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REVIEW ARTICLE

NEUROPHYSIOLOGICAL MECHANISMS OF TRIGEMINAL NEURALGIA – FROM DEMYELINATION PATHOLOGY TO CENTRAL SENSITIZATION

NEUROFIZJOLOGICZNE MECHANIZMY NEURALGII TRÓJDZIELNEJ – OD PATOLOGII DEMIELINIZACJI DO SENSYTYZACJI OŚRODKOWEJ

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ABSTRACT

Introduction

Trigeminal neuralgia (TN) is a severe neuropathic pain disorder characterized by brief, electric shock – like attacks within the trigeminal distribution. Although classically linked to neurovascular compression, recent evidence indicates that its pathophysiology extends beyond peripheral mechanisms to include central sensitization and neuroinflammatory processes.

Aim

The aim of this review was to analyze the neurophysiological mechanisms of TN, emphasizing the interplay between demyelination, altered ion channel expression, and central plasticity, as well as to present modern diagnostic and therapeutic approaches targeting these mechanisms.

Materials and Methods

The study is a narrative review drawing on current evidence-based literature concerning the peripheral and central mechanisms of TN, including electrophysiological, neuroimaging, and experimental model data.

Results

Peripheral demyelination at the root entry zone promotes ectopic discharges and ephaptic transmission between adjacent fibers, while upregulation of voltage-gated sodium channels (Nav1.6, Nav1.7) enhances neuronal hyperexcitability. Central sensitization involves activation of microglia and astrocytes releasing proinflammatory cytokines (interleukin-1β, tumor necrosis factor-α, interleukin-6) and neurotrophins (brain-derived neurotrophic factor), contributing to persistent pain. Neuroimaging demonstrates cortical and subcortical reorganization in pain-processing regions. Therapeutic advances include selective sodium and calcium channel blockers and microvascular decompression.

Conclusions

TN arises from an interplay between peripheral demyelination and central neuroplasticity. Understanding these interconnected mechanisms provides a foundation for more targeted and effective therapeutic strategies that address both neuronal hyperexcitability and neuroinflammation.

Keywords: demyelination, trigeminal neuralgia, central sensitization

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STRESZCZENIE

Wstęp

Neuralgia trójdzielna (NT) jest ciężkim zespołem bólu neuropatycznego, charakteryzującym się krótkotrwałymi, napadowymi dolegliwościami bólowymi o charakterze porażenia prądem elektrycznym, zlokalizowanymi w zakresie unerwienia nerwu trójdzielnego. Choć klasycznie schorzenie to wiązane jest z uciskiem naczyniowo-nerwowym, coraz więcej dowodów wskazuje, że jego patofizjologia wykracza poza mechanizmy obwodowe i obejmuje także sensytyzację ośrodkową oraz procesy neurozapalne.

Cel

Celem pracy było przeanalizowanie neurofizjologicznych mechanizmów NT, ze szczególnym uwzględnieniem współdziałania demielinizacji, zmienionej ekspresji kanałów jonowych oraz plastyczności ośrodkowego układu nerwowego, a także przedstawienie nowoczesnych metod diagnostycznych i terapeutycznych ukierunkowanych na te mechanizmy.

Materiał i metody

Praca ma charakter przeglądu narracyjnego, bazującego na aktualnym piśmiennictwie, opartym na dowodach, dotyczącym obwodowych i ośrodkowych mechanizmów NT, obejmującym dane elektrofizjologiczne, neuroobrazowe oraz pochodzące z modeli doświadczalnych.

Wyniki

Demielinizacja obwodowa w strefie wejścia korzenia nerwowego sprzyja powstawaniu wyładowań ektopowych oraz transmisji efaptycznej między sąsiadującymi włóknami, natomiast zwiększona ekspresja kanałów sodowych (Nav1.6, Nav1.7) nasila nadpobudliwość neuronów. Sensytyzacja ośrodkowa obejmuje aktywację mikrogleju i astrocytów, które uwalniają cytokiny prozapalne – interleukinę-1β, czynnik martwicy nowotworów-α, interleukinę-6 – oraz neurotrofiny, takie jak czynnik neurotroficzny pochodzenia mózgowego), co przyczynia się do utrwalenia bólu. Badania neuroobrazowe wykazują reorganizację korowych i podkorowych struktur zaangażowanych w przetwarzanie bodźców bólowych. Postępy terapeutyczne obejmują selektywne blokery kanałów sodowych i wapniowych oraz mikronaczyniową dekompresję.

Wnioski

Neuralgia trójdzielna wynika ze współdziałania demielinizacji obwodowej i ośrodkowej neuroplastyczności. Zrozumienie tych powiązanych mechanizmów stanowi podstawę do opracowywania bardziej celowanych i skutecznych strategii terapeutycznych, ukierunkowanych zarówno na nadpobudliwość neuronów, jak i na neurozapalenie.

Keywords: demielinizacja, neuralgia trójdzielna, sensytyzacja ośrodkowa

Introduction

Trigeminal neuralgia (TN) represents one of the most severe pain disorders in humans, characterized by short, sudden episodes of acute pain resembling an electric shock, affecting areas innervated by the branches of the trigeminal nerve [1]. The estimated incidence ranges from 4.3 to 27 cases per 100,000 people annually, with a higher prevalence among women and individuals over 50 years of age [2].

Although the condition is well characterized clinically, its underlying neurophysiological mechanisms – including demyelination, altered ion channel expression, and central plasticity manifesting as increased excitability of central nociceptive neurons – remain incompletely understood and are the subject of ongoing investigation [3].

The classical form of TN (so-called classical neuralgia) is most often associated with

vascular compression at the root entry zone (REZ) of the trigeminal nerve, leading to focal demyelination and impaired afferent conduction [4]. From a neurophysiological perspective, key processes include ectopic discharges in demyelinated fibers, ephaptic transmission, and upregulation of voltage-gated sodium channels (e.g., Nav1.6, Nav1.7) in reorganized sensory fibers [5].

Moreover, increasing attention is being paid to central mechanisms –particularly the activation of microglia and astrocytes and the resulting neuroinflammatory processes – which shift the understanding of TN from a purely peripheral microstructural disorder toward a network-based functional model involving central sensitization and the remodeling of pain-processing circuits [6].

The aim of this paper is to present and analyze the neurophysiological mechanisms underlying TN, encompassing both peripheral processes (demyelination, ectopic discharges, altered ion channel expression) and central processes (central sensitization, glial cell activation, and cortical reorganization). The study seeks to demonstrate how myelin sheath pathology and channelopathies contribute to the development and persistence of neuropathic pain in TN, as well as to highlight the significance of modern diagnostic and therapeutic methods in the assessment and modulation of these disturbances. This article is a narrative review based on current, evidence-based sources.

Anatomy and neurophysiology of the trigeminal nerve

The trigeminal nerve (*nervus trigeminus*) is the fifth cranial nerve and serves as the main sensory nerve of the face. It transmits tactile, pain, and temperature sensations from the facial region, oral and nasal cavities, and the anterior cranial fossa. In addition, it contains a motor component that innervates the muscles of mastication, allowing it to participate in both motor and somatosensory functions of the head [7].

Anatomical structure of the trigeminal nerve

The trigeminal nerve emerges from the lateral surface of the pons as two roots – a sensory (radix sensoria) and a motor (radix motoria). The sensory neurons are located in the trigeminal (Gasserian) ganglion (ganglion trigeminale), situated in Meckel's cave in the posterolateral cranial cavity. From this ganglion arise three main branches: the ophthalmic nerve (V1, *n. ophthalmicus*), the maxillary nerve (V2, *n. maxillaris*), and the mandibular nerve (V3, *n. mandibularis*). The first two branches are purely sensory, while the third also contains motor fibers that supply the muscles of mastication, including the masseter, temporalis, and both pterygoid muscles [8]. The branches of the trigeminal nerve innervate the skin of the face, the mucous membranes of the nose and oral cavity, the teeth, the tongue, and part of the dura mater. Owing to its extensive sensory distribution, the trigeminal nerve plays a crucial role in integrating somatosensory information from the head [7]. The sensory portion of the nerve contains myelinated Aβ fibers responsible for touch, Aδ fibers transmitting sharp pain, and unmyelinated C fibers carrying dull, diffuse pain sensations, which together allow for the conduction of a wide range of sensory stimuli [9].

Sensory pathways of the trigeminal nerve

Sensory information from the areas innervated by the trigeminal nerve is transmitted to the sensory nuclei in the brainstem, which include the mesencephalic nucleus (*nucleus mesencephalicus n. trigemini*) responsible for proprioception from the masticatory muscles and periodontal tissues, the principal (pontine) sensory nucleus (*nucleus pontinus n. trigemini*) processing tactile and pressure sensations, and the spinal trigeminal nucleus (*nucleus spinalis n. trigemini*) conveying pain and temperature signals. The fibers from these nuclei decussate and form the trigeminothalamic tract, which projects to

the contralateral ventral posteromedial nucleus of the thalamus and subsequently to the primary somatosensory cortex in the postcentral gyrus. As a result, sensory and pain stimuli from one side of the face are processed in the opposite cerebral hemisphere [8].

REZ

REZ represents the transitional region between the peripheral and central parts of the trigeminal nerve and is key to understanding the pathophysiology of TN. It is located on the lateral aspect of the pons, where peripheral myelin produced by Schwann cells transitions into central myelin synthesized by oligodendrocytes [10]. This is the most common site of neurovascular conflict, typically involving the superior cerebellar artery, though the anterior inferior cerebellar artery or pontine veins may also be implicated [11,12]. The resulting focal demyelination leads to impaired afferent conduction, promoting ectopic discharges and ephaptic transmission, where impulses are abnormally transmitted between adjacent demyelinated fibers. These processes underlie the paroxysmal nature of pain in TN [4].

Neurophysiology of impulse conduction in the trigeminal nerve

In the healthy trigeminal nerve, impulses are conducted saltatorily due to the integrity of the myelin sheath and the proper organization of the nodes of Ranvier, ensuring rapid signal transmission. Demyelination slows conduction and promotes the formation of hyperexcitable foci that generate ectopic discharges. Sodium channelopathies also play a crucial role in this process. The NaV1.6 isoform of voltage-gated sodium channels (encoded by the *SCN8A* gene), abundantly expressed in the nodes of Ranvier and trigeminal ganglion neurons, facilitates high-frequency firing and, through gain-of-function changes, increases sodium current – including the resurgent component – thereby enhancing neuronal excitability. This mechanism aligns with the "ignition" model of TN. Neurophysiological studies in affected patients demonstrate disturbances in afferent conduction within trigeminal pathways, consistent with this concept [13].

Pathophysiological mechanisms of TN

TN represents a classical form of neuropathic pain characterized by disturbances in both peripheral conduction and central sensory processing [14]. Its pathophysiology involves the coexistence of peripheral processes such as demyelination and ectopic discharges of sensory neurons, as well as central mechanisms leading to sensitization and reorganization of neuronal networks [15].

Demyelination and ephaptic transmission

In most patients with classical TN, a neurovascular conflict occurs within the REZ, where fibers transition from Schwann cell to oligodendrocyte myelination, making them particularly susceptible to compression [15]. Histopathological studies have demonstrated areas of demyelination and remyelination, as well as direct contact between demyelinated axons [2]. These conditions promote ectopic activity and ephaptic transmission – the pathological transfer of electrical impulses between adjacent, non-insulated fibers – leading to hyperexcitability of sensory neurons and the characteristic paroxysmal pain attacks [4].

Altered ion channel expression

Sensory neurons within the trigeminal ganglion show significant alterations in ion channel expression, particularly involving sodium channels Nav1.3, Nav1.6, and Nav1.7, as well as calcium channels Cav2.2. Increased expression of Nav1.6 and Nav1.7 lowers the depolarization threshold, resulting in neuronal hyperexcitability even in response to minimal mechanical stimuli [16]. Studies by Siqueira *et al.* revealed marked differences in the expression of sodium channel – encoding

genes in patients with TN, including upregulation of Nav1.3 and altered Nav1.7 levels compared to controls, supporting the role of these channels in ectopic firing and neuropathic pain generation. Gain-of-function mutations in the SCN8A gene encoding Nav1.6, reported in TN patients, may further enhance sodium conductance and neuronal excitability [14]. In animal models, inhibition of Nav1.6 and Nav1.7 activity reduces ectopic discharges and alleviates pain symptoms, confirming their critical role in TN pathogenesis [16].

Central sensitization and glial cell involvement

Peripheral nerve injury in TN induces secondary alterations in central pain-processing structures. Increased excitability and reduced activation thresholds of neurons are observed within the spinal trigeminal nucleus (*nucleus spinalis nervi trigemini*) and the somatosensory cortex, reflecting the process of central sensitization. Experimental studies demonstrate astrocyte activation within the trigeminal REZ and elevated infiltration of immune cells in this region [16]. In patients, elevated cerebrospinal fluid concentrations of cytokines and inflammatory mediators indicate the involvement of neuroinflammatory mechanisms [5]. Activated microglia and astrocytes release proinflammatory cytokines – interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), interleukin-6 – and neurotrophins such as brain-derived neurotrophic factor, which enhance synaptic transmission, weaken inhibition mediated by gamma-aminobutyric acid, and sustain neuronal hyperexcitability [17].

Central plasticity and cortical reorganization

Neuroimaging studies using high-resolution magnetic resonance imaging (MRI) with voxel-based morphometry and resting-state functional MRI have revealed concurrent structural and functional brain alterations in patients with classical TN [18]. These include reduced gray matter volume in the right hippocampus and fusiform gyrus, along with increased spontaneous activity in these regions, indicating the coexistence of anatomical and functional deficits. Additional findings of heightened activity in the limbic system, thalamus, basal ganglia, and insular cortex support the involvement of emotional and sensory circuits in pain persistence [18]. This pattern of reorganization reflects neuroplastic adaptation to chronic nociceptive stimulation, with hippocampal and fusiform gyrus hyperactivity potentially serving as compensatory mechanisms. Consequently, TN should not be viewed solely as a peripheral disorder but rather as a dysfunction encompassing the entire pain-processing network, including limbic, sensory, and cortical regions [19].

Experimental models and neurophysiological studies of TN

Neurophysiological studies of TN provide valuable insights into the mechanisms underlying the generation and persistence of pain. Due to the limited availability of human nerve samples, much of the current understanding comes from animal models that replicate the key features of TN, such as paroxysmal pain, ectopic discharges, and central sensitization [4].

Electrophysiological studies

Human neurophysiological testing provides important information on conduction abnormalities within the trigeminal system. The most commonly used diagnostic method is the blink reflex (BR), which evaluates conduction through the reflex arc involving the trigeminal (V) and facial (VII) nerves. In patients with TN, prolongation of the R1 component latency is frequently observed, while R2 responses remain preserved. This finding indicates impaired conduction within the brainstem, particularly in the principal trigeminal nucleus in the pons, reflecting partial dysfunction of afferent fibers. Following

decompression of the brainstem, R1 latency may normalize, demonstrating a correlation between BR changes and recovery of trigeminal conduction [20].

Another diagnostic tool used to evaluate trigeminal function is trigeminal somatosensory evoked potentials, recorded after stimulation of the perioral or buccal region. In TN patients, latency prolongation and amplitude reduction are typically observed on the affected side, indicating partial dysfunction of afferent fibers within the trigeminal sensory pathway [21,22]. In animal research, patch-clamp and extracellular recording techniques are frequently applied to analyze the activity of single neurons in the trigeminal ganglion. Studies in chronic constriction injury (CCI) models show increased frequency of spontaneous action potentials, shortened refractory periods, and prolonged depolarization duration [23].

Experimental models of TN

Among experimental models, partial infraorbital nerve ligation in mice is considered the most representative of TN. It induces sustained mechanical allodynia and neurochemical changes in the dorsal horn of the medullary bulb (decreased calcitonin gene-related peptide and substance P, increased neurokinin-1 receptor), along with activation of microglia, astrocytes, satellite cells, and elevated expression of activating transcription factor 3 expression in the trigeminal ganglion. This model reproduces both the peripheral and central components of trigeminal pain [24]. In CCI and REZ compression models, microglial activation within trigeminal nuclei and elevated levels of proinflammatory cytokines (IL-1β, TNF-α) are also observed, confirming the contribution of inflammatory processes to neuropathic pain persistence [25]. Moreover, pharmacological or genetic silencing of the Nav1.7 sodium channel has been shown to reduce pain-related behavior in animals, underscoring the critical role of this channel in TN pathophysiology [26].

Functional Neuroimaging

Functional and structural MRI studies in TN patients have revealed pronounced alterations in central pain-processing structures, including the thalamus, somatosensory cortex, insula, and cingulate cortex, confirming the presence of central reorganization. Morphometric analyses additionally show gray matter loss within the trigeminal nuclei of the brainstem, while diffusion tensor imaging demonstrates reduced fiber integrity in the REZ, consistent with microstructural damage. Collectively, these findings confirm that TN involves both peripheral and central components [27].

Therapy and neurophysiological modulation of TN

The treatment of TN has traditionally relied on pharmacotherapy and neurosurgical procedures. However, in recent years, novel therapeutic strategies have emerged, focusing on the modulation of neuronal activity and neuroinflammatory processes. The goal of modern therapies is not only to alleviate pain symptoms but also to target the underlying neurophysiological mechanisms responsible for pain chronification [28].

Neurosurgical and interventional treatments

In patients resistant to pharmacological therapy, neurosurgical procedures are used to relieve neurovascular compression or interrupt nociceptive transmission. Microvascular decompression (MVD), which involves separating the offending vessel from the trigeminal nerve, remains the most effective treatment for classical TN. The procedure reduces mechanical compression in the REZ, which can restore normal conduction and decrease ectopic neuronal discharges. Nevertheless, recent studies emphasize that the analgesic effect of MVD cannot be explained solely by mechanical decompression, as some patients continue to experience pain despite technically successful surgery.

This suggests the involvement of additional molecular mechanisms, including oxidative stress and neuroinflammation, in TN pathophysiology [28].

Alternative percutaneous ablative procedures include radiofrequency rhizotomy, glycerol rhizotomy, and balloon compression of the Gasserian ganglion. These techniques cause controlled denaturation of sensory fibers, leading to reduced pain transmission and rapid symptom relief. They show high short-term efficacy (90–97% within the first months post-procedure), although the effect may diminish over time. Despite being less invasive and better tolerated than MVD, these procedures can cause transient or permanent sensory disturbances in the trigeminal distribution area [29].

Pharmacotherapy targeting ion channels

First-line drugs such as carbamazepine and oxcarbazepine act by blocking voltage-gated sodium channels (primarily Nav1.6 and Nav1.7), stabilizing the neuronal membrane and reducing ectopic discharge frequency [9]. Due to their side effects, research is increasingly focused on agents with greater selectivity for specific ion channel subtypes. Preclinical studies have confirmed the efficacy of selective Nav1.7 inhibitors (e.g., vixotrigine, BIIB074), which reduce the excitability of trigeminal ganglion afferent neurons without affecting other neural structures. Another therapeutic approach involves calcium channel blockers targeting Cav2.2 channels (e.g., gabapentin, pregabalin), which inhibit the release of glutamate and substance P at central sensory terminals. Clinical studies have shown that combining gabapentin with baclofen may more effectively reduce pain attack frequency than monotherapy [30].

Antidepressant therapy

Antidepressant treatment plays an important supportive role in managing TN, particularly in patients experiencing chronic pain associated with mood disturbances and emotional strain. These agents exert analgesic effects independent of their mood-regulating properties by inhibiting serotonin and norepinephrine reuptake, thus enhancing descending inhibitory pain pathways in the central nervous system [31]. The most commonly used agents include tricyclic antidepressants (amitriptyline, nortriptyline) and newer serotonin–norepinephrine reuptake inhibitors (duloxetine, venlafaxine), which offer better tolerability and fewer side effects. Clinical studies indicate that duloxetine can effectively reduce neuropathic pain and improve patients' well-being, especially when used in combination with anticonvulsants [32].

Conclusions

TN is a complex neuropathic disorder characterized by concurrent disturbances in peripheral conduction and central plasticity. A key pathological process involves demyelination within the REZ, leading to ectopic discharges and ephaptic transmission, as well as abnormal ion channel expression (Nav1.6, Nav1.7, Cav2.2), which lowers the excitability threshold of sensory neurons. At the central level, microglial and astrocytic activation contributes to neuroinflammation and central sensitization.

Advances in understanding these mechanisms have led to the development of innovative therapeutic approaches, ranging from selective ion channel blockers to modern neurosurgical techniques. Promising results have also been reported for gene and cell-based therapies targeting neuronal activity and neuroinflammation.

TN should therefore not be viewed merely as a result of neurovascular compression, but rather as a manifestation of complex dysregulation across multiple levels of the nervous system. Continued neurophysiological research may pave the way for more precise and effective treatment strategies.

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