Molecular basis of trigeminal nerve disorders and healing

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Abstract. – OBJECTIVE: This review aims to describe trigeminal neuralgia and the molecular basis contributing to the pathophysiology of this condition by focusing on the state of the art.

PATIENTS AND METHODS: An electronic search of PubMed was performed using the following keywords: "trigeminal neuralgia" AND "classification", "pathophysiology," "molecular basis" and "mitochondrial role."

RESULTS: Mitochondrial abnormality, whether functional or morphological, can contribute to neurological disorders. Additionally, one recent finding showed that gain-of-function mutation in the voltage-gated sodium channel NaV1.6 contributes to the pathophysiology of trigeminal neuralgia by increasing the excitability of trigeminal nerve ganglion neurons. It also exacerbates the pathophysiology of vascular compression. Healing of the trigeminal nerve is controlled by many molecular signaling pathways, including extracellular-signal-regulated kinase, c-Jun, p38, Notch, and mitogen-activated protein kinases.

CONCLUSIONS: More investigations regarding the gain-of-function mutation of NaV1.6 sodium channels are essential for the diagnosis and treatment of trigeminal nerve disorders, regardless of whether these are associated with vascular compression or not.

Key Words
   Trigeminal neuralgia, Classification, Pathophysiology, Molecular basis.

List of Abbreviations

AAN, American Academy of Neurology, ATP, adenosine triphosphate, CCI, chronic constriction injury, CN V, fifth cranial nerve, CSD, current source density, DI/S1, segment 1 of domain I, Drp1, dynamin-related protein 1, EFNS, European Federation of Neurological Societies, ENT, ear-nose-throat, ERK, extracellular-signal-regulated kinase, GNDF, glial cell-derived neurotrophic factor, JAK, Janus kinase, JNK, c-Jun N-terminal kinase, MBP, myelin basic protein, Mfn1, mitofusion 1, MRI, magnetic resonance imaging, mtDNA, mitochondrial DNA, MVD, microvascular decompression, NRF1, nuclear respiratory factor 1, NRF2, nuclear respiratory factor 2, Nrg1, neuregulin 1, NVC, neurovascular compression, PGC-1a, peroxisome proliferator-activated receptor gamma coactivator-1a, PNS, peripheral nervous system, REZ, root entry zone, ROS, reactive oxygen species, STAT, signal transducer and activator of transcription, TFAM, mitochondrial transcription factor A, TG, trigeminal, TN, trigeminal neuralgia, TRG, trigeminal ganglion, TRPA1, transient receptor potential cation channel, UCP5, uncoupling protein, V1, ophthalmic branch of trigeminal nerve, V2, maxillary branch of trigeminal nerve, V3, mandibular branch of trigeminal nerve, WT, wild-type.

Introduction

Trigeminal neuralgia is one of the most common peripheral neuropathic disorders of patients presenting at dental clinics.

Trigeminal neuralgias (TN) can produce excessively intense acute facial pain of a very exhausting nature[1]. It is characterized by recurring events of unilateral disturbance that cause transient electric shock-like stabbing pain, with sudden onset and termination, and with limited distribution in one or more of the trigeminal nerve branches[2]. Painful attacks can be evoked by any kind of simple activity at the area of nerve distribution, such as light touch or even slight movement, and pain attacks can occur repeatedly at many intervals or they might be continuous[3]. The condition is not life-threatening per se but the symptoms are excruciating and distressing[4,5] and patients are usually terrified of the pain attacks, which adversely affect their daily functioning and quality of life[6]; these patients typically present with higher anxiety and depression levels[7]. Eating is a primary issue in patients with trigeminal neuralgia and this dilemma places them between the need to avoid chewing – to prevent pain – and patterns of disordered food and drink intake, which put individuals at risk of nutrient deficiency[8]. In most idiopathic cases, the usual age for pain onset is between 40 and

60 years, although onset may occur in the second and third decades, most often in females[9].

There are many different types of lesions that may affect the nerve tracks and/or pathways. The tracks of the trigeminal nerve pair include the sensory nuclei and the sensory root and branches, up to the skin. The pathways of CN V include the cervical spine, the brainstem, the nerve root, as well as its three divisions: the ophthalmic, maxillary, and mandibular branches (V1, V2, and V3), respectively[1]. To manage trigeminal neuralgia, a vast range of medical and surgical approaches are obtainable and helpful[10-14], but treatment can be expensive[4,5].

This review aims to describe trigeminal neuralgia and the molecular basis contributing to the pathophysiology of this condition by focusing on the state of the art.

An electronic search of PubMed was performed using the following keywords: "trigeminal neuralgia" AND "classification", "pathophysiology," "molecular basis" and "mitochondrial role."

Classification of trigeminal neuralgia

There are two main clinical types of trigeminal neuralgia that vary from each other according to their etiology.

Essential Neuralgia

The most common type is essential neuralgia, also referred to as classic TN, which affects the vast majority of TN patients[15,16] and is mainly caused by neurovascular compression[1]. However, TN could be absolutely "essential", i.e., without specific causality or pathological condition[1]. Essential neuralgia is clinically distinctive and its characteristics are summarized in Table I.

Etiologies of essential neuralgia

Neurovascular Compression

The physiopathological mechanism of neurovascular compression is not yet fully understood[17]. Ultrastructural studies on trigeminal root biopsies revealed axonal loss, demyelination (destruction of normally myelinated structures), and dysmyelination (abnormal myelination) consistent with neurovascular compression (NVC) of the trigeminal nerve[18]. Frequent microtraumas caused by vascular pulsation of the compressing vessels may enhance a demyelination zone with abnormal remyelination and the formation of neoreceptors that are able to produce ectopic impulses. This struggle can only occur in a particular zone of the nerve, which corresponds to a delicate area of the nerve known as the root entry zone (REZ) or transition zone between central myelin (oligodendroglia) and peripheral myelin (Schwann cells). This transition does not occur where the nerve emerges, but takes place in the nerve root to various extents according to the nerve itself. For the trigeminal nerve, REZ is 2-6 mm from the emergence of the brainstem. Usually, the presence of two main conditions can confirm neurovascular compression: first is the presence of a touch between REZ and the blood vessels (veins or arteries) and second is when the neurovascular compression is perpendicular with the nerve axis.

Table I. Description of essential trigeminal neuralgia.

Clinical appearance	• Acute intensive paroxysmal electrical shock-like painful attacks
Pain induction	• Pain attacks are easily induced by skin touch over the trigger zone or even during movement
Pain location and involvement	• Pain is always unilateral and restricted to one or two branches: typically the maxillary and the mandibular branches
Pain duration	• Pain flashes last for a second and regenerate frequently for some minutes • When the painful episode terminates, a refractory period takes place; meanwhile, the trigger zone can be contacted without any pain evoked
Etiological factors	• Neurovascular compression • Multiple sclerosis • Structural defects in the cerebellum such as Chiari's malformation • Abnormal structure that may stretch the trigeminal nerve root such as lesions of the cerebello-pontine angle
Investigation	• Neurological examination of these patients is routine • Some patients show a normal MRI scan
Treatment	• Sodium channel inhibitors are the first line of treatment to relieve pain

Table II. Description of secondary trigeminal neuralgia.

Clinical appearance	• Usually dull continuous pain
Pain induction	• Pain lacks the trigger zone
Pain location and involvement	• Pain involves all three trigeminal nerve branches
Pain duration	• Painful paroxysms last 3–4 hours
Investigation	• This might be normal • This could indicate hypoesthesia, deterioration of other cranial nerves, or impaired central nervous system
Etiological factors	• Any pathological lesion on the CN V pathway

Diagnosis is clearly visible when the contact between blood vessels and the nerve is accompanied by a mass impact (pressure) on the nerve's tract[17].

Presence of a structural lesion or factors secondary to an underlying disease (Table I).

Secondary Neuralgia

This type of pain is clinically different from that of essential neuralgia. The characteristics of secondary neuralgia are summarized in Table II.

Etiology of secondary neuralgia

All pathologies that involve the 5th cranial nerve pathway may be responsible for secondary neuralgia. Therefore, it is crucial to understand both the nerve anatomy and its pathways for precisely locating the defective zones and giving the definitive diagnosis. Some lesions associated with secondary neuralgia present in specific anatomical areas[19-21].

Lesions of the Trigeminal Nuclei

Several pathologies that affect the brainstem and the cervical spine can involve the nuclei of the trigeminal nerve. The principally reported lesions include tumor, multiple sclerosis, ischemia, hemorrhage (cavernoma), and syringomyelic cavitation[1].

Trigeminal Root Lesions Involving the Cave of Meckel and Cisterns

In this anatomical zone, the involvement of the root could either result from a benign origin, such as Schwannoma or sarcoidosis, or the origin might be malignant, such as lymphoma, perineural extension, metastases, or carcinomatous meningitis. Furthermore, the trigeminal nerve root might be exposed to external compressions such as in the cases of Schwannoma of vestibulocochlear nerve and epidermoid cysts[1].

Cavernous Sinus Lesions

Cavernous sinus lesions could be primary, like aneurysms, Schwannoma, or meningioma.

Some lesions of the cavernous sinus may extend from another lesion located on the skull base into the cavernous sinus, such as metastases, chordomas, and chondromas, or from an ENT lesion that extends perineurally that might be (due to vicinity) intermittent such as cystic adenoid carcinomas[1].

Distal Branches Lesions

Schwannomas were observed as lesions that affect the trigeminal distal branches and cause neuralgia. There are other pathological conditions that are non-specific such as perineural extension of an ENT cancer or sarcoidosis. Sometimes distal branch pathology of the trigeminal nerve results in muscular atrophy; this situation is markedly observed when the mandibular branch of trigeminal nerve is affected, leading to unilateral atrophy of masticatory muscles due to the common pathway of the sensory root with the motor root[1].

Pathophysiology

Although the mostly observed etiology associated with neurological hyperactivity disorder is neurovascular compression, its biochemical mechanism is still not fully understood. It has been proposed that the presence of signs and symptoms might be the result of the pulsating compression applied by arteries at the root entry/exit zone of the cranial nerve[22]. Accordingly, demyelination takes place at the trigeminal root entry zone[23], and ectopic impulse production is the consequence[24]. When

the pain trigger zones are stimulated, TN is provoked due to the ephaptic cross-talk between sensory fibers and those responsible of transmitting the pain stimuli. This fact explains the frequent involvement of the TG root entry zone in cases of demyelinating diseases. The prompt clinical improvement and electrophysiological recovery following microvascular decompression indicate two various mechanisms. First, the prompt subsiding of symptoms and distress, which is clinically visible, possibly demonstrates cessation of the ectopic production of impulses and their ephaptic propagation to the proximal fibers[24]. The second process to be taken into account is that the developed neural conductivity indicates the prompt revival of the physiological role of large-caliber rapid-conducting fibers that are not demyelinated[25]. The understanding of such phenomena may provide the interpretation of pain occurrence in some zones that are not innervated by the trigeminal nerve; however, pain is elicited by loud noises or even by light. In addition to the demyelination process, other factors are involved in retarding the restoration of the neuronal membrane potentials and excitability following a TN attack. One of these factors is impairment of production of the mitochondrial ATP due to insufficient blood supply of the compressed nerve root that is caused by neurovascular compression[26]. Following a rush of impulses, nerve hypoperfusion results in delayed restoration of the ionic gradient, a decrease in extracellular fluid, and an increase in resistance to the ionic current between closely juxtaposed demyelinated axons[26].

BKCa Channels' Role in Trigeminal Neuralgia

BKCa channels have a significant role in modifying the mechanical pain threshold related to trigeminal neuralgia (Table III).

## Molecular basis of trigeminal neuralgia

Mitochondrial role

It is well known that in eukaryotes, the cell's primary energy producing system is the mitochondrion. Abnormality in mitochondrial function and morphology might result in various neurological disorders as neuronal activity is highly dependent on energy[27]. Recently, abundant scientific proof has illustrated the participation of mitochondria in the development of pain related to inflammation and neuropathy[28]. Reactive oxygen species (ROS) production can be increased in the trigeminal nucleus, which is located at the medulla oblongata, when the sensory neurons of the trigeminal nerve are mechanically evoked[29]. Genetic and biochemical research have distinguished that migraine sufferers show increased production of ROS with reduced mitochondrial respiratory chain enzymes activity. Additionally, a specific mitochondrial DNA (mtDNA) variants were also identified to predispose a migraine[30,31]. Quality control within mitochondria is carried out by the dynamic interplay of fission, fusion, and mitochondrial biogenesis (Figure 1). Fission is a process that divides the deteriorated mitochondrion into healthy and abnormal parts, whereas fusion brings about an incorporation of matrix content (respiratory enzymes) within the mitochondrion's membranes[32]. The processes of mitochondrial fission and fusion are brought about by dynamin-related protein 1 (Drp1) and mitofusin1 (Mfn1), respectively. Mitochondrial dynamics comprising both fission and fusion have a considerable role in preserving both the functional and morphological aspects of mitochondria when cells undergo oxidative stress[33]. Oxidative stress evokes mitochondrial fission and, consequently, mitochondrial biogenesis is disturbed[34,35]. In turn, increased

Table III. Role of BKCa channels in trigeminal neuralgia.

Following chronic constriction injury	• BKCa channels' downregulation • Decreased threshold intensity of action potential • Reduced overall BKCa currents • Increased levels of ERK, p38, and c-Jun N-terminal kinase
NS1619 (BKCa channel opener)	• Increased mechanical pain threshold • Increased threshold intensities of action potential in chronic constrictive injury
IbTX (iberiotoxin)	• It is a BKCa channel inhibitor • Blocks the mechanical pain threshold
Reversal of mechanical allodynia after CCI	• ERK1/2 antagonist U0126　　Considerably heighten BKCa currents • P38 antagonist SB203580　　　in the condition of CCI trigeminal neuralgia • JNK antagonist SP600125

Figure 1. Mitochondrial biogenesis is tightly regulated by peroxisome proliferator activated receptor gamma coactivator-1a (PGC-1a). Mitochondrial morphology is maintained by both fusion and fission. These two processes are mediated mainly by: Mitofusion1 (Mfn1) and Dynamin related protein1 (Drpl) respectively. Following mitochondrial fusion, the abnormal mitochondrial portion undergoes degradation.
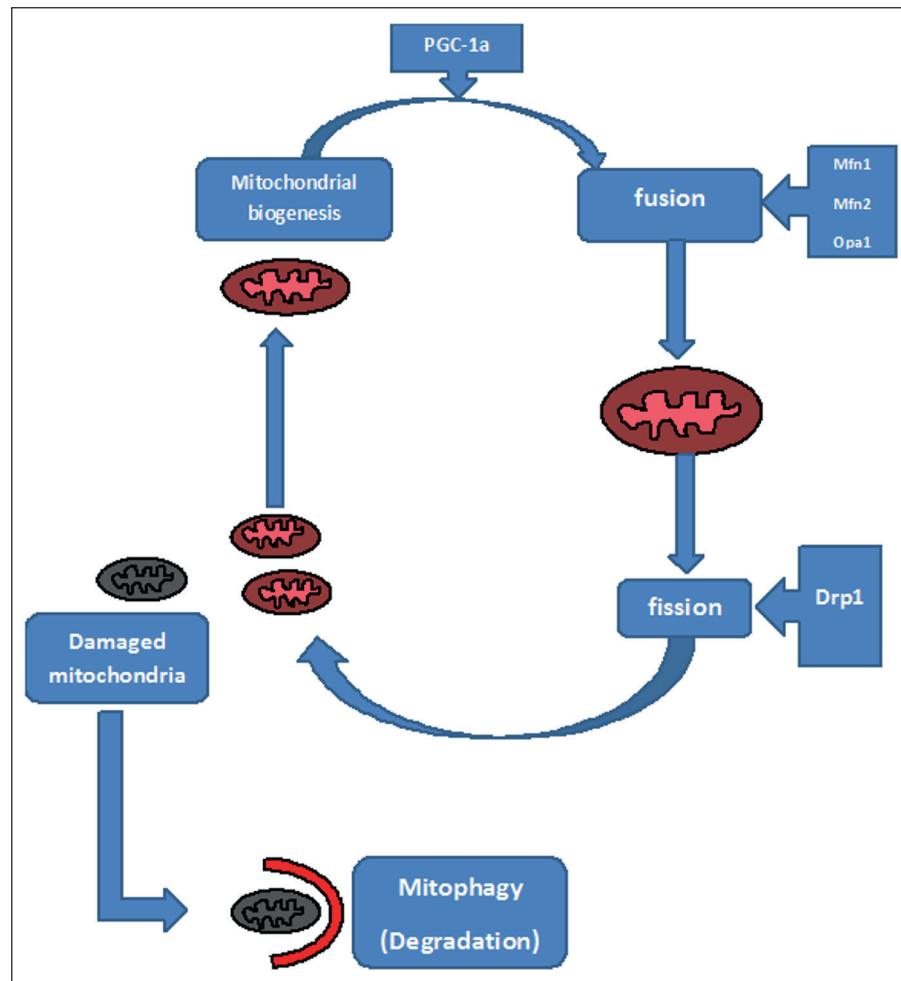
ROS production is caused by the disturbed mitochondrial dynamics and biogenesis[36,37] (Figure 2). Nociceptive signaling can be activated by ROS through activating the transient receptor potential cation channel (TRPA1)[38]. The uncoupling protein (UCP5), which reduces the mitochondrial membrane potential and consequently decreases ROS generation, might provide a neuroprotective influence after current source density (CSD) stimulation[39].

Mitochondrial biogenesis responds to metabolic signals via raising the actual mitochondrial mass with mtDNA replication[40]. It is strictly organized by peroxisome proliferator-activated receptor-gamma coactivator-1a (PGC-1a) and its downstream regulators comprise nuclear respiratory factor1 (NRF1), nuclear respiratory factor 2 (NRF2), and mitochondrial transcription factor A (TFAM)[41]. Low expression of PGC-1 can result in the reduced generation of ATP and excessive formation of ROS when cells are exposed to

oxidative stress[36]. Mitochondrial biogenesis increases the number of mitochondria available to supply the required energy in response to various pathologic and physiologic situations[40]. This process is complicated in that it needs a coordinated fulfillment of mtDNA replication and the translation, synthesis, and import of nuclear DNA-encoded proteins for presenting to the mitochondrial reticulum as well as membrane suitable for the threshold potential of mitochondrial membrane[40]. TFAM is responsible for ordering mtDNA replication and transcription[42].

Mutations in the Voltage-Gated Sodium Channel Nav1.6

Gain-of-function mutations in peripheral sodium channels NaV1.7, NaV1.8, and NaV1.9 are genetically and functionally linked in rare and common painful disorders in which TN is not included[43-45]. Although infantile epileptic encephalopathy has been shown to be caused by gain-of-
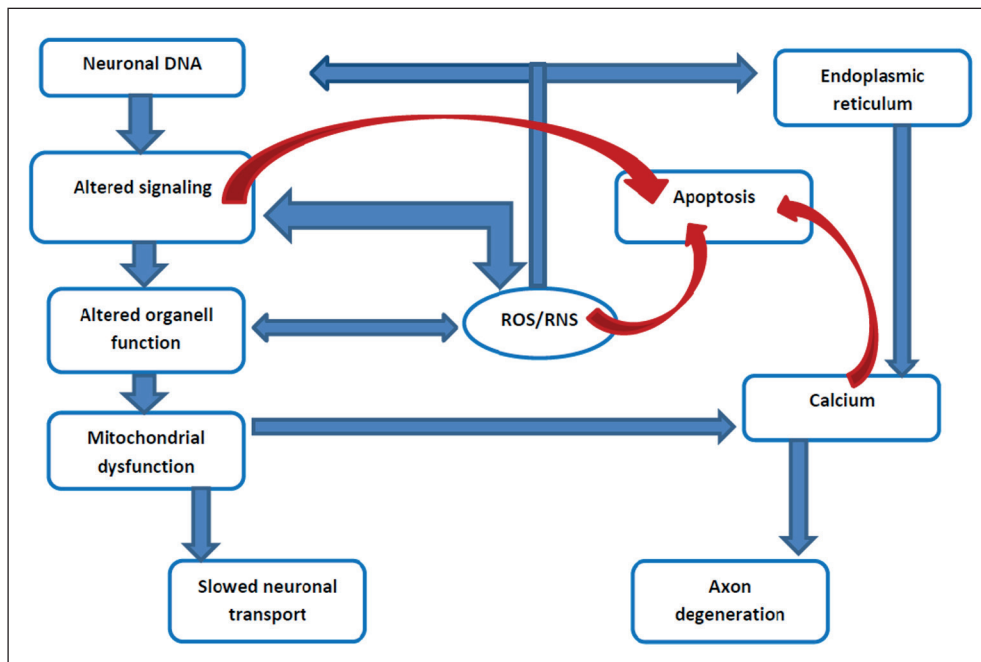
Figure 2. A model illustrating different processes that participate peripheral nerve degeneration. ROS/RNS adversely affect neuronal DNA, neuronal endoplasmic reticulum, neuronal signaling and organell functions. This influence leads consequently to axonal degeneration and/or neuronal apoptosis.

function mutations of NaV1.6[46-48], there has been no genetic proof for a role of this channel in human pain disorders. One study reported a novel NaV1.6 mutation in an individual with TN which supports the role of NaV1.6 in the pathophysiology of TN, adding to the spectrum of excitability disorders linked to this channel. The study illustrates a novel NaV1.6 mutation in TN and represents that this mutation induces transitory and resurgent sodium currents and results in the reinforced provocation in trigeminal neurons. It has been suggested that this gain-of-function NaV1.6 mutation may cause exacerbated pathophysiology of vascular compression and participates in TN. The genetic and functional data produced in that study support a link between gain-of-function mutation in NaV1.6 and human pain disorders, thus expanding the clinical-genetic spectrum of excitability disorders caused by this channel. Early-onset seizures and intellectual disabilities present with human NaV1.6 mutations in infantile epileptic encephalopathy[49] may mask any pain phenotype in the involved people.

Tanaka and collaborators present an interesting paper with a detailed description about the biophysical alterations that result due to the substitution of methionine 136 by valine (MET-126Val) in sodium channel Nav1.6 in a study case of typical TN[50]. The mutation substitutes a highly conserved residue in transmembrane segment 1 of domain 1 (DI/S1) of the channel and produces an increase in peak transient and resurgent currents of NaV1.6. In addition, it lowers the threshold for action potential in trigeminal ganglion (TRG) neurons and increases the neuronal-triggered response and the part of neurons that fire at a higher rate than those expressing wild-type (WT) channels. The authors proposed that the role of voltage-gated sodium channels in TN is compatible with an appropriate response to carbamazepine and evidence indicates the role of NaV1.6 with the pathophysiology of various forms of pain, including TN. One study finds support the notion that Met136Val channels produce an increase in the resurgent current in TRG neurons, thus providing the physiological basis for the increased triggered firing of TRG neurons expressing these channels[51].

Whole-exome screening of a number of relevant ion channel genes and functional testing in relevant cell background increase confidence in utilizing this method to detect pathogenic mutations in pain disorders of unknown etiology[49].

Table IV. Role of BKCa channels in trigeminal neuralgia.

Signaling pathways activated in Schwann cells	• Mitogen-activated protein kinase • Notch • JAK-STAT
Wallerian degeneration	• Degeneration of the nerve axon distal to the injury site • Schwann cells lack the expression of Krox20 and other myelin genes along with the myelin sheath itself • Increased expression of transcription factors in association with immature Schwann cells
Bands of Bunger	• Unique columnar structures formed by dedifferentiated Schwann cells, along which the regenerating axons grow
Following successful axonal regeneration	• Schwann cells retrieve their contact with axons and initiate differentiation again to myelinating cells

Molecular Signaling for Peripheral Nerve Healing

PNS is characterized by sturdy regenerative response following peripheral nerve injury[52]. A complex series of cellular events are induced following peripheral nerve injury and summarized in Table IV and Figure 3.

ERK Signaling in Schwann Cells

Briefly following peripheral nerve injury, extracellular signal-regulated kinase (ERK) is activated by phosphorylation[53,54] and stimulates Schwann cells to dedifferentiate *in vitro*[54,55]. Moreover, ERK signaling is demanded for Schwann cell differentiation and myelination *in vivo*, probably by mediating the effects of Neuregulin 1 (Nrg1) signals (Table V)[56].

Figure 3. A demonstration of Schwann cell response to peripheral nerve injury. First, the distal axonal area undergoes Wallerian degenerative process where Schwann cells dedifferentiate (grey cells) and aid in phagocytosis of their myelin sheathes (small red circles) and they recruit macrophages (orange cells) for eliminating myelin debris. During this stage, Schwann cells represent increased activity of multiple signaling pathways including: ERK, JNK/c-June, Notch and p38. Following successful axonal regeneration, Schwann cells begin remyelination process resulting in reduced thickness myelin; to compensate the thickness, Nrg-III is overexpressed to restore the full myelin thickness. If Nrg-I is conditionally eliminated from Schwann cells, sever regenerative defects take place.
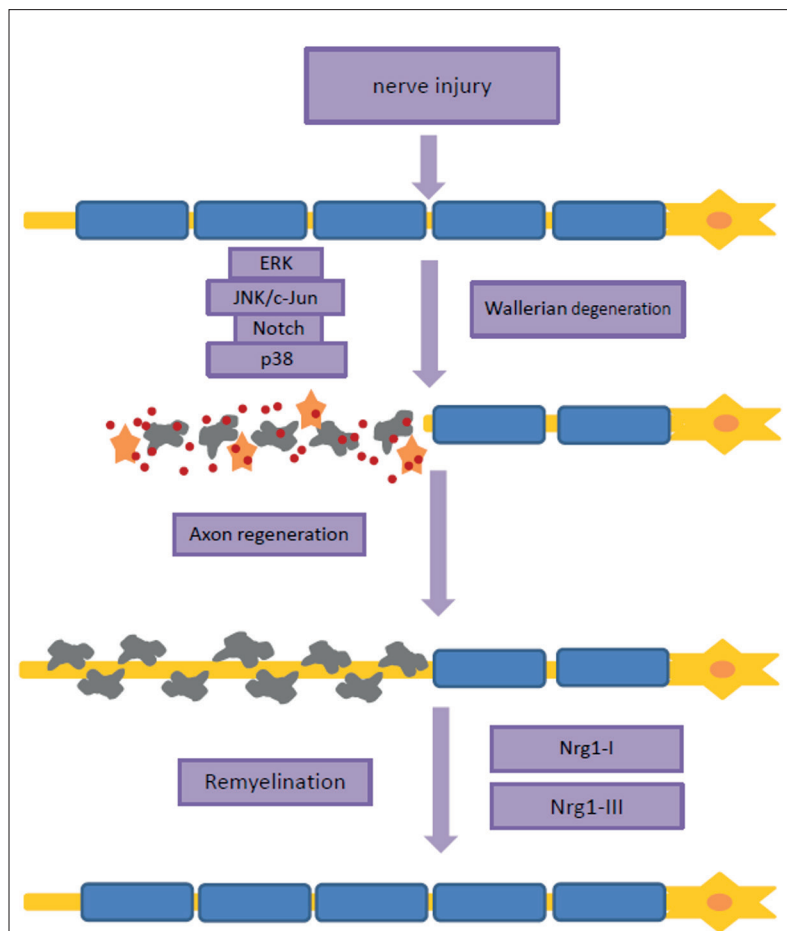
Table V. Role of extracellular-signal-regulated kinase in the peripheral nerve regenerative response.

Activation	• ERK is activated by phosphorylation, briefly following peripheral nerve injury
Role	• Stimulation of Schwann cells differentiation and myelination, probably by mediating the effects of Nrg1 signals • When ERK signaling increase, peripheral nerves undergo a process highly similar to Wallerian degeneration including: • Demyelination • Schwann cell proliferation • Recruitment of inflammatory cells to the nerve • Activation of c-Jun

c-Jun and the Schwann Cell Injury Response

c-Jun is a factor expressed in immature Schwann cells and has an important role in regulating factors that affect neuronal survival. These roles are discussed in Table VI.

Diagnosis and Treatment

Many diagnostic approaches are utilized to investigate TG pain neurophysiology; however, the guidelines of both the European Federation of Neurological Societies (EFNS) for evaluating the neurological pain and the American Academy of Neurology (AAN)-EFNS for management of trigeminal neuralgia advise the most dependable and valuable investigation for trigeminal neuralgia diagnosis is recording the neurophysiological reflexes of the nerve[57].

MRI should be routinely considered during the assessment of TN patients to exclude central intracranial lesions[58].

Much effort and attention have been paid to the treatment modalities with medications being considered as the first-line treatment. The majority of patients respond well to initial (pharmaceutical) treatment; however, some patients are resistant to any treatment modality. Various anti-epileptic agents are potentially beneficial in suppressing TN pain attacks with carbamazepine considered the medication of choice[59-61] where generally 80% of conditions exhibit entire pain relief[62]. Usually, when first-line treatment fails or is intolerable by the patient due to its severe side effects, surgical options can be considered[62]. Some effective treatment modalities include radiofrequency thermo-coagulation, balloon compression, percutaneous glycerol rhizolysis and microvascular decompression (MVD). Moreover, radiosurgery (gamma knife) has been evolved as a recent treatment modality[63,64] increasingly used as an effective treatment applied for patients who refuse surgical management. It is aimed at damaging or functionally suppressing cells by applying special high dose radiobiological impact and thereby resulting in its therapeutic consequence[65].

Table VI. Role of c-Jun in peripheral nerve regeneration.

Function	• c-Jun is a transcription factor
Expression	• c-Jun is expressed in immature Schwann cells
Regulation	• Downregulated in the mature myelinating cells • Upregulated and phosphorylated in Schwann cells following nerve injury
Conditional ablation of c-Jun in Schwann cells	• More neuronal death following nerve injury • Defects in axonal regeneration • Reduced functional recovery
Processes that require c-Jun	• Downregulation of myelin structural genes such as P0 and MBP • Upregulation of trophic factors associated with regeneration such as GDNF and BDNF • Upregulation of markers of immature Schwann cells such as p75NTR and Krox24 • Activation of GNDF and Artemin in Schwann cells to mediate paracrine signaling required for neuronal survival
Role of c-Jun mutant Schwann cells	• Formation of bands of Bunger with aberrant structure following nerve injury • Deficiencies in phagocytosis of myelin following nerve injury, which participates in delayed Wallerian degeneration

Conflict of Interests:

The Authors declare that they have no conflict of interests.

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