We Are Trigeminal and Different

The trigeminal nerve supplies all sensory innervation to the head and associated structures. This is "our" nerve, and it is inevitably involved in the multitude of painful disorders that we manage on a daily basis. Despite distinct embryogenic origins and processing capabilities, trigeminal neurons and cell bodies should not be significantly different from their spinal counterparts. The anatomical set-up is similar, with afferent neuronal cell bodies, both spinal and trigeminal, located in the dorsal root (DRG) and the trigeminal (TG) ganglia, respectively. The DRG and TG structures are similar, and they are essentially homologs of each other. The clearest anatomical differences are the proximity of the trigeminal system to the CNS and the relatively long trajectory of afferent axons in the spinal system. Additionally, the TG is the only sensory ganglion of the body that resides within the CNS.

Clinical and laboratory observations, however, suggest differences between the trigeminal and spinal systems that may underlie dissimilar functional properties and response to injury or disease. There may be subtle differences between these two systems, the basis and consequences of which are still unclear. One interesting difference: The trigeminal system is the only nerve involved in spontaneous denervation during shedding of deciduous teeth. Is that indicative of any differences that may be of consequence?

Evidence in animal models suggests that the trigeminal nerve is more resistant than the spinal system in developing neuropathic pain (NP) following insult or disease. Moreover, sprouting of sympathetic nerves around large ganglionic neurons following injury is not observed in the TG, but is present in the DRG, and cervical sympathectomy does not alter trigeminal NP behavior, but does so in the spinal system. Together with a rich vascular supply to trigeminally innervated regions (ie, the trigeminovascular system), these may explain some differences in the clinical phenotypes of trigeminal vs spinal pain syndromes. For example, clinically diabetic neuropathy is a common source of NP in the limbs and trunk involving classical signs of paresthesia and allodynia. In the trigeminal system, these effects are not pronounced, and there is a sparsity of reports of typical painful diabetic neuropathic pain or indeed neuropathy at all. Insults to trigeminal nerve branches such as microinjuries (eg, tooth extraction, root canal treatment) or macroinjuries rarely result in chronic NP and are consistently reported at a lower prevalence than following injury to the spinal system. Complex regional pain syndrome, a disabling painful disorder resulting from mild to severe nerve injury that commonly presents in the extremities and is accompanied by sensory, vascular, and muscular problems, has no true equivalent with all of these diagnostic features in the trigeminal system.

Conversely, pain syndromes such as migraine, cluster headache, and trigeminal neuralgia exist only in the trigeminal system. Taken together, these findings suggest that the spinal and trigeminal systems may differ, particularly in the way they respond to injury. How and why remain a mystery.

Gene expression data may offer some insights. Studies in naïve animals reveal differences in expressed genes between the DRG and the TG, indicating that different molecular mechanisms are involved in the baseline functionality of the two systems. The animal data seem to align well with human data on the DRG and TG. It has recently been shown that spinal and trigeminal neuropathies caused by trauma are accompanied by differentially regulated genes within the DRG and TG. The genes involved suggest that neuroinflammatory signaling and other related pathways are involved. These studies are limited due to the fact that they are "whole-ganglion" analyses and do not indicate from which type of neuron or nonneuronal cell present in the ganglia the changes originate.

Yet, overall, the message is that the trigeminal system is different. As molecular techniques improve, we may be able to use these data to identify protective genes and pathways that may be novel targets for pain intervention and to elucidate some of the fascinating differences in diseases present exclusively in the trigeminal system.[1–3]

Rafael Benoliel
Editor-in-Chief

References

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William Maixner, DDS, PhD
(1952–2020)

The fields of pain and temporomandibular disorders (TMDs) have benefitted greatly from research produced by many individuals. The evidence accrued over the years has changed our understanding from the occlusion and craniofacial structure(s) as the focus of interest to the recognition that TMDs are a set of complex disorders that require the biopsychosocial model for their understanding, that it is inappropriate to consider TMDs solely as a localized condition, that TMDs exist within a spectrum of pain disorders, and that structural factors alone have relatively little importance. While many investigators have contributed collectively to this summary of current knowledge, William "Bill" Maixner had an encompassing vision regarding the complexity of TMDs, which developed over several decades. Bill eventually developed one of the largest research teams for studying TMDs, as well as research that has yielded nearly 60 publications in the past 10 years and that has contributed substantially to this summary. Bill, who passed away on Monday, November 2, 2020, was a friend, a colleague, and a mentor to many.

Bill was born in Ottumwa, Iowa, and received his BS, DDS, and PhD from the University of Iowa. After his research fellowship at the National Institutes of Health in the laboratory of Ron Dubner, who remained a lifelong friend, collaborator, and mentor, Bill spent the next 30 years at the School of Dentistry, University of North Carolina at Chapel Hill (UNC), and was eventually named the Mary Lily Kenan Flagler Bingham Distinguished University Professor. While at UNC, Bill had many roles: associate dean for Academic Affairs, co-director of the Oral and Maxillofacial Pain Program, and director of the Center for Pain Research and Innovation. The activity he may be most remembered for, and one that certainly changed the field of TMDs, was the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study, which Bill initiated—with colleagues—as a pre-OPPERA study and then with two sequential major multi-site studies to investigate risk factors for first-onset TMD and factors that affect the transition from acute pain to chronic pain. The OPPERA study was notable for its design, size, depth, and commitment to discovery of new insights. OPPERA findings dramatically changed our understanding of not only TMDs but also all pain conditions, and the study is well-regarded around the world as a benchmark.

Bill extended a kind and very personal invitation in 2004 for me to join the emerging OPPERA group. That personal touch was one of Bill's particularly unique and wonderful skills—one that contributed greatly to his research team. Bill pursued his own particular hypotheses of interest and provided a wide space for everyone to contribute equally to the overall study hypotheses, analyses, and writing. A large part of our success within OPPERA was that Bill led with an easy hand, always generous to share the podium and leadership. His sense of humor, joy, and openness with the collaborative research process was always present.

Toward the end of the second OPPERA study, Bill envisioned new research directions, as well as a clinical setting where the insights from the OPPERA findings could be implemented. Duke University offered such an opportunity, and Bill joined Duke in 2016 as the Joannes H. Karis, MD, Professor of Anesthesiology, director for the Center for Translational Pain Medicine at Duke University Medical Center, and vice chair for Research at Duke Anesthesiology.

After Bill moved to Duke, the OPPERA team continued with its work, a testament to the character of the research team that Bill had so strongly had made an imprint on. While Bill received many career accolades and awards, he seemed most rewarded by the progress of our research and its impact on the field—and, by implication, how it would change expected clinical care. For the many people who had the opportunity to collaborate professionally with Bill, his encompassing vision, easy touch, consistent encouragement, and soft humor linger as defining qualities. Both the fields of pain and TMDs owe much to Bill's contributions.

Richard Ohrbach
Associate Editor