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Mini Review

Potential Involvement of Mitochondrial Dysfunction in Major Depressive Disorder: Recent Evidence

Abstract

Major depressive disorder (MDD) is a leading cause of morbidity and mortality, and it is a common psychological disorder in the world. Present antidepressants modulate monoamine systems directly or indirectly, because MDD is classically considered as a neurochemical disease, in which monoamine systems are perturbed including serotonin, noradrenaline or dopamine systems. However, recent evidences suggest that MDD is associated with the impairments of synaptic plasticity or cellular resilience to stress. Cellular resilience is maintained by mitochondria with the supplying cellular fuel or ATP. In addition, it is suggested that mitochondrial functions in neurons influence synaptic plasticity. Therefore, impairment of mitochondrial function can be the cause of the MDD. The present review article summarizes the recent evidences about the association between mitochondrial impairment and MDD, and it suggests that improvement of mitochondrial function become a potential drug target for MDD.

Abbreviations

CMS: Chronic Mild Stress; ETC: Electron Transporting Chain; GSH: Glutathione; MDA: Malondialdehyde; MDD: Major depressive disorder; mtDNA: Mitochondrial DNA; OXPHOS: Oxidative phosphorylation; ROS: Reactive oxygen species; SOD: Superoxide dismutase; TCA: Tricarboxylic acid

Introduction

Major depressive disorder (MDD), a common psychological disorder, is a leading cause of morbidity and mortality worldwide; however, its pathophysiology remains largely unknown. An epidemiological study showed that 4.3% of the world's population has had MDD at least once in their lifetime [1]. Although the number of patients is still increasing, existing medicine is not adequately effective in most cases. Almost all medicines for MDD are based on the "monoamine theory". This theory was originally established based on knowledge of the mechanism of action of imipramine, which inhibits the reuptake of monoamines, including serotonin and noradrenaline into the presynaptic terminal, leading to an increase of monoamines in the synaptic cleft, and resulting in an antidepressant effect [2]. Therefore, most medicines used in MDD treatment affect the monoamine system [3]. However, it is also known that one-third of MDD patients are resistant to existing antidepressants [4]. Thus, new drug targets, which are not based on the monoamine theory, are required.

Mitochondria have now emerged as the apparent pathological basis or drug target for MDD [5]. There is a recent report by the CONVERGE consortium showing the mitochondrial relationship with MDD, which suggested that two loci on chromosome 10 contribute to risk of MDD: one near the SIRT1 gene, and the other in an intron of the LHPP gene [6]. LHPP is an enzyme whose function is not fully understood, and SIRT1 is important for energy-producing cell structures called mitochondria [7]. This study was the first to show robust genetic links to MDD. In addition, co-morbidity of mitochondrial disorders and psychiatric disorders was previously reported in a study focused on patients with mitochondrial disorders [8]. Co-morbidity of MDD was assessed by Fattel et al. in 36 adults who suffered from mitochondrial disorders. Fifty four percent of these patients fulfilled the criteria for lifetime MDD, and this prevalence is much higher than the 15% lifetime prevalence rate of depression in the general population [9]. In addition, 18 patients, from a cohort of 68 children confirmed with mitochondrial disease, were more likely to be affected by MDD (50%) than normal children (10%) which is the norm scores of an American population. Moreover, child behavior checklist T-scores for withdrawn/ depressive behavior is significantly different between the groups of mitochondrial disease and norm of American population [10]. Thus, in the present review article, we discuss the recent advances in knowledge on mitochondrial dysfunction in MDD, and suggest mitochondrial deficit as a new drug target for MDD.

The cellular energy horse, mitochondria

Classically, mitochondria have been considered a source of production of ATP or its metabolites to fulfill cellular energy demands. Multiple carbon substrates are used for the production of ATP, such as pyruvate from glycolysis, glutamine or other amino acids and fatty acids. These carbon substrates are introduced into the tricarboxylic acid (TCA) cycle in the mitochondrial matrix and used for generation of NADH and $FADH_2$. NADH and $FADH_2$ work as electron donors, and deliver electrons to the electron transporting chain (ETC). The transportation of electrons is coupled with the pumping out of protons from the mitochondrial matrix to the inter membrane space by complexes I, III and IV, located in the mitochondrial inner

membrane. This pumping of protons creates proton gradients across the inner mitochondrial membrane, and generates a proton motive force, composed of a small chemical component and a large electrical membrane potential. This proton motive force is used by Complex V to generate ATP from ADP and phosphate, in a process called oxidative phosphorylation (OXPHOS) [11,12]. Specifically, the brain uses 20% of the total oxygen consumed by the body at rest, but represents only 2% of body mass [13]. In addition, neurons are critically and almost exclusively dependent on mitochondrial OXPHOS as a major source of ATP, and have a limited capacity to upregulate energy supply through glycolysis when OXPHOS is compromised [14,15].

Mitochondria as an intracellular calcium store

Mitochondria have been shown to be responsible for the clearance of cytosolic Ca^{2+} in cells and are able to accumulate a large amount of Ca^{2+} [16]. Mitochondrial Ca^{2+} uptake is regulated in a sophisticated manner, and consequently affects multiple cellular processes. The mitochondrial Ca^{2+} uptake from cytosol to the mitochondrial matrix controls the rate of energy production through the modulation of Ca^{2+}-sensitive metabolic enzymes. TCA cycle enzymes are highly sensitive to changes in concentration of Ca^{2+}, which presumably binds directly to isocitrate dehydrogenase and α-ketoglutarate dehydrogenase, whereas pyruvate dehydrogenase is activated by the Ca^{2+}-sensitive pyruvate dehydrogenase phosphatase. Complex IV and complex III may also be regulated by intramitochondrial Ca^{2+}. Matrix Ca^{2+} may also regulate OXPHOS through an effect on the adenine nucleotide trans locator and on F1Fo-ATP synthase [15,17,18]. This modulation of energy production occurs with a spatial and temporal profile similar to intracellular Ca^{2+} signaling, and regulates mitochondrial motility and morphology [19].

Reactive oxygen species (ROS) as a byproduct of ETC

Mitochondria are a very important source of reactive oxygen species (ROS) in most mammalian cells. The production of ROS is important because it underlies oxidative damage in many diseases and contributes to retrograde redox signaling from organelles to the cytosol and nucleus. Superoxide (O_2^-) is the proximal mitochondrial ROS, and predominantly produced in Complex I. The generation of O_2^- within the mitochondrial matrix depends critically on proton motive force, the NADH/NAD^+ and $CoQH_2$/CoQ ratios and the local O_2 concentration [20]. Because mitochondria are the major producers of ROS in mammalian cells, mitochondrial DNA (mtDNA) is prone to oxidative damage. Many studies have consistently shown that 8-oxo-dG, one of the common products of DNA oxidation, is detected at higher levels in mtDNA than in nuclear DNA, suggesting that mtDNA is more susceptible to oxidative damage. As mtDNA encodes essential components of oxidative phosphorylation and protein synthesis machinery, oxidative damage-induced mtDNA mutations that impair either the assembly or the function of the respiratory chain will in turn trigger further accumulation of ROS [21].

Mitochondrial dysfunction in MDD

Altered ETC or OXPHOS: Alteration of the expressions and activity of complexes in ETC, or mitochondrial oxygen consumption have been studied in postmortem brain, skeletal muscle or platelet biopsies from MDD patients in comparison to normal healthy controls.

Postmortem brain: Postmortem brain Decreased expression of complexes of the ETC was reported in patients with MDD compared to healthy controls. The functional Complex I assembly requires 3 catalytic subunits, such as the 24, 51 and 75-kDa subunits. The expression of the 24 kDa subunit was significantly decreased in the prefrontal cortex of MDD patients in comparison with that of normal healthy controls [22]. In addition, the expression of the 24, 51 and 75-kDa subunits were significantly decreased in the cerebellar lateral hemispheres, and 24-kDa subunit was significantly decreased in the prefrontal cortex of MDD patients [23]. Not only decreased expressions but also decreased activity were reported in MDD patients, as Complex I activity was significantly reduced in the prefrontal cortex of MDD patients [24]. Additionally, altered mitochondrial function and amino acid metabolism are associated with MDD. Abdellah et al. found a significant reduction in the rate of the neuronal TCA cycle in glutamatergic neurons by carbon-13 MRS, implicating the glutamatergic system and mitochondrial energy metabolism in the pathology of MDD [25].

Peripheral tissue: It is known that mitochondrial activity in peripheral tissue is related to brain function to some extent. In intact platelets, physiological respiration, the maximal capacity of the electron transport system and respiratory rate after Complex I inhibition are decreased in MDD patients who have reached partial remission, compared to normal healthy controls [26]. In addition, in muscle biopsies, the mitochondrial ATP production rate and the enzymatic activity ratio between NADH-cytochrome c reductase and cytochrome c oxidase, or between succinate-cytochrome c reductase and cytochrome c oxidase, was lower in MDD patients in comparison with normal healthy controls [27]. However, in another study, Complex I activity was measured by assessing NADH ferricyanide reductase activity, and no difference in enzymatic activity was observed between mitochondrial preparations from platelets of MDD patients with recurrent MDD and those of healthy controls [28].

Animal studies: In a mouse model of MDD developed more than 20 years ago, the chronic mild (or unpredictable or variable) stress (CMS) model was developed as an animal model of depression. The foundation of this model was that following long-term exposure to a series of mild, but unpredictable stressors, animals would develop a state of impaired reward salience that is akin to anhedonia. In this state, the hypothalamic–pituitary–adrenal axis (HPA) is activated, which results in the release of corticosteroid hormones from the adrenal glands [29,30]. Rezin et al., showed that the activity of Complexes I, III and IV was reduced without affecting Complex II and creatine kinase activity in both the cerebral cortex and the cerebellum. This reduction was associated with reduced sweet food ingestion and increased adrenal gland weight after 40 days of CMS [31]. In addition, a single infusion of ketamine at low dose robustly decreases depressive symptoms in humans [32]. Acute administration of ketamine reversed the reduction of Complex I, III and IV activity in cerebral cortex and cerebellum with associated reversal of the reduction of sweet food ingestion and increased adrenal gland weight mediated by CMS [33]. A different study carried out by another group also suggested that CMS reduced Complex I, II and V activity, and led to anhedonia, reduced sucrose intake, and depressed behavior including increased immobility in a forced swim test [34].

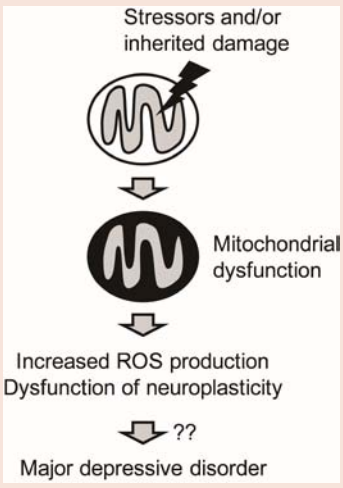

Figure 1: Schematic model of the relationship between mitochondrial dysfunction and major depressive disorder. A combination of stressors and/or inherited mitochondrial damage either on nuclear or mitochondrial DNA mediates mitochondrial dysfunction. Increased ROS production or dysfunction of neuroplasticity is followed by occurred by insufficient mitochondrial function in brain. As a result, this mitochondrial dysfunction might contribute in pathophysiology of major depressive disorder.

Conversely, Garabadu et al. showed in their mouse model of MDD that activities of the mitochondrial respiratory Complexes I, II, IV and V are increased by stress and re-stress, and this increment is prevented by treatment with risperidone [35]. Not only the activity of the mitochondrial complexes, but also the functions of the mitochondria itself were reduced in the mouse model of MDD. The isolated mitochondrial oxygen consumption rate is frequently measured to assess mitochondrial activity. The mitochondrial oxygen consumption rate was attenuated, and the mitochondrial membrane potential was dissipated in hippocampus, cortex, hypothalamus, brain and liver in a mouse model of MDD produced by CMS or chronic restraint stress. In this model, the mal-effects of stress on mitochondria were associated with depressive-like behavior in a tail suspension or forced swimming test [36-38]. In addition, chronic administration of corticosterone can also be used to create a useful rodent model for MDD as well as CMS. Mouse models of MDD created by both CMS and corticosterone treatment showed reduced energy production in the cortex and striatum and reduced mitochondrial membrane potential in the prefrontal cortex. These mitochondrial deficits were associated with depressive-like behavior in a sucrose preference test and a forced swim test, as well as anxiety-related behavior in an open field test and novelty suppressed feeding test [39]. Not only repetitive exposure to stressors but also a single exposure to stress can affect mitochondrial activity. Short (30 min) and acute single stress exposures decrease the oxygen consumption rate in the brain mitochondria of mice [40]. On the other hand, mitochondrial dynamics including their mobility or their number also affect mitochondrial function. Increased synaptosomal mitochondrial levels in the hippocampus were observed in a mouse model for MDD created by neonatal isolation before weaning followed by social isolation [41]. In addition, Chen et al. investigated the mitochondrial number and volume in the CA1 region of the hippocampus in a genetic animal model of MDD, the Flinders-sensitive line rats ("depressed" rats) and their corresponding controls, the Flinders-resistant line rats. The results showed a significantly reduced number of and enlarged size of mitochondria in the CA1 region of Flinders-sensitive line rats in comparison with Flinders-resistant line rats. Treatment with imipramine, a tri-cyclic antidepressant, canceled the reduction of the number of and enlargement of mitochondria in the CA1 region of Flinders-sensitive line rats [42].

Overall, mitochondrial activity is reduced in MDD patients and most of the rodent models of MDD. Notably, this decrement of mitochondrial activity can be mediated by acute and single stress exposures, and is prevented by antidepressant treatment.

ROS and its derivatives

Postmortem brain: Glutathione (GSH) is the major free radical scavenger in the brain. Diminished GSH levels elevate cellular vulnerability towards oxidative stress, characterized by accumulating reactive oxygen species. In postmortem prefrontal cortical samples, levels of reduced, oxidized, and total glutathione and GSH peroxidase are significantly decreased in depressive conditions compared to a control group [43]. Conversely, immunoblotting analysis showed similar expression levels of carbonylated proteins, which are oxidized proteins, in a mitochondrial sample obtained from the prefrontal cortex of MDD patients in comparison with normal healthy controls [24].

Peripheral tissue: Peripheral samples are obtained from leukocytes, platelets, erythrocytes, mononuclear cells, plasma or serum from blood or urine. The contents of oxidative stress markers in each of the tissues of MDD patients in comparison with normal healthy control are as follows. Malondialdehyde (MDA), which originates from lipid peroxidation, was increased in many tissues such as plasma [44] (Bilici et al., 2001), erythrocytes [44,45], leukocytes [46], mononuclear cells [47] and serum [48]. Moreover, the degree of symptoms of MDD affects the level of malondialdehyde (MDA). Prior research has suggested that MDD patients with melancholia have more impairment, because recurrent episodes and the risk for MDD are higher in the co-twins of probands with the melancholic subtype [49]. Interestingly, Bilici et al. showed that (i) MDD with melancholia was characterized by significantly higher MDA levels than MDD without melancholia, and (ii) subchronic treatment with SSRIs reduced MDA levels [44]. Hydrogen peroxide was increased in mononuclear cells (Moreno-Fernandez et al., 2012) and erythrocytes [45], and nitric oxide was increased in leukocytes [46] and platelets [50]. DNA oxidation is increased in urine [51], mononuclear cells [52] and leukocytes (Especially in mtDNA) [53]. Total oxidant status is increased in leukocytes [46] and serum [54]. Not only in patients with MDD but also in healthy college students, serum reactive oxygen metabolites and the biological antioxidant potential, as indices of oxidative status, are significantly correlated with depressive symptoms as assessed by the Beck Depression Inventory [55]. Thus, ROS and its derivatives, even in peripheral tissues, are frequently correlated with major depressive symptoms.

Contents of molecules defensive against oxidative stress in each tissue have not been consistent across studies, as is the case with oxidative stress markers. These molecules are frequently decreased, but in some cases increased in patients with MDD, in comparison with healthy controls. The contents of these molecules in MDD patients, in comparison with normal healthy controls, are as follows.

The activity of superoxide dismutase (SOD), which is the enzyme to catalyze the dismutation of superoxide anions, was decreased in leukocytes [46] and serum [48], but was increased in erythrocytes [44] and mononuclear cells [56]. In addition to the activity of SOD, gene polymorphisms (Ala-9Val or Ile-58Thr) on MnSOD, mitochondrial SOD, affected its transportation to the mitochondrial matrix and its activity, and the prevalence of polymorphisms was significantly associated with the symptoms of MDD in the female Polish population [57]. Total antioxidant capacity is decreased in leukocytes [46], serum [54] and urine [58]. In addition, Cumurcu et al. showed that, after 3 months of antidepressant treatment, total oxidant status is decreased and total antioxidant capacity is increased, compared with pretreatment values [54]. Coenzyme Q10 and vitamin C are also known as antioxidants whose expressions are decreased in mononuclear cells [47] and serum [58].

Animal studies: In animal research, many kinds of experimental models for major depressive disorder, such as chronic restraint stress, CMS, social isolation stress, chronic corticosterone treatment or chronic forced swim are used in studies focusing on the relationship of ROS and its derivatives to depressive behavior of rodents. Lucca et al. focused on 5 different brain regions to examine molecules related to ROS. Protein carbonyl (prefrontal, hippocampus, striatum and cortex), MDA (cerebellum and striatum) and catalase (cerebellum, hippocampus, striatum, and cortex) were increased in the indicated brain regions. Additionally, the activity of SOD (prefrontal, hippocampus, striatum and cortex) was decreased in a rat model of MDD. All of these changes were associated with depression-like behavior, such as a decrease in sweet food intake [59,60]. In addition, levels of MDA were increased, and total antioxidant capacity, glutathione peroxidase activity, and catalase activity were decreased in frontal cortex, hippocampus, and striatum in a mouse model of MDD created by CMS. These molecular changes were associated with depressive-like behavior, such as decreased sucrose preference or increased immobility in a forced swim test [61]. In addition, MDA content and the expression of carbonylated protein or fluorescence of dihydroethidium (fluorescent indicator of ROS) were also increased in the hippocampus or whole brain region, which was associated with depressive-like behavior in the tail-suspension and forced swimming tests, and by chronic restraint stress, which is another chronic stress paradigm used widely [37,62]. Superoxide anion is increased in the cerebrum and cerebellum of rats after performance of a chronic forced swimming test for 15 days [63]. Pharmacologically, antidepressants can affect oxidative stress, and alternatively, antioxidants can affect depressive-like behavior in mice. Moretti et al. administrated fluoxetine as an antidepressant or ascorbic acid as antioxidant through oral gavage for 14 days in a mouse model of MDD created by CMS. Depressive-like behavior in a tail suspension test was increased with a significant association to increments in MDA content (cerebral cortex and hippocampus), and decrements of catalase activity (cerebral cortex and hippocampus), glutathione reductase activity (hippocampus) and reduced levels of glutathione (cerebral cortex) in a mouse model of MDD. Interestingly, repeated administration of not only fluoxetine but also ascorbic acid significantly reversed CMS-induced depressive-like behavior as well as oxidative damage [64].

On the other hand, repeated corticosterone injections induced depressive behavioral and neurochemical manifestations in rodents [65,66]. Additionally, physical activity and exercise improved depressive symptoms [67,68]. Liu and Zhou showed that both CMS and chronic corticosterone injection increased the fluorescence of H2DCF-DA, an ROS indicator, and decreased GSH and SOD activity— effects that are associated with depressive behavior. However, physical exercise mitigated these effects [39].

Thus, ROS and its derivatives are potentially increased in both central and peripheral tissues, in association with symptoms of major depressive disorder, in human studies as well as rodent studies. The amount of molecules for ROS clearance, such as SOD, catalase and GSH shows discrepancy between the studies. These amounts might be decreased as a reason for the increment of ROS, or in some cases they might be increased for the clearance of ROS, in a compensatory manner. It will be necessary to do further research to clarify the role of antioxidants. Nonetheless, ROS may be involved in major depressive disease.

Mitochondrial DNA (mtDNA) modification

mtDNA is a 16.5 kb circular DNA sequence carried within mitochondria, composed of a light and a heavy strand. Both strands contain 37 genes, including 13 that encode protein subunits of the oxidative phosphorylation complexes. The remaining genes encode ribosomal RNA and tRNA molecules that are essential for the transcription and synthesis of mitochondrially encoded proteins. Human mtDNA is prone to oxidative injury because mtDNA is not protected by histones and mitochondria themselves generate ROS during ATP synthesis [69]. Oxidative damage can induce point mutations, delete mtDNA and lead to a lack of or decrease in transcription from mtDNA. Thus, we conclude that there is a relationship between mtDNA deficit and MDD.

Postmortem brain: Shao et al. showed that mtDNA common deletion was increased in a postmortem brain sample from the dorsolateral prefrontal cortex from MDD patients compared to normal controls. In addition, the expressions of 13 transcripts from mtDNA were examined, and the results showed that the expressions of the transcripts were not significantly changed when these expressions were normalized with d-loop content, an intramitochondrial control, in the MDD patient in comparison with a normal control [70]. Similarly, Torrell et al. determined the expressions of genes encoded in mtDNA, the copy number of mtDNA and deletion of mtDNA in postmortem brain samples from occipital cortex from patients with schizophrenia, bipolar disorder and MDD. Although no significant differences were observed in gene expressions encoded in mtDNA and copy number of mtDNA, a larger number of MDD and schizophrenia patients tended to have a deletion of mtDNA, compared with patients who had bipolar disorder and normal controls [71]. The increase in deletion of mtDNA was not reproduced in a study conducted by another group. Mamdani et al. examined the somatic mitochondrial common deletion in post mortem brain samples from patients with MDD, and found no significant change in the global accumulation of common deletion in patients with MDD in comparison to normal controls [72]. Because there is an insufficient number of samples and studies with post-mortem samples to draw conclusions about the relationship of mtDNA modifications to abnormalities in the brains of MDD patients, further study with post-mortem samples is necessary.

Peripheral tissue: Gardner et al. performed long-PCR and

southern blot techniques to detect mtDNA deletions in muscle biopsies, and their results showed that deletions of mtDNA were more frequent in patients with MDD than in normal healthy controls [27]. Cai et al. examined the relationship between mtDNA content and MDD with whole-genome sequencing of saliva DNA samples from 11,670 patients, with a mean coverage of 102X for the mitochondrial genome. From this procedure, they estimated the amount of mtDNA for each individual. They observed a highly significant association between MDD and the amount of mtDNA. Interestingly, the mtDNA content was also significantly correlated with both the total number of stressful life events and childhood sexual abuse [38]. In addition, the relationship between the mtDNA content and the number of stressful life events was also examined by Tyrka et al., who reproduced same result. More specifically, childhood adversities such as childhood parental loss and maltreatment are associated with higher mtDNA content in leukocytes [73]. Conversely, Kim et al. investigated the mtDNA content of leukocyte DNA samples from 142 community-dwelling women of old age, who were divided into control and MDD patients with a 15-question geriatric depression scale or who were taking medication. The results showed that the MDD group had significantly lower mtDNA content than the control group [74]. Chang et al. compared 40 MDD patients to 70 healthy control subjects of median age in terms of the mtDNA content of their leukocytes, and their results showed that the mtDNA content of MDD patients was significantly lower than that of the healthy control group [53]. In addition, He et al. found no significant differences between MDD patients and healthy controls in mtDNA content of leukocytes in 427 young adult populations [75].

Thus, although leukocyte mtDNA contents might vary depending on the study, the result of Cai et al. might be reliable because of its detection power, considering the study's sample size [76]. Interestingly, two groups showed that mtDNA content is increased, depending on stress history, which might suggest that mtDNA content might change in response to stress.

OMIX or GWAS analysis in major depressive disorder

Human study: Human study Studies employing OMIX experiments with postmortem brain samples are very difficult, because the expression of mitochondrial-related genes is easily changed by agonal or pH factors. Therefore, the interpretation of postmortem brain studies involving broad mitochondrial gene expression and related pathway alterations must be monitored to control for strong effects of agonal-pH state [77].

Beasley et al. identified disease-specific protein changes within the anterior cingulate cortex in psychiatric disorders including MDD with 2-D gel electrophoresis followed by mass spectrometric sequencing, and suggested that mitochondrial dysfunction is an important component of the neuropathology of major psychiatric disorders including MDD [78]. More recently, the CONVERGE consortium carried out low-coverage whole-genome sequencing of 5,303 Chinese women with recurrent MDD and 5,337 controls screened to exclude major depressive disorder. These researchers identified, and subsequently replicated in an independent sample, two loci contributing to risk of MDD; one of them was located on chromosome 10 near the SIRT1 gene [6]. In addition, rs10997875 in the SIRT1 gene was associated with MDD in the allele/genotype analysis in the Japanese population, suggesting that rs10997875 in SIRT1 might play a role in the pathophysiology of MDD [79]. In addition, Abe et al. used RT-qPCR to measure the mRNA levels of seven SIRT isoforms (SIRT 1 to 7) in peripheral white blood cells of patients with MDD or bipolar disorder during depressive and remissive states, and compared the results to those from normal healthy controls. The SIRT1, 2 and 6 mRNA levels were decreased significantly in MDD and bipolar disorder patients, who were in a depressive state compared to healthy controls. However, the expression of those mRNAs in both MDD and bipolar disorder in patients in a remissive state were comparable to those of healthy controls [80]. Thus, these studies explain the significance of SIRT1 in MDD. The mitochondria are actually the most important target of the SIRT1. SIRT1 knockout canceled resveratrol-mediated increased mitochondrial biogenesis and function, while mice overexpressing SIRT1 increased mitochondrial biogenesis and function in skeletal muscle [81]. In addition, morphological and functional mitochondrial abnormalities were observed in adult hearts lacking SIRT1, suggesting that SIRT1 is essential for the maintenance of mitochondrial integrity [82].

Animal studies: Some studies have shown a mitochondrial relationship to MDD by investigation of transcriptome analysis in rodents and fish models of MDD, and some studies have also investigated the effect of antidepressants on these models of MDD. As shown previously, CMS could produce depressive-like behavior in mice. Liu et al. performed proteomics analysis by differential 2-D gel electrophoresis with brain samples, and the set of altered proteins identified by proteomics implied abnormal energy mobilization [39]. In another case of CMS in fish, fifteen days of exposure to CMS appeared to induce an anxiety- and mood disorder- related phenotype. The expression profiles of total brain proteins obtained from control and CMS samples were analyzed by proteomics of 2-D gel electrophoresis and followed by mass spectrometric analysis. As a result, 18 proteins were found to be regulated, and the most affected process was mitochondrial function. Four out of the 18 differentially regulated proteins were mitochondrial proteins [83]. In addition, the first etiological mouse model for MDD produced by the replacement of the homologous mouse DNA sequence with pathogenic 6-base human CREB1 promoter sequence was developed by Zubenko and Hughes [84]. Zubenko et al. investigated differential hippocampal gene expression and performed pathway analysis in this etiology-based mouse model of major depressive disorder. In this study, pathway analyses highlighted 11 KEGG pathways including the OXPHOS pathway in the mitochondria [85]. The effect of antidepressants on mitochondrial function is reliable evidence for the relationship between mitochondrial deficits and MDD. St John's wort, a traditional herbal product, is as effective as standard antidepressants in the treatment of mild to moderately severe MDD [86]. Wong et al. studied hypothalamic gene expression in rats treated with St. John's wort or imipramine, and found six common transcripts in response to both treatments. These transcripts are relevant to two molecular machines including the mitochondria [87]. It is also known that not only the drug treatment but also the environmental enrichment paradigm has an antidepressant effect. Rats in enriched conditions display increased expression of energy metabolism enzymes, while rats in isolated control conditions exhibit decreased expression of similar proteins [88]. These reports suggest that gene expression

related to mitochondria is associated with depressive symptoms, even in cases where the symptoms were recovered by the treatment.

Inherited deficit on mitochondria

Human studies: Mitochondrial disorders are clinical phenotypes associated with mitochondrial dysfunction; in particular, abnormalities of OXPHOS, which can be caused by mutations in mtDNA or nuclear genes [89,90]. When combining the results of the epidemiology data on childhood and adult mitochondrial diseases, the minimum prevalence is at least 1 in 5,000 and could be much higher [91]. Persons with mitochondrial disorder should note the high prevalence of psychiatric problems, e.g. lifetime diagnoses included 54% MDD, 17% bipolar disorder and 11% panic disorder [9]. In addition, there is a higher likelihood of MDD in children diagnosed with mitochondrial disease (50%) than in normal children (10%) [10]. In another study, MDD was found in 5 out of 35 children and adolescents (14%) with various mitochondrial disorders. However, for pediatric MDD, the ratio is in general between 3 and 4% in children and adolescents [92,93]. Two studies revealed that a several-fold increased likelihood of developing MDD can be maternally inherited along with the mtDNA, which strongly argues that mtDNA sequence variants may induce mitochondrial dysfunction that can predispose individuals towards the development of MDD [94-96]. Thus, MDD could be associated with abnormal energy metabolism mediated by mitochondrial deficits.

Animal studies: Many kinds of genetically engineered mice are produced through the increasing ease of genetic manipulation. The modification of mitochondrial-related genes or the manipulation of mitochondrial heteloplasmy has resulted in depressive symptoms in mice. The maternal inheritance of animal mtDNAs is both virtually universal and highly concerted with specific systems that actively exclude the paternal mitochondria and mtDNAs during fertilization. To investigate the dynamics of germline mtDNA segregation, Sharpley et al. prepared mice that are heteroplasmic for 129S6 and NZB mtDNAs, backcrossed onto a C57BL/6J nuclear background. The heteroplasmic mice were found to be less fit, less depressive and show less anxiety than their homoplasmic counterparts [97]. Similarly, Gimsa et al. studied the behavior and neuroendocrine regulation under social disruption stress of C57BL/6J mice, in which host mitochondria originating from C57BL/6J mice were substituted by mitochondria from AKR/J (C57BL/6J-mt$^{AKR/J}$) or FVB/N (C57BL/6J-mt$^{FVB/N}$) strains. C57BL/6J-mt$^{FVB/N}$ mice were significantly more anxious in the elevated plus-maze test than C57BL/6J-mt$^{AKR/J}$ and C57BL/6J mice at base line, and they showed a reduced corticosterone response and an activation of serotonergic and dopaminergic neurotransmitter systems [98]. In addition, forebrain expression of a mutated form of mtDNA repair enzyme, UNG, induced oxidative stress in hippocampus, and was associated with a lack of anxiety-like responses in mice [99]. Additionally, forebrain expression of a mutated form of mtDNA polymerase, POLG, induced accumulation of mtDNA defects, and caused mood disorder-like mental symptoms with similar treatment responses to bipolar disorder [100]. Thus, the mitochondrial heteroplasmy or the accumulation of mtDNA mutations caused abnormalities in mood such as anxiety or depression. On the other hand, DISC1 was identified in a Scottish family through characterization of a balanced chromosomal translocation found to be associated with major mental illnesses including MDD [101] In addition, a fraction of DISC1 was localized to the inside of mitochondria, and reduction in DISC1 function induced mitochondrial dysfunction, evidenced by decreased mitochondrial NADH dehydrogenase activities, reduced cellular ATP contents and perturbed mitochondrial Ca^{2+} dynamics, suggesting that DISC1 is important for mitochondrial function [102]. In addition, DISC1 participates directly in mitochondrial trafficking, which is essential for neural development and neurotransmission [103]. It is reported that gene-environment interactions may also underlie a variety of neuropsychiatric disorders including MDD. Although these environmental factors can interact with each other, individual responses vary, mainly because of different genetic pre-dispositions among individuals. Niwa et al. showed that an environmental stressor, isolation stress during adolescence, can elicit behavioral deficits including MDD-like behavior only when combined with an appropriate genetic risk, brain specific dominant-negative DISC1 over-expression [104].

Potential sites of action of mitochondrial deficiency in the nervous system

In the brain, there are billions of synapses establishing complex neuronal networks which process and store information, and synaptic function defines brain activity. In presynaptic modulatory function by mitochondria, neurotransmitter release by the presynaptic terminal requires mitochondrial ATP, because presynaptic vesicular recycling largely relies on activity-stimulated ATP synthesis to maintain function [105,106]. Not only the production of ATP, but the state of axonal mitochondria, including presence, absence or movement in or out of the presynaptic terminal, also dynamically modulate neurotransmitter release [107]. Similarly, dynamin-related protein, Drp1, which is involved in mitochondrial fission, is necessary for extremely polarized cells such as neurons to maintain the normal spatiotemporal properties of mitochondria that are essential for the synaptic functions or responses to Ca^{2+} [108].

Mitochondria also regulate postsynaptic functions, including morphogenesis of spines or dendrites and synaptic plasticity, and alternatively, synaptic activity impacts mitochondrial positioning. In synaptic formation, normal synapse density and activity-dependent synapse formation depend critically on the proper distribution and function of mitochondria in dendrites [109]. In dendritic formation, genetic manipulations of mitochondrial complex I subunits cause an unexpected outgrowth of dendritic arbors and ectopic structures in sensory neurons of *Caenorhabditis elegans* [110]. Similarly, control of the mitochondrial distribution in developing neurons may be essential for the establishment of the precise branching pattern of dendritic arbors and resulting functional neural circuits. Altered mitochondrial distribution causes dendritic abnormality by overexpressing Mfn1, a mitochondrial shaping protein, or the Miro-binding domain of TRAK2, a truncated form of a motor-adaptor protein in neocortex of mice [111]. In addition, the mitochondrial membrane potential is correlated with dendritic arborization in hippocampal neurons of mice [112]. Drp1 could affect not only the presynaptic but also post-synaptic function. The phosphorylation of Drp1 at Ser656 increased mitochondrial length and dendrite occupancy, enhancing dendritic outgrowth but paradoxically decreasing synapse number and density [113]. Thus, mitochondria may play important roles in controlling fundamental processes in synaptic modification, including neurite

outgrowth, neurotransmitter release and dendritic remodeling, suggesting mitochondrial deficiency may affect neuroplasticity.

Summary

The story of mitochondria in MDD is growing in reliability because multiple lines of evidence, such as the decrement of mitochondrial activity in MDD, the increment of ROS production in MDD, a large scale genetic approach to identify the mitochondrial relationship with MDD, the co-morbidity of MDD with inherited mitochondrial dysfunction and pharmacological treatment support the role of mitochondrial dysfunction in MDD.

Although many papers have reported on the relationship between mitochondrial dysfunction and MDD, we do not think all of the MDD pathophysiologies can be explained by mitochondrial dysfunction only. Individual MDD patients may have different symptoms, degrees of symptoms or pharmacological tolerance. However, the actual problem in MDD is that some populations of MDD patients are resistant to the present antidepressants, which are based on monoamine theory. We need to evaluate new medicines or drug targets for such resistant cases of MDD. Although further research is necessary to elucidate whether mitochondrial dysfunction is the cause or the result of MDD, it is surely true that mitochondrial dysfunction is a potential drug target for MDD.

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