From Pain to Movement: A Tribute to Professor Barry J. Sessle

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This tribute article to Professor Barry J. Sessle summarizes the 6 presentations delivered at the July 1, 2008 symposium at the University of Toronto. The symposium honored 3 "giants" in orofacial neuroscience, Professors B.J. Sessle, J.P. Lund, and A.G. Hannam. The 6 presentations paying tribute to Sessle spanned the period from the early phase of his career up to some of his most recent studies with colleagues in Asia, Europe, and Australia as well as Canada. The studies have included those providing an improved understanding of the cortical control of sensory inputs in pain perception (presented by R. Dubner) and in the control of mastication and swallowing, as well as brainstem mechanisms of orofacial pain (K. Iwata, G. Murray). His current activities in his laboratory and in Denmark are also highlighted (L. Avivi-Arber, P. Svensson). The potential transfer of basic research discoveries toward drug development in pain control that stem from some of his research is also described (B. Cairns). The final section of the paper includes a commentary from Professor Sessle. J OROFAC PAIN 2008;22:287–296

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The Postdoctoral Years

Ronald Dubner was the initial presenter. He first noted that he had known Professor Sessle for the past 40 years, since the time Sessle arrived at the National Institutes of Health (NIH) in 1968 as a young postdoctoral scientist from Australia. He was the first of many Visiting Fellows to join Dubner at the Neural Mechanisms Section of NIDR, which eventually became the Neurobiology and Anesthesiology Branch of the National Institute of Dental and Craniofacial Research (NIDCR). He had previously completed his dental degree at the University of Sydney, Australia, and just recently his PhD with Ian Darian-Smith at the medical school of the University of New South Wales in Sydney; his PhD studies were published in *Science,* the *Journal of Physiology,* and *Brain Research.*

Dubner noted that they initiated a study together of afferent and corticofugal inhibition in the trigeminal system, mechanisms thought to be important for sensory discrimination in the somatic system. The purpose of the study was to: *(1)* identify a feedback pathway between the trigeminal brainstem nuclei and the face projection area of the cerebral cortex in the cat; and *(2)* observe the presence of presynaptic modification of corticofugal fibers by afferent peripheral nerve stimulation. They demonstrated this by using a method first described by Pat Wall and modified by

Darian-Smith[1]: A change in excitability of the neuron's axonal ending produced by the conditioning stimulus was reflected as a difference in the probability of occurrence of the antidromic response recorded from the neuronal cell body region. A higher probability of occurrence of neuronal single unit activity indicated an increase in excitability referred to as presynaptic depolarization.

Their first paper was published in *Nature* in 1969[2] and demonstrated presynaptic depolarization of corticofugal fibers participating in such a feedback loop. Presynaptic depolarization at that time was considered a measure of presynaptic inhibition, which was a newly discovered inhibitory mechanism in somatosensory pathways. They also utilized the same method to show that neurons in the ventrobasal thalamus and the posterior thalamic nucleus exhibited both corticofugal and afferent presynaptic mechanisms. Of interest was the finding of presynaptic hyperpolarization as well as presynaptic depolarization on thalamic afferents and primary trigeminal afferents. At the time, this finding was of great significance because of the postulate by Melzack and Wall that presynaptic hyperpolarization was an important mechanism of facilitation in the "gate control theory" of pain.[3]

Dubner and Sessle also participated in a subsequently published conference[4] on orofacial function held in Honolulu in January 1970, organized by Yojiro Kawamura of Japan and Dubner. It was supported by the US-Japan Cooperative Science Program. This conference brought together leading scientists in the area of orofacial sensory and motor mechanisms. Its long-lasting contribution was that it led to multiple future collaborations between Japanese, Canadian, and US scientists in the Sessle and Dubner laboratories in future years, as also noted below.

The collaborations between Dubner and Sessle did not end with the conclusion of Sessle's visiting fellow appointment in 1971. In the late 1970s, Dubner and Sessle collaborated in Toronto and provided the first documentation of descending modulatory mechanisms affecting identified trigeminal nociceptive neurons. Also, in 1978, Sessle and Dubner, together with Arthur Storey, wrote a book on the neural basis of oral and facial function.[5] Dubner related the origins of the book: it goes back to the 1960s when Storey, a Canadian dentist, neuroscientist, and orthodontist, and Dubner were seeking doctoral degrees in physiology at the University of Michigan. Storey subsequently took a position at the University of Toronto Faculty of Dentistry. During Sessle's stay at the NIDR, Storey contacted Dubner and indicated that the University of Toronto wanted to recruit another neuroscientist. Dubner recommended Sessle to Storey, and Sessle was offered, and ultimately accepted, the position. The rest is history. The 3 of them decided that the audience for the book would be neuroscientists, academic dentists, and physicians with an interest in sensorimotor function of the head and neck. The book was very successful and is utilized even today. In 1990 it was declared a Science Citation Index citation classic as a result of being cited in more than 200 publications.[6] This is considerable for a book, especially one that had been first published 12 years earlier.

Sessle and Dubner were subsequently asked by Jim Lund and Gilles Lavigne to participate with them as editors of a book geared to teachers of oral biology, oral medicine, and facial pain and to students in dental and medical schools. Most of the chapters were first presented as papers at a symposium held in Vancouver in 1999, preceding the annual meeting of the International Association for Dental Research (IADR) that year. The book was first published in 2001 and dedicated to Art Storey, who passed away in 1998. A second edition has recently been published[7]; indeed, it was released to coincide with the July 1 symposium and the subsequent IADR meeting in Toronto.

Dubner noted that Sessle's list of awards and honors are too long to enumerate. It is very clear that he has excelled as a researcher, educator, and administrator. He is a leader in his chosen field. He strives for and always reaches a high level of achievement in his work as well as his hobbies and vocations.

Impact of Sessle's Work on Research in Asia

The next speaker, Koichi Iwata, noted that Professor Sessle has been and still is a very important scientist in Asian trigeminal neuroscience, and the impact of his work on Asian neuroscience, especially in the fields of orofacial motor control and trigeminal pain mechanisms, has been enormous. Twenty Japanese scientists as well as a dozen scientists and graduate students from other parts of Asia have worked with Sessle in Toronto. Most of them have subsequently made great contributions to the basic research in the fields of trigeminal sensory and motor functions. In the case of the Japanese scientists, their collaborative research with Professor Sessle started in 1978. Professor Sumino was the first researcher from

Japan to work with him. Almost 30 scientific articles coauthored by Sessle and Japanese scientists have been produced from his laboratory in the past 29 years.

Several of these collaborations involved studies with Iwata, who illustrated this with some recent examples, including ones fostered by a Joint Japan/Canada Collaborative Research Program award that they currently hold. One recent paper[8] described the underlying mechanisms of trigeminal neuropathic pain following regeneration of the injured inferior alveolar nerve. It represents the first paper reporting changes in trigeminal brainstem nociceptive neurons produced by regeneration of the injured trigeminal nerve and should improve our understanding of trigeminal neuropathic pain mechanisms. Another recent paper[9] has described the organization of nociceptive neurons in brainstem subnucleus caudalis (Vc) and upper cervical spinal cord (C1-C2) following noxious stimulation of intraoral structures and facial skin. This paper has provided novel information on the functional differences of Vc and C1-C2 nociceptive neurons involved in oral and facial pain. A particular focus of Sessle's group at the moment is on astroglial involvement in acute and chronic orofacial pain models in rats following trigeminal nerve injury or pulp inflammation. Their studies, including collaborative experiments with Iwata's group, have documented the involvement of the glutamate-glutamine shuttle in astroglia in central sensitization of Vc nociceptive neurons in these models. Since central sensitization is considered a fundamental process critical in the development and maintenance of chronic pain conditions, these studies are providing a better understanding of mechanisms involved in trigeminal neuropathic and inflammatory pain conditions.

The Primary Sensorimotor Cerebral Cortex and Jaw Muscles: A Canadian and Australian Collaboration

Gregory Murray, the next presenter, pointed out that another research focus of Professor Sessle's activities has been on orofacial motor control. His studies, starting in the mid-1980s, have characterized a critical role for the face sensorimotor cerebral cortex in voluntary and semi-automatic orofacial movements. Some of these studies involved collaborative research with Murray and Iven Klineberg and their colleagues at the University of Sydney, focusing on the functional properties of single motor units within the superior head of the human lateral pterygoid muscle (SHLP). Most recently, the Toronto and Sydney groups have collaborated to study the effects of experimental orofacial pain on human jaw muscle activity and rat motor cortical excitability. Murray elaborated upon the Toronto-based and Sydney-based studies.

Cerebral Cortical Control of Primate Orofacial Movements

He first pointed out that there is abundant evidence for a critical role for the face region of the primary motor cerebral cortex (face MI) in the control of orofacial movements. Early studies suggested that the face MI is important in the production of facial and tongue movements but has only a limited role in jaw-closing movements.[9–11] The relative role of the face MI in the production of facial and tongue movements as distinct from jaw movements was studied in 2 sets of experiments in awake monkeys in Sessle's laboratory. In the first,[10] face MI, which had been previously defined by intracortical microstimulation (ICMS), was reversibly inactivated by cooling. Trained monkeys performed a tongue protrusion task and a biting task that required minimal target force levels for successful task performance. During cooling, there was a significant reduction in the success rates for the performance of the tongue protrusion task but not for the performance of the biting task, although it could affect the rate of bite force application. These data documented the essential role for face MI in the generation and fine control of voluntary tongue movements and a role in the fine control of jaw-closing movements.

In the second set of experiments,[11] single neuronal recordings were made at ICMS-defined sites to establish a neuronal correlate for these different behavioral relations. In the ICMS-defined tongue region of face MI (tongue-MI), a significantly higher proportion of neurons were related to the tongue-protrusion task than to the biting task; the reverse was found for neurons within the ICMS-defined jaw region of face MI. Tongue-MI neurons that were related to the tongue protrusion task were located at sites from which ICMS evoked a variety of tongue twitch movements, and the neurons exhibited different patterns of activity during the tongue-protrusion task and received different peripheral origins of mechanosensory afferent input. The data suggested that there were different efferent zones within tongue-MI that were deployed differentially, in terms of magnitude and pattern of neuronal activity, to produce the appropriate change in tongue shape and position

required for performance of the tongue-protrusion task. Additional studies[12] suggested that tongue-MI also plays a role in the regulation of semi-automatic tongue movements, such as swallowing. Another set of additional studies that employed many of the same techniques described above identified an important role for the face somatosensory cortex (face SI) in the fine control of voluntary tongue and biting movements.[13,14]

Definition of Functional Properties of Single Motor Units Within the Lateral Pterygoid Muscle

Murray noted that there is good evidence for multiple representation of evoked movements within face MI.[9–11] This very sophisticated control system implies that the system being driven, ie, the musculature, is also very sophisticated. There is indeed good evidence that the jaw muscles are functionally complex, with sophisticated internal architectures.[15] The lateral pterygoid muscle, in particular its superior head (SHLP), is a poorly understood jaw muscle that has been implicated as playing a critical role in the etiology of temporomandibular disorders (TMD). In 18 human subjects, SHLP single motor units were intramuscularly recorded at computed tomography–verified sites during horizontal (eg, protrusion) and vertical (eg, opening) jaw tasks (recorded by a jaw-tracking device) and at resting postural jaw position.[16] The data suggested differential activation within SHLP during the different jaw movements and raised the possibility of functional heterogeneity within SHLP, namely, selective activation within subcompartments of the SHLP to allow the appropriate force vector to be applied to the condyle.

Experimental Orofacial Pain and Human Jaw Muscle Activity and Rat Motor Cortical Excitability

Since the effects of pain on movement are not well understood, the next set of collaborative studies that were highlighted by Murray were those that examined the effects of experimental pain on the activity of jaw muscles during goal-directed tasks in humans and on the excitability of the face MI in rats. In the human studies,[17] mandibular movement was tracked and electromyographic (EMG) activity was recorded from bilateral masseter and right posterior temporalis, anterior digastric, and the inferior heads of lateral pterygoid muscles in 22 asymptomatic subjects at postural jaw position and during 3 tasks: *(a)* protrusion, *(b)* contralateral (left) movement, and *(c)* open jaw movement. After control trials, 4.5% hypertonic saline (compared to 0.9% isotonic saline) injected into the right masseter muscle produced significant effects on EMG activity that varied with the task in which the muscle participated, irrespective of whether the muscle was an agonist or an antagonist in the tasks. These data suggest that under constrained goal-directed tasks, the relation between pain and motor activity may not be clear cut.

The mechanisms of some of these effects of pain on jaw muscle activity may possibly be mediated by effects of nociceptive inputs on supraspinal centers. Therefore, in the rat study,[18] ketamine-anesthetized rats were used to determine if lingual algesic chemical (glutamate) stimulation affected face MI excitability defined by ICMS. Left and right genioglossus ICMS thresholds, but not anterior digastric ICMS thresholds, were significantly increased (up to 350%) in the glutamate infusion group compared with intact and isotonic saline infusion groups. These dramatic and long-lasting effects of glutamate on ICMS-evoked genioglossus activity contrast with its weak effects only on genioglossus activity evoked from the internal capsule or hypoglossal nucleus. This is the first documentation that intraoral noxious stimulation results in prolonged neuroplastic changes manifested as a decrease in face MI excitability, and raises the possibility that pain-related disturbances in motor function may involve changes in motor control exerted by MI.

Murray concluded by noting that Sessle's contributions over the past 40 years to orofacial sensory and motor research have been enormous. Despite all the significant recognition that he has received, he remains unaffected, is totally approachable, and has a wonderful sense of humor.

Milestones in Research on Brain Neuroplastic Mechanisms and Oral Sensorimotor Functions: The Student Perspective

The next speaker was Limor Avivi-Arber, who first noted that Professor Sessle's major contributions to brain research related to orofacial sensory and motor functions are significant milestones in orofacial neuroscience research, and that his many pioneering and innovative research activities could not be achieved without his global network of humming nodes and the creativity and dedication of his students and postdoctoral fellows. She reviewed recent work from Sessle's laboratory, especially from her own perspective, that of a

graduate student, taking in the many investigations ongoing in the laboratory that underscore the neuroplastic capabilities of the brain at 2 levels: functional reorganization of motor representations within the primary motor cortex representing the orofacial area (ie, face MI) in monkeys and rats following manipulations to the oral tissues or training in a novel motor task; and the involvement of brainstem glutamatergic and purinergic receptors and glial cells in trigeminal central sensitization leading to orofacial pain states and reflected in functional reorganization of nociceptive mechanoreceptive fields and neuronal properties within the trigeminal brainstem complex and the thalamus following experimentally induced inflammation or nerve damage.

Neuroplastic changes may occur at the peripheral, subcortical, or cortical level, and have been associated with adaptation to changes in sensory inputs, altered motor functions, and acquisition of novel motor skills. It is well known from clinical studies that injury to the nerves supplying the oral tissues as well as modification to the occlusion as a result of dental attrition or loss of teeth and the subsequent restoration with dental prostheses are associated with adaptive and often maladaptive behaviors to the altered oral state. Furthermore, these behaviors may improve with time as patients learn to adapt to the altered oral environment (eg, refs 19, 20). To study the possible mechanisms underlying these adaptive processes, ongoing studies in Sessle's laboratory have utilized the ICMS technique to investigate whether face MI neuroplastic mechanisms may be associated with various alterations in the oral environment in anesthetized rats and with the training of novel motor task in awake monkeys and in humans.[9,18,21,22] These studies have demonstrated that different manipulations to the oral tissues are associated with specific yet sometimes different ICMS-defined neuroplastic changes and that different neuroplastic changes may occur at different points of time. Bilateral trimming of the rat's mandibular incisors for 1 week or less is associated with a significantly decreased anterior digastric (AD) representation within face MI that is reversed once the teeth are allowed to erupt back into occlusion. On the other hand, unilateral extraction of the rat mandibular incisor is associated 1 week later with face MI neuroplastic changes reflected in a significantly increased AD representation and a lateral shift of its center of gravity. Furthermore, unilateral transection of the lingual nerve supplying the tongue results in time-dependent face MI changes in AD and genioglossus representations, suggesting that loss of sensory inputs may be associated with neuroplastic changes in face MI motor representations. Correlated ICMS studies in awake monkeys and investigations using transcranial magnetic stimulation (TMS) in humans further suggest that neuroplasticity within face MI is a necessary condition for the primate's ability to perform a novel tongue-task and that pain can modulate these face-MI neuroplastic changes.[9,21,23,24] The correlated findings in rats mentioned earlier further support the effect of pain in inducing face MI neuroplasticity,[18] and its possible disruption of motor function (see above).

There is also evidence from Sessle's laboratory several years ago that neuroplastic changes associated with orofacial alterations (eg, endodontic therapy) may also occur at subcortical levels (eg, brainstem).[25,26] Of particular interest to pain research are their recent findings of trigeminal central sensitization, which is considered a crucial process underlying the development and maintenance of acute and chronic pain following peripheral nerve injury or inflammation that contributes to the clinical manifestations of hyperalgesia, allodynia, pain spread and referral. Studies in the Sessle laboratory were the first to document central sensitization in trigeminal nociceptive pathways, eg, that application of the inflammatory irritant mustard oil to the rat's tooth pulp induces central sensitization in functionally identified trigeminal nociceptive neurons in the brainstem subnucleus caudalis and involve both glutamatergic and purinergic (P2X) processes within caudalis; central sensitization can also be induced in the thalamus, where it is dependent on the functional integrity of caudalis.[27–30] Furthermore, recent studies in his laboratory have revealed the crucial involvement in trigeminal central sensitization also of glial cells, in particular the glutamate-glutamine shuttle in astrocytes.[31,32] Blocking the glutamate-glutamine shuttle in astroglia can markedly attenuate the development and maintenance of caudalis central sensitization, but not normal nociceptive processing, in functionally identified Vc nociceptive neurons. These novel findings document a new player (glial cells) in trigeminal pain mechanisms and raise the possibility of new targets for drug development to control pain.

In conclusion, Avivi-Arber remarked that a student working in the Sessle laboratory gains extensive research expertise and insights into a variety of mechanisms underlying orofacial function. Of particular note are findings that various manipulations to the oral tissues, as well as learning novel oral motor skills, may be associated with significant cortical and subcortical neuroplastic changes.

These changes may be related to the animal's ability to learn to adapt to the altered oral environment, but they may also be related to sensorimotor disorders and pain. Understanding these neuroplastic mechanisms in animals and in humans is of clinical significance, as it may provide future scope for improved therapeutic strategies for the control of orofacial pain and for the restoration of vital oral sensory and motor functions such as eating and speaking, thereby improving quality of life of patients suffering from severe sensorimotor deficits.

A Human Approach to Bruxism and Orofacial Pain Research

Peter Svensson was the next presenter and highlighted the significance of sensory-motor integration in the orofacial region, with a particular reference to the contribution from Professor Sessle's laboratory studies in animal models to human research. He noted its direct bearing on conceptual models of how pain and motor function are interrelated. The "vicious cycle" model predicted a mutually reinforcing relationship between pain and muscle hyperactivity, ie, pain would lead to muscle hyperactivity, which would lead to more pain. This model was challenged by Lund and colleagues in the pain-adaptation model, which suggests that motor function would be adjusted to painful input by decreasing the agonist muscle activity and increasing the antagonist muscle activity, ie, leading to slower and less forceful movements, which should allow recovery and facilitate healing (see Lund Tribute article).

Influence of Nociception and Pain and Muscle Activity

Svensson stated that a simple and straightforward approach to "open" the vicious cycle is to apply nociceptive or painful stimuli and observe the muscle activity, for example, with the use of EMG recordings. He outlined how Sessle's group had pioneered this research field and developed animal models to test the effect of various substances (eg, hypertonic saline, mustard oil, capsaicin) on jaw-closer, jaw-opener, and cervical muscle EMG activity.[34–38] These models demonstrated robust and consistent increases in EMG activity in the examined muscles. One interpretation of these results was that a nociceptive input, indeed, was associated with muscle hyperactivity but in both agonist and antagonist muscles. Thus, the jaw was unlikely to move but rather to be maintained by a "splinting" response in the same position. Human experimental pain studies have, however, failed to show the same kind of EMG increases when the jaw is held in a relaxed position, but a recent study in humans nevertheless documented that experimental glutamate-evoked pain in the jaw muscle as well as neck muscle was associated with a remarkable EMG increase in the neck muscles.[39] There is, indeed, good electrophysiological evidence from Sessle's laboratory for a significant convergence of trigeminal and cervical nociceptive inputs on nociceptive neurons in Vc,[40] which may be part of the underlying mechanisms for the observed EMG responses. Further evidence from human experimental studies performed in collaboration with Sessle have also shown that jaw or neck muscle pain modulates brainstem-mediated reflex responses,[41,42] indicating a bilateral interaction between the trigeminal and cervical motor systems. Nociceptive and painful inputs appear to be strong modifiers of motor function, but caution is needed when animal and human experimental studies are extrapolated to the clinical condition because a multitude of factors related to the type, intensity, duration, and stimulus quality, as well as interspecies differences, contextual, and motivational aspects of pain, may further complicate the relationship between pain and muscle activity.[43]

Influence of Muscle Activity on Pain

Svensson then mentioned that the other question related to the vicious cycle is how muscle activity and pain (or nociceptive behavior) are related. In the orofacial literature, bruxism is frequently suggested to cause hyperactivity, leading to pain and thereby initiating the vicious cycle. Sessle has also contributed to the understanding of bruxism physiology.[44] Over the last decades several experimental bruxism studies have been performed in healthy subjects (for a recent review see ref 45). The outcome of these studies is a short-lasting muscle pain or soreness with some resemblance of delayed-onset muscle soreness (DOMS). Nevertheless, repeated clenching tasks do not lead to increased levels of pain but on the contrary a decrease in pain and unpleasantness as well as increases in maximal voluntary bite force levels.[46] There is also emerging evidence that patients with high EMG activity during sleep have less pain than patients with little EMG activity.[45] These findings challenge the traditional view that bruxism is a strong risk factor for orofacial muscle pain and again underline the necessity to consider other neurobiological and psychosocial parameters.

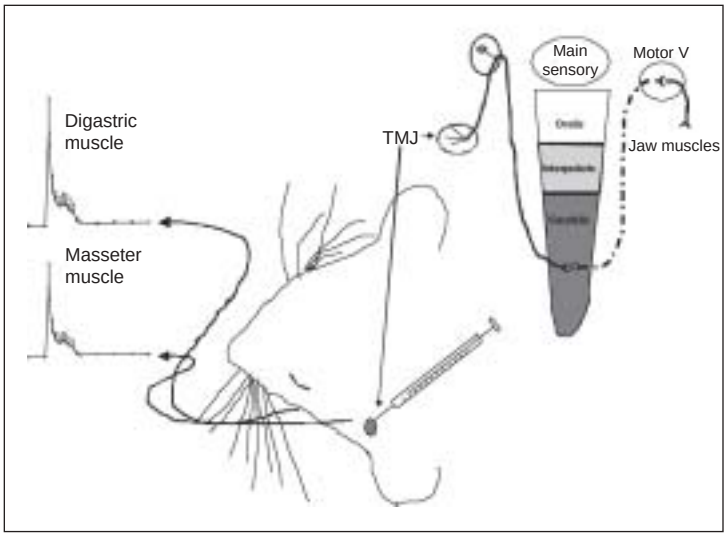

Fig 1 Illustration of the TMJ-jaw muscle reflex pathway. Injection of an algesic substance into the rat TMJ evokes reflex jaw muscle activity that can be measured in the jaw-opener (digastric) and closer (masseter) muscles. The reflex pathway includes TMJ afferent fibers that pass through the trigeminal ganglion en route to the subnucleus caudalis of the trigeminal sensory nuclear complex. An as yet undefined pathway *(dotted line)* connects the output of caudalis to the trigeminal motor nucleus.

Svensson concluded by noting that the interaction between Sessle's group at the University of Toronto, Brian Cairns at the University of British Columbia, Lars Arendt-Nielsen and Peter Svensson at Aalborg University and the University of Aarhus, Denmark, and Sigvard Koop and colleagues at the Karolinska Institute has been successful in the attempt to apply a translational approach to the study of orofacial motor physiology and pain. Complex interactions between pain, nociceptive activity, and muscle activity have been identified in their human studies and animal models, but the data clearly indicate that the era of the vicious cycle is over and that more elaborate models need to be formulated.[47]

Pain and Implications to Drug Development From Discoveries in the Sessle Laboratory

Brian Cairns was the final Tribute speaker and first expressed his great good fortune to have joined Professor Sessle's laboratory at a time when the laboratory was becoming increasingly interested in pharmacological mechanisms of craniofacial pain. He provided a brief summary of some of the findings generated from a unique TMJ pain model developed and used by Sessle and his laboratory.

The Temporomandibular Joint (TMJ)-Jaw Muscle Reflex Model

As illustrated in Fig 1, the acute TMJ injury model wherein injection of several algogenic substances evokes a reflex bilateral coactivation of the jaw opener and closer muscles was initially described by the Sessle laboratory in the late 1980s.[34] Subsequently, they showed that injection of the inflammatory irritant mustard oil (MO) into the rat TMJ also reliably evokes reflex jaw muscle activity.[38] The trigeminal subnucleus caudalis is a critical relay in this TMJ-jaw muscle reflex pathway, as demonstrated by findings that surgical or ibotenic acid lesions of Vc permanently inactivated the reflex, while application of lidocaine to the trigeminal subnucleus caudalis resulted in a reversible suppression of the TMJ-jaw muscle reflex.[35,48] In subsequent studies it was shown that application of NMDA or non-NMDA receptor antagonists to the Vc also significantly attenuated TMJ-evoked reflex jaw muscle activity, which indicated that excitatory amino acid receptor mechanisms in Vc contribute to TMJ-evoked reflex jaw muscle activity.[49]

Peripheral Excitatory Amino-Acid (EAA) Receptor Mechanisms

Cairns next related a study characterizing the MO-evoked TMJ-jaw muscle reflex model, where it was discovered that preapplication of the noncompetitive NMDA receptor antagonist MK-801 into the TMJ attenuated the reflex,[50] suggesting that peripheral EAA receptor activation could contribute to the evoked reflex jaw-muscle activity. Subsequent research indicated that both NMDA and non-NMDA EAA receptor subtypes are located within the TMJ and may contribute to the reflex jaw-muscle activity. A sex-related difference in the magnitude of the reflex response evoked by activation of peripheral EAA receptors that appeared to be dependent on the female sex hormone estrogen was also determined.[51] Despite the potential role of peripheral EAA receptors in TMJ nociceptive mechanisms, injection of the NMDA receptor antagonist ketamine into the TMJ of patients with TMJ arthralgia did not result in effective analgesia.[52]

GABA Receptor Mechanisms

In addition, Cairns noted how the TMJ-jaw muscle reflex model was also used in the Sessle laboratory to investigate the role of peripheral GABA receptor mechanisms located within the TMJ and how their activation might affect this nociceptive reflex. Injection of GABA into the TMJ did not evoke jaw-muscle reflexes, but its coinjection with glutamate suppressed glutamate-evoked jaw-muscle reflexes.[53] These effects of GABA were shown to be mediated through activation of $GABA_A$ receptors in the TMJ. No human studies have yet evaluated the potential analgesic effect of peripheral $GABA_A$ receptor activation in craniofacial tissues.

Opioid Receptor Mechanisms

Cairns also commented that initial work by the Sessle group with the TMJ-jaw reflex model also suggested that central opioid receptor suppressive mechanisms were engaged to limit the reflex duration.[54] Subsequent studies indicated that injection of morphine into the TMJ can significantly attenuate the TMJ-jaw muscle reflex in male rats through activation of peripheral mμ opioid receptors but that female rats are significantly less sensitive.[55,56] These findings have not yet translated well into treatment of TMJ pain in humans, where results of intra-articular morphine for TMJ arthralgia so far have been at best inconclusive.[57]

Cairns concluded by noting 1 apparent disadvantage of the acute TMJ injury model is that in spite of the fact that it has provided a wealth of information about the TMJ nociceptive pathway, these findings have not been readily translated into effective pain treatment for TMD sufferers. This may reflect several limitations in this animal model, not the least of which is the acute nature of the noxious stimulus, which does not really replicate the chronic nature of TMD pain in humans. In addition to joint pain, many TMD patients will also suffer symptoms of masticatory and cervical muscle pain and headache (particularly chronic tension type and/or migraine) as well as a host of comorbid conditions, such as irritable bowel syndrome and interstitial cystitis, which cannot be easily replicated in animal models. Nevertheless, consistent with the increased prevalence of TMD in women, there appear to be sex-related differences in nociceptive processing from the rat TMJ. The mechanisms underlying sex-related differences in the rat still require further elucidation and may yet reveal novel approaches for therapeutic interventions for TMD-related joint pain.

Sessle Response

At the end of each of the 6 presentations, Professor Sessle thanked the presenter and remarked on the presentation and his own personal relationships with each presenter. He also acknowledged the impact on his academic career of his MDS mentors Mark Jolly and David Cameron at the University of Sydney, his PhD supervisor Professor Ian Darian-Smith at the University of New South Wales, and his postdoctoral mentor Dr Ron Dubner. He also acknowledged the late Art Storey who had guided him so well in his early academic years at the University of Toronto. Sessle also thanked the 80 or so students, postdoctoral fellows, and visiting scientists, many of whom were present at the symposium, who had worked with him so effectively and collegially in Toronto and who had played a large part in his own academic and research successes. In particular he singled out Dr Jimmy Hu, his long-time collaborator, who had just retired from the University of Toronto on the very day before the July 1 symposium.

In addition, Sessle made note that his many collaborations also included ones with the other 2 "giants" being honored at the symposium, eg, his very first book was coedited with Alan Hannam[58] and his most recent book[59] was coedited with Jim Lund (and Lavigne and Dubner); he and Lund also

did some collaborative studies together and coauthored several journal papers and book chapters. Sessle also remarked about the cadre of 200 or so students and postdoctoral fellows from various parts of the world that Hannam, Lund, and he had trained, many of whom had taken up academic posts. He noted that they were making their own mark in orofacial neuroscience research or its clinical application, and so the orofacial neuroscience field, especially that related to orofacial pain and motor control, was in very good hands. Nonetheless, he felt that he still "had some good years left" before his retirement for collaboration with some of them and others and thus contribute a bit more to the field of orofacial neuroscience.

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