CRITICAL REVIEWS IN ORAL BIOLOGY & MEDICINE

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The Role of Sensory Fiber Demography in Trigeminal and Postherpetic Neuralgias

APPENDIX

A Summary of the Function of Trigeminal Sensory Fibers in a Healthy System

Non-nociceptive and nociceptive stimuli are transduced into action potentials by specialized end organs or free nerve endings in the skin. Tactile-induced action potentials are transmitted mainly by large myelinated *A*β fibers, which are low-threshold mechanosensitive. These fast-conducting fibers, with a mean conduction velocity of 50 m/sec, may also transmit nociceptive signals after nerve injury (Costigan *et al*., 2009; Devor, 2009), as we will discuss in detail later in this Appendix. In contrast, *A*δ and *C*-fibers transmit action potentials related to thermal and mostly painful stimuli (Okeson, 2005; Wall *et al*., 2006). *A*δ are lightly myelinated small fibers and are activated by stimulation, usually described as brief and sharp pain, at a rate of 15 m/sec. The second fibers, the polymodal non-myelinated *C*-fibers, are smaller and slower (1 m/sec) and related to noxious inputs described mostly as burning. Derived from their conduction velocity, *A*δ and *C*-fibers' noxious inputs may be responsible for first and second pain, respectively, clinically representing two successive and distinctive sensations following an isolated noxious stimulation (Ploner *et al.*, 2002; Strigo *et al.*, 2002; Basbaum *et al*., 2009). In addition, *A*δ nociceptors are subdivided into type I (HTM: high-threshold heat and mechanical nociceptors), which mediates the pain provoked by pinprick and other intense mechanical stimuli, and lower-threshold type II nociceptors that mediate first pain after noxious heat (Julius and Basbaum, 2001; Basbaum *et al*., 2009). In the same way, the C-fibers are also subdivided into two classes. The peptidergic population releases substance P and calcitonin-gene-related peptide (CGRP) and expresses TrKA neurotrophin receptors. The non-peptidergic group binds IB4 isolectin and expresses P2X3 receptors (Julius and Basbaum, 2001; Basbaum *et al.*, 2009). Apparently, there is a distinct connection of each kind of C-fiber in the dorsal horn of the spinal cord and in the trigeminal subnucleus caudalis. For instance, while peptidergic C-fibers terminate in the lamina I and outer lamina II, non-peptidergic fibers terminate in inner lamina II (Basbaum *et al*., 2009). Nevertheless, most C-fibers terminate in the superficial layers of the spinal or caudalis dorsal horn and are scarce in the deep layers as well as in the subnucleus oralis of the trigeminal brainstem nuclear sensory complex (TBNSC). However, it seems that interneurons provide connections between the superficial and deep layers of the subnucleus caudalis or spinal cord, and also between the superficial layers of the subnucleus caudalis and more rostral subnuclei (Dallel *et al.*, 1998, 2003; Woda, 2003).

Trigeminal Neuropathic Pain of Dental Origin

When neuropathic pain is related to a tooth extraction or endodontic treatment (previously referred to as 'phantom tooth pain'), the more common symptom described by patients a dull and poorly localized burning (Leeuw, 2008), which is characteristic of second pain and thus related to C-fiber activity. In fact, the great majority of pulp afferent fibers (about 70-80%) are unmyelinated. They are especially located in the core or pulp proper, and are responsible for the transmission of the C-fiber type of pain of dental origin (Reader and Foreman, 1981; Johnsen *et al.*, 1983; Byers, 1984; Närhi *et al.*, 1992; Mengel *et al.*, 1993; Nair and Schroeder, 1995; Ten Cate, 1998; Bender, 2000; Abd-Elmeguid and Yu, 2009), while the A-fibers are mainly located at the pulp-dentin border in the coronal portion of the pulp and are responsible for the mediation of sharp pain induced by dentinal stimulation and pre-pain sensation. Here, it is important to comment that some of the myelinated axons that enter the tooth pulp gradually lose their myelin coat as the nerve bundles ascend coronally. Nevertheless, as demonstrated by previous studies in human premolars, at the juxta-apical level, about 87% of axons are non-myelinated C-fibers and only 13% are A-fibers (Nair *et al.*, 1992; Nair, 1995; Nair and Schroeder, 1995).

Effects of Pharmacological Treatments for TNP in the Function of Trigeminal Sensory Fibers

Various studies have identified some similarities between neuropathic pain and epilepsy. The increased activation of N-methyl-D-aspartate (NMDA) receptors in neuropathic animal models

has also been documented in specific neurons in epilepsy (Dickenson, 1995; Backonja, 2000). Sodium channel blockers, which include anticonvulsants (such as carbamazepine and Lamotrigine), tricyclic antidepressants (*e.g.* amitriptyline), and topical local anesthetics, have similar effects on the functioning of sensory fibers in both diseases (Rogers *et al.*, 2006; Cummins *et al*., 2007). Carbamazepine, a gold standard treatment for typical-TN, is an anticonvulsant that suppresses spontaneous firing of afferent sensory fibers, without disturbing the regular input transmission (Tremont-Lukats *et al.,* 2000). This mechanism helps to explain the effects of this drug in trigeminal neuropathic pain, since injured sensory fibers exhibit spontaneous or ectopic firing, which depends on voltage-sensitive sodium channels (Fox *et al.*, 2003). In fact, abnormal expression of specific sodium channels (*e.g*., NAV 1.7 and NAV 1.8) was recently demonstrated in patients with trigeminal neuralgia (Siqueira *et al.,* 2009). Nevertheless, the mechanism of action of anticonvulsants is not restricted to sensory fibers, but may also affect cortical activity, since a fMRI experiment with rats showed that Lamotrigine decreases somatosensory cortex response to paw stimulation; however, there is no effect on the regional cerebral blood flow (rCBF) baseline (Kida *et al*., 2001). Other anticonvulsants, such as gabapentin and pregabalin, are especially effective for patients with PHN (Finnerup *et al.*, 2005; Attal *et al.*, 2006). However, apparently their action is related more to calcium than to sodium channels (Fox *et al.*, 2003). They bind to the $Ca_V\alpha_2\delta$ auxiliary subunit of the presynaptic voltage-gated calcium channels, inducing conformational changes that inhibit the abnormally intense neuronal activity by reducing the synaptic release of glutamate and other neurotransmitters (Tuchman *et al.*, 2010). In the case of atypical-TN, the use of antidepressants provides additional or solo benefits when symptoms do not respond to anticonvulsant therapy (Delvaux and Schoenen, 2001), with odds ratio and number-needed-to-treat of 4.1 and 2.8, respectively (McQuay *et al.,* 1996; Saarto and Wiffen, 2007).

Efficacy of Surgical Treatments for TNP Based on Sensory Fiber Involvement: Why is Microvascular Decompression so Successful in Typical-TN?

Surgical procedures for TNP are, in a sense, empirical: They aim either to spare or to damage, to various degrees, the sensory fibers involved. However, most of them provide short-term pain relief. Unfortunately, in the long term, this positive immediate outcome can diminish, with pain recurrence and possible worsening of the pre-surgical symptoms. The significant pain relief in typical-TN achieved by microvascular decompression (MVD) surgery corroborates the hypothesis that vascular compression plays a major role in its etiology (Sindou *et al.*, 2006). This is credited to the partial selective impact of compression on myelinated fibers, while the unmyelinated C-fibers are relatively spared at the upper level of REZ. In the long term, pain recurrence rates for MVD are 15% (Taha and Tew, 1996). MVD is also associated with lower rates of post-surgical sensory disturbances, depending on the surgeon's skills and experience (Kalkanis *et al.,* 2003; Sindou *et al.*, 2006), especially regarding the risks associated with craniotomy. Percutaneous balloon compression (PBC) of the trigeminal ganglion, another surgical procedure for TNP, also produces low occurrence of corneal anesthesia and anesthesia dolorosa (Skirving and Dan, 2001), with 21% pain recurrence (Taha and Tew, 1996), but with significantly high rates of motor dysfunction in a long-term follow-up period due to possible compression of motor myelinated fibers. Neuroablative methods, such as radiofrequency, glycerol trigeminal rhizotomy, and gamma knife radiosurgery, have even higher pain recurrence, because of their non-selective harmful effects on all types of sensory fibers. Consequently, it is not unusual to observe typical-TN patients who endured neuroablative surgical procedures reporting recurrent pain not only as evoked, but also as constant and spontaneous, with more atypical-TN pain qualities. This switch from typical-TN to atypical-TN could be related to the extent of the damage by neuroablative procedures to increasing amounts of C-fibers, instead of to the initial predominance of A-fiber dysfunction. Nevertheless, the presence of these atypical symptoms seems to reduce the overall benefits of additional surgical procedures in TNP disorders.

The goal in TNP treatment is to modulate symptoms to a bearable level for patients without affecting their quality of life. Taking into consideration other existent comorbid conditions (*e.g*., sleep disorders, and depression), the development of step-by-step and multidisciplinary treatment approaches with the "do not harm" motto has led to improvement in patient outcome and compliance. This conservative view translates into initial medicinal therapy followed by surgical procedures that, if indicated and allowed by the patient's health status, should avoid unnecessary further damage of the nervous system milieu, especially the afferent sensory fibers.

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