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REVIEW ARTICLE

Mitochondria: A Connecting Link in the Major Depressive Disorder Jigsaw

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Abstract: ***Background*:** Depression is a widespread phenomenon with varying degrees of pathology in different patients. Various hypotheses have been proposed for the cause and continuance of depression. Some of these include, but not limited to, the monoamine hypothesis, the neuroendocrine hypothesis, and the more recent epigenetic and inflammatory hypotheses.

***Objective*:** In this article, we review all the above hypotheses with a focus on the role of mitochondria as the connecting link. Oxidative stress, respiratory activity, mitochondrial dynamics and metabolism are some of the mitochondria-dependent factors which are affected during depression. We also propose exogenous ATP as a contributing factor to depression.

***Result*:** Literature review shows that pro-inflammatory markers are elevated in depressive individuals. The cause for elevated levels of cytokines in depression is not completely understood. We propose exogenous ATP activates purinergic receptors which in turn increase the levels of various pro-inflammatory factors in the pathophysiology of depression.

***Conclusion*:** Mitochondria are integral to the function of neurons and undergo dysfunction in major depressive disorder patients. This dysfunction is reflected in all the various hypotheses that have been proposed for depression. Among the newer targets identified, which also involve mitochondria, includes the role of exogenous ATP. The diversity of purinergic receptors, and their differential expression among various individuals in the population, due to genetic and environmental (prenatal) influences, may influence the susceptibility and severity of depression. Identifying specific receptors involved and using patient-specific purinergic receptor antagonist may be an appropriate therapeutic course in the future.

Keywords: Major depressive disorder, mitochondria, ATP, purinergic receptors, neuroinflammation, PBAIDs.

1. THE MDD JIGSAW

Neuropsychiatric ailments such as major depressive disorder (MDD), bipolar disorder, anxiety disorders and schizophrenia are widely prevalent and are a major impediment to daily life activities and to one's profession. MDD is a serious mood disorder that affects thought, sleep and appetite, and is accompanied by prolonged unpleasant mood, inability to experience pleasure and resignation from matters of the world. As per the World Health Organization report, unipolar depressive disorders itself accounts for a worldwide 65.5 million disability-adjusted life years [1]. Despite their wide prevalence, aetiology of neuropsychiatric disorders remains a puzzle from the time of Hippocrates (460-370 BC) who associated 'melancholia' with black bile. Research in the later part of last century identified monoamines and corticotropins in the pathophysiology of MDD and led to the development of selective serotonin reuptake inhibitors (SSRIs) that are widely used for the treatment of depression and anxiety disorders. However, responsiveness to drugs and psychotherapy is variable and patient-dependent. Lack of mental health awareness and the social stigma attached to these disorders further isolate the potentially treatable patients.

There have been various hypotheses proposed for the onset of depression; however, none of the current theories complete the jigsaw. Besides the monoamine and neuroendocrine hypotheses, some of the newer players identified include neurotrophic or growth factors, epigenetic mechanisms, and cytokines and other pro-inflammatory molecules. More recently, mitochondria have been implicated in the pathophysiology of depression [2-4]. This review frames an insight into mitochondrial alterations in psychiatric disorders in relation to all the proposed hypotheses on depression to

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date. Originally considered to be just the organelles responsible for energy production in the form of ATP, mitochondria have come across as very dynamic organelles involved in cellular signalling, apoptosis and autophagy. Within the neurons, mitochondria are responsible for plasticity at the axonal synapses and in the dendritic spines [5]. Mitochondrial dynamics have been associated with various neurodegenerative disorders such as Parkinson's disease and Huntington's disorder [6, 7]. Dysfunction in mitochondrial bioenergetics has also been implicated in MDD [8]. MDD patients are often characterised with deficits in energy metabolism suggesting a direct association with decreased mitochondrial ATP production [9]. Chronic mild stress was shown to inhibit the mitochondrial complexes I, III and IV in the cerebral cortex and cerebellum of rats which could be reversed with the administration of *N*-methyl-D-aspartate (NMDA) antagonist, ketamine [10]. Peripheral blood leukocytes of MDD patients show significantly lower numbers of mitochondrial DNA (mtDNA) copy numbers compared to control subjects as also the extent of DNA damage in terms of nucleotide oxidation or strand breaks [11, 12]. Serum levels of 8-hydroxy-2'-deoxyguanosine, a marker for increased oxidative stress, was found to be increased, while serum levels of antioxidants such as vitamin E were significantly lower in MDD patients compared to healthy volunteers [13, 14]. However, MDD patients also showed significantly elevated activities of superoxide dismutase 1 (SOD1) and catalase (CAT) enzymes [15]. Dietary intake of antioxidants, ω3 fatty acids, vitamin B family members and magnesium have been suggested to prevent the onset of mood disorders by preventing oxidative stress on mitochondria [16]. Modulation of various mitochondria-associated genes has been observed in MDD patients including an upregulation of adenine nucleotide translocase 4 (ANT4) responsible for releasing adenosine triphosphate (ATP) to the cytosol in exchange for adenosine diphosphate (ADP) [17]. These reports suggest mitochondria may play an important role in the pathophysiology of MDD. To further explore this possibility we present in this review the possible involvement of mitochondria to each of the proposed theories for MDD in an attempt to find a unifying hypothesis. While it may not single out mitochondrial dysfunction as the cause of MDD, it brings about a newer approach to address depression through understanding the role mitochondria in MDD. In addition, we also suggest the role of exogenous ATP in MDD through its action on purinergic receptors leading to an increase in the levels of inflammatory mediators. Use of purinergic receptor antagonists may be considered for therapeutic option in the future.

2. MITOCHONDRIA AND THE MONOAMINERGIC HYPOTHESIS

One of the earliest theories of depression, the monoaminergic concept relies on the fact that depletion of monoamines correlates to clinical features of depression [18]. Evidences for this hypothesis comes indirectly based on the action of reuptake inhibitors which aim to increase synaptic serotonin (5-HT) or norepinephrine levels by inhibiting their respective transporters or by the inhibition of monoamine oxidase (MAO) responsible for their degradation (Fig. **1**). Accordingly, the two classes of antidepressant drugs – tricyclic antidepressants and the newer class of selective serotonin reuptake inhibitors (SSRIs) or norepinephrine selective reuptake inhibitors (NRIs) and the MAO inhibitors – have been in use for more than 60 years despite the fact that only about 50% individuals show remission in response to these drugs [19]. A major drawback of this theory is the lack of direct measurement of monoamines in MDD patients. Furthermore, depression is not seen in healthy volunteers where monoamines are experimentally depleted [20].

Other evidences for the role of monoamines in depression come from the observation that several 5-HT receptors are found to be decreased in MDD patients while the levels of MAO is elevated [21]. Various 5-HT receptors have been implicated to play a role in MDD and the recently approved novel drug vortioxetine not only acts as SSRI but also modulates the functions of various 5-HT receptors [22, 23]. However, conventional antidepressants fail in patients with treatment-resistant depression suggesting the possibility of other pathways involved in MDD [24].

MAOs are bound to the outer membrane of mitochondria and have been shown to contribute to oxidative stress [25]. Irreversible MAO inhibitor, L-deprenyl, inhibits state 3 respiration and increases SOD activity in the rodent striatum [26]. Agonist for the norepinephrine β2 receptor, formoterol, showed increased carbonylcyanide p-trifluoromethoxyphenylhydrazone (FCCP)-uncoupled oxygen consumption rate, mtDNA copy number and expression of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) and multiple mitochondrial genes in primary renal cells and in mice [27]. A similar effect on mitochondrial biogenesis was observed with agonists for 5-HT receptors 5-HT1F and 5-HT2 group [28, 29]. Various antidepressant drugs such as paroxetine, nortriptyline and venlafaxine have been shown to increase energy metabolism in various brain regions in the rat through increased activity of mitochondrial complexes I, II and IV [30]. These studies show an important relationship between monoamine receptors and mitochondrial activity in MDD (Fig. **1**). While the increase in MAO has been shown to increase oxidative stress within the cell, thereby further enhancing depression, activation of various monoamine receptors are involved in neuroprotective actions through increased respiration and mitochondrial biogenesis.

3. MITOCHONDRIA AND THE NEUROENDOCRINE HYPOTHESIS

Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis has been implicated in MDD [31]. This involves impairment of the corticosteroid receptor-mediated feedback leading to increased secretion of corticotropin-releasing factor (CRF) in the hypothalamus. The importance of the HPA axis in MDD is clearer in cases involving prenatal stress and maternal separation [32]. The HPA axis also serves as the medium through which the gastrointestinal microbiota mediates its effect on the host which also includes depression and anxiety [33]. The HPA axis connects to the monoaminergic system as well with CRF and related peptides being able to act and influence the action of serotonergic neurons in the brain stem thereby affecting stress responsive behaviour [34]. CRF receptor antagonist, CP-316,311, was even tested in a small trial involving MDD patients but failed in its efficacy [35]. An attractive therapeutic possibility is the CRF

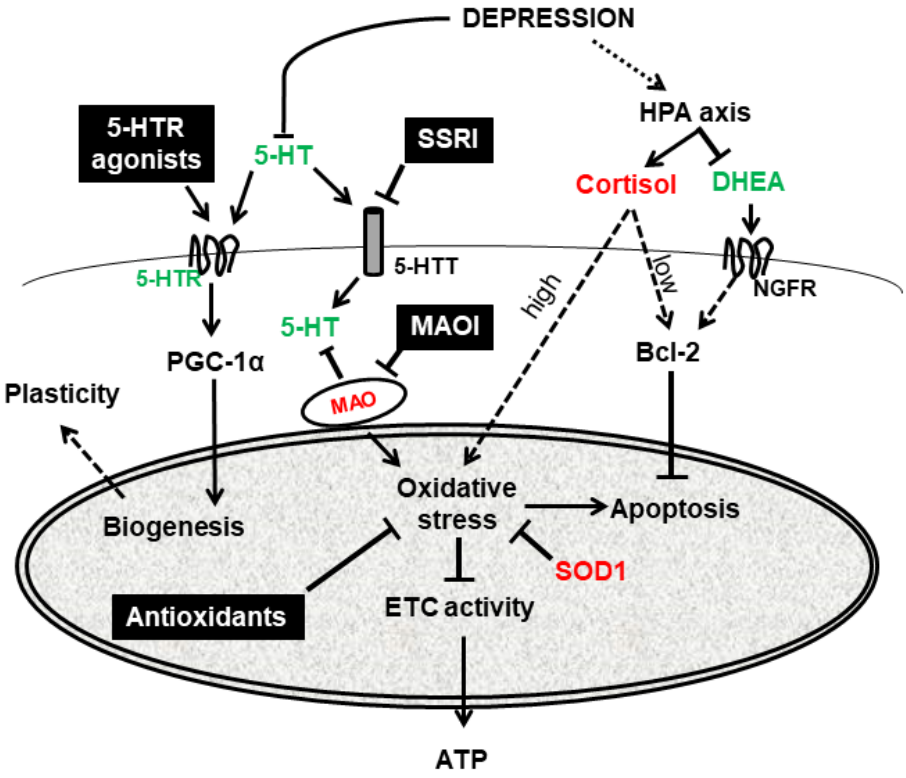

Fig. (1). Mitochondria and monoamine hypothesis in MDD pathophysiology. Depression leads to reduced serotonin levels and dysregulation of the HPA axis, both of which contributes towards increased oxidative stress in the cell and reduced electron transport chain (ETC) activity. Levels of monoamine oxidase (MAO), superoxide dismutase (SOD) and cortisol have been shown to be increased in MDD patients while that of dehydroepiandrosterone (DHEA) and serotonin receptors (5-HTR) are reduced. DHEA interacts with nerve growth factor receptor (NGFR) and is neuroprotective through inhibition of apoptosis. Current approaches to target depression are depicted in the black boxes and include selective serotonin reuptake inhibitors (SSRIs), MAO inhibitors (MAOI), antioxidants and 5-HTR agonists. 5-HTR agonists increase neuronal plasticity by increasing mitochondrial biogenesis through increasing the expression of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α).

binding protein whose expression increases in the brain during acute stress and has been implicated in MDD [36].

Stress mediates chronic increased levels of cortisol and a decrease in the levels of dehydroepiandrosterone – the latter binds to various neurotrophic receptors thereby preventing neuronal apoptosis [37]. On the other hand, glucocorticosteroids have been shown to increase oxidative stress in cultures [38], increase telomerase activity [39] and compromise the activity of mitochondrial manganese SOD in chronic isolation stress model in rats [40]. Chronic mild stress also increases the levels of catalase thereby creating an imbalance between catalase and SOD activities in the brain and predisposing the individual to depression [41]. While at higher doses corticosterone enhanced kainic acid-induced toxicity of primary neurons, at lower levels, corticosterone treatment was neuroprotective with glucocorticoid receptors complexing with the anti-apoptotic B-cell lymphoma 2 (Bcl-2) protein and translocating to the mitochondria [42]. The fate of the neuron thereby depends on the decision at the level of mitochondria and the various anti-apoptotic and anti-oxidative players whose levels depend on the levels of corticosterone released which in turn depends on the duration and degree of stress (Fig. **1**).

4. MITOCHONDRIA AND THE NEUROTROPHIC HYPOTHESIS

Chronic stress affects neuronal plasticity and this forms the basis for the neurotrophic hypothesis for depression [43]. Evidences for this comes from the observation that neurogenesis is higher in mice living in enriched environments compared to littermates living in standard cages [44]. Neurogenesis is mediated by various neurotrophic factors including brain-derived neurotrophic factor (BDNF) whose levels go down in depression and are increased with antidepressant therapy [45]. Loss of neurotrophic factors leads to the activation of the intrinsic cell death pathway in neurons [46]. An increase in the levels of BDNF mRNA by 48% was seen in a study where patients were given eight weeks of treatment with antidepressant drugs [47]. Plasma BDNF has also been considered as a marker for response to antidepressant therapy [48].

Neuroplasticity is inherently linked to mitochondria which must provide the energy required for neuronal remodelling [49]. The neuroprotective effects of BDNF occur through an increase in respiratory control index through a mitogen-activated protein kinase kinase (MEK)-Bcl2 pathway [50]. The neuroprotective effect was inhibited by rote-

none, a mitochondrial complex I inhibitor. The increased efficiency of oxygen utilization by BDNF allows for the plasticity of neurons in the brain (Fig. **2**). An important transcription factor downstream of BDNF pathway is cyclic AMP response element-binding protein (CREB), which is involved in neurogenesis and whose levels are lowered in depression but are reversed by the action of antidepressants [51]. Mitochondrial activity and the levels of BDNF, CREB, and various genes involved in energy metabolism were elevated in mice undergoing exercise which also show reduced anxiety and depressive behaviour [52]. This suggests that mitochondrial activity is associated with increased neurogenesis thereby implicating their role in MDD.

5. MITOCHONDRIA AND EPIGENETICS HYPOTHESIS

Unlike schizophrenia, where various genetic loci have been identified, studies by the MDD Working Group of the Psychiatric genome-wide association studies (GWAS) Consortium did not result in the identification of any single-nucleotide polymorphism (SNP) for MDD [53, 54]. However, genetic polymorphisms associated with MDD have been identified for BDNF, 5-HT receptors and transporter, catechol-O-methyltransferase (COMT), glucocorticoid receptor gene (NR3C1) and many others [55]. Epistatic interactions among them, such as between 5-HT transporter and BDNF, have been identified which involves the HPA axis and CREB protein [56].

Studies among identical twins show relatively higher rates of discordance for MDD suggesting the importance of environmental factors for disease vulnerability [57]. Stress-mediated epigenetic changes include events such as DNA methylation and histone acetylation [58, 59]. Epigenetic modifications in response to early life stress play an important role in the pathophysiology of MDD in the adult [60]. In the glucocorticoid receptor-impaired mice, where the HPA axis fails regulation through feedback, epigenetic changes were observed in genes regulating neurotransmitter release and circadian rhythm [61]. Glucocorticoid receptor expression is also reduced in pups devoid of maternal grooming due to increased methylation of its promoter region [62].

DNA and histone methylation events use S-adenosylmethionine (SAM) as the methyl donor which is regenerated in the cytosol from methionine using the one-carbon metabolic pathway which utilizes the vitamin folate [63]. Mitochondria play a key role in this pathway by providing the one-carbon unit formate which is utilized for re-methylation of homocysteine to methionine. Polymorphism in the genes involved in this pathway, such as methylenetetrahydrofolate reductase, affects DNA and histone methylation and increases the risk for neuropsychiatric diseases [64]. SAM has been successful as a second-line therapeutic option in patient's non-respondent for SSRIs [65]. Efforts to counter increases in homocysteine level and more large-scale controlled trials would be required for considering SAM as a supplementary antidepressant [66, 67]. These observations suggest an indirect role of mitochondria in reduced gene expression in psychiatric patients through epigenetic modulation (Fig. **2**).

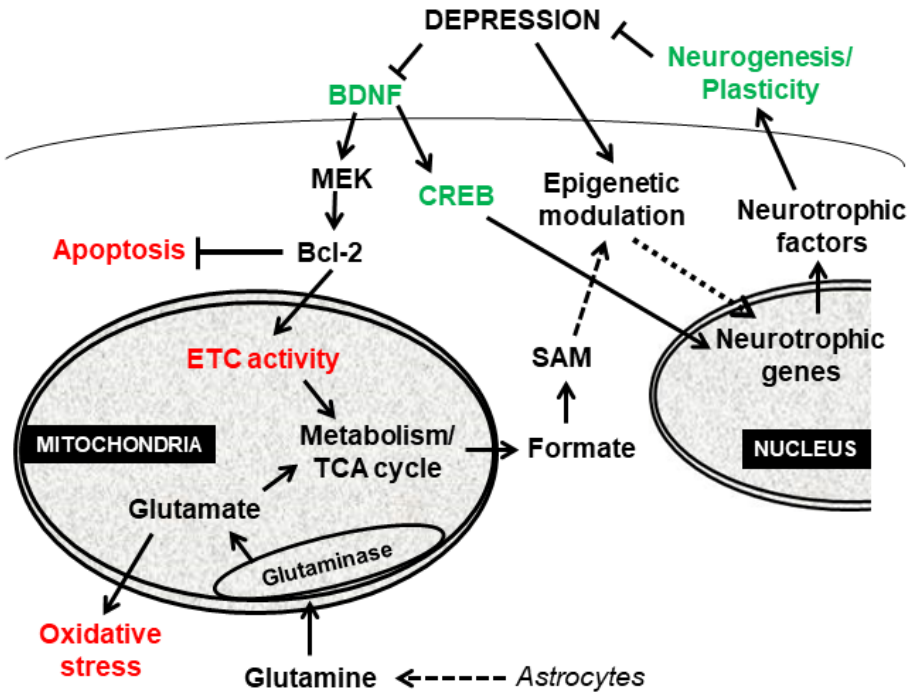

Fig. (2). Mitochondria and neurotrophic hypothesis in MDD pathophysiology. Chronic stress affects neuronal plasticity through decreased availability and transcription of neurotrophic factors such as brain-derived neurotrophic factor (BDNF). BDNF enhances mitochondrial activity through a bcl-2-dependent pathway. Loss of signalling by BDNF reduces neuronal plasticity and induces apoptosis. Mitochondria provide the substrate for formation of S-adenosylmethionine (SAM) which is required for various epigenetic modulations within the cell including of the genes responsible for neuronal plasticity. The density of astrocytes is also reduced in MDD individuals thereby affecting glutamine-glutamate ratio. Astrocytes transfer glutamine to the neurons, which is reconverted to glutamate by the mitochondrial glutaminase-2.

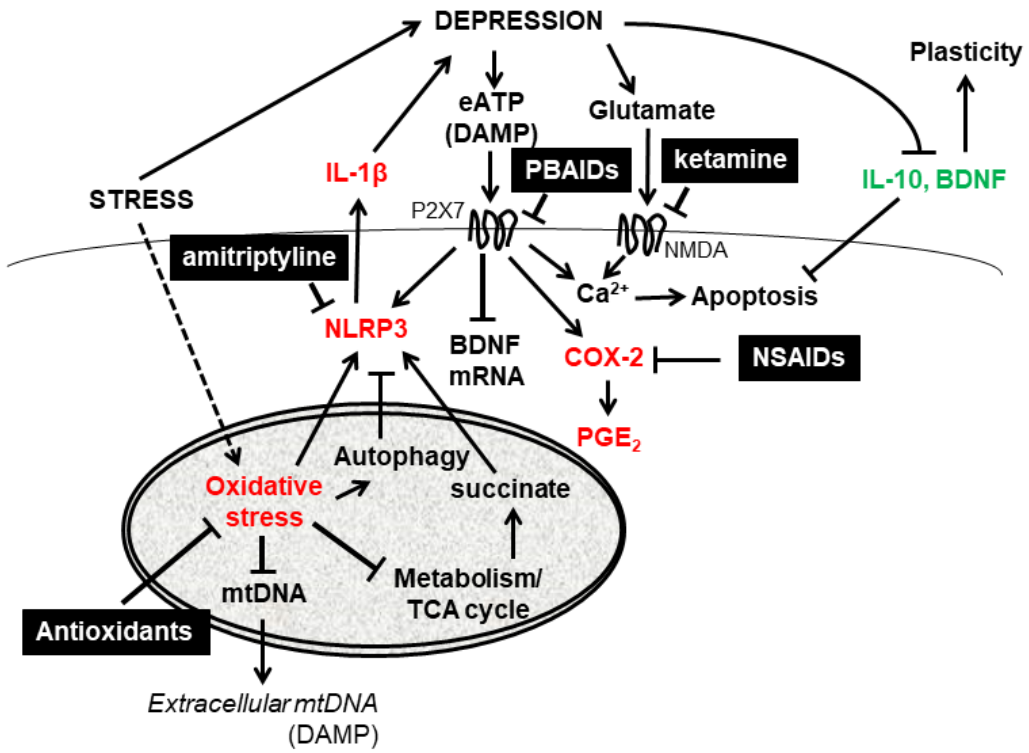

Fig. (3). Mitochondria and neuroinflammatory hypothesis in MDD pathophysiology. Stress causes release of inflammatory cytokines and prostaglandin E_2 (PGE_2) whose levels are increased in depression while that of BDNF and interleukin 10 (IL-10) are reduced. Stress-mediated oxidative stress is responsible for release of danger-associated molecular patterns (DAMPs) such as mitochondrial DNA (mtDNA) and ATP. Exogenous ATP further enhances depression through increased cytokine and PGE_2 synthesis *via* NLRP3 inflammasome and cyclooxygenase 2 (COX-2) activation. Inflammasome formation is enhanced by the TCA cycle intermediate succinate and reduced during autophagy. In addition to antioxidants and amitriptyline, other approaches to target depression include ketamine, non-steroidal anti-inflammatory drugs (NSAIDs) and P2 receptor-based anti-inflammatory drugs (PBAIDs).

The differential response of MDD patients to antidepressants is also due to differential expression of microRNAs (miRNAs). Among the various miRNAs, miR-146a-5p, miR-146b-5p, miR425-3p and miR-24-3p have been suggested to play an important role in treatment response [68]. In a genetic rat model of depression, miR-101b, which targets glutamate transporter, has been found to be downregulated [69]. In astrocytoma cells, miR-101 has been shown to reverse the methylation of promoter of PR domain containing 16 (PRDM16) leading to disruption of mitochondrial function, reduced ATP synthesis and initiation of mitochondria-dependent apoptosis [70]. Stress-regulated miR-124 is epigenetically regulated in MDD [71]. miR-124 is involved in mitochondrial fatty acid oxidation in prostate cancer cells through modulation of the carnitine cycle and in regulation of apoptosis through inhibition of Bim, thereby preventing Bax translocation to mitochondria, in a mouse model of PD [72, 73]. Suggestions for use of miRNAs in MDD therapeutics, therefore, have been suggested [74].

6. MITOCHONDRIA AND THE NEUROINFLAMMATION HYPOTHESIS

Stressors not only affect monoamine and growth factor levels but also mediate an increase in the levels of cytokines such as interleukin-1β (IL-1β), tumour necrosis factor α (TNF-α) and interleukin-6 (IL-6) [75]. Elevated levels of immune markers were identified in psychiatric patients as early as the late 1960s [76]; however, evidences for monoaminergic and neuroendocrine hypotheses were stronger. Interest in the inflammatory hypothesis returned when a relationship was demonstrated between prenatal infection and adult-onset schizophrenia [77]. Early-life inflammation is related to anxiety through adult life [78]. Meta-analysis studies showed that patients suffering from MDD had higher levels of plasma IL-6, TNF-α and soluble interleukin 2 receptor [79]. This is often accompanied by an absence of the counter-balancing, immunoregulatory interleukin-10 levels [80]. In about one-third of the patients with chronic inflammatory diseases such as multiple sclerosis or chronic hepatitis C, recombinant interferon α treatment promoted depressive mood which could be reduced with the use of antidepressants [81]. Antidepressants and anti-depression therapies such as electroconvulsive therapy reduced the levels of various inflammatory cytokines [82, 83]. Similarly, anti-inflammatory compounds such as the cyclooxygenase 2 (COX-2)-specific inhibitor, celecoxib, possess antidepressant activity as well [84].

Inflammatory cytokines increase mitochondrial reactive oxygen species (ROS) and lipid peroxidation which has been shown to be increased in patients with MDD [85]. ROS, in turn, increase the expression of various pro-inflammatory cytokines. Rats treated with lipopolysaccharide (LPS) ex-

hibit increased oxidative stress and mitochondrial dysfunction leading to neuronal loss [86]. Cellular stress releases mtDNA and formyl peptides into the serum where they act as mitochondrial damage-associate molecular patterns (DAMPs) leading to the activation of the innate immune system (Fig. **3**) [87]. Several recent animal and clinical studies provide further evidences on mitochondrial dysfunction due to high serum levels of pro-inflammatory cytokines and leading to increased depression [88]. Various antioxidant and anti-inflammatory compounds, therefore, have been suggested as therapeutic options for the treatment of depression [89].

7. MITOCHONDRIA AND THE GLUTAMATERGIC HYPOTHESIS

An interesting but lesser researched hypothesis for depression implicates the role of glutamate receptors. Evidence for this hypothesis comes from the observation that the non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, ketamine, mediates a rapid antidepressant effect which sustains up to seven days in therapy-resistant MDD patients [90]. It is hypothesized that inhibition of NMDA receptors by ketamine results in inhibition of eukaryotic elongation factor 2 kinase (eEF2K) and increased translation of BDNF [91]. Evidences on the role of other glutamatergic receptors, and their modulation by 5-HT receptors or crosstalk with inflammatory signalling, have also been observed [92, 93].

Several magnetic resonance spectroscopy studies showed a consistent reduction in the levels of glutamine/glutamate ratio in MDD, especially in the frontal and cingulate cortices [94-96]. Increased levels of glutamate metabolites have also been observed in frontal cortices of patients with post-stroke depression and late-life depression [97, 98]. On the other hand, notable increase in glutamine levels was seen in the occipital and parietal cortices of medication-free depressive patients [99]. The ratio of glutamine to glutamate is maintained through the glutamate recycling pathway in the astrocytes, whose density is prominently reduced in post-mortem brain tissue of MDD patients [100]. Astrocytes transfer glutamine to the neurons where it is reconverted to glutamate by the mitochondrial glutaminase [101]. The rate of glutamate recycling thereby depends on the mitochondrial TCA cycle and the neuroenergetic demand [102]. Any impairment of mitochondrial activity in the neurons, therefore, adversely affects the glutamate recycling and overall neuronal activity. Imaging studies show a reduction in mitochondrial energy production by 26% in glutamatergic neurons in MDD patients [103]. Neuronal glutaminase-2 has also been implicated in the regulation of neurogenesis through p73-dependent pathway [104] and in the modulation of mitochondrial metabolism which is p53-dependent [105]. The glutamatergic hypothesis, thereby, links neuronal metabolism with mitochondrial dysfunction and modulation by glial cells in the pathology of MDD (Fig. **2**).

8. MITOCHONDRIA AND THE PURINERGIC HYPOTHESIS

Purinergic signalling has been identified to play an important role in a variety of neurological disorders ranging from neuropathic pain through ischemia, traumatic brain injury, neurodegenerative disorders, epilepsy, migraine, multiple sclerosis and schizophrenia, to name a few [106]. While cells maintain a high level of intracellular ATP, it has been considered as a DAMP when present in excess in the extracellular milieu [107]. The danger association was first observed in lipopolysaccharide-primed macrophages and microglia which show enhanced release of mature IL-1β in response to exogenous ATP [108]. We have previously hypothesized the role of ATP in neuroinflammation wherein its release from injured cells acts as the "second-hit" leading to enhanced release of pro-inflammatory mediators following the "first-hit" due to infection or injury [109]. Neuronal stress increases the levels of exogenous ATP eventually leading to the development of a chronic low-grade inflammation within the brain and the development of neuropsychiatric ailments (Fig. **3**). This makes the purinergic hypothesis a prequel to the neuroinflammation hypothesis.

Extracellular ATP acts through various members of the ionotrophic P2X receptors or through G protein-coupled P2Y receptors while its breakdown product, adenosine, acts through A1, A2a, A2b and A3 receptors [106]. While we have previously discussed the role of these receptors in neuroinflammation [109], the evidence for their role in neuropsychiatric disorders is limited. The eventual effect depends on the type of receptor on which ATP binds which is dependent on the concentration of ATP determined in turn by the activity of ectonucleotidases [110]. In addition, it also depends on the cell-type – neuronal, astrocyte or microglia – on which these receptors are present, with purinergic signalling considered to be the "re-normalizing" factor when imbalance occurs in neuron-glia signalling [111]. ATP released by astrocytes mediates antidepressant-like effects in a mouse model of depression [112]. While that study implicated the role of $P2X_2$ receptors as having antidepressant-like activity, the other promising receptors thus far identified to play a role in depression include $P2X_7$, $P2Y_1$ and A2a receptors [113-115]. These are supported by associated gene polymorphism studies in humans and the antidepressant phenotype of $P2X_7^{-/-}$ mice [116-118]. $P2X_7$ receptors have been implicated in learned helplessness behaviour, in LPS-induced depression, and in the chronic unpredictable stress model [119-121]. The antidepressant nature of $P2X_7$ knockout mice was shown to be due to elevated levels of basal BDNF, lack of glutamate release, increased 5-HT availability and enhanced neurogenesis – thus linking many of the above hypotheses proposed for depression (Fig. **3**) [122].

Mitochondria are affected due to increasing oxidative and nitrosative stress caused by the increased production of cytokines and prostaglandin E_2 (PGE_2) by exogenous ATP [109]. On the other hand, mitochondria also play an important role in maintaining purine levels within the brain. Compared with non-depressed control subjects, purine metabolism is altered in MDD patients [123]. A magnetic resonance spectroscopy study also supported the finding of a lower level of nucleoside triphosphate in the basal ganglia of patients with major depression [124]. In addition, purine-mediated calcium levels are altered due to dysfunctional mitochondria leading to impaired synaptic plasticity in depressed patients [5, 125]. Recently it was also shown that neurotoxic agents that act on

mitochondria are also capable of affecting neuronal PGE_2 synthesis and process length [126]. Since neuronal processes play an important role in mood, neurotoxic agents that affect mitochondrial health may also play an important role in depression. One such neurotoxic agent is 1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline (TaClo) which can be potentially formed within the brain of individuals exposed to trichloroethylene or chloral hydrate [127]. Parkinsonism-like symptoms have been observed in patients occupationally exposed to trichloroethylene [128]. These observations suggest that environmental toxins that affect mitochondrial function can be detrimental to neuronal function as well as interneuronal communication through loss of process length.

The inflammasome is a multimeric protein complex consisting of an intracellular sensor such as a nod-like receptor (NLR), the adaptor protein apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and the precursor procaspase 1. Exogenous ATP activates inflammasome causing maturation of caspase 1 and processing of IL-1β [129]. Of all the NLRs, NLRP3 has been implicated in depression acting through IL-1β [130]. Stress causes release of ATP leading to stimulation of $P2X_7$ receptors and activation of inflammasome [131]. Antidepressants such as amitriptyline inhibit IL-1β production along with NLRP3 in MDD patients [85]. In addition to its effect on glutamate receptors, ketamine also mediates antidepressant-like activity in a chronic restraint stress model through decreases in pro-inflammatory cytokines and downregulation of the $P2X_7$ receptor [132]. The inhibitory effect of ketamine is observed in both LPS-induced microglial cells [133] and lipoteichoic acid-induced macrophages [134]. Such immunomodulatory role of ketamine has also been suggested towards its antidepressive activity in astroglial cells [135]. NLRP3 activation by extracellular ATP stimulation requires intact mitochondria as a prerequisite [136]. Autophagy prevents inflammasome formation and its blockage leads to accumulation of ROS within the mitochondria leading to activation of NLRP3 [137]. Increased levels of succinate in the mitochondria also increase IL-1β formation in LPS-treated macrophages [138]. The exact mechanism by which mitochondrial dynamics is associated with NLRP3 inflammasome activation is unknown. Since both mitochondrial dynamics and NLRP3 inflammasome are key participants in MDD aetiology and have been related to one another, further research is required to understand the convergence among the three.

CONCLUDING REMARKS

The major depressive disorder is a multifactorial disease with an unclear aetiology and, because of which, recovery is inconsistent or not the same across patients. Depression imposes a significant burden on both the sufferers and society at large [139]. Keeping in view for a common denominator among the various hypotheses proposed for depression, we found the involvement of mitochondria at various levels (Figs. **1**-**3**). Despite their important role in oxidative phosphorylation, calcium homoeostasis, apoptosis, cellular signalling and metabolism, mitochondrial dynamics and generation of reactive oxygen species play a crucial role in the pathogenesis of MDD as reviewed here. Markers of oxidative damage have been identified in depressed patients while antidepressants have been shown to affect mitochondrial function [12, 30]. Mitochondria are also required for neurite outgrowth [126, 140]. Insulin resistance in the brain causes depression-like symptoms through mitochondrial dysfunction and altered dopamine turnover [141]. These and many other evidences suggested in this review point to mitochondrial involvement in the pathogenesis of MDD.

We have also described the role of exogenous ATP in the pathogenesis of depression through its binding to purinergic receptors (Fig. **3**). While $P2X_7$ receptors are primarily involved in the formation of inflammasome, which has been shown to cause depression [121], other purinergic receptors also contribute to inflammation as described previously [109]. $P2Y_6$ receptors trigger a change in phenotype of microglia from surveillance cells to phagocytic cells, while $P2Y_{12}$ receptors are responsible for their chemotaxis [142, 143]. Astrocytic $P2Y_1$ receptors cause reactive gliosis although ATP released by astrocytes mediates antidepressant-like activity through $P2X_2$ receptors located on neurons [112, 144]. These observations suggest that the diversity of P2 receptors and their cellular localization determines their effect in mediating inflammation within the brain. P2 receptor antagonists can function as anti-inflammatory drugs, coined as P2 receptor-based anti-inflammatory drugs (PBAIDs), which may also be an effective antidepressant in inhibiting the formation of inflammasome and PGE_2 responsible for chronic stress [109]. However, the diversity of P2 receptors and contrasting functions pose challenges for therapeutic targeting. For example, $P2X_4$ receptors mediate neurophagic activity of microglial cells during stroke but are also essential for post-ischemic recovery where they are responsible for the release of BDNF [145, 146]. This makes $P2X_4$ receptors pro-inflammatory during stroke but antidepressant-like during recovery phase. Similarly, A2a knockout mice show altered anxiety behaviour and its blockade by caffeine prevents depression in chronic unpredictable stress model [115, 147]; however, A2a receptors are also activated by inosine, the breakdown product of adenosine, which mediates an antidepressant-like effect in the tail suspension model in mice [148]. Hence, more studies are required to identify the contributory roles of P2 receptors to be successfully used as PBAIDs in the treatment of MDD.

In this review, we have highlighted the involvement of mitochondria in the various hypotheses proposed for MDD. Targeting mitochondria therapeutically can be generalized to all MDD patients; however, mitochondrial function depends on age, occupational exposure, exercise, diet and metabolic capacity of the person, all of which varies between patients. Similar challenges pose for the use of P2 receptors for therapeutically targeting inflammation or depression. More studies are warranted to identify suitable pathway/target protein underlying the pathophysiology of MDD.

LIST OF ABBREVIATIONS

5-HT	=	Serotonin
ATP	=	Adenosine Triphosphate
BDNF	=	Brain-derived Neurotrophic Factor

CREB	=	Cyclic AMP Response Element Binding Protein
CRF	=	Corticotropin-Releasing Factor
DAMPs	=	Damage Associated Molecular Patterns
HPA	=	Hypothalamus-Pituitary-Adrenal Axis
IL-1β	=	Interleukin-1β
LPS	=	Lipopolysaccharide
MAO	=	Monoamine Oxidase
MDD	=	Major Depressive Disorder
NLRs	=	Nod-Like Receptors
NMDA	=	*N*-Methyl-D-Aspartate
PBAIDs	=	P2 Receptor-Based Anti-Inflammatory Drugs
PGC-1α	=	Peroxisome Proliferator-Activated Receptor γ Coactivator 1α
PGE_2	=	Prostaglandin E_2
SAM	=	S-Adenosylmethionine
SSRI	=	Selective Serotonin Reuptake Inhibitor
TNF-α	=	Tumour Necrosis Factor α

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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