Progress in Molecular Biology Research on Neuropathic Pain

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Abstract: Neurogenic pain is a pain caused by damage and disease to the body's nerves. With the continuous deepening of molecular biology research, neuropathic pain is closely related to genes and cytokines. This article summarizes the genetic mechanisms of neuromolecular biology and elucidates the effects of related genes and cytokines on neuropathic pain

Keywords: Neurogenic Pain; Cytokines; Genes; Rheumatic Diseases

Introduction

When local tissue injury occurs, neuropathic pain is manifested as local pain. However, in diabetes virus infection, inflammatory reaction and autoimmune diseases, because the disease affects the somatic sensory nervous system, neuropathic pain is manifested as the widespread application of molecular biology of systemic pain and the extensive development of research on the correlation between cytokines and genes of neuropathic pain, which indicates that many gene expressions are involved in the pathogenesis of neuropathic pain, such as CXCR2, GRK1 Genes such as L12B and TNFSF8. Clinical studies have also found that genetic mutations and abnormalities can lead to neuropathic pain. In addition, the release of inflammatory factors and cytokines can also lead to neuropathic pain, and the involvement of cytokines before and after inflammation is also considered one of the causes of neuropathic pain.

1. The concept and treatment principles of neuropathic pain

1.1 The concept of neuropathic pain

Myeloid nerve fibers play an important role in the pathological mechanism of peripheral neuropathic pain. Sensory nerve fibers are a type of myelinated nerve fibers that can cause neuropathic pain in areas with peripheral and central skin sensory abnormalities. Examination of sensory nerve fibers is considered an important means of diagnosing sensory abnormalities in the body. Diseases of the nervous system itself, such as syringomyelia and demyelinating diseases, can lead to peripheral and central neuropathic pain.

Pathological neuropathic pain (NP) is a common disease that puzzles modern people. It is pain directly caused by the sensory nervous system injury of the trunk or diseases (such as cancer, trauma and diabetes). Most NP patients have persistent burning pain, compression or compression pain, stabbing pain or mechanical abnormal pain, and may be accompanied by induced pain, which is a common source of chronic pain [1]. If NP is not effectively improved, it can cause patients to experience low mood, sleep disorders, and seriously affect their quality of life . It is estimated that there are approximately 90 million patients with NP in China, and drug therapy is currently the main method. The most common drugs include anticonvulsants, antidepressants, opioid analgesics, and N-methyl-D-aspartate (NMDA) antihypertensive agents . Gabapentin is a type of ion channel receptor antagonist, currently used as a first-line medication for neuropathic pain. However, due to its psychological side effects, long-term use can make patients feel depressed, aggressive, and even increase the risk of suicide , and the long-term effects may not be as expected. The occurrence of NP is often related to nociceptive factors, and various factors such as peripheral nerve injury and inflammation can lead to the activation of spinal cord glial cells. Inflammatory mediators, cytokines, and other substances are released in large quantities, further activating glial cells

and promoting pain sensitization in central nervous system neurons, forming a positive feedback regulatory process that causes chronic pain to persist and not heal through neuroimmune regulation . Research has shown that epidermal growth factor receptor (EGFR) and its homologous receptors promote pain sensitization, inhibit EGFR, and strongly reduce inflammation and chronic pain in patients [2]. EGFR exhibits a genetic correlation with the development of chronic pain, and the importance of this pathway has been confirmed in mouse models of inflammation and chronic pain. Inhibition of EGFR can significantly reduce the harm caused by NP. Inhibiting the activation of EGFR can alleviate neuropathic pain and pain hypersensitivity to mechanical, thermal, and cold stimuli induced by chronic compression of the unilateral dorsal root ganglion (DRG) in rats. Clinical studies have shown that EGFR inhibitors, such as cetuximab, panizumab, gefitinib, and erlotinib, can improve NP, 2]. EGFR may represent a potential target for treating chronic compressive nerve injury (CCI) in rats. After binding with corresponding ligands, EGFR can activate multiple signaling pathways within the cytoplasm, including the PI3K/Akt signaling pathway. ChenYT et al. found that bimodulin induces cartilage damage during osteoarthritis by acting on EGFR to activate the PI3K/AKT pathway. AlaaeldinR et al. found that fatty acid glucosides inhibit inflammatory responses by inhibiting the EGFR/Akt/PI3K pathway. We used SPF grade Sprague Dawley (SD) male rats, weighing 250 or 300g[3].

The standard examination for patients with neuropathic pain should include the following aspects: touch, acupuncture, compression, cold stimulation, hot stimulation, tremor, and "sum". The response to these stimuli can be classified as normal, decreased, or enhanced pain perception. Stimulation induced (positive) pain is divided into hyperalgesia and anodynia, and is classified based on whether the stimulus is dynamic or static. You can evaluate tactile sensation by gently stimulating the skin with cotton, acupuncture sensation by stimulating the skin with sharp needles, deep pain sensation by gently pressing on muscles and joints, cold and hot sensations by measuring the response to warm stimuli, and tremor sensation by responding to the tuning fork.

1.2 Treatment principles of neuropathic pain

1.2.1 Medication treatment:

When using medication to treat neuropathic pain, the choice should be based on the basic pathogenesis of each patient. The drugs used to treat chronic neuropathic pain mainly include anticonvulsants, tricyclic antidepressants, N-methyl-D-aspartate (NMDA) antagonists, ion channel blockers, non-steroidal anti-inflammatory drugs (NSAIDs), local anesthetics, capsaicin receptor blockers, antihypertensive drugs, morphine like drugs, and GABA receptor agonists. In recent years, some new types of drugs have also emerged, such as gabapentin and anti-tumor drugs[4].

1.2.2 Neuromodulatory surgery:

The neuromodulation method of stimulating the spinal cord or motor cortex by placing electrodes in the epidural space or cerebral cortex has gradually been widely used to treat refractory central and peripheral neuropathic pain. The principle of this method is to stimulate the target nerve that can generate pain appropriately through electrodes, thereby generating a numb feeling to cover the pain area and achieving the goal of alleviating pain. Clinical indications: neuropathic pain (such as post back surgery syndrome, radiculopathy, chronic regional pain syndrome, and peripheral nerve injury), local ischemic pain (such as peripheral vascular disease and pharyngitis), seizures, Parkinson's syndrome related motor disorders (such as tremors, paralysis, rigidity, and motor disorders), and other functional disorders. The main methods of neural regulation include spinal cord stimulation (SCS) and cerebral motor cortex stimulation (MCS)[5].

2. Molecular biological mediators of neuropathic pain

Some special biological molecules are involved in neuropathic pain. Nerve injury can cause changes in mirna expression, as well as downregulation of potassium ion channels and glutamate transporters, leading to high expression of nerve growth factor. A series of mirnas were also observed in the dorsal root ganglia of the spinal cord, such as miR-182 and mir-96. Other studies have observed that the epigenetic modification of acute and chronic neuropathic pain proteins is mainly the methylation of histidine, while histone deacetylase can alleviate neuropathic pain. Neurological damage activates

peptide or non peptide genes, leading to the activation of G protein binding receptors and glutamate induced release. G protein binding receptors can also trigger peripheral immune cells.

In addition, synaptic transmission is mediated by glutamic acid amino acids, and this transmission is completed through special receptors AMPARS or NMDAR, indicating the correlation between central sensation and hyperalgesia. Most excitatory neurotransmitter transmission is completed by glutamate through special receptors AMPARS and NMDAR, and excitatory neurotransmitter transmission can be fast or slow. Male neuropathic pain is mainly caused by microglia, while female neuropathic pain is mainly caused by the invasion of T lymphocytes. In addition to excitatory neurotransmitters, glutamate is also considered the main transmitter of pain transmission, acting through metabolic or ionic receptors, which are mainly present in astrocytes, microglia, and oligodendrocytes. Research has confirmed that certain genes are associated with pain (such as those involved in the occurrence of pain in erythematous limb pain), mainly specific genes related to metabolic processes and ion channels, such as MPZ, PRKCA, GCH1COMT, and SCN11A[6].

3. A Study Model of Neurogenic Pain

A study has established an animal model of neuropathic pain using rats. This model is based on the detection of nerve damage at the ipsilateral sciatic nerve junction in the hind paws of experimental rats. After several hours of partial nerve damage, experimental rats may exhibit abnormal pain, spontaneous pain, and hyperalgesia. Another experiment is the L5/16 position spinal nerve ligation model in rats. The animal model mechanism is not entirely clear, but experimental rats can be recorded with long signals of mechanical abnormal pain and hyperalgesia. In addition, axonotomy is a clear model that causes neuropathic pain. The entire sciatic nerve is transected, which can project into the middle area of the rat's hind paw. Peripheral sensory neurons are responsible for multiple sensory inputs and are a mixed cell group, making it difficult to directly obtain peripheral sensory neurons for pain research. At present, a more advanced research method is to extract embryonic stem cells, use small molecule inhibition method to amplify functionally consistent sensory neurons from stem cells, and then simulate in vivo pathophysiology to study peripheral nerve injury.

4. Neurogenic pain related to 4 diseases

Diseases often involve the sensory nervous system, which can cause local neuropathic pain and sensory nerve conduction, leading to overall pain. Its characteristics are migratory and uncertain.

4.1 Pain in metabolic and rheumatic diseases

The interaction between axons and Schwann cells is the premise to ensure the integrity of nerve cells. Research shows that Schwann cell disease will lead to axon deformation. Single nucleotide adenosyltransferase is considered to play a key role in diabetes neuropathy. High or low glucose environment of diabetes can cause diabetes related neuropathic pain. Fibromyopathy often leads to loss of somatosensory nerves, but it has central nervous pain and changes in nerve conduction signals, causing small fiber neuropathy. For the diagnosis of rheumatic immune diseases, it is generally necessary to have symptoms of pain[7].

4.2 Pain caused by tumors

Neurogenic pain caused by tumors is receiving increasing attention. Chemotherapy drugs can cause neuropathic pain in tumor patients, while invasive growth of the tumor itself can also cause neuropathic pain. In the early stages of tumor development, its growth involves the nervous system, which can block nerve conduction, accompanied by inflammatory reactions and invasive nerve cell deformation. In the later stages, tumors often manifest as neuropathic pain caused by chemotherapy drugs

4.3 Pain in central system diseases

The blood-brain barrier is the main component that maintains the integrity of the nervous system, and any pathological injury can alter its permeability, causing damage to the central nervous system. The pathophysiology of thalamic pain syndrome in the damaged area of the central nervous system is very complex, distributed in the cerebral cortex, opioid

receptors, and long-chain fatty acid receptors. Post stroke pain is caused by the dysfunction of the spinal thalamic pathway, which is an ascending pathway for pain and warmth transmission in the spinal cord, in chronic neuropathic pain after central nervous system injury.

5. Summary

Neurogenic pain is a chronic disease state that is the result of multiple pathophysiological mechanisms and other metabolic pathways being interrelated. With the continuous deepening of molecular biology research, pain related genes and proteins are constantly recognized, and the mechanism of pain occurrence will become increasingly clear, providing a theoretical basis for pain treatment.

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