Oxygen - Mitochondrial fuel as a missing link in depressive pathophysiology

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Author Contributions

MM and RNM conceptualized the model, with critical contribution from AB and ITK. RNM and MM reviewed the literature and wrote the manuscript. AB and ITK edited and revised the manuscript.

Abstract

Major depressive disorder (MDD) causes enormous individual suffering and socioeconomic costs. Biochemical mechanisms leading to MDD are poorly understood and therapy success is not satisfactory. At present, there is evidence of low-grade inflammation, oxidative stress, and most interestingly, a disturbed energy metabolism in MDD and other mental disorders. Mitochondria play a central part in energy production and stress signaling. Mitochondrial electron transport chain uses molecular oxygen (O_2) as final electron acceptor during adenosine triphosphate production attributing a crucial role to an intact O_2 supply. Adaptation to altered O_2 availability by the highly conserved hypoxic response is essential for maintaining allostasis. Previous research confirmed the role of O_2 metabolism in the pathophysiology of MDD. In this perspective article, we compile the evidence linking O_2 transport, O_2 homeostasis, and mitochondrial energy metabolism to MDD. Furthermore, we hypothesize that inflammation and oxidative stress-related alterations in O_2 transport might lead to a hypoxic response, which explains changes in O_2 homeostasis and energy metabolism in MDD. Our forthcoming studies will investigate the interplay between energy metabolism and O_2 homeostasis in MDD that aim to improve the overall understanding of the pathophysiology of MDD and to guide medical and psychological diagnostics towards a holistic strategy.

Introduction

Prevalence of major depressive disorder (MDD) is escalating, and it is a leading cause of disability and socioeconomic burden worldwide [1]. Yet, the pathophysiology of MDD is still not clear. Success of selective serotonin reuptake inhibitors in animal models led researchers to identify MDD as a lack of monoaminergic neurotransmitter availability in the brain [2, 3]. However, mixed success rate and relapses after remission indicate that monoaminergic antidepressants do not seem to sustainably cure the disease [4, 5]. Finding better treatments depends on a more profound understanding of the disorder's biological underpinnings. Unfortunately, the current understanding of the pathophysiology of MDD is not sufficient to prompt therapeutic applications.

Recent transdisciplinary research has established mitochondrial functioning as an element in the pathophysiology of MDD and confirmed various physiological aberrations, including reduced mitochondrial energy production in immune cells, blood platelets, and muscle cells [6–8] as well as reduced energy production and adenosine triphosphate (ATP) shortage in the brain of MDD patients [9, 10], indicating MDD as a chronic state of systemic energy deficiency. Reduced cellular energy production limits the functionality of cells in depressed patients, leading to the characteristic findings in MDD, namely, lack of energy, fatigue, difficulties in concentration, memory consolidation, and emotion regulation problems as well as dysregulated inflammatory processes [6, 7, 11]. However, the physiological mechanisms underlying the altered mitochondrial function in MDD is unclear.

In this article, we propose a novel model of MDD as a hypoxic state, which could explain the dysregulation of the energy metabolism in the disease. For this purpose, we reviewed previous research about relevant processes that are associated with hypoxic response, i.e. oxygen (O_2) transport and homeostasis, and their role in cellular energy production. We propose that inflammation- and oxidative stress-related alterations in O_2 transport and utilization result in a

low-grade hypoxic state that might affect mitochondrial functioning in MDD. After a short summary of the energy production and related processes, evidence of a disturbed O₂ transport in MDD is presented. Afterwards, molecular adaptation processes regulating O₂ homeostasis upon hypoxic conditions and MDD will be described and specified in the context of mitochondrial functioning. Finally, main findings are recapitulated and integrated into our novel model of MDD pathophysiology.

Cellular energy production and oxidative stress

Biological energy is provided in cells consecutively by utilization of carbohydrates, production of electron carriers, establishment of a proton gradient, and final synthesis of ATP. Detailed information about the biological processes that are discussed in this paper can be found in Table 1. Briefly, carbohydrates are used during glycolysis, pyruvate oxidation, and citric acid cycle to provide the reduction equivalent nicotinamide adenine dinucleotide (NADH) [12]. In the subsequent oxidative phosphorylation (OXPHOS), electrons provided from NADH are passed across the mitochondrial electron transport chain (ETC), where O₂ serves as the final electron acceptor, to pump protons out of the inner membrane. The resulting proton gradient is used to synthesize ATP, which is essential for all kinds of biochemical processes in living organisms [13]. However, due to disturbances or adaptive reprogramming of OXPHOS, excessive amounts of reactive oxygen species (ROS) can be produced. The imbalance between ROS and antioxidants is termed as oxidative stress. It is an intrinsic cellular demand to maintain ATP production and ROS formation at defined levels. As O₂ is crucial to OXPHOS, it is vital to any cell to maintain adequate O₂ supply, regulate its consumption, and adapt to altered O₂ availability.

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MDD as a low-grade hypoxic state: Disturbances in oxygen availability and transport

This section focuses on the mechanisms and elements of O₂ transport as well as their alterations in MDD and other mental disorders. Lower O₂ levels in the tissue due to alterations in O₂ transport and utilization might trigger a hypoxic response, which affects mitochondrial functioning and O₂ homeostasis.

After being inhaled into the lungs, driven by a partial pressure gradient, O₂ passively diffuses across the blood-air barrier and passes through the membrane of erythrocytes where it binds to hemoglobin. Hemoglobin consists of four globular protein subunits, each containing a central iron atom (Fe²⁺) that is reversibly oxidized to Fe³⁺ with O₂ binding. With this conformation, one hemoglobin molecule can bind a maximum of four O₂ molecules. After binding to hemoglobin, O₂ is distributed across the body via blood circulation. Where needed in tissues, O₂ passively diffuses from blood to cells, and subsequently, into mitochondria to take role in ETC [14].

Particularly, hemoglobin's affinity to O₂ in pulmonary and systemic capillaries is what brings O₂ to the circulation, and releases it from the circulation. It is regulated in an "*oxyhemoglobin equilibrium*", which depends on the *oxygen dissociation curve* (ODC). ODC depicts the association between partial O₂ pressure (pO_2) and O₂ saturation in hemoglobin. It has a sigmoidal shape, meaning the binding of the first O₂ to Fe²⁺ bolsters the second O₂ binding, and as the number of O₂ molecules bound to hemoglobin increases, more pO_2 is required for additional O₂ binding to hemoglobin [14]. The process is the opposite for unbinding. ODC is influenced by core physiological factors, namely body temperature, carbon dioxide concentration (pCO_2), pH -levels, and 2,3-diphospho-glycerate (2,3-DPG) concentration. Increasing body temperature, pCO_2 , and 2,3-DPG, and decreasing pH result in a right shift in the ODC, meaning more pO_2 is necessary to saturate hemoglobin, leading to decreased O₂-hemoglobin affinity [15].

Factors that may cause a shift in ODC are found to be altered in MDD and other mental disorders. In particular, increased body or brain temperature was shown in individuals with MDD or schizophrenia, respectively [16, 17]. Decreased brain pH was reported to be common in schizophrenia, bipolar disorder, and autism spectrum disorder [18], while higher venous blood pH was found in MDD patients [19]. In individuals with Alzheimer's disease and non-Alzheimer dementia, lower venous erythrocyte 2,3-DPG levels were found compared to controls [20]. These findings might indicate less affinity of hemoglobin to O_2 in MDD and other mental disorders.

As suggested before, the central transition element of hemoglobin is iron. Thus, the iron metabolism and its highly conserved regulation are crucial for the O_2 supply system as well as for the aerobic energy production. Studies reported associations between MDD risk and alterations in the iron metabolism, i.e., decreased ferritin, transferrin, hemoglobin, and erythrocyte counts [21–24]. Similarly, individuals with MDD show lower serum iron levels than controls [25]. However, other studies reported no association between MDD and serum iron, ferritin, and hemoglobin levels [26, 27]. Therefore, certain alterations in iron metabolism might be only relevant in certain subgroups of MDD. On the other hand, alterations in the iron regulation, rather than a huge effect in the steady-state level of iron parameters might be more likely in MDD. This hypothesis is supported by previous findings: While iron levels appear to be reduced in the blood of MDD patients, iron seems to accumulate in their brain, depicting a dysregulation in iron metabolism in MDD [28]. Moreover, increased levels of hepcidin were found in MDD patients with brain iron load [29]. Noteworthy, in order to restore and maintain O_2 supply, hepcidin is induced via the influence of erythropoietic activity, hypoxia, and inflammation [30]. The important role of hepcidin was previously shown in a chronic mild stress-induced MDD model in rats, reporting increased iron and hepcidin mRNA levels in the hippocampi of stressed animals [31]. Therefore, compensatory alterations in hepcidin-

dependent iron regulation in MDD might be a more reliable indicator of iron metabolism status compared to steady-state iron parameters.

Increased MDD prevalence was observed in patients displaying dysfunctions in O₂ transport, such as iron-deficiency anemia [32] and sickle cell anemia [33]. Diseases that prevent sufficient air inhalation such as chronic obstructive pulmonary disease [34], asthma [35], and COVID-19 [36] have also been associated with higher MDD risk, compared to general population. Higher MDD rates were also found in people with chronic hypoxic conditions such as coronary heart disease and stroke [37].

Environmental factors like air pollution and altitude are known to reduce O₂ availability and O₂ saturation in humans, and lead to psychopathology. Accordingly, exposure to traffic-related air pollution evoked depressive symptoms in children [38], and air pollution was linked to a higher risk for suicide [39]. Similarly, a positive association between altitude and suicidal risk was observed [40]. Another study reported that students moving from a low altitude to a high altitude developed more depressive and anxiety symptoms compared to a control group that remained at low altitude [41]. These findings led to the interpretation that conditions which limit the O₂ availability such as altitude and asthma might create a mild hypoxic state in individuals, resulting in mood disorders. Researchers speculated that hypoxic response can decrease serotonin synthesis [42], increase inflammatory response [43], or affect brain bioenergetics [44] and thus lead to suicide and MDD.

The studies mentioned above point towards an association of MDD and a disturbed O₂ transport as well as decreased cellular O₂ availability. Indeed, a case-control study performing venous blood gas analysis reported higher venous pO_2 along with lower venous pCO_2 in MDD patients compared to controls, which was interpreted as tissue hypoxia. A positive correlation between venous pO_2 and depressive symptoms was also observed, exhibiting a reduced O₂ utilization in MDD [19]. Moreover, compared to controls, less O₂-saturated hemoglobin was observed in the

frontotemporal cortex of MDD patients during a verbal task [45, 46], highlighting the relevance of O₂ insufficiency in cognitive symptoms of MDD.

Altogether, studies provide evidence for O₂ insufficiency in MDD in conditions both with and without a scarce of O₂, suggesting relative tissue hypoxia as one contributing factor in the pathophysiology of MDD. Hypoxia provokes systemic compensatory metabolic reactions throughout the whole body, at the foremost, affecting mechanisms responsible for O₂ homeostasis and cellular energy provision.

Alterations in oxygen homeostasis in hypoxia and major depressive disorder

The next section addresses molecular response mechanisms upon alterations in O₂ availability. Additionally, we will outline the link between the cellular response to hypoxia and the energy metabolism. Based on this, it will be demonstrated that changes in the energy metabolism upon hypoxia response might play a role in the pathophysiology of mental disorders, highlighting MDD.

In 2019, the Nobel Prize in physiology or medicine was awarded to Kaelin Jr, Ratcliffe, and Semenza for their work on cellular sensing and adaptation to O₂ availability. Their key finding was the discovery of Hypoxia Inducible Factor-1 (HIF-1) as the major mediator of hypoxia response. The heterodimeric transcription factor HIF-1 consists of subunit HIF-1 α and HIF-1 β , which are ubiquitously expressed [47]. As illustrated in Figure 1, under normoxic conditions, HIF-1 α is rapidly degraded via the proteasome. Depending on Fe²⁺ and O₂, prolyl hydroxylase domain enzymes (PHD) hydroxylate HIF-1 α [48], which serves as a signal for ubiquitination by the von Hippel-Lindau protein (VHL) [49] and the subsequent proteasomal degradation of HIF-1 α [50]. Due to PHD's dependency on molecular O₂, hypoxia results in both PHD inhibition and HIF-1 α stabilization [51]. Therefore, O₂ sensing can be attributed to PHD.

insert Figure 1 around here

Another proposed mechanism for HIF-1 α stabilization is the generation of ROS. Researchers inhibited the hypoxic response by blocking ROS generation at mitochondrial ETC complex III [52, 53]. Increased production of ROS leads to catalytic inactivation of PHD via oxidation of Fe²⁺ to Fe³⁺ [54]. Furthermore, it was shown that low pO_2 leads to an increased reduction state of ETC's cytochrome c that results in a preservation of O₂ consumption even under lower O₂ abundance [53]. These changes in redox status might lead to elevated ROS production, but the mechanisms are still not fully understood. Altogether, these findings place mitochondria as the central element in the response to hypoxia as well as the source of adaptive regulation, which will be addressed next.

Along with HIF-1, HIF-2 is another important regulator of hypoxic response. HIF-1 and HIF-2 activation depend on the tissue, the time course and severity of hypoxic response, and the type of hypoxic response [55]. Therefore, in this article HIF-1 and HIF-2 will be together referred as Hypoxia Inducible Factors (HIFs) in order to ensure simplicity. HIFs fulfill an important part in the adaptation to altered O₂ supply and mitochondrial ROS production. They act as transcription factors on certain genes via binding to hypoxia-responsive elements (HRE) that initiate gene expression. This regulates O₂ homeostasis as well as parts of the energy metabolism, e.g., glycolysis and anaerobic respiration [56]. HIF-mediated changes in O₂ homeostasis result in increasing O₂ delivery and/or decreasing O₂ consumption [56]. In order to increase O₂ delivery, HIF targets the vascular endothelial growth factor (VEGF) that induces angiogenesis, and erythropoietin (EPO) that induces erythropoiesis [57, 58]. In line with our hypothesis, higher plasma EPO levels were reported in MDD patients compared to controls, indicating increased erythropoiesis in MDD [59]. Although studies are not entirely consistent, there is evidence for higher blood levels of VEGF in MDD [60].

As mentioned above, HIFs also take part in the regulation of the energy metabolism. Improving the O₂ supply in response to deficits appears straightforward, but the implementation of a

metabolic change seems to be rather complicated. In conditions of insufficient O₂ supply, a metabolic shift towards glycolysis and anaerobic respiration counteracts ROS production, diminishes O₂ demand, and maintains ATP provision to some extent [56]. Glucose transporter 1 (GLUT1), lactate dehydrogenase A (LDHA), and pyruvate dehydrogenase kinase 1 (PDK1) are important proteins in the energy metabolism and are directly targeted by HIFs. HIF-1 dependent upregulation of LDHA leads to an increased conversion of pyruvate to lactate [61], while induction of PDK1 inhibits the conversion of pyruvate to acetyl CoA [62]. By increasing cellular glucose concentration (through GLUT1), elevated anaerobic respiration (via LDHA), and inhibition of aerobic respiration (via PDK1), HIFs decrease O₂ consumption while promoting glycolysis rather than OXPHOS. Higher expression of *HIF-1*, *GLUT1* and *LDHA* genes were reported in patients with MDD [63]. Researchers recently found the connection between MDD-like phenotypes and increased *GLUT-1* expression in an animal model [64]. In line with these results, a study reported downregulation of citric acid cycle metabolites in immune cells of patients with MDD [65]. Findings in certain mental disorders support the hypoxia-mediated shift towards glycolysis. Increased pyruvate was found in the blood of patients with bipolar disorder [66] and posttraumatic stress disorder [67]. A meta-analysis reported decreased pyruvate in the blood of MDD patients [68] which might be due to increased LDHA activity. Increased lactate was found in the blood of posttraumatic stress disorder patients [67], ventricular cerebrospinal fluid of MDD patients [69], and in the brain of schizophrenia and bipolar disorder patients [70].

Taken together, the highly conserved HIF regulation constitutes an essential mechanism for adaption to hypoxic conditions. As a response to decreased O₂ availability and/or elevated ROS production, HIF stabilization induces both improvement of the O₂ supply and metabolic reprogramming. There is evidence of such metabolic changes in mental disorders indicating a

possible contribution to the pathophysiology. Please see Table 2 for a summary of hypoxic response related alterations in MDD.

Disturbances in mitochondrial function and biogenesis during hypoxic conditions and major depressive disorder

This section focuses on mitochondrial functioning, and how it might be influenced by hypoxic response in mental disorders. In general, mitochondrial research in psychology has gained importance in recent years. Many studies report allostatic processes, namely adaptations to certain stressors such as chronic life stress or trauma, which lead to mitochondrial allostatic load and contribute to MDD symptomatology. However, many of these allostatic processes are poorly characterized.

Alterations in mitochondrial function and biogenesis have been established to be critical factors in MDD pathophysiology [71]. These factors are also regulated during hypoxic conditions through HIFs [72]. Therefore, the link between mitochondrial function and the previously described shift towards glycolysis seems plausible. In order to regulate the energy metabolism in hypoxic conditions, citric acid cycle is inhibited via PDK1, and the ETC is remodeled [72]. During hypoxic conditions, ETC adapts its complexes to prevent additional ROS production also while inactivating complex I [73]. Moreover, it was proposed that optimal O₂ consumption is achieved under hypoxic conditions via a change in complex IV (COX) subunit COX4-1 to COX4-2 [74] .

However, such hypoxia-related reprogramming comes at the cost of less efficient ATP production, which is also observed in MDD [9, 10]. As already described, studies reported a disturbed mitochondrial energy production in several cell types of MDD patients [6–8]. Conceivably, this alteration in MDD could be the result of hypoxic stress-related reprogramming of the mitochondrial complexes. Indeed, downregulation of mitochondrial

complexes I, III, and IV was reported in gastrocnemius muscle and hippocampus tissue of “depressed” rats [75]. A meta-analysis showed similar effect in humans with MDD, reporting decreased activity in mitochondrial complex I and IV [76].

Another response to hypoxia is the downregulation of ATP-demanding processes. This is achieved by degradation of Na-K-ATPase as well as diminished global mRNA translation through the suppression of rapamycin complex 1 (mTORC1) [77]. These mechanisms might lead to an overall reduction in the regulatory capacity. The mechanism underlying this downregulation is not yet fully understood. Most probably, ROS that are generated during hypoxia at the mitochondrial complex III trigger the increase of cytosolic calcium [78]. Elevated calcium concentration activates Ca^{2+} /calmodulin-dependent kinase kinase (CaMKK), followed by activation of AMP-activated protein kinase (AMPK) [79]. AMPK itself inhibits mTORC1 and promotes endocytosis of Na-K-ATPase [80]. Remarkably, reduced activity of Na-K-ATPase was shown in a rat MDD model [75], and in patients with MDD and schizophrenia [81]. Alterations in the protein’s signaling are well established in bipolar disorder [82]. Moreover, decreased expression of the gene coding for Na-K-ATPase was reported in MDD patients compared to controls [83].

As another adaptation to hypoxia, HIFs limit the overall mitochondrial O_2 consumption through decreasing the mitochondrial mass by inducing mitophagy and suppressing mitochondrial biogenesis [72, 84]. Mitophagy refers to mitochondrial autophagy, the process to degrade damaged or unwanted mitochondria [85]. HIFs seem to promote mitophagy through activation of BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3) and BCL2/adenovirus E1B 19 kDa protein-interacting protein 3-like (BNIP3L/NIX) [86, 87] as well as PINK1/Parkin [88]. The role of mitophagy in MDD is not exactly clear. A study reported increased mitophagy induced by acute mental stress in rats [89]. Mitophagy was suggested to be impaired in MDD [90], and higher PINK1 but lower Parkin levels in PBMC were reported in patients compared

to healthy controls [91]. As for mitochondrial biogenesis, in hypoxic conditions, HIFs suppress peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1 α), which is the main regulator of mitochondrial biogenesis [92]. This suppression seems to also happen in MDD. Less expression of *PGC-1 α* and other mitochondrial biogenesis-related genes were observed in individuals with MDD, compared to controls [93]. Moreover, decreased citrate synthase activity was reported in MDD compared to controls, indicating lower mitochondrial mass in MDD [94].

During hypoxic conditions, mitochondrial dynamics are regulated not only to decrease OXPHOS, but also to reduce ROS production and induce mitophagy [72]. Mitochondrial dynamics, namely fusion and fission, rapidly adapt according to altered cellular needs [95]. Mitochondrial fusion helps retaining optimal functionality upon genotoxic events in the mitochondrial DNA through merging with other undamaged mitochondria, sharing their functional proteins. Mitochondrial fission promotes mitophagy to degrade old or damaged mitochondria [96]. In healthy cells, these processes are well-balanced, but severe cellular stress can lead to apoptosis and consequently to increased mitochondrial fission [96]. Hypoxic stress also regulates mitochondrial dynamics by inducing fission [72]. Mitochondrial allostatic load caused by psychological and physiological stress is also thought to lead to accumulation of mitochondrial damage that promotes fission [97]. Increased mitochondrial fission was observed in peripheral CD4⁺ cells of “anxious” mice, compared to control mice [98]. In addition, decreased expression of a fusion protein was found in nucleus accumbens of highly “anxious” rats [99]. MDD as a disorder associated with mitochondrial allostatic overload might involve similar shifts in mitochondrial dynamics. Indeed, a recent study reported evidence indicating increased fission related mitochondrial fragmentation in MDD [91].

Taken together, we showed several complex mechanisms that occur in mitochondria as a response to hypoxia. Most interestingly, the same mechanisms were associated with mental

disorders such as MDD (Table 2). However, cells might benefit from these adaptations due to optimization of O₂ consumption, downregulation of ROS production, and switching to glycolysis to retain ATP production even in suboptimal conditions for OXPHOS. On the other hand, a conceivable drawback might be a global reduction in a variety of metabolic processes. As a result, such regulations might lead to a diminished response capacity towards additional stressors, which is designated as allostatic load.

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Stress-related inflammation and oxidative stress in major depressive disorder might lead to low-grade hypoxia and altered mitochondrial function

In this section, we will elucidate why the hypoxic response might occur in MDD, and how it is associated with other processes that are related to the disease, specifically inflammation and oxidative stress.

In stress-related disorders, it is commonly accepted that activation of the hypothalamic-pituitary-adrenal axis via secretion of stress hormones (e.g. cortisol) can lead to elevated levels of proinflammatory cytokines in the bloodstream, and subsequently to increased oxidative stress [100, 101]. For MDD, meta-analyses ascertained elevated levels of certain proinflammatory parameters [102] as well as increased oxidative stress [103]. Both processes can contribute to altered O₂ transport in MDD, thus promoting hypoxia. Chronic inflammation might lead to anemia through indirect downregulation of erythropoiesis [104], most likely by influencing the iron homeostasis [105]. Consequently, elevated ROS are capable of damaging hemoglobin-containing erythrocytes that are essential for O₂ transport [106]. Both oxidative stress and hypoxia may result in metabolic reprogramming via induction of HIFs as already described before. Moreover, this reprogramming probably counteracts increased production of ROS and maintaining optimal ATP production under hypoxic conditions.

Our model (Figure 2) proposes that chronic stress leads to low-grade inflammation, elevated oxidative stress, and impaired O₂ transport, promoting a low-grade hypoxic state. To counteract these challenges, hypoxic response leads to a metabolic shift towards glycolysis, anaerobic respiration, mitochondrial fission and mitophagy, decreased mitochondrial functioning and content, and a diminished ATP production. Hypoxia can in turn induce inflammation [107] and oxidative stress [108], leading to a vicious cycle which can elucidate the pathophysiology of MDD. This model can also help explain the etiology of comorbid MDD, or other related symptomatology such as cognitive symptoms and fatigue, in infectious diseases such as COVID-19 [36, 109]. Inflammation in COVID-19 can cause damage in the lungs and endothelium [110], limiting the O₂ transport to the circulation. Decreased O₂ levels in tissues might then provoke a hypoxic response [111] through altered mitochondrial function and ROS production [112], leading to a vicious cycle. Inflammation and oxidative stress-related neurotoxic events as well as lack of energy to fulfill certain physiological processes can explain the MDD symptomatology in COVID-19.

In this perspective, we mainly focused on alterations in O₂ transport which can lead to a possible hypoxic state in MDD. Other diseases have been previously associated with hypoxia, and its role in their pathophysiology have been discussed. For instance, it has been suggested that hypoxia in sepsis, termed “cytopathic hypoxia”, might be the outcome of deficits in mitochondrial respiration rather than O₂ transport [113]. Although it is accepted that inefficient production of mitochondrial ATP is not responsible for hypoxia signaling, inflammation-related damage in mitochondrial membrane and altered complex activities might increase mitochondrial ROS production while cellular O₂ consumption is reduced [114]. Consequently, ROS might act as signaling molecules even in normoxic conditions, leading to stabilization of HIF-1 α . Inflammation-related microvascular flow abnormalities in MDD [115] can also lead to dysregulation in cellular O₂ utilization leading to hypoxia. However, inflammation-related

deficits in O₂ utilization and our model involving O₂ transport are not mutually exclusive. Since MDD is a heterogeneous disorder, either or both processes can occur.

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Conclusion

MDD as a stress-related mental disorder entails multiple physical and psychological symptoms that arise out of various biochemical alterations. Chronic or long-term stress prevalent in MDD is likely to result in inflammation and oxidative stress, and this can lead to maladaptive alterations in transport and utilization of the mitochondrial fuel O₂, possibly provoking hypoxic response. Hypoxia can in turn reduce mitochondrial mass, shift the energy production from mitochondrial respiration towards anaerobic respiration, influence mitochondrial structure and function, and limit the overall energy demand. To date, the body of available evidence on O₂ transport and homeostasis as well as mitochondrial function is limited to mostly cross-sectional and correlational designs. Therefore, longitudinal and intervention studies, which also consider the heterogeneity of the disease, are needed for more reliable findings. Our upcoming project (Kaupp et al., in preparation) aims to assess the validity of our model conceptualizing MDD as a low-grade hypoxic condition using a longitudinal randomized controlled trial where we treat MDD patients with cognitive-behavioral therapy. We aim to describe the causal relationship between psychological stress, mitochondrial function, and O₂ homeostasis as well as identify reliable biomarkers of MDD, altogether expanding our understanding of MDD pathophysiology. Thereby, our research might inspire the development of improved and individualized treatment strategies for this highly heterogeneous disease.

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Table 1: Explanation of Important Terms.

Glycolysis, pyruvate oxidation and citric acid cycle	One glucose forms two pyruvates during glycolysis. In aerobic conditions, pyruvate is oxidized to acetyl coenzyme A (Acetyl CoA) with the help of pyruvate dehydrogenase and NAD^+ . Acetyl CoA then enters the citric acid cycle. During metabolization of carbohydrates by glycolysis and citric acid cycle, reduction equivalents (NADH and FADH_2) are formed to serve as fuel for subsequent mitochondrial ATP production [116].
Oxidative phosphorylation (OXPHOS)	Electrons provided by NADH and FADH_2 are continuously transported across the mitochondrial electron transport chain (ETC) and terminally transferred to O_2 . During this process, a proton gradient is established and used to synthesize ATP [116].
ETC complexes	ETC consists of four protein complexes that transfer electrons, and pump protons from mitochondrial matrix to intermembrane space using the free energy released after the electron transfer, thus establishing the proton gradient (except for Complex II). NADH is oxidized in Complex I and its electrons are transferred to Coenzyme Q (CoQ). Succinate, an intermediate of the citric acid cycle, transfers electrons to FADH_2 in Complex II to be carried to CoQ. The electrons from CoQ are transferred to Complex III. Cytochrome c accepts electrons from Complex III and donates electrons to Complex IV. There, the final electron carrier O_2 is reduced to H_2O . Finally, ATP synthase (i.e., Complex V) uses the proton gradient formed by ETC complexes to catalyze ATP production from ADP and a phosphate group [116].
Anaerobic respiration (lactate formation)	In conditions where O_2 is scarce, pyruvate from glycolysis is fermented to form lactate, with the help of lactate dehydrogenase and NADH [116].
Angiogenesis	Formation of new blood vessels. This process helps with tissue oxygenation. When O_2 is scarce, certain cells (including neurons) secrete vascular endothelial growth factor (VEGF), regulated by HIFs, to trigger angiogenesis [117].
Erythropoiesis	Production of erythrocytes (red blood cells) that start at the bone marrow and end at the blood stream. Hematopoietic stem cells are

	differentiated into reticulocytes, which lose their organelles and turn into hemoglobin-containing mature erythrocytes that are released in blood stream. Erythropoietin (EPO) is the main regulator of the process. Iron proteins and certain vitamins (e.g. Vitamin B12) are also regulators of erythropoiesis [118].
Ferritin	The iron storage protein. Its levels are mostly controlled by the iron content in the body, like the many iron proteins. Another function of ferritin is to protect the cell components from iron-induced oxidative damage [119].
Transferrin	Transports iron in plasma to bone marrow for erythropoiesis and to the other cells. Other functions of the protein are iron uptake from the gut where absorption occurs, and regulation of hepcidin [120].
Hepcidin	The main regulator of systemic iron homeostasis. Its role is to maintain iron absorption and release. Therefore, it protects the body from iron overload and deficiency [120].

Table 2. Summary of Findings Regarding Hypoxia Related Processes in Major Depressive Disorder

Adaptations related to hypoxic response	Provoked process in hypoxia	Findings in MDD patients compared to controls
Increased O ₂ delivery	Erythropoiesis	Increased plasma EPO [59]
	Angiogenesis	Increased serum [121] and plasma [60] VEGF
Decreased O ₂ consumption	Metabolic re-programming	Increased expression of <i>LDHA</i> and <i>GLUT1</i> [63], increased CSF lactate [69]
	Decreased citric acid cycle flux	Decreased citric acid cycle metabolites in PBMC [65]
Alterations in mitochondrial function and biogenesis	Decreased mitochondrial mass	Decreased expression of mitochondrial biogenesis genes [93]
	Disturbed dynamics	Increased fragmentation and impaired mitophagy [91]
	Remodeling ETC complexes	Decreased complex I and IV activity [76]
	Decreased ATP demand	Decreased enzymatic activity [81] and gene expression [83] of NA/K ATPase

ATP, adenosine triphosphate; EPO, erythropoiesis; ETC, electron transport chain; GLUT1, Glucose transporter 1; LDHA, lactate dehydrogenase A; MDD, major depressive disorder; PBMC, peripheral blood mononuclear cells; VEGF, vascular endothelial growth factor.

Figure 1. Hypoxia-inducible factor 1 regulates cellular response to hypoxia. Under normal oxygen (O_2) concentrations, Hypoxia-inducible factor 1-alpha (HIF-1 α) subunit is hydroxylated by prolyl hydroxylase domain protein (PHD). Hydroxyl groups signal binding to Von-Hippel-Lindau protein (VHL), which mediates ubiquitination and the subsequent proteasomal degradation of HIF-1 α . Low O_2 level and increased reactive oxygen species (ROS) inhibit PHD activity and stabilize HIF-1 α . HIF-1 heterodimer (HIF-1 α /HIF-1 β) binds to HIF-1 responsive elements (HRE) and regulates transcription of genes involved in angiogenesis, erythropoiesis, and glycolysis.

Figure 2. Proposed model of major depressive disorder as a low-grade hypoxic condition.

Chronic stress leads to an induction of inflammation and oxidative stress via the hypothalamic–pituitary–adrenal (HPA) axis. Inflammation and oxidative stress disturb oxygen (O₂) supply elements. Decreased O₂ supply affects mitochondrial function and reactive oxygen species (ROS) production, which induces Hypoxia Inducible Factor (HIF) response. Consequently, metabolic reprogramming shifts oxidative phosphorylation towards anaerobic respiration and glycolysis. Additionally, mitochondria are restructured to optimize O₂ consumption and adenosine triphosphate (ATP) production as well as reduce ROS production. Despite these adaptations, ATP production is decreased leading to energy shortage.