 doi:10.20944/preprints202207.0130.v1

Review

Mitochondrial Impairment: A Common Motif in Neuropsychiatric Presentation? The Link to the Tryptophan-Kynurenine Metabolic System

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Abstract: Nearly half a century has passed since the discovery of cytoplasmic inheritance of human chloramphenicol resistance. The inheritance was then revealed to take place maternally by mitochondrial DNA (mtDNA). Later, a number of mutations in mtDNA were identified as a cause of severe inheritable metabolic diseases with neurological manifestation, and the impairment of mitochondrial functions has been probed in the pathogenesis of a wide range of illnesses including neurodegenerative diseases. Recently growing number of preclinical studies has revealed that animal behaviors are influenced by the impairment of mitochondrial functions and possibly by the loss of mitochondrial stress resilience. Indeed, as high as 54% of patients with one of the most common primary mitochondrial diseases, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome, present psychiatric symptoms including cognitive impairment, mood disorder, anxiety, and psychosis. Mitochondria are multifunctional organelles which produce cellular energy and play a major role in other cellular functions including homeostasis, cellular signaling, and gene expression, among other. Mitochondrial functions are observed to be compromised and to become less resilient under continuous stress. Meanwhile, stress and inflammation have been linked to the activation of the tryptophan (Trp)-kynurenine (KYN) metabolic system, which observably contributes to development of pathological conditions including neurological and psychiatric disorders. This narrative review discusses the functions of mitochondria and the Trp-KYN system, the interaction of the Trp-KYN system with mitochondria, and the current understanding of the involvement of mitochondria and the Trp-KYN system in preclinical and clinical studies of major neurological and psychiatric diseases.

Keywords: Keywords: mitochondria; stress resilience; plasticity; stress; kynurenine; Alzheimer's disease; neurodegenerative; depression; anxiety; psychiatric

1. Introduction

Mitochondria are double membrane-bound cell organelles abundant in the cytosol of eukaryotes. The most prominent role of mitochondria is the production of high energy storage molecule adenosine triphosphate (ATP) which is directly usable to the host cells [1-3]. For the ultimate energy production, mitochondria employ a variety of metabolic activities, including tricarboxylic (TCA) cycle, oxidative phosphorylation (OXPHOS), ketogenesis/ketolysis, fatty acid oxidation, and glutamate metabolism, among others [4-9].

Each component forms a complex metabolic network and dynamically adapts to the cellular environment to ensure the optimal energy supply. Mitochondrial malfunction can occur due to the defects of proteins directly or indirectly responsible for the OXPHOS or to the dysfunction of cellular mechanisms outside of mitochondria [10-13]. However, the role of mitochondria is not limited to cellular energy production. Mitochondria stores calcium ions [14]. The mitochondria constantly communicate and interact with other organelles including the nucleus, the endoplasmic reticulum (ER), lysozymes, and peroxisomes, signaling in fundamental processes such as gene expression, cell division, cell differentiation, antiviral signaling, autophagy, and apoptosis [15].

Accumulating evidence is revealing that the enzymes and the metabolic products of the tryptophan (Trp)-kynurenine (KYN) system actively influences metabolisms of mitochondria and participates in normal ageing as well as the pathogenesis of mitochondrial diseases, neurodegenerative diseases, and psychiatric disorders [16,17]. The enzymes of the Trp-KYN system are under the direct influence of inflammation, oxidative stress, antioxidant system, and downstream bioactive metabolites [18]. The Trp-KYN system produces a wide range of biomolecules such as oxidants, antioxidants, neurotoxins, neuroprotectants, anti-inflammatory agents, and immune modulators [19].

Normal functions of mitochondria are typically compensated in mitochondrial diseases, a heterogenous group of chronic, genetic, and often inherited metabolic disorders caused by mitochondrial dysfunction resulting in the impairment of cellular energy production [20]. The prevalence of inherited mitochondrial diseases is estimated to occur one 5000 live births, and they are the most common inborn errors of metabolism [21]. Primary mitochondrial disease (PMD) is caused by the pathogenic mutation of mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) encoding either the proteins of OXPHOS or the proteins affecting the energy production of OXPHOS. Secondary mitochondrial diseases (SMDs) can be hereditary, caused by the genes not encoding the proteins responsible for the OXPHOS function, but for mtDNA transcription or expression, homeostasis, or metabolism [22]. Furthermore, mitochondrial dysfunction can be caused by acquired multifactorial diseases such as diabetes, cancer, heart or kidney disease, or neurodegenerative diseases [23,24].

Mitochondrial malfunction occurs in other conditions including normal ageing, neurodegenerative diseases, and psychiatric disorders. Age-related physiological changes are strongly associated with mitochondrial malfunction with decreased mtDNA volume and mitochondrial integrity, which results from cumulative damage to mtDNAs due to oxidative stress [25]. Mitochondrial dysfunction also occurs in most of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's diseases (PD), Huntington's disease (HD), Friedreich's ataxia (FA), and amyotrophic lateral sclerosis (ALS) [26]. Psychiatric disorders include mood disorders such as major depressive disorder (MDD) and bipolar disorder (PD), schizophrenia (SCZ), autism spectrum disorder (ASD), attention deficit hyperactive disorder (ADHD) [27].

This narrative review discusses the functions of mitochondria, the Trp-KYN system, the interaction of the Trp-KYN system with mitochondria, the mitochondrial environment upon the activation of Trp-KYN system, and the link to neuropsychiatric presentation in clinical and preclinical settings in search for possible diagnostic biomarkers and novel interventional targets for mitochondria-associated diseases.

2. Mitochondria in the central nervous system

The brain accounts for only 2% of body weight; however, it consumes as much as 20% of body's total oxygen supply [28]. The estimated number of one to two million mitochondria is present per cell to supply cellular energy to the brain. Mitochondria take responsibility for the production of cellular energy and the proper conduction of neural circuits in the nervous system [29-33]. Mitochondria is multifunctional organelles maintaining calcium homeostasis and signaling to other organelles in the cell as well as with other mitochondria at distance [34,35]. Furthermore, mitochondria are highly plastic in

 doi:10.20944/preprints202207.0130.v1

morphology, functions, and cell cycle, depending on tissue type and need of cells [36]. Mitochondria can be even transferred cell to cell [37].

2.1. Mitochondrial bioenergetics

Glucose, other sugars, and some amino acids are broken down in the cytosol to three-carbon molecule pyruvate which transfers into the mitochondria. Pyruvate is degraded to two carbon molecule acetyl coenzyme A (acetyl-CoA) which enters the second stage of cellular respiration, the TCA cycle that takes place in the matrix of mitochondria. Initially, Szent-Györgyi reported a cyclic chemical reaction between a four-carbon molecule oxaloacetate and two four-carbon molecules fumarate and L-(-)-malate (the Szent-Györgyi cycle). Later, Krebs has revealed the larger cyclic biochemical reactions in which a two-carbon molecule "triose" bonds with oxaloacetate to form a six-carbon molecule citrate, which is then oxidized to a five-carbon molecule alpha-ketoglutarate, and four-carbon molecules succinyl-CoA, succinate, fumarate, and malate, subsequently, thus forming the TCA cycle (the Krebs cycle) [38]. "Triose" was eventually identified as a product of pyruvate and coenzyme A, acetyl-CoA [39,40]. The TCA cycle employs eight different enzymes, reproducing one molecule of oxaloacetate, two molecules of carbon dioxide, water, three molecules of nicotinamide adenine dinucleotide (NADH), and one molecule of flavin adenine dinucleotide ($FADH_2$) and guanosine triphosphate (GTP). GTP is readily converted to ATP. In the TCA cycle most of high-energy storage molecule ATP is consumed by NAD^+ and FAD to form NADH and $FADH_2$ [29] (Figure 1). The NAD^+ excess has been reported to improves mitochondrial function and thus prolong life span in mice [30].

16-18 carbon chain fatty acids transported by plasma albumin diffuse into the cytosol using a protein transporter. Consuming ATP, fatty acid is transformed to acyl coenzyme A (acyl-CoA) that cross the inner membrane of mitochondria by carnitine-acyl-CoA transferase. The beta-oxidation takes place in the mitochondrial matrix in which acetyl-CoA, water and five ATP molecules are produced by shortening two carbon chain until an acyl-CoA molecule is reduced to an acetyl-CoA molecule [31].

Amino acids are recycled to produce new proteins, but when they are in excess, or cells are under starvation amino acids are catabolized to supply energy. All essential amino acids except histidine, alanine, and cysteine are involved in mitochondrial metabolic pathways. All essential amino acids are converted to pyruvate in cytosol, which enters to mitochondria to fuel in the TCA cycle [36].

NADH and $FADH_2$ transfer their energy to the third stage of cellular respiration OXPHOS consisting of the electron transport, chemiosmosis, and ATP synthesis. The electron transport chain (ETC) generates a proton (H^+) gradient across the inner membrane and the subsequent return of the H^+ to the matrix produces ATP from ADP by ATP synthetase. The ETC is a group of protein complexes composed of NADH coenzyme Q reductase (Complex I), coenzyme Q, succinate dehydrogenase (Complex II), cytochrome bc1 complex (Complex III), and cytochrome c oxidase (Complex IV). NADH donates an electron to Complex I, generating three H^+ gradients, while $FADH_2$ donates an electron to Complex II, generating two H^+ gradients. ATP synthetase (Complex V) utilizes a proton gradient across the inner membrane to synthesize ATP from ADP and inorganic phosphate (Pi) [32]. In general, three to four protons are required to produce one ATP with 42% efficiency of energy conservation [33].

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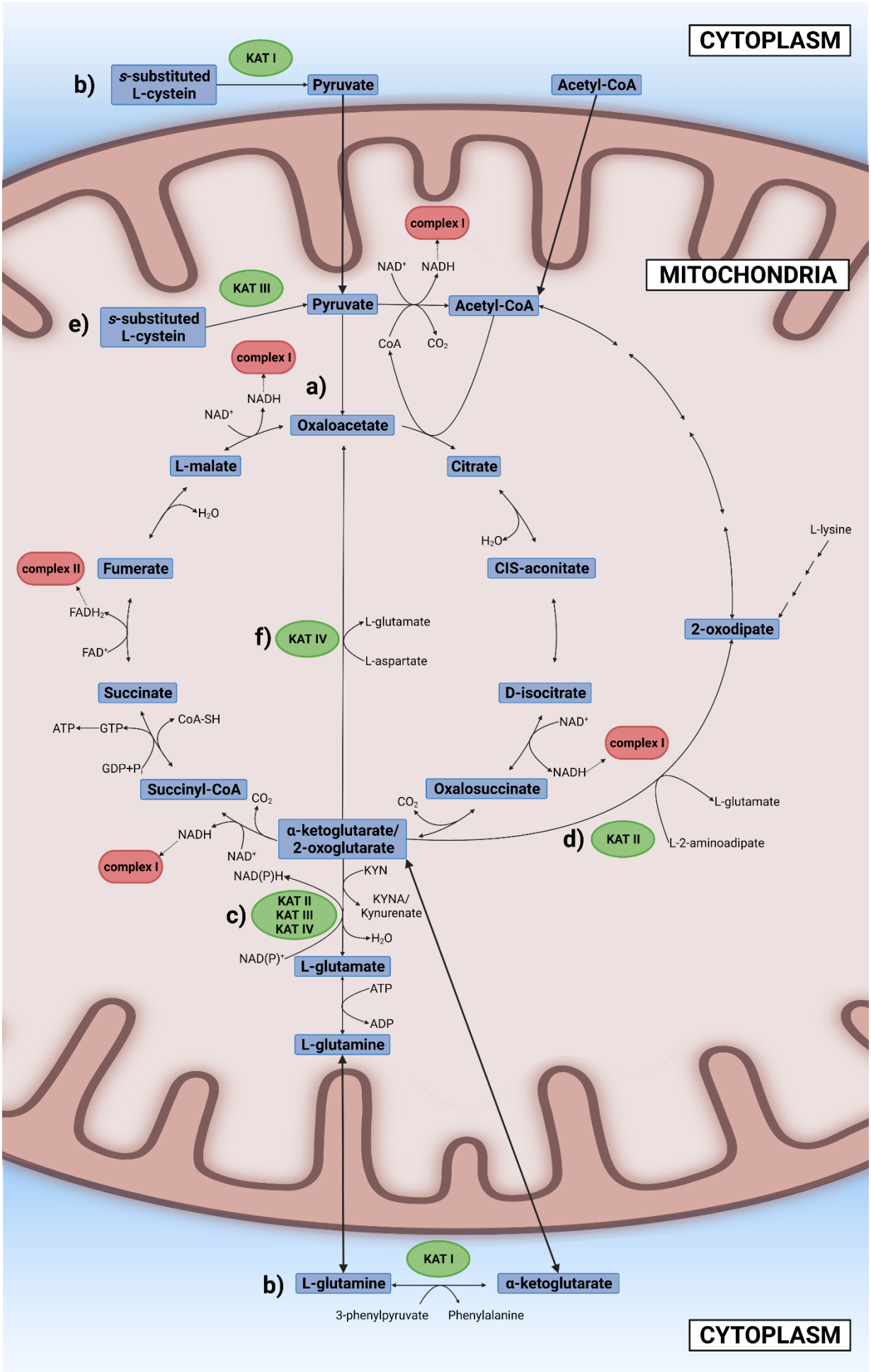

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Figure 1. The tricarboxylic acid cycle and its interface with the tryptophan-kynurenine metabolic system. (**a**) The tricarboxylic acid (TCA) cycle is initiated with acetyl coenzyme A (acetyl-CoA) reacting with oxaloacetate to form citrate. Citrate is oxidized to alpha (α)-ketoglutarate (2-oxoglutarate) with the formation of nicotinamide adenine dinucleotide (NADH). α-ketoglutarate is oxidized to succinyl coenzyme A (succinyl-CoA) with the formation of NADH. Succinyl-CoA is converted to succinate with the formation of adenosine triphosphate (ATP). Succinate is oxidized to fumarate with the formation of flavin adenine dinucleotide ($FDAH_2$). Fumarate is hydrated to malate which is oxidized to oxaloacetate to end the cycle. (b) Cytosolic kynurenine aminotransferase (KAT) I catalyzes the reaction of an *S*-substituted L-cysteine to pyruvate. (c) KAT I also catalyzes the reaction of L-glutamine to 2-oxoglutarate. (d) Mitochondrial KAT II, KAT III, and KAT IV catalyzes the reaction of α-ketoglutarate to L-glutamate. (e) KAT II catalyzes the reaction of 2-oxoglutarate to 2-oxoadipate which is eventually degraded to acetyl-CoA. (f) Mitochondrial KAT III catalyzes the reaction of an *S*-substituted L-cysteine to pyruvate. (g) Mitochondrial KAT IV catalyzes the reaction of 2-oxoglutarate and L-aspartate to oxaloacetate and L-glutamate.

2.2. Other mitochondrial functions

Mitochondria plays an important role in cellular calcium homeostasis. The concentration of calcium ions in the intermembrane space is the same as that in the cytosol due to the high permeability of outer mitochondria membrane. A higher concentration of mitochondrial calcium ions enhances ATP production; however, severe calcium overloads are associated with pathological conditions [34,35,41].

Mitochondria constantly communicate with other cellular organelles such the nucleus, the ER, lysozymes, and peroxisomes. The coordinated interaction of mitochondrial and nuclear factors is required for mitochondrial gene expression participated by mitochondrial ribonuclease P, ribosomal RNAs, transfer RNAs, introns, and a protein [42]. The nucleus sends signals to the mitochondria by anterograde regulation to modulate mitochondrial biogenesis upon stressful events. On the other hand, mitochondria constantly transmit information on mitochondrial status and cellular stress to the nucleus by retrograde signaling [43].

Mitochondria and the ER are at a close contact through mitochondria through the mitochondria-associated membrane to exchange information on energy production, calcium homeostasis, lipid transport, and apoptosis [44]. Lysosomes digest macromolecules including carbohydrates, lipid, proteins, and nucleic acids, respond against foreign substances such as bacteria and virous, and maintain the integrity of cellular membrane. Lysosomes interact with mitochondria to transport amino acids, lipids, and calcium ion [45]. Mitochondria and peroxisomes function in concert in fatty acid metabolism. Mitochondria degrade long-chain fatty acids to supply acetyl-CoA and produce ATP, while peroxisome performs beta-oxidation to generate hydrogen peroxide and anabolic metabolic metabolism such as plasmalogen and bile acid synthesis [46].

Mitochondria undergo cell division during mitosis, forming equal amounts of cell soma to daughter cells in interaction with the ER and cytoskeleton [47]. Morphology, functions, and dynamics of mitochondria change upon tissue differentiation [48]. Mitochondria constantly divide and fuse, controlling their morphology and functions. The fusion takes place by initially merging the outer membrane and subsequently the inner membrane of two mitochondria. The continuous events of fusion and division generate mitochondrial networks [49]. Mitophagy is mitochondrial autophagy in which double-membraned vesicle autophagosomes deliver mitochondria to lysosomes for destruction. microRNAs play an important role in regulation of protein expression responsible for autophagy [50].

Mitochondria also induce an immune response by the activation of mitochondrial antiviral-signaling protein which leads to the secretion of cytokines by the virally infected cells [51]. Furthermore, mitochondria induce mitochondrial apoptosis through mitochondrial outer membrane permeabilization (MOMP) which leads to the disruption of mitochondrial outer membrane and the release of intermembrane space proteins such as cytochrome c [52].

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3. Tryptophan-kynurenine metabolic systems

The aromatic amino acid L-Trp is an essential component for the biosynthesis of proteins and a substrate for the production of neurotransmitters and hormones [53]. Acute Trp deprivation increases pain sensitivity, motor activity acoustic startle, and aggression, while chronic Trp deficiency induces ataxia, cognitive impairment, and dysphoria [54,55]. A meta-analysis showed decreased levels of Trp in blood samples of patients with major depressive disorder, and BP [56]. Trp is catabolized in the serotonin (5-HT) and KYN metabolic system. More than 95% of L-Trp enters the KYN system producing several biomolecules. The main enzymes of the KYN system are tryptophan 2,3-dioxygenase (TDO), indoleamine 2,3-dioxygenases (IDOs), kynurenine formamidase (KFA), kynurenine 3-monooxygenase (KMO), kynurenine aminotransferases (KATs), and kynureninase (KYNU). The metabolites are L-KYN, kynurenic acid (KYNA), 3-hydroxy-L-kynurenine (3-HK), quinolinic acid (QUIN), and NAD^+. Those metabolites possess a wide range of biological properties such as oxidative, antioxidative, neurotoxic, neuroprotective, cognition enhancing and impairing, and/or immunomodulating properties and have attracted growing attention as potential biomarkers and therapeutic targets [19,57] (Figure 3).

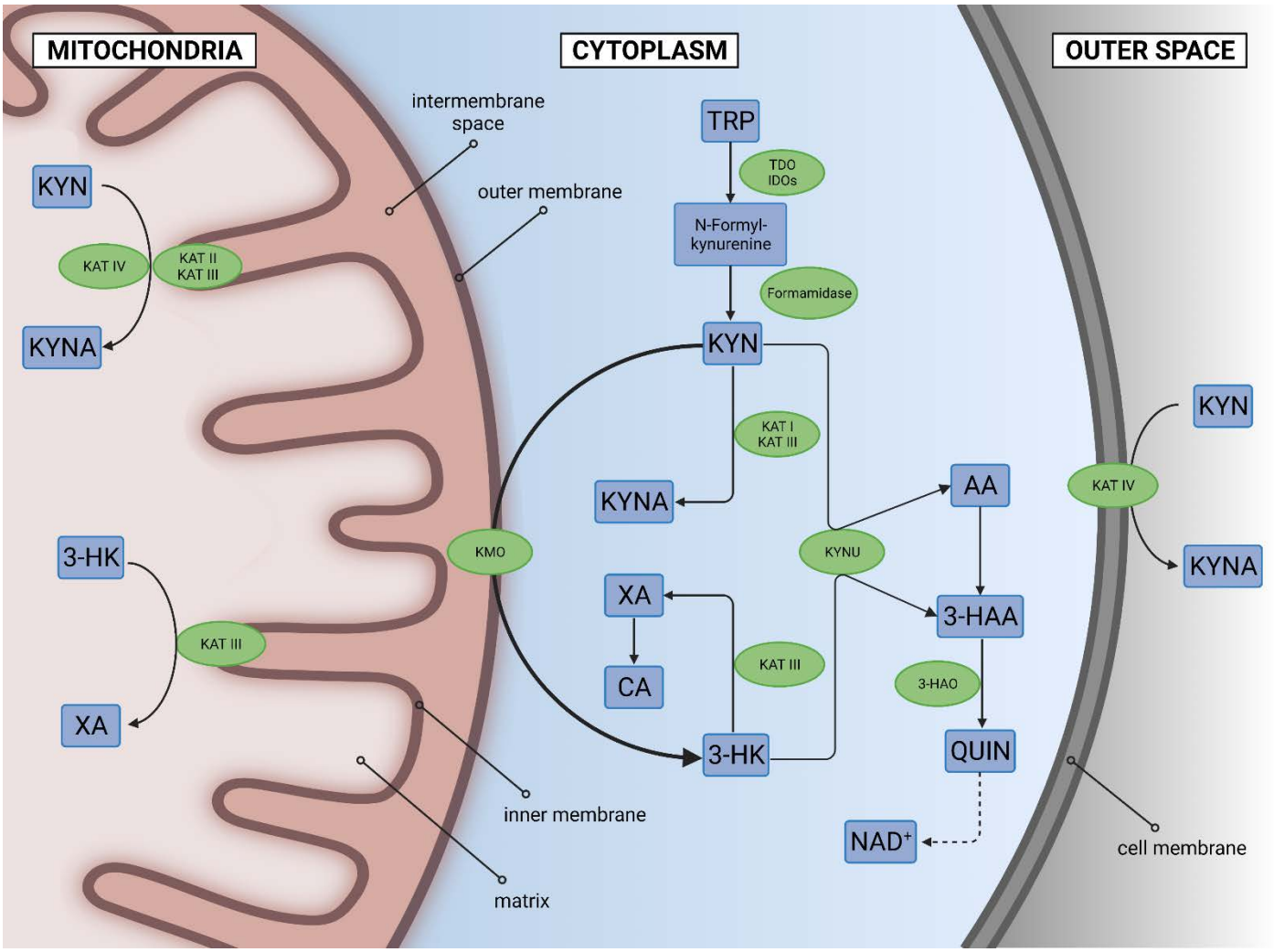

Figure 3. The tryptophan (Trp)-kynurenine (KYN) metabolic system and the subcellular location of the enzymes. More than 95% of L-Trp enters the KYN system producing multifarious biomolecules. The main enzymes of the KYN system are tryptophan 2,3-dioxygenase (TDO), indoleamine 2,3-dioxygenases (IDOs), kynurenine formamidase (KFA),

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kynurenine 3-monooxygenase (KMO), kynurenine aminotransferases (KATs), and kynureninase (KYNU). Most of enzymes are located in the cytosol. However, KMO is located in the outer membrane of mitochondria; KAT II and KAT III are in the inner membrane of mitochondria; and KAT IV is in the matrix of mitochondria and in the plasma membrane. The main metabolites are L-KYN, kynurenic acid (KYNA), 3-hydroxy-L-kynurenine (3-HK), quinolinic acid (QUIN), and nicotinamide adenine dinucleotide (NAD^+) which exhibit a wide range of biological properties such as oxidative, antioxidative, neurotoxic, neuroprotective, cognition enhancing and impairing, and/or immunomodulating properties.

3.1. Tryptophan 2,3-dioxygenase, indoleamine 2,3-dioxygenases, and kynurenine formamidase

TDO and IDOs are a heme-containing enzymes that catalyze the oxidation of L-Trp to N-formyl-L-kynurenine. This is the first rate-limiting step of the Trp-KYN system, which regulates the systemic level of Trp in the body. IDO1 also catalyzes D-Trp. TDO is a cytosolic enzyme encoded by gene *tdo2*, stimulated by the stress hormone cortisol and downward metabolite 3-HK [17,58]. Human *tdo2* gene polymorphisms are associated with attention deficit hyperactivity syndrome, Tourette syndrome, MDD, ASD, and SCZ [59,60]. *tdo2*$^{-/-}$ mice exhibited less anxious behavior, increased exploratory activities, and increased cognitive function, with increased concentration of Trp, 5-HT, 5-hydroxyindoleacetic acid, and/or KYN in the plasma, hippocampus, or midbrain [61,62]. However, it was later reported that anxiolytic and exploratory behaviors is less prominent in *tdo2*$^{-/-}$ mice [63,64]. Thus, the behaviors of *tdo2*$^{-/-}$ mice remain inconclusive.

IDOs are cytosolic enzymes with two isoforms. IDO1 is encoded by gene *ido1* and expressed in various parts of the body including the brain, while IDO2 is encoded by gene *ido2* and expressed in limited type of tissues as kidney, liver, or antigen presenting cells [65,66]. The two isoforms differentiate in kinetics, substrate specificity, and function. IDOs are upregulated by pro-inflammatory cytokines and lipopolysaccharide while downregulated by anti-inflammatory cytokines and antioxidant enzyme superoxide dismutase [17].

ido1$^{-/-}$ knockout mice showed diurnally hypolocomotive behavior with higher brain 5-HT levels and attenuated nociceptive sensation and depressive-like behavior [62,67]. Furthermore, Bacille Calmette-Guérin (BCG) elicited proinflammatory cytokines, but BCG-induced depressive-like behavior was not induced in *ido1*$^{-/-}$ knockout mice [68]. However, another study reported that *ido1*$^{-/-}$ knockout mice did not exhibit any significantly diferent behavior, compared to the wild type, in comprehensive behavioral assessments including the domain of cognitive function, negative valance system, motor function, social interaction, and pain sensitivity [69]. *Ido2*$^{-/-}$ knockout mice increased exploratory activity during light phase [62]. *ido1* polymorphism is asscociated with the susceptibility of interferon α treatment-induced depression in patients with chronic hepatitis C [70]. The common polymorphisms of *ido1* and *ido2* genes are associated with the outcome of a selective serotonin reuptake inhibitor (SSRI) citalopram treatment [71].

N-formyl-L-kynurenine hydrolyses to L-KYN spontaneously or enzymatically via KFA. The enzyme is encoded by gene *afmid*; predominantly cytosolic; expressed in the liver and kidney; and participates in glyoxylate and dicarboxylate metabolism [72]. KFA is stimulated by proinflammatory cytokine interferon-γ. L-KYN is an antioxidant and an aryl hydrocarbon receptor (AHR) agonist [73]. A meta-analysis showed decreased levels of KYN and an increased KYN/Trp ratio in blood samples of patients with MDD [56]. No study regarding KFA polymorphism or gene knockout has been reported.

3.2. kynurenine 3-monooxygenase

KMO is encoded by gene *kmo* and catalyzes the rate-limiting step of redox reaction from L-KYN to 3-HK. KMO is located in the outer membrane of mitochondria and is expressed in many tissues of the body including the brain glial cells microglia [74]. KMO is stimulated by oxygen molecules, pro-inflammatory cytokines, and downward metabolite NADH, while it is inhibited by the superoxide dismutase and anti-

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inflammatory cytokines [17]. 3-HK generates free radicals to elicit excitotoxic injury. The oxidant molecule 3-HK may function as an antioxidant in a certain condision [75]. A meta-analysis showed decreased ratio of KYNA/3-HK in blood samples of patients with MDD [56].

kmo$^{-/-}$ knockout mice have been generated to study the transgenic effects on the metabolites of the Trp-KYN metabolites. The levels of 3-HK were lower in the liver, brain, and plasma; the levels of QUIN were greatly lower in the liver and plasma, while slightly lower in the brain; the levels of KYN, KYNA, and anthranilic acid (AA) were substantially higher, but depending on a tissue; and the levels of NAD^+ were not different, compared to the wild type [76]. *kmo*$^{-/-}$ knockout mice showed lower contextual memory function, more anxious-like behavior, and higher horizontal activity upon a D-amphetamine challenge. The behaviors were associated with the elevated levels of KYNA in the brain, especially in the cerebellum. [77].

A small sample study reported that KMO single nucleotide polymorphism (SNP) rs1053230 polymorphism was potentially associated with lower CSF KYNA concentrations in SCZ patients [78]. KOM polymorphism has been associated with the cognitive dysfunction. The *KMO* rs2275163C>T C (risk) allele was related to the lower cognitive performace in healthy controls and it is more promominent in SCZ patients. Furthermore, other KMO polymorphism showed a trend effect in cognitive funtion [79].

3.3. Kynurenine aminotransferases

KATs belongs to transferases, specifically transaminases, employing pyridoxal 5'-phosphate (PLP). KATs typically catalyze substrates L-KYN and 2-oxoglutarte to 4-(2-aminophenyl)-2,4-dioxobutanoate and L-glutamate and then the unstable former product forms KYNA via intramolecular cyclization [80]. Kynurenine--oxoglutarate transaminase 1 (aka KAT I) encoded by gene by gene *kyat1*, kynurenine/ α-aminoadipate aminotransferase (KAT/AadAT, aka KAT II) encoded by gene *aadat*, kynurenine--oxoglutarate transaminase 3 (KAT III) encoded by gene *kyat3*, and aspartate aminotransferase (mAspAT, aka KAT IV) encoded by gene *got2* are isofoms representing KATs. KATI is located in the cytosol; KAT II is in the inner membrane of mitochondria; KATIII is in the inner membrane of mitochondria and the cytosol; and KATIV is in the matrix of mitochondria and the plasm membrane [81-84]. KYNAs are allosterically regulated by α-ketoglutarate in cooperation with KYN [85].

KAT I also catalyzes the reactions of the reaction of an S-substituted L-cysteine and H_2O to a thiol, NH_4, and pyruvate and of 3-phenylpyruvate and L-glutamine to 2-oxoglutarate and L-phenylalanine (Figure 1b). 2-oxoglutarate is the same as α-ketoglutarate [81]. Mitochondrial KAT II, KAT III, and KAT IV may compete for the substrate α-ketoglutarate of the TCA cycle, supplying L-glutamate in glutamine metabolism (Figure 1c) [82-84]. KAT II also catalyzes the reaction of 2-oxoglutarate and L-2-aminoadipate to 2-oxoadipate and L-glutamate. 2-oxoadipate is an intermediate molecule of L-lysin catabolism, which further degraded to glutaryl coenzyme A, and finally to acetyl-CoA, forming a side loop of the TCA cycle (Figure 1d) [82]. KAT III catalyzes the reactions of 3-HK and glyoxylate to glycine, H_2O, and xanthurenic acid (XA), of glyoxylate and L-KYN to glycine, H_2O, and KYNA, and of an *S*-substituted L-cysteine and H_2O to a thiol, NH_4^+, and pyruvate (Figure 1e) [83]. Furthermore, mitochondrial KAT IV catalyzes the reaction of 2-oxoglutarate and L-aspartate to L-glutamate and oxaloacetate, thus bypassing the TCA cycle and participating essential amino acid aspartate metabolism (Figure 1f) [84]. Thus, KAT enzymes relays molecules between the TCA cycle and glutamate, lysine, and aspartate metabolisms.

KYNA is a receptor antagonist of glutamate receptors including ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and N-methyl-D-aspartic acid (NMDA) receptors [86]. KYNA's action depends on its concentration at AMPA receptor and cognitive function [87,88]. KYNA's action at the α-7 nicotinic acetylcholine

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receptor in vivo remains controversial [89]. KYNA is a G-protein-coupled receptor 35 (GPR35) ligand and an AHR agonist. A meta-analysis showed decreased to ratios KYNA/KYN, KYNA/QA and KYNA/3-HK in patients with MDD, a decreased level of KYNA and a decreased ratio of KYNA/QA in patients with BD [56]. XA is an AHR agonist, may be Group II metabotropic glutamate receptor agonist, and the glutamate vesicular transporter (VGLUT) inhibitor [90,91]. A meta-analysis revealed the lower XA level in blood of patients with BP and a significant lower level of XA was observed in the serum of SCZ patients [92,93].

The intracerebroventricular (i.c.v.) administration of KYNA was reported to enhance memory function at low doses but impair it at higher doses in passive avoidance test of mice [94]. Furthermore, i.c.v. KYNA and synthetic KYNA analogues showed antidepressant-like effects in modified forced swim test of mouse [95,96].

aadat$^{-/-}$ (aka *kat2*$^{-/-}$) knockout mice exhibited transitory hyperlocomotive activity and abnormal motor coordination during postnatal day17 to 26 with transiently reduced total brain KAT activity and KYNA levels during the first month, which returned to normal levels later [93]. Three-week old *kat2*$^{-/-}$ knockout mice showed significantly increased cognitive functions including object exploration and recognition, passive avoidance, and spatial discrimination with significantly reduced levels of KYNA in the hippocampus [97]. Intriguingly, homozygous *got2*$^{-/-}$ knockout mice result in embryonal death *in utero* [98]. No study has been reported regarding KATs variants associated with psychiatric symptoms.

3.3. Kynureninase

KYNU is a PLP-dependent hydrolase, encoded by gene *kynu*, which catalyses L-KYN to AA and L-alanine and 3-HK to 3-hydroxyanthranilic acid (3-HAA) and (3-arylcarbonyl)-alanines. The enzyme also has cysteine-conjugate-beta-lyase activity. KYNU is located in the cytosol [99]. However, there is a report that the enzyme has no activity for L-KYN and is inhibited by L-KYN and D-KYN. AA inhibits the TCA cycle and respiratory chain complexes I–III, interfering with mitochondrial function [100]. 3-HAA is also biosynthesized from AA by spontanous hydroxylatin. AA was once thought to be water-soluble vitamin L_1 and is possibly related to an endogenous anti-inflammatory derivatives in the celluar environment, as the molecule is a pharmaceutical precursor of nonsteroidal anti-inflammatory agents such as mefenamic acid and diclofenac [101]. 3-HAA can be either an oxidant or an antioxidant depending on the cellular condition. AA and 3-HAA suppress pro-inflammatory cytokines and invoke anti-inflammatory cytokine interleukin [IL]-10 [102].

kynu$^{-/-}$ knockout mice have been generated; however, no study has been reported regarding neurological and psychiatric diseases. Homogyzgous variant KYNU p.V57Efs*21 and heterozygous KYNU variants p.Y156* and p.F349Kfs*4 were identified in patients with vertebral, cardiac, renal, and limb defects syndrome 1, autosomal recessive congenital malformation, characterized by vertebral segmentation abnormalities, congenital cardiac defects, renal defects, and distal mild limb defects. The NADH levels of patients is significantly lower [103]. KYNU SNP rs2304705 has been associated with essential hypertension and 50% reduction of enzyme activity, but the activity reduction was not observed in another SNP [104].

In humans, increased levels of pro-inflammatory cytokine IL-1, associated with reduced levels of hippocampal neurogenesis, have been reported in depressed patients and in animal models of depression [105,106]. Identifying the mechanisms by which inflammatory cytokines block neurogenesis in the human brain would provide insight that might be used to manage inflammation-associated mental health disorders, including the discovery of new diagnostic and treatment therapies for depression [107,108]. Recently, the potential of a novel approach, the time-frequency decomposition of heart rate vairiability, has gained attention in the evaluation of the abnormal fear learning that

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characterizes several neurological and psychiatric disoders [109] also, several studies have suggested the effectiveness of non-invasive brain simulation to interfere and modulate the abnormal activity of neural circuits such as amygdala-medial prefrontal cortex (PFC)-hippocampus involved in the acquisition and consolidation of emotional memories, which are altered in psychiatric disorders, such as fear-related disorder including anxiety disorder, phobias, post-traumatic stress disorder (PTSD), or depression [110-112].

3.3. 3-hydroxyanthranilate 3,4-dioxygenase, and toward the tricyclic carboxylic cycle

3-hydroxyanthranilate oxidase (3-HAO) is the most active enzyme of Trp-KYN metabolic system, encoded by gene *haao*. The non-heme iron dependent enzyme 3-HAO catalyzes 3-HAA to 2-amino-3-carboxymuconate semialdehyde (ACMS), which spontaneously cyclizes to QUIN. The enzyme is located in the cytosol [113]. QUIN forms a highly reactive free radical and is a NMDA receptor agonist which elicits excitotoxicity [114]. The concentration QUIN is increased upon immune activation and decreased by immune suppressant dexamethason [115,116]. QUIN inhibits around 35% succinate dehydrogenase, an enzyme involved in the TAC cycle and in the respiratory chain [117]. *haao* gene variants HAAO p.D162* and HAAO p.W186* were identified in patients with vertebral, cardiac, renal, and limb defects syndrome 1 and the NADH level of the patients were significantly lower [103].

Quinolinate phosphoribosyltransferase (QPRT) catalizes QUIN to nicotinic acid mononucleotide (NaMN), which is converted by NaMN adenyltransferase to nicotinic acid adenine dinucleotide (NaAD). Finally, NAD synthetase converts $NaAD^+$ to NAD^+. ACMS is catalized by 2-amino-3-carboxymuconate-6-semialdehyde decarboxylase (ACMSD) or picolinate carboxylase to 2-aminomuconic-6-semialdehyde (AMS) that nonenzymatically cyclized to picolinic acid (PIC) [17]. The significantly lower levels of PIC were observed in ASD [118]. XA is converted to cinnabarinic acid (CA) by autoxidation. CA is also produced from 3-HK or QUIN. CA is an AHR agonist and the reduced concentration of CA in the PFC is linked to SCZ [119]. 2-aminomuconate semialdehyde dehydrogenase (AMSD) catalyzes the conversion of AMS to 2-aminomuconic acid, which is further degraded to acetyl-CoA that replenishes the TCA cycle [101].

Currently, research is focusing on finding scientific frameworks for understanding the relationship between molecular regulation of higher order neural circuits and neuropathological alterations, and how this may lead to PFC dysfunction and to the symptoms of mental illness. The deficit in control and motor inhibition, which depend on aberrant neural activity in the PFC associated with serious impulsivity problems are characterized in psychopathological and psychiatric conditions including MDD, SCZ, obsessive-compulsive disorder (OCD), and PD, among others [120,121].

Furthermore, functional alterations in the PFC affects the memory and learning abilities of psychiatric and brain-damaged patients. The human ventromedial PFC is responsible for the capacity of associative learning [122,123] Hypoactivation in the ventromedial PFC with hyperactivation in the dorsal anterior cingulate cortex are reported in patients with PTSD and SCZ [124,125]. These evidence suggests that PFC dysfunctions cause impairment of aversive learning and emotional memory circuits, which might be transversal across many psychiatric disorders in humans.

4. Diseases linked to mitochondrial dysfunction

The activity of neurons depends on mitochondrial function to elicit membrane excitability, execute neurotransmission, and maintain neuroplasticity [126]. Mitochondria are located throughout the cytoplasm of neurons, but more mitochondria are found in energy-demanding areas such as in the sites of branching axons, synaptic contacts, and glial processes [127]. The volume fraction of mitochondria is the highest in the cortical layer IV and mitochondrial volume is higher in dendrites than axons in rats [128]. The dynamics

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of mitochondria is governed by mitochondrial fission, fusion, mitophagy, motility, and anchoring. Furthermore, mitochondria play a crucial role in axon degeneration and regeneration [128,130].

Mitochondrial dysfunction affects any part of the body, but the most vulnerable organs are those with high energy requirements, such as the central nervous system (CNS), peripheral nervous system, heart, and musculoskeletal system [131]. Mitochondrial diseases often go misdiagnosed or undiagnosed due to a wide range of manifestation, including fatigue, muscle weakness, visual or hearing loss, seizures, strokes, dementia, severe constipation, diabetes, thyroid or adrenal dysfunction, and heart, liver, or kidney failure, in addition to poor growth, developmental delays, learning disabilities, and ASD in children [132]. The conditions can appear in adolescence and in adulthood [133]. The mitochondrial dysfunction also exhibits psychiatric symptoms such as depression, cognitive impairment, psychosis, and anxiety [134]. Currently, there is no cure for mitochondrial diseases and the mainstay of the treatment remains symptom-relieving or progression-delaying measures, which vary from patients to patients and depend on the mitochondrial disease and its severity [135].

4.1. Primary mitochondrial diseases

PMD are a clinically heterogenous group of uncurable, chronic, and genetic conditions caused by the mutations of mtDNA. PMD commonly affect the nervous system of developmental stage, predominantly affecting skeletal muscles but presenting many non-specific symptoms from muscle weakness to seizure [136]. The mutations of the genes may encode proteins functioning for OXPHOS, mtDNA replication and expression, mitochondrial dynamics, homeostasis, and quality control, mitochondrial metabolism, metabolism of cofactors, and metabolism of toxic compounds, among others [137].

The severe form of PMD typically present early in life, but the milder forms tend to have later presentations [138]. Primary mitochondrial myopathy (PMM) causes progressive external ophthalmoplegia, frequently presented with diplopia, bilateral ptosis, or a head tilt. Progressive external ophthalmoplegia can be a part of syndrome with facial muscle weakness or paralysis, swallowing difficulty, slurred speech, or breathing difficulty. Furthermore, PMM may show involvement of the muscles of the neck, shoulder, arms, hips, or legs, presenting cramping stiffness, weakness, pain, or paralysis the affected muscles. Exercise intolerance is a common symptom [139]. Mitochondrial encephalomyopathy is characterized by neurological involvement of infancy or childhood, such as vision loss, sensorineural hearing loss, migraine, ataxia, or seizures. Other neurological manifestation includes dysphagia, dysarthria, myasthenia, or muscle rigidity. Some patients experience peripheral neuropathy. Developmental delays, failure to thrive, or short statue is a common finding in children [140]. In addition, many genetic disorders present mitochondrial myopathy or encephalomyopathy as a part of main symptoms involved in multiple organ systems [141].

The diagnosis is made clinically, but very difficult and not always confirmed by a DNA mutation. The causative gene mutations can be located in both mtDNA and nDNA [142]. 413 genes have been associated with PMDs. PMDs caused by mtDNA are estimated to have a prevalence of 1 in 5,000 cases, while PMDs caused by nDNA are estimated to have prevalence of 1 in 35,000 [143]. The mutations can be either inherited or spontaneous. The mutations of nDNA can be inherited either autosomal dominantly or autosomal recessively. The mutations of mtDNA are inherited only maternally [144]. A variety of clinical manifestations in a single family may be due to heteroplasmy of mtDNA or the different number of mutant mtDNAs in daughter cells as a result of mitosis. Currently, there is no cure for mitochondrial diseases and the mainstay of the treatment remains symptom-relieving or progression-delaying measures, which vary from patient to patient and depend on the mitochondrial disease and its severity [135].

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Leigh syndrome is a neurodegenerative disorder, and it is the most prevalent mitochondrial disease in childhood. We know more than 75 genetically mutations, which appear in the basis of the disorder [145]. A recent study shown a reduction in the L-KYN and 3-HAA levels in blood with French Canadian variants of Leigh syndrome patients. In addition to this, the level of indoxyl sulfate increased in these patients which suggest a shift in Trp metabolism to indol pathway [146]. Trp can metabolizes not only into KYN or 5-HT, but also to indoxyl sulfate. Thus, Trp can transform to indole by tryptophanase and indole metabolizes to indoxyl by cytochrome P450 2E1. Thereafter, sulfotransferase can convert indole to indoxyl sulfate [147].

Leber hereditary optic neuropathy is accompanied by a degeneration of retinal ganglion cells, causing loss of vision [148]. The patients usually have some mutations in the genes, which encode complex I in the ETC. In patients with Leber hereditary optic neuropathy, have found a decrease levels of Trp and glutamate, suggesting the possible role of the Trp-KYN metabolic system in the pathomechanism of disease [149,150].

4.2. Secondary Mitochondrial Dysfunction

SMD can be caused by genes not encoding proteins for OXPHOS or mitochondrial functions, secondary to other illness such as cancer, sepsis, infectious, or metabolic, neuromuscular, neurodegenerative, and psychiatric diseases, by drugs such as tetracycline and valproate, by environmental factors including alcohol, cigarette smoke, carbon monoxide, asbestos, and metals, and antiretroviral, tetracycline, valproate, and aminoglycosides therapy, or in consequence of normal ageing [151]. Therefore, SMD can be inherited or acquired and is in contrast to PMD, which can only be inherited. Diagnosis of SMD is made based on clinical signs of mitochondrial dysfunction with negative or equivocal DNA tests. But it is often difficult to distinguish SMD from PMD, but important for the prognosis and treatment. Sometimes the treatment of PMD is effective to SMD [22].

4.3. Neurological disesases linked to mitochondrial dysfunction

The loss of stress resilience and functional impairment of mitochondria have been linked to neuropsychiatric symptoms comorbidities of neurological diseases such as AD, PD, HD, ALS, FA, and Charcot-Marie-Tooth disease [152,153,154]. Preclinical animal research plays a major role in revealing the involvement endogenous peptides, neurohormone, and metabolites including KYNs [155-157].

4.3.1. Alzheimer's disease

AD is the most common chronic neurodegenerative disease with an insidious onset of progressive cognitive dysfunctions, particularly memory impairment, but it progresses to motor, sensory, motor, and autonomic dysfunctions in later sage [158]. The age-related impairments in the ability to process contextual information and in the regulation of responses to threat are related to structural and physiological alterations in the PFC and medial temporal lobe [159]. Brain autopsy and imaging studies reveal the atrophy of the brain including the frontal, temporal, parietal, entorhinal cortices, amygdala, and hippocampus [160]. Not specific to AD, but the deposition of amyloid beta (Aβ) peptide and tau protein is also a characteristic finding [161].

More than 170 genetically manipulated mouse models of AD have been created. Most transgenic mouse models of AD are designed to overexpress genes associated with early onset familial type of AD, such genes *APP*, *PSEN-1* and *PSEN-2* genes and the mouse strains are characterized with the pathological deposition of Aβ peptide [162]. Mitochondrial dysfunction including decreased mitochondrial respiration and pyruvate dehydrogenase protein was observed in the brain of triple transgenic mice of AD (3xTg-AD) at age of 3 months, while mitochondrial Aβ level is significantly increased in 3xTg-AD at age of 9 months. Mitochondrial impairment was even detected in embryonal neurons of 3xTg-AD [163]. Mitochondrial impairments were reported in a transgenic mouse expressing human amyloid precursor protein with the Arctic mutation (TgAPParc) mice at age of six

 doi:10.20944/preprints202207.0130.v1

months. The mitochondrial membrane potential was decreased; an amount of reactive oxygen species was increase; and oxidative DNA damage were increased. The mitochondrial abnormality is more prominent in TgAPParc mice at age of 24 months [164]. Mitochondrial dysfunction was also observed in transgenic mice carrying the APP_{SWE} and $PSEN1_{dE9}$ mutations, heterozygous sodium dependent vitamin C transporter ($SVCT2^{+/-}$) knockout mice, and transgenic APP/PSEN1 mice with heterozygous SVCT2 expression at age of 4 months [165]. However, familial AD accounts for less than 5% of AD. Recently, human Aβ-knock in (KI) mouse has been engineered, which mimics a late onset type. hAβ-KI mouse develops age-dependent phenotypic and behavioral alterations and may be more relevant to study polygenic and multifactorial pathogenesis of AD [166].

The ratio of KYN/TRP was increased in the plasma and CSF of patients with AD and an increased 3-HK/KYN ratio in samples from CSF was positively correlated with amounts of t-tau and p-tau peptides, while plasma KYN and PIC inversely correlated with p-tau and t-tau, respectively [167-172]. The levels of KYNA were found to be decreased in the plasma of AD patients [169]. AD had strong effect sizes for shared deficits in complex I and IV in the peripheral blood, frontal cortex, cerebellum, and substantia nigra [173].

4.3.2. Parkinson's disease

PD is a progressive neurological disorder that affects the motor system with muscle rigidity, tremors, and changes in speech and gait. PD patients frequently experience non-motor symptoms (NMS) such as sensory complaints, mental disorders, sleep disturbances, and autonomic dysfunction. NMS often occurs in PD due to the loss of dopamine-producing cells and the presence of Lewy bodies in the brain, having negative impacts on the quality of life and causing major challenges for disease management [174,175]. Studies in healthy individuals have revealed that modulation of autonomic nervous system responses is fundamental for behavioral regulation [176,177]. The pathogenesis of PD is considered to be largely due to the denervation of dopaminergic nigrostriatal nervous system and the aggregations of α-synuclein [175].

In a familial form of PD, mutations have been identified in genes encoding mitochondrion-associated proteins such as mitochondrial phosphatase and tensin homologue (PTEN)-induced kinase 1 (PINK1), Parkinson juvenile disease protein 2 (parkin), DJ-1 (Parkinson disease protein 7), and coiled-coil-helix-coiled-coil-helix domain containing 2 (CHCHD2) [178]. PINK1 knockout mice may use a prodromal model of PD, as the mice show olfactory and gain disturbances [179]. The Parkin knockout mouse is a classic transgenic PD model, while there are few studies using DJ-1 knockout rats [180]. Homozygous CHCHD2 knockout mice mimic PD pathology in an age-dependent manner: indistinguishable at birth, but fragmented mitochondria in dopaminergic neurons compared to the wild type [181]. NADH:Ubiquinone Oxidoreductase Core Subunit S2 (NDUFS2) is a subunit of complex I in neurons that produce dopamine. Mitochondrial complex I (MCI)-Park model that lacks the gene encoding NDUFS2 shows neurodegeneration [182]. However, transgenic mice that lack the gene encoding another complex I subunit NDUFS4 do not show neurodegeneration in dopaminergic neurons [183]. Complex I inhibitors 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and rotenone are used for pharmacological models of PD, while 6-hydroxydopamine (6-OHDA) injections applied for oxidative stress model of PD [184]. Various types of α-syn transgenic mice do not develop significant nigrostriatal degeneration [185].

Significant lower activities of KATI and KATII with a decreasing tendency of plasma KYNA levels were observed in the plasma samples of PD patients. Increased 3-HK levels in CSF and a lower KYNA/KYN ratio, increased QUIN levels, and higher QUIN/KYNA ratio were reported in plasma of PD patients [186,187]. In addition, it is reported that the single nuclear polymorphism variants of IDO1 influence the age onset of PD [188]. PD had strong effect sizes for shared deficits in complex I and IV in the peripheral blood, frontal cortex, cerebellum, and substantia nigra [173].

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4.3.3. Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune demyelinating neurodegenerative disease leading to the damage of neurons in CNS. More common symptoms of MS range widely from motor and autonomic dysfunctions to psychobehavioral disturbances including pain, cognitive and emotional changes, and depression [189]. The neural lesion characteristic in MS is numerous plaques which are glial scars in the white matter and spinal cord [190]. The pathogenesis and progression of MS is ascribed at least partly to mitochondrial dysfunction including reduced fidelity in gene expression, inadequate DNA repair, lower ATP supply, and increased reactive chemical species, and among others [191]. Monitoring the redox status in patients with MS has been proposed to assess stress resilience and thus predictive biomarkers for therapeutic agents [192].

The most characterized animal models of MS are experimental autoimmune/allergic encephalomyelitis (EAE), Theiler's murine encephalomyelitis virus-induced chronic demyelination, and toxin-induced demyelination [193]. After three days immunization in EAE abnormal mitochondrial morphology appears such as vacuolization, swelling, and crista dissolution [194]. Focal intra-axonal mitochondrial alteration proceeds focal axonal degeneration leading to axon fragmentation, which is triggered by macrophage-derived reactive chemical species [195]. Furthermore, the mitochondria of the spinal cord axon are depolarized, fragmented, and trafficking impaired in EAE mice [196]. Cuprizone produces cellular megamitochondria, leading to ATP shortage, reactive chemical species production, and ER stress in oligodendrocytes [197]. In addition, cuprizone mobilizes iron molecules from ferritin by chelating copper, leading to iron-mediated lipid peroxidation. The ferroptosis also leads to producing more reactive chemical species via the Fenton reaction [198,199]. Upon the withdrawal of toxin treatment, the mitochondria reverse to normal original morphology [199,200].

Up to only a half of polymorphic loci is identified in the nuclear genome in MS inheritance. The rest of inheritable polymorphic variants may lie in the mitochondrial genome and interaction of mitochondrial and nuclear genes. The allele m.9055*G is found to be mitochondrial variant associated with MS. The mitochondrial variants m.4216, m.4580, or m.13708 in biallelic combinations with nuclear gene variants of IL7R, CLEC16A, CD6, CD86 or PVT1 is found to be associated with MS [201]. Regarding KYNs, the significantly decreased levels of KYNA were observed in the plasma and the brain tissue of mice treated with cuprizone [202].

The KYN/TRP ratio was significantly increased in serum of MS patients. The QA levels were elevated, while NADH was decreased. 3-HK was found to be significantly higher in MS groups. The QA/KYNA ratio was higher in primary progressive MS, secondary progressive MS, and relapsing-remitting MS. KYNA levels were the highest in primary progressive MS, but lower in progressive MS [203]. Significantly elevated QA/KYN and QA/KYNA ratios were observed in the CSF of the relapsing subgroup of relapsing-remitting MS. TRP, KYNA, and QA levels were increased in primary progressive MS, while TRP and KYNA levels were decreased in secondary progressive MS [204]. KYNA levels were significantly increased in the plasma of MS patients [205].

4.3.4. Huntington's disease

HD is a fatal autosomal-dominant disease characterized by progressive and irreversible motor dysfunctions leading to coordination and gait difficulties and cognitive and behavioral changes. Degeneration and neural loss of the striatum, particularly the caudate nuclei, targeting the cerebral cortex, pallidum, thalamus, brainstem, and cerebellum, are specific neuropathological findings in HD [206]. An abundance of ballooned neurons in the cerebellum, thalamus, and brain stem are a characteristic finding [161]. Mutant huntingtin (HTT) protein is associated with ballooning cell death.

The R6/1 and R6/2 mice are the first transgenic mice generated with a gene containing the promoter and exon 1 of human HTT with 115 or 150 CAT repeats, respectively. The

 doi:10.20944/preprints202207.0130.v1

transgenic mouse exhibits cognitive and motor deficits, irregular gait, clasping, weight loss, and seizure, resulting in early death [207]. The R6/2 model has exhibited age-dependent changes in mitochondrial respiration in different regions of the brain [208]. The bacterial artificial chromosome transgenic mouse model of HD which carries full-length mutant HTT with a mixture of 97 CAG-CAA repeats exhibits progressive motor dysfunction, synaptic dysfunction, late-onset neuropathology, and neural degeneration [209]. Many knock-in models of HD have been generated [210]. The knock-in mice have the advantage in carrying a certain mutation under the endogenous *Hdh* promoter. Some models develop behavioral, molecular, cellular, and neuropathological phenotypes at an early age [210]. The role of aggregates remains unclear. The development of aggregates inhibitors has been under extensive research; however, the aggregates may not play an important role in the pathogenesis [211]. The homozygous HdhQ111 knock-in mutant huntingtin was found to be associated with the outer mitochondrial membrane, directly induced mitochondrial permeability transition (MPT) pore opening, and significantly decreased the Ca^{2+} threshold to trigger MPT pore opening [212]. Knock-in mouse models exhibit the slow progression of behavioral abnormalities and thus, they may help revealing the pathomechanisms of HD and identifying a new target for therapeutic intervention [213].

The lower levels of TRP and higher levels of KYN together with the higher KYN/TRP ratios were found in the serum of HD patients, suggesting the up-regulation of IDO activity [214]. The higher levels of 3-HK and QA and the higher activity of #-HAO were observed in the striatum [215,216]. In contrast, the lower levels of KYNA and the lower activity of KAT were found in the plasma and the brain [217,218]. The levels of AA are found to be well correlated with the inflammatory status and the number of CAG repeats [219]. Thus, AA may be a potential prognostic biomarker for HD.

4.3.5. Amyotrophic Lateral Sclerosis

ALS is a progressive neurodegenerative disease causing the dysfunction of neurons controlling voluntary muscles. ALS often begins with fasciculation, myasthenia, or dysarthria, progressing to the involvement of the muscles responsible to move, speak, eat, and breathe [220]. Mitochondrial impairment is an early pathological event in ALS, leading to the death of motor neurons. The dysfunction of mitochondria affects calcium homeostasis, mitochondrial respiration, ATP production, mitochondrial dynamics, and apoptotic signaling. This is caused by the accumulation of ALS-associated mutant proteins such as superoxide dismutase 1 (SOD1), transactive response (TAR) DNA binding protein 43 kDa (TDP-43), fused in sarcoma, chromosome 9 open reading frame 72 (C9orf72) gene product, and the C9orf72 GGGGCC repeat expansion-associated glycine/arginine dipeptide repeat protein [221].

Current rodent ALS models include the Friend leukemia virus B (FVB)-C9orf72 bacterial artificial chromosome (BAC) mouse that carries *C9orf72* mutations most associated with ALS, Cu/Zn SOD1-G93A mouse that encodes the human SOD1 protein containing the G93A mutation, and TDP43-Q331K mouse model that mildly overexpresses human mutant TDP-43 [222]. The FVB-C9orf72 BAC mice develop paralysis and the loss of neuromuscular junction integrity, but the pathological manifestation depends on mouse strain. The Cu/Zn SOD1-G93A mice show progressive motor dysfunction and loss of motor neurons, but it also depends on mouse strain and there is no evident upper motor neuron loss. The TDP43-Q331K mice develop progressive motor dysfunction with motor neuron and axon degeneration, but the progressive degeneration is limited in time, and it does not lead to death [222]. Morphological abnormalities have been observed in ALS models. Mitochondria were swollen in an induced pluripotent stem cells (iPSC) model of C9orf72-associated ALS [223]. The abnormal cluster formation of mitochondria was observed in the axon of SOD1 G93A transgenic mice [224]. The less elongated and more spherical mitochondria were isolated from the motor neuron of SOD1 G93A transgenic mice [225]. Expression of wild type or ALS TDP-43 mutants lead to abnormal morphology including aggregated, fragmented and vacuolated mitochondria [226].

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The environmental factors are considered to play a role in the pathogenesis of ALS and tabaco smoke has been linked to the of ALS. The exposure to bisphenol A (BPA), a chemical used in the production of polycarbonate plastics and beta-sitosterol beta-D-glucoside (BSSG), an estrogen receptor-binding phytosterol have been found neurotoxic to motor neurons and thus, those compounds have been applied to environmental models of ALS [222]. BPA induces neurotoxicity and neurodegeneration through alternation of mitochondrial functions leading to fission and apoptosis by translocation of dynamin-related protein 1 (Drp1) from the cytosol [227]. The neurotoxic effects of BSSG appears to be caused by mitochondrial production reactive oxygen species associated with succinate oxidation (Complex II) [228].

Significantly increased TRP, KYN, and QA in serum and CSF, and significantly decreased PA in serum were observed in ALS. The neuronal and microglial expression of IDO and the levels of QA were increased in the motor cortex and spinal cord of ALS patients [229]. The levels of KYNA in ALS remains inconclusive: studies showed significantly higher levels in the CSF, significantly lower levels in the serum, or no significant difference between healthy control and ALS patients [230]. Thus, the levels of KYNA may depend on the subgroup, the severity, and the stage of ALS and further study may reveal a potential role of KYNA measurement for biomarkers.

4.3.6. Migraine

Migraine is a primary headache disorder, characterized mostly by a headache on one side of the head. The exact pathomechanism of the disease is not fully known, but morphological and biochemical studies shown that the pathophysiology of migraine is linked to mitochondrial dysfunction [231]. Abnormal mitochondria have been identified in patients with migraine with aura [232] and with familial hemiplegic migraine [233]. In addition, increased levels of lactate were shown in blood and cerebrospinal fluid of patients with migraine, which clearly suggests a defective oxidative function [234,235]. Th activities of mitochondrial enzymes including monoamine oxidase, succinate dehydrogenase, NADH dehydrogenase, cyclooxygenase, and citrate synthetase were found reduced in the platelets of migraineurs [236,237]. Furthermore, the biochemical changes were restricted to enzymes of the respiratory chain encoded by mtDNA [232]. OXPHOS has been found impaired in the brain of patients with migraine during and between migraine attacks [238-240]. This impairment is seen as increased levels of ADP, decreased levels of organic phosphate, and a decreased phosphorylation potential [241]. Reyngoudt et al. found that brain ATP decreased by 16% between attacks in patients with migraine without aura compared with healthy controls [242].

The mitochondrial involvements in migraine have been reported in animal models of migraine. The rodent inflammatory soup model revealed that mitochondria were small and fragmented, and that the number of mtDNA was significantly reduced in the trigeminal neurons. Furthermore, fission protein Drp1 was increased while fusion protein Mitofusin1 (Mfn1) was decreased, suggesting that mitochondrial dynamics was under disturbance after repeated dural stimulation [243]. The same chronic migraine model also showed that the trigeminal nucleus caudalis decreased spare respiratory capacity, the amount of ATP to be produced by oxidative phosphorylation in case of a sudden increased demand [244]. Neuroprotective, antiepileptic, and migraine-prophylactic agent valproic acid stabilized mtDNA copy number, restored ATP level, and maintained the mitochondrial membrane potential in a rat model of nitroglycerin-induced trigeminovascular activation [245].

In the serum of chronic migraineurs, the levels of L-KYN, KYNA, 3-HK, 3-HAA, 5-HIAA, and QUIN were decreased, while the levels of L-Trp, AA, and XA were significantly higher compared to healthy controls [246]. The similar results were observed in patients with episodic or chronic cluster headache [247]. The levels of L-Trp, L-KYN, KYNA, 3-HAA, 5-hydroxyindolacetic acid, PIC, and melatonin were decreased in the plasma of episodic migraineurs in the interictal period. The tendency was more prominent

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in those without aura. In addition, the levels of 3-HAA, 5-hydroxyindolacetica acid, and melatonin were increased in the ictal period [248]. The expression of KAT-II enzyme was decreased in the upper cervical spinal cord (C1-C2) in nitorglycerin-induced trigeminovascular activation of rats [249]. Preclinical and clinical findings suggests that mitochondrial dysfunction and KYN metabolites play a role in the pathomechanism of migraine [250]. Furthermore, KYNs are also involved in the pathogenesis of chronic pain and their adjacent position to serotonin metabolism is drawing close attention to development of anti-migraine drugs [251,252].

4.4. Psychiatric disorders linked to mitochondrial dysfunction

Growing number of researchers cast more attention on the contribution of mitochondria in mental health, susceptibility by genetic variants, and its interaction with environmental factors. Clinical and preclinical studies are revealing evidence that the organelles play a key role in psychiatric disorders and neurodevelopmental disorder such as MDD, generalized anxiety disorder (GAD), PTSD, SCZ, ADHD, and ASD. Furthermore, preclinical animal research plays a major role in revealing the involvement of endogenous neurotransmitters, neurohormones, and metabolites [253-256].

4.4.1. Major depressive disorder

MDD is a mental disorder with at least two weeks of low mood, often accompanied by low self-esteem, loss of interest, low energy, and pain without a cause. The lifetime prevalence of MDD ranged from 2 to 21% [257]. The monoamine hypothesis has been prevailing for the pathogenesis of depression. The hypothesis holds that depression is caused by depletion of 5-HT, norepinephrine, or dopamine in the CNS [258]. The atrophic lesion and synaptic impairment in the PFC and hippocampus and hypertrophy and increased synaptic activity in the nucleus accumbens and amygdala are observed [259]. SSRIs are commonly used as first-line treatment for MDD. However, only 42-53% of patients treated with SSRIs see an improvement and medication for treatment-resistant depression remain a challenge [260]. Furthermore, psychotherapy is an effective treatment of choice, which can serve as a powerful measure for patients who cannot tolerate medication and KYNs may be potentially useful as prognostic biomarkers [261].

Chronic mild stress (CMS) model of depression showed decreased ATP production, decrease hippocampal NA^+, K^+-ATPase activity, and anhedonia in sucrose preference test [262]. The damaged structure, impaired respiration rated, and altered membrane potentials of mitochondria were observed in the hippocampus, hypothalamus, and the cortex of CMS mice which exhibit anhedonia in sucrose preference test and depression-like behavior in tail suspension test (TST) [263]. Furthermore, SSRI fluoxetine reversed that NA^+, K^+-ATPase activity, mitochondrial respiration, and sucrose preference in chronic unpredictable stress model [264]. Thus, mitochondrial dysfunction may be involved in depression-like behavior.

Transgenic models for depression have been generated by manipulating genes responsible for the metabolism of 5-HT. Tryptophan hydroxylase (TPH) is the rate-limiting enzyme in 5-HT biosynthesis. The *Tph1*−/− mice produced a normal level of 5-HT in the brain and showed no significant change in behavior [265,266]. The *Tph2*−/− mice exhibited depressive-like behavior in TST and anxiety-related behavior in marble burying test [247]. However, it was reported that Tph2 null mutants (*Tph2*−/−) mice showed slightly reduced depression-like and anxiety-like behaviors but significantly increased fear conditioning responses. The behaviors including impulsivity, aggressiveness, and emotional reactivity of *Tph2*−/− mice are sex-dependent [268]. The double knockout *Tph1*/*Tph2*−/−mice showed depressive-like behavior in TST and anxiety-related behavior in marble burying test but antidepressive-like behavior in forced swim test (FST) with reduced levels of 5-HT in the brain and periphery [269]. In addition, knock-in of TPH2 variant (R439H) in mice showed depression-like behavior in TST [270].

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MDD patients showed moderate effect sizes for similar abnormality patterns in the expression of complex I of samples from frontal cortex, cerebellum and striatum [173]. The levles of TRP, KYN and KYNA were decreased in the plasma of MDD patients, and the levels of QUIN was increased in MDD patients without antidepressant treatment. The immunoreactivity of QUIN was increased in the PFC and hippocampus of the postmortem brain tissues from MDD patients [271,272]. KYN analogues have been under extensive research in search for novel antidepressants [273].

4.4.2. Generalized anxiety disorder

GAD is a mental disorder characterized by excessive, uncontrollable and irrational anxiety. GAD has a combined lifetime prevalence of 3.7% [274]. 5-HT, dopamine, norepinephrine, and gamma-aminobutyric acid (GABA) are linked to anxiety [275]. The amygdala in the middle of the brain which processes emotion, memory, and fear are involved in GAD [276]. Benzodiazepines such as alprazolam, clonazepam, diazepam bring relief in 30 mins; SSRIs are the first line of treatment in GAD; and cognitive behavioral therapy is the most effective form of psychotherapy [277].

An increasing number of preclinical studies are revealing that anxiety is linked to mitochondrial functions including bioenergetics, oxidative stress, neurosteroid production, biogenesis, and apoptosis [278]. The mitochondrial dysfunction is located in the nucleus accumbens (NAc) which interfaces motivation and action, playing a key role in motivation, aversion, reward, and reinforcement learning. The shell of NAc is considered to be part of the extended amygdala [278]. The outbred Wiser rats which exhibit anxiety-like behavior showed the reduced expression of the mitochondrial GTPase mitofusin-2 (MFN2) in the NAc, altered mitochondrial morphology and functions, and the morphology of medium spiny neurons (MSNs) projecting from the NAc. The behavioral, mitochondrial, and neuronal phenotypes were reversed by the viral overexpression of MFN2 [279]. Furthermore, more anxious rats are prone to become subordinate during social encounter with less anxious rats and a social hierarchy is linked to the mitochondrial bioenergetic profiles of the NAc. Thus, anxiety appears to directly influence social dominance mediated by mitochondrial functions [280].

The levels of KYN were reduced in endogenous anxiety and normalized after treatment in the plasma samples. [281]. The levels of KYN were lower in people with Type D personality, the joint tendency towards negative affectivity and social inhibition [282].

4.4.3. Post-traumatic stress disorder

PTSD is a behavioral and mental disorder that develops after experiencing a traumatic event. Individuals with PTSD suffer from flashbacks, nightmares, severe anxiety, and uncontrollable thoughts regarding the event [283]. The lifetime prevalence of PTSD ranges from 6.1 to 9.2 percent [284]. PTSD is considered to be caused by insufficient integration of a trauma memory into the hippocampal-cortical memory networks, forming fragmented, incomplete and disorganized intrusive memories [285]. The primary treatment of PTSD is psychotherapy and SSRIs such as sertraline and paroxetine are considered first-line therapy for PTSD [286].

Animal models of PTSD are revealing the pathogenesis of PTSD. The genetic factors contributing to the development of PTSD include the stress response system such as the hypothalamic–pituitary–adrenal (HPA) axis, neuroplasticity such as brain-derived neurotrophic factor (BDNF), and monoamine neurotransmission such as serotoninergic, dopaminergic, glutamatergic, and GABA-ergic system [287]. FK506-binding protein 51 (FKBP5) is a co-chaperone which modulates glucocorticoid receptor activity. FKBP5$^{-/-}$ mice prevents age-induced impairment of stress resilience [288]. Chronic variate stress increases the bed nucleus of the stria terminalis pituitary adenylate cyclase activating polypeptide (PACAP) [289]. The pituitary adenylate cyclase 1 receptor type 1 knockout (PAC1R−/−) mice show reduced anxiety [290]. The BDNF promotor IV-disrupted mutant Bdnf-e4 mice and BDNF Met-Val mutant mice showed impair fear extinction [291,292].

 doi:10.20944/preprints202207.0130.v1

Serotonin 1A receptor knockout 5-HT1AR-/- mice show increased fear memory to contextual cues [293]. 5-HT transporter (5-HTT) gene knockout 5-HTT$^{-/-}$ mice show impaired stress response and impaired fear extinction with abnormal corticolimbic structure [294]. Dopamine is degraded by catechol-*O*-methyltransferase (COMT). COMT gene knockout COMT-/- mice showed an increased response to repeated stress exposures [295]. GABA is synthesized from L-glutamic acid by glutamic acid decarboxylase (GAD). 65-kDa isozyme of glutamic acid decarboxylase (GAD2) knockout GAD6-/- shows increased generalized fear and impaired extinction of cued fear [296,297]. GABA receptor subunit B1a knockout GABAB1a−/− mice shows a generalization of conditioned fear to nonconditioned stimuli [298]. Cannabinoids directly interact with GABAegic neurotransmission. Cannabinoid 1 receptor knockout CB1R−/− mice show an increased response to repeated stress exposures [299].

Mitochondrial functions are linked to PTSD-like behavior in preclinical studies. Following exposure to a trauma, mice with PTSD-like symptoms exhibit the reduced activities of mitochondrial electron transport in the cerebellum and the dysfunction of fatty acid oxidation in cerebellum and plasma. The activity of cerebellar mitochondrial electron transport complex is negatively correlated with PTSD-like symptoms [300]. Abnormal apoptosis has been observed in the brain areas closely associated with emotion and cognition, including the hippocampus, the amygdala, and the medial PFC in single prolonged stress model of PTSD [301]. In addition, decreased kynurenine pathway potentiates resilience to social defeat effect on cocaine reward [302].

No clinical study was reported regarding the peripheral or CSF samples of KYNs in patients with PTSD. KYN metabolites are monitored in clinical settings as evidence of inflammatory responses contributing to sleep deprivation and the formation of intrusive memories [303].

4.4.4. Bipolar disorder

BD is a mental disorder characterized by mood oscillations with episodes of mania and depression. A large cross-sectional survey of 11 countries found the overall lifetime prevalence of BD was 2.4% [304]. Neuroimaging and postmortem studies have found abnormalities in a variety of brain regions, and most commonly implicated regions include the ventral PFC and amygdala [305,306]. Dysfunction in emotional circuits located in these regions have been hypothesized as a mechanism for BD. The left side of the hippocampus regulates verbal and visual memory. This part of the brain also helps regulate how you respond to situations emotionally. When your mood shifts, your hippocampus changes shapes and shrinks [307]. Patients with BP showed diminished GABA neurotransmission. Thus, low GABA levels can result in excitatory toxicity [308].

There have been no established animal models of BD that exhibit both manic and depressive episodes. Typical current animal models of mania involve drug-induced hyperactivity or genetically modified animals that exhibit continuous hyperactivity. Targeting circadian rhythm genes to disrupt mechanisms regulating the circadian rhythm has been widely used to create animal models for BD [309].

The most common model is the *ClockΔ19* mutant mouse. These mice carry a deletion at exon 19 of the *Clock* gene, resulting in a dominant-negative protein, unable to activate transcription [310]. Mutant mice exhibit mania-like behavior and altered sleep patterns [311]. The dominant negative mutant of mtDNA *Polg1* transgenic mice showed recurrent hypoactive periods [312]. The withdrawal of lithium provoke depression in the mice, while antidepressant medications alleviate depressive symptoms [313]. Thus, the transgenic strain appears to be a good animal model for BD.

Meta-analysis revealed that BD showed moderate effect sizes for similar abnormality patterns in the expression of complex I of samples from frontal cortex, cerebellum and striatum [173]. The dysfunctional mitochondrial hypothesis is one of current hypotheses attempts to explain the origin of mood disorders. Many studies have confirmed that mood

 doi:10.20944/preprints202207.0130.v1

stabilizers affect mitochondrial functions, even though the exact mechanism or localization of action is unknown [314].

Regarding the KYN system a case-control study showed that KYNA levels were reduced and the 3-HK/KYN and 3-HK/KYNA ratio was increased in BD compared to healthy control [315]. However, a meta-analysis reported no significant difference of TRP and KYN levels, KYN/TRP and KYNA/QUIN ratios in serum from BD patients [316] KYNA was significantly increased in CSF of BD patients [317]

4.4.5. Substance use disorders

Substance use disorder (SUDs) is a mental disorder affects the brain and behavior leading to an inability to control the use of a drug or medication. The exact cause of SUDs is not known, but the known risk factors are the genes, the action of the drug, peer pressure, emotional distress, anxiety, depression, and environmental stress [318]. In addition to an impaired control, common substances are alcohol, sedatives, caffeine, hallucinogens, inhalants, stimulants and tabaco, among others [319]. The main brain area associated with SUDs is the limbic system, comprising of the cingulate gyrus, amygdala, hippocampus, PFC, ventral tegmental area, and the nucleus accumbens. The system is related to reward, emotion, and punishment [320].

The mitochondrial copy number were found to be reduced in blood samples of patients with opioid use disorder; however, the link between changes in the reward neural circuitry and the peripheral measurements remains unclear [321]. No clinical study was found regarding KYNs in patients with SUDs. Although there are few studies, growing attention is paid to a relationship between KYN metabolites and SUDs, the alteration of the Trp-KYN system, and a potential approach to SUDs including ethanol, nicotine, cannabis, amphetamines, cocaine and opioids [322]. Furthermore, 5-HT concentration was significantly higher and the KYN/5-HT ratio was significantly lower in plasma of patients with cocaine use disorder (CUD-induced MDD than those with MDD but there were no differences between CUD-primary MDD and MDD. It may suggest that the TRP-KYN pathway participates less in CUD-induced MDD [323].

4.4.6. Schizophrenia

SCZ is a mental disorder characterized by abnormally interpret reality, hallucinations, delusions, apathy, lack of social functioning, and extremely disordered thinking and behavior. cognitive symptoms including difficulty in concentration and attention, and memory impairments can be subtle [324]. SCZ is generally considered to be a neurodegenerative disorder with neurodevelopmental antecedents. The underlying changes occur before the onset of symptoms arising from the interaction between genes and the environment, leading to deficits in the neural circuitry in age of 18-25 [325]. Maternal infections, malnutrition, and complication during pregnancy and parturition are risk factors [326]. Many people with SCZ have hypertension, disturbance of lipid metabolism, and other mental disorders, including SUDs, MDD, GAD, and OCD [327-329].

Disrupted in schizophrenia 1 (DISC1), encoded by the *DISC1* gene, is a protein which plays a role in presynaptic regulation of dopamine. DISC1 alterations increase the risk of SCZ [330]. DISC1 also plays various roles in many other cellular functions including mitochondrial transport, fission, and fusion. The dynamic processes of mitochondrial transport, fission, and fusion determine mitochondrial morphology, localization, and network [331]. DISC1 mouse models display abnormal changes relevant to SCZ. The neuroanatomical changes include displaced dentate granule neurons, altered axonal targeting, reduced dendrite growth, and dendritic spine density. The behavioral abnormalities include impairment of working memory [332].

Neurodegenerative changes in SCZ are caused by a series of malfunction including mitochondrial impairment, oxidative stress responses, and the activation of immune responses, leading to chronic low-grade inflammation [17]. Clinical studies linked mitochondrial impairment with increased risk of SCZ and suggested abnormal mitochondrial dynamics contribute to compromising normal neural connectivity in the brain of SCZ

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[333,334]. Furthermore, meta-analysis revealed that SCZ showed moderate effect sizes for similar abnormality patterns in the expression of complex I in samples from frontal cortex, cerebellum and striatum [173].

Regarding the Trp-KYN metabolic system, the ratios of KYN and KYN/TRP was higher in the serum of SCZ patients [335]. Meta-analyses showed increased KYN and KYNA levels in CSF samples of SCZ patients and increased levels of KYNA in plasma, CSF, brain tissue or saliva, respectively [53,336]. Thus, the KYN system is activated in SCZ and elevated KYNA levels are considered to contribute to the impairment of cognitive function. However, another meta-analysis reported that KYNA levels and the KYNA/3-HK ratio were not altered and the KYNA/KYN ratio was decreased in SCZ, suggesting the presence of differential pattern between SCZ and mood disorders [53].

4.4.7. Autism spectrum disorder

ASD is a neurodevelopmental disorder characterized by persistent deficits in social interaction, restricted-repetitive patterns of behavior, and the loss of interests or activities [337]. These social impairments may be related to the interpretation of social signals [338]. Potentially threatening situations such as others' proximity can trigger a number of physiological responses that help regulate the distance between themselves and others during social interaction, showing the critical role of social signal interpretation in social interaction [339]. Individuals with ASD have social impairments, potentially due to the lack of social signal interpretation, and therefore resulting unable to interpret these signals to guide appropriate behaviors. The prevalence of mitochondrial diseases is higher in the population of ASC that general population and up to a half of children with ASD showed evidence of mitochondrial dysfunction [340]. However, most mitochondrial disease associated-ASD is not associated with genetic abnormalities, suggesting secondary mitochondrial impairment such as environmental factors [340].

Animal models of ASD include prenatal exposure to valproate during pregnancy, inbred strains of mice expressing autism traits, and genetical modification targeting autism-related genes including mtDNA [326,341]. Insertion of mtDNA *ND6* gene missense mutation ($ND6^{P25L}$) exhibits ASD endophenotypes including autism-like behaviors and electroencephalographic profiles and correlates with mitochondrial respiration and increased reactive oxygen species of the brain, suggesting a link to mitochondrial dysfunction [342]. Preclinical studies also showed links between the pathogenesis of ASD and maternal immune activation, maternal microbiota profile, and exposure to nutritional and toxic metals during mid-fatal development [343-345].

The alteration of the tryp-KYN metabolic system was also observed in patients with ASD. The levels of KYNA were significantly lower and the ratio of KYN/KYNA was significantly higher in the serum of children with ASD [346]. The ratio of KYN/Trp and the levels of KYN and QUIN were significantly higher in blood samples of ASD patients, but there was no significant difference in KYNA and the levels of PIC were significantly lower in ASD patients [347]

4.4.8. Attention dificit hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD) is a behavioral and neurodevelopmental disorder characterized by inattention, hyperactivity, and impulsivity, which are pervasive, impairing, and otherwise age inappropriate [348]. ADHD is associated with SUDs, alcoholism and other mental disorders including MDD, GAD, and ASD [349]. Furthermore, multidirectional relationships between stress, anxiety, and inflammation in the pathogenesis of ADHD are discussed recently [350].

Patched domain-containing protein (*Ptchd*) is a membrane protein with a patched domain. The deletion of *Ptchd* gene has been identified in patients with intellectual disability and autism spectrum disorder. The *Ptchd1* KO mice exhibits ADHD-like behavior. No changes in Trp and 3-HK were found, but significant increased levels of KYN, KYNA, AA, and 3-HK were observed in the serum of the *Ptchd1* KO mice. Meanwhile, no changes in KYNA levels, but significantly increased levels of AA, 3-HK, and 3-HAA were observed

 doi:10.20944/preprints202207.0130.v1

in the frontal cortex of *Ptchd1* KO mice [351]. A clinical study showed that the lower concentrations of Trp, KYNA, XA, 3-HAA were found in the serum of patients with ADHD and that higher levels of Trp and KYN were associated with higher scores of ADHD symptoms [352].

Mitochondria may be sensitive to psychological stress in early life [353]. People who experienced childhood trauma appear to possess a larger number of mitochondrial genomes per cell [354]. Indeed, mtDNA copy number was observed higher in the peripheral blood of ADHD patients, which suggests a possible link to mitochondrial impairments in the pathogenesis of ADHD [355].

7. Conclusion and future perspective

This review article recapitulated the involvement of mitochondria with an emphasis on its connection to the Trp-KYN metabolic system in clinical manifestations of neuropsychiatric symptoms and advances in preclinical research in major neurological and psychiatric disorders. Growing evidence has revealed that mitochondria have a close link to KYN metabolism and that mitochondrial dysfunction and the activation of the KYN system contribute to the pathogenesis of neuropsychiatric disorders. Extensive clinical and preclinical research has helped delineate multifunctional facets, compartmentalization, and dynamic nature of mitochondria including cell differentiation, cell-type determination, cell movement, and pattern formation. The pathological changes in functions, morphologies, and dynamics have been probed in mitochondrial diseases as well as diseases linked to mitochondrial dysfunction. For example, functional magnetic resonance imaging, measurements of fibroblast mitochondrial spare respiratory capacity, the NAD^+/NADH ratio, or Complex II levels, and a combination of detection of amyloid and/or tau protein and signs of neuronal injury on brain imaging or cerebrospinal fluid sampling are emerging techniques to assess mitochondrial functions.

However, little is known about the reversibility, plasticity, and/or resilience of mitochondrial functions, integrity, dynamics, and/or network formation. Measurement of such parameters is of particular importance. Revealing the link between mitochondria and the KYN metabolic system may be a promising option for this direction of research. Development of mitochondrial stress test, for example, which assess recoverability may help early detection of mitochondria-related diseases and possible application of prophylactic measures. For this purpose, engineering fine preclinical models high in construct, face and predictive validity is an essential step. Two-hits models consisting of a certain genetic susceptibility and environmental trigger with pharmacological agents which initiate neuropsychiatric manifestations would help develop preventive measures, understand the pathomechanism, make accurate diagnosis, delay disease progression, and choose the most appropriate therapeutic option.

Abbreviations

AA	anthranilic acid
Acetyl-CoA	acetyl coenzyme A
ACMS	2-amino-3-carboxymuconate semialdehyde
ACMSD	2-amino-3-carboxymuconate-6-semialdehyde decarboxylase
acyl-CoA	acyl coenzyme A
AD	Alzheimer's disease
ADHD	attention deficit hyperactive disorder
AHR	aryl hydrocarbon receptor

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ALS	amyotrophic lateral sclerosis
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMS	2-aminomuconic-6-semialdehyde
AMSD	2-aminomuconate semialdehyde dehydrogenase
Aβ	amyloid beta
ASD	autism spectrum disorder
ATP	adenosine triphosphate
BAC	bacterial artificial chromosome
BCG	Bacille Calmette-Guérin
BD	bipolar disorder
BPA	bisphenol A
BSSG	beta-sitosterol beta-d-glucoside
CA	cinnabarinic acid
CMS	chronic mild stress
C9orf72	chromosome 9 open reading frame 72
EAE	experimental autoimmune/allergic encephalomyelitis
ER	endoplasmic reticulum
ETC	electron transport chain
FA	Friedreich's ataxia
$FADH_2$	flavin adenine dinucleotide
FVB	Friend leukemia virus B
GABA	gamma-aminobutyric acid
GAD	generalized anxiety disorder
GTP	guanosine triphosphate
GPR35	G-protein-coupled receptor 35
H^+	proton
HD	Huntington's disease
5-HT	serotonin
i.c.v.	intracerebroventricular
IDO	indoleamine 2,3-dioxygenase
3-HAA	3-hydroxyanthranilic acid
3-HK	3-hydroxy-L-kynurenine
3-HAO	3-hydroxyanthranilate oxidase
HTT	huntingtin
iPSC	induced pluripotent stem cells
KAT	kynurenine aminotransferase
KFA	kynurenine formamidase
KI	knock-in
KMO	kynurenine 3-monooxygenase
KYN	kynurenine
KYNA	Kynurenic acid
KYNU	kynureninase
MDD	major depressive disorder

MELAS	mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes
MPT	mitochondrial permeability transition
MS	multiple sclerosis
mtDNA	mitochondrial DNA
NaAD	nicotinic acid adenine dinucleotide
NADH	nicotinamide adenine dinucleotide
NaMN	nicotinic acid mononucleotide
nDNA	nuclear DNA
NMDA	N-methyl-D-aspartic acid
NMS	non-motor symptoms
OCD	obsessive-compulsive disorder
OXPHOS	oxidative phosphorylation
Pi	inorganic phosphate
PINK1	phosphatase and tensin homolog (PTEN)-induced kinase1
PD	Parkinson's diseases
PFC	prefrontal cortex
PIC	picolinic acid
PLP	pyridoxal 5'-phosphate
PMD	primary mitochondrial disease
PMM	Primary mitochondrial myopathy
PTSD	post-traumatic stress disorder
QPRT	quinolinate phosphoribosyltransferase
QUIN	quinolinic acid
SCZ	schizophrenia
SNP	single nucleotide polymorphism
SMD	secondary mitochondrial dysfunction
SOD1	superoxide dismutase 1
SSRI	selective serotonin reuptake inhibitor
succinyl-CoA	succinyl coenzyme A
SUD	substance use disorder
TDP-43	transactive response (TAR) DNA binding protein 43 kDa
TDO	tryptophan 2,3-dioxygenase
TPH	tryptophan hydroxylase
Trp	tryptophan
TST	tail suspension test
XA	xanthurenic acid

Author Contributions: Conceptualization, M.T.; Writing-original draft preparation; M.T., E.S., H.P.; Writing-review and editing, M.T., F.T., E.S, Á.S., L.V.; Visualization; Á.S.; Project administration, L.V.; Funding acquisition, M.T., L.V.

Funding: This research was funded by National Scientific Research Fund OTKA138125, MTA-JSP-050609, and ELKH-SZTE. Helga Polyák was supported by the New National Excellence Program of the Ministry for Innovation and Technology from the source of the National Research, Development and Innovation Fund [ÚNKP-21-3] and EFOP-3.6.3-VEKOP-16-2017-00009.

Conflicts of Interest: The authors declare no conflict of interest regarding this review article.

 doi:10.20944/preprints202207.0130.v1

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