PERIPHERAL RECEPTOR TARGETS FOR ANALGESIA
NOVEL APPROACHES TO PAIN MANAGEMENT

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PERIPHERAL RECEPTOR TARGETS FOR ANALGESIA
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Knowledge of pain mechanisms has advanced significantly since Wall and Melzack launched the gate control theory in the late 1960s. Since then, an exponential increase in the number of scientific papers on this topic has been seen. This has lead to a significant increase in our understanding of the fundamental aspects of the pain system and its pharmacology, but unfortunately, this has so far not been reflected in the number of new pharmacological compounds available for the treatment of pain. Aspirin, morphine, and lidocaine are still among the most widely used analgesic drugs. However, in more recent years, other centrally acting drugs (e.g., anticonvulsants, antidepressants), not developed or intended for the management of pain, have found their place in modern polypharmacological treatment regimes. Besides lidocaine, antitumor necrosis factor alpha (TNF-α) and, to some degree, nonsteroidal anti-inflammatory drug (NSAID), compounds targeting peripheral sites for pain relief, have been largely neglected. The present book is therefore an important contribution in the process of conceptualizing peripheral sites as possible targets for the development of new pain management treatments. This approach could also potentially reduce the well-known significant adverse effects associated with centrally acting analgesic drugs, such as drowsiness, somnolence, and mental clouding as well as gastrointestinal ulceration that is a problem with chronic use of NSAIDs. Such unintended side effects can significantly impact the quality of life of chronic pain patients.

Despite these apparent advantages of local analgesics for the treatment of pain, many results from this approach, for example, topical application of analgesic drugs, are disappointing. One reason for failures of this approach is a lack of appreciation of the peripheral pain transduction mechanisms and the diversity of receptors that may be involved in these mechanisms. This book, by reviewing the role of peripheral receptor mechanisms in the transduction of pain, should provide a framework for the development of rationally designed treatments with locally applied analgesics and promote further basic and clinical studies on potentially interesting peripheral receptor targets.

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The main purpose of *Peripheral Receptor Targets for Analgesia: Novel Approaches to Pain Management* is to bring together in one text much of the diverse body of work on peripheral receptor mechanisms of pain. I hoped, by doing this, to allow the reader to compare work done on various receptor targets to determine which targets might be the most useful to pursue in their own research. Thus, the topics I have chosen for the book should be of interest to health sciences researchers and clinicians (physicians, dentists, pharmacists, nurse practitioners, physiotherapists, and others) as well as researchers in the pharmaceutical industry. Nevertheless, I believe that this book will also be attractive to senior undergraduate and graduate students in the health sciences whose research interests include pain. The book is organized into introductory chapters to provide the reader with a general sense of the importance of peripheral mechanism of pain, followed by select topical chapters focusing on specific receptor targets. The book finishes with chapters that discuss avenues for selective delivery of analgesic agents. I intend that this book will not only provide interesting reading but also serve as useful reference for those interested in the field of pain research.

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PART I

PERIPHERAL MECHANISM IN CLINICAL PAIN CONDITIONS
CHAPTER 1

Role of Peripheral Mechanisms in Craniofacial Pain Conditions

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1.1 INTRODUCTION

The craniofacial region is the site of some of the most common acute and chronic pain conditions [1,2]. There are various types of headaches that are common and specific to this region, and toothaches are one of the most
common reasons for people to seek dental treatment. Moreover, a significant proportion (~10%) of the population may suffer from craniofacial musculoskeletal pain (e.g., so-called temporomandibular disorders or TMD), and many of the chronic types of craniofacial pain are more commonly reported by women.

Acute pain is a transient signal that something is wrong and has a significant value to the person as an alert signal of tissue damage or potential damage. In contrast, chronic pain, which is usually considered as pain persisting for 3–6 months or more, may not have this protective and learning value, and the pain may become a disease or disorder in itself. Associated emotional or health-related stresses may also affect the patient by reducing his or her quality of life and can lead to undesirable changes such as loss of appetite and libido, and sleep disturbances, as well as reduced social interactions with the patient’s family and friends. In addition to its emotional and social consequences to the patient and others, chronic pain will become an increasing socioeconomic burden as population demographics in most countries change, with more people being middle-aged or elderly, the age span when many chronic pain conditions are prevalent.

These considerations especially apply in the case of pain in the face and mouth because of the special psychological and emotional meaning and importance that this region has in eating, drinking, speech, sexual behavior, and expression of emotions and because the craniofacial tissues are densely innervated by free endings of nociceptive afferents and have an extensive somatosensory representation in the central nervous system (CNS). These various factors also may explain why many people find it unpleasant and painful to go for a routine dental examination.

There is considerable evidence that peripheral mechanisms play a significant role in the etiology or pathogenesis of many of the craniofacial pain conditions, and in recent years, insights have been gained into the neural and nonneural processes involved. This chapter will review these processes and indicate their documented or potential role in these conditions.

### 1.2 FEATURES OF PERIPHERAL TISSUES IN THE CRANIOFACIAL REGION

The craniofacial region is unique in the multiplicity of sensory functions manifested in this part of the body, for example, pain, temperature, touch, taste, smell, proprioception/kinesthesia, and detection and discrimination of the hardness, texture, and viscosity of substances or objects placed in the mouth. It is also characterized by a wide variety of tissues that include facial skin, cornea, oral mucosa, teeth and periodontal tissues, periosteum, bone, cartilage, muscles, joints (temporomandibular joint [TMJ]), ligaments, and fascia. These tissues have a rich blood supply and most have a dense innervation that subserves the various sensory functions of the craniofacial region.
The craniofacial tissues on the left or right side are innervated almost exclusively by branches of the ipsilateral trigeminal (V) sensory nerve, although some small parts of the craniofacial region are supplied by other cranial nerves or cervical nerves. The ophthalmic branch or first division of the V nerve supplies principally the supraorbital tissues (e.g., forehead skin) and cornea; its maxillary branch or second division mainly innervates the infraorbital skin, upper lip, maxillary mucosa, and teeth; and the mandibular branch or third division supplies mainly the skin of the low jaw, lower lip, mandibular mucosa, and teeth. Many V primary afferent fibers terminate in these tissues as sense organs (receptors) that are quite complex in their structure and that respond to tactile stimulation (e.g., low-threshold mechanoreceptors) or to other forms of mechanical stimuli such as stretch or tension (e.g., proprioceptors). These receptors are mainly associated with large (Aβ)- or medium (Aδ)-sized afferents that convey the tactile or proprioceptive information into the CNS. Other primary afferents may terminate as free nerve endings, many of which respond to noxious stimuli and which are termed nociceptors. These nociceptive afferents are either small-diameter, myelinated (Aδ) primary afferent fibers or even smaller (and even slower conducting) unmyelinated (C) afferent fibers, although there is evidence that in some conditions, Aβ-afferents may take on a nociceptive function. It is important to note that not all of the Aδ- and C-fiber afferents conduct nociceptive information: some are associated with receptors that respond to non-noxious cooling, warming, or even tactile stimuli. In addition, there are other types of receptors (e.g., gustatory, olfactory) that are supplied by afferents in other cranial nerves.

1.3 PERIPHERAL NOCICEPTIVE MECHANISMS IN THE CRANIOFACIAL REGION

1.3.1 General Features of Nociceptors and Chemical Mediators

The craniofacial nociceptive Aδ- and C-fiber afferents mentioned above convey sensory information as nerve impulses (so-called action potentials) from the nociceptors into the CNS and thereby provide the brain with sensory-discriminative information about the spatial and temporal qualities of the noxious stimulus. The peripheral basis for coding the intensity and duration of the noxious stimulus is closely related to the frequency of the nerve impulses and the duration of the nerve impulse discharge of the nociceptive afferent fibers. The peripheral feature of particular importance for localization of the stimulus is the receptive field of the fiber, that is, the area of skin, mucosa, or deep tissue from which the afferent fiber and its associated receptors can be excited by a threshold stimulus. The receptive field of most nociceptive afferent fibers is usually less than 1 mm², and the threshold for their activation from the receptive field is very high and in the noxious range. Noxious stimuli, particularly in superficial tissues, usually also activate other receptors such as
mechanoreceptors that code for touch, and these help determine the location and quality of the sensation perceived. In tissues that appear to have no such low-threshold mechanoreceptors, such as tooth pulp and muscles, noxious stimuli may give rise to a different quality of pain sensation.

The activation of the nociceptive afferent stems from the tissue damage produced by the noxious stimulus causing the release from the tissues of chemical mediators (e.g., prostaglandins, bradykinins) that activate the free nerve endings of the afferent. This can result in the production of action potentials in the $\text{A}_\delta$- and/or $\text{C}$-fiber afferents, which are conveyed into the CNS and may elicit the perception of transient or acute pain. It has become evident in recent years that the processes by which the nociceptive endings are activated are extremely complex and varied between endings and that a multitude of factors and mechanisms can influence their excitability. Subsequent chapters in this book deal at length with these, so only a brief overview is provided here, followed by an outline of findings specifically in craniofacial tissues.

Broadly speaking, the activation of nociceptive afferent endings involves subcellular compartmentalization and signaling pathways, extracellular matrix, cytoskeleton, and intracellular organelles as well as extracellular processes (see References 3–7). Briefly, the subcellular elements and signaling pathways involve numerous intracellular second messenger pathways, networks, and cascades that involve cyclic adenosine monophosphate (cAMP), protein kinases A and C (PKC), mitogen-activated protein (MAP) kinases, and nitric oxide just to name a few. These processes are also very much involved in the sensitization (see below) as well as activation of the afferent endings and manifest considerable plasticity. In addition, components of the cytoskeleton and extracellular matrix as well as organelles within the endings (e.g., intracellular and extracellular scaffolding proteins, and mitochondria) are involved in modulating the excitability of the nociceptive afferent endings; sex hormones may also have a role through local regulatory functions and gene transcription.

A number of extracellular factors and chemical mediators can also influence the excitability of the nociceptive afferent endings. These are outlined in Figure 1.1 and include damage to peripheral tissues, which often results in inflammation, and may also involve products released from the cells of the immune system or from the blood vessels. Substances synthesized in and released from the afferent fibers themselves may influence the excitability of the nociceptive afferents, for example, neurotrophins such as nerve growth factor, and neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) may cause platelets, macrophages, mast cells, and other cells of the immune system to release inflammatory mediators such as histamine, serotonin (5-HT), bradykinin, and cytokines. Under certain conditions, the excitability of the nociceptors may also be modulated by substances, such as norepinephrine, that are released from sympathetic efferents innervating the tissues. In some situations, damage to the afferents themselves may occur and may lead to abnormal nerve changes that are associated with ectopic or aber-
Many of these factors increase the excitability of the nociceptors at the site of injury; this is termed nociceptor or peripheral sensitization. Sensitized nociceptors exhibit spontaneous activity, lowered activation thresholds, and increased responsiveness to subsequent noxious stimuli that appear to contribute, respectively, to the spontaneous pain, allodynia, and hyperalgesia that are characteristics of many chronic or persistent pain conditions. The inflam-
matory mediators as well as some of the substances released from the afferent fibers may also cause edema (swelling), redness, and local temperature increases, which, along with pain, are the cardinal signs of inflammation; this process has been termed neurogenic inflammation.

The chemicals may also diffuse through the peripheral tissues and act on the endings of adjacent nociceptive afferents, and so, more nociceptive afferents send their signals into the CNS, thus contributing to the spread and increased size of the painful area. The increased afferent barrage into the CNS from this increased nociceptor activity may also lead to functional changes in central nociceptive processing that contribute to persistent pain. One such series of changes that is especially important in mechanisms underlying pain is *central sensitization*. This central process is involved in the so-called secondary hyperalgesia, which refers to the increased sensitivity to noxious stimuli well beyond the site of original tissue injury. In contrast, peripheral processes involving peripheral sensitization of nociceptive afferent endings at the injury site seem mainly to account for the increased pain sensitivity at the injury site itself (primary hyperalgesia).

These peripheral sensitizing events reflect, in a sense, a form of functional plasticity, and recent studies suggest an added element of complexity in these peripheral plasticity processes. The nociceptive afferent endings may manifest a “primed state” where basal nociceptive thresholds are normal but instead of being sensitized for physical (e.g., mechanical) stimuli, the ending is sensitized against sensitizing agents such that far lower concentrations of inflammatory mediators for instance are sufficient to elicit, in this primed state, much augmented excitability of the ending. This primed state is PKC-dependent and can last for weeks and so could represent an important factor in pain chronicity (see Reference 7).

Also noteworthy is that the nociceptive afferent fibers can undergo phenotypic switches under certain conditions (see References 3, 6, 8, and 9). For example, they can change in response to peripheral inflammation, with alterations in the expression of certain nociceptor receptors or ion channels (e.g., voltage-gated sodium channels). Transcription of neuropeptides, brain-derived neurotrophic factor (BDNF), and ion channels, and translation of transient receptor potential (TRP) channels may occur and enhance peripheral (and central) sensitization. Transcriptional changes may also occur after nerve injury and be involved along with sympathetic efferent sprouting in the development of abnormal, ectopic discharge patterns in the afferents that are often a feature of neuropathic pain. These changes may be manifested in the afferent ganglion cell body as well as in the afferent fiber itself and contribute to the spontaneous nature, allodynia, and hyperalgesia of neuropathic pain.

Compared with studies of spinal nerve fibers, investigations of V afferent endings and ganglion cells have been much fewer but have revealed several analogous changes following V nerve injury or craniofacial inflammation, but some notable differences include the apparent lack of sympathetic efferent sprouting in the V ganglion after nerve injury, time course differences in the
abnormal afferent discharge patterns, and differences in the up- or down-regulation of neuropeptide and ion channel expression in the ganglion cells or their peripheral afferent endings (see References 10 and 11).

Additional receptor mechanisms that are involved in pain have been discovered in peripheral nerve endings themselves. They include receptor subtypes for 5-HT, adenosine triphosphate (ATP), bradykinin, nerve growth factor, and opioidergic peptides as well as several TRP receptors such as the transient receptor potential vanilloid 1 (TRPV1) receptor that responds to protons (H⁺), heat, and chemicals like capsaicin, the ingredient in hot peppers that produces pain. It should also be noted that chemical mediators long thought to be involved in nociceptive transmission or modulation within the CNS (e.g., the excitatory amino acid glutamate and opioid-related substances such as enkephalins) can also act peripherally on the nociceptive afferent endings. For example, glutamate is synthesized by primary afferent cell bodies. It can excite nociceptive afferents supplying craniofacial musculoskeletal tissues, initiate central sensitization and sustained sensorimotor behavior in animals, and produce a transient pain in humans by activating glutamate receptors (N-methyl-D-aspartate [NMDA] and non-NMDA receptors) located on the afferent endings. These effects in animals and humans are significantly greater in females. In contrast, the well-known centrally acting narcotic analgesic drug morphine also has actions in peripheral tissues as it can depress the activity of nociceptive afferents by interacting with opioid receptors on their afferent endings. In addition, the powerful central inhibitory neurotransmitter gamma-aminobutyric acid (GABA) can also act peripherally and depress nociceptive afferent excitability. Several of these chemical mediators may influence afferent excitability indirectly by acting on other cells in these tissues (e.g., mast cells, macrophages, platelets, keratinocytes, endothelial cells), which themselves have several of the same receptors and ion channels existing in the afferent endings and release many of the mediators mentioned above.

The multiplicity of peripheral chemical mediators, receptors, and ion channels, and intracellular channels involved in peripheral nociceptive activation, sensitization, and related events (e.g., inflammation) are all potential targets for the development of new and more effective therapeutic approaches. Knowledge of the chemical mechanisms involved in the activation or sensitization of the nociceptive afferents has led to the development of therapeutic agents targeting specific peripheral mechanisms. For example, common non-steroidal anti-inflammatory drugs (NSAIDs) including salicylates such as aspirin, as well as many newly developed analgesics such as cyclooxygenase (COX)-2 inhibitors, have their principal analgesic and anti-inflammatory actions in peripheral tissues (e.g., on prostaglandin E₂ [PGE₂] synthesis). They can reduce inflammation associated with tissue injury, modulate nociceptive afferent excitability, and alter the hyperalgesia associated with short-term craniofacial pain conditions. A cautionary note, however, is warranted to offset any sense of optimism that a peripherally based pharmacological cure for pain is “around the corner.” The multiplicity of processes, many of which
act in parallel, also means that interception of any one or a few is unlikely to have a major therapeutic impact. The development of effective agents that act further downstream on the consequences of the increased afferent excitability induced by noxious stimulation would seem a more useful and fruitful avenue (see Reference 7).

1.4 PERIPHERAL PROCESSES IN SPECIFIC TISSUES

1.4.1 Facial Skin
The craniofacial region has a dense innervation, especially in the intraoral and perioral region. Three major classes of nociceptive afferent fibers supplying facial skin have been described [12,13]: (i) Aδ mechanothermal nociceptive afferents that respond to intense thermal and mechanical stimuli; (ii) high-threshold mechanoreceptive afferents that respond best to intense mechanical stimuli (most of these conduct in the Aδ range, although some may have conduction velocities in the Aβ- and C-fiber ranges); and (iii) C-polymodal nociceptive afferent fibers that are excited by strong mechanical and thermal, as well as chemical stimuli that include agonists for ATP, 5-HT, bradykinin, and TRP channels. Some chemical stimuli may also act on the Aδ nociceptive afferent endings.

1.4.2 TMJ and Masticatory Muscles
The endings of many of the small-diameter afferents innervating the TMJ and masticatory muscles may respond to a wide range of peripheral stimuli that cause pain in humans. These include heavy pressure, algesic chemicals, and inflammatory agents [12,14] and likely also ischemia especially in the case of muscle nociceptive afferent fibers if it is prolonged and associated with muscle contractions. Several recent studies utilizing immunohistochemical, electrophysiological, and behavioral approaches have provided evidence for peripherally acting agonists for glutamate, TRPV1, GABA, and opioid receptors, just to name a few, as having modulatory effects on these deep craniofacial afferents [14–18]. There is also evidence from animal and human studies that sex differences may exist in some of these effects and have clinical implications (see below).

1.4.3 Cranial Vessels and Meninges
Cranial vessels and the meninges are supplied by small-diameter V afferent fibers that can be activated by noxious stimuli [19,20]. Their activation may also be associated with the subsequent development of vasodilatation related to neurogenic inflammation. The activation and modulation of these afferents by peripheral neurochemical processes (e.g., 5-HT) are thought to be important factors in the initiation and control of certain headaches such as migraine (see below).
1.4.4 Periodontium and Oral Mucosa

As well as a dense innervation supplying low-threshold mechanoreceptors, the periodontal ligament and oral mucosa have free nerve endings, which are associated with Aδ- and C-fiber nociceptive afferents. Although the subject of limited investigation, they have been found to respond to mechanical, thermal, and/or chemical stimuli [12,13] and, in general, appear to have properties similar to nociceptors in other tissues. Interestingly, some periodontal nociceptive afferents branch to innervate the pulp of an adjacent tooth, and the responsiveness of some mucosal nociceptive afferents may be influenced by biomechanical factors in the tissues.

1.4.5 Cornea

Nerve fibers supplying the cornea penetrate into the corneal epithelium and terminate as free nerve endings, which are thus very exposed to changes in the external environment. The most prominent sensations evoked by stimuli of different types applied to the corneal surface are of pain and irritation, although a cooling sensation may also be perceived. These observations are consistent with corneal afferent recordings in experimental animals, which have shown that the cornea contains mechano-nociceptors and polymodal nociceptors as well as low-threshold cold receptors [21].

1.4.6 Tooth Pulp

The tooth pulp is a highly vascular and richly innervated tissue that is exquisitely sensitive to stimulation (for review, see References 22–24). The pulp (the “nerve of the tooth”) is encompassed in dentine, which, in the coronal part of the tooth, is itself covered by enamel. Both the pulp and the dentine are innervated, and intradental afferents can respond to a variety of stimuli that predominantly, if not exclusively, produce pain. As well as small-diameter (Aδ- and C-fiber) afferents supplying the tooth, sympathetic afferents and Aβ-fibers also contribute to the innervation. The role of the Aβ-fibers is unclear, but their presence has been used as an argument that pain may not be the only sensation evoked from the pulp. While it appears that a hydrodynamic mechanism is largely responsible for activation of many intradental afferents, thermal and chemical stimuli may directly activate some afferents. The afferents may also manifest peripheral sensitization, and many of the peripheral chemical processes, receptors, and ion channels underlying their activation and sensitization appear to be similar to those identified in other tissues (see 1.3.1 above), including intraneural neuropeptides (e.g., substance P, CGRP, TRP and ATP receptors, and a number of chemical mediators [e.g. histamine, 5-HT, opioids, cytokines, and kinases]); several of these also contribute to pulp inflammatory, repair, and regenerative processes. A special feature of the pulp that should be noted is that while its nociceptive mechanisms are in a dynamic plastic state
like that in other tissues (see above), it has a very low compliance because of its encasement in hard tissues. This has been thought to be a factor contributing to the exquisite sensitivity of the tooth in some inflammatory states.

1.5 CRANIOFACIAL PAIN CONDITIONS AND ROLE OF PERIPHERAL MECHANISMS

This section briefly describes some of the most common or intriguing pain conditions in craniofacial tissues and outlines the contribution that peripheral mechanisms may make to each. It is important to note that these pain conditions may in addition or instead involve central neural processes (e.g., central sensitization) that may also contribute (see References 9, 11, 25, and 26). These pain conditions are listed according to the proposed mechanism-based classification of pain (Table 1.1).

1.5.1 Injury and Inflammatory-Related Pain

Trauma and inflammation are not only natural consequences of some dental procedures (e.g., tooth extraction, oral surgery) but can also be associated with

**TABLE 1.1. Suggested Classification of Pain according to Underlying Mechanisms.**

<table>
<thead>
<tr>
<th>Transient Pain</th>
<th>Tissue Injury Pain (Inflammatory Pain)</th>
<th>Nervous System Injury Pain (Neuropathic Pain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nociceptor specialization*</td>
<td>Primary afferent</td>
<td>Primary afferent</td>
</tr>
<tr>
<td>• Sensitization</td>
<td></td>
<td>• Acquisition of spontaneous and stimulus-evoked activity by nociceptor axons and cell bodies at loci other than peripheral terminals</td>
</tr>
<tr>
<td></td>
<td>• Recruitment of silent nociceptors</td>
<td>• Phenotype changes</td>
</tr>
<tr>
<td></td>
<td>• Alteration in phenotype</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hyperinnervation</td>
<td></td>
</tr>
<tr>
<td>CNS mediated</td>
<td>• Central sensitization recruitment, summation, and amplification</td>
<td>CNS mediated</td>
</tr>
<tr>
<td></td>
<td>• Deafferentation of second-order neurons</td>
<td>• Central sensitization</td>
</tr>
<tr>
<td></td>
<td>• Disinhibition</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Structural reorganization</td>
<td></td>
</tr>
</tbody>
</table>


*Specialization refers to specific membrane and neurochemical properties of nociceptors and associated afferent nerve fibers that allows them to be differentially activated by different types of brief noxious stimuli (e.g., mechanical, heat, or chemical).
specific pain conditions, which will be noted below. In addition, trauma normally involves injury of more than one type of tissue, and the clinical manifestation will depend on which tissues are involved, for example, deep pain usually has features quite distinct from those of pain occurring in superficial tissues (e.g., skin, mucosa) in terms of its localizability (diffuse vs. localized) and quality (aching, cramping vs. sharp, burning). Similarly for inflammation, which is a natural consequence of tissue injury, the clinical manifestations may differ depending on the physical properties and functions of the involved tissue; for example, inflammation in the tooth pulp (pulpitis) is associated with clinical characteristics that are different from those associated with gingival inflammation (gingivitis), probably in part due to the relative rigidity of dentine and enamel (also see above).

This leads us to consider one of the most common types of craniofacial pain. The teeth are a common source of pain [27]. Toothaches (odontalgias) are usually associated with reversible or irreversible pulpitis. Toothaches can have a “sharp” or a “dull” quality and sometimes a “throbbing” component, and the pain may also be exacerbated by hot and cold stimuli. The pain intensity can be very severe, particularly in the acute stages, with bouts of pain lasting minutes to hours. While the tissue damage is highly localized, the pain may spread and be referred to the ipsilateral face and jaw. Periapical periodontitis is also common and is often the consequence of irreversible pulpitis. In the acute stage, periapical periodontitis manifests severe pain that is difficult to localize, and often mechanical and thermal hyperalgesia. Mechanical hyperalgesia but more moderate pain is characteristic of the chronic stage. Other more special types of toothaches are cracked or partially fractured teeth, barodontalgia, and referred pain from remote and other craniofacial sites.

Inflammation can also occur in other craniofacial tissues and cause pain. For example, gingivitis and periodontitis involve, respectively, inflammation of the gingiva (gums) and periodontal tissues (around the root of the tooth). They are also very common inflammatory conditions, but surprisingly, they usually do not produce symptoms of pain. Why is unclear, but it could be related to the release of peripheral modulators that dampen the excitability of the gingival or periodontal nociceptive afferent endings; this requires further study through the development of specific models. Maxillary sinusitis involves inflammation of the lining of the maxillary sinus that often occurs in relation to nasal colds and is associated with cheek pain and tenderness of zygomatic arch tissues and teeth. Inflammatory conditions in the TMJ (synovitis and capsulitis) or jaw muscles (myositis) can occur after injury, systemic infections or localized inflammatory reactions (e.g., osteoarthritis), or systemic inflammatory states (rheumatoid arthritis) [28].

These many and varied painful conditions associated with local tissue injury and inflammation likely involve some common mechanisms underlying the pain. Studies in animal models of pulpitis, sinusitis, myositis, and arthritis for example, have provided evidence indicating that nociceptive afferents supply
ing these affected tissues are activated and sensitized in these models by chemical mediators and processes that are generally similar to those noted earlier [14,17,22,24,29]. Mechanisms within the CNS (e.g., central sensitization) have also been shown to be involved [11,25].

1.5.2 Neuropathic Pain

There are several craniofacial pain conditions that are neuropathic in origin [9,30,31]. Postherpetic neuralgia is a relatively common complication of acute herpes zoster infection and can affect the V nerve (usually its ophthalmic branch). Damage to or loss of the large peripheral afferent fibers with loss of myelination is a feature of postherpetic neuralgia and is generally thought to lead to changes in central nociceptive transmission and modulation, although peripheral processes may also contribute (e.g., inflammation of the involved cutaneous sites; see Reference 30). Trigeminal neuralgia is much less common, fortunately, because it is an excruciatingly painful neuropathic condition. Trigeminal neuralgia has a paroxysmal character, with sudden, unilateral, brief, stabbing, recurrent pain especially in the distribution of the maxillary or mandibular branches of the V nerve. The electric shocklike jolts of pain are usually triggered by light mechanical contact of a specific location in the perioral or intraoral region. Between the pain attacks, the patient is largely asymptomatic, with no clear changes in somatosensory sensitivity. The etiology and pathogenesis of trigeminal neuralgia are still unclear, although it can be secondary to multiple sclerosis, benign or malignant brain tumors, or facial trauma. There is some evidence that it might arise from a mechanical distortion of trigeminal afferents, which induces ectopic discharges of the afferents, but central mechanisms are undoubtedly involved in its pathogenesis [30–32].

Extraction of a tooth and endodontic treatment by their very nature involve deafferentation as well as peripheral nerve injury. Although these procedures are very common in dental practice, it is interesting that only a very low proportion of patients complain about persistent neuropathic pain. It has been suggested that this low incidence of neuropathic pain is because the high vascularization of the orofacial tissues facilitates regeneration and because the injured nerves are usually quite small in number compared with those in the limbs where neuropathic pain following trauma is more common. Pain can also appear when a peripheral branch of the V nerve is injured, for example, during maxillofacial surgery or placement of dental implants, but hypoesthesia and numbness are more common [31,33]. Atypical odontalgia and atypical facial pain may also represent neuropathic pain conditions due to peripheral events associated with deafferentation (e.g., tooth extraction, endodontic therapy) as well as long-term neuroplastic changes especially in the CNS (e.g., central sensitization). Atypical odontalgia can be difficult to distinguish from conventional odontalgias as pain may be localized to the site or to the tooth where the tooth or tooth pulp used to be before it was removed. As a consequence, the patient may receive excessive and unnecessary dental treatment