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Mitochondrial dysfunction in schizophrenia and psychotic disorders: Implications for antipsychotic drug mechanisms

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Summary

Background: *Schizophrenia (SCH) is a severe neuropsychiatric disorder associated with complex neurobiological alterations and suboptimal therapeutic outcomes. Increasing evidence indicates that mitochondrial dysfunction may contribute to SCH pathophysiology through impaired energy metabolism, oxidative stress, altered calcium homeostasis, and dysregulation of neuronal function. This review aims to summarize current knowledge regarding mitochondrial abnormalities in schizophrenia and to explore their potential involvement in the mechanisms of action of antipsychotic drugs.*

Subjects and Methods: *A comprehensive review of the current literature was performed, focusing on human studies, cellular and animal models investigating mitochondrial alterations in schizophrenia, as well as studies evaluating the effects of antipsychotic medications on mitochondrial structure and function.*

Results: *Available evidence demonstrates structural, molecular, and functional mitochondrial abnormalities in schizophrenia, including alterations in mitochondrial density, respiratory chain activity, oxidative phosphorylation, ATP production, and redox regulation. Antipsychotic drugs influence mitochondrial pathways in a complex and drug-specific manner. Some antipsychotics may impair mitochondrial respiration and increase oxidative stress, whereas others may exert compensatory or protective effects. Mitochondrial alterations may also contribute to cognitive impairment, negative symptoms, treatment response variability, and metabolic adverse effects associated with antipsychotic therapy.*

Conclusions: *Mitochondrial dysfunction represents an important component of schizophrenia pathophysiology and a potential therapeutic target. The interaction between mitochondrial pathways and antipsychotic drug effects highlights mitochondria as a possible pharmacodynamic interface for personalized treatment strategies. Further in vivo studies and biomarker-based approaches are required to clarify drug–mitochondria interactions and improve therapeutic outcomes in schizophrenia.*

Keywords: *Schizophrenia; mitochondrial dysfunction; antipsychotic drugs; oxidative stress; energy metabolism*

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INTRODUCTION

Schizophrenia (SCH) is a chronic and severe mental disorder characterized by both structural and functional alterations in the brain. Despite significant advances in pharmacological treatment, it remains a major therapeutic challenge, as clinical outcomes are often suboptimal. Multiple studies have pointed to abnormalities in mitochondrial (MTH) function and dysregulation of energy homeostasis in the pathophysiology of SCH (Ciobica et al., 2011; Loga-Zec et al.,2023).

Structural abnormalities, including alterations in mitochondrial shape, density, and number, have been consistently reported in postmortem brain studies. Early investigations demonstrated a significant reduction in mitochondrial cross-sectional profiles in the caudate and putamen, as well as decreased mitochondrial density in oligodendrocytes. Furthermore, patients with SCH have

List of abbreviations:

SCH	schizophrenia
MTH	qmitochondria
APs	antipsychotic drugs
ETC	electron transport chain
OXPHOS	oxidative phosphorylation
ATP	adenosine triphosphate
ROS	reactive oxygen species

been shown to exhibit 26–30% fewer mitochondria per synapse in the striatum compared to healthy controls (Xu & Yang, 2022).

Additional studies have identified membrane pathology and reduced synaptic and mitochondrial density in the anterior cingulate cortex, with changes localized to specific cortical layers (Roberts et al., 2022).In addition to structural alterations, mitochondrial functional impairments have also been documented. Reduced activity of cytochrome c oxidase within the mitochondrial electron transport chain (ETC) has been observed in multiple brain regions, including the frontal cortex, caudate nucleus, and temporal cortex. Notably, a marked reduction in Complex IV activity has been reported in the frontal and temporal cortices (Park et al., 2021). These findings are consistent with broader evidence indicating disrupted energy metabolism in SCH (Yuksel et al., 2021).Mitochondrial dysfunction in SCH encompasses a wide spectrum of structural, genetic, molecular, and biochemical abnormalities, ultimately leading to altered oxygen consumption and impaired ATP synthesis (Padurariu et al., 2013; Ene et al., 2023). However, interpretation of these findings remains challenging, as mitochondrial alterations may be influenced by the effects of antipsychotic drugs (APs) and other commonly prescribed medications (Chan et al., 2020).

Despite increasing evidence, uncertainties remain regarding whether mitochondrial dysfunction represents a primary feature of SCH or a secondary effect related to treatment. Therefore, the aim of this review is to summarize the current evidence on mitochondrial involvement in schizophrenia and to explore its potential role in disease pathophysiology and therapeutic strategies.

THE ROLE OF MITOCHONDRIA IN SCHIZOPHRENIA

Developing new and most effective therapeutic strategies requires a deep understanding of pathogenetic mechanisms of SCH (Ni & Chung 2020; Ni et al., 2022). It is a highly phenotypically diverse neurodevelopment disease as a result of interaction between SCH risk loci and environmental risk factors (Guloksuz et al., 2019). Studies using postmortal tissue samples from SCH patients, showed a great involvement of multiple circuit components with various cell types during SCH pathogenesis A common characteristic of SCH abnormality is its compromised metabolism/mitochondrial function (Scaini et al.2018) Various important functions of mitochondrial such as: synaptic transmission, Ca^{2+} signaling generation of action potentials) and ion homeostasis coincide with various aspects of neuronal dysfunctioning in SCH. Metabolic/mitochondrial abnormalities observed in various SCH research areas such as postmortem studies, imaging studies, genetic studies, induced pluripotent stem cell (iPSC) studies, animal model studies suggest that mitochondrial dysfunction is a potential therapeutic target in the treatment of SCH (Sanders et al.,2017; Fernandez et al., 2019). One of the core pillars of emerging induction of antipsychotic drugs as a novel treatment strategy that target and mitigate mitochondrial dysfunction is of overt importance for optimizing treatment of SCH (Panizzutti, 2023). Administration of antipsychotic drugs affects mitochondrial functions – oxidative phosphorylation (OXPHOS) especially. Haloperidol, chlorpromazine, fluphenazine as well as risperidone and clozapine inhibit the activity of complex I (dose-dependent inhibition) in the brains of individuals with schizophrenia. Haloperidol and fluphenazine induce broad inhibition of Complex I, while this effect is not observed with clozapine (Cikánková et al., 2019).

Previous studies investigated olanzapine's effects on mitochondrial function. it was shown that after receiving a single injection of olanzapine, male Wistar rats exhibited increased activity of complex I (CI), complex II (CII), and citrate synthase (CS) in the prefrontal cortex, striatum, and hippocampus. However, there was a decrease in the activity of complex IV (CIV). Chronic olanzapine treatment increased CII-CIII activity in the striatum but decreased CII activity in the cerebellum and CIV activity in the hippocampus (Emmerzaal et al., 2021). These findings not correlated with the extrapyramidal side-effects of antipsychotic drugs; thus, complex I inhibition may be associated with the side-effects of these drugs. The activity of complex II was found to be reduced or unchanged after the chronic antipsychotic treatment (Cikánková et al., 2019). Studies have observed that despite the presence of abnormal complex I activity in patients with schizophrenia, antipsychotic drugs have a comparable impact on complex I-driven respiration in lymphocyte-derived cell lines of both patients and healthy individuals (Bar-Yosef et al., 2020).

This review summarizes findings on relevant mitochondrial mechanisms underlying SCH, and the potential impact of psychoactive drugs including primarily APs. The summarized data suggest that APs impair mitochondria function by decreasing Complex I activity and ATP production and dissipation of the mitochondria membrane potential. At the same time, in the brains of patients with SCH, APs treatment may normalize gene

expression modules enriched in mitochondrial genes that are decreased in SCH. This indicates that APs may have both positive and negative effects on mitochondria (Chan et al., 2020). There has been increasing interest in the role of mitochondrial dysfunction in the pathophysiology of schizophrenia. Mitochondrial dysfunction is increasingly recognized as a key component in the pathophysiology of schizophrenia (SCH), with consistent evidence of both structural and functional alterations.

Despite limitations, accumulating evidence supports a link between mitochondrial dysfunction, neurotransmitter dysregulation, and clinical manifestations of SCH, particularly cognitive deficits and negative symptoms. These observations highlight mitochondrial pathways as promising therapeutic targets and emphasize the need for integrative approaches that combine molecular, pharmacological, and clinical data.

In vitro effects of novel antipsychotics on mitochondrial function

In vitro examinations of novel APs disclose important and statistically significant drug-induced changes in selected mitochondrial parameters (Ľupták et al., 2021). Tested substances displayed a decrease in the: electron transport chain (ETC) complexes activities (except complex IV activity, which increased in brexpiprazole (BREX) and loxapine (LOX), mitochondrial respiration rate and ATP formation. Decline in the ETC activity complexes leads to: an ineffective OXPHOS system, decreased ATP formation and excessive reactive oxygen species (ROS) production. High drug concentrations could lead to lack of energy and higher oxidative stress which may cause neuronal damage. Increased ROS production was noticed for all tested substances. In the therapeutic drug concentration range, cariprazine (CAR) and lurasidone (LUR) expressed little but significant inhibition of complex I-linked respiration, on the contrary, therapeutic drug concentrations did not show inhibition effect on complex II-linked respiration. Tested APs besides adverse effects such as decreased ATP production and increased ROS production act as a partial or weak MAO-A inhibitor therefore suggesting they could have a possible augmentative antidepressing effect in the treatment of affective disorders. BREX and LOX partially inhibited MAO-B indicating their role in neuroplasticity and neuroprotection. Inhibition of monoamine oxidase could be an attractive effect of novel APs. Beyond cognitive and negative symptoms, mitochondrial dysfunction in schizophrenia may also contribute to affective dysregulation, given the central role of mitochondrial energy metabolism, redox balance, and calcium signaling in mood regulation (Scaini et al., 2018, Ben-Shachar, 2017). Cell cultures and notably in vivo animal brain studies are required to elucidate the relationship of mitochondrial activity, SCH pathophysiology and the mitochondrial impact of novel APs in vivo .

Molecular basis of antipsychotic drug action: mitochondrial and metabolic links

The information on the molecular basis of antipsychotic action provided a more complete picture as to how antipsychotic drugs modulate cellular outputs and processes. Several studies in humans, human cell culture systems and animal models have been performed to elucidate some of the potential mechanisms underlying schizophrenia pathology. There are multiple lines of evidence suggesting a disruption in metabolism that compliment the data on antipsychotic mechanism of action. For instance, genetic studies of mitochondrial proteins have noted decreased expression of Opa1 one of the enzymes they cause mitochondrial fusion (Koshiba et al.,2004) that correlate to increased schizophrenia risk (Rosenfeld et al., 2011, Engmann et al., 2011). In addition, increased glutamine dehydro-genase activity including that of both GLUD1 and GLUD2 has been noted in the prefrontal cortex of schizophrenia patients compared with healthy controls (Burbaeva et al., 2003). GLUD1 is basally more active than GLUD2 (Spanaki et al., 2012) and likely contributes towards this increased activity (Burbaeva et al., 2003). In schizophrenia, glutamatergic synapses are differentially affected depending on the brain region, treatment status, and treatment response (Roberts et al., 2022).

Findings from recent studies findings suggest that the disruption of APs- induced bioenergetics may be cause to an underlying mechanism of APs diabetogenic effects. APs also influence the MTH of pancreatic cells. This finding proved the effect of medications on MTH to be generic in different cell types**.**

Therefore, antipsychotic drugs may affect glucose utilization, and, at least in vitro, affect mitochondrial complex one (MCI). The findings overall are consistent with MCI dysfunction in schizophrenia, but also highlight the need for in vivo studies to determine the link between MCI dysfunction and symptoms in patients. If new imaging tools confirm MCI dysfunction in the disease, this could pave the way for new treatments targeting this enzyme (Whitehurst & Howes, 2022).

Numerous studies have explored the relationship between second-generation antipsychotics (SGAs)—such

as olanzapine and clozapine—and their prominent metabolic side effects. These include weight gain, insulin resistance, and dyslipidemia, which may be partially explained by mitochondrial dysfunction. Treatment with SGA, drug alternatives and non-pharmacological interventions can cause various side effects so determine the root of metabolic impairments is of significant interest (Mortimer et al.,2023).

Establishing the optimal treatment approach of treatment for patients psychosis through adequate polypharmacy or personalized medicine will have, in the short term, favorable outcomes for patients quality of life. Reducing the risk of metabolic side effects should be one of the objectives in long term treatment with new ADs

Mitochondrial pathways as a therapeutic interface between schizophrenia pathophysiology and antipsychotic treatment

Metabolic dysfunction was also observed to be a common thread in multiple studies of human schizophrenia patient tissue. Given that antipsychotic drugs have been shown to alter transcription and protein abundance of several of the specific genes indicated in mitochondrial and metabolism defects, the cellular processes regulating metabolism appears to be a site of interplay between known schizophrenia pathology and the action of antipsychotic drugs. Mitochondria are also a target for psychotropic drugs by virtue of the drugs' modulatory effect on the expression of mitochondrial genes expression and on levels of proteins involved in the tricarboxylic acid cycle, the respiratory chain, apoptosis, autophagy and mitochondrial network dynamics (BenShachar, 2017; Kazemi et al., 2018; Scaini et al., 2018;Bar-Yosef et al., 2020).

This interplay has also been investigated in animal models. In a study by Amiri et al., the effects of post-weaning social isolation stress (PWSI) on mitochondrial function and the expression of immune-inflammatory genes in the prefrontal cortex (PFC) of normal and stressed rats were investigated as an animal model of schizophrenia. To achieve this, rats were subjected to eight weeks of PWSI, and subsequently divided into control and PWSI groups that were further split into subgroups receiving either clozapine (CLZ) treatment or no treatment. The rats were treated with a dose of 2.5 mg/kg/day for 28 days. The results showed that PWSI caused schizophrenic-like behaviors in rats, mitochondrial dysfunction, and activation of genes related to innate immunity in the PFC. Chronic administration of CLZ alleviated the behavioral impairments, mitochondrial dysfunction, and immune-inflammatory responses induced by PWSI in the rat PFC. These findings provide insight into the mechanisms of action of CLZ and the relationship between immune-inflammatory responses and mitochondrial dysfunction in the pathophysiology of schizophrenia.(Amiri et al., 2021).

Mitochondria as a relevant target for psychotropic drugs

In particular, based on multiple lines of evidence suggesting that mitochondrial dysfunction is a key component in the neurobiology of neuropsychiatric disorders and a target of psychotropic drugs. (Scaini et al., 2018; Rosenfeld et al., 2011; van Rensburg et al., 2022). Zhang et al. (2024) proposed that mitochondrial parameters in lymphocytes might be associated with schizophrenia pathophysiology and with antipsychotic-induced weight changes. These mitochondrial alterations may also be linked to cognitive dysfunction, particularly impairments in language processing. Zhang et al. (2024) suggest that mitochondrial lymphocytes could be entangled with the pathophysiology of SCH and the weight variations induced by the APDs furthermore it could be associated with cognitive impairments, notably in language function.

In schizophrenia model organisms, antipsychotic drugs restores normal cortical nitric oxide NO levels. (Morales-Medina et al., 2021).Current in vitro study of cell line cultures and their data is leaving the tested hypothesis uncertain because of the absence of local cell environment that includes interactions with different cell types and biological pathways which may be limiting the tested hypothesis. Therefore, more in vivo studies are necessary to support the current findings (Elmorsy et al., 2021).

Authors showed an in-vitro drug-specific mitochondria-related effect profile in healthy controls-derived lymphocytes. This, along with disparate clustering of typical vs. atypical antipsychotic drugs support the relevance of mitochondrial function parameters as a tool for personalized treatment prediction. The profiles are comprised of respiration parameters and mitochondrial function-related proteins but not of their mRNA, which was not affected by the 24 ^{h} drug treatment. The latter is in line with a previous study reporting lack of haloperidol effect on mRNA expression of complex I subunits in a human neuronal cell line (Brenner-Lavie et al., 2009) and with the comprehension that mRNA and protein levels are not always affected to the same extent by intra and/or extra-cellular processes (Payne 2015;Vogel & Marcotte,

Table 1.

Author and Year	Antipsychotic Drug(s)	Effects on Mitochondrial Functions
Shaju at al., 2025	Risperidone	Reduces mitochondrial respiratory chain complex I activity, contributing to mitochondrial dysfunction
Pirc Marolt et al., 2023	Aripiprazole	Persistent mitochondrial hyperpolarization with reduced oxidative phosphorylation and a compensatory shift to glycolysis
Kramar et al., 2022	Aripiprazole	Oxidant conditions increased the activity of antioxidant enzymes and upregulated genes and proteins associated with oxidative stress response in aripiprazole-treated cells
Amiri et al., 2021	Clozapine	Alleviated the behavioral impairments, mitochondrial dysfunction, and immune-inflammatory responses induced by PWSI in the rat PFC
Emmerzaal et al., 2021	Olanzapine	Increase in the activity of CII–CIII in the striatum; decrease in CII activity in the cerebellum and CIV activity in the hippocampus
Bar-Yosef et al., 2020	Antipsychotic drugs	Effects on mitochondrial gene expression
Cikánková et al., 2019	Haloperidol, Fluphenazine	Inhibition of complex I
Kazemi et al., 2018	Antipsychotic drugs	Effects on the expression of mitochondrial genes
Scaini et al., 2018	Antipsychotic drugs	Modulation of proteins involved in apoptosis, autophagy, and mitochondrial dynamics
Oliva et al., 2017	Chlorpromazine	Inhibition of cytochrome c oxidase (COX)
Ben-Shachar, 2017	Antipsychotic drugs	Altered expression of mitochondrial genes and respiratory chain proteins
Payne, 2015; Vogel & Marcotte, 2012	Haloperidol	Emphasized dissociation between mRNA and protein levels; short-term exposure affects post-transcriptional mechanisms
Brenner-Lavie et al., 2009	Haloperidol	No significant effect on mRNA expression of complex I subunits in a human neuronal cell line

2012), this lack of effect could indicate that short-term in-vitro exposure to psychotropic drugs affects post-transcriptional mechanisms.

During the study, (Ouyang et al., 2021) consistent plasma levels of cf-mtDNA were monitored between the first-episode patients with SCH and the HCs. After administration of APs, plasma cf-mtDNA levels were reduced and related to the PANNS scores. Plasma level of cf-mtDNA between the first-episode patients with SCH and the HCs were similar. This result suggests that this plasma parameter does not have any significance with schizophrenic risk. These results propose that the plasma cf-mtDNA reduction, in a drug-free first episode patients with SCH after 8 weeks of APDs treatment and the change in PANSS scores, was associated with the change in the plasma cf-mtDNA levels.

Quantification of plasma cf-mtDNA levels may be a convenient tool in the assessment of clinical progression in first-episode patients with schizophrenia.

Disease-specific mitochondrial sensitivity to antipsychotic drugs

However, 25% of the metrics impacted by standard medications were only observed in patients, with haloperidol affecting proteins associated with mitochondria and perphenazine influencing parameters related to respiration. Disease-specific alterations in medication interaction sites may be the underlying cause of drug-specific differences between patients and controls. Both perphenazine and haloperidol are known to participate in redox processes, but in different ways. Perphenazine is an oxidation substrate, while haloperidol possesses oxidation potency (Bar-Yosef et al., 2020).

Also, aripiprazole, protects liver cells against oxidative stress. This finding could be relevant for schizophrenia patients with high-oxidative-stress-risk lifestyles and needs to be validated in vivo. Oxidant conditions increased the activity of antioxidant enzymes and

upregulated genes and proteins associated with oxidative stress response in aripiprazole-treated cells (Kramar et al., 2022).

These data suggest that the patients are more susceptible to oxidoreductive load. The findings of the in-vivo drug treatment effects in patients provide additional evidence for mitochondria being a relevant target for psychotropic drugs. The selective and coordinated down-regulation of energy production genes in schizophrenia is consistent with the effects of chronic reductions in pyramidal neuron firing, and enhancement of this activity may serve as a therapeutic target (Glausier et al., 2020; Bar-Yosef et al., 2020).)

Notably, in treatment-responsive patients, short-term antipsychotic therapy did not sufficiently improve mitochondrial dysfunction. In contrast, prolonged treatment was associated with restored mitochondrial activity**,** highlighting the importance of treatment duration in modulating mitochondrial outcomes. Taken together, these findings reinforce mitochondria as a pharmacodynamic interface in schizophrenia and support the development of biomarker-guided strategies for individualized psychotropic therapy.

CONCLUSION

This review summarizes current evidence on the role of mitochondrial dysfunction and its modulation by antipsychotic drugs in schizophrenia. Accumulating data support the involvement of mitochondrial abnormalities in the pathophysiology of SCH, encompassing alterations in energy metabolism, calcium homeostasis, oxidative stress, and apoptotic pathways. These disturbances may contribute not only to disease mechanisms but also to variability in treatment response.

The effects of APs on mitochondrial function appear to be complex and heterogeneous. While some agents may impair mitochondrial processes by disrupting oxidative phosphorylation and increasing oxidative stress, others may exert partially protective or compensatory effects over time. These findings highlight mitochondria as both a potential contributor to disease pathology and a promising therapeutic target. Importantly, the evidence remains limited by inconsistencies across experimental models and the confounding effects of pharmacological treatment. Future research should aim to clarify the molecular mechanisms underlying drug–mitochondria interactions and to identify reliable biomarkers that predict treatment response and resistance. A better understanding of mitochondrial dysfunction may facilitate a shift from a predominantly neurotransmitter-based model of schizophrenia toward an integrated bioenergetic framework.

Such an approach could support the development of novel therapeutic strategies targeting mitochondrial pathways, with the potential to improve cognitive deficits, negative symptoms, and overall functional outcomes in patients with SCH.

Ethical considerations: Does this study include human subjects? NO

Conflict of interest: No conflict of interest'

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