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A Novel Pathophysiological Mechanism Contributing to Trigeminal Neuralgia

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Trigeminal neuralgia (TN) is a form of neuropathic pain that affects the fifth cranial nerve, the most widely distributed nerve in the head. Although TN has been associated with a variety of pathological conditions, neurovascular compression on the trigeminal nerve as it exits the brainstem is the most frequent reported cause. This compression causes progressive demyelination of the nerve and subsequent aberrant neural transmission. Although several studies have clarified some pathophysiological mechanisms underlying TN, the molecular basis remains vague. Very recently the substitution of methionine 136 by valine (MET126Val) in sodium channel $Na_v1.6$ in a case study of typical TN has suggested a new possible mechanism for TN. The findings of this new mutation provide novel information that warrants further conclusive investigation.

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Trigeminal neuralgia (TN) is a debilitating form of facial pain leading to serious discomfort and reduction in quality of life. This disease has an annual incidence of about 4.5 per 100,000, with a female-to-male ratio of 2.3 (1). In its classic form, TN is characterized by paroxysmal and recurrent painful attacks lasting for fractions of a second, with distribution to one or more divisions of the trigeminal roots. Patients suffering from TN describe an unbearable, excruciating discomfort, sometimes severe enough to lead to suicidal thoughts. The painful attacks, generated by the stimulation of triggers points corresponding to the facial emergence of the trigeminal nerve, are often produced by normal stimuli such as light touch, shaving, toothbrushing or eating. According to the International Classification of Headache Disorders, the etiology of TN is divided into a classical form, caused by vascular compression of the trigeminal nerve root, and a symptomatic form, caused by other factors such as tumors, vascular disorders and demyelination in multiple sclerosis (2). Among several pathophysiological mechanisms, several lines of evidence have contributed to promoting the role of vascular compression in the posterior fossa as a causative factor of TN. In this regard, in 1932 Dandy (3) proposed compression of the trigeminal nerve at its point of entry into the pons from arterial vessels (the superior cerebellar artery) as a possible cause of TN. Subsequently, the concept of vascular compression of cranial nerves in the posterior fossa has been further investigated in numerous clinical and autoptic studies. Currently, we know that patients with trigeminal neuralgia, hemifacial spasm, glossopharyngeal neuralgia and other cranial nerve dysfunction syndromes may have blood vessels close to the respective cranial nerves, and that separating the blood vessel from the nerve by interposing a soft implant between them (microvascular decompression) may be curative (4–6). Although neurovascular compression is considered the etiological factor most frequently observed in hyperactivity syndromes of the cranial nerves, the biochemical mechanisms underlying nerve dysfunction are still unclear. Among the many theories proposed, it has been suggested that these clinical syndromes result from pulsatile compression by arteries at the root entry/exit zone of the cranial nerve, a junctional area between central and peripheral myelin (7).

Accordingly, the pain is attributed to hyperactivity or abnormal discharge arising from the gasserian ganglion, injured nerve roots and the trigeminal nucleus in the brainstem (8). Any possible explanation underlying the pathophysiology of such a disease should account for both the abnormal generation of sensory impulses and their spreading through fibers

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that normally have different functional activities. It has been pointed out that the pathological substrate of this condition is mainly associated with demyelination of the trigeminal root entry zone (9). In this regard, experimental evidence exists about ectopic impulse generation from demyelinated axons (10). Accordingly, the pulsatile compression would result in progressive demyelination and subsequent ephaptic coupling, leading to aberrant impulse generation and spreading. The ephaptic cross-talk between sensory fibers and those delegated to painful stimuli transport can account for TN following tactile stimulation of trigger points. The frequent involvement of the trigeminal nerve root entry zone in patients suffering from demyelinating diseases reflects the fact that fibers subserving light touch and those involved in the generation of pain are in closest proximity in this region. Therefore, when demyelination occurs in this region, ephaptic cross-talk between the two pathways is most likely to happen (11).

The rapid clinical and electrophysiological recovery that often follows microvascular decompression has led to questioning of the central role of demyelination in the development of TN. However, it can be argued that clinical improvement and electrophysiological recovery reflect two different processes. First, the rapid relief of clinical symptoms probably indicates termination of the ectopic generation of impulses and their ephaptic spreading to the adjacent fibers (10). The resolution of nerve compression would allow separation of the demyelinated axons, thus preventing ephaptic cross-talk. The second process to be considered is that the improvement in nerve conduction reflects the rapid functional recovery of the large-caliber, fast-conducting fibers that are not demyelinated (12). This is most likely to occur during conduction of high-frequency trains of impulses. The knowledge that clinical improvement can be dissociated from conduction recovery in some patients following microvascular decompression supports the concept that these are two distinct processes involved in the same pathological condition.

Despite the progress achieved in recent years, the pathogenesis of some phenomena related to TN remains unclear. These include the occurrence of pain in areas outside the field of innervation of the V nerve, and even lights or loud noises. These findings require the involvement of central pathways still under investigation.

Another point under debate is the occurrence of a refractory period of seconds to minutes after an attack of TN, during which further attacks cannot be provoked. Experimental studies have shown the length of time during which the nerve fibers are refractory to further excitation (13). However, the duration of the refractory period in these experimental studies is much shorter than that in patients with TN. Accordingly, besides demyelination, other factors could delay the restoration of membrane potentials and excitability after an episode of TN. These include impairment of mitochondrial ATP production due to inadequate blood perfusion of the compressed nerve root from neurovascular compression (11). After a burst of discharges, nerve hypoperfusion would generate a delay in restoring the ionic gradient, a reduction in extracellular fluid and an increase in resistance to the ionic current between closely juxtaposed demyelinated axons (11).

Whether remyelination occurs following microvascular decompression and plays a role in the initial symptomatic recovery is unclear. Apparently, remyelination cannot explain the immediate relief from neuralgia, although it has been reported in spontaneous remission. In the long term, however, it is possible that remyelination can help to ensure sustained symptomatic relief (13).

Though several studies have clarified some physiopathological mechanisms underlying TN, the molecular basis remain elusive.

In this issue of *Molecular Medicine*, Tanaka and collaborators present a detailed and interesting paper describing the biophysical changes caused by the substitution of methionine 136 by valine (MET126Val) in sodium channel $Na_v1.6$ in a case study of typical TN (14). 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 $NA_V1.6$. It also reduces the threshold for action potential in trigeminal ganglion (TRG) neurons and enhances the neuronal evoked response and the fraction of neurons that fire at a higher rate than those expressing wild-type (WT) channels. As suggested by the authors, the role of voltage-gated sodium channels in TN is consistent with a favorable response to carbamazepine, and several lines of evidence associate the role of $NA_V1.6$ with the pathophysiology of different forms of pain, including TN. The findings of this study support the notion that Met136Val channels produce an increase in the resurgent current in TRG neurons, thus providing the physiological basis for enhanced evoked firing of TRG neurons expressing these channels.

Even if the data are preliminary and limited by the single case analyzed, the study highlights a possible molecular basis in TN, thus extending our knowledge of cranial nerve dysfunction by vascular compression. Although the study represents a basic premise for future investigations, important issues still need to be addressed. First, it would be interesting to understand what happens following neurovascular decompression treatment and whether a relationship exists between such a mutation and ephaptic transmission. Also, it would be interesting to address whether the discovery of an $Na_v1.6$ mutation can be extended to all cases of nerve dysfunction, such as hemifacial spasm, vertigo or spasmodic torticollis, which we know are associated with vascular compression.

Overall, the conclusions, well supported by the reported data, provide novel information that warrants further conclusive investigation.

DISCLOSURE

The authors declare that they have no competing interests as defined by *Molecular Medicine* or other interests that might be perceived to influence the results and discussion reported in this paper.

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