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Schwann cells and trigeminal neuralgia

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Abstract

Schwann cells are components of the peripheral nerve myelin sheath, which supports and nourishes axons. Upon injury of the trigeminal nerve, Schwann cells are activated and cause trigeminal neuralgia by engulfing the myelin sheath and secreting various neurotrophic factors. Further, Schwann cells can repair the damaged nerve and thus alleviate trigeminal neuralgia. Here, we briefly describe the development and activation of Schwann cells after nerve injury. Moreover, we expound on the occurrence, regulation, and treatment of trigeminal neuralgia; further, we point out the current research deficiencies and future research directions.

Keywords

Schwann cells, trigeminal neuralgia, brain-derived neurotrophic factor, nerve growth factor, P2X receptor

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Introduction

Trigeminal neuralgia (TN) is a severe type of paroxysmal neuralgia that occurs in the distribution area of the facial trigeminal nerve. The patient experiences a series of painful symptoms and sensations, such as knife cutting and needling, which are among the most painful. It has a reported annual incidence of approximately 12.6 per 100,000 with symptoms on the right side having a higher incidence than those on the left.[1] Further, it has a higher incidence among women than among men.[1–3] Currently, the etiology and pathogenesis of TN are not unified, and the trigeminal nerve demyelination theory is considered the pathogenic basis of TN.[4] The treatment for TN includes therapeutic and surgical interventions. Carbamazepine and Oxcarbazepine are the most commonly used drugs, and surgical treatment includes microvascular decompression and gamma knife therapy, and traditional Chinese acupuncture also has curative effect on TN.[5–8]

Schwann cells (SCs), which are derived from neural crest cells, are the cells responsible for forming the myelin sheath of the trigeminal nerve. They can secrete various neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin 3, and neurotrophin 4/5, and can produce extracellular matrix proteins such as matrix metalloproteinase 9[9]; they play a role in neuron nourishment. In addition, they are involved in the pathogenesis and healing process of neuropathic pain.

Overview of SCs

SCs, which are glial cell types, are mainly distributed in the peripheral nervous system. They migrate and differentiate from neural crest cells and develop into precursor SCs that enter the SC lineage.[10] Recent studies have reported an association between the upregulation of transcription factor sox2 and the entry of neural crest precursor cells into the SC lineage.[11–13] In addition, transcription factor FoxD3 might be an important factor for the differentiation of neural crest cells into the SC lineage. This is because its expression inhibits the development of neurons and melanocytes, which are the other

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differentiation lineages of migrating neural crest cells.[14] In addition to proliferation and differentiation of neural crest cells into the SC lineage, sox10 also regulates the myelination of SCs.[15] These transcription factors might affect TN by regulating SC regeneration and myelin formation.[12,16,17] With extensive cell proliferation and differentiation, the SCs separate the axons into bundles, a process known as "radial sorting." Here, the SCs wrap around the axons and separate them into small bundles. At this time, SCs are divided into either myelinating or nonmyelinating SCs. Nonmyelinating SCs, which are also called Remark SCs, retain the ability to proliferate and differentiate.

As an important component of the peripheral nerve myelin sheath, SCs play an important role in the structure and composition of peripheral nerves. SCs can provide support and nourishment of peripheral nerve axons through the release of various cytokines that regulate axon growth.[18,19] Furthermore, they play a vital role in the growth and regeneration of peripheral nerves. The activity of SCs is affected by their interaction with axons.[14,18] SCs are closely related to the physiological states of nerve axons and they mutually interact[18]; so, a change in one side inevitably affects the other. Therefore, peripheral nerve injury that causes pain affects SCs,[18,20] and SCs play a significant role in neuropathic pain.[9,21] SCs have a complex signaling system involved in the production and regulation of neuropathic pain, as well as damaged nerve repair, by releasing numerous NGFs.[9]

SC activation

SCs up- or downregulate related genes to allow adaption to tissue injury and promote injury repair.[9,14] After peripheral nerve injury, myelinating and nonmyelinating SCs convert into repair SCs in order to promote nerve repair and regeneration.[9] This phenotype shift, known as SC activation, involves downregulation of myelin-related genes and upregulation of some neurotropic factors. SC activation has both positive and negative effects on pain conduction. A study has reported an increased level of BDNF after inferior alveolar nerve injury, which corresponds to the pain occurrence; contrastingly, the levels decrease with laser treatment, which corresponds to pain reduction. BDNF upregulation has been proved to be involved in the occurrence or conduction of TN; NGF upregulation is helpful in the improvement of pathologic neuralgia.[22] In conclusion, the substances released by the activated SCs include those that produce or promote pain as well as those that reduce it.

SCs undergo demyelination and rapidly downregulate myelination-related genes, including Egr2, cholesterol synthase, structural protein P0, and myelination basic protein.[23]

Furthermore, there is an upregulation of related SC-derived molecules, including L1, P75, and glial fibrillary acid protein.[9,14,20,24] Here, a new cell phenotype that is different from that of precursor and immature SCs is formed.[9] Upregulated genes include neurotrophic factors and surface proteins that promote axonal elongation and survival of injured neurons, such as glial cell line-derived neurotrophic factor, BDNF, and neurotrophin 3,[25] and immune response-related cytokines, including tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), leukemia inhibitory factor (LIF), and monocyte chemotactic protien-1 (MCP-1).[9,20,23] A recent study reported a significant upregulation of proteins related to purine metabolism after activation of SCs.[26] As described below, this is probably related to pain hypersensitivity following nerve damage.

SCs and production of TN

The relation between SCs and TN mainly involves two aspects. After trigeminal nerve injury, axons degenerate and demyelinate due to compression or inflammation.[27] Activated SCs destroy the myelin sheath and engulf axon fragments and the detached myelin sheath, which leads to TN.[28,29] Otherwise, activated SCs secrete molecules that induce hypersensitivity to pain, which leads to a decreased pain threshold that triggers TN.[9,14]

Trigeminal nerve demyelination, which is considered an important cause of TN, is caused by trigeminal nerve injury;[30,31] meanwhile, neurons in the trigeminal semilunar ganglion are activated to form the ignition focus.[32] Upon compression or inflammation-induced stimulation of the peripheral branches of the trigeminal nerve, these neurons are activated and produce abnormal impulses. The outgoing impulse from the center can also be transformed into an abnormal afferent impulse, too.[33] Following a short-circuit through axon demyelination and repeated superposition, the positive feedback amplifies impulses and generates a strong discharge phenomenon, which is clinically manifested as the production of severe pain by mild stimulation.[32,34]

SCs are important factors in trigeminal nerve demyelination. Following nerve injury, SCs are activated and acquire the ability to differentiate and phagocytize.[9,15] The activated SCs not only lose their original ability to maintain the myelin sheath but also begin to degrade and engulf it.[20,35] Myelin degradation is generally considered to occur in two stages. During the early stage of injury, only SCs remove myelin.[20] Subsequently, with the secretion of a large number of macrophage chemokines by SCs, macrophages join in the myelin removal. Myelin removal can reduce compression injury during nerve regeneration and eliminates potential myelin regeneration inhibitors.[15] However, demyelination inevitably causes TN.[36]

As aforementioned, activated SCs regulate the expression of several molecules, including those associated with TN. In addition to the expression of pain-causing molecules, SCs can act as pain signal transducers by receiving pain signals, releasing the corresponding molecules, and participating in pain conduction.

Calcitonin gene-related peptide (CGRP) is an important neuropeptide that is mainly found in the trigeminal ganglion (TG) and spinal dorsal root ganglion and is synthesized and released by sensory neurons.[37] It promotes central excitability through inhibition of substance P (SP) degradation and prolongs SP-induced local neuroinflammation and pain in tissues. Further, CGRP can promote injured nerve repair.[38,39] There have been recent reports of CGRP receptors on SCs in the peripheral nervous system.[40] The fact that CGRP is an important neuralgia-causing substance suggests that SCs play an important role in TN pathogenesis and the nerve repair process. Studies have reported an upregulation of CGRP expression in the axon proximal to the nerve injury[38]; further, CGRP has been reported to reduce the pain threshold, which causes TN.[41] Moreover, denervated SCs secrete matrix metalloproteinase, which leads to CGRP release and TN aggravation. Given the presence of CGRP receptors on SCs, prolonged exposure to CGRP, e.g. after nerve damage, increases release of IL-1β,[39] which induces hypersensitivity to pain and subsequently pathologic neuralgia.[42]

SP is widely found in the peripheral nervous system and is an important molecule that mediates the production and conduction of pain; moreover, it plays an important role in neuropathic pain.[43] Its biological function is mediated by the activation of three different neurokinin (NK) receptors, namely, NK1, NK2, and NK3, and has a preferential affinity for the NK1 receptor.[44] Large amounts of SP can directly induce sensory neuron excitability, which leads to hyperalgesia.[43] SP, which is the main messenger of harmful information, can be synthesized by TG cells and delivered to the trigeminal sensory nucleus and the peripheral head and face through central and peripheral synapses, respectively.[45,46] Studies have reported that after nerve injury, SCs synthesize and release NGF, which can promote SP synthesis.[47] Moreover, treatment with SP receptor blockers can alleviate TN caused by infraorbital nerve injury.[43] As the upstream SP signal source, activated SCs release a series of neurotrophic factors, cytokines, and extracellular matrix, which can increase the local SP levels and cause TN.

SCs and the TN regulatory mechanism

There is currently great interest in the adenosine triphosphate (ATP)-induced pain theory in the field of neuropathic pain. Briefly, abnormally increased extracellular ATP causes glial cell activation and transmits pain signals through purine cell membrane receptors.[48–51] ATP receptors are divided into P1 and P2 receptors; further, P2 receptors are divided into P2X and P2Y subtypes.[50]

The P2X receptor is an ion channel-type receptor whose most common agonist under physiological conditions is ATP. However, ATP metabolites, namely, adenosine diphosphate and adenosine monophosphate, cannot activate P2X receptors.[52] ATP activation of the P2X receptor causes Ca^{2+} influx into cells, which increases the intracellular Ca^{2+} concentration in TG neurons.[50] In the inferior alveolar nerve injury model, increased P2X3 receptor expression in the TG has been reported, which suggests that the P2X3 receptor is involved in TN occurrence or conduction.[53] P2X4 receptors are mainly located in the lysosomes of SCs in the peripheral nervous system. In in vitro cultured SCs, TNF-α enhances P2X4 receptor protein synthesis and promotes P2X4 receptor transport to the SC surface; moreover, BDNF release is dependent on P2X4 receptor activation.[54,55] Upon nerve damage, TNF-α release promotes P2X4 receptor expression; ATP activates the P2X4 receptor, which leads to BDNF release (see Figure 1).[54]

As mentioned before, high BDNF levels are involved in TN development. BDNF is an important member of the neurotrophic factor family. It is synthesized by primary sensory neurons in humans, packaged in vesicles, and transported along the axis to the periphery. To exert its function, BDNF must bind to the trkB receptor.[56,57] The binding of BDNF to the trkB receptor promotes N-methyl-D-aspartic acid (NMDA) receptor upregulation and K^+-Cl^- co-transporter (KCC2) receptor downregulation[58–60] with both processes leading to pain occurrence.[59] Blocking the BDNF- trkB B receptor interaction has been reported to alleviate abnormal pain caused by peripheral nerve injury.[61,62] In addition, as a member of the neurotrophic factor family, BDNF can repair injured nerves.[63]

Not only can BDNF cause TN but also NGF. Previous studies on NGF have focused on its therapeutic effect on TN. However, recent studies have reported that NGF can also mediate pain generation and conduction. Monoclonal antibodies against NGF have been shown to improve chronic neuropathic pain.[64] NGF exerts its biological effects by binding to its high-affinity receptor, the trkA, which is distributed across primary sensory neurons.[65] Upon nerve injury, the distal SCs are stimulated and secrete large NGF amounts; further, NGF and its receptor complex have been observed at the proximal stump of injury axons. NGF activation of the trkA receptor has been reported to increase the levels of SP, CGRP, and transient receptor potential vanilloid 1 (TRPV1) receptors.[60] As aforementioned, SP and CGRP can cause TN. The TRPV1 receptor is closely

related to pain transmission, and its activation can cause the influx of cations such as Ca^{2+}, causing pain.

In summary, we present a pathway of the involvement of SCs in TN. After peripheral nerve injury, TNF-α expression increases;[66] then, TNF-α binds to TNF-α receptors (TNFR) on the SCs and induces SCs to express the P2X4 receptor;[67] P2X4 receptor is activated by ATP which is released by neurons and SCs to mediate Ca^{2+} influx and increased BDNF release.[68,69] BDNF binds with the trkB receptor that leads to KCC2 downregulation and NMDA receptor upregulation, which lays the foundation for pain production. Increased Ca^{2+} influx leads to increased release of the excitatory neurotransmitter, Glu, which activates NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, leading to hyperalgesia and hypersensitivity.[70] NGF expression is upregulated in injured SCs. NGF activation of the trkA receptor can lead to the upregulation of the SP, CGRP, and TRPV1 receptors. SP activates the NK1 receptor, while CGRP inhibits SP degradation, leading to TN. Moreover, NGF can promote BDNF expression and thus cause TN.

TN treatment

There are two main causes of TN. One is the abnormal discharge activity in the trigeminal nerve system, while the other is trigeminal nerve damage, including rupture, compression, and inflammation.[31,71]

Before 1871, Torusseau first proposed the epileptiform pain symptoms of TN, and some scholars observed abnormal discharge phenomena in the ventral thalamus and cerebral cortex in the TN model.[72] This suggests that abnormal discharge of the ventral thalamus and cerebral cortex might cause TN. Moreover, chronic electrical stimulation of the central sulcus motor cortex in patients with TN was reported to have an effective response rate of 40%∼100%,[73] which suggests an association between abnormal electrical activity in the brain and TN. The aforementioned findings confirm that abnormal central discharge is an important cause of TN. Based on this etiology, carbamazepine and oxcarbazepine are commonly used as curative treatments for TN. In addition, lamotrigine and baclofen are considered second-line drugs for TN.[74]

Many studies have reported that SCs can relieve neuropathic pain[9,14,15] by remyelinating injured nerves. In addition, we have previously reported that SC transplantation can reduce neuropathic pain caused by nerve injury.[75] We microencapsulated SCs in alginic acid and transplanted microencapsulated SCs and non-microencapsulated SCs into the region surrounding the injured sciatic nerve in the rat model of chronic constriction injury. After 14 days, under electron microscopy, we found that the myelin sheaths in the injury areas healed better than those without SCs. More importantly, after transplantation of SCs, the expression levels of P2X2 and P2X3 which participate in the transmission of algesia and nociception information by primary sensory neuron[76] were also decreased.[75]

Nerve injury can be divided into axonotmesis and neurotmesis. After axonotmesis, the basal laminae of the SCs remain intact. After axon regeneration to the distal stump, the axon remains in its inherent basal lamina.[19] After neurotmesis, there is disruption of the axons, SCs, and the basal lamina. The response of SCs to axonotmesis and neurotmesis is similar. After nerve injury, nerve fibers at the distal end of the injury site, as well as axons and myelin sheaths of unequal length at the proximal end, disintegrate and degrade via a process known as Waller degeneration.[77] SCs are activated and dedifferentiate into repair SCs that promote nerve repair. These cells have regained the ability to proliferate and differentiate, and the axons are demyelinated; simultaneously, SCs engulf and clear nerve debris. SCs at the injured proximal stump proliferate and differentiate, forming tissue bridges at both ends of the damaged area that connect to the damaged nerve and form Bungner bands in the basilar canal.[78] This guides the extension of the regenerative axons and induces the formation of a new myelin sheath. The formation of Bungner bands provides the necessary guidance and support for nerve regeneration.[9,14,15]

However, the therapeutic method of SC transplantation is only at the animal trial stage, and there have been no relevant clinical reports. Moreover, there are several factors to consider regarding SC transplantation, such as the many problems associated with transplantation and whether to opt for autotransplantation or allotransplantation. Obtaining SCs in the human body for autologous transplantation and overcoming immune rejection in allotransplantation are some of the main unresolved concerns. Moreover, as previously mentioned, various substances secreted by SCs can cause pain. Therefore, ensuring that the treatment of neuropathic pain caused by nerve injury does not aggravate the pain remains challenging. Since the cell is active, it can also secrete molecules besides the therapeutic factors and thus cause side effects that are currently unrecognized. There is a need for further research to address these concerns.

The use of drugs to treat TN is more economical and feasible than transplantation. As previously explained, it is known that TN occurrence is related to the secretion of BDNF and NGF by SCs and that BDNF and NGF require their corresponding receptors, namely, trkA and trkB receptors, respectively, to exert their effect.

SCs are an important source of BDNF source, and secretion is dependent on the t-type voltage-gated calcium channel.[79] The use of appropriate receptor blockers for neuralgia has shown some efficacy.[80] BDNF release is

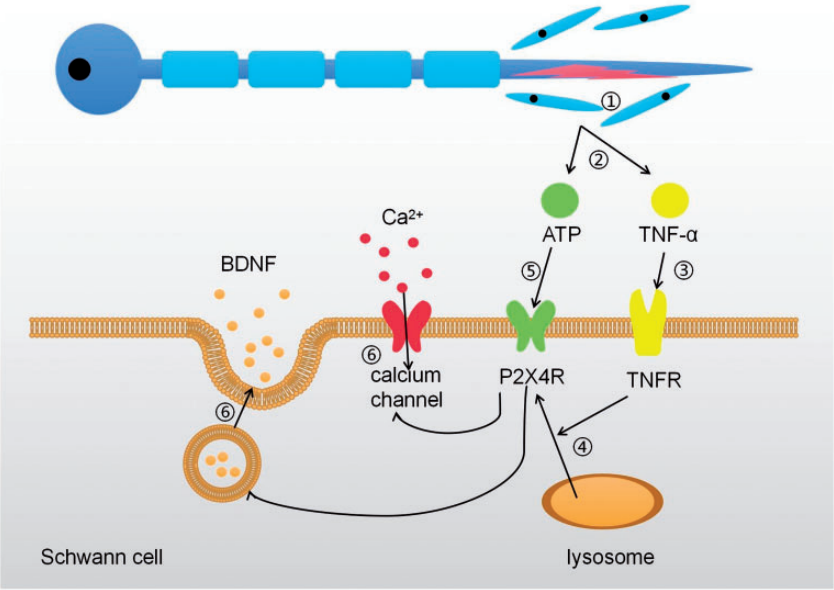

Figure 1. ① After axonal injury, Schwann cells are activated to form repair Schwann cells. ② Injury nerves release TNF-α and Schwann cells release ATP. ③ TNF-α activates TNFR on Schwann cells, ④ and promotes P2X4R synthesis and transport from lysosomes to cell membranes. ⑤ ATP binds to P2X4R on Schwann cell membrane, and ⑥ BDNF release and calcium influx increase.
BDNF: brain-derived neurotrophic factor; ATP: adenosine triphosphate; TNF-α: tumor necrosis factor alpha; TNFR: TNF-α receptor.

dependent on the activation of the P2X4 receptor. Studies on mice with defective P2X4 receptors have found that the GluN1 subunit of the NMDA receptor is not phosphorylated and that the KCC2 receptor is not downregulated in the neuropathic pain model. However, these two processes are dependent on the BDNF-trkB signaling pathway; therefore, there is no increase in BDNF release, and pain hypersensitivity does not occur when the P2X4 receptor is inhibited.[81] The P2X4 receptor is also a potential therapeutic target. Studies using the new P2X4 receptor-selective blocker, NP-1815-PX, have found that it has analgesic effects on neuropathic pain caused by nerve injury.[82] After P2X4 receptor activation, SCs release more BDNF that acts on the trkB receptor and causes pain. Therefore, it is possible that blocking the trkB receptor might help treat TN. Theoretically, blocking the interaction between BDNF and trkB is important for pain treatment; however, there are currently no relevant reports. NMDA receptor upregulation is one of the effects of BDNF-trkB signaling, and studies have shown that using NMDA receptor blockers can reduce TN symptoms.[83,84]

NGF expression by SCs is upregulated after injury. However, the molecular mechanism behind the release of NGF by SCs remains unclear. Some studies have suggested that syntaxin-4 related to SNAP23 can regulate NGF release by SCs and that syntaxin-4 and SNAP23 inhibition can significantly reduce the cytoplasmic effect of NGF.[85] The exertion of the biological effect of NGF requires initial trkA receptor activation. Theoretically, blocking the interaction between NGF and the trkA receptor could be beneficial for neuropathic pain. In fact, monoclonal antibodies against NGF have been reported to improve chronic neuropathic pain.[64,86,87]NGF-induced trkA receptor activation increases CGRP expression. CGRP is an important pain-causing substance and has been targeted in the clinical treatment of TN. Monoclonal antibodies against CGRP have achieved satisfactory efficacy in the clinical treatment of migraine.[88] Moreover, CGRP can cause pain by inhibiting SP degradation, and administration of SP receptor blockers has been used in TN treatment.[43] However, some studies have advised caution in migraine treatment using CGRP monoclonal antibodies.[89]

The drug treatment is just pain relief. Compared with drug treatment, the advantage of transplantation of SCs is that it can repair the damaged nerve more quickly and treat TN etiologically.[9,14,75] However, as mentioned above, SCs can release pain-causing substances that cause TN, such as BDNF and NGF. BDNF can repair nerves treating pain etiologically[63] but can activate trk B receptors that cause or exacerbate pain.[62] This poses a problem for transplanting SCs to treat TN. Other disadvantages of applying SCs for TN include immune problems associated with transplantation.

Conclusion and prospects

In conclusion, SCs are activated after trigeminal nerve damage. This causes demyelination and induces SCs to

secrete various neurotrophic factors, including NGF and BDNF, both of which contribute directly or indirectly toward TN. TN is regulated by two key pathways, namely, the NGF-trkA and BDNF-trkB signaling pathways, which are dependent on, interact with, and promote each other. These two pathways contain many targets for TN treatment, such as the trkA, trkB, and P2X4 receptors, as well as CGRP. SCs are an important source of these two neurotrophic factors. Therefore, SCs play an important role in the production, transduction, and treatment of TN.

Trigeminal nerve injury is one of the main causes of TN. After trigeminal nerve injury, the SCs are activated to upregulate the expression of neurotrophic factors such as BDNF and NGF, which in turn causes TN. However, the ability of NGF and BDNF to repair damaged nerves is widely recognized. In fact, these neurotrophic factors can repair injured nerves and eliminate the cause of pain. In other words, NGF and BDNF can both cause and be used to treat pain. In fact, there is no contradiction between pain occurrence and its treatment. Pain generation is a biological self-protection mechanism where the therapeutic effect of neurotrophic factors is retained, and pain is alleviated in the treatment process. In other words, there is a need for further research to separate the two pathways of pain treatment and occurrence. However, current studies have largely focused only on the pain pathway of neurotrophic factors. Although their role in nerve injury treatment is widely recognized, there have been no reports regarding their therapeutic effects. Further research on the neurotrophic factor pathway for repairing injured nerve could provide new clues on novel methods for the clinical treatment of TN.

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