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The therapeutic potential of natural medicine puerarin for depression

Yuchao Guo

Tianjin University of Traditional Chinese Medicine, Tianjin. China

Abstract. The incidence of depression has steadily increased in recent years, making it one of the most prevalent mental disorders. As the pursuit of new antidepressant drugs has attracted wide attention in the pharmaceutical community, the therapeutic effects of traditional Chinese medicine have also been extensively explored. Puerarin is commonly used as a vasodilator in the treatment of coronary heart disease including angina and myocardial ischemia, cerebral infarction, retinal vein occlusion, and sudden deafness. However, the potential of puerarin in the treatment of depression is very great, so this article reviews the latest research progress of puerarin in the mechanism of depression in recent years, and discusses its application prospect in depression. In addition, we also discuss the related pathological mechanism of depression, which provides new insights for further understanding of depression. However, despite the great potential of puerarin, further studies are needed to elucidate its specific mechanism of action and evaluate its effectiveness in human subjects.

Keywords: puerarin depression neuroinflammation brain-gut axis.

1. Introduction

Depression is a chronic relapsing neuropsychiatric disorder characterized by anxiety, reduced thinking, and delayed thinking. Other symptoms are also present, including irritability, depression, worthlessness or guilt, low energy, insomnia, lethargy, changes in appetite or weight, difficulty concentrating, suicide attempts or thoughts of death or suicide[1], and it carries a substantial socio-economic burden, including increased healthcare expenditures and increased suicide rates[2]. Although there are many treatments for major depression, many patients do not respond adequately to conventional antidepressants. In the trials of sequential treatment regimens for depression relief, most patients achieved cumulative remission only after four consecutive treatments, and the most commonly used antidepressants in clinical practice have many side effects, including common cardiovascular side effects, gastrointestinal side effects, liver toxicity and sexual dysfunction[2]. Therefore, more effective treatment methods for depression are needed[3]. Efforts to develop new antidepressant drugs have been challenging, in part because our understanding of the pathophysiology of depression and antidepressant mechanisms is still in its infancy[4]. An in-depth understanding of the pathological mechanisms of depression is of great significance for our development of new antidepressant drugs. In addition, plant medicine has the potential to provide an encouraging approach to the treatment of human diseases. Many effective components contained in natural plants have become an important source for the development of new drugs[5]. At the same time, traditional Chinese medicine has a significant therapeutic effect on patients with coronary heart disease accompanied by anxiety or depression, and the most active compounds in traditional Chinese medicine can act on pathological targets such as coronary heart disease, anxiety and depression at the same time[6]. Puerarin, a highly bioactive component isolated from Puerarin root, has a wide range of pharmacological properties and has shown a wide range of pharmacological effects in a variety of central nervous system diseases such as Alzheimer's disease, Parkinson's disease, cerebral ischemia, depression, and spinal cord injury, which has attracted more and more attention worldwide[7]. This article reviews the latest research progress of puerarin in the mechanism of depression in recent years, and discusses its application prospect in depression. In addition, we also discuss the related pathological mechanism of depression, which provides new insights for further understanding of depression.

2. Pathological mechanisms of depression

Worldwide, the incidence of depression is increasing every year, causing a very large economic and social burden. Moreover, the pathological mechanisms of depression and the mechanisms of drug therapeutic effects are complex and unclear[8]. It is difficult to fully reveal the pathogenesis of depression using only one hypothesis, so several theories have been proposed to explain the pathogenesis of depression in recent years, including the monoamine hypothesis, which is based on the deficiency of biogenic amine systems, especially serotonin and norepinephrine, and the dysregulation of the neuroendocrine system, also known as hypothalamic-pituitary-adrenal (HPA) axis dysfunction. This theory is based on the increased activity of HPA axis to reduce the feedback inhibition of endogenous glucocorticoids, the neuroplasticity hypothesis, the inflammation theory, and the brain-gut axis theory. These theoretical studies have shown that depression is a complex mental disorder involving multiple neurotransmitters, brain regions, circuits, and various biochemical substance systems[9]. Great progress has been made in elucidating the role of multi-organ interaction in the pathogenesis of depression and the discovery of new treatment methods and multi-target regulatory strategies, which further reveals the disease characteristics of depression. None of these hypotheses can fully explain the pathological basis of depression, and many mechanisms proposed by these hypotheses are interactive[8]. Therefore, there is an urgent need for mechanistic understanding of the pathophysiology of depression, which may open the way to the development of new therapeutic strategies.

2.1. The monoamine hypothesis

Symptoms of depression can be improved by drugs that act through various mechanisms to increase monoamine synaptic concentrations. This finding led to the monoamine hypothesis of depression, which was first proposed more than three decades ago[10]. The monoamine hypothesis is a widely accepted theory that attempts to explain that the biological basis of major depression is caused by the depletion of monoamine neurotransmitters, namely norepinephrine and serotonin. This hypothesis of monoamines as the pathophysiological basis of major depression has led to the design and widespread use of selective serotonin reuptake inhibitors [11]. However, the monoamine hypothesis focuses solely on the role of neurochemical deficits, and this single hypothesis cannot provide a complete explanation for the effects of antidepressants and has major limitations. Examples include why antidepressants are also effective in other disorders such as panic disorder, obsessive-compulsive disorder, and bulimia, or why all drugs that enhance serotonergic or noradrenergic transmission are not necessarily effective in depression. However, despite these limitations, it is clear that the development of the monoamine hypothesis is important for understanding depression and for developing safe and effective therapeutic drugs[10].

2.2. Neuroendocrine dysfunction theory

The HPA axis is a complex and robust system. It consists of a series of neuroendocrine pathways that maintain physiological homeostasis in stressful environments. Homeostasis is mainly achieved through the control of circulating glucocorticoid levels, with cortisol being the major downstream glucocorticoid in humans. Cortisol has multiple physiological functions, including the regulation of mood[12]. Glucocorticoids act on almost all parts of the body and play a role in various physiological processes by activating glucocorticoid receptor (GR), exerting anti-inflammatory and immunosuppressive effects, regulating neuronal function in the limbic system. However, upregulated glucocorticoids also bind to GRs located in several brain regions, including the hypothalamus and pituitary gland, maintaining HPA axis homeostasis through a negative feedback loop. Dysregulation and imbalance of the HPA axis have been observed in a large proportion of clinical cases of depression and are thought to be caused by GR-dependent negative feedback dysfunction of the HPA axis[13]. The fact that antidepressant treatment can normalize cortisol levels suggests that the negative feedback effect of cortisol at the limbic hypothalamic level is less effective in patients with depression. A return to full response can be achieved with antidepressant treatment. The time course

of antidepressant action on corticosteroid receptors is consistent with its long-term effects on HPA system activity and is closely associated with clinical improvement in depression[14]. Major alterations in the hypothalamic-pituitary-adrenal cortex (HPA) system, which can be reversed by successful antidepressant treatment, are common in patients with depression, and these changes are associated with a dysfunctional GR system[14].

2.3. Neuroplasticity hypothesis

Neuroplasticity is a general term used to describe the anatomical and physiological changes of the brain in response to various stimuli. By responding to them and affecting changes in structure, function and connectivity, the neuroplasticity hypothesis of depression proposes that neuroplasticity dysfunction is the main pathological mechanism of the disease[15]. Impaired neuroplasticity can be caused by a variety of risk factors, including neurotransmitter imbalance and insufficient brain-derived neurotrophic factor (BDNF)[16]. One of the most important evidence of reduced neuroplasticity in certain brain regions in depression comes from neuroimaging, that is, reduced hippocampal volume in depression[17], and hippocampal vulnerability predispositions to hippocampal dysfunction that translates into cognitive and emotional disorders, both of which are important psychopathology disorders in MDD. The molecular mechanism behind this can be attributed to a reduction in BDNF expression, which leads to the loss of neurons and synapses, thereby reducing neuroplasticity[15]. Ketamine may act on depression based on neuroplasticity. Ketamine increases the expression of BDNF mRNA in the hippocampus to improve depression, but it has the problems of inducing psychotic symptoms and abuse in clinical application[17] Therefore, the non-toxic side effects of Chinese herbal medicine are the first choice for the treatment of depression. In addition, an important contributor to neural plasticity is adult hippocampal neurogenesis, which is the process by which adult neural stem cells generate new neurons. Changes in dendritic morphology and density, neurogenesis, growth factor expression, and neurotransmitter production may all contribute to changes in functional connectivity underlying behavioral and cognitive deficits in depression. These injuries have been targeted for antidepressant action and reversal of neuroplasticity deficits associated with symptom improvement. Although a growing body of research suggests that neuroplasticity is involved in the pathogenesis of depression, more research is needed to discern the etiology of the disease and how pathological outcomes can be more specifically reversed[18].

2.4. Neuroinflammation theory

Mood disorders are associated with elevated inflammation. Interventions using pharmacotherapy and neuromodulation to treat psychiatric disorders have been shown to reduce inflammation while alleviating symptoms. Targeting neurocircuit dysfunction, neuromodulation therapies to treat affective disorders by reducing neuroinflammation may provide a better understanding of disease pathogenesis. And objectively evaluate the efficacy of physical therapy[19].Proinflammatory systemic diseases that cause neuroinflammation and subsequent changes in brain regions involved in emotion regulation have been suggested as potential mechanisms in the pathophysiology of depression [20]. Most of the evidence linking depressive symptoms to inflammatory processes consists of three main concepts: (1) Systemic diseases with inflammatory processes increase the risk of depression. (2) Proinflammatory markers were increased in patients with depression. (3) Pro-inflammatory agents often induce psychiatric side effects, and there is evidence that patients with major depression have elevated levels of circulating cytokines[11]. Thus, conditions that affect systemic inflammation and subsequent neuroinflammation, as well as those that can induce alterations in brain regions associated with emotion regulation, may contribute to understanding the pathophysiology of depression[20]. In addition, inflammation activates the kyrenine pathway, and reductions in excitotoxic or neuroprotective metabolites have been found in cerebrospinal fluid or plasma samples from patients with major depression and suicide attempts. Prolonged dysregulation of the kynurenine pathway with more excitotoxic metabolites production has also been observed in suicide attempters, and the severity of symptoms is associated with an increased inflammatory burden. Various subtypes of depression, such as immune-related depression, postpartum depression, and

depressive episodes in patients with bipolar disorder also show activation of the kynurenine pathway, and kynurenine metabolites and morphological changes may also be associated with prefrontal cortex thickness in patients with depression[21].

2.5. Brain-gut axis theory

The mammalian gut contains a large number of microorganisms, including bacteria, archaea, fungi, viruses and some protozoa, and its metabolism, immune system and signaling are closely related to the microbiota. Therefore, the gut and gut microbiota can respond to and influence other organs as a whole[16],the brain-gut axis (tightly connecting the brain, gut and gut microbiota) is a two-way signaling mechanism between the gastrointestinal tract and the central nervous system, and the interaction between microbiota and intestinal epithelium can cause physiological changes in the brain and affect mood and behavior[22, 23]. Patients with depression often have gut-brain dysfunction, because factors such as psychological stress and illness damage one or more pathways of the gut-gut axis, which may lead to dysfunction of the gut-gut axis and lead to depression. According to the gut microbiome hypothesis, the gut microbiome can affect the brain and behavior through the gut-brain axis, which is also known as the microbiota-gut-brain axis. In order to emphasize the importance of microbiota, the gut microbiota hypothesis suggests that depression is closely related to gut microbiota, and the dysfunction of microbiota-gut-brain axis is the main pathological basis of depression[16]. Depression is strongly associated with changes in the gastrointestinal microbiota. Depression can change the composition of intestinal flora, and the disorder of gastrointestinal flora can further cause stress response and aggravation of depression[24]. Regulating intestinal flora is an effective method for the treatment and prevention of depression, and the intestinal flora of patients with depression is significantly different from that of healthy controls. Some studies have found that the diversity and richness of microbiota in patients are decreased, and fecal microbiota transplantation can transmit depressive symptoms[16]. The structural disorder of gut microbial system plays a crucial role in depression. The gut-brain axis shows the potential link between the digestive system and the central nervous system. At present, it has become an emerging trend to treat diseases by targeting intestinal microorganisms and combining the gut-brain axis mechanism[24].

3. Related mechanisms of puerarin in the treatment of depression

Puerarin has been shown to have a good antidepressant effect. The main antidepressant mechanism is related to regulating intestinal flora imbalance and inhibiting inflammatory response in hippocampus, serum and colon. Puerarin reduced pro-inflammatory factors, increased anti-inflammatory factors and improved damaged colon tissue in depression-like rats by down-regulating TLR4/NF-κB pathway[25]. Puerarin alleviated depression-like behavior and intestinal flora imbalance in rats, and significantly reduced the abundance of harmful bacteria. In addition, puerarin enhanced BDNF and IκB-α expression and inhibited NF-κB expression in the hippocampus. The potential mechanism of puerarin's antidepressive-like effects is closely related to the bidirectional communication of microbiota-gut-brain axis[26].

Shengmagen decoction, a traditional Chinese medicine compound with puerarin as its main bioactive ingredient, can alleviate depression-like behaviors in sleep-deprived mice. The main mechanism of action is to reduce the levels of TNF-α, IL-4 and IL-13, increase the level of melatonin, inhibit the p38 MAPK, STAT1 and NF-κB pathways, reduce the production of VEGF and inhibit the phosphorylation of ERK[27], In addition, puerarin treatment improved the depressive symptoms of diabetic mice, mainly by activating GLP-1R and phosphorylating the key Wnt signaling proteins β-catenin and mTOR, which are closely related to hippocampal neuroplasticity and depression. In addition, the phosphorylation levels of ERK and CREB were increased after puerarin treatment, which are essential for the survival of nerve cells. In addition, BDNF was also significantly increased, which protected nerve cells from damage. Puerarin also increased 5-HT content and decreased corticosterone content, IL-1β and IL-6 levels. GLP-1R/Wnt pathway also plays an important role in

the regulation of glucose metabolism in the body, and the dual effect of puerarin has certain unique advantages in the treatment of complications such as diabetes with depression[28].

Puerarin can improve sucrose preference and depression-like behavior in rats, mainly by inhibiting the TLR4/cPLA2/COX-2 pathway and reducing PGE2 production, thereby improving intestinal mucosal barrier dysfunction and neuroinflammatory damage. IL-6 and TNF-α are the two most studied proinflammatory markers in the blood of patients with major depression. Puerarin treatment reduced the levels of IL-6 and TNF-α in plasma and hippocampal tissue, significantly reduced inflammatory damage, and thus reversed depressive-like behavior[29].

Puerarin can improve the depression induced by LPS in mice. Puerarin reduces the inflammation and depression behavior of LPS-stimulated mice by inhibiting the RagA/mTOR/p70S6K pathway, weakening the accumulation of mTORC1 near lysosomes and reducing the production of pro-inflammatory cytokines IL-6 and IL-1β[30].

Puerarin effectively ameliorated depression and pain in neurological survivor (SNI) mice. Further mechanistic studies revealed the uniqueness of puerarin: puerarin significantly promoted the activation of CREB pathway, and puerarin induced the expression of BDNF rapidly and continuously. Collectively, these results suggest that puerarin may ameliorate SNI-induced depression and pain by activating ERK, CREB, and BDNF pathways. Puerarin can be used as a new lead compound for the development of new therapies for depression and pain comorbidities[31].

Puerarin treatment was effective in reducing the anhedonia and desperate behavior caused by chronic stress because puerarin improved sucrose preference and immovability time. In addition, the results showed that puerarin increased FGF-2 expression in the hippocampus. In contrast, infusion of the FGFR1 inhibitor SU5402 into the brain not only blocked the antidepressive-like effects of puerarin, but also abolished the effects of puerarin on hippocampal neurogenesis enhancement and neuroinflammation inhibition. These findings provide new insights into the mechanism by which FGF-2 / FGFR signaling is required to regulate neurogenesis and neuroinflammation for the antidepressive-like effects of puerarin[32]. The antidepressant effect of puerarin is mediated by α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor(AMPAR)-induced mTOR signaling pathway and is associated with increased BDNF release. In addition, GluR1 phosphorylation at its PKA site was significantly increased after puerarin treatment. The antidepressive-like effects of puerarin require activation of the AMPAR-mtor signaling pathway, correlate with increased BDNF levels and promote AMPAR, demonstrating that puerarin may have antidepressant properties mediated by the glutamatergic system[33].

4. Summary and Prospect

The natural product puerarin is a promising antidepressant candidate, and this article reviews the potentially relevant mechanisms of puerarin in the treatment of depression; however, there are many limitations in the study of the antidepressant effect of puerarin. Most of the current literature reports are based on animal or cellular models, and the relationship between targets and molecular mechanisms needs to be further studied. Given the depth of basic research on depression, we should actively promote the transformation of scientific results into practice, and strengthen the clinical research and treatment of depression. In addition, depression is a very complex disease, its pathological mechanism is still unclear, and its diagnosis and treatment methods are limited. Existing theories and hypotheses do not fully explain the pathogenesis of major depression. This article discusses the underlying mechanisms of current depression[11]. In addition to the monoaminergic hypothesis, we also discuss widely accepted theories, Including neuroendocrine hypothesis, HPA axis hypothesis, neuroinflammation hypothesis, neuroplasticity hypothesis and brain-gut axis hypothesis to discuss the potential etiology and pathogenesis of depression. A more complete understanding of the pathophysiology of MDD may significantly improve our ability to develop preventive and more effective treatments that can help reduce the burden and suffering caused by MDD. Understanding the cellular processes driving these changes and the symptoms they cause may provide key insights

into new therapeutic approaches [8]. All of these mechanisms are supported by evidence from clinical studies or animal models associated with major depression[13]. However, more details need to be further clarified in order to provide potentially better clinical treatment effects for the development of corresponding treatment methods.

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