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Mitochondrial dysfunction and mitophagy in ADHD: Cellular and molecular mechanisms

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by persistent, age-inappropriate levels of inattention and/or hyperactive-impulsive behaviors. Previous investigations reveal that disrupted mitochondrial physiological homeostasis may contribute to ADHD. Several factors, including environmental factors, metabolic dysregulation, oxidative stress, neuroinflammation, and genetic abnormalities, can lead to mitochondrial dysfunction and impaired mitophagic pathways. Several investigations have been established a connection between mitochondrial dysfunction in ADHD and variations in monoaminergic genes, including dopamine receptors, dopamine transporters, norepinephrine transporters, serotonin transporters, and synaptic genes. The interplay between mitochondrial homeostasis and mitophagy in ADHD provides a promising research area and understating this interaction may help in the investigation of pathophysiological mechanisms and the innovation of novel therapeutic approaches to ADHD. Accordingly, this review explores previous studies that have investigated the mitochondrial abnormalities and dysfunctions in mitophagy at the cellular and molecular level in the development of ADHD.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a childhood condition characterized by persistent, age-inappropriate levels of inattention and/or hyperactive-impulsive behaviors that occur in a variety of situations. In accordance with the DSM-5 criteria, ADHD can be classified into three types based on the unique pattern of symptoms: combined, predominantly inattentive, and predominantly hyperactive-impulsive (Mahrous, 2024). A re-analysis of the Global Burden of Disease (GBD) data indicates that approximately 5 % of school-aged children globally suffer from ADHD, making it the most common neurodevelopmental disease (Christiansen, 2021). In up to 75 % of these children, impairing symptoms of ADHD continue throughout adulthood (Veronesi, 2024). ADHD in adults frequently causes difficulty with organization, job performance, and social interaction impairments. Furthermore, it is usually linked to other mental diseases, such as mood disorders and substance use disorders (Barth, 2021). It has been reported that these behavioral conditions can enhance the risk of suicide and criminal activities, thereby negatively affecting families and society (Shen and Zhou, 2024). Although ADHD is a common neurodevelopmental disorder, the exact pathological mechanisms remains elusive, and diagnosing this pathological condition currently relies mainly on a series of behavioral symptoms without relevant biomedical and biological considerations. Therefore, understanding the

Abbreviations: 5-HTR, 5-Hydroxytrptamine Receptors; 6-OHDA, 6-Hydroxydopamine; ADHD, Attention-Deficit/Hyperactivity Disorder; ATP, Adenosine Triphosphate; ATPs, ATP Synthases; COXs, Cytochrome *C* Oxidases; CYTB, Cytochrome *B*; DAT, Dopaminergic Transporter; DBH, Dopamine Beta-Hydroxylase; DRD, Dopaminergic Receptor D; GAD, Glutamic Acid Decarboxylase; HSF1, Heat Shock Transcription Factor; IMM, The Inner Mitochondrial Membrane; mGluRs, Metabotropic Glutamate Receptors; MOMP, Mitochondrial Outer Membrane Permeabilization; NDs, NADH Dehydrogenases; NET1, Neuroepithelial Cell Transforming Gene 1; OMM, The Outer Mitochondrial Membrane; OXPHOS, Oxidative Phosphorylation; ROS, Reactive Oxygen Species; SOD1, Superoxide Dismutase 1; TCA, Tricarboxylic Acid; TDP-43, TAR DNA-Binding Protein 43; TPH2, Tryptophan Hydroxylase 2.

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pathophysiological consequences of ADHD is crucial for approaching effective preventive and interventive strategies in clinical practice (Lee, 2019). Emerging evidence has revealed that ADHD's pathophysiology is associated with an induction of oxidative stress (Shen and Zhou, 2024; Wu et al., 2024). Neurons' homeostasis has been shown to fundamentally depends on mitochondria to produce ATP and regulate ion and redox states (Alvarez-Arellano, 2020). Therefore, impairment of the physiological homeostasis of mitochondria could be a risk factor for ADHD (Verma, 2016). This review aims to provide a comprehensive overview of the pathogenic role of mitochondrial abnormalities and mitophagic molecular dysfunctions in ADHD pathogenesis.

2. Mitochondria

Mitochondria are critical organelles that play a role in energy production, cell signaling, and cell fate. The majority of cell types have many mitochondria, which take up 10 to 40 % of the total volume of the cell. They serve as a center for a variety of signaling pathways involved in cell survival and cell death. It is covered by a double membrane made up of the inner mitochondrial membrane (IMM) and the outer mitochondrial membrane (OMM). There are many crucial genes in mitochondria that contribute to mitochondrial activity. These genes include NADH dehydrogenases (NDs), cytochrome *B* (CYTB), cytochrome *C* oxidases (COXs), and ATP synthases (ATPs). ND1-6 genes encode NADH ubiquinone oxidoreductase core subunits 1 to 6. These genes are important in the mitochondrial respiratory chain particularly the complex 1 assembly. ND 1–6 maintains the NADH/NAD^+ ratio, which is essential for cell metabolism (Sharma et al., 2009; Grivennikova et al., 2020; Posakony et al., 1977). CYTB is a subunit encoded in the mitochondrial genome and considered an important component of respiratory chain complex III. It leads to oxidizes ubiquinol and reduces cytochrome, which contributes to the electrochemical gradient across mitochondrial membranes (Flores-Mireles, 2023). COX or complex IV genes are crucial in cellular oxygen consumption and ATP generation. COX 1–3 are encoded by the mitochondrial DNA involved in several redox-regulated processes, including the reduction of oxygen to water in the mitochondrial respiratory system (Timón-Gómez, 2018; Yoshikawa et al., 2012). (***Summarized in*** Fig. 1).

At the neuronal level, mitochondria play crucial physiological roles in neuronal homeostasis (***summarized in*** Fig. 2). These roles present in many key functions, including the following:

a. Production of the bioenergetic carrier adenosine triphosphate (ATP).

Mitochondria are the cell's energy production center. They produce adenosine triphosphate (ATP) by oxidative phosphorylation, particularly in neurons, which have high energy needs (Saraste, 1999). Acetyl-CoA is oxidized in the tricarboxylic acid (TCA) cycle as part of the mitochondrial bioenergetic function to produce NADH and FADH2, which deliver electrons to the electron transport chain to produce an electrochemical gradient across the IMM that is used to generate ATP (Mitchell, 1961).

b. ROS Regulation

Mitochondria primarily function to produce ATP for the cell. Reactive oxygen species (ROS) production is a byproduct of this activity, which depends on oxidative phosphorylation (OXPHOS). OXPHOS is responsible for 90 % of the ROS production (Kausar et al., 2018). ROS are primarily generated in mitochondria. Additionally, they have antioxidant mechanisms that control ROS levels and protect against oxidative stress, both of which are essential for the survival of neurons (Sena and Chandel, 2012). ROS at low levels have physiological functions, while elevated levels of ROS for an extended period can oxidize proteins, lipids, and nucleic acids, causing cellular dysfunction and apoptosis (Sena and Chandel, 2012; Hamanaka and Chandel, 2010).

c. Calcium Regulation

The amount of calcium within cells is regulated by mitochondria, which can take in excess calcium, protecting the neuron from its damaging effects and preserving appropriate signaling (Rizzuto et al., 2000). When the local $[Ca^{2+}]_c$ rises, the uniporter that mitochondria use to take in Ca^{2+} may act like a channel and remain open (Rizzuto et al., 2000). The electrochemical potential gradient for Ca^{2+} determines the amount of Ca^{2+} that enters the matrix via this pathway. Initially, the gradient is generated and maintained via mitochondrial respiration, which creates a significant potential gradient. The mitochondrial membrane potential (m) is typically estimated to be in the range of 150–200 mV or so negative to the cytosol, along with a low resting intramitochondrial Ca^{2+} concentration $[Ca^{2+}]$m, which is primarily maintained by the mitochondrial Na^+–Ca^{2+} exchanger (Rizzuto et al., 2000; Duchen, 2000).

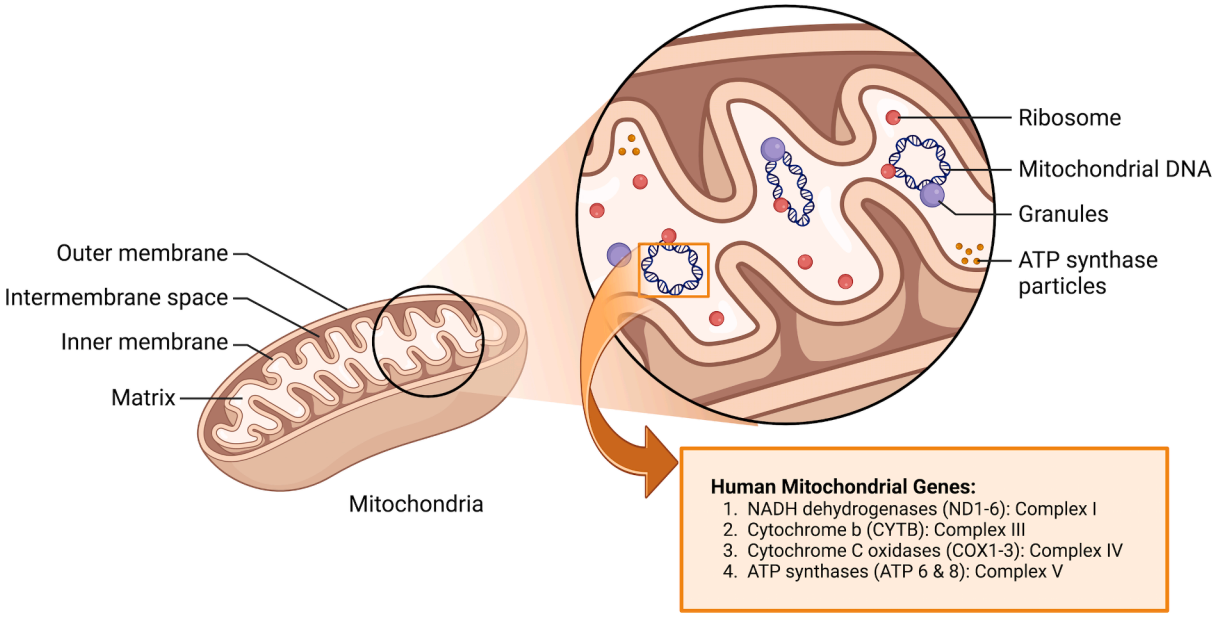

Fig. 1. The important structural components of the double-membrane organelle mitochondria () and the BioRender Science Template was created by Eunice Huang with "
Adopted from (Andrieux, 2021BioRender.com").

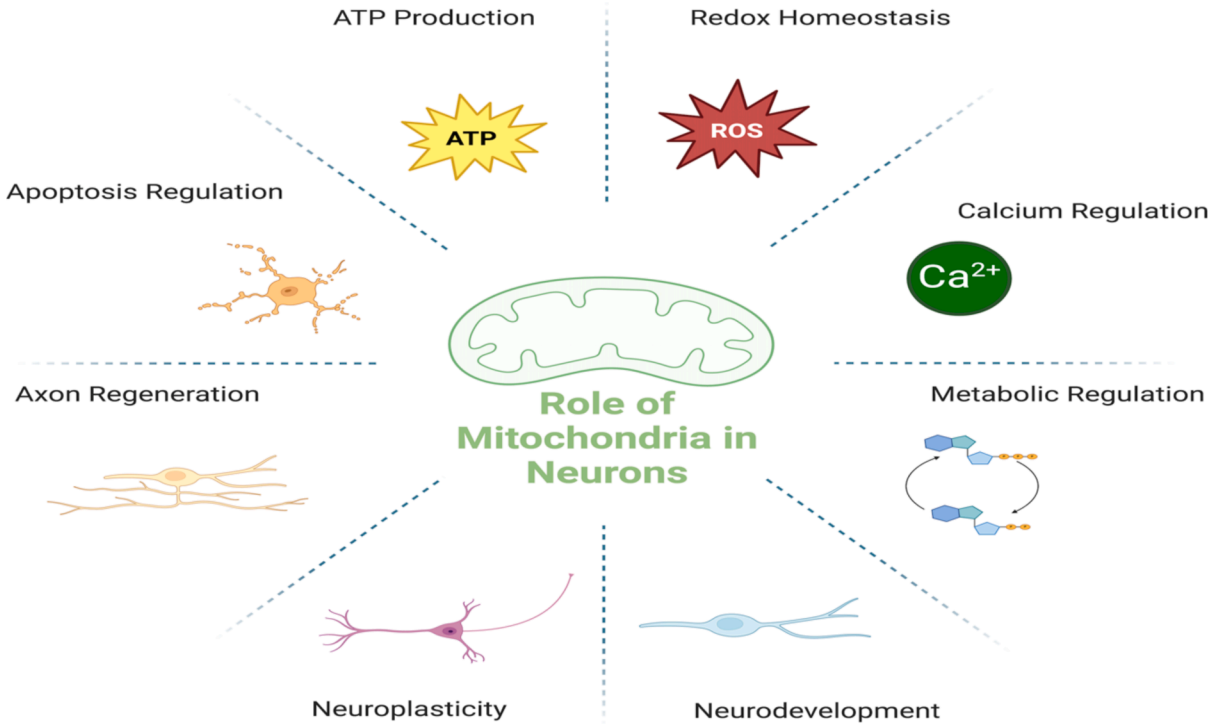

Fig. 2. Crucial physiological roles of mitochondria in neuronal homeostasis (*Created with "BioRender.com"*).

d. Metabolite synthesis.

Mitochondrial metabolites play two distinct roles in a cell: They play a part in energy metabolism, and serve a significant signaling role (Sciacovelli and Frezza, 2016). The tricarboxylic acid (TCA) cycle, which generates intermediates for the production of chemicals such as amino acids and lipids, is one of the metabolic pathways in which mitochondria are engaged. These molecules are necessary for the structure and function of neurons (Frezza, 2017).

e. Apoptosis Regulation

Apoptosis, or "programmed cell death," is mostly regulated by mitochondria through a process known as mitochondrial outer membrane permeabilization (MOMP) and controls the activation of caspase and cell death (Oberst et al., 2008; Tait and Green, 2013). This process causes the release of proteins that initiate or regulate the apoptotic cascades. These proteins, such as cytochrome *c* and apoptosis-inducing factor (AIF), which are often present in the space between the inner and outer mitochondrial membranes, can be crucial during the process of development and in response to cellular stress (Green and Kroemer, 2004).

f. Neuroplasticity.

Numerous characteristics and roles of mitochondria in neuroplasticity have been identified, including that they (i) move quickly through and among subcellular compartments (such as the axon shaft, dendrites, and presynaptic terminals) (Zinsmaier et al., 2009), (ii) undergo fission and fusion, which are important for the synaptic plasticity necessary for learning and memory functions (Liesa et al., 2009), (iii) respond to electrical stimulation and the activation of growth factor and neurotransmitter receptors (e.g., move, modify energy production, take up or release calcium) (Macaskill, 2009), and (iv) serve as signaling outposts that include kinases, deacetylases and other signal transduction enzymes (Stowe and Camara, 2009; Cheng et al., 2010; Mishra and Chan, 2014).

g. Neuroprotection

They provide neuroprotection by altering cellular stressor responses, such as hypoxia (Mattson and Kroemer, 2003). When exposed to hypoxia, mitochondria undergo fission and become single organelles, possibly to encourage mitophagy, maintain physiologically low levels of ROS generation, and retain integrity via a reduction in respiratory activity (Fuhrmann and Brüne, 2017).

3. Mitochondrial dysfunction

Mitochondrial dysfunction is a key factor in the development of various diseases, including neurological disorders, metabolic syndromes, and cancer. Gaining insight into the mechanisms that cause mitochondrial dysfunction and its various clinical manifestations is essential in the development of successful therapeutic approaches. Mitochondrial dysfunction can result from a variety of sources, including as genetic mutations, oxidative stress, metabolic dysregulation, and environmental influences (Waseem, 2021; Prasun, 2020; Palmer et al., 2021). Mitochondrial dysfunction can have significant implications, as it impairs the synthesis of ATP and increases oxidative stress, which, in turn, affects cellular function and viability in a widespread manner. Mitochondrial malfunction has been linked to the development of various diseases, such as neurodegenerative disorders, metabolic disorders, cardiovascular diseases, and cancer. For example, it has been reported that impaired mitochondrial dynamics and mitophagy are reportedly associated with diabetic endothelial dysfunction and cardiac microvascular injury (Zhang et al., 2023). Furthermore, the dysregulation of mitochondrial metabolic genes, such as hub mitochondrial genes, contributes to immune infiltration in septic cardiomyopathy (Li, 2024). A previous study showed that voltage-dependent anion-selective channels (VDACs) mediates the opening of the mitochondrial membrane-permeability transition pore (mPTP) and impaired these channels results in increased ROS and mitochondrial damage (Chang, 2024). In addition, mitochondrial sirtuins (mito-SIRTs), which are nicotinic adenine dinucleotide^{+}(NAD^{+})-dependent histone deacetylases, include SIRT3, SIRT4, and SIRT5. These mito-SIRTs play crucial roles in cancer progression (Shen, 2024). SIRT3 acts as a tumor suppressor gene by activating the mitochondrial pyruvate dehydrogenase complex, inhibiting glycolysis and promoting apoptosis in cancer cells (Fan, 2014). SIRT4 levels are downregulated in cancer cells and this deficiency results in dysregulating glutamine, increasing proliferation, and enhancing tumor migration. However, overexpression of SIRT4

stops the cell cycle and prevents tumor growth (Tucker, 2024). SIRT5 also acts as a tumor suppressor by reducing the mitochondrial membrane potential (ΔΨm) and impairing mitochondrial redox homeostasis, which subsequently prevents cancer cell growth and migration (Lu, 2019). Due to the significant impact of mitochondrial malfunction on various diseases, there is an increasing focus on discovering treatments that specifically address mitochondrial functions. Possible approaches encompass the utilization of antioxidants and substances that eliminate harmful free radicals, substances that enhance the production of new mitochondria, substances that regulate the development and structure of mitochondria, and substances that modify metabolic processes and therapies that target specific genes. As our knowledge of the intricate relationship between mitochondrial dysfunction and disease advances, innovative therapeutic approaches that specifically target mitochondria have significant potential for enhancing patient outcomes in various clinical diseases (Zong, 2024).

4. Mitochondrial dysfunction in neurological disorders

Recent research has shed light on the potential role of mitochondrial dysfunction in the pathophysiology of neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), and Huntington disease (HD). Emerging evidence has shown that AD is characterized by the disruption of the DNA repair system, alteration of calcium homeostasis, and reduction of cytochrome *c* oxidase activity. Inherited changes in mtDNA have been found to possibly contribute to AD pathogenesis. AD brains exhibited a notable elevation of oxidative biomarkers, including 8-hydroxydeoxyguanosine (8-OHdG) and 8- hydroxyguanosine (8-OHG) in both mitochondrial and nuclear DNA (Wang, 2020). In addition, PD models reportedly exhibited defective oxidative phosphorylation complex assembly, increased oxidative stress, and disrupted mitochondrial morphology (Subramaniam and Chesselet, 2013). Most notably, a decrease in mitochondrial complex enzyme 1 is significantly prevalent in PD. Mutations in Pink1 and LRRK2 genes result in mitochondrial dysfunction-induced free radicals and depleted ATP in dopaminergic neurons in PD patient brains (Moon and Paek, 2015). Furthermore, increased oxidative damaged mitochondria and decreased mitochondrial membrane potential have been observed in ALS models. Mutations in superoxide dismutase 1 (SOD1) and TAR DNA-binding protein 43 (TDP-43) lead to impair mitochondrial calcium uptake and subsequently induces mitochondrial dysfunction in ALS (Wood, 2021). Also, reduced respiratory chain complex function, increased ROS, and altered mitochondrial activity have been reported in HD models. Deficiency in heat shock transcription factor (HSF1) in HD results in the inhibition of mitochondrial biogenesis (Liu, 2022).

5. Mitophagic molecular dysfunctions in ADHD pathogenesis

Mitophagy is a highly regulated process by which damaged or dysfunctional mitochondria are selectively targeted for degradation. It plays a crucial role in maintaining mitochondrial quality control, cellular energy metabolism, and redox balance. The dysregulation of mitophagy has been implicated in several neurodegenerative disorders, and recent evidence suggests its involvement in ADHD (Shafique, 2023). Studies have reported alterations in mitochondrial structure, function, and bioenergetics in individuals with ADHD. These abnormalities include decreased mitochondrial membrane potential, impaired oxidative phosphorylation, and increased oxidative stress. Collectively, these findings suggest a potential link between mitochondrial dysfunction and the pathophysiology of ADHD. Emerging evidence suggests that impaired mitophagy may contribute to the accumulation of damaged mitochondria in individuals with ADHD. Dysfunctional mitophagy can lead to the release of ROS and pro-inflammatory molecules, which can further exacerbate neuronal dysfunction and contribute to ADHD symptoms (Öğütlü et al., 2022). Understanding the molecular mechanisms underlying mitophagy dysregulation in ADHD is crucial for developing targeted therapeutic interventions. Targeting mitophagy pathways holds promise as a potential therapeutic strategy for ADHD. Modulating mitophagy regulators, such as Parkin, PINK1, and BNIP3, may help restore mitochondrial function and alleviate ADHD symptoms. Additionally, interventions aimed at reducing oxidative stress and enhancing mitochondrial biogenesis could offer potential benefits in mitigating ADHD-related impairments. Furthermore, some experimental studies revealed that mitochondrial genetic variation contribute to ADHD pathogenesis. For example, mitochondrial gene NADH Ubiquinone Oxidoreductase Complex Assembly Factor 2 (NDUFAF2) and Uncoupling Protein 2 (UCP2) mutation was reported in ADHD children (Lesch, 2011; Giannoulis, 2024). In addition, variation in mitochondrial organization genes (e.g. Prps18c, Letm1, Uqcrc2) induces mitochondrial damage and reduces mitochondrial OXPHOS activity, resulting in decreased mitochondrial respiration and increased oxidative stress in the ADHD brains (Giannoulis, 2024; dela Peña, 2014). Mitochondrial pathway genes, such as caspases (3,7, and 9) and Bcl2 were identified as candidate causal pathways in apoptotic signaling that contribute to ADHD susceptibility (Giannoulis, 2024; Lee and Song, 2014).

Recently, polymorphisms of monoaminergic genes, such as dopamine receptors, transporters for dopamine, norepinephrine, and serotonin, as well as synaptic genes became considered risk factors for ADHD, which will be discussed below thoroughly (***summarized in*** Fig. 3).

a. Dopaminergic pathway:

Many studies have revealed that ADHD is associated with disruption of dopaminergic functions (Russell, 2011; Volkow, 2011). In addition, the density of dopamine receptors in different brain regions of ADHD patients is significantly lower compared with those of healthy individuals (Medin, 2013). Dopaminergic receptor D (DRD) and transporter (DAT) genes, including DRD1, DRD2, DRD4, and DAT1, play a potential role in ADHD pathogenesis. Case control studies reported that children with ADHD have exhibited DRD1 polymorphisms (Ribasés, 2012; Bobb, 2005). The hypofunction of DRD1 mediates GABAergic inhibitory synaptic transmission which could contribute to ADHD pathophysiology (Satoh et al., 2018). In addition, DRD2 polymorphisms are reportedly associated with the ADHD-like phenotype and are a risk factor for anxiety disorders in ADHD patients (Mariggiò, 2021; Fraporti, 2019). Emerging evidence has revealed that DRD4 polymorphisms also contribute to the etiology of ADHD (Qian, 2018; Bidwell, 2011). In addition, DRD4 knockout mice models exhibit the ADHD phenotype (Avale, 2004). DAT1 regulates the dopamine reuptake from the synapses, and downregulation of DAT1 reduces its reuptake, which subsequently increases the dopamine metabolism (Ernst, 1999). Both DAT knockout and hypofunctional animal models exhibited hyperactivity. A case control study that investigated the association between organophosphate pesticide exposure and ADHD in Taiwan children, reported that oxidative stress, lipid peroxidation, and dopamine receptor polymorphisms were observed in those children (Chang, 2018). Linked to mitophagy, the loss of dopamine neurons is associated with alterations in Pink1, Parkin, and LRRK2 genes (Giguère, 2019). Most importantly, impaired energy metabolism and disrupted dopamine system have been found in ADHD animal models (Dimatelis, 2015). Interestingly, methylphenidate, a dopamine-reuptake inhibitor, is the most effective drug in ADHD treatment, as it maintains mitochondrial homeostasis in response to oxidative stress by increasing mitochondrial regulatory proteins (such as Parkin), decreasing ROS production, and increasing GSH, SOD, and ATP levels (Rieder, 2024; Zhu, 2018).

b. Serotonergic pathway:

Serotonin mediates many effects through its interaction with GABAergic, dopaminergic, glutamatergic, and acetylcholine neurons (Lladó-Pelfort, 2012; Zhang, 2002; Lucki, 1998). Tryptophan hydroxylase 2 (TPH2), highly expressed in the cortex, is a rate-limiting enzyme that mediates serotonin synthesis from tryptophan (Park, 2013).The mutation of TPH2 has been found to be a risk factor for genetic

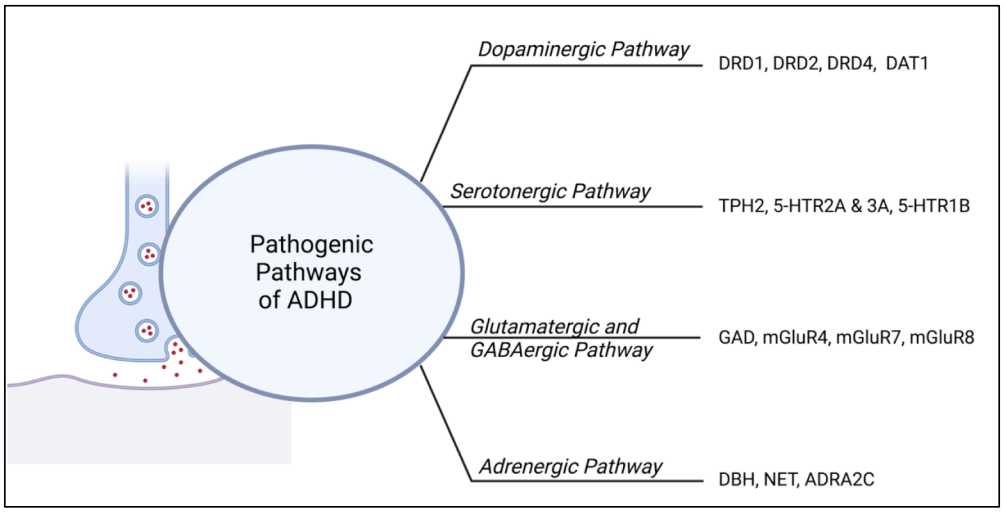

Fig. 3. polymorphisms of monoaminergic genes, such as dopamine receptors, transporters for dopamine, norepinephrine, and serotonin, as well as synaptic genes are considered as risk factors for ADHD (*Created with "BioRender.com")*.

predisposition to ADHD in children (Abo El Fotoh, 2020; Brookes, 2006). In addition, 5-hydroxytrptamine receptors (5-HTR), such as 1A, 2A, and 1B, play an important role in regulating serotonin signal pathways in the brain, particularly in the hypothalamus and cortex (Brown, 2005; Serretti et al., 2007; Bouwknecht, 2001). The mutation of 5-HTR1A is reportedly associated with ADHD phenotypes (Shim, 2010; Park, 2013). Although few studies have examined 5-HTR2A and 5-HTR3A models, mutation of these genes could be associated with ADHD (Quist, 2000; Yamashita et al., 1989; Hou, 2018). A *meta*-analysis study found an association between 5-HTR1B genetic variant and ADHD pathogenesis (Hou, 2018). Most importantly, 5-HTRs mediate critical cellular functions including cell proliferation and differentiation through MAPK signaling pathways, which are tightly regulated by mitochondrial calcium, ROS, and ATP generation (Ding, 2024; Wang, 2016). Therefore, alterations to these genes could have a significant influence on mitochondrial homeostasis and mitophgic pathways.

c. Glutamatergic and GABAergic pathway:

Glutamate is considered a major excitatory neurotransmitter in the brain, and can be converted to GABA, an inhibitory neurotransmitter, by an enzyme called glutamic acid decarboxylase (GAD). Glutamate and GABA both play a crucial role in ADHD via regulating dopamine signaling and mediating dopamine metabolism, respectively. ADHD children reportedly exhibit high glutamate levels and low GABA levels (Kessi, 2022; Courvoisie, 2004). Due to this imbalance, ADHD patients experience some symptoms such as inattention, hyperactivity, and impulsivity. In addition, GAD polymorphism children are more susceptible to ADHD disorder (Bruxel, 2016). Moreover, mutations in metabotropic glutamate receptor (mGluR) genes could contribute to ADHD pathogenesis. For example, mGluR4 and mGluR7 polymorphisms are associated with ADHD disorder in the Chinese children (Zhang, 2021). An in-vivo study showed that mGluR8 null mutant mice exhibited the hyperactivity phenotype (Fendt, 2010). According to a genome-wide copy number variation study, approximately 10 % of ADHD patients carry mGluR gene variants that may contribute to ADHD pathogenesis (Elia, 2011). A study showed that mGluRs may contribute to neuronal protection against oxidative stress-induced cellular injury (Spillson and Russell, 2003). Furthermore, mGluRs modulate mitochondrial membrane potential and promote neuronal plasticity (Chong et al., 2003). Glutamate excitotoxicity induces the accumulation of Parkin on neuronal mitochondria which associated with mitophagy and oxidative stress (Van Laar, 2015). In addition, a recent systematic review reported that mGluR7 deficiency induces glutamate-mediated excitotoxicity through mitochondrial dysfunction, oxidative stress, and neuroinflammation (Zaki-Dizaji, 2024).

d. Adrenergic pathway:

Norepinephrine plays an important role in regulating cognition, memory, and stress. Alterations of neuronal norepinephrine homeostasis have been reported as a risk factor for CNS disorders. For example, the excessive reuptake of norepinephrine and depletion of its level in synaptic cleft have been observed in ADHD. This notion has been supported by the positive effect of norepinephrine reuptake inhibitors in ADHD patients. A *meta*-analysis study has revealed that polymorphisms of adrenergic genes can negatively alter methylphenidate and atomoxetine efficacy in ADHD therapy (Yuan, 2021; Gul, 2022). The hypofunction of numerous adrenergic genes, such as dopamine beta-hydroxylase (DBH), neuroepithelial cell transforming gene 1 (NET1), and Alpha-2C-adrenergic receptor (ADRA2C), is reportedly associated with ADHD phenotypes (Kessi, 2022). DBH mediates norepinephrine synthesis via dopamine hydroxylation. Clinical studies found that ADHD patients exhibited lower activity of DBH compared with healthy individuals and this hypofunction is associated with ADHD symptoms (Pliszka, 1994; Rogeness, 1989). NET1 (*also named SLC6A2*) is a presynaptic gene that encodes norepinephrine transporters. It also mediates intrinsic neuronal activity, visual memory, and attention (Shang et al., 2021). Polymorphisms of this gene have been reported in ADHD female patients (Anney, 2008). ADRA2C regulates adenylate cyclase inhibition as a result of its activation by catecholamine. Although it has not been confirmed yet, ADRA2C polymorphism is associated with the ADGD subtype (Cho, 2008). A study showed that the 6-hydroxydopamine (6-OHDA), a neurotoxin that is commonly used to develop animal models of Parkinson's disease, reduces DBH and induces mitochondrial ROS production, which subsequently leads to the lysosomal degradation of cupper-trafficking protein such as ATP7A, which is essential for redox balance in mitochondria (Kondo, 2021; Bhattacharjee, 2016). ATP7A regulates copper transport to mitochondria and protects it from excessive copper toxicity. ATP7A dysfunction leads to abnormal mitochondrial redox status, which results in reduced mitochondrial glutathione and increased oxidative stress (Bhattacharjee, 2016). Recently, excessive copper has been reported to significantly induces microglia activation and neuroinflammation via increasing ROS production and reducing mitophagic genes such as Parkin and PINK1 expression (Zhou, 2022).

6. Neuroinflammation-induced mitochondrial dysfunction in ADHD pathogenesis

Neuroinflammation has been linked to ADHD incidence. Increased maternal expression of inflammatory mediators such as cytokines could

be a risk factor for ADHD. Cytokines can trigger dopaminergic pathways, particularly dopamine deficits. In addition, it has been reported that neuroinflammation mediates glial activation, oxidative stress, and neurotransmitter metabolism alteration. Furthermore, alteration of immune response, inflammatory-related gene polymorphisms, and prenatal exposure to toxins alter offspring brain development and has been linked to the occurrence of ADHD (Miller, 2013; Thürmann, 2019). A recent study has assessed the oxidative and inflammatory parameters in ADHD patients and found that oxidative stress and inflammatory mediators (e.g. IL1-ß, IL-6, and TNF-α) levels were significantly higher in the ADHD patients compared with healthy individuals (Koç, 2023). The elevated oxidative stress that observed in the ADHD model is associated with low cellular and mitochondrial respiration, low ATPase levels, and loss of mitochondrial membrane potential (Verma, 2016). Most importantly, neuroinflammation is considered one of the stressors that induce mitochondrial stress, subsequently promoting mitophagic pathways and the ubiquitination of mitochondria (Gao, 2024). Taken together, neuroinflammation-induced oxidative stress could alter mitochondrial bioenergetics, subsequently contributing to ADHD pathogenesis.

7. Perspectives and conclusion

Mitochondria are the cellular powerhouses that mediate many functions, including ATP generation, cellular proliferation, calcium homeostasis, and redox regulation. Accordingly, mitochondrial dysfunction contributes to oxidative stress, cell apoptosis, and inflammatory responses. Abnormal alterations in mitochondria stimulate many processes such as mitochondrial fission, fusion, and degradation. The elimination of degraded mitochondria can be achieved by mitophagy. Evidence suggests that mitophagy and mitochondrial DNA stability are influenced by cellular stressors, such as inflammation and oxidative stress. How mitochondrial dysfunction and impaired energy metabolism contribute to pathogenesis of various neuropsychiatric disorders, including ADHD, has gained attention. In this disorder, patients exhibit increased ROS generation, neuroinflammation, and certain genetic variation affecting mitochondria homeostasis and mitophagy. Emerging evidence reveals that the disruption of mitochondrial functions in ADHD lead to impaired normal autophagy and mitophagy processes, elevated mitochondrial Ca^{+2}, and accelerated cellular apoptosis (Kessi, 2023). Although numerous studies have linked mitochondrial dysfunction in ADHD with polymorphisms of monoaminergic genes, such as dopamine receptors, transporters for dopamine, norepinephrine, and serotonin, as well as synaptic genes (Kessi, 2022), more research is needed to examine the progression of mitochondrial function in ADHD patients. Furthermore, future studies should investigate the influence of lifestyle factors, such as food, exercise, and sleep on mitophagy and mitochondrial homeostasis in ADHD. In addition, investigating and understanding the interplay among mitochondrial dysfunction, mitophagy, and cellular stressors in ADHD phenotypes would help to reveal therapeutic targets that may improve the ADHD patient outcomes. Nevertheless, there are some limitations to studies investigating the role of mitochondrial dysfunction and mitophagy in the ADHD, including limited availability of well-characterized findings on ADHD animal models and human postmortem brains to support ones that derived from cell models. In addition, there is a lack of comprehensive multi-omics, mitochondrial functional analysis, and the high-throughput screening of mitochondrial targeting-biomarkers and drug candidates for mitochondrial phenotypic associated with the ADHD pathogenesis.

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CRediT authorship contribution statement

Mohammed M. Almutairi: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Abdulrahman Althekair:** Writing – review & editing, Writing – original draft, Conceptualization. **Fahad Almutairi:** Writing – review & editing, Writing – original draft, Conceptualization. **Mohammed Alatabani:** Writing – review & editing, Writing – original draft, Conceptualization. **Abdulaziz Alsaikhan:** Writing – review & editing, Writing – original draft, Conceptualization.

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