Chapter 5

Musculoskeletal referred pain to the craniofacial region

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Introduction

Pain in the craniofacial region can have multiple sources. Obviously, pain may arise from trauma or noxious stimulation of particular structures, for example skin, muscle, joint, tendon, bone, or teeth, resulting in localized pain. However, extrasegmental structures may also induce craniofacial pain. 'Referred tenderness' was originally used in the first reports of referred sensations (Head, 1893), but this is now known as referred pain. In the spinal system, clinical examples of pain perceived in the knee or thigh may arise from an arthritic hip joint, and often distant pain is perceived due to palpation of myofascial trigger points (TrPs) (Simons et al., 1999). In visceral pain conditions, referred pain (and not localized pain) is frequently felt in somatic structures distant from the affected visceral organs. Although known for many years, the definition of referred pain as felt away from the pain locus is not fully operational when it comes to pain spreading from a structure; for example, pain from the trapezius muscle may be perceived as a large area covering the trapezius muscle and also the neck and head. In this chapter, pain felt both distant from and outside of the pain origin is defined as referred pain.

The purpose of this chapter is to present the nociceptive capacity of various structures and their capability to mediate pain referral and cause sensitization. Major findings on the topic of pain referral mechanisms originate from studies on extremity muscles, which will be presented together with specific examples of referred pain in the craniofacial region.

Pain in the craniofacial region from myofascial trigger points

Definition

Although there are different definitions of myofascial trigger points (TrPs), the most accepted defines a TrP as 'a hyper-irritable spot within a taut band of a skeletal muscle that is painful on compression, stretch, overload or contraction, which causes a referred pain pattern and autonomic phenomena' (Simons et al., 1999). Clinically, TrPs are classified as active and latent. Active TrPs are those in which local and referred pain reproduces any sensory or motor symptoms reported by the patient and the symptoms are recognized by the patient as his or her usual pain (Simons et al., 1999). Latent TrPs are those in which local and referred pain does not reproduce any familiar or usual symptoms in the patient (Simons et al., 1999). The relevance of 'pain recognition' is discussed in the current Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) (Peck et al., 2014; Schiffman et al., 2014). It has been clinically observed that active TrPs induce a larger referred pain area and higher pain intensity than latent TrPs (Hong et al., 1997). In addition, this clinical distinction has been substantiated by a study showing higher levels of chemical mediators and other proinflammatory substances, for example substance P, bradykinin, and serotonin, in the vicinity of active TrPs compared with latent TrPs (Shah et al., 2005).

Sensitization mechanisms of trigger points

The referred pain evoked by TrPs is most likely mediated by a central mechanism (see the section below), whereas TrPs per se likely result from peripheral mechanisms where sensitizing agents cause increased pain sensitivity in very localized points (Shah et al., 2005). Findings also indicate the presence of nociceptive and non-nociceptive hypersensitivity at TrPs (Li et al., 2009; Wang et al., 2010b) in which a spinal dorsal horn mechanism may be involved (Kuan et al., 2007). Obviously, active TrP pain is processed at supraspinal levels and TrP hyperalgesia has been demonstrated to excite various brain areas associated with the pain

experience (Niddam et al., 2008; Niddam, 2009). A recent study found that individuals with TrPs exhibited microstructural brain abnormalities mainly distributed in the limbic system and the brain areas involved in the pain neuromatrix (Xie et al., 2016).

Trigger points in temporomandibular disorders

Pain patterns in TMDs can be composed of referred pain patterns from muscle TrPs located in the neck, shoulder, and masticatory muscles. Simons et al. (1999) described the referred pain pattern from several muscles and also how referred pain can spread to the head or face (see the illustrations of referred pain patterns in Chapter 8 of this textbook). Although these muscles refer pain to the face (trigeminal innervated area), they can also refer to the head and neck (cervically innervated area), mimicking headaches. It has therefore been suggested that a number of different muscles are involved in the pathophysiology of TMDs (the masseter), and headaches (upper trapezius and suboccipital muscles) (Conti et al., 2016; Svensson, 2007).

Few clinical studies have investigated the presence of TrPs in patients with TMDs. Wright (2000) reported that the upper trapezius, lateral pterygoid, and masseter muscles were the most common sources of referred pain into the neck and craniofacial regions. Nevertheless, this study did not include a control group and patients were not examined in a blinded fashion (Wright, 2000). Fernández-de-las-Peñas et al. (2010) conducted a blinded, controlled study, where patients with myalgic TMD and healthy controls were examined for TrPs in the neck, shoulder, and head musculature. This study found that TrPs in the masticatory muscles (the masseter and temporalis), were more prevalent than TrPs within the neck and shoulder muscles (the upper trapezius, suboccipital and sternocleidomastoid muscles) (Fernández-de-las-Peñas et al. 2010). These findings support the notion that masticatory muscle TrPs are more likely to play a role in TMDs, whereas neck and shoulder TrPs are more likely to play a greater role in headaches. This hypothesis was confirmed by a clinical study showing that referred pain was more pronounced in the orofacial region in patients with TMDs, whereas in female patients with fibromyalgia it was more pronounced in the cervical spine (Alonso-Blanco et al., 2012). Experimental pain studies also support this notion (see the next section).

Experimental musculoskeletal referred pain

Intramuscular injections of hypertonic saline have been widely used to study referred pain from muscles (Graven-Nielsen, 2006) (Figure 5.1). Other deep structures, such as tendon, ligament, intervertebral disc, periosteum and joint structures, may also evoke referred pain but have been less extensively investigated. In contrast to the superficial pain experienced

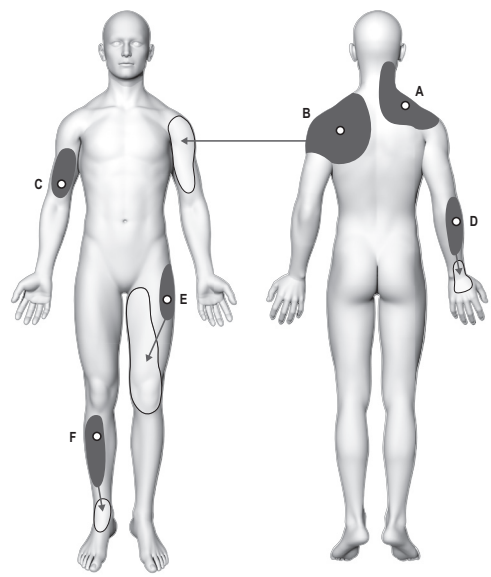

Figure 5.1
Typical enlarged local pain areas (shown in dark gray) and distinct referred pain areas (shown in white) experienced after intramuscular hypertonic saline injection (site denoted by white dot) into the trapezius (A), infraspinatus (B), biceps brachii (C), brachioradialis (D), vastus lateralis (E) and tibialis anterior muscles (F).

with visceral pain referral (Ness et al., 1990), muscle or deep tissue pain often evokes referred pain also perceived in deep structures (Kellgren, 1938). This can make it difficult to separate out which deep structures are the sources of pain and which are merely exhibiting referred symptoms.

Experimental investigations of pain in the pericranial muscles and nearby joints, ligaments, and muscles in the cervical spine have revealed that these structures are able to produce various patterns of referred pain. For example, early pioneering work has shown that injection of hypertonic saline into both the suboccipital muscles (Kellgren, 1938) and the cervical paravertebral muscles (Feinstein et al., 1954) is able to evoke a deep pain in the forehead region, similar to a headache. Similarly, hypertonic saline-induced pain from the atlanto-occipital joint (Campbell & Parsons, 1944), splenius capitis (Falla et al., 2007), and sternocleidomastoid muscle is also commonly felt about the cranium, in the parietofrontal, oculofrontotemporal, and occipitoparietal regions respectively.

Interestingly, however, there are clear differences between muscles in the extent of referred pain, with some muscles, for example the tibialis anterior and infraspinatus, giving rise to very distinct areas of pain, while other muscles, for example the biceps brachii, primarily give rise to local pain (Graven-Nielsen, 2006). This is also true in the craniofacial region, as was demonstrated when Schmidt-Hansen et al. (2006) systematically mapped saline-induced pain from muscles with trigeminal (masseter, anterior temporalis, posterior temporalis), and/or cervical (trapezius, splenius capitis and sternocleidomastoid) innervation (Figure 5.2). This study observed that the masseter and anterior temporalis muscles commonly produced trigeminal referral of pain to the face, jaw and parietofrontal region; whereas the posterior temporalis muscle also referred pain into cervical territories, such as the occipitotemporal region and occasionally the upper cervical region. The trapezius muscle almost exclusively produced pain in upper cervical regions; whereas splenius and sternocleidomastoid muscles produced referred pain both in the craniocervical region and into the ophthalmic trigeminal territory, as previously purported to be comparable to headache pain. These findings are consistent with prior investigations of experimental pain in pericranial musculature (Jensen & Norup, 1992; Svensson & Graven-Nielsen, 2001). Hence there appears to be a clear distinction between trigeminally and cervically innervated muscles with only limited functional overlap observed, despite the extensive convergence between these systems reported in animal studies (Sessle et al., 1986).

Originally, it was reported that referred pain followed a segmental pattern (Kellgren, 1938) and was thus restricted to the dermatome, myotome or sclerotome of the spinal segment innervating the painful

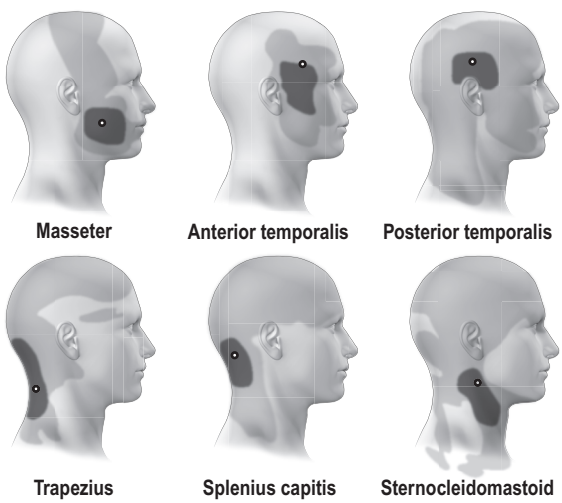

Figure 5.2
Pain distribution, as drawn on a body chart, following hypertonic saline injections into the masseter, anterior and posterior parts of the temporalis, trapezius, splenius capitis, and sternocleidomastoid muscles. Dark gray shapes represent the most commonly drawn pain areas (> 5 subjects), light gray shapes represent the combined extent of the pain areas (≥ 1 subject), and white dots denote the injection sites. Based on original data from 20 subjects presented in Schmidt-Hansen et al. (2006).

structure. However, this is no longer considered to be accurate. The distribution of both clinical and experimentally induced referred pain does not always follow a strict segmental pattern. In fact, referred pain in areas three segments distant to an electrically stimulated lumbar dorsal root segment has been reported (Bogduk, 1980). Consistent with this, TrPs in the temporalis muscle (mandibular division of the trigeminal nerve) can refer pain to the teeth (maxillary division of trigeminal nerve), and TrPs within the suboccipital (C1) and splenius capitis (C2–C4) muscles can result in referred pain in the trigeminally innervated temple region (Simons et al., 1999). Thus, referred pain from muscle tissue most likely extends into the territories innervated by neighboring segments to the afferent nerve supplying the painful structure.

Another interesting feature of referred pain is the semidirectionality of its occurrence, with referral toward the distal joint being most common in the extremities. For example, inducing experimental pain in the tibialis anterior muscle will commonly evoke referred pain in the ankle, but strong experimental pressure-induced pain at the ankle will not evoke pain in the tibialis anterior muscle (Graven-Nielsen, 2006). In contrast, there are some examples of bidirectional referred pain from muscle (Feinstein et al., 1954), which are certainly well-illustrated in the craniofacial region. Here, experimental jaw-muscle (masseter) pain can refer pain to the teeth (Svensson et al., 1998), and odontogenic (tooth) pain can often mimic jaw-muscle and facial pain (Falace et al., 1996). Similarly, as already highlighted, temporomandibular structures can give rise to neck pain and headache-like referred symptoms, and the temporalis and upper cervical muscles can give rise to referred jaw and facial symptoms.

Clinically, osteoarthritis in the hip joint is often accompanied by complaints of knee pain (and vice versa), which may in some cases be the only symptom and illustrates pain referral from a joint. Fairly localized pain is however induced by stimulation of the fat pad of the knee (Joergensen et al., 2013). In contrast, experimental electrical facet joint stimulation induces low back pain and pain referral into the anterior leg, ipsilaterally, proximal to the knee, similar to what is observed clinically in facet joint pain (O'Neill et al., 2009). Pain patterns from cervical joints have been extensively studied typically by joint provocation followed by recordings of the referred pain areas. As an example, the pain patterns from the cervical zygapophyseal joints were assessed by distending the joint capsule in healthy volunteers with injections of contrast medium under fluoroscopic control (Dwyer et al., 1990). The referred pain patterns that result from stimulation of the upper cervical spine zygapophyseal joints have also been described by Aprill et al. (2002). The opposite approach was used in patients where the referred pain areas from the zygapophyseal joint pain were eliminated by selective nerve blocks (Cooper et al., 2007). Cervical facet joints are therefore likely to be a source of headache pain, due to the characteristic pain referral pattern to the head and neck. Limited information exists from stimulating the TMJ. One study injected glutamate into the TMJ, producing pain that was fairly localized in the orofacial region with a few cases of pain being in the occipital region (Alstergren et al., 2010).

In addition to pain, the region of referral may also exhibit changes in sensitivity to cutaneous and deep mechanical stimuli. However, the direction of such changes is still debated, with the seminal experimental studies showing hyperalgesia in the region of referred pain (Feinstein et al., 1954; Kellgren, 1938) and later experimental studies showing hypoalgesia in the region of referral (Graven-Nielsen et al., 1998). Clinical studies are also difficult to interpret in this respect as often generalized hypersensitivity may exist, meaning both local and remote sites will be affected regardless of the presence of referred pain in the remote region.

Temporal and spatial characteristics of referred pain

The appearance of referred pain is commonly delayed in comparison to the appearance of local pain. When using single bolus hypertonic saline injections, referred pain occurs approximately 20 seconds after the relatively instant perception of local pain (Graven-Nielsen

et al., 1997). Similarly, continuous intramuscular electrical stimulation induces immediate and constant local nociceptive activity, and hence relatively immediate local pain, but referred pain is again delayed, appearing approximately 40 seconds later (Laursen et al., 1997). Further to this, prolonged exposure to experimental muscle pain, from either hypertonic saline infusion (Graven-Nielsen et al., 1998) or painful mechanical stimulation (Gibson et al., 2006), produces referred pain more frequently than during the initial phase or during a briefer painful exposure period. Together this indicates that referred pain is, at least to some extent, a time-dependent process.

In addition, the occurrence and area of referred pain may be related to the intensity of overall pain (Graven-Nielsen, 2006; Jensen & Norup, 1992). Similarly when referred pain develops in addition to local pain, the local and referred pain intensities are clearly well correlated (Graven-Nielsen, 2006). Given the relationship between pain intensity and the size of the pain area, however, it is possible that local pain may expand into the area of referred pain. In this case there is no longer true referred pain according to the definition (that is, pain not confined to the local pain area), and hence the prevalence of referred pain may be underestimated. Consistent with this, less than half of the intramuscular hypertonic saline injections seem to provoke true referred pain, but many participants (more than 60%) develop pain far from the injection site, or pain that spreads from the injection site into typical regions of referral (Graven-Nielsen, 2006). The location of painful stimulation in a muscle may also play a role in the development and extent of referred pain, with higher pain intensity and larger referred pain areas observed following hypertonic saline injection into the motor endplate zone compared to a control site (Qerama et al., 2004). However, this difference was not observed when using capsaicin (Qerama et al., 2004) and may instead be due to the difference in evoked pain intensity between sites with hypertonic saline. Pain intensity would therefore appear to be the primary determinant for the induction of referred pain from muscle.

In some instances, participants develop only referred pain and not local pain. This is an interesting conundrum, similar to what is often seen with referred pain from the viscera (Ness & Gebhart, 1990), and it is not entirely clear why this occurs. Potentially it is the result of anatomical variation, the excitation of different intramuscular nociceptive groups, or differences in descending modulatory systems, but it is yet to be confirmed.

The need for afferent somatosensory information from the referred pain area

To induce referred pain, somatosensory input from the periphery is at least partly involved. Differential nerve block techniques have demonstrated this, showing reduced referred pain intensity following blockage of myelinated afferents in the referred pain area (Laursen et al., 1999). Interestingly, the blockage of unmyelinated afferents conferred no greater pain reduction, suggesting that the proprioceptive fibers may be the most important peripheral component for the development of referred pain (Laursen et al., 1999). However, referred pain has also been induced in regions of complete sensory loss, for example following spinal cord injury, nerve lesion, amputation or regional anesthetic, with unchanged or only slightly decreased pain intensity (Feinstein et al., 1954; Harman, 1948; Kellgren, 1938; Whitty & Willison, 1958). Hence, the amount of peripheral somatosensory input required for referred pain induction varies depending on the location, structure, and central facilitatory mechanisms.

Experimental pain referral in musculoskeletal pain and headache

The presence of chronic musculoskeletal pain and headache conditions changes the behavior of experimentally induced muscle pain. Hypertonic saline injections into the anterior temporalis muscle result in larger pain areas of referral in patients with chronic and episodic tension-type headaches when compared to healthy controls (Schmidt-Hansen et al., 2007). Larger areas also resulted from injections into

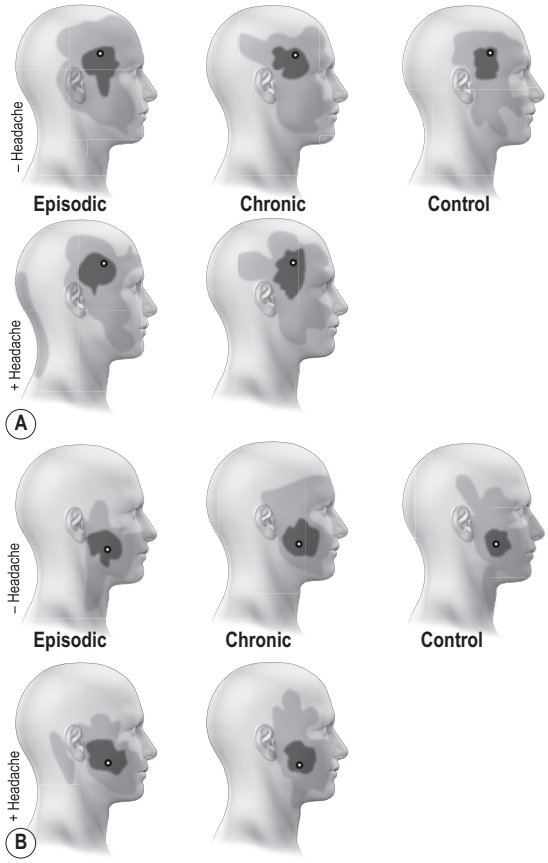

Figure 5.3
Pain areas induced by hypertonic saline injection (0.5 mL, 5.8%) into the temporalis anterior (A) and masseter (B) muscles in patients with headache and healthy participants. Patients with frequent episodic or chronic tension-type headache were assessed both during (+) and without (–) ongoing headache, and were found to demonstrate larger pain areas than healthy participants, especially for the temporalis anterior muscle. Dark gray shapes represent the most commonly drawn pain areas (> 5 subjects), light gray shapes represent the combined extent of the pain areas (≥ 1 subject), and white dots denote the injection sites. Based on original data from Schmidt-Hansen et al. (2007).

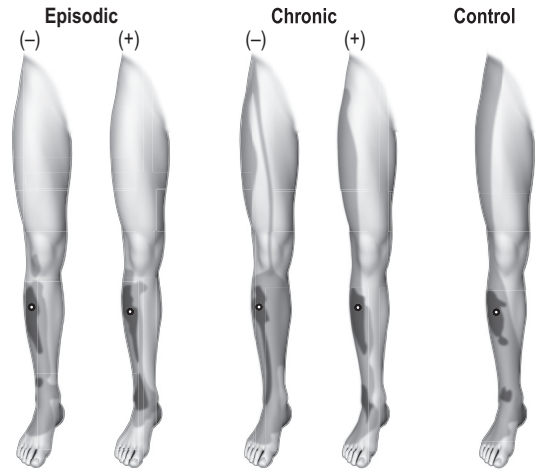

Figure 5.4
Pain areas induced by hypertonic saline injection (0.5 mL, 5.8%) into the tibialis anterior (TA) muscle in patients with headache and healthy participants. Patients with frequent episodic or chronic tension-type headache were assessed both during (+) and without (–) ongoing headache. Dark gray shapes represent the most commonly drawn pain areas (> 5 subjects), light gray shapes represent the combined extent of the pain areas (≥ 1 subject), and white dots denote the injection sites. Based on original data from Schmidt-Hansen et al. (2007).

adjacent and distant sites, for example the masseter (Figure 5.3) and tibialis anterior (Figure 5.4) muscles (Schmidt-Hansen et al., 2007), suggesting generalized sensitization in these patients. Such differences are also seen in widespread pain conditions, such as fibromyalgia, with higher pain intensity and larger referred pain areas in response to hypertonic saline injection than in matched healthy controls (Arendt-Nielsen & Graven-Nielsen, 2003). Fibromyalgia patients also commonly showed significant proximal referral of pain, unlike the predominantly distal referral patterns observed in healthy controls, which may also be indicative of sensitized central pain mechanisms. Larger areas of referred pain, following hypertonic saline injection into normally nonpainful muscles,

have also been observed in patients with chronic whiplash-associated disorder (Johansen et al., 1999), TMD pain (Svensson et al., 2001), symptomatic knee osteoarthritis (Bajaj et al., 2001), and low back pain (O'Neill et al., 2007). These enlargements in referred pain areas suggest the presence of sensitized central pain processing or a loss of efficient descending inhibition, potentially as a consequence of the ongoing noxious input.

Mechanisms of referred pain

Animal experiments using single neuron recordings have shown extensive convergence in the caudal trigeminal sensory nucleus complex between cervical and trigeminal afferents (Sessle et al., 1986). This convergent-projection theory is one of the earliest neuroanatomical explanations for referred pain, suggesting that the convergence of multiple afferents onto the same spinal neuron gives rise to referred pain by precluding higher brain regions from accurately identifying the original source. However, this explanation fails to account for the delayed onset of referred pain. Instead, referred pain may be partly due to central hyperexcitability and the development of new receptive fields (Graven-Nielsen, 2006; Mense & Simons, 2001; Neugebauer & Schaible, 1990). The former, central hyperexcitability, is supported by findings of reduced frequency of referred pain in healthy subjects when treated with a low dose of ketamine (an NMDA-receptor antagonist) to antagonize central hyperexcitability (Schulte et al., 2003). The latter, development of new receptive fields, has been demonstrated in animal studies following noxious muscle stimulation (Hoheisel et al., 1993; Hu et al., 1992). There is assumed to be an extensive and complex network of collateral synaptic connections for each muscle afferent to different dorsal horn neurons (Mense & Simons, 2001), some of which are fully functional under normal conditions, and others which are latent. Ongoing strong noxious input may activate these latent synaptic connections, allowing for greater convergence of afferent inputs from nearby regions, and hence give rise to the delayed emergence of referred pain.

Sensitization of craniofacial pain mechanisms

Both peripheral and central sensitization processes are implicated in the development and maintenance of craniofacial pain conditions. Peripheral sensitization generally occurs with injury- or inflammation-related activation of muscle and/or joint nociceptive afferents (Cairns, 2010; Sessle 2011). Peripheral muscle nociceptors may be activated by a number of substances (Mense, 2009), but perhaps the two most important factors are the release of adenosine triphosphate (ATP) and protons (H+). The resulting neuronal activation stimulates neuropeptide release from the free nerve ending, termed neurogenic inflammation. Known substances involved in this process include substance P (SP), bradykinin (BK), calcitonin-gene-related peptide (CGRP), serotonin (5HT) and prostaglandin E2 (PGE2) (Xanthos & Sandkühler, 2014), and also tumor necrosis factor alpha (TNFα) and nerve growth factor (NGF) which can further sensitize muscle nociceptors (Mense, 2009).

Inflammation, caused by increased joint loading, remodeling and hence release of proinflammatory mediators (TNFα and interleukins [ILs]) may be the most potent driver of pain in some conditions (especially joint-related conditions). This up-regulation of proinflammatory mediators can then cause greater release of inflammatory substances, such as SP, BK, CGRP and PGE2, causing neurogenic inflammation and the hallmark inflammatory signs of redness, edema, warmth and pain (Takeuchi et al., 2004). Peripheral glial cells may also be involved in peripheral sensitization, as has been seen in some animal models of orofacial pain (Zhao et al., 2015). In these studies, satellite glial cells were activated in response to stress (a known contributor to many chronic orofacial conditions), which is associated with an over-release of proinflammatory mediators and the development of mechanical allodynia (Zhao et al., 2015). As may be expected, plasma levels of proinflammatory cytokines (such as IL-1β, IL-6, IL-10 and TNFα) have been demonstrated to be elevated in patients with TMD (Park & Chung, 2016;

Takahashi et al., 1998). Interestingly, the magnitude of cytokine elevation in these patients was associated with the level of disability and sleep disturbance (Park & Chung 2016), suggesting that TMD may be one condition where the inflammatory process is indeed a potent driver of pain and disability, and that this inflammation may be maintained or further exacerbated by factors such as sleep quality and stress.

Strong excitation of nociceptive-specific afferents (C fibers) from deep tissues can cause prolonged hyperexcitability of dorsal horn neurons that may be responsible for hyperalgesia (Woolf, 2011). If this hyperexcitability or sensitization is limited to second-order neurons, pain and hyperalgesia will be limited to the innervated field; but if such sensitization advances to third-order neurons, this may underlie the widespread pain reported by groups of patients with craniofacial pain conditions (Burstein et al., 2000). Consequently, the more widespread a musculoskeletal pain condition becomes, the more signs of generalized hypersensitivity are demonstrated (Carli et al., 2002).

For a range of TMDs, widespread changes in mechanical pain detection thresholds (Ayesh et al., 2007; Fernández-de-las-Peñas et al., 2009), along with enhanced temporal summation of pain (Maixner et al., 1995), and after-sensations (Sarlani et al., 2004) have been observed. Similar local and widespread changes in pain sensitivity, and facilitated temporal summation, have also been shown in patients with chronic tension-type headache (Abboud et al., 2013; Ashina et al., 2006), migraine (Burstein et al., 2000) cluster headache (Fernández-de-las-Peñas et al., 2011), and to a lesser extent in individuals with episodic tension-type headache (Bendtsen & Jensen, 2000). Such observations cannot solely be explained by peripheral sensitization or neurogenic inflammation and instead implicate central nociceptive processes, such as central hyperexcitability and a loss of descending inhibition. (See Chapters 4 and 6 of this textbook for further information on the effect of sensitization mechanisms on TMDs.)

Pain modulatory systems

Increasing evidence suggests that chronic pain conditions are associated with disturbed balance between descending pain inhibition and facilitation – a phenomenon which may play a role in maintaining the sensitization of central pain mechanisms (You et al., 2010). To quantify descending inhibitory function, a counterirritation analgesia paradigm is used, whereby a tonic painful stimulus is applied extrasegmentally to alter the perception of pain in response to a particular painful stimulus. The reduced pain sensitivity that is produced is thought to result from the activation of medullary inhibitory projections that act postsynaptically to inhibit spinal and trigeminal wide dynamic range neurons in the dorsal horn (Le Bars et al., 1975). This paradigm and the effect it produces is termed diffuse noxious inhibitory control (DNIC) in animals or conditioned pain modulation (CPM) in humans (Yarnitsky et al., 2010). CPM can be evoked experimentally by applying a tonic nociceptive conditioning stimulus (such as tonic pressure or submersion of an extremity into ice water) while concurrently or sequentially applying a segmentally distinct acute nociceptive test stimulus (such as a pressure or thermal pain detection threshold or defined supra-threshold stimulus). The magnitude of the CPM effect is then quantified as the difference between the acute nociceptive stimulus rating with and without conditioning, with an improvement during conditioning normally expected (that is, increased pain detection threshold or lowered evoked pain). However, as the CPM effect reflects the net sum of descending pain inhibition and facilitation, in many patients with chronic pain there tends to be a reduced inhibitory effect (Yarnitsky, 2015).

Interestingly, the ability of the craniofacial region to drive CPM has not been extensively investigated. It is clear that spinal nociceptive systems can produce inhibitory effects on pain perception in the craniofacial region, and it seems that the reverse is also possible, despite it often being overlooked. One conditioning