Proceedings of the International Conference on Social Psychology and Humanity Studies
DOI: 10.54254/2753-7048/8/20230017

The Effect of Microglia on Depression

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Abstract: This paper focuses on the relationship between microglia and depression. Depression is affected by multiple structures, cells, and hormones, including the hippocampus, amygdala, hypothalamic-pituitary-adrenal axis, gut microbiota, stem cells, and glucocorticoids. This paper explores the relationship between microglia and structures, how these structural changes lead to increased concentrations of microglia leading to depression, and current treatment options for depression. Treatment options include drug therapy, electroacupuncture, and stem cell therapy. All of these treatments significantly impact the cure of depression and, at the same time, affect the overactivated microglia cells. It is concluded that the production of depression is closely related to microglial cells.

Keywords: microglia, neuroscience, psychology, depression

1. Introduction

1.1. The Basic Information about Microglia

Microglia is the only cell in neural tissue derived from mesoderm. The cell body is small and short rod-shaped. Microglia are few, accounting for about 5% of all glial cells. This cell is a phagocyte that settles in the brain. Under inflammatory stimulation, its antigenicity is enhanced, its morphology is extended, and its function is active. Microglia are found in all brain parts, and there are five times more microglia in gray matter than in the white case. There were more microglia in the hippocampus, olfactory lobes, and basal ganglia than in the thalamus and hypothalamus and the least in the brainstem and cerebellum. It also has some biological functions. Multiple synapses and plasticity characterize microglia. Microglia are necessary for the proper development of the nervous system. It regulates the number of neurons in the central nervous system.

1.2. The Basic Information about Depression

Depression is now the most common mental illness, with continuous and long-term low mood as the primary clinical characteristics, and is the most critical type of modern mental illness. Depression is the most common and disabling mental illness worldwide, with about 4.4% of the population suffering from depression. Depression has become the number one killer of human life, the fourth primary disease in the world. But the causes of depression are still unclear. The cause of depression is very complex and may be composed of genetic, biological, and environmental factors. The number of people worldwide suffering from depression has reached 322 million, accounting for about 4.4 percent of the total population. Until now, many people believed that personality defects cause

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depression and that the disease can be overcome by will, but ignore that mental illness stems from abnormal brain function.

1.3. The Basic Information of the Hippocampus

The hippocampus is located between the thalamus and the brain's medial temporal lobe. The hippocampus is a part of the limbic system and is mainly responsible for the storage and orientation of short-term memory. The hippocampus may relate to depression and nervousness. The hippocampus is also strongly associated with depression. There is evidence that the hippocampus volume is smaller in people with recurrent depression than in ordinary people. Because the hippocampus is an essential structure for storing memories and regulating emotions, people with depression are less able to control their emotions and memory.

1.4. The Basic Information of the Amygdala

The almond-shaped amygdala is part of the limbic system. It's the part of the brain that produces emotions, recognizes and regulates them, and controls learning and memory. The amygdala is generally divided into two parts, namely the basolateral nucleus group and the medial cortex group. Functionally, the amygdala is an essential structure for emotional learning and memory. In addition, it affects emotions. When the amygdala is stimulated, the organism experiences fear.

2. The Relationship Between Microglia and Depression

2.1. The Effect of Microglia Activation and Depression

When people are exposed to external stimuli such as craniocerebral injury and mental stress, microglia will be overactivated and show undesirable morphology. Microglia in the central nervous system release an excess of proinflammatory cytokines, which stimulate the formation of inflammatory cells. Overexpression of these proinflammatory factors can cause microglia to lose their ability to protect nerves, thus causing inflammation in the body. Experiments have shown that depressed patients have higher concentrations of proinflammatory cytokines than the average person, and when these subjects are treated with anti-inflammatory drugs such as ibuprofen and microglial proinflammatory cytokines are reduced, depression-like behaviors gradually decrease [1].

2.2. The Relationship Between Microglia and Hippocampus

One of the leading causes of depression is thought to be the loss of neurons in the hippocampus. In animal studies, antidepressant drugs have been found to promote neuronal cell regeneration in the hippocampus and reduce depression-like behavior in mice. The neuronal regeneration area in adult mammals' hippocampus mainly exists in the subgranular area of the dentate assembly of the hippocampus and the subventricular site of the subventricle of the forebrain. Because the overactivation of microglia leads to inflammation in the brain, it induces the differentiation and migration of neural stem cells [2]. In the chronic bondage experiment, the mice showed depression-like behavior. The morphology and number of microglia in the hippocampus of these mice were changed. In behavioral experiments, the knockdown of specific signaling factors and activators of transcription in microglia in the hippocampus of mice showed a decrease in depression-like behavior. Immunostaining cells in the dorsal anterior cingulate cortex of middle-aged suicidal individuals with depression revealed elevated concentrations of microglia at rest [3].

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2.3. The Relationship Between Microglia and Amygdala

The amygdala is located in the dorsomedial part of the anterior temporal lobe, the hippocampus, and a little anterior to the tip of the inferior horn of the lateral ventricles. Mainly through the lateral olfactory stria, stria terminals, and ventral amygdala efferent pathway, it has two-way interaction with the medial frontal lobe, orbitofrontal gyrus, septum, insomnia, preoptic area, hippocampus, hypothalamus, thalamus, striatum, temporal tegmental cortex, insular tegmental cortex, tectal cortex, temporal pole, motor cortex, and brainstem reticular structure. Functionally, the amygdala plays a vital role in the generation, recognition, and regulation of emotions, particularly fear, and in controlling learning and memory. Studies have shown that depressed patients experience varying degrees of atrophy in the amygdala's lateral and basolateral parts. Cell-specific transcriptional analysis showed that inflammatory mediators were released from both adjacent cells, the expression of chemokine two was selectively increased in microglia, and IL-1β was more expressed in monocytes [4].

2.4. Hyperactivation of Microglia

The main effect of microglia is to protect the nervous system, but overactivation can produce a large number of toxins. Due to excessive activation of Indoleamine (2,3) -dioxygenase, accumulation of quinolinic acid, a neurotoxic product, can lead to neurological disorders and neurodegenerative diseases. Gene-specific mutations in microglia lead to microglia hyperreactivity or hyperactivation of microglia. Overactivation of microglia activates IDO and leads to overactivation of microglia, which leads to toxin accumulation and ultimately leads to depression. Animal experiments showed that using IDO competitive antagonists reduced the inhibitory behavior of mice. If IDO activation induced by LPS induced by microglia was used, the depression-like behavior of the mice was aggravated [5,6].

3. The Relationship Between Microglia and the HPA Axis

The hypothalamic-pituitary-adrenal axis is an essential part of the neuroendocrine system. The limbic structure in the brain consists of three basic structures—the paraventricular nucleus of the hypothalamus, the anterior pituitary gland, and the adrenal cortex. There are a large number of neurons in the parathalamic nucleus that secrete two polypeptide hormones. These two polypeptide hormones play a vital role in regulating the human body. These two polypeptide hormones also act on the anterior pituitary gland and adrenal cortex. This causes the anterior pituitary gland to release adrenotropic hormone, which stimulates the production of glucocorticoids in the adrenal cortex. Glucocorticoids create negative feedback; that is, they act against the paraventricular nucleus of the hypothalamus and inhibit the production of two polypeptide hormones. A significant target of glucocorticoids is the brain's hippocampus, which is an integral part of regulating the HPA axis [7]. And depression formation and response and microglia activation have a great relationship. The HPA axis formed and released hormones are glucocorticoids. When individuals are chronically stressed, the HPA axis is continuously activated, which induces the HPA axis to release large amounts of glucocorticoids. With the release of a large number of glucocorticoids, the content of glucocorticoids in individuals gradually increases, thus inducing the activation of microglia. This causes microglia to release glucocorticoid receptors and halocorticoid receptors. Glucocorticoid receptors induce hippocampal neuroinflammation, which changes the hippocampal structure and can lead to depression. Microglia, rich in glucocorticoid receptors, can cause allergic reactions, leading to inflammation in the brain and depression-like behavior [8].

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4. Relationship Between Microglia and Intestinal Flora

Gut microbiota is normal microbes in the body that affect people's ability to resist various diseases and respond to multiple drugs. There are also many beneficial species in the intestinal flora that can participate in the metabolism of proteins and sugars. At the same time, vitamins, which are essential for human beings, will cause harm to the human body once lacking. Intestinal flora is divided into significant flora and minor flora. These bacteria are many living in the human gut and have specific physiological effects on the human body, which is indispensable to the human body. Secondary flora is highly mobile and may cause particular harm to the human body. They are all related to the microecological balance in the human body[9]. Experiments have found that if fecal samples from depressed patients are transplanted into germ-free mice, the mice will exhibit depression-like behavior. It has been found that SCFA produced by gut microbes during the degradation of dietary fiber affects microglia homeostasis in mice. In germ-free mice, microglia were reduced in number and functionally impaired. This results in impaired innate immunity in germ-free mice, which further affects their neural circuits. LPS induces microglial activation and influences depression-like behavior. But it was found that LPS failed to act in the gut of germ-free mice to cause depression-like behavior. This suggests that gut microbiota may be an essential mediator of LPS response to guide depression-like behavior.

5. Therapy

5.1. Electroacupuncture Therapy

Electroacupuncture, a usual traditional Chinese medicine treatment method, has been proven to have good clinical efficacy in treating depression. However, the specific mechanism of action still needs to be studied.

Nod-like receptor 3 (NLRP3) is a cytosolic pattern recognition receptor, often structurally expressed in microglia, and can promote a series of immune-inflammatory responses and inhibit neurogenesis. Inhibition of NOD-like receptors reduces depression-like behavior. Experiments showed that adult mice were stressed for one hour a day. After completion, the NLRP3 blocker MCC950 was injected, and electroacupuncture was used. After behavioral testing, the mouse hippocampus was dissected. The subgranular area of the dentate gyrus of hippocampus tissue was detected by immunofluorescence double labeling. The test results showed that the fluorescence intensity of NLRP3 and Iba-1 protein in the subgranular region of the hippocampus dentate gyrus was enhanced in the model group. In contrast, the fluorescence intensity of NLRP3 and Iba-1 protein in the subgranular region of hippocampus dentate gyrus was weakened in the experimental group. This suggests that electroacupuncture significantly inhibits microglial activity, which could also be used to reduce symptoms of depression [10].

5.2. Minocycline

Minocycline, also known as the marvel line, is a broad-spectrum tetracycline antibiotic. It can combine with tRNA to achieve the bacteriostatic effect. Minocycline has a broader antibacterial spectrum and antibacterial activity than similar drugs. The antibacterial range is identical to that of tetracycline. Minocycline probably plays an antidepressant role by inhibiting microglia from preventing central monocyte recruitment, thereby reducing IL-1β release. Minocycline is a candidate drug for treating neuroinflammation, which can cross the blood-brain barrier and has anti-inflammatory and neuroprotective effects. Minocycline can effectively inhibit the occurrence of depression in patients and animal models, and its mechanism is to prevent MG activation and value-added mediation. But minocycline also has several side effects. It may cause dysregulation of the gut

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microbiota and increase microglia activity. So minocycline doesn't solve the problem [11].

5.3. Inhibitory Effect of PARP14 on Microglia

PARP14 is one of 18 family members of poly-adenosine diphosphate-ribose polymerases (PARP), which clefts ADP-ribose from NAD+ molecules and transfers it to target proteins, Posttranslational single ADP ribosylation of the protein was realized. PARP14 affects the activity of microglia. Il-1βm RNA can cause hyperactivation of microglia, leading to brain inflammation. It was found that the mRNA and protein expression level of PARP14 in the hippocampus of the chronic stress mouse model was higher, and the mice showed depression-like behavior. Moreover, the mRNA expression of IL-1β in the hippocampus of mice increased. These results suggest that PARP14 promotes the overactivation of microglia, triggering inflammation in the brain and leading to depression-like behavior in individuals. If we try to knock down PARP14 expression in microglia, we may be able to reduce patients' depression-like symptoms [11].

5.4. Stem Cell Treatment

Stem cells are divided into totipotent stem cells, pluripotent stem cells, and unipotent stem cells. Stem cells have a solid ability to regenerate, reproduce and differentiate. Stem cells are more abundant in newborns, and most scientists take stem cells from the umbilical cord of newborns and culture them.

NSC stem cells were discovered in the human forebrain in the 20th century, and their role is to differentiate into various glial cells. It renews itself and produces new neurons and glial cells. The study found that NSC stem cells play a role in regulating mood in the adult hippocampus and may be able to cure depression. NSC stem cells also have many advantages. It is readily available and can be extracted from the forebrains of fetuses, infants, and adults. Second, it can migrate to areas where microglia cause inflammation.

The second is i PSC technology. The technique involves the introduction of a specific binding factor, such as transcription factor 4, which causes adult somatic cells to be reprogrammed into embryonic stem cells. Studies have shown great success with this technique for depression. It can induce the somatic cells of depressed patients so that the nerve differentiation of depressed patients is impaired and the proliferation of neuropluripotent stem cells is reduced. This method involves genome editing, which can be done to create many of the cell types we want. The technique holds promise for treating depression and relieving the suffering of those suffering from it [12].

6. Conclusion

The cause of depression is related to microglia. Activation of microglia increases the concentration in various parts of the brain, which can lead to depression. There is evidence that concentrations of microglia are much higher than usual in the brains of depressed patients and animal models subjected to chronic bondage. Many factors lead to microglia activation, and there is evidence that the imbalance of intestinal flora and the imbalance of HPA axis hormone may lead to microglia activation. Activation of microglia leads to changes in the hippocampus and amygdala, resulting in depressive behavior. This can reduce the size of the hippocampus, loss of emotional control, and memory loss.

Many treatments can be used to suppress the activity of microglia and the treatment of depression. The use of minocycline, traditional Chinese medicine electroacupuncture, and stem cell therapy listed in this paper are mainly put into clinical research. They all have a prominent role in the treatment of depression.

The focus and highlight of this paper are that we can find appropriate methods (various treatment methods mentioned above) to relieve the pain of patients with depression by studying microglial cells'

mechanism and action mechanism. In the future, this technology will be used, which gives doctors a new way of thinking about treatment and a new method of treatment. So we believe this is an up-and-coming technology. At the same time, the study of microglia on the mechanism of depression sheds new light on the further development of antidepressant drugs.

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