International Journal of General Medicine

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REVIEW

Treatment of Depression with Acupuncture Based on Pathophysiological Mechanism

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Abstract: Depression is a prevalent mental disorder and has a profound impact on an individual's psychological and physical well-being. It is characterized by a persistently depressed mood, loss of interest, energy loss, and cognitive dysfunction. In recent years, more and more people have changed to mental diseases, such as depression, anxiety, mania and so on. In the incidence of depression, covering all ages, but still mainly young and middle-aged women. Traditional treatments for depression mainly rely on medication and psychotherapy, but these methods are not effective for all patients and are often accompanied by certain side effects. Therefore, finding safe and effective alternative or adjuvant treatments has become a priority. Here we highlight the research progress of acupuncture in the treatment of depression and to explore the mechanism of acupuncture in the treatment of depression. Acupuncture treatment of depression is an ancient and effective method, the mechanism involves multiple biological pathways, for example, by regulating neurotransmitter levels, regulating the neuroendocrine axis, improving neuroplasticity, anti-inflammatory and other effects, improving emotional state and play an antidepressant role. To provide evidence to support the widespread use of acupuncture in clinical practice. We hope to provide new treatment ideas and methods for patients with depression, and even reduce the incidence of depression.

Keywords: acupuncture, depression, mechanism

Introduction

Depression is a global mental health problem that has a wide impact on the global population. Its pathogenesis is broad and influenced by multiple factors, such as genetics, psychology, social environment, and natural environment. Studies[1] have shown that depression differs significantly between genders. Women are twice as likely as men to develop depression. This gender difference may be closely related to biological, social, and cultural factors.[2] Although the occurrence of depression is not restricted by age, it shows different characteristics in different age groups.[3] For example, adolescents and young adults may be more vulnerable, but older adults may also develop depression. Notably, some other diseases or life states are also prone to trigger depression, such as postpartum depression[4] and post-stroke depression (PSD),[5] which further highlights the complexity of depression and its broad public health impact. In addition, depression is associated with other psychiatric disorders.[6] Anxiety disorders are also prevalent mental health disorders and have a significant impact on individuals' lives and society. Depression and anxiety can occur independently, but there have also been case reports of both. We believe that understanding the cognitive neuroscience aspects of these diseases is essential for preventive measures and early intervention.

Although many antidepressant drugs have been developed on the market, such as estazolam, diazepam, phenobarbital. However, these drugs, while being treated, can also bring side effects to patients and produce adverse effects. Fatal, some drugs are also addictive.[7] Tianeptine is an opioid agonist which is addictive and prescribed as an antidepressant in many countries. However, Tianeptine is not approved for medical use in some countries. According to a case report, a prenatal mother used Tianeptine in a context of dependence on dietary supplements. The baby developed severe withdrawal symptoms shortly after birth. Some patients developed gastrointestinal symptoms such as nausea, vomiting, diarrhea, and

Received: 4 November 2023
Accepted: 21 January 2024
Published: 31 January 2024

epigastric discomfort after oral administration of 5-HT drugs, and these side effects may be due to the excitatory effect of 5-HT on intestinal smooth muscle during its action in the intestine.[8] 5-HT may also have effects on sexual function, such as decreased libido and erectile difficulties. These side effects may be due to the modulation of sex hormones by 5-HT during neurotransmitter modulation.[9]

Therefore, finding a treatment that is less harmful to depressed patients looks very important in the current medical environment. We focused our attention on a well-known non-pharmacological treatment, acupuncture. Acupuncture includes a variety of specific treatments, including conventional acupuncture, electroacupuncture, auricular acupuncture, intradermal acupuncture. Acupuncture has been available for thousands of years. According to the theory of "eight principles" and the concepts of syndrome differentiation of "viscera" and "meridians and collaterals", fine acupuncture is inserted into specific acupoints to correct the imbalance of yin and yang in the body. The aim of this study is to explore the physiopathological mechanism of acupuncture in the treatment of depression, hoping to improve the clinical non-drug treatment of depression, reduce the adverse reactions caused by antidepressant drugs, promote the recovery of patients with depression, reduce the burden of society and families in medical treatment. Similarly, we prefer to be able to reduce the occurrence of depression from the root cause.

Pathogenesis

Neurotransmitter Imbalance

One major pathogenesis of depression involves an imbalance of neurotransmitters.[10] Neurotransmitters are chemical messengers in the brain that transmit signals between nerve cells and affect various functions of the brain, including mood regulation, stress response, sleep, and appetite. Studies have shown that abnormal levels of these neurotransmitters may be present in the brains of depressed patients, which can affect mood, sleep, and regulation.

Serotonin is a neurotransmitter that plays an important role in emotional regulation and emotional stability in the brain, especially in inhibiting negative emotions and enhancing positive emotions. Serotonin is also important for the regulation of sleep.[11] Insufficient serotonin may lead to sleep disturbance, which is one of the common symptoms of depression. Serotonin has also been implicated in appetite regulation.[12] Depressed patients may experience loss of appetite or excessive appetite, which may be associated with changes in serotonin levels.[13] Depressed patients usually show abnormally low serotonin levels. This may therefore lead to depression symptoms such as depressed mood, sleep problems, and appetite changes.[14] Many antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), improve depressive symptoms by increasing serotonin levels in the brain.[15]

Dopamine (DA) is another neurotransmitter that is associated with reward, motivation, and affect. DA neurons are one of the crucial neurons involved in the pathogenesis of depression. DA and its receptors are now recognized targets for the treatment of several neuropsychiatric disorders, including Parkinson's disease and schizophrenia. In depressed patients, imbalances in the DA system may lead to a decreased perception of rewards and pleasures, making people tedious and indifferent. Anhedonia is considered a core feature of depression.[16] Dopamine transporter (DAT) is one of the main factors that maintains DA stability in the synaptic cleft. Increasing evidence[17] suggests that there is reduced availability of DAT in depressed patients, and treatment directed at DAT provides clinical improvement in depressed patients.

Abnormal Neural Circuits

Depression is associated with abnormalities in specific neural circuits in the brain. For example, brain regions such as amygdala, cingulate gyrus, and prefrontal cortex (PFC) may show abnormal activity in depressed patients.[18]

PFC is important in the pathogenesis and treatment of depression. The PFC is part of the brain responsible for performing cognitive functions, affective regulation, and decision-making. The association between depression and PFC abnormalities has been demonstrated by several neuroimaging and neurobiological studies. Some studies have found that depressed patients may experience decreased gray matter volume or altered white matter integrity in the PFC. These structural changes may be associated with certain symptoms of depression, such as depressed mood, cognitive dysfunction, and difficulty concentrating.[19]

Functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) have shown[20] that PFC activity may be reduced in depressed patients, particularly in the face of negative stimuli or stressful events. Positron emission tomography showed that depressed patients had lower PFC gray matter volume and cerebral blood flow values, while cerebral blood flow in this region was closely related to depressive symptoms.

The cingulate gyrus is a brain region implicated in affective regulation and affective responses. Depressed patients may show abnormal activity patterns in the cingulate gyrus, usually characterized by enhanced negative emotions and diminished positive emotions.[21] It has been found[22] that the cingulate gyrus plays an important role in self-related information processing, and the cingulate gyrus in depressed patients may be associated with their negative self-evaluation. Depressed patients tend to have attentional biases toward negative information, while the cingulate gyrus plays an important role in attention control and selective attention.

The amygdala is also a critical region of the brain responsible for emotional processing.[23] The amygdala of depressed patients may be more sensitive to negative emotional stimuli, which may lead to affective hyperreactivity and anxiety. Neuroimaging studies[24] have also found that patients with depression may experience structural and functional abnormalities in the amygdala, such as gray matter volume reduction and changes in connection strength. Some antidepressant treatments,[25] such as pharmacotherapy and cognitive behavioral therapy,[26] may improve symptoms of depression by altering amygdala activity.

Genetic Factors

Genetic factors play an important role in the pathogenesis of depression. Family studies and twin studies[27] suggest that genetic factors contribute to susceptibility to depression. In monozygotic twins, if one twin suffers from depression, the other twin has a significantly higher risk of disease than dizygotic twins.[28] Depression is clustered in families. If a person's first-degree relative has depression and a specific gene or genetic variant is transmitted in the family, the risk of depression in this person is higher than in the general population.[29] The genetic risk of depression is complex and often involves the interaction of multiple genes. Different genetic variants may interact to make individuals more vulnerable to or uncomfortable with the effects of depression. Researchers have identified several genetic loci associated with depression, such as 5-HTTLPR (a genetic polymorphism associated with serotonin transporter).[30] However, no single gene has been found to be strongly associated with depression, and the onset of depression is generally considered to be the result of a combination of polygenes and environmental, life events, psychosocial, and other factors.

Inflammation and Immune System

Some studies have shown[31] that inflammation and abnormal activity of the immune system may be associated with depression, and inflammatory responses and immune molecules may play a role in the pathophysiology of depression. Inflammatory mediators can affect the neurotransmitter system, particularly DA, 5-hydroxy tryptamine (5-HT), norepinephrine (NE), and other neurotransmitters related to mood regulation. Certain inflammatory factors, such as IL-6 and TNF-α, may increase in inflammatory states, and high levels of these molecules are associated with the development and progression of depression. These cytokines can affect the synthesis, release, and reuptake of neurotransmitters, thereby disturbing neurotransmitter balance and leading to the development of depression.[32]

Inflammation may reduce the production of neuroprotective factors, such as brain-derived neurotrophic factor (BDNF).[33] One study showed that BDNF levels were significantly lower in patients with major depression.[34] BDNF plays an essential role in signaling, neuronal development, regulation of plasticity in the central nervous system, and treatment of neurological diseases, while its reduction is associated with an increased risk of depression.[35] Chronic inflammatory conditions can lead to decreased BDNF levels because some cytokines in the inflammatory response can interfere with BDNF production and signal transmission. Decreased BDNF levels may lead to abnormal function of neurons and instability of neural networks.[36] BDNF is not only essential for neuronal survival but also has an important impact on neuronal plasticity, including synaptic plasticity.[37] Plasticity is a critical mechanism for brain adaptation and learning, and it is associated with emotional stability and cognitive function. Decreased BDNF may lead to impaired neuronal plasticity, which in turn impacts emotional regulation and cognitive function. Chronic inflammation may reduce the formation of new neurons, particularly in brain regions such as the hippocampus that are closely related to emotional

regulation and cognitive function. This may be associated with the pathogenesis of depression because structural and functional abnormalities of the hippocampus are associated with depression.[38]

Persistent inflammatory conditions can lead to sustained activation of the immune system, releasing inflammatory mediators such as C-reactive protein and IL-1. These molecules can cross the blood-brain barrier and directly affect brain function, leading to emotional and cognitive abnormalities.[39]

Acupuncture

Acupuncture, as an ancient and unique non-pharmacological treatment, stimulates the nervous system of the human body by inserting and rotating needles at specific acupoints and exerts analgesic, muscle relaxation, anti-inflammatory, mild anxiolytic, and antidepressant effects. Acupuncture can induce the brain and spinal cord to produce a variety of neurotransmitters and neurohormones, such as endorphins and serotonin.[40] These bioactive substances have positive effects on relieving pain, improving mood, and enhancing the body's ability to cope with stress. By relaxing vascular smooth muscle and dilating blood vessels, acupuncture may help to improve local blood flow, which in turn promotes tissue repair and reduces pain.[41] In addition, acupuncture may reduce the inflammatory response by inhibiting the activity of certain inflammatory cells while helping to relax tense muscles and improve muscle flexibility and joint mobility, which may help improve various diseases of the motor system.[42] In terms of endocrine, acupuncture may adjust hormone levels, for example, by adjusting the pituitary-adrenal axis to affect cortisol levels.[43] Acupuncture may also modulate the immune system by affecting the activity of immune cells and cytokine production, for example, by adjusting the gut-brain axis, which in turn enhances the body's resistance to disease.[44] Acupuncture stimulates the body's own regulatory and reparative mechanisms by altering connective tissue structure and neurotransmitter levels, prompting the flow of energy and blood to rebalance.[45] Finally, acupuncture may produce relaxation and calming effects that help reduce anxiety and improve sleep quality, providing support for the overall health and psychological well-being of patients.[46] Acupuncture has been widely used in the treatment of depression in recent years. Although its exact mechanism of action is not yet fully understood, a large number of studies have shown that acupuncture may exert antidepressant effects through several mechanisms.

Modulating Neurotransmitter Levels

Acupuncture is thought to affect the levels of some major neurotransmitters in the brain.[47] Acupuncture enhances activity in certain key areas of the brain, such as the amygdala, hypothalamus, and brainstem, thereby promoting the release of neurotransmitters such as serotonin, DA, and NE. These neurotransmitters play an important role in regulating mood and coping with stress, and their increased levels are often associated with a reduction in depressive symptoms. Acupuncture increases the levels of these neurotransmitters in the brain and thus acts as an antidepressant.

Researchers[48] investigated the effect of acupuncture on depressive behavior induced by chronic stress and its effect on the central nervous system. They imposed chronic restraint stress (CRS) on male mice for 14 to 28 days, followed by acupuncture treatment for 7 to 14 days. Through open-field experiments, the investigators assessed depressive behavior in mice and explored the role of c-Fos and 5-HT related mechanisms in cranial neural activity by studying 5-HT1A and 5-HT1B receptors. The results showed that mice treated with acupuncture showed a significant improvement in depressive behavior, whereas the control group did not. Changes in neural activity were observed in the hippocampus, cingulate cortex, motor cortex, insular cortex, thalamus, and hypothalamus. Acupuncture increased 5-HT1A receptor activity in the cortex, hippocampus, thalamus, and hypothalamus, as well as 5-HT1B receptor activity in the cortex and thalamus. This suggests that acupuncture can effectively reduce depressive behavior in mice by regulating the activity of the central nervous system and the activity of serotonin receptors.

Karatay[49] assessed the effect of acupuncture treatment on serotonin and substance P levels in fibromyalgia patients. The results showed that serotonin levels significantly increased while substance P levels decreased in the real acupuncture group. This suggests that acupuncture may improve depressive symptoms and pain by directly increasing serotonin levels and decreasing substance P levels. Wei[50] investigated the effect of acupuncture on neurotransmitter gene expression in the brain tissue of rats with PSD. When comparing the contents of neurotransmitters in the cerebral cortex of rats in each group, it was found that the contents of 5-HT and NE in the cerebral cortex of rats in the model group were

significantly decreased compared with those in the normal group. Compared with the model group, the contents of 5-HT and NE in the cerebral cortex of rats in the acupuncture group and drug group were significantly increased. 5-HTT mRNA levels can be used as a potential biomarker of treatment response in patients with major depressive disorder.[51] When comparing the expression of 5-HTT mRNA in the brain tissue of rats in each group, the 5-HTT mRNA expression levels in the hippocampus, raphe nucleus, and locus coeruleus nucleus were significantly decreased in the model group compared with the normal group. Compared with the model group, the expression levels of 5-HTT mRNA in these brain regions were significantly increased in the acupuncture and drug groups. Ding[52] divided rats into five groups, including an acupuncture group, and measured the levels of 5-HT, 5-HIAA, and tryptophan (Trp) in PFC tissue using radioimmunoassay by recording the percentage of sucrose consumed to assess depression-like behavior. The depression model group showed a significant decrease in sucrose consumption, 5-HT levels, and 5-HT1A receptor binding constant, and an increase in Trp content in the PFC after a 3-week experiment. Compared with the depression model group, the acupuncture group showed improvement on these parameters. It is suggested that acupuncture alleviates depressive behavior in rats, which may be achieved by regulating serotonin levels and receptor activity in the PFC and is associated with up-regulation of 5-HT/5-HIAA and down-regulation of Trp content in the PFC. This result supports the effectiveness of acupuncture in treating depression.

Electroacupuncture is a type of acupuncture. Electroacupuncture (EA) may exert its antidepressant effects by regulating dopaminergic correlates in the PFC, with DAT playing a key role.[53] Behavioral tests[54] found that electroacupuncture treatment was able to alleviate depression-like behaviors triggered by chronic unpredictable mild stress (CUMS). EA improves neural function by enhancing synaptic transmission in the ventromedial prefrontal cortex (vmPFC) and upregulating spontaneous excitatory postsynaptic current amplitudes. Electroacupuncture treatment resulted in the improvement of depressive symptoms in rats, which was accompanied by an increase in TAAR1 and PKA expression. TAAR1, as a novel target for modulating the dopaminergic nervous system and related diseases, is also an intracellular G-protein-coupled receptor capable of elevating cAMP levels and downstream signaling, such as cAMP-dependent PKA. Phosphorylation of DAT may be a downstream effect of TAAR1, cAMP, and PKA activation. At the molecular level, EA treatment reversed the increase in total DAT and p-DAT expression in vmPFC, as well as the decrease in the p-DAT/total DAT ratio, and activated TAAR1, cAMP, and PKA. Phosphorylation of monoamine transporters by PKA can modulate signaling cascades in corresponding neurons and thus exert their regulatory effects.

Acupuncture enhances the release of NE by stimulating neurons, thereby activating the downstream cAMP-PKA signaling pathway, further regulating gene expression, improving the survival and functional status of neurons, and helping to alleviate depressive symptoms.[55] In addition, acupuncture can also inhibit the activity of the NE transporter, reduce the reuptake of NE, increase the concentration of NE in the synaptic cleft, enhance its effect on receptors on the postsynaptic membrane, and play an antidepressant role. Long-term acupuncture treatment can also adjust the sensitivity of NE receptors, optimize receptor function, and enhance the biological effects of NE. Through these mechanisms, acupuncture may exert neuroprotective effects, improve neuronal status, and improve depressive symptoms.[56]

Modulation of the Neuroendocrine Axis

Acupuncture exerts its antidepressant effect by regulating the neuroendocrine axis in the body, particularly the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis plays a critical role in coping with stress and regulating mood.[57] In depressed patients, the activity of the HPA axis is often enhanced, leading to increased cortisol levels in the body. In one case,[58] acupuncture relieved depression-related symptoms by improving HPA axis function and enhancing hippocampal activity. This suggests that acupuncture can be used as an alternative therapy to medication and psychotherapy to reduce suicidal ideation and improve HPA axis function by regulating cortisol secretion.

Acupuncture was found to be able to reduce cortisol levels in the blood and reduce hyperactivity of the HPA axis, thereby relieving depressive symptoms.[59] This effect may be a reflection of a homeostatic mechanism achieved by restoring the balance between sympathetic and parasympathetic nerves.[60] In this way, acupuncture can not only reduce depressive symptoms but also regulate neuroendocrine balance in the body and promote physical health.

Improving Neuroplasticity

Neuroplasticity refers to the ability of the nervous system to adapt to environmental changes during life, including the strengthening or weakening of neural synapses, the formation of new neural synapses, or the disappearance of existing synapses. Neuroplasticity tends to be compromised in depressed patients. Changes in synaptic plasticity are key pathological factors leading to the development of depression, mainly manifested as changes in the structure, number, and function of synapses. Acupuncture is thought to promote the growth and reconstruction of nerve cells in the brain and improve neuroplasticity, thus acting as an antidepressant.[61]

In the research field of brain injury-related diseases, acupuncture treatment has shown its potential effect, which can enhance the expression of synapse-related proteins and promote the recovery and improvement of neuronal injury through the regulation of mTORC pathway.[62] Dendritic spines, as tiny projections on the dendritic membrane, are critical regions for synaptic maturation and function.[63] In addition, the synaptic structural proteins PSD95, Synapsin I, and the excitatory glutamate receptor GluR1 play important roles in maintaining the structural and functional plasticity of synapses. Therefore, changes in the number and morphology of dendritic spines, as well as expression levels of synapse-related proteins such as PSD95, Synapsin I, and GluR1, are often used as indicators to assess synaptic plasticity.[64] Previous studies[65] have shown that BDNF is an essential factor in the formation and functional maintenance of synaptic connections in neurons, while mTORC1 is a key link in the regulation of synaptic protein repair and synthesis. Activation of the BDNF/mTORC1 signaling pathway plays a crucial role in enhancing synaptic plasticity. BDNF release increases expression of proteins involved in the mTORC1 signaling pathway, including p-mTORC1, phosphorylated extracellular regulated kinase, phosphorylated protein kinase B, and phosphorylated ribosomal S6K protein kinase, as well as synapse-related proteins Synapsin I, PSD95, and GluR1 in the PFC.[66]

TrkB is a high-affinity receptor of BDNF, and its binding can activate intracellular signaling, promote neuronal growth, development, functional expression, and nerve repair, and play an antidepressant role. Mice lacking TrkB showed increased depression-like behavior, whereas BDNF expression was regulated by CREB, and its overexpression was associated with mood disorders. CREB forms a positive feedback loop with BDNF/TrkB signaling and enhances each other's signaling.[67]

The hippocampus, as part of the limbic nervous system, is involved in the development and rehabilitation of depression. Previous studies[68] found severe neuronal damage and abnormal cell structure in the CA1 region of the hippocampus in PSD rats. PSD is associated with oxidative stress damage in the central nervous system, which impacts mood and behavior in rats. In PSD rats, MDA increased, SOD and CAT activities decreased in the hippocampus, and oxidative stress levels were correlated with depressive behavior. Mood disorders also decrease BDNF expression in the hippocampus. In the hippocampus of PSD rats, CREB/BDNF/TrkB signaling pathway activity is decreased, and depressive symptoms are aggravated.[69] The results also showed that acupuncture could improve the neurological function and depressive symptoms of PSD rats, decrease the oxidative stress level of hippocampal neural tissue, increase the expression of BDNF and CREB and the phosphorylation level of CREB, and regulate the CREB/BDNF/TrkB signaling pathway, which was consistent with the effect of antidepressant drugs. Reducing oxidative stress, increasing BDNF expression, and enhancing CREB/BDNF/TrkB signaling pathway activity are key to improving PSD symptoms.

Ning[70] hypothesized that the rapid antidepressant effects of acupuncture are achieved by modulating synaptic plasticity. The results showed that acupuncture treatment could effectively shorten the immobility time of two depression model mice in a forced swimming test, indicating that it had an antidepressant effect. At the molecular level, acupuncture treatment was able to inhibit the expression of M1-AchR while promoting the expression of proteins such as GluR 1, GluR 2, BDNF, p-mTOR, synapsin I, and PSD 95 and increasing the density of dendritic spines in PFC neurons. These results suggest that acupuncture treatment may exert its rapid antidepressant effect by inhibiting the expression of M1-AchR and activating the "glutamate tide"-AMPA receptor activation-BDNF release-mTORC 1 pathway in the PFC, thereby promoting synaptic protein expression and regulating synaptic plasticity. This provides a possible molecular mechanism for an acupuncture treatment of depression.

GABA, as an inhibitory neurotransmitter in the brain, is involved in the regulation of mood, while it also plays an important role in the regulation of sleep. Repeated transcranial magnetic stimulation (rTMS), as a non-invasive

stimulation technique, acts on nerve cells in the cerebral cortex or deep tissues through magnetic fields generated by coils to regulate neural circuit function and transmitter metabolism, thereby promoting brain plasticity and nerve injury repair.[71] Low-frequency rTMS can positively promote GABA release, regulate mood, and adjust the sleep cycle. Yan[72] observed the effect of acupuncture combined with rTMS on depressive mood and sleep quality in insomnia patients with comorbid mild-to-moderate depressive disorder. The results showed that after treatment, the clinical symptoms of the patients in the observation group improved, and the serum GABA and BDNF levels increased.

Anti-Inflammation

Depression is often associated with an increased inflammatory response. Chronic inflammation is now thought to be associated with depression.[73] Depressed patients have repeatedly been observed to have activated inflammatory pathways, as evidenced by increased proinflammatory cytokines, increased acute phase proteins, and increased expression of chemokines and adhesion molecules.

Acupuncture is considered to have anti-inflammatory effects and is able to reduce the production and release of inflammatory factors (eg, TNF-α, IL-1β, IL-6, etc.).[74] These inflammatory factors play an important role in the development of depression, and acupuncture helps to reduce depressive symptoms by inhibiting the production of these inflammatory factors. Acupuncture can also promote the release of anti-inflammatory factors (such as IL-10) in vivo. Anti-inflammatory factors are able to resist the effects of inflammatory factors, and by increasing the levels of anti-inflammatory factors, acupuncture helps to control the inflammatory response in the body, which in turn exerts antidepressant effects.[75] Many experiments and clinical trials have investigated the effect of acupuncture on inhibiting inflammation.

In a depression-like behavioral model in mice, S. Kwon found[76] that acupuncture could have an antidepressant-like effect after chronic systemic inflammation/immune response induced by Bacillus Calmette Guerin Vaccine vaccination by regulating the aggravated tryptophan-kynurenine metabolic pathway and hippocampal dopaminergic nerve conduction. Other studies[77] have found that rat models of CUMS have higher expression of HMGB1, IL-1β, IL-18, IFN-γ, IL-6, and TNF-α in the hippocampus, and the relationship between HMGB1 and pyroptosis in depression has been demonstrated. Following CUMS stimulation, NLRP3 is activated and binds pro-caspase-1 via ASC oligomerization, which in turn activates caspase-1. Subsequently, caspase-1 activates pyroptosis by cleaving GSDMD. Acupuncture can relieve depression-like behavior by inhibiting activation of the NLRP3 inflammasome. Recent studies[78] have shown that NLRP3-mediated pyroptosis, in particular, is associated with depression. Chen found that acupuncture treatment restored CUMS-induced behavioral performance and reversed NLRP3-mediated inflammatory responses and pyroptosis in the hippocampus of CUMS rats. In this study, expression of NLRP3, caspase-1, and GSDMD was significantly upregulated in the hippocampus of depression model rats. Therefore, acupuncture may exert antidepressant effects by regulating NLRP3-mediated pyroptosis, which may be related to the pathogenesis of depression.[79]

Conclusions

Acupuncture treatment for depression is an ancient and effective method, and its mechanism involves multiple biological pathways. Acupuncture plays an antidepressant role by regulating neurotransmitter levels, regulating the neuroendocrine axis, improving neuroplasticity, anti-inflammation, and other effects, and improving the emotional state. Overall, acupuncture treatment provides a safe and effective alternative or adjunctive therapy that holds new promise for depressed patients. Although some people may benefit from it, the effectiveness of this approach varies from person to person and has some limitations and potential risks. First, the quality and quantity of research on acupuncture treatment remain insufficient to make it a widely recognized medical treatment. Second, if not performed properly, it may cause side effects such as infection, bleeding, and needle stick injuries. In addition, acupuncture treatment usually requires multiple treatments, and each treatment may take longer, which may be inconvenient for the patient. Finally, because acupuncture treatment is deeply influenced by TCM philosophy, it may not be compatible with the cultural background and belief system of some people, which may also affect the patient's acceptance and effect of treatment. Therefore, when considering the use of acupuncture treatment, it is best to consult a healthcare professional to ensure that this treatment is appropriate for the individual's health status.

Abbreviations

SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; DAT, dopamine transporter; DA, dopamine; PFC, prefrontal cortex; fMRI, functional magnetic resonance imaging; EEG, electroencephalography; NE, norepinephrine; 5-HT, 5-hydroxy tryptamine; BDNF, brain-derived neurotrophic factor; CUMS, chronic unpredictable mild stress; vmPFC, ventromedial prefrontal cortex; HPA, hypothalamic-pituitary-adrenal; PSD, post-stroke depression; rTMS, repeated transcranial magnetic stimulation.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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.

Funding

Funding information is not available.

Disclosure

There are no conflicts of interest.

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