

## Review

## Orofacial pain

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Pain in the oral and craniofacial system represents a major medical and social problem. Indeed, a U.S. Surgeon General's report on orofacial health concludes that, "...oral health means much more than healthy teeth. It means being free of chronic oral-facial pain conditions..." [172]. Community-based surveys indicate that many subjects commonly report pain in the orofacial region, with estimates of >39 million, or 22% of Americans older than 18 years of age, in the United States alone [108]. Other population-based surveys conducted in the United Kingdom [111,112], Germany [91], or regional pain care centers in the United States [54] report similar occurrence rates [135]. Importantly, chronic widespread body pain, patient sex and age, and psychosocial factors appear to serve as risk factors for chronic orofacial pain [1,2,92,99,138]. In addition to its high degree of prevalence, the reported intensities of various orofacial pain conditions are similar to that observed with many spinal pain disorders (Fig. 1). Moreover, orofacial pain is derived from many unique target tissues, such as the meninges, cornea, tooth pulp, oral/nasal mucosa, and temporomandibular joint (Fig. 2), and thus has several unique physiologic characteristics compared with the spinal nociceptive system [23]. Given these considerations, it is not surprising that accurate diagnosis and effective management of orofacial pain conditions represents a significant health care problem.

Publications in the field of orofacial pain demonstrate a steady increase over the last several decades (Fig. 3). This is a complex literature; a recent bibliometric analysis of orofacial pain articles published in 2004–2005 indicated that 975 articles on orofacial pain were published in 275 journals from authors representing 54 countries [142]. Thus, orofacial pain disorders represent a complex constellation of conditions with an equally diverse literature base. Accordingly, this review will focus on a summary of major research foci on orofacial pain without attempting to provide a comprehensive review of the entire literature.

**2. Physiologic studies on trigeminal pain**

Several reviews are available that document the historical development of physiologic research on the trigeminal nociceptive

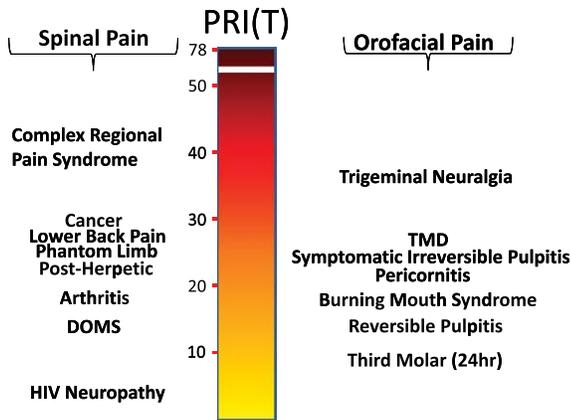
system [33,53,114,120,149]. More recent studies have characterized differences in electrophysiological [82], anatomical [10], or pharmacological [42,80] properties of trigeminal afferents innervating distinct target tissues. Collectively, many of these studies provide support for the hypothesis that target tissue interactions with trigeminal neuron terminals, via either soluble factors such as neurotrophins [48], or by integrin binding to extracellular matrix molecules [22,25], regulate the expression or trafficking of neuronal proteins, including ion channels and receptors [90,139] or second messenger signaling pathways [25]. Thus, the presence of unique target tissues innervated by trigeminal afferent fibers likely contributes to differences in the responsiveness of these neurons. A recent review characterizes differences between the trigeminal and spinal afferent systems under basal conditions [23]. Table 1 illustrates differences between the trigeminal and spinal systems after various forms of injury. Collectively, these studies indicate that the trigeminal system has many unique features that may contribute to distinct response patterns to tissue injury.

The hypothesis of peripheral regulation of neuronal phenotype has been expanded by the recognition that estradiol selectively alters gene transcription in trigeminal neurons with increased expression of neuropeptides, such as prolactin, that are capable of sensitizing neuronal responses to capsaicin or noxious heat [49]. Additional studies have demonstrated that trigeminal peptidergic neurons undergo morphological changes ("sprouting") in response to injury-induced inflammation in target tissues [33]. In contrast, there is a lack of sympathetic fiber sprouting in trigeminal ganglion cells, unlike the well-recognized occurrence in the spinal system [19,29,63]. Thus, an emerging body of evidence reveals the dynamic and specific responsiveness of the trigeminal system to either injury of its various target tissues or to the presence of certain gonadal steroids.

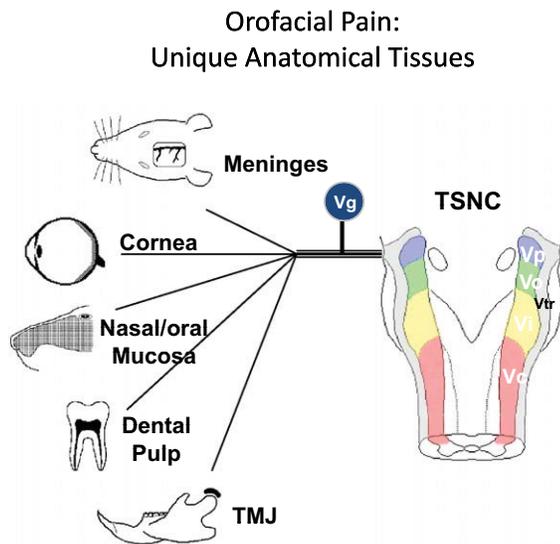
Other studies have employed cultured trigeminal ganglia (TG) to evaluate cellular mechanisms of neuronal activation. For example, cannabinoids activate a calcineurin pathway leading to the rapid dephosphorylation and desensitization of transient receptor potential cation channel, subfamily V, member 1 (TRPV1), thereby contributing to an ionotropic mechanism for peripheral cannabinoid antinociception [4,5,89,133]. Moreover, accumulating evidence indicates a functional cross-desensitization between TRPV1 and TRP subfamily A, member 1 (TRPA1) on trigeminal neurons, possibly via formation of a heteromer [4,6,146,147]. Additional studies have used cultured TG to demonstrate that opioid receptors are

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**Fig. 1.** Comparison of pain intensity among spinal and orofacial pain disorders using the McGill Total Rank Pain Index (PRI(T)). The PRI(T) is an ordinal scale consisting of the sum of the ranks of words in each of the 20 sub-categories on the McGill Pain Questionnaire and ranges from 0 to 78. Data taken from: [14,35,71,73,116,117,150,164,176,183,184].



**Fig. 2.** Unique target tissues innervated by the trigeminal sensory system. Taken from Bereiter et al. [23], with permission.

expressed on sensory neurons but are not coupled to inhibitory signaling pathways under basal experimental conditions. Instead, pretreatment with arachidonic acid or with agonists to receptors coupled to  $G\alpha_q$  signaling pathways (eg, bradykinin, trypsin) is required to induce the rapid development of a functional competence for opioid receptor signaling to  $G\alpha_i$  pathways leading to inhibition of neuronal activities [24,25,60,131,132]. These cellular findings are consistent with the observation that opioids have little efficacy for peripheral antinociception under basal conditions, but rapidly gain functional competence following injection of inflammatory mediators [145] or the development of inflammation.

Recent studies have employed cultured trigeminal neurons to identify endogenous TRPV1 agonists [130,134]. Heating of isolated superfused peripheral tissue to a noxious temperature range leads to the release of oxidized linoleic acid metabolites (OLAMs), including 9- and 13-hydroxyoctadecadienoic acid (HODE). The administration of synthetic 9- and 13-HODE (and their oxoODE metabolites) selectively activates TRPV1, leading to inward currents, increased accumulation of intracellular calcium, and triggering exocytosis of neuropeptides from TG neurons and thermal allodynia. These effects are blocked by TRPV1 antagonists and are

observed only in trigeminal neurons from wild-type mice but not TRPV1 knockouts [130]. Moreover, the intracellular delivery of compounds that block OLAM formation (eg, nordihydroguaiaretic acid) or a combination of anti-9- and anti-13-HODE antibodies both significantly inhibit heat-evoked activation of trigeminal neurons. Collectively, these findings strongly implicate the OLAMs as a family of endogenous TRPV1 agonists. Interestingly, the pronounced effect of TRPV1 antagonists for blocking heat hyperalgesia in inflammation as well as mechanical allodynia (after intrathecal administration) has led to the hypothesis that an endogenous TRPV1 system might be activated under conditions of tissue injury. In support of this hypothesis, the administration of anti-OLAM antibodies produces a peripherally mediated thermal antinociception and a centrally mediated blockade of mechanical allodynia in the complete Freund's model of inflammation [130,134]. Thus, the OLAM system appears to contribute to acute heat detection by TRPV1 and to regulate more persistent conditions such as inflammatory pain.

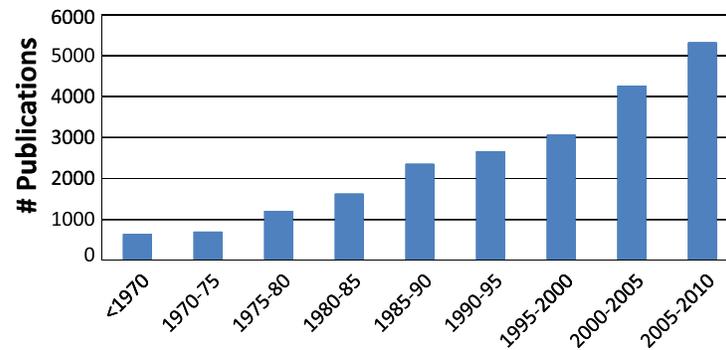
Future research directions may include preclinical studies focusing on mechanisms underlying differences between trigeminal and spinal pain conditions, mechanisms of sex-dependent differences in pain transduction and processing, and on the biological basis and pharmacological regulation of acute and chronic orofacial pain conditions. Many of these studies would be promoted by the development of standardized preclinical pain models and assessment methods.

In addition to research on the biological mechanisms of nociceptive transmission, numerous clinical studies have described strong psychosocial/disability components to orofacial pain. Indeed, some diagnostic classification schemes differentiate the dimension of tissue contributions from psychosocial/disability factors [55] contributing to orofacial pain disorders. These studies demonstrate that the orofacial pain patient is confronted with a complex, multidimensional disorder that is best managed with appropriate treatment for all underlying factors [2,46,56,61,85,97,154].

### 3. Studies on trigeminal inflammatory disorders

Many translational studies have evaluated acute inflammatory injury to the trigeminal system. The dental impaction pain model has been developed as a standard clinical method for evaluating many analgesic drugs [43,45,115]. Other investigators have used this model of acute inflammatory pain to evaluate preemptive anesthesia [66,68], activation of endogenous opioid analgesic systems [70,78,104,105], local release of inflammatory mediators as collected by implanted microdialysis probes [50,67,77,162], other physiologic mechanisms [76], or the association of genetic polymorphisms with postoperative pain [95,96,98]. This clinical model has several notable advantages, including participation of relatively healthy subjects not taking concurrent drugs, standardized surgical procedures leading to reduced variance, and relatively large numbers of potential participants. Collectively, these studies on patients undergoing surgical dental extractions have contributed greatly to evaluation of analgesics, anesthetics, and anxiolytics, as well as basic biological research on human subjects.

Other studies have focused on chronic inflammation of the oral and craniofacial region. Clinical studies on irreversible pulpitis in teeth ("toothache") have demonstrated that this condition of bacterial-induced inflammation/necrosis is associated with significant changes in expression of ion channels [8,16,83,110,178,182], receptors [106], and neuropeptides [32,33]. Moreover, inflammation of a single tooth in patients appears sufficient to trigger central sensitization [59,94,127,151]. Animal studies on inflammation in the trigeminal region have demonstrated target-site-dependent differences in sensitization/activation [62,79,175] as well as sex-dependent differences in neuronal activities [20,126,168].



**Fig. 3.** Rates of articles published on orofacial pain. Data were acquired from a PubMed search (August 2010) using the search criteria of: (orofacial or trigeminal or temporomandibular or dental or tooth) and (pain or headache or hyperalgesia or allodynia or nociceptor or nociceptive).

Future research directions on trigeminal inflammatory disorders may include preclinical and translational clinical studies focusing on mechanisms underlying the development and maintenance of inflammatory hyperalgesia/allodynia. Importantly, the clinical condition of pulpitis results in a very restricted pain locus (often within a tissue volume of <200  $\mu$ L), intense pain reports [73], and dynamic neuronal and immunoplasticity. Thus, the pulpitis pain model is important not only from the perspective of high prevalence [108] and health care disparity [174], but also serves as a useful model for translational research [27].

#### 4. Studies on trigeminal neuropathic disorders

The orofacial region has unique neuropathic pain disorders not seen in the spinal system, including trigeminal neuralgia and glossopharyngeal neuralgia [15]. Numerous clinical reports document these and other orofacial neuropathic or neuritic/neuralgic pain conditions and their responsiveness to surgical or pharmacological treatments [15,38,118,124,129,168,184]. Several etiologic factors appear to contribute to the development of neuropathic pain disorders. Proposed mechanisms include injury/compression to the trigeminal nerve, inflammatory insult (possibly including glial contributions), or infection with herpes virus [3,15,17,40,124,125,177]. However, not all injuries to the trigeminal nerve lead to neuropathic pain disorders; indeed, the incidence of neuropathic pain after injury to orofacial structures is relatively low after dental treatment [34,109,137], facial trauma [17], orthognathic surgery [39], tooth extraction [26,36,143,173], or placement of dental implants [72]. This apparent resistance of the trigeminal system to development of neuropathic conditions is an interesting clinical observation that should prompt preclinical research comparing trigeminal to spinal afferent systems for susceptibility to neuropathic pain disorders. It is interesting that the trigeminal system appears programmed for periodic loss of innervated structures during postnatal development, with the shedding of 20 deciduous teeth per person, with minimal development of neuropathic pain conditions.

Several risk factors for trigeminal neuralgia have been found, including multiple sclerosis [44,140] and hypertension [93]. Additional studies have reported changes in the expression of ion channels (eg, NaV1.3, 1.7, 1.8, TRPA1) in surgical biopsies collected from patients suffering from neuropathic orofacial pain [119,153]. Animal models of trigeminal neuropathic pain have been developed and include chronic constriction injury of the infraorbital nerve as well as transection of the inferior alveolar nerve [3,177]. Interestingly, both preclinical and clinical studies have implicated constriction of peripheral nerves as an etiologic mechanism for inducing neuropathic pain via alteration in primary afferent functions [81], although certain cortical changes have been reported as well [28]. This has led to the development of clinical surgical decompression procedures to treat patients with trigeminal neu-

ralgia [166,167]. Several preclinical studies have implicated ion channels and endothelin receptors as well as glial mechanisms in contributing to the development of these models of neuropathic pain conditions [11,40,81,125].

#### 5. Studies on chronic trigeminal myofascial and joint pain

The diagnosis and management of many chronic orofacial pain conditions has been greatly hampered by confusion in determining etiologies from the temporomandibular joint versus myofascial sources. This has led to clinical studies difficult to interpret and diagnostic classifications that did not have a strong biological basis due to the lack of differentiation between joint and muscle contributions to the patient's pain condition. Clinical studies on myofascial pain or temporomandibular dysfunction (TMD) were considerably improved by the development of the Research Diagnostic Criteria [55,56], which highlighted the need for developing standardized diagnostic methods and definitions. Considerable evidence has been published demonstrating that patient sex/gender and exposure to sex steroids serve as risk factors for developing chronic orofacial pain conditions [61,65,100–103]. However, this is not observed in all studies, and other risk factors such as chronic widespread body pain, a prior history of physical abuse, or health anxiety have also been reported to be associated with the development of chronic orofacial pain disorders [1,55,61,92,100,107]. The reasons why some but not all studies detect sex/gender as a significant risk factor for orofacial pain disorders is not clear, but may be due to differences in patient populations, case definitions, or experimental approaches. Related preclinical studies have demonstrated that trigeminal neurons express estrogen receptors and undergo dramatic changes in gene expression [9,21,49] or firing rates [62] following exposure to estradiol.

Other clinical studies have focused on synovial fluid levels of inflammatory mediators to test for other possible biological mechanisms [31,160] or have evaluated the role of peripheral glutamate receptors in triggering myofascial pain [7,12]. A very interesting approach is the application of genetics to patients with TMD. A haplotype of the catechol-O-methyltransferase gene in patients is associated with reduced responsiveness to experimental pain and to reduced risk for TMD [47]. Moreover, a mechanistic hypothesis for the protective effect of this haplotype has been advanced [121], and TMD patients with this catechol-O-methyltransferase haplotype respond with increased analgesia from drugs such as propranolol [169].

#### 6. Studies on other orofacial pain conditions

Many other orofacial pain disorders also have been evaluated. The trigeminal autonomic cephalgias include cluster headache,

**Table 1**  
Comparison of the trigeminal and spinal afferent systems after injury.

Marker	Injury model	Comparison	Authors
Galanin	Axotomy	TG ~ DRG for upregulation	Arvidsson et al. [13]; Zhang et al. [185]
NPY	Axotomy	TG ~ DRG for upregulation	Arvidsson et al. [13]; Zhang et al. [185]
Sympathetic fiber sprouting into ganglion and basket formation	Axotomy or CCI	TG: No DRG: Yes	Bongehiellm et al. [29]; Benoliel et al. [19]
Sympathetic fiber sprouting into ganglion	NGF infusion icv X 14d	DRG > TG	Nauta et al. [122]
SNS/PN3 = NaV1.8	Axotomy	TG: Downregulation followed by normalization DRG: Persistent downregulation	Bongehiellm et al. [30]
Ankyrin(G)	Axotomy	TG: Persistent downregulation	Bongehiellm et al. [30]
Ectopic firing of afferents	Axotomy	TG < DRG	Tal and Devor [165]
Augmented excitability	Axotomy	TG ~ DRG	Tal and Devor [165]; Zhang et al. [186]; Cherkas et al. [37]
Frequency and rhythmicity of spontaneous discharges	Tight ligation of infraorbital vs sciatic nerves	DRG had significantly greater spontaneous discharge rate than TG neurons for both myelinated and unmyelinated fibers. DRG afferents had rhythmic discharge rates (not seen with TG)	Tal and Devor [165]
Satellite glial cells	Axotomy	TG ~ DRG for upregulation of GFP, proliferation	Woodham et al. [181]; Stephenson et al. [158]; Cherkas et al. [37]
NOS	Axotomy	TG ~ DRG for upregulation	Hokfelt et al. [84]
P2X3 & ATF-3 expression	Partial axotomy	TG ~ DRG	Tsuzuki et al. [171]
GM3 ganglioside.	Knockout GM2/GD2 and the GD3 synthase gene	Facial wounding > Rest of the body	Inoue et al. [87]
Peripheral chromatolysis	LiCl	With peripheral nerve degeneration	Levine et al. (2004)
Sensory neuropathy with neuronal degeneration	Sjogren's Syndrome	TG ~ DRG	Malinow et al. [113]
Infectivity of contralateral ganglia	Herpes simplex virus-1 (HSV) infection	70% of TG contralateral to side of HSV injection produced infections after inoculation, whereas only 10% of contralateral DRG produced infections.	Thackray et al. [170]
HSV polypeptide ICP4 (VP175) expression in ganglia	Herpes simplex virus-1 (HSV) infection	TG ~ DRG	Pepose et al. [136]
Viral replication and degradation of host cells, mRNA	Herpes simplex virus-1 (HSV) infection	TG ~ DRG with wild-type HSV more virulent in both ganglia than HSV mutants lacking virion host shutoff (vhs) protein	Smith et al. [156]
Infectivity of ganglia	Simian varicella virus (SVV)	TG ~ DRG	White et al. [179]
Substance P in ganglia	Streptozotocin-diabetes	TG had 26% reduction ( $P < 0.01$ ), but DRG = 11% non-significant reduction	Robinson et al. [144]
Substance P in ganglia	mf rat (mutilated foot; an autosomal recessive sensory neuropathy with reduced pain responsiveness)	DRG < TG	Scaravilli [148]
Caspase-3 mediated neuronal apoptosis	Knockout of Rb (retinoblastoma tumor suppressor protein)	TG ~ DRG for protection from apoptosis in double knockout of Rb and caspase-3 compared to single Rb knockout	Simpson et al. [152]
Number of neurons in ganglia	TRKA knockout	TG ~ DRG for extensive neuronal loss	Smeyne et al. [155]
Reactivation of virus	HSV mutant with gamma 34.5 gene deletion	TG > resistant to reactivation than DRG	Spivack et al. [157]
Wide-spread numbness and pain 4–12 d after antibiotic treatment	Acute sensory neuronopathy syndrome in humans	TG ~ DRG	Sterman et al. [159]
Pain	Trigeminal neuralgia in humans	TG: Yes (max/mand divisions > ophthalmic) DRG: No equivalent	Jannetta [88]; Sweet [161]; Wilkins [180]; Goya et al. [69]; Hamlyn [74,75]; Tacconi and Miles [163]
Spontaneous behavior	Formalin	OVX females exhibited significantly greater increase in formalin hyperalgesia after orofacial injection (upper lip) compared to hind paw injection. Result is consistent with hypothesis of a difference in sex steroid regulation of nociception between TG and DRG systems	Pajot et al. [128]

SNS, sensory neuron specific; PN3, peripheral nerve sodium channel type 3; NOS, nitric oxide synthase; P2X3, purinoceptor 3; ICP4, infected cell protein 4; TG, trigeminal ganglia; DRG, dorsal root ganglia; NPY, neuropeptide Y; CCI, chronic constriction injury; NGF, nerve growth factor; NOA, ATF-3, activating transcription factor 3; OVX, ovariectomized.

paroxysmal hemicrania, and unilateral neuralgiform headaches [41]. This collection of pain disorders is characterized by unilateral head pain in association with autonomic features such as tearing

and conjunctival involvement, and considerable research has shed light on pain referral patterns and issues related to proper diagnosis and treatment [18,51,58,64,86]. Most cases of trigeminal auto-

onomic cephalgia reflect primary headaches, although rare cases may be associated with pituitary tumors [41]. Pain is a major aspect of oral cancer [57] and often represents the initial symptom that prompts patients to seek health providers. Pain due to oral cancer may be due to soluble factors released from tumor cells, a localized inflammatory response to the tumor, or even nerve entrapment. Several recent studies have implicated the endothelin system and proteases (eg, PAR-2 receptor activation) in mediating mechanical allodynia experimental models of oral cancer pain [52,141]. Burning mouth syndrome is a rare disorder, commonly characterized by spontaneous burning pain and mechanical allodynia. Although idiopathic, it has many features of neuropathic pain and has been reported to be associated with altered peripheral expression of voltage-gated sodium channels [16].

## 7. Discussion

Orofacial pain disorders comprise a major and expensive component of health care and collectively have a high prevalence rate, a large range in pain intensity with a commensurate, often devastating impact on quality of life [149]. Although there are many common aspects of pain transduction and processing between the trigeminal and spinal systems, there are numerous examples of unique features in the peripheral and central components of the trigeminal pain system. Accordingly, ongoing basic and clinical research focused on acute and chronic orofacial pain conditions is required to understand the unique features of this pain system and to develop and evaluate better ways to treat patients with orofacial pain.

A major barrier for improved patient care and translational research is the lack of validated diagnostic criteria. Although efforts have been made to classify TMD patients with the Research Diagnostic Criteria for TMD, headache patients with the International Headache Society criteria, and orofacial pain with the American Academy of Orofacial Pain standards, clinical research indicates that each of these 3 methods is incomplete for comprehensive diagnosis of orofacial pain patients [18]. Thus, further research is critically required to establish a comprehensive, sensitive, and specific diagnostic classification scheme for all orofacial pain patients. This would provide a critical contribution to practitioners and foster the development of a powerful dataset for clinical research. In addition, recent studies have incorporated quality-of-life indices, which provide important additional information on clinical outcomes [123].

Taken together, orofacial pain conditions represent a highly prevalent spectrum of pain disorders with pain intensities similar to those observed with many chronic spinal pain conditions. However, the unique anatomical, biochemical, and associated psychosocial components provide compelling evidence for specific research focused on orofacial pain disorders.

## Conflict of interest statement

The author denies any conflicts of interest.

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