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REVIEW ARTICLE

Recent advances in low-level laser therapy on depression

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ABSTRACT

Photobiomodulation (PBM), as a form of light therapy, has been applied broadly in the medical practice. The biological photoreceptors use small-molecule cofactors called chromophores to detect light and convert a physical signal into a biochemical signal transmission cascade. Visible light (380–780 nm) can activate specialized photoreceptors to stimulate vision and regulate circadian rhythm. Compared with visible light, near-infrared (NIR) light (780–1,100 nm) has better tissue penetration depths, enabling us to carry out non-invasive low-level laser therapy (LLLT) for different tissues. Mitochondrial cytochrome c oxidase is the main NIR photoreceptor. The basic effect is to promote the generation of ATP through the respiratory chain. LLLT can enhance blood circulation, alleviate inflammation, promote muscle damage repair, stem cell proliferation and so on. The neuroprotective effect of LLLT on central nervous system (CNS) diseases has been preliminarily verified in animal models, which is expected to improve the cognitive function of Alzheimer's patients, motor symptoms of Parkinson's patients and mental disorders of patients with depression, thus improving the quality of life of patients. Understanding its protective effect and mechanisms will contribute to better therapeutic application in the future. In this review, we will discuss the antidepressant effect of LLLT, its possible mechanisms, and existing problems with its applications.

1 Introduction

The origin of sunlight in heliotherapy can be tracked to ancient China, Egypt, and Greece. Physicist Theodore Harold Maiman invented the first operable laser in 1960. Photobiomodulation (PBM) was discovered shortly after the invention of the laser. Beginning in 1967, Professor Mester found that low-energy laser radiation accelerated healing of wounds and damaged hairs in laboratory mice. Since then, the non-invasive low-level laser therapy (LLLT) is practiced as part of physical therapy in many parts of the world. In recent years, LLLT has been emphasized because of its beneficial brain effects among many non-drug interventions [1, 2]. The main mechanism of LLLT is the ability of cells to absorb red light (620–750 nm) and near-infrared (NIR) light (780–1,100 nm) through chromophores, including flavins, iron–sulfur centers, or heme [3]. During this process, cytochrome c oxidase (CCO) activity is enhanced, and ATP synthesis is elevated [4].

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In addition, energy absorption of ion channels from LLLT leads to the release of calcium ions, thus activating downstream transcription factors and gene expression [5].

The brain is one of the most energy-consuming organs. To perform normal brain function, it depends on an efficient metabolism and energy supply. However, energy metabolism and mitochondrial function are disrupted, promoting a vicious circle of impaired function in many neurodegenerative diseases. Depression, Alzheimer's disease, and Parkinson's disease have been characterized by decreased energy metabolism [6–9]. As we all know, mitochondria provide energy for cells to carry out vital functions. Studies have found that ATP can mediate antidepressant-like effects through P2X2 receptors in the cortex [10]. There is an urgent need for therapeutic strategies to enhance and restore brain energy against neurodegenerative diseases [6].

Depression is a severe emotional disorder with high incidence, high suicide, and high recurrence rates, ranking second in the total burden of disease in China [11]. The core symptoms of depression are anhedonia，unbearable negative emotions, and disturbed sleep or appetite [12]. A combination of factors (biological, psychological, and social factors) that have been identified as being responsible for the development of depression. At present, there is still a lack of clear insight of the pathophysiology mechanism of depression, and it is difficult to design appropriate individual treatment programs. Patients are facing the problems of longer duration of treatment and high recurrence rate. There is an urgent need for new flexible treatment strategies with few side effects [13–15]. Light therapy, or photobiomodulation, is a non-invasive photoceutical approach with therapeutic applications in ophthalmology, neurology, and psychiatry in recent years. Animal studies have shown that LLLT has a positive effect on central nervous system (CNS) diseases. Not only can LLLT modulate oxidative stress, increase ATP synthesis and enhance the function of mitochondria, it also acts on specific neural circuits to achieve antidepressant treatment. However, its neuroprotective mechanism needs to be further clarified [16–18]. We attempted to explain the possible mechanism by which LLLT produces neuroprotection and its contribution to depression. In addition, new insights regarding the CNS benefits of abdomen-targeted LLLT are also within the scope of this review. This will provide guidance for patients to carry out daily care and disease prevention.

2 Effector molecule of LLLT

The initial biological reaction to light therapy is the absorption of photon energy by the target tissue. Endogenous or exogenous chromophores with unsaturated groups and their related chemical bonds are the main photoreceptors to absorb photon energy. Photoreceptors absorb energy for photochemical reactions and produce electron transition. Common specialized photoreceptors involved in this response are chlorophyll and rhodopsin. For example, a rod opsin binds to 11-cis-retinal chromophore, which constitutes visual pigment. The pigments in the rods and three types of cones turn retinal to absorb a specific wavelength of light [19]. The photon absorption results in the isomerization of retinal from the 11-cis to the all-trans conformation and triggers a conformational change in the protein that initiates a cascade of events in the cell [20, 21]. Cyclic nucleotide-gated ion channels are closed, and the release of synaptic transmitters is inhibited by membrane potential hyperpolarization. Finally, it regulates the visual signals into the brain.

In addition, the light absorption of nonspecific photoreceptor molecules (which can absorb light

of a specific wavelength, but are not necessary for specific photoreceptors) is widely used [22–24]. Among these molecules, Tina Karu's research team determined for the first time that the mitochondrial enzyme CCO is the basic molecule for LLLT to produce benefits [4]. CCO is an oxidase containing heme and copper centers. It is also the terminal mitochondrial complex IV on the electron transport chain [25]. It receives electrons from cytochrome c and catalyzes the reduction of O_2 to H_2O coupled with the function of proton pump. The research shows that the absorption spectrum of CCO in different oxidation states is very similar to the action spectrum of photobiological reactions [26]. LLLT acts on CCO in the mitochondrial respiratory chain to absorb photons to increase the activity of co-promote and the synthesis of ATP. The underlying effects of LLLT are shown in Fig. 1.

Since the basic effect is the absorption of photons by the chromophore, which directly leads to the increase in ATP synthesis. Besides, LLLT can promote the mitochondrial membrane potential ($\Delta\Psi_M$), inducing the rise of reactive oxygen species (ROS). The secondary effect is modulating the concentration of NO and Ca^{2+} [5, 27]. These molecules can act as messengers and activate downstream signaling pathways [28].

3 LLLT and depression

Depression is a complex disease with multiple contributing factors, which may explain why it is difficult to achieve significant results with a single drug treatment. Many hypotheses have been summarized and proposed: monoaminergic hypothesis, hypothalamic–pituitary–adrenal (HPA) axis changes, inflammation, decreased nerve regeneration and neuroplasticity, epigenetic changes, etc. The pathways involved in the above hypotheses are all interrelated [12].

Genetic and environmental stress acting through immunologic and endocrine responses initiate structural and functional changes in brain regions, resulting in dysfunctional neurogenesis and neurotransmission which then manifest as a constellation of depression symptoms [29–31]. Currently, the drugs used to treat depression are based on the dysfunction of the monoaminergic neurotransmission hypothesis, increasing the level of brain 5-hydroxytryptamine (5-HT) or norepinephrine (NE), playing an antidepressant role [32]. Nonetheless, drug treatment, such as 5-HT selective reuptake inhibitor, has limited effect and may also bring serious side effects [13]. Its pathogenesis and treatment scheme still need to be further explored.

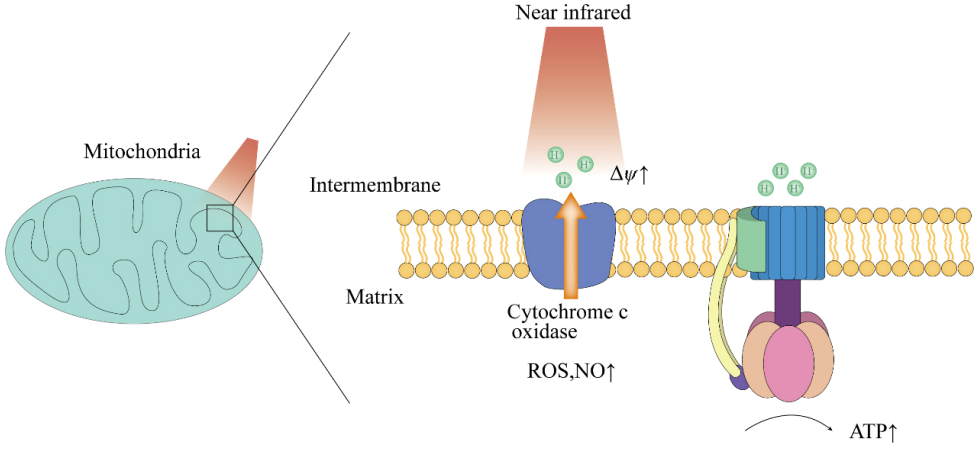

Figure 1 Cytochrome c oxidase is the primary effector molecule of LLLT. Its metal centers absorb photon energy and facilitate electron transfer. The pumping of H^+ into the intermembrane space increases the membrane potential and ATP biosynthesis. Dissociated NO from the binuclear center and elevated ROS further activate downstream transcription factors.

From the perspective of energy supply, brain energy metabolism is affected by the endocrine regulation of appetite and systemic energy, which are damaged in the process of disease and aging [6]. It is worth noting that patients with depression show mitochondrial dysfunction and impaired energy metabolism in different brain regions [33, 34], characterized by lack of energy, difficulty in concentration, and fatigue [7, 35]. Therefore, CCO may be a potential target for LLLT to improve depression. In the transcranial application of LLLT, NIR energy is transmitted to the cerebral cortex. Studies have shown that the expression and activity of ATP biosynthesis and mitochondrial complex IV in the prefrontal cortex (PFC) are significantly increased after LLLT and can improve the depression-like behavior of mice [36].

At the neurotransmitter level, LLLT can increase the levels of 5-HT and NO in the PFC and hippocampus of depressed mice to achieve the effect of antidepressant [37]. Brain-derived neurotrophic factor (BDNF) plays a role in neurogenesis, and antidepressant interventions can improve its level [38, 39]. Studies have shown that LLLT increases the expression of BDNF in hippocampal neurons induced by oxidative stress [40]. Moreover, depression is related to inflammatory response and oxidative stress [41–45]. LLLT's anti-inflammatory effect and the ability to reduce excessive ROS production in the process of oxidative damage may be beneficial in the remission of depression [46, 47], and decrease the risk for inflammation-related diseases [48]. At the level of depression-related receptors, LLLT can improve glutamate transporter-1 (GLT-1)-mediated glutamate uptake and glutamate receptor activity by saving the loss of astrocytes in the cerebral cortex and hippocampus, upregulating the expression of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors in the postsynaptic membrane, finally reducing glutamate excitotoxicity, and improving depression-like behavior [49].

Light can influence the circadian rhythm and mental health. Dysregulated activity in certain brain regions and neural circuits has been linked to susceptibility and resilience to depressive-like states. Studies using humans and animal models have demonstrated the ability of light to influence emotion-related behaviors and activity of the brains regions [50, 51]. Ren and colleagues mapped retinal ganglion cells projection to the dorsal raphe nucleus and superior colliculus, identifying these circuits as potential targets for light-dependent regulation of depression [52, 53]. Decreased medial prefrontal cortex (mPFC) neural circuits activity or hippocampal functions correlates with depression-like behaviors [43]. Therefore, LLLT may restore the functions of mPFC and hippocampal to modulate the stress axis and attenuate depressive disorder [36, 54, 55].

LLLT can not only alleviate the level of serum cortisol and reduce depression-related behavior in chronic mild stress (CMS) rat model [56, 57], but also have a positive effect on human depression and anxiety in transcranial applications at both 810 and 945 nm wavelengths [58, 59]. Clinical studies have shown that LLLT can enhance the efficacy of attention bias modification in treating depressive symptoms [60]. LLLT shows antidepressant ability in patients with major depressive disorder (MDD) [61, 62]. Combined with its capability to regulate cerebral blood flow and inflammatory factors [47, 59], LLLT has great potential in controlling the progress of depression and is suggested to be a mild and convenient adjuvant treatment for depression. In the future, the ideal parameters, safety, and effectiveness of LLLT are going to be further clarified

4 LLLT acts on the distal intestine

As early as more than ten years ago, scholars

summarized the indirect effect of remote photobiotherapy on the target tissue and first described it as "remote PBM" [63]. For example, LLLT targeting the back rather than the head can produce distal neuroprotection [64]. The distal intestinal tissue-targeted LLLT has not been applied to the model of depression yet.

In the development of depression, three important factors are worthy of attention: the HPA axis is involved in stress, the abnormally activated immune system, and the unbalanced intestinal microbiota [65]. There is increasing evidence of a link between gut microbiota imbalance and various neurological and psychiatric disorders, including depression. The microflora composition of patients with depression, especially related to metabolites of carbohydrates and amino acids, has changed [66–69], indicating higher energy demand in MDD [67]. Some microflora with a high abundance in clinical anxiety and depression are considered to be related to gastrointestinal inflammation [70]. Gut microbiota imbalance induces depression-like behavior through the microbiota–gut–brain axis, and microbiota–gut–brain axis has emerged as a novel therapy target in depression [71, 72]. The balance of microflora is crucial to normal physiological activities, because changes in bacterial composition can be sensed by the brain, which then regulates appetite and body temperature through the neuronal activity of hypothalamus [73]. Therefore, the gut microbiota can act as a potential regulator of anxiety and depression [74, 75], and specific probiotic strains have been shown to regulate host behavior through the vagus nerve [76]. Clinical evidence also supports therapeutic strategies in which probiotics help reduce negative thoughts associated with sadness [77].

The energy of LLLT can penetrate the abdominal wall of mice and directly act on the intestinal flora [78], suggesting that the benefit of LLLT may help to establish a new balance among the dysfunctional intestinal flora of patients with depression. LLLT is demonstrated to change the microflora in mice and increase the number of probiotics [79]. The gut–brain axis links the emotional and cognitive centers of the brain with peripheral intestinal functions. NIR light energy applied to the abdomen area may therefore influence mood and neuropsychological issues through the following aspects (Fig. 2): (1) protecting the integrity of gastrointestinal barrier [80, 81]; (2) alleviating intestinal inflammation and inflammatory factor levels in circulation [82, 83]; thereby reducing negative emotions and the risk of disease [84, 85]; (3) stimulating the production of neurotransmitters and hormones acting on the CNS in the gut [86]; modulating the balance of gut flora; (4) modulating the vagus nerve which plays an important role in fighting depression and regulating reward circuits [87–89]; (5) preventing ischemia-reperfusion injury and providing neuroprotection by increasing NO concentration [90, 91]; reducing blood pressure and the risk of high stress response [92–94]; (6) stimulating bone marrow-derived mesenchymal stem cells (MSCs) to migrate to the brain and release nutritional factors conducive to axon growth.

In the future, we can cooperate with transcranial applications to jointly prevent the development of depression.

5 Neuroprotective mechanisms of LLLT

LLLT effectively improves depression-like behavior and has regulatory effects on neurotransmitters, glutamate receptors, and inflammatory factors. After LLLT, the ability of learning and memory has also been enhanced [95], accompanied by neurogenesis in the hippocampus [55]. In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's

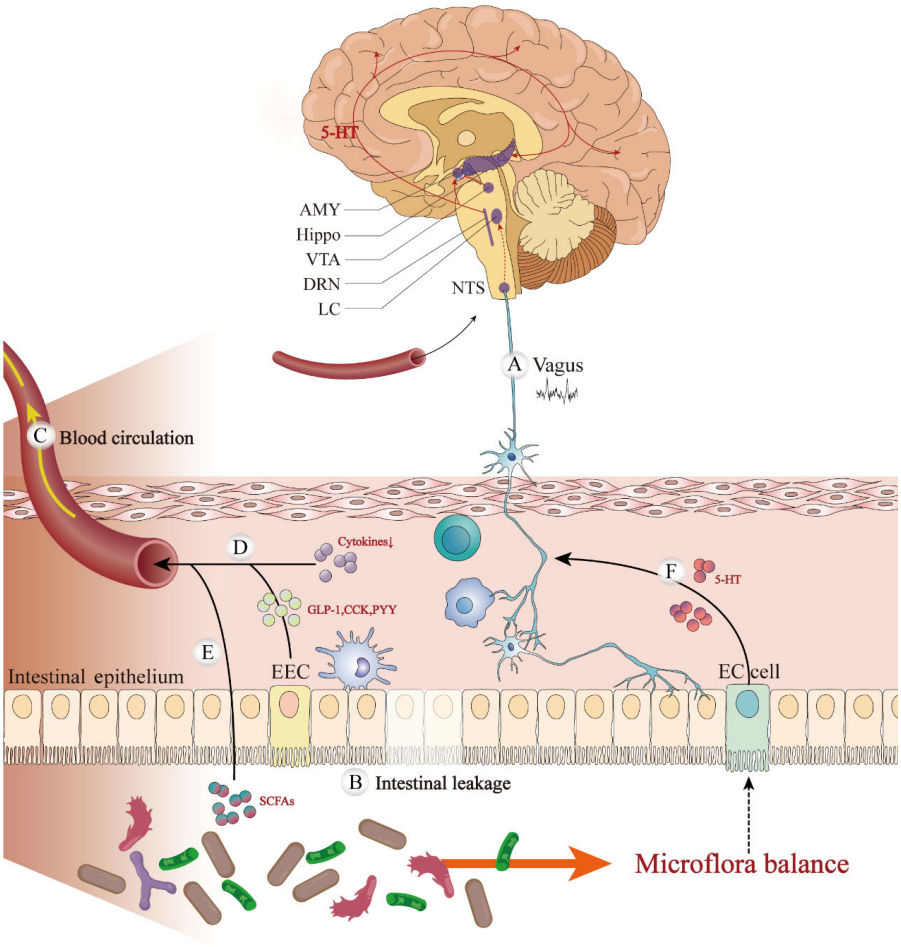

Figure 2 Abdominal LLLT protects brain through gut brain axis. (a) LLLT directly stimulates vagus nerve and activates monoaminergic neurons to play a neuroprotective role; (b) The wound healing effect of LLLT can provide gastrointestinal barrier protection and maintain intestinal homeostasis. (c) Vasodilation and blood pressure lowering effects may play a role in alleviating anxiety. (d) The content of inflammatory factors in circulating media decreases after LLLT therapy, which determines the brain's ability to withstand stress such as anxiety and depression. In addition, LLLT stimulates the bone marrow to produce proliferating MSCs that migrate to the brain, and the neurotrophic factors released by MSCs regulate neuroplasticity, which helps repair abnormal synaptic connections in the brain of depressed patients. (e) The energy transferred by LLLT helps to establish a new balance of intestinal flora. Intestinal microorganisms regulate the gut brain axis through hormones, neurotransmitter precursors, and metabolites. The vagus nerve dependence of probiotics in the treatment of depression suggests that LLLT may regulate depression-related circuits through vagus nerve. (f) LLLT directly stimulates the production of neurotransmitters and transcription factors. AMY, amygdala; CCK, cholecystokinin; DRN, dorsal raphe nucleus; EEC, enteroendocrine cell; EC, enterochromaffin; GLP-1, glucagon-like peptide-1; PYY, peptide YY; SCFA, short-chain fatty acid.

mouse model, LLLT is delivered to the distal end of the brain, providing cerebral neuroprotection [96–98]. Since Parkinson's patients often have gastrointestinal symptoms that precede motor symptoms, this unintended consequence might be in line with the gut flora-targeted therapy theory, which is predicated on a reciprocal exchange of circulating mediators [99–102]. What is the mechanism behind these results?

Among the secondary mechanisms described by Karu, cyclic adenosine monophosphate (cAMP), the second messenger, was shown to increase after LLLT [103, 104]. As a hydrolysate of ATP, the increase of cAMP also directly affects the increase of ATP. cAMP can activate the downstream protein kinase A (PKA)/cAMP-responsive element binding protein (CREB) signaling pathway. Extracellular signal regulated kinase (ERK) is also involved in the regulation of this pathway [105]. Studies have shown that

LLLT activates ERK/CREB to up-regulate the expression of BDNF [40, 106]. This pathway is related to the antidepressant-like effect of (R)-ketamine [107], which is consistent with the neurotrophic factor theory of depression treatment [108]. Moreover, one study has shown that LLLT has the ability to rescue the down-regulation of AMPA receptors induced by chronic unpredictable mild stress (CUMS) through the cAMP/PKA signaling pathway [49]. Phosphorylation of tryptophan hydroxylase 2 (TPH2) by PKA promotes the interaction of 14-3-3 with TPH2, further promoting stability, which is conducive to the synthesis of 5-HT transmitter [109].

LLLT can increase the synthesis of ROS under normal conditions. Still, it can increase the mitochondrial membrane potential to the baseline level and reduce the production of reactive oxygen species under oxidative stress [110]. This may also be involved in the anti-inflammatory mechanism of LLLT [42]. It also suggests that the application of LLLT should be at an appropriate dose. NF-κB is a redox-sensitive transcription factor that plays a central role in inflammatory response [111]. Studies have shown that 810 nm LLLT has anti-inflammatory effects on activated dendritic cells. The significant decrease in NF-κB activity suggests that it may be involved in the anti-inflammatory effect [112]. The anti-inflammatory effects of light therapy in diseases such as wound healing, arthritis, and muscle injury have been well-reviewed [113].

The core feature of depression and other mental diseases is excitotoxicity caused by excessive glutamate release in acute and chronic stress [114]. *In vitro* experiments have proved that LLLT can reduce oxidative stress and decrease the concentration of Ca^{2+} to protect cerebral cortical neurons from excitotoxicity [115]. LLLT may also activate PI3K/Akt/NF-κB to up-regulate GLT-1 and reduce the extracellular glutamate levels [49]. PI3K/Akt is an intracellular signal transduction pathway that can promote proliferation, survival, growth, angiogenesis, and other events. Studies have shown that this pathway can be activated by LLLT [116, 117]. LLLT may antagonize depression by activating PI3K-Akt-mTOR-BDNF signaling pathway through Ca^{2+} influx induced by ATP-binding receptor P2X2 [118, 119]. Besides, the involvement of PI3K/Akt/GSK-3β in the anti-apoptotic process suggests the possibility of treating some GSK-3β-driven neuronal degenerative diseases [120].

Moreover, LLLT can stimulate the migration of bone marrow stem cells to the damaged area [121, 122]. The nutritional factors released by these cells can also promote cell survival and play a significant role in CNS injury [123, 124]. This may explain why applying LLLT to distal tissues can also produce neuroprotective effects, together with anti-inflammatory effects. The possible neuroprotective mechanisms of LLLT under depression or stress are illustrated in Fig. 3.

In conclusion, the energy of all cell activities comes from ATP. ATP can drive ion pumps to regulate ion exchange. For example, the vacuolar proton ATPase participates in forming proton electrochemical gradients to regulate the uptake and release of neurotransmitters [125]. Secondly, as the main source of brain energy, it participates in synaptic transmission, axonal transport, and the maintenance of cytoskeleton structure. These processes may be disordered in depressed patients with impaired energy metabolism [33, 34]. Therefore, improving energy metabolism by targeting CCO is one of the important mechanisms of LLLT.

6 Conclusions

So far, we are still able to use its excellent penetrability to perform non-invasive combination therapy, or to amplify beneficial signaling pathways by molecular signals involved in laser

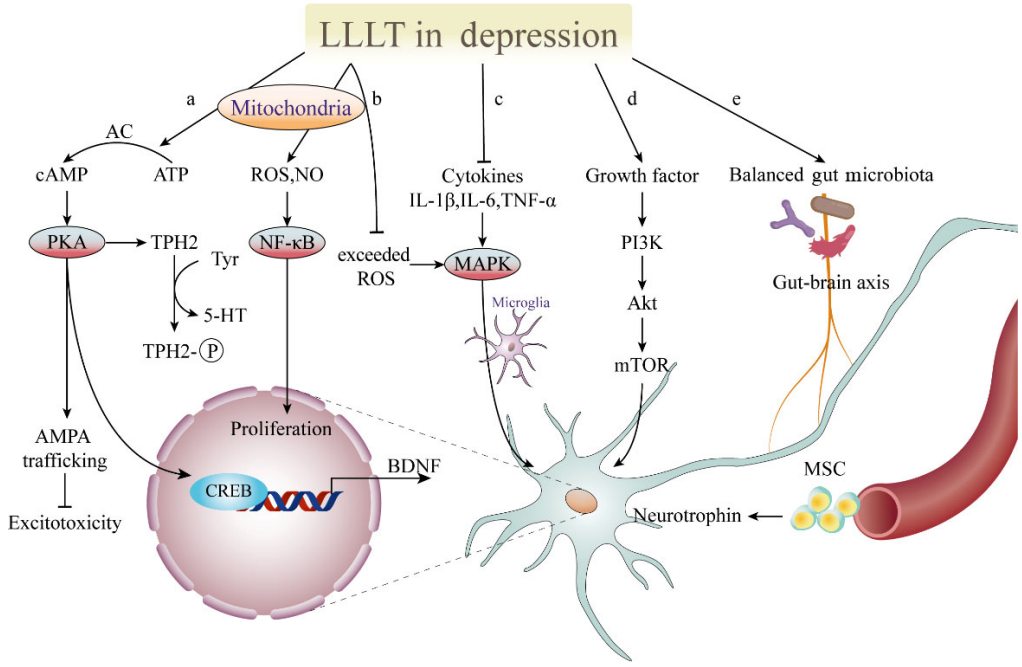

Figure 3 The possible neuroprotective mechanisms of LLLT under depression or stress. (a) The cAMP/PKA pathway is involved in LLLT effect on depression therapy. Phosphorylation of AMPA receptor subunit by PKA is conducive to glutamate transmission under stress, and can buffer the excitotoxicity induced by Ca2+ influx; cAMP/PKA-CREB pathway enhances both BDNF mRNA and protein expression which regulates neuronal survival and growth; Phosphorylation of TPH2 by PKA promotes its stability and facilitates 5-HT synthesis; (b) effects of LLLT on the homeostasis of ROS. NIR photons are absorbed in cell mitochondria, producing ROS and releasing NO, which leads to gene transcription via activation of transcription factors (NF-κB and AP1). Under certain circumstances, LLLT corrects mitochondrial membrane potential to normal levels and reduces oxidative damage to neurons by excessive ROS level; (c) LLLT significantly reduces inflammatory cytokines production and inhibites MAPK and NF-κB pathway, further inhibiting inflammation and anhedonia; (d) low-level light may exert a prosurvival effect on cells via the activation PI3K/AKT/mTOR. In addition, LLLT can promote the proliferation of bone marrow mesenchymal stem cells (MSCs), which release neurotrophic factors in the process of migration to the damaged area, playing a neuroprotective role; (e) LLLT may reverse the imbalance of gut microbiota. Circulating metabolites produced by microorganisms are thought to affect the central nervous system via the gut–brain axis. AC, adenylate cyclase.

therapy. Deep penetration is enough to reach certain deep brain tissues or organs to initiate protective and repair functions, and prevent muscle atrophy in patients who have lost normal exercise ability. Besides, the increase of mitochondrial production capacity in healthy cells will lead to the squeezed living space of diseased cells.

Nonspecific photoreceptors show broad application prospects in photodynamic therapy and optogenetics. NIR emissive luminogen performs well in photodynamic antibacterial therapy [126]. Upconversion nanoparticles (UCNPs) materials can be used to tune specific wavelength emission. The NIR light penetrating the tissues is converted to light of specific wavelength to stimulate the ventral tegmental area (VTA) to release dopamine (DA), or inhibit the habenular nucleus (Hb) to regulate the brain neuron activity of patients with depression [127]. The chromophore of human body tissue in response to LLLT can be CCO, photosensitive ion channel, or effector molecules in some provital pathways. It should be emphasized that as a chromophore, it needs to have good absorption of high wavelength light in order to achieve sufficient penetration efficiency in human application. There is crosstalk in the downstream signal pathway activated by LLLT. Its neuroprotective mechanism needs to be fully explored to promote clinical use in some nervous system diseases.

Nowadays, there are infrared physiotherapy instruments to assist in the treatment of muscle injury, arthritis, and other symptoms. However, there is no specific disease-matching light dose, which brings uncertainty to the use. The role of LLLT in treating CNS diseases is not widely understood. More clinical evidence is needed. Nevertheless, the neuroprotective function and psychological benefits shown by LLLT are still attractive to us.

Declaration of conflicting interests

The authors declare there are no conflicting interests regarding the content of this article.

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