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Cuprizon - Induced MS Mouse Model of Breviscapine: The Role and Mechanism of the Study

Zou Yuan[1], Zheng Chin-Ri[2], Xu Junming[3]

[1]Graduate Student, PTSD and AD, Research Center of Biomedical Engineering, Kunming Medical University, Key Laboratory of Stem Cell and Regenerative Medicine, Yunnan Province, Kunming 650500, China
E-mail: 469380021[at]qq.com

[3]Graduate Student, Neural Stem Cells, Research Center of Biomedical Engineering, Kunming Medical University, Key Laboratory of Stem Cell and Regenerative Medicine, Yunnan Province, Kunming 650500, China
Corresponding author E-mail: *462492369[at]qq.com*

[2]Laboratory of Probiotics and Therapy Research, Institute of Biosciences, University of Botra, Malaysia (Sarden, Selangor, Malaysia 43400)

Abstract: ***Multiple sclerosis (Multiple sclerosis, MS) is a progressive, autoimmune disease of the human central nervous system (Central Nervous System, CNS) with myelin loss as the main pathological change. It is characterized by immune cell infiltration, myelin and oligodendrocyte loss and axonal injury. Studies have found that oligodendrocyte progenitor cell maturation disorder may be the main cause of myelin regeneration failure in animal models of multiple sclerosis, neural precursor cell transplantation can improve animal behavior defects by promoting myelin regeneration. Transplantation of neural stem cells (Neural Stem Cells, NSCs) for the treatment of neurological diseases has advantages that are not available by conventional treatment methods such as drugs and surgery. Hence, how to promote endogenous myelin regeneration is one of the main directions of MS research.***

Keywords: multiple sclerosis; breviscapine; neural stem cells

1. Introduction

Previous studies have found that breviscapine can improve the ability of spatial learning and nerve regeneration, and has the potential of small molecular drugs as regenerative therapy for neurodegenerative diseases. At the same time, there is growing evidence that glutamate (the main central nervous system excitatory neurotransmitter) plays a role in the pathology of multiple sclerosis in inflammatory demyelinating diseases. Therefore, in this study, we selected breviscapine, assuming that breviscapine reduces glutamate excitotoxicity by regulating glutamatergic system. Promote the differentiation, proliferation and differentiation of stem cells and the differentiation and maturation of oligodendrocyte precursor cells (Oligodendrocyte precursor cells, OPC) to oligodendrocytes (Oligodendrocyte cells, OL), thus playing a neuroprotective role. using a cuprizone -induced multiple sclerosis model, we treated it with breviscapine to investigate the effect of breviscapine on myelin regeneration, neural stem cells, progenitor cells, and neural lineage cells in adult mice and how to promote the mechanism of myelin regeneration.

1) Research status of multiple sclerosis

(Multiple Sclerosis) Multiple sclerosis MS) is a common inflammatory demyelinating disease of the central nervous system, It's good for young people, It is the main cause of adult neuropathic disability. Because of its high incidence, chronic course of disease and young and middle-aged predisposition, it has attracted much attention. According to the latest atlas released by the International Federation of multiple sclerosis, An estimated 9.5 per cent increase in the number of MS cases between 2008 and 2013, As many as 2.3 million [1] were affected. At present MS there is no effective radical therapy, Its treatment methods mainly include recurrence treatment, disease modification treatment and symptomatic treatment [2-4], The main clinical treatment is disease correction. MS pathological features are inflammation, Neuroglial hyperplasia, Demyelinating, axonal injury and synaptic loss [5]. MS plaques are localized demyelinating areas, Inflammatory cell infiltration varies, Mainly in the brain, [6] in the white matter of the spinal cord and optic nerve. The neurological dysfunction in MS patients was mainly caused by myelin loss, but there was significant spontaneous myelin regeneration in the early stage of MS. With the progress of the disease, myelin loss increased, myelin regeneration decreased, resulting in the decline of nerve function. Therefore, how to promote endogenous myelin regeneration is one of the main directions [8] MS research.

(Neural stem cells,) Neural stem cells NSCs) widespread in mammalian embryos and adult central nervous system, It is a kind of precursor cells with self-renewal ability and multi-differentiation potential, With self-replicating, Proliferation, Migration and differentiation into neurons, ability of oligodendrocytes and astrocytes [9]. neuronal loss [10] are often found after brain injury and in

neurodegenerative diseases. oligodendrocytes produce myelin, which can effectively carry out nerve conduction [11] in the central nervous system (CNS), respectively. Loss of astrocyte function and responsiveness leads to brain aging and neurodegenerative disease [12]. Therefore, the number of neurons, oligodendrocytes, and astrocytes may be key factors in assessing the ability of nerve regeneration. Neurogenesis occurs mainly in two regions of the adult brain, That is, the lateral inferior ventricular region (SVZ) and the subgranular region (SGZ) of the hippocampal dentate gyrus lining [13]. Significant compensatory neurogenesis in the hippocampal striatum and dentate gyrus was also found in neurodegenerative diseases [14-15], These findings provide hope for the development of new therapies.

The current treatment challenge is to find effective treatments to stop disease progression and reverse established nerve damage. Emerging disease-relieving immunomodulators (e.g., fingomod and dimethyl fumarate) cannot prevent progressive neurodegenerative processes. Therefore, cell replacement therapy aimed at overcoming neuronal cell loss and myelin regeneration failure and increasing endogenous myelin repair ability is considered an alternative treatment option. Stem cell-based therapies have emerged to solve this problem. At present, there are two main ways to repair the damaged central nervous system, one is the transplantation therapy [16] of stem / progenitor cells, the other is to activate endogenous repair and regeneration ability. therapeutic strategies utilizing endogenous NSCs have great potential because it avoids complex processes that generate exogenous NSCs, which involve lengthy differentiation protocol [17]. currently, available drugs and recombinant cytokines or soluble factors require in-depth investigation to exploit their potential to initiate endogenous myelin regeneration.

2) Neuroprotective effects of 2. breviscapine on multiple sclerosis

Natural compounds derived from medicinal plants have long been considered as a rich source of new therapeutic agents. Breviscapine, a bioactive flavonoid, is a herb widely used in many inflammatory diseases in traditional medicine. Breviscapine has the functions of clearing heat and detoxifying, bacteriostatic and anti-inflammatory, anti-oxidation, anti-allergic and anti-tumor, and central nervous protection [18-19]. Traditional Chinese medicine treatment has the advantages of less side effects and low toxicity. It can play a more comprehensive and three-dimensional therapeutic effect on diseases through its unique multi-target effect, especially in alleviating difficult and complicated diseases, and plays an irreplaceable role in western medicine [20-21]. Previous studies have found that breviscapine can improve the ability of spatial learning and nerve regeneration, and has the potential of small molecular drugs as regenerative therapy for neurodegenerative diseases. A large number of studies have shown that breviscapine has a significant neuroprotective effect on many neurological diseases, including Alzheimer's disease, Parkinson's disease and stroke dicyclohexanone-oxaloyl dihydrazone (Cuprizone) is the most common drug [22] used to induce demyelination.

Cuprizone is a copper chelator. Copper ketone model is [23] a model of toxic demyelination are 8 weeks old C57BL⁄6 mice fed with 0.2% copper ketone for 6 weeks leading to oligodendrocyte death and subsequent reversible demyelination. Spontaneous myelin regeneration [24] can be seen on the 4th day after copper ketone withdrawal. Suitable for demyelinating toxicity mechanism and therapeutic intervention. For this project, dicyclohexanone oxaloacetate dihydrazone (cuprizone,) is selected CPZ) To establish a mouse model of multiple sclerosis to study the effect of breviscapine on myelin regeneration, and the effect of breviscapine on the behavior of model mice and on hippocampal neural stem cells, progenitor cells and neural lineage cells.

3) Mechanism of Breviscapine's Neuroprotective Effect by Regulating Glutamaterin System

Neurogenesis is a multistep process that includes the proliferation, fate determination, migration and neuronal maturation of endogenous neural progenitor cells. Cell fate determines entry into neurons or glial cells is one of the key steps. Recently, various studies have shown that glutamate has [25] toxic effects in MS animal models. Glutamate is the main excitatory neurotransmitter in the central nervous system and plays a central role in the complex communication network between neurons, astrocytes, oligodendrocytes and microglia. A variety of abnormal triggers, such as energy deficiency, oxidative stress, mitochondrial dysfunction and calcium overload, may lead to abnormal [26] of glutamate signaling. thus, disorders of glutamate homeostasis may actually affect all physiological functions and interactions of brain cells, leading to excitotoxicity. Excitotoxicity is a pathological process in which glutamate overstimulation destroys or kills nerve cells. Although neuronal degeneration and death are the ultimate consequences of multiple sclerosis (MS), it is now widely accepted that changes in peripheral glial cell function are key features of disease progression. It occurs after excess extracellular glutamate accumulation in the central nervous system and subsequent excessive stimulation of glutamate receptors. almost all aspects of glutamate homeostasis are pathologically altered in MS, suggesting that glutamate excitotoxicity is an important mechanism in the pathogenesis of the disease.

Glutamate affects neuronal growth and maintains synaptic plasticity by N- methyl- D- aspartate receptors (N-methyl-D-aspartate receptor, NMDA-R), and is closely related to cognitive functions such as brain development regulation and learning and memory. NMDA receptors are of particular interest to pharmacologists, Because there are many ligand binding and regulatory sites, these sites provide potential therapeutic targets as control points and intervention points. Previous studies have shown that, NMDARs present in oligodendrocyte lineage cells (OLs), and damage to myelin under pathological conditions. This also shows that, NMDAR priority is in the OLs process,

actively involved in axon - OL interactions, and regulate OPC differentiation and myelin formation. Our previous findings suggest that, Breviscapine promotes neural stem cell proliferation, Inhibition of neural stem cell apoptosis, promote the proliferation and differentiation of oligodendrocyte progenitor cells and mature [27], Promote myelin regeneration, and then improved behavioral deficits in cuprizone-induced multiple sclerosis model mice. Therefore, we hypothesize that breviscapine can reduce glutamate excitotoxicity by stripping off the toxic components in NMDAR signal transduction outside synapses without affecting the normal physiological function of synapses. Activation of NMDAR signals promotes stem cell differentiation, proliferation and differentiation, OPC to OL differentiation and maturation, thus playing a neuroprotective role.

2. Research Significance

The study of the proliferation, differentiation and regeneration of neural stem cells in the central nervous system can provide scientific evidence for understanding the pathological characteristics of demyelinating diseases, provide strategies and ideas for understanding the pathogenesis and related regulatory mechanisms of demyelinating diseases, and have important theoretical and practical significance for the clinical diagnosis and treatment of demyelinating diseases. Simultaneous control of glutamate release and metabolism can provide a viable treatment to limit subsequent damage associated with excitotoxicity. Collaborative efforts to find potentially effective drugs in MS that work at non-immune sites or do not have exclusive immunosuppressive properties can be regarded as unconventional methods of disease management. however, compounds designed to antagonize the agonist effects of administration alone or in combination with other therapies on NMDA may provide real therapeutic prospects for patients with MS and cns-related diseases.

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