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The etiological contribution of GABAergic plasticity to the pathogenesis of neuropathic pain

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Abstract

Neuropathic pain developing after peripheral or central nerve injury is the result of pathological changes generated through complex mechanisms. Disruption in the homeostasis of excitatory and inhibitory neurons within the central nervous system is a crucial factor in the formation of hyperalgesia or allodynia occurring with neuropathic pain. The central GABAergic pathway has received attention for its extensive distribution and function in neural circuits, including the generation and development of neuropathic pain. GABAergic inhibitory changes that occur in the interneurons along descending modulatory and nociceptive pathways in the central nervous system are believed to generate neuronal plasticity, such as synaptic plasticity or functional plasticity of the related genes or proteins, that is the foundation of persistent neuropathic pain. The primary GABAergic plasticity observed in neuropathic pain includes GABAergic synapse homo- and heterosynaptic plasticity, decreased synthesis of GABA, down-expression of glutamic acid decarboxylase and GABA transporter, abnormal expression of NKCC1 or KCC2, and disturbed function of GABA receptors. In this review, we describe possible mechanisms associated with GABAergic plasticity, such as central sensitization and GABAergic interneuron apoptosis, and the epigenetic etiologies of GABAergic plasticity in neuropathic pain. Moreover, we summarize potential therapeutic targets of GABAergic plasticity that may allow for successful relief of hyperalgesia from nerve injury. Finally, we compare the effects of the GABAergic system in neuropathic pain to other types of chronic pain to understand the contribution of GABAergic plasticity to neuropathic pain.

Keywords

Gama-aminobutyric acid, plasticity, epigenetic, mechanism, neuropathic pain

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Introduction

The central nervous system (CNS) has numerous excitatory and inhibitory neurons that are crucial for the integration of somatosensory information.[1] Gama-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the spinal dorsal horn and brain of mammals.[2] GABA is excitatory in immature mammalians, while in mature mammals, it produces inhibitory effects in extensive areas of the CNS including the cerebral cortex, amygdala, hippocampus, and spinal dorsal horn.[3,4] Several recent behavioral and physiological studies indicate GABA synaptic inhibition plays an important inhibitory function in the transmission of nociceptive information in the spinal cord or brain,

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including neuropathic pain.[5–7] The GABAergic pathway starts with the release of GABA by presynaptic terminals, followed by transport via the GABA transporter, which regulates rapid removal of extracellular GABA and thereby ends its inhibitory synaptic transmission.[8] Thus, plasticity along the GABAergic pathway after nerve injury may be responsible for the generation and development of neuropathic pain.

Indeed, pain sensation represents an imbalance of the excitatory and inhibitory states in the CNS. Many factors contribute to GABAergic transmission and synaptic plasticity related to neuropathic pain. For example, in chronic constriction injury (CCI), increased apoptosis of GABAergic interneurons (GABAn) in the spinal dorsal horn plays a crucial role in the development of neuropathic pain. Apoptosis is the result of key proteins in mitochondrial apoptotic pathways being activated; inhibition of GABAergic interneuron apoptosis can suppress ongoing neuropathic pain.[9] Similarly, CCI rats show reduced GABA levels and decreased neuronal activity. Glutamic acid decarboxylase (GAD) is a key synthetic enzyme for GABA,[10–12] especially GAD67. Thus, GAD can act as a marker for GABA neurons, indicating their number and functional changes, and can also be used as a potential target of gene therapy for neuropathic pain.[13,14] Furthermore, GABA mediates synaptic inhibition by acting on its ionotropic receptor $GABA_A$ and metabotropic receptor $GABA_B$; both of these are also involved in the development of numerous neuropsychiatric disorders.[15] Neuropathic pain-induced hypersensitivity can be reversed by a $GABA_A$ receptor agonist, suggesting the importance of the GABAergic inhibitory pathway in the maintenance of chronic pain.[16] In addition, studies from the University of Texas MD Anderson Cancer Center[17,18] that consider paclitaxel-induced neuropathic pain indicate that it leads to reduced GABA-mediated membrane hyperpolarization, resulting in a depolarizing shift of spinal dorsal horn neurons by increasing the presence of the Na^+-K^+-$2Cl^-$ cotransporter-1 (NKCC1) protein, while traumatic nerve injury impairs GABA synaptic inhibition through K^+-Cl^- cotransporter-2 (KCC2) protein degradation. These neuropathy-related changes in GABAergic transmission are proposed to be associated with the epigenetic etiologies of neuropathic pain.[19–22]

`In this review, we discuss the current knowledge and advances of the role of the GABAergic system in neuropathic pain. We first describe the GABAergic transmission pathway in CNS inhibition and then focus on factors related to the modulation of GABAergic plasticity involved in neuropathic pain. The possible mechanisms underlying GABAergic plasticity for the onset or maintenance of neuropathic pain and therapeutic advances that focus on the GABAergic system are considered. Finally, the effects of the GABAergic system in other types of chronic pain are presented briefly.

GABAergic transmission in CNS inhibition

Developmental switch of GABAergic transmission from excitation to inhibition

Excitatory and inhibitory neurons in the CNS interact to maintain chloride and calcium homeostasis, which plays a crucial role in pathophysiological responses.[1,23,24] In the immature mammalian brain, GABA interneurons depolarize and become excitatory due to high intracellular chloride concentrations $[Cl^-]i$.[25] In mature neurons, an increase in synapses with upregulated expression of KCC2 and downregulated expression of NKCC1 lead to an increased chloride influx and postsynaptic hyperpolarization.[23,26] Therefore, KCC2 and NKCC1 are key factors in the developmental switch of the GABAergic system from excitation to inhibition. The early excitatory activity of GABA-promoted neuronal outgrowth and synapse formation in developing neurons, and the successful switch to inhibitory actions with maturation, allows for a more diverse and functional network.[25,27]

Synthesis, transport, and distribution of GABA in the CNS

The GABAergic pathway, glutamatergic neurons, and glial cells are metabolically interrelated.[15,28,29] GABA in the mammalian brain is primarily synthesized from GAD and released from interneurons in the spinal cord. GAD most often occurs in one of its two common isoforms, GAD65 and GAD67, which are encoded by the Gad1 and Gad2 genes, respectively. Studies have reported that GAD67 controls more than 90% of basal GABA synthesis, while GAD65 is crucial to inhibitory neurons releasing GABA.[30] Fractionation and immunohistochemical analyses reveal that GAD67 is distributed throughout the cell, and GAD65 is located preferentially near neuronal synaptic vesicles, suggesting that GAD65 is crucial to the release of GABA from the axon terminals.[31,32]

The GABA transmission system plays an important role in regulating the clearance of extracellular inhibitory transmitters and maintaining homeostasis in the CNS.[33] The metabolization of GABA depends on the catalytic action of GABA transporters (GATs), of which four main types are present: GABA transporter-1 (GAT-1), GABA transporter-2 (GAT-2), GABA transporter-3 (GAT-3), and GABA transporter-4 (GAT-4). GATs are typically located at the plasma membrane of neurons and near the astrocytes that transport extracellular GABA into the cell. A catalytic cracking reaction removes excess GABA to maintain

homeostasis.[33] The GABAergic inhibitory pathway produces inhibitory effects throughout the CNS, including in the cerebral cortex, amygdala, hippocampus, and spinal dorsal horn.[3,4] An innovative positron emission tomography paradigm was recently applied to reveal the exact distribution of GABA in healthy subjects for the first time.[34] In the mammalian spinal dorsal horn, GABA appeared in about 25%, 30%, and 40% of laminae I, laminae II, and laminae III neurons, respectively.[4]

GABA receptors: A fundamental factor of GABA-mediated synaptic inhibition

GABA receptors, the binding and interaction sites for GABA-mediating synaptic inhibition, include ionotropic receptors $GABA_A$ and $GABA_C$, and the metabotropic receptor $GABA_B$.[15] The $GABA_A$ receptor is a class of ligand-gated Cl^-channels of physiological and therapeutic significance that are commonly targeted by therapeutic drugs for anxiety disorder and other pathophysiological conditions and diseases.[35,36] Numerous experiments have indicated the binding sites of GABA are in the extracellular domain of $GABA_A$ receptors, which belong to the pentameric ligand-gated ion channel superfamily. $GABA_A$ receptors typically contain five subunits: two copies of the α subunit, two copies of the β subunit, and one copy of either the γ or δ subunit, which constitute different forms of one integration.[37,38] In contrast, the diverse $GABA_B$ receptors are primarily distributed in pre- or postsynaptic sites; they are part of the GTP-binding protein-coupled receptor family and mediate the long-term inhibitory actions of GABA by regulating the K^+ and Ca^{2+} channels.[39] $GABA_B$ receptors are heterodimers, consisting of two different subunits: $GABA_{B1}$ and $GABA_{B2}$.[40,41] $GABA_C$ receptor is one isoform of $GABA_A$ receptors, which is mainly expressed in the retina.

GABAergic plasticity: A critical modulator in the etiological mechanism of neuropathic pain

The plasticity of the GABAergic system provides extensive flexibility in neural circuits, allowing adaption to changing environments and maintenance of normal physiological activities. Diverse types of GABAergic neuron cells exhibit different characteristics, such as distinct anatomical locations, physiological characteristics, and capacities for plasticity.[42–44] Neuronal network dynamics, such as neural differentiation, migration, proliferation, and neurite outgrowth facilitation, are modulated by GABA synthesis, transport, release and reuptake, and GABA receptor composition.[45,46]

GABA-related synapse plasticity

A recent article reviewed both form and function of GABAergic synapses related to long-term plasticity.[44] The review indicated that an initial study showed plasticity in GABAergic synapses on excitatory neurons (heterosynaptic inhibitory plasticity) and on inhibitory neurons (homosynaptic inhibitory plasticity) in the form of long-term potentiation (LTP) and/or depression (LTD) of inhibitory postsynaptic potentials (IPSPs).[47] Subsequent studies using electrophysiological and molecular biological analyses revealed bidirectional GABAergic inhibitory plasticity in numerous areas of the brain including the neonatal hippocampus, lateral superior olive, deep cerebellar nuclei, brain stem, and in dopaminergic neurons of the ventral tegmental area.[48–51]

Homosynaptic inhibitory plasticity in the hippocampus and cortex have also been confirmed in several studies.[52–55] For example, one monosynaptic form of homosynaptic plasticity occurs when GABAergic inhibitory synapses from a single inhibitory neuron with a specific subtype to act on a postsynaptic excitatory neuron. These inhibitory neurons can change their activity strength in response to nociceptive stimulation.[53] Crucial factors of GABAergic synapses are those that regulate activity strength, including modulating the integration of inhibitory and excitatory inputs or responding to various input stimulation patterns. As a result, increased activity may enlarge the scope of functions that the GABAergic inhibitory-induced plasticity performs in different neuronal circuits. Activity patterns for homosynaptic inhibitory plasticity occur with different time and space during the modulation of neural circuits. In the immature hippocampus, a spike-timing-dependent LTP of inhibition (STD-LTPi) is induced by excited GABA postsynaptically; stimulation in afferent axons elicits an action potential 15 ms before postsynaptic firing, enhancing GABA postsynaptic currents onto CA3 pyramidal neurons, while stimulation in afferent axons elicit an action potential 15 ms after postsynaptic firing, leading to the depression of postsynaptic currents. Further investigations suggest these mechanisms lead to STD-LTPi, where this type of GABAergic plasticity is expressed presynaptically and fired postsynaptically.[54] In adult hippocampal slices, in vitro electrophysiology methods show a GABAergic inhibitory action is induced by hyperpolarization. In this condition, homosynaptic plasticity of GABAergic synapses is observed in the form of STD-LTDi dependency on postsynaptic Ca^{2+}-influx by voltage-gated Ca^{2+} channels and on depolarization induced by chloride influx on KCC2.[55]

Central sensitization is one of the most important mechanisms for maintain of chronic pain, including neuropathic pain. And LTD in spinal dorsal horn inhibitory

neurons is a crucial factor for central sensitization.[56] LTD of transmission occurred at the synapses of afferent neurons, many of which are GABAergic neurons. Decreased GABA level and GABAergic inhibitory transmission in the spinal cord after peripheral nerve injury is consistent to the LTD of GABAergic neurons.[10,57] On the other hand, some direct evidences revealed that intense afferent stimulation could induce LTP in excitatory spinothalamic tract neurons and LTD in inhibitory GABAn in the synaptic plasticity that occurs in neuropathic pain.[7,58]

Functional plasticity: Neuropathy-related changes in GABAergic transmission

Previous behavioral studies have revealed that after a nerve injury, maladaptive changes can occur in injured sensory neurons along the nociceptive pathway in the CNS, resulting in nociceptive phenotypes—spontaneous pain or pain hypersensitivity.[59] Among the changes, several studies have indicated that neuropathic pain is accompanied by a reduced GABAergic inhibitory function[9,16,60] (see Table 1 for a summary). Therefore, an understanding of molecular changes in GABAergic transmission and mechanisms plays a crucial role in understanding neuropathic pain. In the following discussion, we give an overview of molecular changes that occur in neuropathic pain.

GABA plays an indispensable role in control of neuronal excitability via control of homeostasis during neuropathic pain. Decreased GABAergic inhibition is an important component in neuropathic pain.[16] The GABAergic pathway starts with the release of GABA by presynaptic terminals; GABA is then transported via GAT to rapidly remove the extracellular GABA, leading to an end of the inhibitory synaptic transmission.[8] Thus, plastic changes along the GABAergic pathway after a peripheral nerve injury may be responsible for the generation and development of neuropathic pain.

Decreased synthesis of GABA. Many neuropathic pain conditions are associated with reduced synaptic inhibition, such as occurs with a decreased GABA level, since GABA is a key inhibitory neurotransmitter in the GABAergic transmission. GAD is the key regulatory enzyme in the synthesis of GABA. Both isoforms GAD65 and GAD67 are significantly reduced in various neuropathic pain models. For example, concentration of GABA and GAD65/67 in neuropils decreases in the ipsilateral dorsal horn of mice that have undergone a partial sciatic nerve ligation (PSL).[61] Furthermore, fluorescent microscopy reveals that GAD65 positive nerve terminals are decreased in the superficial spinal dorsal horn in CCI model rats.[64] In addition, a decreased level of spinal GABA in CCI model rats is related to a decline in GAD67 expression.[11] As noted above, GAD67 is thought to be responsible for >90% of basal GABA synthesis, whereas GAD65 appears to be crucial for inhibitory neurons to release GABA. In addition to these distinct functions, GAD65 and GAD67 are found in different locations in the CNS. For example, both are expressed in superficial spinal GABAergic neurons within different laminae: GAD65 is mainly distributed in laminae I–II, whereas GAD67 is abundantly expressed in deeper laminae.[65] Therefore, the functional reduction of GAD65/GAD67 in the CNS may play a role in the persistent hyperalgesia of neuropathic pain by decreasing levels of the inhibitory transmitter GABA.

Molecular changes related to GABA uptake in neuropathic pain. GABA is synthesized in presynaptic neurons, stored in the synaptic vesicles, and then released into the synaptic cleft. Therefore, GABA levels in the GABAergic transmission pathway depend on the release and uptake of GABA from the synaptic cleft. As noted above, specific GATs rapidly take up extracellular GABA and maintain cellular levels of GABA. Among the four isoforms of GATs (GAT1–4), GAT-1 and GAT-3 are both abundant in the CNS regions associated with nociceptive

Table 1. Expression of GABAergic plasticity-related molecules under various neuropathic pain models.

Pain models	Position	Forms of GABAergic plasticity	Reasons	References
CCI	ZI, Spinal cord,	↓GABA	GABAergic neuron apoptosis	9,16
SNL	Spinal cord	↓GABA neuron and dysfunction of surviving GABA neurons	Oxidative stress	60
SNI	Spinal cord	↓GABA	GABAergic neuron apoptosis	10
PSL	Spinal cord	↓GABA and GAD65/67	GABAergic neuron apoptosis	61
TNP	Trigeminal ganglion and Sp5C	↑NKCC1, ↓KCC2	NA	62
SCI	PO	Inability of $GABA_B$ receptor	NA	63

CCI: chronic constriction injury; SNL: spinal nerve ligation; SNI: spared nerve injury; SCI: spinal cord injury; PSL: partial sciatic nerve ligation; TNP: trigeminal neuropathic pain; ZI: zona incerta; Sp5C: trigeminal nucleus caudalis; PO: posterior thalamic nucleus; ↑: increased or upregulated; ↓: decreased or downregulated; NA: not available.

transmission. Hyperalgesia in the CCI model has been tied to a reduction in spinal GAT-1 and GAT-3 levels, leading to the depletion of spinal GABA from neuronal terminals.[66–68] In preclinic studies, intrathecal injection of SNAP5114, a selective GAT-3 inhibitor, created an antinociceptive effect in both neuropathic and inflammatory pain models.[68]

Expression of NKCC1 and KCC2 in neuropathic pain. Various mechanisms to maintain homeostasis occur in the CNS, including changes in the actions of neuromodulators, synaptic plasticity, and ionic concentrations and currents.[69,70] The GABAergic inhibition pathway acts as more than a modulator of neural network excitability. In the CNS, highly interconnected networks involving inhibitory neurons, electrical, and synaptic neurons provide an extensive range of physiological and anatomical properties propitious to modulating a broad neural network.[71–73] NKCC1 and KCC2 associated with GABAergic transmission contribute to the maintenance of homeostasis in the CNS. Indeed, many neuropathic pain models indicate notable changes in NKCC1 and KCC2 protein abundance. A recent study found that an impaired peripheral nerve affects the expression of NKCC1 and KCC2 in various areas, such as the spinal cord, dorsal root ganglia (DRG), primary somatosensory (S1) cortex, and ventral posterolateral (VPL) nucleus of the thalamus.[74] In the two months, following formation of a sciatic nerve lesion, mechanical and thermal hyperalgesia developed, accompanied by increased NKCC1 protein in the DRG, reduced KCC2 in the spinal cord, and later downregulation of KCC2 levels in the VPL and S1. Moreover, paclitaxel-induced neuropathic pain led to a reduced GABA-mediated membrane hyperpolarization that resulted in a depolarizing shift of neurons in the spinal dorsal horn via increased NKCC1 protein. In contrast, traumatic nerve injury impairs GABA synaptic inhibitory transmission by degradation of the KCC2 protein. Decreased spinal KCC2 expression is considered crucial for the initiation or maintenance of neuropathic pain, with the time since peripheral nerve injury determining the ongoing alteration of inhibitory signals.[75] Similarly, the downregulation of KCC2 is observed in the trigeminal nucleus caudalis (Sp5C) in trigeminal neuropathic pain. The application of voltage-sensitive dye-induced optical imaging of evoked synaptic responses reveals that downregulation of KCC2 changes excitatory currents by reducing postsynaptic GABA inhibition.[62] Taken together, this body of evidence suggests that NKCC1 and KCC2 play key roles in the initiation and/or maintenance of hyperalgesia in neuropathic pain.

Activity of GABA receptors in neuropathic pain. The neuropathy-induced decrease of GABA synaptic inhibition is largely due to the diminished ability of its receptors, ionotropic receptors $GABA_A$ and $GABA_C$, and metabotropic receptor $GABA_B$; these are involved in the onset of numerous neuropsychiatric disorders.[15] GABAergic inhibition results most frequently from the interaction between GABA and its activated receptors, which induces membrane hyperpolarization and decreases the frequency of action potentials. Indeed, GABA receptors have been found to be closely associated with neuropathic pain produced by several means. For example, a reduced expression of the δ subunit of the $GABA_A$ receptor was observed in substantia gelatinosa (SG) neurons in the spinal dorsal horn in CCI mice. The diminished GABAergic-related IPSPs in SG neurons suggest the $GABA_A$ receptor plays an important role in neuropathic pain. Hypersensitivity, such as tactile allodynia and thermal hyperalgesia, in normal rats can be produced by spinal injection of the $GABA_A$ receptor antagonist bicuculline or the $GABA_B$ receptor antagonist phaclofen.[76] In addition, transient allodynia is generated by application of a $GABA_A$ receptor antagonist that may disrupt GABAergic transmission in the basolateral nucleus of the amygdala.[77] Thus, reversal of the disrupted GABAergic pathway in basolateral amygdala could alleviate pain symptoms. These changes at the GABA receptor level that result in hyperalgesia related to nerve injury, combined with the antinociceptive effects of GABA receptor agonists, supports the hypothesis that GABA receptors are key components for the generation and maintenance of neuropathy hyperalgesia.

Mechanisms of neuropathy-related GABA plasticity

Central sensitization

Neuronal plasticity-induced activity-dependent central sensitization is widely involved in neuropathic pain development. In 1983, Woolf[78] proposed spinal central sensitization as a typical form of long-lasting synaptic plasticity in the spinal dorsal horn induced by nociceptive peripheral stimuli. Formation of central sensitization can facilitate nociceptive processing, leading to the amplification of input signals within the CNS and related pain hypersensitivity. Central sensitization provides a mechanism for several effects of hyperalgesia, including (1) why pain perception can be induced by A or C fibers with low threshold; (2) why pain perception can be aggravated by repeated stimuli at a fixed intensity; and (3) why extensive sensitivity can be observed outside the impaired nerve territory or beyond areas of tissue injury.[79–81]

Central sensitization in the CNS is activity dependent, and it can induce the establishment of both homo- and heterosynaptic potentiation typically triggered by a burst of activity in nociceptors.[82,83] Notability, heterosynaptic

facilitation is considered an especially prominent neuropathic change in central sensitization. During the development of neuropathic pain after peripheral nerve damage, responses to nociceptor-specific inputs may be enhanced through long-lasting facilitation of Aβ- or C-fibers with low threshold at different topographic locations. Classic LTP typically occurs on a single dendritic spine and is coactivated by two inputs. In contrast, heterosynaptic LTP refers to synapse plasticity that occurs by a change in synaptic strength that spreads from activated synapses to their non-activated neighbors. However, heterosynaptic facilitation may last for less time than homosynaptic LTP. Furthermore, as well as pre- and postsynaptic changes, central sensitization includes increased excitability in the postsynaptic membrane.[59] Moreover, multiple changes of neuronal plasticity during neuropathic pain are observed.

Neuronal plasticity is not restricted to the spinal cord; functional neuroimaging research has identified areas activated by noxious stimuli in the brain, including the nucleus accumbens, medial prefrontal cortex, insula, anterior cingulate cortex (ACC), periaqueductal gray, amygdala, rostroventral medulla, and locus coeruleus.[84] Of note, functional magnetic resonance imaging studies indicate that activated pain regions in the brain differ between acute nociceptive pain and chronic pain, and that similar noxious stimuli activate different pain areas in healthy subjects than in those experiencing chronic pain.[83,85]

Apoptosis of GABAn

Peripheral nerve ligation and central nerve injury both provoke apoptosis of GABAn, primarily in the spinal dorsal horn. The spinal cord injury (SCI) neuropathic pain model predicts decreased GABAergic inhibitory interneurons in the superficial spinal dorsal horn, and this is supported by the observation of decreased immunohistochemical staining of GAD65/67 and GAT-1. Although the cause and possible mechanisms of cell death are controversial, some studies regarding the effects of GABAergic interneuron loss in neuropathic pain provide insight. Specific deletion of functional N-methyl-D-aspartate type glutamate receptors in spinal nerve injury rodents reduces the loss of GABAergic neurons, providing evidence that glutamate excitotoxicity leads to cellular degeneration.[86] Different kinds of reactive oxygen species are responsible for distinct spinal synaptic plasticity in spinal nerve ligated mice.[7] Among the reactive oxygen species, behavioral and electrophysiological outcomes suggest that [O_2] can regulate both GABAn-LTD and spinothalamic tract neurons-LTP, while [OH] is primarily related to GABAn-LTD. In brief, the discovery of apoptosis, or loss of GABAn, in the superficial spinal dorsal horn contributes to neuropathic pain. This becomes an important origin for changes in the expression of related genes, or protein changing, leading to the reduced level of GABA, GAD65, GAD67, and GAT-1 induced by nerve injury. Therefore, further research into the mechanisms will be indispensable for revealing the causes of apoptosis in inhibitory neurons that is associated with neuropathic pain.

Epigenetic etiologies of GABAergic plasticity in neuropathic pain

Epigenetic mechanisms for neuropathic pain are rarely investigated. One potential epigenetic form is methylation and acetylation modification. Epigenetic changes in gene expression may have a vital function in ongoing neuropathic pain, through the regulation of transcription and the expression of involved pro- or anti-nociceptive genes.[19–22]

Methylation modulation. DNA methylation is a characteristic and early-formed epigenetic mechanism in mammals that is primarily responsible for the stable expression of functional genes related to complex physical changes.[87] In a latest clinical prospective study,[88] the ingenuity pathway analysis of genes with DNA methylated positions for both chronic postsurgical pain and Child Anxiety Sensitivity Index revealed an enrichment of several canonical pathways, including GABA receptor, which supports GABA hypofunction contributing to the maintenance of pain. DNA methylation triggered by methyltransferases (DNMTs) inhibits gene expression. Blocking nerve injury-induced DNMT3a may be a prospective adjuvant therapy for opioid use in management of neuropathic pain.[89] Further, several previous studies indicate that reduced GAD67 contributes to the downregulated spinal GABA of CCI rats, and that this central enzyme in the GABAergic pathway is coded by the gene GAD1 promoter.[10,11] In addition, there is some evidence that abnormal DNA methylation of the GAD1 promoter can regulate GAD67 expression in the psychotic brain.[90,91] DNMTs and methyl-DNA binding domain proteins (MBDs) are the primary regulators for DNA methylation. To confirm the relationship of DNA methylation and GAD67 expression in neuropathic pain, one recent study examined mRNA levels of GAD67, DNMTs, and MBDs in the CCI model.[92] DNMT3a and DNMT3b expression increased significantly, while MBD2 expression decreased; a reduced GAD67 expression and increased methylation of GAD1 promoter were also observed in the spinal dorsal horn in CCI rats on the 14th day postsurgery. These discoveries provide evidence for the hypothesis that decreased GAD67 resulting from abnormal DNA methylation of the GAD1 promoter may be closely related to the neuropathic pain of CCI. This suggests that DNA methylation may be involved in neuropathic pain through regulation of GABAergic inhibitory pathway.

Acetylation modification. Evidence accumulated from research on different animals suggests that abnormal transcription of nociceptive genes occurs in inflammatory or neuropathic pain as the result of altered acetylation or deacetylation of histone proteins.[93] Most studies indicate an increased expression or enhanced activity of histone deacetylases under inflammatory or nerve injury conditions. In addition, the activity of histone deacetylase enzymes affects neural modulation. Recent studies suggest that deacetylase enzymes are involved in epigenetic regulation during induction of acute or chronic pain.[94,95] For example, recent animal studies show that nerve injury can up-regulate histone deacetylase level, resulting in a decreased histone acetylation that contributes to the induction of pain. Likewise, histone deacetylase inhibitors can produce analgesic effects in the treatment of inflammatory pain or neuropathic pain by increasing acetylated histone protein.[96–99] The relationship between histone acetylation modification and GABAergic inhibitory plasticity has also been revealed in research on mechanisms. Decreased histone acetylation during neuropathic pain can result in decreased expression of GAD65 or GAD67, leading to reduced synaptic GABAergic inhibition.[100,101] In addition, epigenetic modification of KCC2 gene expression modulated by histone acetylation affects efficacy of GABAergic inhibitory neurotransmission in the spinal dorsal horn.[102]

GABAergic plasticity: A potential target for neuropathic pain treatment

Decrease the GABAergic neuron apoptosis

Increased apoptosis of GABAn after peripheral nerve injury has been observed in several animal investigations (see Table 2 for a summary). The reduced proportion of neurons with primary afferent-evoked IPSPs in the superficial spinal dorsal horn decreased by 17% and 28% in CCI and spinal nerve injury rats, respectively.[10] In addition, treating CCI rats with hyperbaric oxygen therapy at 2.4 atmospheres absolute for 1 h once every day for seven days can significantly alleviate mechanical allodynia by inhibiting GABAergic neuron apoptosis.[9] Application of the GAT antagonist tiagabine can also reverse neuropathic hyperalgesia induced by SCI, suggesting that reduced GABAergic neurons may play an important role in neuropathy symptoms.[103]

Return to the normal level of GABA and NKCC1/KCC2

GABA is the most important neurotransmitter in the inhibitory transmission pathway, making prominent contributions to the initiation and maintenance of nociceptive hyperalgesia that results from various kinds of nerve injury. Therefore, returning GABA to its normal levels for those experiencing neuropathic pain is a valuable therapeutic target for clinical treatment strategies in patients with neuropathy diseases. In animal research in PSL mice, physical exercise was found to relieve hyperalgesia by suppressing the process of GAD65/67 reduction of GABA related to PSL, and thus protected the GABA level between interneurons and neuropils in the superficial spinal dorsal horn.[61] Systemic injection of donepezil exerts antinociception in spinal nerve ligated rats by increasing spinal extracellular acetylcholine concentration, leading to the elevation of GABA release in the spinal cord.[105] In another study, the efficacy of spinal cord stimulation was associated with an increased expression level of GAD65, reflecting an augmented GABA release following spinal cord stimulation. In addition, in order to confirm whether increasing the level of spinal GABA is effective for central neuropathic pain produced by SCI, a herpes simplex virus vector with GAD67 coding was transduced to the DRG in SCI rats. Results suggest that herpes simplex virus-induced gene transfer to the DRG may be a promising therapeutic measure in neuropathic pain after SCI by increasing GABA synthesis.[110]

Upregulated NKCC1 and downregulated KCC2 in various regions, such as the spinal cord, DRG, S1, and VPL, after different kinds of nerve injury are largely responsible for the maintenance of homeostasis in the CNS. Indeed, many preclinical studies have confirmed an important role for the reversal of NKCC1 and KCC2 expression in the treatment of neuropathic pain. Several interesting studies indicate physical exercise, including increasing-intensity treadmill exercise, performed in the early postinjury period can improve functional recovery after nerve injury. The mechanism for this effect may be a blocking of the dysregulation of NKCC1/KCC2 and the collateral sprouting that takes part in the early stages of nerve injury recovery.[104]

Activation of GABA receptors

GABA exerts antinociceptive effects by binding with the GABA receptors on postsynaptic membranes; this is indicative of the crucial role that the activity of GABA receptors plays in neuropathic pain. In CCI rats, microinjection of a $GABA_A$ receptor agonist (muscimol) into the zona incerta can lead to alleviation of pain hypersensitivity induced by a damaged peripheral nerve.[16] In the rat model for chronic compression of the DRG, spinal application of $GABA_A$ receptor agonist muscimol (5 nmol) or $GABA_B$ receptor agonist baclofen (25 nmol) successfully suppresses both mechanical hypersensitivity and spinal wide-dynamic-range neuronal excitability.[107] Moreover, in a mechanical study on the intrathecal

Table 2. Therapeutic advances targeting on GABAergic plasticity in neuropathic pain.

Drugs	Targets and areas	Neuropathic pain models						
		CCI	SNL	SNI	SCI	PSL	CCD	CPSP
HBO	↓GABAergic neuron apoptosis, spinal cord	2.4 ATA for 1 h once for seven days, ↓mechanical allodynia[9]	NA	NA	NA	NA	NA	NA
Physical exercise	↑GAD65/67, GABA, spinal cord	NA	NA	NA	NA	↓mechanical allodynia[61]	NA	NA
	↑KCC2,↓NKCC1, DRG	NA	NA	NA	NA	↓mechanical allodynia[104]	NA	NA
Donepezil	↑GABA release, spinal cord	NA	ip., ↓mechanical allodynia[105]	NA	NA	NA	NA	NA
Muscimol	Activation of $GABA_A$, spinal cord	NA	NA	i.t., ↓mechanical allodynia[106]	NA	NA	i.t., ↓mechanical allodynia[107]	NA
Baclofen	Activation of $GABA_B$,Spinal cord	NA	NA	NA	i.t., ↓thermal hyperalgesia[108]	NA	i.t., ↓mechanical allodynia	NA
SNAP5114	Activation of $GABA_A$ and $GABA_B$ receptors, spinal cord	i.t., ↓mechanical allodynia and thermal hyperalgesia[68]	NA	NA	NA	NA	NA	NA
14,15-EET	Activation of AP-$\delta GABA_A$ pathway, VPL	NA	NA	NA	NA	NA	NA	intrathalamic, ↓mechanical allodynia[109]

CCI: chronic constriction injury; SNL: spinal nerve ligation; SNI: spared nerve injury; SCI: spinal cord injury; PSL: partial sciatic nerve ligation; CCD: chronic compression of dorsal root ganglion; CPSP: central post-stroke pain; HBO: hyperbaric oxygen therapy; ATA: atmospheres absolute; DRG: dorsal root ganglion; EET: epoxyeicosatrienoic acid; AP: allopregnanolone; VPL: ventral posterolateral nucleus; i.t.: intrathecal; ip.: intraperitoneal;↑: increased or upregulated; ↓: decreased or downregulated; NA: not available.

application of SNAP5114, a selective GAT-3 inhibitor, an antinociceptive effect occurred via activation of both $GABA_A$ and $GABA_B$ receptors.[68] Except in peripheral nerve injury, increasing the activation of GABA receptors also plays a role in neuropathic pain related to a central lesion. In central post-stroke pain rats, intrathalamic application of exogenous 14,15-epoxyeicosatrienoic acid into the VPL nucleus can attenuate mechanical allodynia through the allopregnanolone (AP)-$\delta GABA_A$ signaling pathway.[109]

Effects of the GABAergic system in other type of chronic pain

Given existing evidence regarding the contribution of the GABAergic system in neuropathic pain models, we are interested in looking for GABAergic inhibition that may be related to other types of chronic pain, such as inflammatory pain, bone cancer pain, or chronic visceral pain. In complete Freund adjuvant-induced chronic inflammatory pain mice, there are no changes in the protein levels of $GABA_A$ subunits, but reduced GAT expression is observed in the ACC.[111] Cancer-induced bone pain (CIBP) is a challenge in patients with advanced cancer. Zhou et al.[112] provide the first evidence suggesting downregulated $GABA_B$ in the spinal dorsal horn plays a role in the development and maintenance of CIBP. Furthermore, in one kind of chronic visceral pain—zymosan-induced cystitis in both neonatal and adult rats, a decreased expression level of spinal KCC2 and vesicular GAT occurs relative to the control group. In addition, hypersensitivity is improved by an miR-92b-3p inhibitor through upregulation of spinal KCC2 and GAT, indicating an important role for the spinal GABAergic system in zymosan-induced cystitis.[113] In summary, research on the GABAergic system in chronic inflammatory, CIBP, and chronic visceral pain is limited, but existing studies suggest partial roles and mechanisms that depend on GABAergic plasticity in the spinal cord and ACC. Therefore, further investigation is warranted on more potential mechanisms of GABAergic plasticity.

Concluding remarks

Electrophysiological and molecular biological changes of the central GABAergic inhibitory pathway contribute to neuropathic pain. Many researchers have focused their attention on the GABA-modulated mechanism of neuropathic pain following nerve injury. We review evidence in behavioral research that reveals the GABAergic pathway effects on the generation and development of the neuropathic pain threshold by testing the expression of related factors, such as GABA, GAD, GAT, KCC2, and NKCC1, which play important roles in the GABAergic pathway. The patterns of GABAergic inhibitory plastic synapses are broadly divided into synaptic plasticity and functional changes in GABAergic system molecules. In addition, we present potential GABAergic plasticity mechanisms related to neuropathic pain, including central sensitization, apoptosis of GABAn, and epigenetic etiologies of GABAergic plasticity. Neuropathy-related changes in GABAergic inhibitory plasticity that occur with neuropathic pain lead to decreased inhibitory potential in the spinal dorsal horn, disturbing homeostasis and playing a crucial role in neural circuit activity. Thus, therapeutic measures in light of the GABAergic system are shown in our review to provide some insight for the readers. Finally, we briefly look for features of the GABAergic system in other types of chronic pain for increased understanding and knowledge.

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