Post-Traumatic Trigeminal Neuropathy

Subjects: Neurosciences

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Painful traumatic trigeminal neuropathy (PTTN) is a chronic neuropathic pain that may develop following injury to the trigeminal nerve. Etiologies include cranio-orofacial trauma that may result from dental, surgical, or anesthetic procedures or physical trauma, such as a motor vehicle accident. Following nerve injury, there are various mechanisms, including peripheral and central, as well as phenotypic changes and genetic predispositions that may contribute to the development of neuropathic pain.

neuropathic pain pathophysiology trauma

1. Introduction

The trigeminal nerve (TN), or fifth cranial nerve, provides sensory–motor function via its three branches: V1, V2, and V3. It transmits information regarding temperature, pain, and touch in the face and provides motor function mainly to the masticatory muscles. When there is a noxious stimulus in the TN region, sensory afferents composed of myelinated Aδ-fibers and non-myelinated C-fibers transmit that information to the primary somatosensory cortex and limbic system [1].

When the nerve is injured, it may manifest on a spectrum of symptoms from no pain to tingling to attacks of severe pain. Trigeminal neuralgia may arise from etiologies including vascular compression, space-occupying lesions, multiple sclerosis, and trauma. When trauma causes injury to the sensory components of the TN resulting in pain, it is termed post-traumatic trigeminal neuropathy (PTTN), a diagnosis of exclusion, with a prevalence of 1.55 to 3.3% [2][3][4].

2. Pathophysiology

Trauma to the TN can be caused by cranio- or orofacial trauma, such as motor vehicle accidents, dental procedures (endodontic treatment, molar extractions), or other surgeries (Caldwell–Luc approach, rhizotomies, nerve blocks). Other injuries may include implant therapy and local anesthetic injections; however, iatrogenic injuries rarely result in chronic neuropathic pain.

While the exact mechanism of PTTN is not entirely understood, researchers attempt to summarize current literature. The majority of evidence comes from animal models of neuropathic pain that study injury to the spinal nerve. The cascade of events from peripheral to central in the nervous system result in major changes to neurons and their environment and may be affected by genetic variations [5][6].

3. Peripheral Mechanisms

Generally, nerve damage results in altered neuronal electrical activity, peripheral sensitization, and nociceptor activation. The release of inflammatory mediators leads to reduced thresholds and therefore increased excitability of the peripheral terminal membrane. The inflammatory response then causes blood vessel dilation, recruitment of white blood cells, and mast cell degranulation, which further decreases the threshold. This leads to swelling and further nociceptor activation that is transmitted through pain and temperature fibers to the cortex. However, in neuropathic pain, this process is dysregulated, manifesting as changes to membrane composition and ion flow, causing an amplified and cyclical response.

In neuropathic pain, patients may feel increased amounts of pain from noxious stimuli or even pain from non-painful stimuli, termed hyperalgesia and allodynia, respectively. This atypical pain is a manifestation of peripheral sensitization or increased responsiveness of nociceptors and decreased thresholds.

4. Chemokines and Cytokines

Several pre-clinical studies have investigated the roles of cytokines and chemokines, such as CCL2/receptor CCR2 [7], CXCL13/CXCR5 [8], CXCL2 [9], and CXCL10/CXCR3 [10], in neuropathic pain. Animal studies have shown that overexpression of CCL2/CCR2 is found in the medullary dorsal horn in a model of chronic neuropathic pain. Furthermore, CCR2 antagonists have been found to inhibit nociceptive signaling [11]. Intrathecal injection of CXCL13, known to be upregulated in the spinal cord following spinal nerve ligation [12], has been found to induce mechanical allodynia and increase the activation of ERK and production of TNF-α and IL-1β. Conversely, inhibition of CXCL13 and CXCR5 decreases mechanical allodynia. Similarly, CXCL10 has been found to induce pain hypersensitivity in wild-type mice, but not those lacking CXCR3, and CXCR3 is elevated in mice with chronic constriction injury. CXCL2 is upregulated in pre-clinical studies of injured sciatic nerves [13]. It has been further found to be increased in animals following induction of chronic neuropathic pain via infraorbital nerve constriction [9], and consequently, anti-CXCL2 injection into the trigeminal ganglion decreases pain behavior.

In the realm of pre-clinical models investigating chronic pain, the CX3CL1/R1 signaling pathway plays a pivotal role in modulating nociceptive signaling within the central nervous system (CNS) [14]. The initial modulation occurs at the synapse between primary afferents and dorsal horns in the spinal cord. Notably, following peripheral nerve injury, the pronociceptive sFKN/CX3CR1 pathway demonstrates a significant impact, leading to thermal and mechanical hypersensitivity. This effect is attributed to the induction of intracellular phosphorylation of microglial p38 MAPK, ultimately resulting in the release of pro-inflammatory cytokines IL-1β, IL-6, and NO. Chronic pain models consistently reveal an elevation in both sFKN and CX3CR levels. Moreover, in diverse preclinical models, the absence of CXCR1, as evidenced by CXCR1 knockout mice, consistently correlates with deficits in both traumatic and nontraumatic chronic pain, aligning with reduced microglial activity. These findings collectively underscore the critical involvement of the CX3CL1/R1 signaling pathway in the pathogenesis of chronic pain and emphasize its potential as a therapeutic target for intervention.

5. Ion Channels

Current evidence is expanding that ion channels, including sodium, calcium, and potassium channels, play a critical role in the development of pain in the trigeminal system. Many changes result in an increased firing of action potentials. For example, phosphorylation of both tetrodotoxin-resistant voltage-gated sodium channels, Nav1.8 and Nav1.9, decreases the activation threshold and increases excitability. The tetrodotoxin-sensitive sodium channels, Nav1.7 and Nav1.3, have been found to be dysregulated in contrasting directions. In patients with trigeminal neuralgia, Nav1.7, has been found to be downregulated, while Nav1.3, a reducer of nociceptive threshold, is upregulated. Interestingly, Nav1.3 is highly expressed during the embryonic period and decreases to low levels after birth [15]; however, it can upregulate upon nerve injury, increasing excitability, resulting in pain [16].

Calcium-activated potassium channel expression has been found to be decreased following infraorbital nerve ligation, and an agonist of the channel results in increased pain threshold (i.e., mechanical allodynia) [17]. A preclinical model of orofacial pain has found that nerve injury downregulates the voltage-gated potassium channel, Kv7.2 [18], and that downregulation results in increased excitability of the trigeminal ganglia neurons and induced trigeminal neuralgia-like behavior [19].

Dozens of variants for voltage-gated channels have been discovered. Recent studies have found missense mutations in both genes that encode the pore forming α1 subunit of the voltage-gated calcium channels, Cav3.1 and 3.2, resulting in gain of function and contributing to chronic pain [20][21]. Animal models of neuropathic pain involving chronic constriction injury of the infraorbital nerve have demonstrated that non-coding RNAs are involved in the development of trigeminal pain [6][22]. Following nerve injury, micro RNAs are downregulated in the dorsal root ganglion, which is thought to increase pain [23]. These miRNAs have been shown to target Nav1.7 [24]. In a study that upregulated miR-182, Nav1.7 was inhibited, reducing excitability and alleviating pain [25]. Micro RNAS target other voltage-gated sodium channels [26], as well as potassium [27] and calcium [28] channels, with downstream effects on neuropathic pain.

6. Ectopic Activity and Spontaneous Pain

Neuropathic pain is characterized by a phenomenon known as ectopic activity, in which spontaneous activity arises along axons within nociceptive pathways and cell bodies in sensory ganglia. This spontaneous activity occurs when a segment of the axon or cell body becomes excessively excitable, leading to the generation of spontaneous action potentials (SAs) [29][30][31].

There are two distinct forms of spontaneous ectopic activity: type 1, which involves subthreshold membrane potential oscillation [31], and type II, which lacks such oscillations. In the ganglia, there are two types of conductance: a voltage-dependent sodium conductance that is physically activating and a voltage-independent conductance attributable to potassium leak. It is proposed that these conductances generate membrane potential oscillations, and when oscillation sinusoids reach threshold amplitude, ectopic firing occurs [32]. Damage to nerves leads to alterations in ion channels, affecting aspects such as their expression, movement, or functionality. This can

result in heightened persistent sodium currents or reduced potassium leak currents, both active in the vicinity of the resting potential. These changes may contribute to the relative depolarization of the resting potential, which is often linked with spontaneous activity [33]. Furthermore, hyperpolarizing cationic currents, specifically I_h, play a role in enhancing the excitability of sensitized peripheral fibers. The I_h current density and rate of firing increases in the sensory ganglia and trigeminal ganglion neurons in peripheral nerve injury [34][35][36][37]; blocking of these currents reduces mechanical allodynia and ectopic discharge following nerve injury [35][38].

In cases where there is inflammation surrounding a nerve without any damage to the nerve's axon, there is an increase in spontaneous activity, triggering heightened mechanosensitivity, which may serve as a source of pain. Prolonged inflammation, if sustained, may potentially result in subsequent damage to the nerve. This progression to secondary nerve damage is a notable consequence [39][40][41]. Furthermore, inflammatory mediators released as a result of nerve injury as well as inflammation (i.e., bradykinin and adenosine triphosphate (ATP)) increase the amount of small-diameter sensory neurons positive for T-type Cav channels [42] that regulate peripheral sensory neuron excitability. This results in an increase in Cav currents in sensory neurons resulting in hypersensitivity [43][44][45][46]. Silencing of Cav3.2 has shown anti-nociceptive effects in animal models of neuropathic and inflammatory pain [43][47] and pharmacological inhibitors of T-type Cav channels has been shown to have analgesic effects in animal pain models [48][49][50].

Additionally, both animal and clinical electrophysiological studies have demonstrated altered firing properties of Aβ, Aδ and C fibers during the spontaneous activity associated with painful neuropathies [30][51][52]. Anticipated outcomes suggest that the occurrence of spontaneous burning or sharp pain is likely attributable to the spontaneous activity in C and Aδ fibers. Conversely, the spontaneous activity in Aβ fibers is expected to be associated with the manifestation of paresthesia and dysesthesia, which are commonly observed in neuropathies [33]. However, results of animal studies have shown that during the onset of pain, Aβ fibers (large-diameter myelinated afferents) comprise the majority of spontaneous activity. These afferents typically signal information about touch and vibration and directly contribute to spontaneous and evoked pain [53]. Thus, ectopic discharge in Aβ fibers, which in pathologic conditions become nociceptors themselves by undergoing a phenotypic switch, is a source of neuropathic pain [53]. Stimulation of previously injured Aβ fibers has also been shown to induce c-fos expression [54][55][56]. These findings provide further evidence for the idea that the activity in damaged Aβ fibers could be a dual contributor, both instigating pain and initiating central sensitization.

Studies have also found a mechanism of central sensitization that occurs via the unmasking of allodynia circuits [57]. In addition, glycine receptors in the dorsal horn may provide a therapeutic target. In [58], glycine blockade via an injection of a glycine receptor antagonist into the cisterna magna of a rat produced tactile allodynia through local circuits while selective inhibition of gamma isoform of protein kinase C and glutamate NMDA in the circuits disrupted them and prevented allodynia. It has also been shown that glycine inhibition can induce a dynamic mechanical allodynia resistant to morphine in cells lacking neurokinin 1 receptors [59]. These findings altogether suggest that in neuropathic pain, there exists a pathway that is then disinhibited, allowing Aβ afferents to access both deep and superficial dorsal horn laminae, resulting in mechanical allodynia [60].

To summarize, injury to every part of the pathway has been associated with neuropathic pain. Animal studies confirm multiple sites for generation of ectopic spontaneous activity along axonal projections and from the cell bodies within sensory ganglia [29][31][61]. Nerve injury affects a number of cells (immune cells, glia, and neurons) present at each of these anatomical levels, and each of these cells contribute to the development of neuropathic pain [62], communicating through gap junctions, synaptic transmission, and cell-to-cell signaling [63][64][65]. In situations of pathology, particularly after nerve injury, intensified communication among various cellular components may establish an environment conducive to heightened spontaneous activity [33]. Moreover, the alteration in characteristics of Aβ fibers (phenotypic switching) and their ectopic discharge play a role in the development of neuropathic pain and the accompanying sensory changes.

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