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REVIEW

Targeting Mitochondrial Homeostasis: The Role of Acupuncture in Depression Treatment

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Background: Depression is a common mental health disorder characterized by persistent feelings of sadness, loss of interest or pleasure, and a range of physical and cognitive symptoms. It affects people of all ages and can significantly impact their daily functioning and quality of life. Mitochondrial homeostasis plays an important role in the pathogenesis of depression. Mitochondrial homeostasis includes mitophagy, mitochondrial oxidative stress, mitoptosis, mitochondrial biogenesis, and mitochondrial dynamics. The regulation of mitochondrial homeostasis is the key link in the prevention and treatment of depression.

Methods: In this article, we focus on the core link of depression-mitochondrial homeostasis and summarize the research progress of acupuncture targeting mitochondrial homeostasis in the treatment of depression in recent years, so as to provide ideas and experimental basis for the research and formulation of more appropriate depression treatment strategies.

Results: Acupuncture has been found to regulate mitochondrial homeostasis (by modulating mitochondrial autophagy, reducing mitochondrial oxidative stress, inhibiting mitochondrial fission, inducing mitochondrial biogenesis, and maintaining mitochondrial dynamics), alleviate depression-like behavior, and regulate signal pathways and key proteins.

Conclusion: Here, we highlight the role of acupuncture in the treatment of depression. A comprehensive exploration of the impact of acupuncture on mitochondrial homeostasis could potentially present a novel mechanism for treating depression and offer fresh perspectives for the treatment of patients with clinical depression.

Keywords: depression, mitochondria, homeostasis, acupuncture, mitophagy, review

Introduction

Depression has become one of the most common public health diseases in the world and the incidence is increasing year by year. People suffering from the disease often show self-neglect, loss of interest, eating disorders, insomnia, despair, lack of concentration, and even suicidal tendencies, and the recurrence rate and disability rate account for a considerable proportion. The disease affects more than 350 million people around the world.[1] With the increase of population and the sharp increase of modern social pressure, the social problems caused by depression are becoming more and more serious. A study predicts that depression will become the second largest disease burden in the world in 2030.[2]

The pathogenesis of depression is very complex, including hypothalamus-pituitary-adrenal axis regulation disorder, insufficient serotonin content, inflammation and cytokines, brain-gut axis imbalance, hypothalamus-pituitary-thyroid axis inhibition, etc. The neural substrate of depression refers to the abnormalities of related neuron activities and neurotransmitters in the brains of patients with depression. Studies have shown that patients with depression often have abnormalities related to neurotransmitters, including dysregulation of neurotransmitters such as serotonin, norepinephrine and dopamine.[3,4] These neurotransmitters play an important role in regulating mood and mental state, and abnormal levels may contribute to the development of depression. The study also found that synaptic plasticity in patients with depression may be affected by abnormal release and reuptake of neurotransmitters, changes in synaptic structure,

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inflammation and stress response. These factors may lead to the imbalance of synaptic plasticity, which in turn affects emotional regulation and cognitive function.[5]

Drug intervention is still one of the main methods for the treatment of depression. Monoamine drugs, such as selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRI), were first introduced at the turn of the century and have since become standard treatments for depression.[6] Currently, SSRI antidepressants have replaced tricyclic antidepressants (TCAs) as the first choice of antidepressants. There are 6 kinds of SSRIs commonly used in clinic: fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram and escitalopram. SSRI and SNRI drugs are thought to work by increasing the number of neurotransmitters in the brain, such as 5-hydroxytryptamine (5-HT) and dopamine (DA) in synaptic spaces.[7–10] Since the application of molecular biology in medicine, non-monoamine drugs, such as ketamine and angomelatine, have become one of the most popular drugs, which are effective in relieving symptoms and improving prognosis of patients with depression.[11,12] Despite this, the therapeutic effect of existing mainstream antidepressants still has considerable limitations, such as SSRIs taking several weeks to take effect, the drug cycle is long, and it is easy to relapse, and some patients do not respond to various drugs. Therefore, it is particularly important to find new treatment strategies.

As a non-drug therapy, acupuncture has great potential in the treatment of depression and can replace or assist drug therapy to improve the curative effect.[13] Compared with drug therapy, acupuncture has the advantages of low cost and less side effects.[14,15] As early as 1984, a study confirmed that acupuncture has a unique therapeutic effect on depression.[16] The report shows that the overall efficacy of various acupuncture methods in the treatment of depression after 6 weeks is about 70% to 83.7%, which is equivalent to or even higher than that of antidepressant western drugs.[17] The results of Meta-analysis showed that acupuncture could significantly reduce the degree of depression compared to the routine treatment group, the sham acupuncture group, and the antidepressant treatment group, and there was a significant correlation between the increase in acupuncture treatment times and the decrease in severity of depression.[18] The latest research has proved that acupuncture can treat depression in many ways (Table 1).

New research has shown that acupuncture can treat depression in a variety of ways, including targeting mitochondrial homeostasis. Mitochondria are one of the most important organelles in the human body, it was once regarded as a simple "living energy metabolism factory", which synthesizes adenosine triphosphate to supply energy for the body.[39] After nearly a century of research, it has been found that it has many functions: regulating gene expression in the nucleus, regulating synaptic transmission in the brain, releasing inflammatory factors and triggering a systemic inflammatory response, affecting the regulation of complex physiological systems.[40] People with depression often have abnormal energy metabolism, including mitochondrial dysfunction. The study found that there are morphological and functional changes in the mitochondria in patients with depression compared to normal people. These mitochondrial abnormalities may lead to disorders of energy metabolism, leading to symptoms of depression. The abnormal function of mitochondria may also lead to the increase of oxidative stress, inflammation and apoptosis. These changes may be closely related to the occurrence and development of depression.[41,42] In addition, mitochondria are involved in the synthesis and regulation of neurotransmitters. Neurotransmitters are chemicals in the brain that transmit neural signals. The abnormal function of mitochondria can lead to abnormal synthesis and release of neurotransmitters, affect the transmission of neural signals and communication between brain regions, and then affect emotional and cognitive function. The study also found that some antidepressants may play a therapeutic role by regulating mitochondrial function. This suggests that repairing mitochondrial function may be a new direction in the treatment of depression.

Mitochondria are highly dynamic organelles that undergo continuous fission and fusion through mitochondrial biogenesis and mitochondrial autophagy to maintain mitochondrial homeostasis.[43] Mitochondrial homeostasis consists of many aspects: mitochondrial autophagy, mitochondrial oxidative stress, mitoptosis, mitochondrial biogenesis, mitochondrial dynamics (Figure 1). Studies have shown that the destruction of mitochondrial homeostasis is an important pathological mechanism for the occurrence and development of depression. In the process of depression, chronic stress will lead to an imbalance of homeostasis of human physiological function and damage the morphology and function of mitochondria through a variety of pathological pathways.

Table 1 Summary of Researches Regarding the Effect of Acupuncture in Depression

Ref.	Model	Number of Animals	Sex	Acupoint	Type/Frequency/Time	Days	Treatment Country/Region	Year	Major Efficacy
[19]	CUMS rat model	36	Male	Fengfu (GV16) Shangxing (GV23)	MA/none/20min	28	China	2023	Inhibit activation of HMGB1/TLR4 in amygdala of CUMS rats Inhibit inflammation
[20]	FS mouse model	200	Male	Baihui (GV20) Yintang (GV29)	MA/none/20min	10	Japan	2023	Increased the expression of neurotrophic factors (NGF, BDNF, NT-3, NT-4/5)
[21]	LPS-induced depression mouse model	18	Male	Taichong (LR3) Yintang (GV29) Baihui (GV20) Hegu (L14)	EA/2Hz/50Hz/20min	14	China	2022	Inhibit collagen type IV trimer, extra cellular matrix organization, and collagen formation Enhance MMP1 and MMP9 Promote synaptic plasticity
[22]	CUMS rat model	36	Male	Fengfu (GV16) Shangxing (GV23)	MA/none/20min	14	China	2022	Suppress NLRP3, ASC, caspase-1, GSDMD, IL-1β, IL-18, HMGB1, IFN-γ, IL-6 and TNF-α Reduce pyroptosis and inflammation
[23]	CUMS rat model	40	Male	Fengfu (GV16) Shangxing (GV23)	MA/none/20min	14	China	2022	Reduce oxidative stress Prevent neuronal apoptosis
[24]	CMS mouse model	40	Male	Baihui (GV20) Shenshu (BL23) Taixi (KI3)	EA/2Hz/15min	21	China	2022	Inhibit NF-κB/NLRP3 inflammatory pathway
[25]	CUMS rat model	32	Male	Baihui (GV20) Yintang (GV29)	MA/none/10min	36	China	2021	Inhibit NLRP3 inflammasome activation and apoptosis
[26]	SI-induced depression rat model	40	Male	Baihui (DU20) Yintang (EX-HN3) Shenshu (BL23) Pishu (BL20) Ganshu (BL18) Xinshu (BL15) Guanyuan (Ren4)	AC/none/none	-	Mexico	2021	Improve sex hormones release Increase BDNF hippocampal levels
[27]	CUMS rat model	32	Male	Shangxing Daling	MA/none/20min	21	China	2021	Increase the level of DA and 5-HT Increase the expression of brain-derived neurotrophic factor signaling and the astrocytes in the hippocampus

(*Continued*)

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Table 1 (Continued).

Ref.	Model	Number of Animals	Sex	Acupoint	Type/Frequency/ Time	Days	Treatment Country/Region	Year	Major Efficacy
[28]	CRS mouse model	27	Male	Yingu (KI10) Ququan (LR8) Jingqu (LU8) Zhongfeng (LR4)	MA/none/30sec	7	Korea	2021	Decrease AST, IL-1β, TNF-α Attenuate leptin insensitivity
[29]	CUMS rat model	40	Male	Baihui (GV20) Yintang (GV29)	EA/2Hz/30min	14	China	2021	Up-regulate the expression level of FGF2 Increase GFAP and the mean optical density of GFAP-immunoreactive astrocyte (GFAP-ir astrocyte)
[30]	CUMS rat model	48	Male	Hegu (LI4) Taichong (LR3)	EA/15Hz/30min	21	China	2021	Decrease hippocampal glutamate, Bax, caspase 3, CaMKII, NR2B Increase Bcl-2, NR2A
[31]	CUMS rat model	120	Male	Baihui (GV20) Shenting (GV24)	EA/2Hz/20min	21	China	2020	Increase CaMKII and CaMKIV
[32]	HIS rat model	75	Male	Zusanli (ST36)	EA/100Hz/2Hz/20min	9	China	2020	Regulate glucose metabolism
[33]	CUMS rat model	40	Male	Baihui (GV20) Yintang (GV29)	EA/2Hz/30min	14	China	2020	Upregulate 5-HT1A receptor Improve synaptic plasticity in the hippocampus
[34]	OVX rat model	32	Female	Sanyinjiao (SP6)	MAI/none/1min	8	Korea	2019	Mitigate ER stress and oxidative stress in amygdala
[35]	CRS mouse model	-	Male	Yingu (KI10) Ququan (LR8) Jingqu (LU8) Zhongfeng (LR4) Shaofu (HT8) Xingjian (LR2)	MA/none/30sec	7/14	Korea	2019	Increase expression of 5-HT1A receptor in the cortex, hippocampus, thalamus, and the hypothalamus Increase 5-HT1B in the cortex and thalamus
[36]	WKY rat model	24	Male	Baihui (GV20) Yintang (EX-HN3)	EA/2Hz/15min	21	China	2018	Decrease 5-HTT protein expression in the hippocampus CA1 region Downregulate the expression of the 5-HT1A protein in the hippocampus CA1 region Restore hippocampus CA1 synaptic plasticity
[37]	CUS rat model	33	Male	Baihui (Du20) Yanglingquan (GB34)	EA/2/100Hz/30min	14	China	2018	Decrease NLRP3, IL-1β, P2X7 receptor, Iba-1, IL-18, TNFα and IL-6 Increase GFAP Alleviate the hippocampal neuroinflammation
[38]	CUMS rat model	40	Male	Baihui (GV20) Yintang (GV29)	MA/none/20min	28	China	2018	Upregulate BDNF in serum and hippocampus Upregulate hippocampal acH3K9 Downregulate hippocampal HDAC2

Abbreviations: CUMS, chronic unpredictable mild stress; FS, forced swimming; LPS, lipopolysaccharide; CMS, chronic mild stress; SI, social isolation; CRS, chronic restraint stress; HIS, heterogeneous intermittent stress; OVX, ovariectomize; WKY, Wistar Kyoto; EA, electroacupuncture; MA, manual acupuncture; AC, acupoint catgut; MAI, mechanical acupuncture instrument; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; NT, neurotrophi; CaMKII, calcium/calmodulin-dependent protein kinase II; GFAP, glial fibrillary acidic protein; acH3K9, acetylation levels in histone H3 lysine 9.

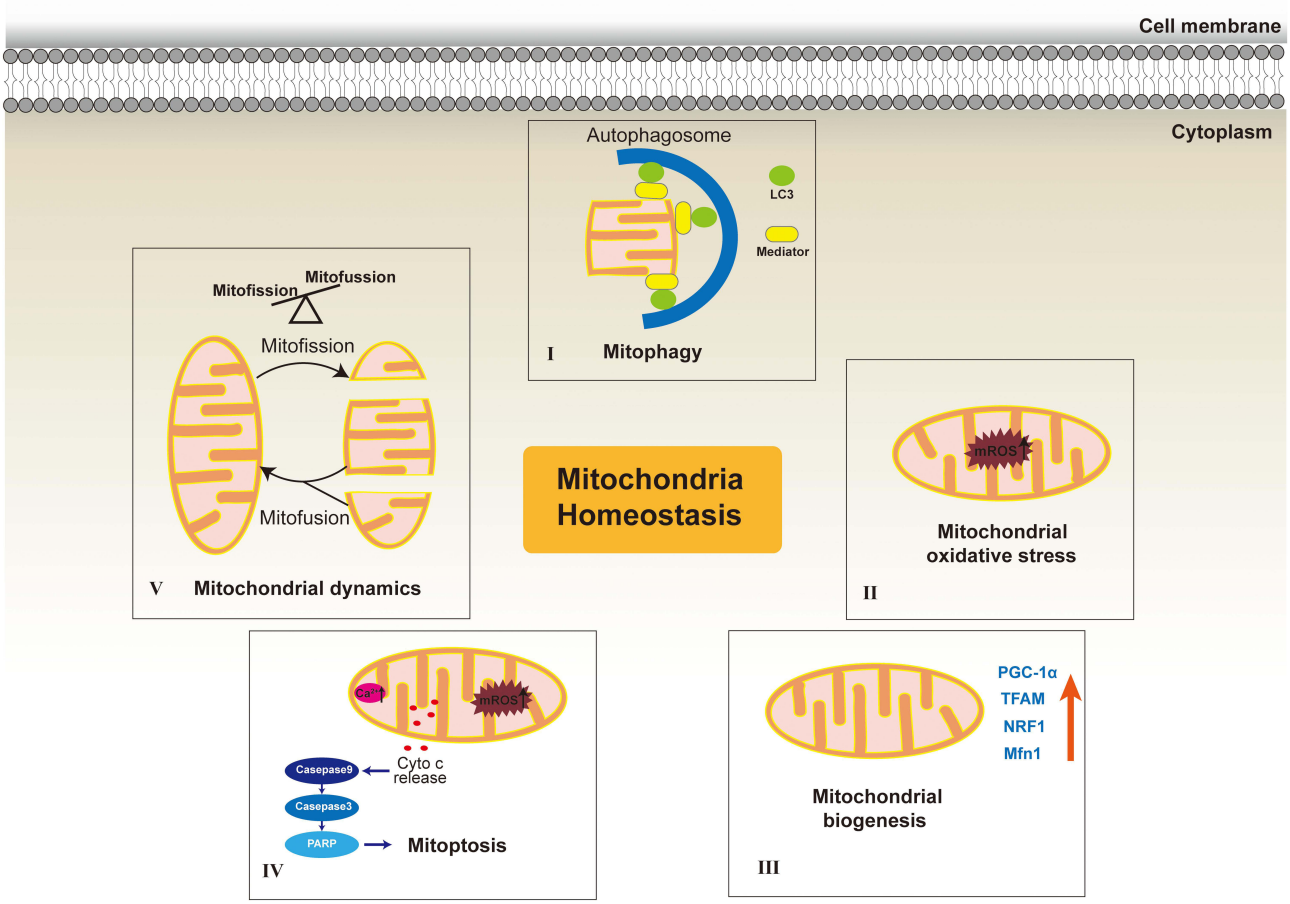

Figure 1 The schematic diagram of mitochondrial homeostasis. (I) The damaged mitochondria are specifically wrapped in autophagosomes and fused with lysosomes to complete the degradation of mitochondria and maintain mitochondrial homeostasis. (II) The imbalance between oxidation and antioxidation in mitochondria produces a large amount of mROS, which leads to mitochondrial oxidative stress. (III) Mitochondrial biogenesis is defined as the process by which cells increase the mass of their individual mitochondria. (IV) With the continuous increase of ROS in mitochondria, the increase of Ca^{2+} released to mediate the imbalance of mitochondrial energy metabolism homeostasis, which led to the release of pro-apoptotic protein cytochrome c (Cyto c) and the activation of apoptotic caspase pathway, the mitoptosis was elicited. (V) Mitochondrial dynamics refers to the dynamic balance between fusion and fission of mitochondria.

Therefore, this paper reviews the related research in order to clarify the new mechanism of acupuncture in the treatment of depression: targeting mitochondrial homeostasis and providing a new strategy for the treatment of patients with depression.

Regulate Mitophagy

Mitophagy is a regulatory mechanism that controls the quality and quantity of mitochondria and maintains the general homeostasis of the structure and function of mitochondria in the cellular environment. It specifically recognizes dysfunction or excess mitochondria, recruits the autophagy structure in the cytoplasm to wrap the mitochondria to be degraded to form autophagosomes, and finally binds to lysosomes to complete the degradation of autophagosomes.[44] Abnormal mitophagy is one of the pathogeneses of depression.[45] When the disturbance of mitophagy occurs, the undegradable damaged mitochondria accumulate in the cell, which leads to the decrease of membrane potential and triggers downstream events such as apoptosis and oxidative stress that destroy the homeostasis of the internal environment.[46]

An animal-model study involving 60 SD rats demonstrated that electroacupuncture partially inhibits mitophagy by partially inhibiting the level of mitophagy in the hippocampus of CUMS rats, reducing the number of autolysomes and the level of Lc3-II/Lc3-I, thus exerting the antidepressant effect.[47] Mitophagy and structural changes of mitochondria are the main causes of neuronal dysfunction.[48] Ge et al[49] established a diabetic model of adult SD rats by using

streptozotocin (STZ) have shown that electroacupuncture promotes mitophagy and improves the learning and memory function of rats by increasing the expression of Disrupted-in-Schizophrenia 1 (DISC1). The down-regulation of DISC1 leads to mitochondrial dysfunction and synaptic plasticity, resulting in cognitive impairment.[50] Studies have shown that electroacupuncture activates mitophagy by regulating the steps in the process of mitophagy, including autophagy induction, phage elongation, vacuole formation and substrate degradation.[51] Zhong et al[52] made the rat model of brain injury induced by middle cerebral artery occlusion (MCAO) demonstrated that electroacupuncture inhibits the activation of NLRP3 inflammatory bodies by regulating melatonin-mediated mitophagy, thus improving the cognitive impairment in stroke rats. It has been found that EA ameliorates nitro/oxidative stress-induced mitochondrial functional damage and decreases the accumulation of damaged mitochondria via Pink1/Parkin-mediated mitophagy clearance to protect cells against neuronal injury in cerebral I/R.[53]

In summary, electroacupuncture can effectively regulate mitophagy, improve mitochondrial dysfunction, and play an antidepressant role in a variety of ways. However, although the mitophagy of depression has been well studied and a certain number of acupuncture and mitophagy studies have been published, the comprehensive study on the effect of acupuncture on mitophagy of depression is still limited.

Reduce Mitochondrial Oxidative Stress

Mitochondria are the main source of reactive oxygen species (ROS), and more than 95% of the ROS in the body come from mitochondria.[54] Extensive studies have shown that mitochondrial reactive oxygen species (mROS) are essential for healthy cell function.[55] ROS is a component of the cellular signal transduction pathway, which can activate various transcription factors and lead to the expression of proteins that regulate inflammation, cell transformation, tumor cell survival, tumor cell proliferation and invasion, angiogenesis, and metastasis. ROS also controls the expression of various tumor suppressor genes (p53, Rb, and PTEN genes) and inhibits tumor progression. Most chemotherapy and radiotherapy drugs act by increasing ROS stress in tumor cells. Sies[56] introduced the concept of oxidative stress, that is, the destruction of oxidative-antioxidant balance. Oxidative stress represents an imbalance between the production and expression of ROS and the ability of biological system to detoxify intermediates or repair damage. Oxidative stress refers to the imbalance caused by excessive ROS or oxidants exceeding the effective antioxidant response of cells. Oxidative stress is harmful because it can lead to cell biomolecule damage and mutation and growth inhibition, and is involved in the occurrence of various diseases such as atherosclerosis, diabetes, cancer, neurodegenerative diseases, and aging.[57] Over the past decade, oxidative stress has emerged as a leading cause of depression.[58,59] Increased ROS and amplified expression of genes controlled by oxidative stress are closely associated with the development of depression.[60]

Previous studies have shown that acupuncture improves depression-like behavior in CUMS rats, which is associated with oxidative stress in the hippocampus. Acupuncture reduces oxidative stress products by regulating the Nrf2/HO-1 signaling pathway, thereby preventing neuronal apoptosis and playing an antidepressant role.[23] Acupuncture has become a common complementary and alternative treatment of depression, an animal experiment in the OVX-induced depression rat model, showed that acupuncture can relieve oxidative stress in the amygdala, change in oxidative stress-related protein (8 - OHDG, BJP, pJNK), play a significant antidepressant effect.[34] Fang et al[61] established a model of ovarian dysfunction by gavage of Tripterygium Glycosides suspension (50 mg·kg-1·d-1) for 14 successive days, demonstrated that acupuncture can increase SOD content, decrease MDA content, and improve the antioxidant stress ability of rats.

In summary, the incidence of depression is closely related to oxidative stress, which can lead to oxidative damage of proteins, lipids and DNA. Studies have confirmed that oxidative stress may be the main influencing factor of cognitive impairment in depression.[62] Both electroacupuncture and manual acupuncture can inhibit oxidative stress.[63] Therefore, an in-depth study of the exact mechanism of acupuncture stimulation of the antidepressant effect by inhibiting oxidation is particularly important for the treatment of depression.

Inhibit Mitoptosis

Apoptosis, also known as programmed cell death, is an active death process in order to better adapt to the living environment. Mitochondria are the center of energy metabolism in eukaryotic cells, and the loss of their normal function will lead to apoptosis, and the caspase feedback cycle in mitochondria further amplifies the effect of apoptosis. Therefore,

mitochondria are called the "life-and-death switch" of apoptosis. Mitochondrial apoptosis pathways include exogenous and endogenous pathways. The stress signals of these two apoptosis pathways are concentrated in mitochondria and regulate apoptosis through proteins of the Bcl-2 family. Bcl-2 in mitochondria induces the opening of the transition pore of permeability of the mitochondrial membrane or precisely changes the permeability of the mitochondrial membrane through the release of Ca^{2+}, thus initiating cell apoptosis procedures. Exogenous stress signal induces caspase-8-mediated Bid activation by binding to death receptors on the cell membrane. In the endogenous mitochondrial apoptosis pathway, BH3 activation is different due to different BH3 structures in different cells, but all can up-regulate the activity of the pro-apoptotic protein BH3. Therefore, whether the activation of Bid in the exogenous pathway or the up-regulation of BH3 activity in the endogenous pathway, can activate the pro-apoptotic molecule Bak, thus forming pores on the mitochondrial outer membrane to release apoptotic factors, that is, the permeability of the mitochondrial outer membrane. In this process, apoptosis-related factors released from mitochondria, such as cytochrome C (CytC), apoptosis-inducing factor (AIF), and mitochondrial-derived second caspase activator (Smac), can trigger apoptosis once these factors are released from mitochondria.

Mitoptosis was first introduced into the scientific literature by Vladimir P. Skulachev in 1999 to represent the programmed death (elimination) of mitochondria in living cells. He proposed that mitoptosis is the driving force behind apoptosis.[64,65] Mitoptosis is a kind of programmed destruction of mitochondria independent of the cystatin pathway, which often leads to the opening of mitochondrial membrane permeability transition pores mediated by reactive oxygen species, structural changes, rupture and fragmentation of mitochondrial membrane system, and its serious consequences can lead to cell death.

It has been found that acupuncture can reduce oxidative stress products, down-regulate caspase 3 expression, up-regulate Bcl-2 expression, inhibit neuronal apoptosis and exert antidepressant effect by regulating Nrf2/HO-1 signal pathway.[23] Guo et al[30] confirmed the antidepressant effect of electroacupuncture in CUMS rats. Electroacupuncture can reduce Bax and caspase 3 levels in the hippocampus, increase Bcl-2 expression, and regulate apoptosis. Dai et al[66] detected the apoptosis rate of hippocampal cells by Annexin V fluorescein isothiocyanate (FITC) / Propidium iodide (PI) (Annexin V-FITC/PI) double-staining, which confirmed that electroacupuncture can inhibit hippocampal cell apoptosis. A scalp acupuncture study also demonstrated the effect of acupuncture on inhibiting cell apoptosis, which found that scalp acupuncture can increase the expression of Beclin1, Parkin, PINK1, NIX in brain tissue, reduce caspase 3, and thus inhibit nerve cell apoptosis.[67]

To sum up, acupuncture can inhibit apoptosis by regulating signal pathways and the expression of key proteins, thus playing an antidepressant role. At present, there are few studies focusing on the regulation of mitoptosis by acupuncture. Combined with the above contents, the mitoptosis is crucial in the pathogenesis of depression. If further studies on the antidepressant effect of the regulation of the mitochondrial apoptosis pathway by acupuncture will certainly promote people's understanding of depression. If we make an in-depth study on the antidepressant effect of acupuncture regulating mitoptosis, it will certainly promote people's understanding of depression.

Induce Mitochondrial Biogenesis

Mitochondrial biogenesis refers to the increase in the number and/or quality of mitochondria and the individual and systematic production of new mitochondria in cells.[68] The increase of the number of mitochondria depends on the biogenesis of mitochondria to produce new mitochondria. The biogenesis of mitochondria is largely regulated at the transcriptional level. A series of transcription factors and transcriptional coactivators are involved in the regulation of mitochondrial biogenesis. It is currently acknowledged that the coordination of mitochondrial biogenesis is achieved by the peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), which plays an integral role in inducing the transcription of genes encoded by both the nuclear and mitochondria.[69] Puigserver et al[70] first found that the ectopic expression of PGC-1α in white adipocytes activated the expression of uncoupling protein-1 (UCP-1) and key mitochondrial enzymes in the respiratory chain, which increased the content of mitochondrial DNA (mtDNA) in adipocytes. Upstream AMP-activated protein kinase (AMPK) binds and activates PGC-1α in muscle by directly phosphorylating two key residues threonine-177 and serine-538.[71] P38 mitogen activated protein kinase (p38MAPK) phosphorylates amino acid residues 262,265,298 directly, inhibits the degradation of PGC-1α protein and increases the half life of PGC-1α.[72]

PGC-1α then binds to the amino acid 180–403 of downstream nuclear respiratory factor 1 (NRF-1) and strongly induces the expression of the NRF-1/2 gene.[73] NRF-1 and NRF-2 directly stimulate the mitochondrial transcription factor A (TFAM) promoter through the binding sites of TFAM-76/58 and TFAM 34/13, respectively, and participate in the activation of the TFAM promoter, which promotes the transcription and replication of mtDNA, and enhances the level of mitochondrial biogenesis.[74,75] In addition to TFAM, PGC-1α-NRF-1/2 pathway also upregulates mitochondrial transcription factors B1 and B2 (TFB1M / TFB2M) and significantly enhances mtDNA transcription.[76,77] PGC-1α promotes mtDNA replication and mitochondrial biogenesis by interacting with its upstream and downstream factors.

A study shows that mitochondrial biogenesis is reduced in patients with major depression. In this study, the expression of genes related to mitochondrial biogenesis in patients' blood monocytes was analysed. Researchers found that the expression of genes related to mitochondrial biogenesis (PGC-1α, TFAM, NRF1) decreased, the expression of antioxidant genes (CuZnSOD and MnSOD) was downregulated, and the level of ATP decreased significantly, indicating that the mitochondrial ability of patients with severe depression is reduced.[78] Tang et al[79] found that electroacupuncture can increase the protein expression of PGC-1α, TFAM, UCP-1, SIRT-1 and PPARγ, and induce mitochondrial biogenesis through PGC-1α-TFAM-UCP1 pathway. Electroacupuncture can up-regulate NRF1 and TFAM expression, increase mtDNA level and mitochondrial volume and number, improve mitochondrial function, and induce mitochondrial biogenesis through CB1R/PGC-α.[80]

To sum up, the decrease of mitochondrial biogenesis is an important cause of depression. Acupuncture can effectively improve the function of mitochondria, increase the level of ATP, up-regulate the expression of PGC-1α, TFAM and NRF-1, and induce mitochondrial biogenesis. Further study on the exact mechanism of mitochondrial biogenesis induced by acupuncture is helpful to solve the difficult problem of depression treatment.

Maintain Mitochondrial Dynamics

Mitochondria adapt to a variety of stress conditions to meet cell energy metabolism and other biological needs through continuous fusion and fission. This biological process is called mitochondrial dynamics. Mitochondria regulate their morphology, quantity, distribution, and function through fusion and fission, and regulate the morphology of mitochondria in two diametrically opposite ways.[81,82] When fusion increases or fission decreases, it promotes the formation of an extended tubular structure of mitochondria, while when fusion decreases and fission increases, mitochondria show a granular structure.[83] The fusion and fission of mitochondria can be regulated by the highly conserved GTPase protein family. The GTPase protein family completes the remodeling of the inner and outer membrane of mitochondria by self-assembly and hydrolysis of GTP. The fusion of mitochondria can be divided into two parts: the fusion of outer membrane and the fusion of inner membrane. The fusion of the outer membrane of mitochondria is accomplished by GTPase proteins mitofusin 1 (Mfn1) and mitofusin 2 (Mfn2) located in the outer membrane of mitochondria, while the fusion of the inner membrane of mitochondria is accomplished by optic atrophy 1 (OPA1). Different from mitochondrial fusion, mitochondrial fission is mediated by a dynamin-1-like protein 1 (Drp1) with a molecular weight of 80 kDa located in the cytoplasmic matrix. The receptor proteins that can recruit Drp1 are distributed on the outer membrane of mitochondria: mitochondrial fission factor (Mff), mitochondrial dynamics protein of 49 and 51 kDa (Mid49/51) and mitochondrial fission protein 1 (Fis1). These proteins can recruit Drp1 to the outer membrane of mitochondria and further form a spiral ring structure, and then drive mitochondrial constriction and transection by hydrolyzing GTP.[84] Abnormal changes in mitochondrial dynamics can mediate the occurrence of depression; especially the overactivation of Drp1 can lead to increased mitochondrial division, resulting in functional abnormalities, damage to the synaptic microenvironment, and inducing depression-like behaviors.[85]

It has been found that electroacupuncture can regulate the mitochondrial dynamics mediated by the HO-1/PINK1 pathway, increase the content of ATP and the level of mitochondrial fusion protein, and maintain mitochondrial homeostasis.[86] Yong et al[87] found that electroacupuncture at "Zusanli" can improve the level of fission and fusion of mitochondria, and have a certain effect on the dynamic balance of mitochondria. By increasing the expression of fusion protein Opa1 and mitotic protein Drp1, a new balance between fusion and fission of mitochondria is established. This balance is beneficial to the synthesis of mitochondrial ATP and the improvement of mitochondrial function.

In summary, when the balance between mitochondrial fusion and fission is disrupted, mitochondrial dynamics will be abnormal and depression will be induced. Electroacupuncture intervention can help mitochondrial fusion and fission to restore balance, increase ATP content, and maintain mitochondrial homeostasis. The research on acupuncture-mitochondrial dynamics-depression is still shallow, and in-depth research on the exact mechanism of acupuncture regulating mitochondrial dynamics may provide new ideas for the treatment of depression.

Regulatory Neuroplasticity

Changes in neuroplasticity play an important role in depression. Depression is an emotional and psychological disorder, which is related to the abnormal function of the nervous system.[88] Acupuncture can interfere with neuroplasticity in many ways so as to assist the treatment of depression. Acupuncture can regulate the levels of a variety of neurotransmitters, such as 5-HT, dopamine and glutamic acid. These neurotransmitters play an important role in the development and occurrence of depression.[89] By regulating the balance of neurotransmitters, acupuncture can affect the neural circuits in the brain associated with mood regulation. In addition, acupuncture can promote the growth and regeneration of nerve cells, which is very important in restoring neurological function and improving symptoms of depression. Acupuncture stimulation can stimulate the brain to release growth factors, such as Neurotrophic factors (NTFs), through signal transduction of the nervous system, thus stimulating the growth and differentiation of nerve cells.[20] Studies have found that patients with depression are often accompanied by chronic inflammation. Acupuncture can improve the symptoms of depression by regulating the function of the immune system and reducing the inflammatory response.[90] Acupuncture can also change the electrical activity pattern of the brain and regulate the interaction between brain regions.[91] This is beneficial for the treatment of depression, because the brain activity of patients with depression is often abnormal. In summary, acupuncture can affect neuroplasticity through many mechanisms and improve symptoms of depression.

Limitations

Currently, there are no human studies to support our proposed mechanism of acupuncture in the treatment of depression by regulating mitochondrial homeostasis. This paper only analyzes the animal experiments, which may have a certain deviation on the results.

Conclusions

Depression seriously harms human physical and mental health, with the symptoms of depression, lack of interest or pleasure, and decreased will and behavior. With the acceleration of the pace of modern life and the increase of social pressure, the incidence rate has increased year by year in recent years. Depression has a high suicide rate, which brings a heavy burden to patients and families. At present, the commonly used drugs for the treatment of depression and other mental diseases have a variety of adverse reactions such as gastrointestinal tract, cardiovascular system and central nervous system, as well as the safety of drug overdose, drug withdrawal syndrome and many other deficiencies. Acupuncture, as a convenient and quick treatment method, can prevent and cure diseases by stimulating the biological function of the human body, significantly improving symptoms, and having no side effects. Studies have demonstrated the efficacy and safety of acupuncture in antidepressant treatment.[15,92] The research on the antidepressant mechanism of acupuncture has become the focus of many studies. At present, studies in various countries have focused on the effects of acupuncture on behavior, neuroendocrine, neurotransmitters, cytokines, neurotrophic regeneration, cellular signal transduction pathways, and related gene proteins. This paper reviews the research on the antidepressant effect of acupuncture by regulating mitochondrial homeostasis. It is found that acupuncture can regulate mitochondrial homeostasis (regulate mitochondrial autophagy, reduce mitochondrial oxidative stress, inhibit mitoptosis, induce mitochondrial biogenesis, and maintain mitochondrial dynamics), reduce depression-like behavior, regulate signal pathways and key proteins. However, the exact mechanism and relationship of acupuncture in the treatment of depression by regulating mitochondrial homeostasis is not clear. Therefore, in-depth study of acupuncture targeting mitochondrial homeostasis may be a new mechanism for the treatment of depression and provide new ideas for the treatment of patients with clinical depression.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that there are no conflicts of interest regarding the publication of this review.

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