Review (Narrative)

GABA-related Synaptic Plasticity in Neuropathic Hypersensitivity

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SUMMARY

It was believed that the role of synapse was simply to send information between the neural network and the other nerve cell or the neuronal cell and the muscle cell. In addition, it was thought that these compounds that were made during the development were relatively strong, as did the solder joining of two electronic components. The thrilling development in neurobiology over the last 40 years has made it possible for most synapses to be extremely plastic. They can change their strength by their own actions or activities in another way. Synaptic structures such as active region, postsynaptic density (PSD) and dendritic spine are strongly correlated with their dimensions and correlate with synaptic intensity. Synaptic plasticity controls the communication between two neurons. The power of communication between two synapses can be compared to the state of the conversation. Neuropathic pain can be classified as peripheral or central to its genesis and is divided into episodic and persistent symptoms. Episodic neuropathic pain occurs during complete remission of the symptoms, while continuous neuropathic pain is a condition for continuous acute pain. Gamma-Aminobutyric acid (GABA) is the inhibitory neurotransmitter in the central nervous system (CNS), which has been identified functioning as an essential modulator of synaptic plasticity in the CNS development and degeneration. We hereby reviewed the role of GABA in synaptic plasticity in the context of neuropathic hypersensitivity.■

KEYWORDS GABA; Synaptic plasticity; Nerve injury; Neuropathic pain; Mechanisms

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THE actual incidence of neuropathic pain is unknown. It is estimated that 1-1.5 percent of the population suffer. Spinal cord, brain or spinal brain damage is less common than peripheral neuropathic pain (PNP). Hypermostypiapitis cervical pain (CNP) was reported in 28 percent of patients with multiple sclerosis, 75% of pollen disease, 60-70% of SCI patients, and 8% of stroke patients. Several sources such as blood vessel compression, radiation, infection, trauma, infection, exposure to neurotoxins and the peripheral nervous system can lead to pathological lesions. Demyelination and axotomy are a means of producing this damage. Several mechanisms have been proposed to explain but not completely understand the neuropathic states (1, 2).

Neuropathic pain develops as a result of lesions or diseases that affect the somatosensory nervous system either peripherally or in the middle. Examples of neuropathic pain include painful polyneuropathy, post-herpetic neuralgia, trigeminal neuralgia and post-pain pain (1). Clinically, neuropathic pain is characterized by persistent or blinding spontaneous pain and increased pain responses to adverse or deleterious irritants. Methods such as screening and evaluation focus on the occurrence and quality of neuropathic pain. Fundamental studies allow the identification of various pathophysiological mechanisms, and the clinical evaluation of symptoms and signs can be used to determine what mechanisms are involved in certain neuropathic pain disorders (3). Neuropathic pain management requires a multidisciplinary approach to medical care. A better understanding of neuropathic pain, and in particular the transmission of physiopathological mechanisms into organoleptic signs, leads to a more effective and specific therapeutic approach.

Synapses have a wide variety of plastic shapes that occur in a wide area of time. As soon as possible (in seconds per minute), relief, augmentation, strength, and depression produce rapid but transient changes in synaptic transmission. These plasticities modify the number of neurotransmitters released by presynaptic endings and are based on changes in Ca^{2+} signaling and synaptic vesicle species in recently active terminals. Durable forms of synaptic plasticity, such as LTP and LTD (3-5), are also based on Ca^{2+} and other intracellular interconnected transmitters. At least some of the synthetic changes produced by these long-term formulations are postsynaptic due to changes in the trade of neurotransmitter receptors, although changes in neurotransmitter release from the presynaptic terminal may also occur. These more robust forms of plasticity, protein phosphorylation, and gene expression modification far outweigh the cycle of synaptic activity and can produce changes in synaptic strength that remain within hours, days, or even more. Long-lasting synaptic plasticity can function as a nerve mechanism for many forms of brain plasticity, such as learning a new behavior or acquiring a new memory (1).

Chronic neuropathic pain syndromes are emphasized because these long-lasting and often disabling states present a much greater challenge to the clinician than acute pain. Peripheral neuropathic pain syndromes have received greater attention in the research literature than central nervous system pain, and study syndrome, such as postherpetic neuralgia and painful diabetic neuropathy, forms the basis for the modern understanding of neuropathic pain (4). Accurate estimates of the prevalence of neuropathic pain are not available, but chronic neuropathic pain can be much more common than commonly observed, and the prevalence is expected to increase in the future. There is considerable consensus that both peripheral and central processes contribute to many chronic neuropathic pain syndromes and that these various mechanisms can qualitatively explain the various symptoms and signs that patients experience. Existing therapies for neuropathic pain and the inability to provide relief to many patients have prompted ongoing studies investigating various approaches to the prevention of neuropathic pain.

Neuropathic pain can be very difficult to treat, with only 40-60% of those who are partially relieved (6). Adjuvants include certain antidepressants (tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors), anticonvulsants (gabapentin and pregabalin) and topical lidocaine. Opioid analgesics are considered useful, but are not recommended as first-line therapy.

A simplified but useful approach is to separate the processes from each other by the following relationship: nociceptive afferents increases firing primary; blocks the activity of neurons in the key structures (for example, due to loss of inhibitory neurons); and central processing (central sensitization) are modified to confirm and maintain normal sensory stability (3). PHN in the continuum seeks irritability one end and segregation in the second While continuity heads through a clinical examination and local capsaicin response results in an application can be distinguished, the impact of this difference in treatment is necessary to investigate the effects of other peripheral processes are not well known, for example, the sympathetic nervous system to facilitate abnormal after the primary permanent nerve damage and nerve injury and inflammation related during the acute phase of herpes zoster may be due to abnormal regeneration of receptor expression and the permanent loss of skin afferents patients with PHN mixture are tracked (6, 7).

SYNAPTIC PLASTICITY

Synaptic Plasticity change is occasionally the result of a change in the synthesis of neurotransmitter receptors. There are many underlying mechanisms that work together to achieve synaptic plasticity, including the number of

synapses in neurotransmitter changes released and changes in the efficiency (8).

The synaptic plasticity of excitatory and inhibitory synapses depends on the release of postsynaptic calcium. The first theory made by national psychologist Donald Hebb in 1949 was the idea that synaptic power to change and that this change depends on their functional level or inactivity. As the probable part of synaptic plasticity was in the warehouses, since become one of the most neuroscientific research subjects (8).

Neuroscientists talk about plasticity in the short and long term. Synaptic plasticity in the short term by changes in synaptic strength that occur in one second: the rapid adjustment will contribute to the importance of this link for the current setting of call volume, but return, "few time after the end of "normal" synaptic plasticity Taking minutes to hours, days, or years, long-term plasticity is a dominant model of how the brain stores information - in other words, our way of creating and memorizing new memories (8, 9).

Word plasticity has a lot to do with word with plastic, and the one who uses plastic or plastic knows that plastic is different from carbide or stone because it is flexible. Plastics bend and change and you can melt them and change their shape, you can customize them as you wish. The idea is that synapses, which are joints between neurons and other neurons, are a plastic feature. In other words, they are changing, mutating not in the genetic sense, but simply changing the form or functions within seconds, minutes, emotions, or even lifetime (9). A lot of people who believe that when you learn something when you encounter something, you will never forget what you will never forget because it is built into your brain by changing the structure and synaptic connections. This is what Synaptic Plasticity offers.

Homosynaptic Plasticity

There are two inherent or homosynaptic plasticity, synaptic synapse and synaptic relief. Synaptic depression and relief are not always synapses. Some synapses have one, but not the other, while some synapses are both. Another type of synaptic plasticity is called post-traumatic potentiation (9). This is an extreme example of relief that is defined as a sustained relative improvement in synaptic strength after a short bar.

Heterosynaptic Forms of Synaptic Plasticity

There are two types of homosynaptic plasticity, as well as two types of heterosynaptic plasticity. Before explaining heterosynaptic plasticity, it is important to study the synapses of the central nervous system. The central nervous system has three main categories of synapses:

- Axosomatic.
- Axodendritic.
- Axoaxonic.

Plasticity indicates that presynaptic inhibition and presynaptic release. Presynaptic blockade is not an esoteric phenomenon. It is very important in the cerebrospinal fluid and directs the diffusion of information to the higher brain centers. The functional potential of the presynaptic cell creates the postsynaptic cell of the EPSP (10).

Short-Term Plasticity

Short-term synaptic plasticity, in contrast to minutes and long-lasting, durable plasticity, lasts tens of milliseconds in minutes. Short-term plasticity can strengthen or weaken synapses. Short-term synaptic improvements are due to the fact that synaptic terminals release emitters better because of the increased likelihood of pre-synaptic action potential. Synapses are magnified for a short period of time as the number of packaged transmitters' increases in response to each operational potential. According to the chronology in which it operates, synaptic improvement is classified as specific nerve relief, synaptic enhancement, or post-tetanic potentiation (11).

Long-Term Plasticity

Long-term depression and long-term potentiation are two forms of long-term plasticity that last for at least one minute in excitatory synapses. LTD and NMDA-dependent LTP have been studied a lot and it has been found that binding of glutamate and glycine or D-serine is required to activate NMDA receptors. Synaptic synapses turned self-modifying, depending on the history of synapses. Recently, several attempts have been made to produce a complete model that would explain most forms of synaptic plasticity (12).

Long-Term Potentiation

A very durable form of synaptic plasticity is called long-term potential (LTP). These may be homosynaptic and heterosynaptic components. If a trip is repeated several times (eg every minute), the amplitude of the EPSP is constant. Tetanus produces post-static potentiation (PTP), which disappears after a few minutes. There is a very sustainable improvement of the EPSP (13). LTP has a voltage because it is a storage mechanism for memory. A certain postsynaptic neuron receives a synaptic input from several sources. There are traditional axosomatic and axodendritic synapses. These can be pathogens or inhibitors. In addition, synaptic responses may be mediated by inotropic and metabotropic receptors. Presynaptic cells can be modulated by presynaptic inhibition and presynaptic excretion. Keep in mind that each postsynaptic cell makes and maintains 10,000 contacts with other cells, and this module can be grouped into every billion cells in the nervous system (13, 14). It is this vast network of synaptic connections and the plasticity of each of these synapses that make the nervous system so special. It is very difficult to overesti-

mate the importance of synaptic transfer. It is important for the basic functioning of the nervous system and seems essential in learning and memory. In addition, changes in synaptic transfer appear to be essential for understanding various neurological disorders such as myasthenia gravis and Parkinson's disease. Synaptic transfer is essential for understanding mental health, such as schizophrenia, anxiety and depression. One of the main topics of neuroscience is to identify the specific transmitter systems associated with these brain diseases and to develop appropriate measures. Finally, most psychoactive drugs affect certain subtypes of synaptic transfer. (15)

NEUROPATHIC HYPERSENSITIVIT

One particular reason why pain develops in neuropathy is unknown. Several theories have been suggested. One theory is that nerve cells, if they can no longer give impulses or organoleptic messages, use spontaneous activity in the nerve cells, which the brain interprets as pain (1-5).

Unlike a disease that occurs as a result of a disorder, neuropathic pain occurs without any associated stimulation. Sometimes, neuropathic pain may be associated with exaggerated or high sensitivity to normal stimulation (such as light contact or feeling of clothing), and these feelings may be interpreted as inappropriate pain.

A particular reason why pain develops in neuropathy is unknown. Several theories have been suggested. One theory is that nerve cells if they cannot give any impulse or organoleptic messages use more spontaneous activity in neurons than the brain interprets as pain (9).

Unlike the pain that occurs in response to the disorder, neuropathic pain occurs without any associated stimulation. Occasionally, neuropathic pain may be a high or exaggerated sensitivity to normal stimuli (such as loose clothing touch or sensation) being connected and these feelings may be mistaken for pain (13).

Symptoms of neuropathic pain generally have negative and positive symptoms and organoleptic symptoms. Nonsensory neurological symptoms and signs depend on the cause and can independently affect pain and disability. Although the International Pain Relief Society neuropathic pain has been defined as "primary disability or primary dysfunction of the nervous system", several researchers have recently argued that integrating the concept of dysfunction makes this definition entirely vague and acceptable (6, 17). The proposed solution is to determine the neuropathic pain caused by the symptoms of the symptoms of the CNS or the peripheral nervous system (or both). Background factors include infection, trauma, metabolic disorders, chemotherapy, surgery, radiation, neurotoxins, hereditary neuro-degeneration, nerve compression, and inflammation and tumor infiltration. Neuropathic neurodegeneration, which refers to neurodegenerative disease, consistent with certain symptoms and signs, provides strong support. However, if no damage can be demonstrated, limitations of existing diagnostic techniques do not always allow the exclusion of neuropathic pain. Diagnosis of neuropathic pain is based on history, systemic examination, physical and neurological research and appropriate laboratory tests, including blood and serological tests, magnetic resonance imaging and electrophysiological studies. In some cases, biopsy of the nerves or skin is needed to make the neurons appear directly.

Sensitive back pain and sensory results for certain pathophysiological mechanisms with therapeutic effects are at an early stage. Clinical examinations of pain mechanisms are labor-intensive and require special equipment; they are not yet useful in routines. In pain diagnoses, it is also difficult to identify the specific mechanisms of neuropathic pain (17, 18).

Peripheral neuropathy causes various peripheral and central nervous processes that can affect permanent pain and abnormal feelings. Inflammation, repair mechanisms in response to neurons and damage to the adverse tissue reaction hyper-sensitivity-primary afferent norepine damage, a phenomenon known as peripheral sensitization. On the other hand, the central nerve cells were inoculated as in the neurons during the years of major functional changes; including space hyperactivity is called central susceptibility. Generally, these sensitizing phenomena are destroyed when the tissue is healed and inflammation is reduced. However, if the primary afferent function is permanently impaired due to injury or nervous system disease, these processes remain unchanged and may be very resistant to treatment (15, 18).

The strong or permanent loss of primary afferent fibers (differentiation) distinguishes peripheral neuropathic pain from another pain. Positive organoleptic phenomena (spontaneous pain, allodynia and hyper-algesia) that are characteristic of patients with neuropathic pain are likely to be manifested by many underlying factors such as ectopic impulse generator tools and neurotransmitters and their receptors and ion channels by de Novo (15). Immediate CNS damage may change sustainably, and in some patients there is a central nervous system neuropathic pain and dysesthesia, sensory therapy. Mechanisms that cause neuropathic pain in the central nervous system are still unclear.

Nonsensory neurological and musculoskeletal disorders can have a significant effect on overall disability. Symptoms and symptoms of the motor system include weakness, fatigue, hypotension, tremors, dystonia, spasticity, ataxia, apraxia and motor disorders. Other musculoskeletal support and symptoms: decreased trajectory, joint stiffness, spontaneous muscle spasms, local muscle pain and myofascial and triggering points. Although in animal models of neuropathic pain mechanisms, many still need to translate and amplify neuropathic pain syndrome, and the results of these models provide valuable information on various neuropathic pain events. Laboratory studies on humans are limited, but they support the idea that animal

models have pathophysiological mechanisms relevant to human neuropathic pain (17).

Distribution of GABA Receptor in the Central Nervous System

Gamma-aminobutyric acid (GABA) receptors are ion channels that are controlled by ligands (also called ionotropic receptors); while GABA receptors are G-linked receptors, also called metabotropic receptors. GABA is a centrally decentralized neurotransmitter in the CNS. As such, GABA limits the activity of neuron excitability in all brain regions. Excessive GABAergic signaling leads to sedation, amnesia, and ataxia, while a slight attenuation of GABA signaling causes excitement, anxiety, agitation, insomnia, and exaggerated responsiveness (14). GABA is synthesized in presynaptic neurons and stored in synaptic vesicles (17); the step of limiting the rate of the process is modulated by the activity of L-glutamic acid decarboxylase acid, an enzyme that promotes the synthesis of GABA. Through nerve activation, GABA is released from the vesicles in a synapse where it can act on postsynaptic receptors or degrade in extracellular space and activate the extracellular receptors of postsynaptic neurons. GABA is then removed from the extracellular space by GABA ladder located on presynaptic neurons and glial cells taking GABA cells in the absence of postsynaptic GABA receptors. Intracellular GABA levels are determined by the release of GABA between presynaptic vesicles and GABA delivery of GABA drivers.

To determine the quantitative distribution of the Gee amino acid receptor types (GABAA and GABAB) in the rat brain, an autoradiographic procedure can be used. Although the concentrations of the two receptor binding sites in some brain regions were similar, the GABAA sites were generally larger than the GABAB sites. The highest concentration of GABAA sites has been observed in prostate tissue, in the cerebellar layer of stomach cells, in the olfactory body and in the thalamic mediator (17). The highest concentration of GABA sites occurred molecular layer of the cerebellum. In addition, the globus pallidus, temporal cortex, posterior lateral thalamus, superior colliculus, pontis raphe magnus nucleus, spinal trigeminal region and gelatinous substance contained substantially GABA B sites as GABA sections. The physiological and pharmacological significance of this heterogeneity is not yet defined.

Changes of GABA Activities after Nerve Injury- Related to Neuropathic Pain

The production, release and activation of the neurotransmitter receptor will change dramatically in response to peripheral damage. Neurotransmitter changes act intracellular - second and third system and substances, such as nitric oxide involved in the expression of genes alter the immediate early genes, such as e-fos and c-micron may also play a role in the maintenance of the interactions of chronic Play pain protein synthesis (18).

A peripheral nerve fund can lead to the development of neuropathic pain. The International Association defines the study of neuropathic pain, pain that was initiated or caused by primary injury or disorders of the nervous system. Although it is generally accepted that this process can be chronic and long-term, it often remains undiagnosed after acute surgery. The peripheral and central nervous system shows significant variability in response to nerve damage (19).

The two major amino acid inhibitors found in the neutron spine, GABA and glycine, are both modified by nerve damage. GABA or glycine antagonistic dorsalhorn within the producing behavior pains such as mechanical allodynia, similar to the neuropathic pain, which is very visible contact with allodynia. The GABA block can also be recruited tacitly earlier (20). If the device is never injured, the GABA level in the back is lowered bilaterally. Back-end glycine-inhibiting neurons may also be more sensitive to massive neuronal discharges caused by neuromuscular injury resulting in the death of these neurons.

Balance Between GABA and Glutamate in the CNS

Like most things in life, balance is the key to the optimal functioning of the nervous system. GABA and glutamate are primarily soothing and stimulating neurotransmitters in the central nervous system and have an opposite effect. Despite their respective roles, GABA and glutamate have many compounds, including their existence on the same biological pathway (16, 20).

Under normal physiological conditions, the activity of glutamate and GABA is balanced. Under stressful conditions, such as inflammation or increased immune system, glutamate activity is increased. When the nervous system is functioning properly, the activity of GABA also increases to compensate for the acceleration of homeostasis restoration.

Glutamate is the precursor of GABA, which means that increasing levels of glutamate lead to an increase in GABA synthesis.

This "allostatic mechanism" is the body's attempt to restore your homeostasis and compensate for disturbing and balancing activities (21). Common disorders of the unbalanced system with glutamate concentrations above the GABA level are anxiety, overheating, sleep disorders and concentration problems.

Change in the GABA Glutamate Balance in Neuropathic Pain

Cortical degradation reflects the balance of acceleration and blockage. Glutamate is the most exciting pathogen and GABA is the most important inhibitory neurotransmitter in the mammalian shell. Changes in the metabolism of glutamate and GABA may play an important role in the con-

trol of cortex degradation (21). Glutamate is a metabolic precursor of GABA that can be traced back to the tricarboxylic acid cycle to synthesize glutamate (22). GABA synthesis is unique among neurotransmitters as it has two different rate regulating enzymes, glutamic acid decarboxylase. The need for a gene that is separated from two chromosomes for GABA synthesis is unclear. Both metabolic products of GABA are present in uniquely high concentrations in the human brain. Pyrrolidinone has a significant effect on the metabolism of GABA in the human brain (23). These two metabolites of GABA have anticonvulsant properties and can have a major impact on cortex degradation.

Despite the cause, the imbalance between glutamate and GABA can lead to symptoms. For a healthy and optimally functioning nerve, the balance of GABA and glutamate is essential (24, 25). Although GABA is the neurotransmitter glutamate in the central nervous system and most prominent, they are irreversibly linked by the same biochemical pathway and balance is the key (26).

CONCLUSIONS

Nociceptive pain is due to the detection of strong or harmful stimuli, including sensory nerves specialized in high-threshold, transmission of action potential spinal cord and next transmission alarm signal to the brain. However, clinical pain such as pain following nerve injury (neuropathic pain) is characterized by pain without stimulation, and nociceptive thresholds are reduced so that normally harmless stimuli produce pain. The development of neuropathic pain affects not only neuronal pathways, but also Schwann cells, ganglion cells of satellite cells of the peripheral immune system, spinal microglia and astrocytes. GABA-related synaptic plasticity is a potential underlying mechanism of nerve injury-induced neuropathic hypersensitivity. It is a promising way for the researchers to identify effective medications of this thorny problem.■

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