκομείο Θεσσαλονίκης,Θεσσαλονίκη, Ελλάδα*

ΙΣΤΟΡΙΚΟ ΑΡΘΡΟΥ: Παραλήφθηκε 3 Νοεμβρίου 2024/ Αναθεωρήθηκε 12 Δεκεμβρίου 2024 / Δημοσιεύθηκε Διαδικτυακά 24 Μαρτίου 2025

----------**ΠΕΡΙΛΗΨΗ**----------

Παρά την εκτεταμένη έρευνα, η ακριβής παθοφυσιολογία της σχιζοφρένειας παραμένει ασαφής, αλλά αυξανόμενα στοιχεία υποδεικνύουν ότι η δυσλειτουργία των μιτοχονδρίων και το οξειδωτικό στρες παίζουν σημαντικό ρόλο στην ανάπτυξή της. Η μιτοφαγία, η επιλεκτική αποδόμηση των κατεστραμμένων ή δυσλειτουργικών μιτοχονδρίων, διαδραματίζει κρίσιμο ρόλο στη διατήρηση της κυτταρικής ομοιόστασης και αναγνωρίζεται όλο και περισσότερο για τις επιπτώσεις της σε διάφορες νευροψυχιατρικές διαταραχές, συμπεριλαμβανομένης της σχιζοφρένειας. Αυτή η ανασκόπηση εξετάζει τις τρέχουσες γνώσεις σχετικά με τη μιτοφαγία και τη σχέση της με τη σχιζοφρένεια. Η αναζήτηση της βιβλιογραφίας πραγματοποιήθηκε στις βάσεις δεδομένων PubMed-Medline και Scopus, και ως αφηγηματική ανασκόπηση, η μεθοδολογία επικεντρώνεται στην ολοκληρωμένη κάλυψη και σύνθεση σχετικών μελετών. Η υπόθεση της ανασκόπησης υποστηρίζει ότι υπάρχει σύνδεση μεταξύ της μιτοφαγίας και της σχιζοφρένειας. Οι όροι που χρησιμοποιήθηκαν στην αναζήτηση ήταν “mitophagy”, “schizophrenia” με τον Boolean όρο “AND”. Η σχέση μεταξύ της μιτοφαγίας και της σχιζοφρένειας είναι σύνθετη και πολυδιάστατη, περιλαμβάνοντας τη δυσλειτουργία των μιτοχονδρίων, τη νευροφλεγμονή, και την ακεραιότητα των ολιγοδενδροκυττάρων και των μικρογλοιακών κυττάρων. Η σχιζοφρένεια συνδέονται με δυσλειτουργική μιτοφαγία και αυξημένο οξειδωτικό στρες. Αυτοί οι εμπλεκόμενοι μηχανισμοί μπορούν να συμβάλουν στην εξήγηση των κοινών συμπτωμάτων, ιδιαίτερα των γνωστικών ελλειμμάτων. Παρά τα υποσχόμενα δεδομένα που συνδέουν τη μιτοφαγία με τη σχιζοφρένεια, η τρέχουσα έρευνα έχει περιορισμούς. Μεγάλο μέρος των στοιχείων για τη δυσλειτουργία της μιτοφαγίας στη σχιζοφρένεια προέρχεται από ζωικά μοντέλα ή μεταθανάτιες μελέτες, τα οποία μπορεί να μην αποδίδουν πλήρως την πολυπλοκότητα της διαταραχής στους ανθρώπους. Επιπλέον, η μελέτη της μιτοφαγίας in vivo είναι ιδιαίτερα δύσκολη, ειδικά στον ανθρώπινο εγκέφαλο, καθιστώντας δύσκολη την άμεση παρατήρηση των διαδικασιών μιτοφαγίας σε ασθενείς με σχιζοφρένεια. Η μιτοφαγία και η δυσλειτουργία της ενδέχεται να συμβάλλουν στην παθοφυσιολογία της σχιζοφρένειας. Τα στοιχεία δείχνουν ότι η εξασθενημένη μιτοφαγία μπορεί να οδηγήσει σε δυσλειτουργία ενεργειακής ρύθμισης, οξειδωτικό στρες και νευροφλεγμονή, όλα εκ των οποίων εμπλέκονται στη σχιζοφρένεια. Παρά το γεγονός ότι χρειάζεται περισσότερη έρευνα, η πιθανή σύνδεση μεταξύ της μιτοφαγίας και της σχιζοφρένειας αποτελεί ένα ιδιαίτερα ενδιαφέρον πεδίο για μελλοντικές μελέτες και ανάπτυξη θεραπευτικών μεθόδων. Η στόχευση της μιτοφαγίας θα μπορούσε να προσφέρει νέες προσεγγίσεις για την αντιμετώπιση των γνωστικών και αρνητικών συμπτωμάτων, δίνοντας ελπίδα για καλύτερα θεραπευτικά αποτελέσματα.

ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ: Μιτοχόνδρια, μιτοφαγία, σχιζοφρένια, δυσλειτουργία μιτοχονδρίων.

Επιμελητής συγγραφέας: Νικόλαος Σταθαράκος, Ψυχιατρική Ενηλίκων, ΓΝΘ «Γ.Παπανικολάου», Λεωφόρος Παπανικολάου, Εξοχή 57100, Θεσσαλονίκη, Ελλάδα, Email: nicstath@gmail.com