

Review Article

Relationships between craniofacial pain and bruxism*

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SUMMARY A still commonly held view in the literature and clinical practice is that bruxism causes pain because of overloading of the musculoskeletal tissue and craniofacial pain, on the other hand, triggers more bruxism. Furthermore, it is often believed that there is a dose–response gradient so that more bruxism (intensity, duration) leads to more overloading and pain. Provided the existence of efficient techniques to treat bruxism, it would be straightforward in such a simple system to target bruxism as the cause of pain and hence treat the pain. Of course, human biological systems are much more complex and therefore, it is no surprise that the relationship between bruxism and pain is far from being simple or even linear. Indeed, there are unexpected relationships, which complicate the establishment of adequate explanatory models. Part of the reason is the complexity of the bruxism in itself, which presents significant challenges related to operation-

alized criteria and diagnostic tools and underlying pathophysiology issues, which have been dealt with in other reviews in this issue. However, another important reason is the multifaceted nature of craniofacial pain. This review will address our current understanding of classification issues, epidemiology and neurobiological mechanisms of craniofacial pain. Experimental models of bruxism may help to further the understanding of the relationship between craniofacial pain and bruxism in addition to insights from intervention studies. The review will enable clinicians to understand the reasons why simple cause–effect relationships between bruxism and craniofacial pain are inadequate and the current implications for management of craniofacial pain.

KEYWORDS: bruxism, pain, trigeminal physiology, jaw motor function

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Overview on craniofacial pain

In this issue of Journal of Oral Rehabilitation, other reviews have covered the complexity of bruxism in terms of criteria, diagnosis, and pathophysiology (1–3). We will start this review with an overview on craniofacial pain mechanisms. Craniofacial pain is simply a topographic term, which includes a great diversity of painful conditions in the cranium and face. The most widely accepted definition of pain is provided by the International

Association for the Study of Pain (IASP) (4): ‘Pain is an unpleasant sensory and emotional experience with actual or potential tissue damage, or described in terms of such damage’. Pain is conceptualized as a complex and multidimensional experience with a sensory-discriminative dimension related to our ability to tell the intensity (how much does it hurt), location (where does it hurt) and quality (how does it hurt) of pain. However, pain also involves an emotional or affective dimension because we may find it unpleasant and it can be associated with suffering, and we will normally also try to compare the pain with previous painful experiences and interpret it in relation to the actual situation

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(cognitive dimension of pain) (5–9). As an example, if you get injured during a competitive sport event you will most likely not pay full attention to the nociceptive information from the injury if you are in the lead and you may be able to ‘bite your teeth together’ and focus on the competition. Once you cross the finish line, you may realize how bad the leg actually hurts. Thus, there are many different cerebral signatures and emotional and behavioural responses associated with acute and chronic pain (8, 10). Still another component of the neuromatrix underlying human pain experience is the motivational dimension, which is the conscious or unconscious drive state for a person to initiate, sustain or direct behaviour in a certain manner (7, 9). This may vary substantially from an acute pain situation, which is a warning or alert signal that something is wrong and requires dental or medical treatment, to a situation where chronic craniofacial pain can be debilitating and the reason and even in rare cases the excuse for the person in pain not to participate in social or work activities, a situation referred to as ‘secondary gain’ (9).

A particular useful way to think about pain is formulated in the so-called bio-psycho-social model, which encapsulates much of this complexity of pain (11). Pain is rarely a question about simply the presence of nociceptive activity (nociceptive pain) or its absence (‘psychological’, ‘delusional’, ‘hallucinatory’ pain) but rather a complex balance or relationship where the same nociceptive activity can be interpreted and expressed by one person very differently from other persons and be associated with quite different responses, and illness behaviour. It is quite a challenge to adopt this more sophisticated view on pain instead of the old Cartesian view that injuries trigger ‘pain signals’ which run in ‘pain fibres’ reaching the ‘pain centre’ in the brain in a one-to-one relationship between injury and pain much the same as electrical current runs in cables and can turn on a lamp (7). The critical point may therefore not be the actual amount of nociceptive input but rather how this afferent barrage is integrated and processed in the central nervous system. From this perspective it may be no surprise if two persons with the same degree of bruxism could have quite different responses in terms of their painful symptoms.

Classification of craniofacial pain

In practical terms, the IASP has classified pain according to its duration (acute or chronic) (4). Often the distinc-

tion between acute and chronic is set to 6 months but this is obviously arbitrary and it may in fact be more relevant to distinguish between pain which subsides within a few weeks after an injury, and pain which lasts beyond the normal tissue healing time (9). Instead of chronic pain, the term *persistent pain* is often used for longer lasting pain because chronic may imply an irreversible event. Furthermore, the IASP classification uses regions to describe pain (pain in the head, face and mouth; cervical region, thoracic region, etc.), and involved organ systems (pain in the musculoskeletal, visceral, cutaneous-subcutaneous, nervous, respiratory, cardiovascular system, etc.). The temporal characteristics should also be considered when classifying pain (single episode, continuous, intermittent, paroxysmal, etc.). Finally, the presumed aetiology of pain can be used to classify pain according to different causes (genetic-congenital, trauma, infection, inflammatory, degenerative, psychological). IASP has used these characteristics to classify >50 fairly localized pain syndromes in the craniofacial region, e.g. trigeminal neuralgia, glossopharyngeal neuralgia, post-herpetic neuralgia, tension-type headache, atypical odontalgia, odontalgia, migraine, and temporomandibular disorders (TMD; for a complete list see Ref. 4). Bruxism is usually believed to be related to the musculoskeletal types of pain such as TMD pain, but also tension-type headache and pains associated with overloading of the tooth pulp and periodontium have been considered relevant. This review will mainly focus on the painful TMD.

Despite the clinical usefulness in classifying pain according to the above-mentioned principles, it may be important from a diagnostic and also therapeutic point of view to classify pain according to the underlying pain mechanisms irrespective of the pain being present in muscle or skin or in the head or toe. Therefore, it is a matter of ongoing discussion in the pain field whether it is indeed possible to classify pain according to the current knowledge of the mechanisms involved (12). The proposed mechanism-based classification has four main categories: nociceptive pain, tissue injury (inflammatory) pain, nervous injury (neuropathic) pain and functional pain (12, 13). A summary of the pain mechanisms is shown in Table 1 and will be further discussed in the following paragraphs.

Basic pain mechanisms

The proposal of a mechanism-based classification of pain (Table 1) is rooted in significant advances in the

Table 1. Mechanism-based classification of pain

Nociceptive pain: transient pain in response to a noxious stimulus

Nociceptor specialization

Tissue injury pain (inflammatory pain): spontaneous pain and hypersensitivity to pain in response to tissue damage and inflammation.

Primary afferent: sensitization, recruitment of silent nociceptors, alteration in phenotype, hyper-innervation

CNS mediated: Central sensitization recruitment, summation, amplification

Nervous system injury pain (neuropathic pain): spontaneous pain and hypersensitivity to pain in association with damage or a lesion of the nervous system.

Primary afferent: Acquisition of spontaneous pain and stimulus-evoked activity by nociceptor axons and somata at loci other than peripheral terminals, phenotype changes

CNS mediated: Central sensitization, deafferentation of second-order neurones, disinhibition, structural reorganization

Functional pain: hypersensitivity to pain resulting from abnormal central processing of normal input

Adapted from Woolf *et al.* (12) and Woolf (13).

understanding of the neurobiological mechanisms involved in different painful conditions. Here, we will highlight some of the unique aspects related to activation and peripheral sensitization of the primary afferent nociceptive fibres, the activation and sensitization of the second-order and/or higher-order nociceptive neurones in the central nervous system (CNS), and finally the endogenous pain-control mechanisms, which include both inhibitory and facilitatory processes.

Peripheral nociceptive mechanisms and sensitization

The nociceptive endings in peripheral tissues can be activated by several types of noxious stimuli (thermal, mechanical, chemical) and then they initiate action potentials in their associated afferent fibres that are conducted towards the CNS. These afferent fibres conducting the 'nociceptive signals' into the CNS are some of the small-diameter myelinated afferents (A-delta) and unmyelinated afferents (C-fibres). In addition to the activation of the nociceptive endings, however, there are also significant changes as a result of tissue-damaging stimuli and inflammatory mediators; these changes include an increased excitability of the nociceptive endings, so-called 'peripheral sensitization' (9, 14, 15). Thus, a great number of factors and chemical mediators including products released from blood vessels or from cells of the immune system can influence

the excitability of the nociceptive afferent endings (15, 16). Substances synthesized in and released from the afferent fibres themselves may influence the excitability of the nociceptive afferents (14–16). Examples include the neurotrophins such as nerve growth factor (NGF), and neuropeptides such as substance P and calcitonin gene-related peptide (CGRP). For example, artificial elevation of NGF in the human masseter muscle is associated with a prolonged period (weeks) of decreased thresholds to pressure stimuli but without spontaneous pain reports (17). Under certain conditions, substances such as noradrenaline that are released from sympathetic efferents innervating the tissues may also modulate the excitability of the nociceptors (14). In some situations, the tissue damage may lead to abnormal nerve changes that are associated with so-called ectopic or aberrant neural discharges. Neuropeptides such as substance P and CGRP (calcitonin gene-related peptide) that are synthesized in the primary afferent cell bodies of nociceptive afferents and are released from their peripheral as well as and central afferent endings 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 (16). The combined release of the neuropeptides and these inflammatory mediators ('inflammatory soup') results in oedema (swelling), redness, and local temperature increases which, along with pain, are the cardinal signs of inflammation of peripheral tissues. This process has also been termed neurogenic inflammation, because it is mainly triggered from nerves themselves (14, 16). Such clear-cut inflammatory changes are, however, not encountered in patients who brux their teeth.

The neuroactive chemicals also act on the nociceptive afferent endings and contribute to the peripheral sensitization of the endings. Sensitized nociceptors exhibit spontaneous activity, lowered activation thresholds, and increased responsiveness to subsequent noxious stimuli. In the clinic, these changes appear to contribute, respectively, to the spontaneous pain, allodynia (pain because of a stimulus which does not normally provoke pain) and hyperalgesia (increased response to a stimulus which is normally painful) that are features of many chronic or persistent pain conditions including myofascial TMD and temporomandibular joint (TMJ) arthralgia (e.g. 18–20).

Additional receptor mechanisms have been discovered recently in peripheral nerve endings that are

involved in pain. They include the vanilloid VRI (or TRPV1) receptor that responds to protons (H^+), heat, and chemicals such as capsaicin, the ingredient in chilli (hot) peppers that produces pain (14, 16) as well as 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). For example, glutamate is synthesized by primary afferent cell bodies. It can excite nociceptive afferents supplying craniofacial musculoskeletal tissues and induce a transient pain in humans by activating *glutamate receptors* [*N*-methyl-D-aspartate (NMDA) and non-NMDA receptors] located on the afferent endings (9, 21). Recent studies have demonstrated significant decreases in pressure pain thresholds associated with spontaneous pain reports in healthy volunteers where glutamate has been applied directly to the masseter muscle (22). These studies in humans are paralleled by studies in rat models with recordings of the primary afferent nerve fibres from the TMJ, temporalis or masseter muscle (21, 23–25). Interestingly, the human and animal studies on peripheral glutamergic mechanisms have also revealed sex-related differences since the glutamate-evoked afferent barrage is significantly greater in female rats than in male rats and healthy women experience significantly more glutamate-induced pain than healthy men (21, 23, 26). Very recently, differences in the expression of the NR2B receptors have also been demonstrated between female and male rats, providing further evidence that there may indeed be a neurobiological rationale for the predominance in women amongst TMD patients for example (27). Such experimental studies have also shown that administration of a NMDA receptor antagonist is able to block the activation and sensitization of the primary afferent nerve fibres (21, 28) and pain and muscle sensitivity in healthy men (25). Interestingly, the NMDA receptor antagonist ketamine does not seem to have an analgesic effect in women (29) or in female myofascial TMD patients (30). Also, the opiate drug morphine can depress the activity of the primary afferent nerve fibres by interacting with opioid receptors on the nociceptive afferent endings (31). Such peripheral opioid receptors do exist in craniofacial tissues, and it has been shown that administration of morphine or other opiate-related chemicals to the TMJ can suppress jaw reflexes and nociceptive behaviour evoked by noxious stimulation of TMJ tissues in animals, and again there are sex differences in these effects (e.g. 32, 33).

The multiplicity of peripheral chemical mediators involved in peripheral nociceptive activation, peripheral sensitization and related events (e.g. inflammation) are all potential targets for the development of new and more effective therapeutic approaches to pain control (14, 15). So far, the neurobiology and characteristics of peripheral tissues in bruxers have not attracted much attention but might provide important clues to its relationship with craniofacial pain.

Central nociceptive mechanisms and sensitization

The trigeminal nociceptive primary afferents release excitatory amino acids (e.g. glutamate) and neuropeptides (e.g. substance P, CGRP) not only in the peripheral tissues as described above, but also in the synapse between the first- and second-order neurones in the trigeminal brainstem sensory nuclear complex. This brainstem complex comprises the trigeminal main sensory nucleus and the trigeminal spinal tract nucleus; the latter is made up of the subnucleus oralis, subnucleus interpolaris and the subnucleus caudalis (6, 9, 34). The release of the excitatory amino acid glutamate from the afferents leads to the activation of nociceptive neurones which predominate in subnucleus caudalis; these nociceptive neurones are of two main types; nociceptive-specific (NS) and wide dynamic range (WDR). Glutamate activates these neurones by a process involving two different ionotropic receptors (i.e. that gate ion channels directly) for glutamate, NMDA and AMPA receptors (alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid), as well as metabotropic glutamate receptors (i.e. that gate ion channels indirectly through the action of G-protein-coupled receptors which utilize intracellular second messengers) (9, 13, 35). These different types of glutamate receptors have different physiological characteristics and actions. Activation of the AMPA receptor is rapid and short-lived. In contrast, the NMDA receptor has a longer period of activation and is important in the processes called 'wind-up' and 'central sensitization' (13). Recent studies have shown that NMDA receptor antagonists in particular can block these nociceptive phenomena in caudalis, which has led to the view that NMDA antagonists through their central actions might be useful analgesics in, for example, neuropathic pain conditions (see Ref. 9, 34). However, a recent randomized and controlled clinical trial failed to show a significant effect of intravenous administration of ketamine on pain reports in patients with atypical

odontalgia (36) although other types of orofacial pain conditions may be more sensitive to blockage of NMDA receptors (37). The potential effects of NMDA receptor antagonists on bruxism-related pain conditions have not been studied but such studies could indicate if central glutamatergic mechanisms were involved in bruxism.

The neuropeptide substance P is also an important contributor to nociceptive mechanisms in the CNS (13). Like glutamate, it also occurs not only in the peripheral endings of small-diameter primary afferents but is also concentrated in primary afferent terminals in the CNS, such as those of subnucleus caudalis. Noxious craniofacial stimulation may cause the release of substance P within caudalis: this then acts on the caudalis nociceptive neurones through neurokinin receptors to produce a long-latency, sustained excitation of the nociceptive neurones that can be blocked in experimental animal models by substance P antagonists (34). A substantial spread of substance P within the trigeminal brainstem sensory nuclear complex has also been shown in response to dental injuries, which may help to explain the potential of spreading and referral of craniofacial pain in some clinical conditions (38).

The anatomy, physiology and neurochemistry of subnucleus caudalis have many features similar to those of the dorsal horn in the spinal cord, an area that is critical in spinal nociceptive transmission (34, 39). Indeed, because of its close functional and structural similarity with the spinal dorsal horn, caudalis is now often termed the 'medullary dorsal horn'. However, there are some distinct differences between subnucleus caudalis and spinal dorsal horn (40). Moreover, different parts of subnucleus caudalis *per se* may have different functional roles since its rostral and caudal portions appear to be differentially involved in the autonomic and muscle reflex responses to noxious craniofacial stimulation (34, 41). Furthermore, caudalis may not be the only component of the trigeminal brainstem complex with a nociceptive role. Like caudalis, more rostral components of the trigeminal brainstem complex (e.g. subnuclei interpolaris and oralis) have NS and WDR neurones and furthermore, lesions of rostral components may disrupt some craniofacial pain behaviours (34, 39). These nociceptive neurones have cutaneous receptive fields that are usually localized to intraoral or perioral areas, and many can be activated by tooth pulp stimulation. The receptive field and response properties of these rostral neurones, coupled with the effects of rostral lesions, suggest that

the more rostral components may play a role in intraoral and perioral nociceptive processing (34).

It has been shown that many caudalis NS and WDR neurones with a cutaneous receptive field also receive convergent afferent inputs from tissues that include tooth pulp, TMJ or masticatory muscle, which are thought to contribute to the spread and referral of pain that is typical of deep pain conditions involving these tissues (34, 39, 42, 43). This extensive convergence of afferent inputs may also contribute to central neuronal changes that can be induced by inflammation or injury of peripheral tissues or nerve fibres. Chemicals released from the peripheral tissues or primary afferent nerve endings themselves by the injury or inflammation may enhance the excitability of peripheral nociceptors (i.e. peripheral sensitization). This in turn may produce a barrage of nociceptive input into the CNS which can lead to prolonged functional alterations in subnucleus caudalis (and spinal dorsal horn) resulting in a state of increased excitability of caudalis neurones (13, 34). For example, the nociceptive afferent activity caused by damage to or inflammation of tooth pulp, TMJ or muscle can induce spontaneous activity, lowering of the activation threshold, receptive field expansion, and enhancement of responses of caudalis NS and WDR neurones; these neuroplastic changes in the properties of the nociceptive neurones are termed 'central sensitization'. Other changes may include a gradually augmenting response to a series of repeated noxious stimuli ('wind-up') (34, 39). Such characteristics have so far not been studied in animal models of bruxism. Central sensitization is not restricted to subnucleus caudalis but also occurs in nociceptive neurones in subnucleus oralis and in higher brain regions such as the ventroposteromedial nucleus of the thalamus (VPM), although caudalis is responsible for the expression of central sensitization in these structures through its projections to both oralis and VPM thalamus (34, 40).

An important point from these recent advances in the understanding of basic pain mechanisms is that the trigeminal and cervical afferent inputs and brainstem circuitry are not 'hard-wired' but are 'plastic' (34, 35). This means that the receptive field and response properties of the nociceptive neurones can undergo changes as a result of unmasking and increased efficacy of some of the extensive convergent afferent inputs to the nociceptive neurones (35). The neurones' responses to these inputs are enhanced and their receptive fields

are enlarged, resulting in a greater number of stronger inputs. In the clinic these phenomena may translate into pain spread and increased areas of pain and hypersensitivity to stimuli (9).

The neuroplastic changes occurring in caudalis nociceptive neurones are relayed not only via ascending pathways to higher brain centres such as VPM thalamus but also onto the trigeminal motoneurones supplying the jaw muscles via the connections that subnucleus caudalis has with brainstem reflex centres such as the trigeminal motor nucleus. Thus the above-mentioned neuroplasticity of the nociceptive neurones in the brainstem may be accompanied by prolonged increases in activity of both jaw-opening and jaw-closing muscles which has been convincingly demonstrated in animal models (34). These prolonged increases in jaw-opening and jaw-closing activity may serve to limit jaw movement in pathophysiological conditions affecting the jaw, for example, when a masticatory muscle is injured or inflamed (34). Theoretically, this interaction between the 'plastic nociceptive sensory system' and jaw motor system could play a role in relation to bruxism. However, it needs to be pointed out that experimental painful stimulation of human jaw-closing muscles mainly evoke, if any, a short-lasting response in the relaxed jaw muscles (44–46) and a consistent decrease (inhibition) of the jaw-closing muscles during agonist action (e.g. during a isometric contraction) (47, 48). The net result of the neuroplastic changes is an increased central excitatory state that is dependent on peripheral nociceptive afferent input for its initiation, but may not be fully dependent on peripheral afferent drive for its maintenance (35). Central sensitization can last for days or even weeks, and if it does not resolve and becomes maintained, it is thought to contribute to the development of persistent pain and to the spontaneous pain and tenderness that characterize many clinical cases of injury or inflammation (9, 13). Central sensitization may also enhance the effect of low-threshold mechanosensitive afferent inputs (which are not normally associated with pain) on nociceptive pathways in conditions associated with peripheral injury or inflammation, and thus could contribute to the allodynia that often is associated with pain conditions. It also can explain the hyperalgesia that is a feature of many acute as well as persistent pain conditions, because it increases the response of central nociceptive neurones to A-delta and C-fibre nociceptive inputs. The increased receptive field size of the noci-

ceptive neurones also appears to represent a central factor contributing to pain spread and referral, and the spontaneous activity of the neurones may contribute to spontaneous pain. A special condition termed 'proprioceptive allodynia' (see below) which may share some of the characteristics of secondary hyperalgesia will be discussed in relation to experimental bruxism models (49–51).

Endogenous pain-modulatory mechanisms

In view of the multidimensional nature of pain, it is not surprising that pain can be modulated by a variety of pharmacologic agents and physical and psychological interventions (7). Several areas in the thalamus, reticular formation, limbic system, and cerebral cortex are involved in the perceptual, emotional, autonomic, and neuroendocrine responses to noxious stimuli by utilizing various excitatory and inhibitory neurochemicals (9). The modulatory effects differ from one person to another, which is consistent with the idea that pain is a highly personal experience that is susceptible to a variety of biological, pharmacological, psychological, genetic and environmental influences. Again this also underlies the clinical observation that the afferent input from nociceptive nerve fibres, e.g. triggered by bruxism not always is linearly related to the self-reported levels of pain symptoms.

The intricate organization of each subdivision of the trigeminal brainstem complex and the variety of inputs to each of them from peripheral tissues or from different parts of the brain provide a particularly important substrate for interactions between the various inputs (9, 34). Other modulation can also occur at thalamic and cortical levels and in the peripheral tissues themselves (52). This modulation is an important element of the gate control theory of pain (53). The central modulatory processes release endogenous neurochemical substances, some of which underlie facilitatory influences on nociceptive transmission, while others exert primarily inhibitory influences that may involve presynaptic or postsynaptic regulatory mechanisms (41, 54). These neurochemicals include opioids such as the enkephalins, serotonin (5-HT), noradrenaline, and GABA (52, 55). These neurochemical substrates are used by pathways that descend from structures elsewhere in the brain onto nociceptive pathways and modify incoming nociceptive signals. These central pathways emanate from the periaqueductal grey

matter, rostroventral medulla/nucleus raphe magnus, anterior pretectal nucleus, locus coeruleus and parabrachial area of the pons as well as the somatosensory and motor areas of the cerebral cortex (52, 56). Electrical or chemical stimulation of these central sites activates descending pathways that project to the trigeminal brainstem complex and can inhibit trigeminal brainstem neuronal and related reflex and behavioural responses to noxious craniofacial stimulation in experimental animals (34, 39). Stimulation of some of these pathways may potentially also relieve pain in clinical conditions. It is also important to note that some of these descending pathways can facilitate nociceptive transmission, and so enhancement of these facilitatory influences could be playing a role in fostering central sensitization (41, 57).

While these descending pathways exert their effects on nociceptive transmission by the release from their endings of neurochemicals such as enkephalins or 5-HT in subnucleus caudalis (34, 52, 56), some chemicals (e.g. enkephalins, GABA) appear to be released from the endings of interneurons contained wholly within the trigeminal brainstem complex (e.g. the substantia gelatinosa of subnucleus caudalis). As well as being activated by some other descending pathways, these interneurons may also be influenced by afferent inputs from peripheral tissues and thus be part of so-called segmental inhibitory mechanisms. Thus some analgesic procedures involving stimulation of peripheral tissues [e.g. transcutaneous electrical nerve stimulation (TENS); acupuncture; diffuse noxious inhibitory controls (DNIC)] conceivably could be exerting an inhibitory influence on nociceptive transmission by involving these segmental mechanisms and/or by activating some of the descending inhibitory pathways.

The enkephalins are one group of several opioid peptide groups that can act on specific opiate receptors in the CNS or peripheral tissues (e.g. μ , δ , κ opiate receptors). The action of the narcotic analgesic morphine on opiate receptors in peripheral tissues was mentioned previously but all three subtypes of opiate receptors are also widely distributed in the CNS. They are concentrated in several sites including the periaqueductal grey, amygdala, anterior cingulate cortex, and trigeminal subnucleus caudalis (34, 52). All three opiate receptor subtypes have been implicated in the modulation of nociceptive processes: some exert facilitatory effects, others are inhibitory. For example, analgesia can be produced by the microinjection of certain

opioids at these intra-cerebral sites. This appears to involve the activation of descending anti-nociceptive pathways that originate in these sites, and the descending inputs inhibit craniofacial nociceptive transmission at the very first relay station, in subnucleus caudalis (34, 52). Suppression of nociceptive transmission can also be induced by the application of opioids directly to subnucleus caudalis. This presumably acts on opiate receptors related to some of these descending inputs to the trigeminal brainstem complex or on opioid-containing neurones intrinsic to the subnucleus caudalis. These inhibitory influences acting *via* the descending pathways or by actions within caudalis itself are thought to contribute to the analgesic efficacy of the narcotic opiate-related analgesics drugs (e.g. morphine and codeine) as well as possibly some of the procedures involving peripheral tissue stimulation (9). A key point here is that neuronal circuitries within the brainstem with both pro- and antinociceptive (facilitatory and inhibitory) components play a pivotal role in gating the nociceptive transmission (10, 52).

An intriguing concept related to painful TMD and many other chronic pain conditions is that they could reflect a dysfunctional state of such endogenous pain-modulatory systems (41, 52, 58–60). A dysfunction reflecting less efficient DNIC mechanisms has been reported, using different experimental paradigms, in patients with myofascial TMD (58–60), and several other chronic pain conditions (61–64). Also in patients with migraine and chronic tension-type headache, deficiencies in DNIC-like pain inhibitory mechanisms have been described (65). It can be speculated that impairment of the endogenous supraspinal pain modulation systems may contribute to the development and/or maintenance of central sensitization in craniofacial pain conditions such as primary headaches (65), however, it is not known if changes in DNIC-like mechanisms are a cause of, e.g. myofascial TMD pain and tension-type headache or if such changes occur in response to the persistent pain problem.

In the field of TMD one of the most exciting new avenues towards a better understanding of the pathophysiology is coming from genetics and in particular the variation in the coding of the catechol *O*-methyltransferase (COMT), an enzyme that metabolizes catecholamines and is critically involved in the pain perception, cognitive function and affective mood (66, 67). An association between COMT haplotypes and sensitivity to experimental painful stimuli has been established

(68–70) and importantly, carriers of the low-pain sensitivity haplotype appear to reduce by 2.3 times the risk to develop a myofascial TMD (68). The influence of COMT activity appears to be mediated through the adrenergic receptor beta-2 (ADRB2) (67) and individuals who carry one haplotype coding for high and one coding for low ADRB2 expression have been shown to display high positive psychological traits, have higher levels of resting arterial pressure, and to be approximately 10 times less likely to develop TMD (69, 70). However, there are numerous receptors and molecules involved in the regulation of nociceptive transmission and several other genes undoubtedly also have implications for the pain sensitivity, e.g. TRPV1, TRPM8, TRPA1, OPRD1 and FAAH (71–74) but the studies noted above imply the need for individually tailored treatment of myofascial TMD pain, e.g. by pharmacological agents that block ADRB2 function. The field of ‘pain genetics’ is promising and is likely to enable us to understand some of the neurobiology underpinning the individual differences in response and behaviour to painful stimuli and this may also have a great impact on the future understanding of the relationship between bruxism and craniofacial pain. One important caveat here is that environmental factors also represent important determinants of how a person may respond to a painful situation (72, 74). Another related caveat is that the phenotypic characteristics of the individuals need to be well described to be linked with the genotypes and this emphasizes the continued need for accurate and valid measures of both bruxism and craniofacial pain.

Epidemiology of craniofacial pain

For a complete review on the epidemiology of craniofacial pain the reader is referred to recent reviews and text books (4, 75–79). Here only TMD will be briefly considered as they are the most relevant for the discussion of the bruxism. The aetiology of most TMD conditions is still unclear, and yet epidemiological studies have indicated that approximately 10% of the population will qualify for a TMD pain diagnosis (80, 81). In addition, several epidemiological studies have shown a remarkable co-morbidity between painful TMD conditions and, e.g. low-back pain, fibromyalgia, chronic fatigue syndrome, and tension-type headache (82–85). Few studies have tried to separate TMJ pain from myofascial TMD pain but the latter appears to be

less prevalent than the former. Most studies have, however, found that TMD pain is almost two times more prevalent in women but it is important to distinguish between the number of TMD cases presenting in the clinic and the number of TMD cases in the community, because behavioural aspects like treatment-seeking patterns and use of health services may bias a neurobiological difference (9). The prevalence of TMD across the lifetime is still debated but there seems to be a peak approximately 45 years for women, although also elderly people may suffer from TMD pain (86). For some types of TMD problems such as TMJ osteoarthritis, there seems to be an increase over the lifespan. There are few good studies on the incidence of TMD pain problems but the persistent types appear to be approximately 0.1%. Some longitudinal studies have shown substantial variations in the time course of myofascial TMD (87) with one-third being persistent over a 5-year period, one-third being remittent and about one-third recurring. Non-painful clicks in the TMJ (disc displacement with reduction – DDwR) are very common (10–35%) but have been shown very rarely to progress to disc displacement without reduction (DDwoR); indeed, none of the 114 adolescents that were followed over a 9-year period progressed from DDwR to DDwoR (88). This strongly indicates that asymptomatic DDwR should be managed by conservative techniques. Other studies have shown that patients with combined diagnosis of DDwR and arthralgia may have a higher risk to progress to a DDwoR (89).

Risk factors

Contemporary epidemiology is nevertheless much more advanced than a basic description of the prevalence and incidence of TMD symptoms and can also be used as an analytic tool. Although the aetiology of most TMD conditions is unclear, this line of research has helped to identify a number of factors likely to be related to TMD pain. These factors are termed risk factors to indicate the probability that TMD pain and the factor are related. A stringent view on these risk factors has suggested that very few of the assumed and often clinically believed etiological factors actually meet the criteria for a statistical relationship (81) (Table 2). It must also be noted that although these factors meet or are close to meeting the statistical criteria, they do not necessarily indicate a straight forward cause–effect relationship; this is exemplified by the risk factor

Table 2. Possible risk factors for temporomandibular disorders

Gender/hormonal factors
Depression/somatization
Multiple pain conditions/widespread pain
Bruxism/oral parafunctions
Trauma
Generalized joint hypermobility
Vulnerable genotypes (COMT/ADRB2)
Occlusal variables
Anterior open bite
Unilateral cross-bite
Overjets >6–7 mm
More than 5–6 missing posterior teeth
RCP-ICP slide >2 mm
Dental wear

Possible risk factors for temporomandibular disorders modified after Drangsholt and LeResche (81), Pullinger *et al.* (90); Seligman and Pullinger (96); Diatchenko *et al.* (68). RCP, retruded contact position, ICP, intercuspal contact position.

Not all the listed factors are supported by sufficient data to suggest causation.

depression which conceivably could be an effect of persistent TMD pain rather than its cause.

Occlusal factors have especially been subject to an intense discussion and continue to be within the dental community. A small number of occlusal factors (e.g. anterior open bite, large horizontal overjet, loss of molar support) appear to be weakly associated with TMD but for many clinicians it is a surprise not to find more occlusal parameters on the list (90–93). Again it must be remembered that a change in occlusion could occur as an effect of an underlying pathology (e.g. osteoarthritis leading to anterior open bite). In particular, many clinicians are surprised not to see deep bite as a significant risk factor because the conventional view has been that deep bite may lead to a posterior displacement of the mandible which then leads to TMJ clicking and degeneration associated with TMJ arthralgia and myofascial TMD pain. This view would at a first glance seem to gain support from a report where 320 persons were followed over 20 years and where deep bite was a significant risk factor (odds ratio 12.5) for dysfunctional problems (94). However, a careful reading of the report shows that although there was a significant correlation between deep bite and some signs and symptoms of TMD, the study could not demonstrate that deep bite was a risk factor for *manifest* TMD pain. In support of this conclusion another study showed in 3033 persons that deep bite

or anterior open bite not was associated with the cardinal signs and symptoms of TMD, i.e. pain, limited opening capacity and joint sounds/noises (95). The current view is that dental occlusion plays only a minor role for development and maintenance of TMD pain and that not more than approximately 25% of the variation of TMD pain can be explained by occlusal factors (90, 91, 96–98). One of the more robust findings is the association between cross-bite and TMD (e.g. 97, 99) but further studies will be needed to identify the odds ratio for manifest types of TMD problems. A challenge for future research is to operationalize and better quantify functional aspects of occlusion since reproducibility and validity of most occlusal examination procedures are poor to modest (100). Clark *et al.* (101) concluded that supracontacts in the occlusion consistently elicited local signs of pain in the tooth and in the periodontium but neither the introduction nor elimination of supracontacts had any significant effects on bruxism. In a recent study, experimental supracontacts were indeed associated with significant reductions of the EMG activity during day-time and none of the subjects developed signs or symptoms of TMD (102). Thus, occlusion does not seem to play a major role for either manifest types of TMD and craniofacial pain or bruxism.

The clinical literature is filled with a palette of studies tying craniofacial pain complaints and bruxism together (e.g. 103–107). For example, Huang *et al.* (108) reported that self-reported bruxism was associated with an odds ratio of 4.8 for myofascial TMD pain and 1.2 for TMJ arthralgia. Carlsson *et al.* (94) in their 20-year follow-up study also reported that bruxism was associated with TMD signs or symptoms according to the Helkimo index. Patients with long-standing sleep bruxism appear to be more likely to have craniofacial pain complaints than to have no pain problems (109). A study based on questionnaires also demonstrated that craniofacial pain was significantly, and positively associated with reports of frequent bruxism (110). In large-scale studies ($n = 12\,468$) in 50- and 60-year-old subjects in Sweden, the strongest risk indicator for craniofacial pain and dysfunction was self-reported bruxism (111). Clenching habits during day-time also appears to be associated with craniofacial pain (112). Two recent studies have prompted myofascial TMD pain patients to report non-functional tooth contact habits during wake-time as well as measures of stress (106, 113). Both studies demonstrated that myofascial

TMD pain patients reported more frequent tooth-contacts than control subjects and had higher levels of stress and tension.

Although many clinical studies cited above have demonstrated significant associations and odds ratios, there are a few caveats to establish a firm cause-effect relationship between bruxism and craniofacial pain (114, 115): First, as noted above, odds ratios only indicate associations and not necessarily the directions of the relationships. Second, most studies have used self-reported measures of bruxism (see Ref. 1, 3), which could be biased by patients perception of oral habits and being 'tense' confounded by statements from dentists. A study related to fibromyalgia tested the associations between actual muscle activity measured by EMG and the patients own perception of being tense as well as muscle tension traits and there were no correlations between these measures (116). In contrast, the perception of being tense correlated with aspects of anxiety proneness (116) indicating that not all 'tense' patients have increased EMG activity or may actually grind or clench their teeth.

The concept of a straight forward relationship between bruxism and craniofacial pain is furthermore challenged by a series of papers where sleep bruxers without painful symptoms have higher EMG activity compared to the sleep bruxers with pain (117, 118). Recently, further support to this notion was obtained by Rompre *et al.* (119) who concluded that sleep bruxers with low frequencies of EMG activity were more at risk of reporting craniofacial pain. Pergamalian *et al.* (120) found that the amount of self-reported bruxism was not associated with more severe muscle pain and remarkably was associated with less pain in the TMJ on palpation. Raphael *et al.* (121) also pointed out that severity of bruxism may not be a predictor of myofascial TMD pain and have recently strengthened this concern by the finding that tooth wear as a proxy of bruxism is negatively associated with measures of muscle sensitivity (122).

In summary, the clinical literature has frequently linked bruxism and craniofacial pain and implied a cause-effect relationship; however, several studies appear to challenge bruxism as a major risk factor for craniofacial pain. One way to further examine such questions is to simulate bruxism and control the muscle activity in experimental models. The following section reviews the outcome of such 'experimental bruxism models' in healthy subjects.

Experimental bruxism models

It is a common and often unpleasant experience that strong physical exercise can cause significant levels of muscle pain and soreness. This has initiated many studies on various human jaw-muscle exercises and development of craniofacial pain. Generally, two types of muscle exercise have been used. One technique is based on repeated or sustained concentric contractions of the jaw-closing muscles. The other method involves repeated eccentric contractions which cause forced lengthening of the muscle fibres (Table 3).

Concentric dynamic and isometric (i.e. same length) contractions will in conditions with overloading and insufficient relaxation periods cause muscle pain probably with the same pathophysiology as ischaemic pain (123). Ischaemia alone cannot produce muscle pain but, in combination with contractions, strong pain develops in humans (124, 125). Accumulation of metabolites such as lactate, potassium, or the lack of oxidation of metabolic products in addition to mechanical determinants such as the number of contractions, duration and force may play a significant role (126–129). Furthermore, hypoxia and the release of bradykinin, prostaglandins, CGRP (see section Peripheral nociceptive mechanisms and sensitization) in association with a reduced pH can cause sensitization of muscle nociceptors leading to pain evoked by mechanical stimulation during contractions (128, 129).

In the masticatory system, many studies have tried to establish human experimental models to induce jaw-muscle pain (for a review see Ref. 130). A combination of dynamic concentric contractions (mastication) and ischaemic block of the superficial temporal artery in healthy subjects has been shown to cause a continuously increasing, dull bilateral, frontal 'headache-like' pain in healthy subjects (131, 132). Sustained or repeated static tooth-clenching tasks in different jaw positions cause intense jaw-muscle pain with a rapid onset (19, 133–139). However, the pain quickly disappears and most studies in healthy subjects have failed to show clinically significant levels of pain in the jaw muscles in the days after such exercise. Christensen performed a series of tooth-clenching studies and concluded that the onset of muscle fatigue and pain by maximal voluntary tooth clenching appeared after approximately 0.5 and 1 min respectively, and the tolerance of clenching endurance was approximately 2 min (134, 140). Clark *et al.* (136) examined the effect

Table 3. Overview of experimental tooth-grinding and tooth-clenching studies

References	Subjects	Mean age	Type of jaw-muscle exercise	Duration	Level of contraction	Outcome measurements	Exercise days	Immediately after	Day 1	Day 2	Day 5	Comments
Christensen 1971 (173)	2 F 7 M	24	Grinding	1800 s	'sound'	PI Category	1	8/9 reports pain	3/9	5/9	—	'Prolonged pain for following days'
Scott & Lundeen 1980 (133)	4 F 11 M	—	Protrusion	300 s	'vigorously'	Intramuscular Pressures PI Category	1	93% reports pain	—	—	—	'Pain ended soon after stop' 'Two subjects had long lasting pain'
Christensen 1981 (134)	10 M	27	Clenching	mean 21 s mean 82 s	100% MVOF	Time to fatigue tolerance Time to pain tolerance	1	—	—	—	—	'Progressive physiological, or peripheral, muscle fatigue accompanied the psychological, or central, endurance of tooth clenching'
Bowley & Gale 1987 (135)	10 F	18–26	Grinding	1800 s	50% MVOF	Four-point scale	1	9/10 reports pain	—	—	—	'Methods did not consistently produce masticatory muscle pain in non-pain subjects'
			Clenching	300 s	70% MVOF	Four-point scale	—	9/10 reports pain	—	—	—	
			Protrusion	300 s	—	Four-point scale	—	7/10 reports pain	—	—	—	
			Clenching	1350 s	70% MVOF	Four-point scale	—	1/10 reports pain	—	—	—	
Clark 1991 (136)	8 M	28	Protrusion	516 s	25–100% MVOF	VAS PDT MVOF	5	No No No	No No	—	—	'Protrusion does not produce sustained pain in masticatory muscles'
Svensson & Arendt-Nielsen 1996 (141)	10 F	24	Clenching	900 s day ⁻¹ 5 days	25% MVOF	VAS PDT PTT MVOF MPQ	5	No No No No	No ↓ ↓	No No No No	No No No No	'Five days of submaximal clenching does not lead to pain or tenderness in masticatory muscles'
Glaros <i>et al.</i> 1998a (137)	3 F 2 M	23–29	Clenching	1020 s days ⁻¹ 8 (max) days	10.0 µV	VAS MPQ	1–8	—	No	—	—	'Pain tended to resolve in 24 h following increase training'
Glaros <i>et al.</i> 1998b (138)	8 F	21–33	Clenching	1200 s/day ⁻¹ 5 days	10.0 µV	Diagnostic outcomes VAS	5	2/5 reports TMD	—	—	—	
Plesh <i>et al.</i> 1998 (139)	7 F 7 M	25	Clenching	endurance	100% MVOF (intermittent, ramp and sustained)	Diagnostic outcomes VAS PDT PTT	2	1/8 reports TMD	No	—	—	'Low-level activity can result in TMJ pain or myofascial pain in some individuals' Only female subjects demonstrated post-exertional pain 24 h later

Table 3. Continued

References	Subjects	Mean age	Type of jaw-muscle exercise	Duration	Level of contraction	Outcome measurements	Exercise days	Immediately after	Day 1	Day 2	Day 5	Comments
Arima <i>et al.</i> 1999 (174)	12 M	26	Grinding	2700 s	50% MVOF	PDT VAS	1	↓	↓	No	—	Grinding caused low levels of pain/soreness the following days
Arima <i>et al.</i> 2000 (147)	10 M	24	Grinding	2700 s	50% MVOF	PDT VAS	1	No	—	—	—	VAS ratings of pain intensity, unpleasantness, and soreness were lower than those in the previous study
Glaros <i>et al.</i> 2000 (222)	10 F	20–51	Clenching	1200 s/day ⁻¹ 5 days	≤2.0 μV	VAS	5	No	No	No	No	'Reports of pain were significantly higher in the group which engaged in the experimental clenching task'
	10 F		Clenching	1200 s/day ⁻¹ 5 (max) days	≥10.0 μV	Diagnostic outcomes VAS	5	0/10 reports TMD	No	No	No	
Svensson <i>et al.</i> 2001 (19)	11 M	24	Clenching	3600 s	10% MVOF	VAS	1	↓	—	—	—	'Low-intensity clenching task can induce subjective and electrophysiological indications of fatigue'
Glaros and Burton 2004 (223)	3 F 4 M	21–35	Clenching	1200 s/day 5 days	≤2.0 μV	VAS	5	No	No	No	No	'These findings confirm previous paratunctional activity increases pain and can lead to a diagnosis of TMD or other pain'
Torisu <i>et al.</i> 2006 (149)	11 F 12 M	26 24	Clenching	1200 s/day 5 days	≥10.0 μV	Diagnostic outcomes VAS	5	0/10 reports TMD	No	—	2/10 reports TMD	'Males tended to have higher levels of fatigue than females'
Hedenberg-Magnussen <i>et al.</i> 2006 (224)	16 F 4 M	45	Clenching	1800 s	50% MVOF	VAS	1	↓	—	—	—	'Pain is developed in masseter muscle during repeated isometric contraction but without increasing levels of Neuropeptide Y'
Torisu <i>et al.</i> 2007 (225)	11 F 12 M	26 24	Clenching	1800 s	10% MVOF	VAS Finger PDT	1	↓	—	—	—	'Jaw-muscle fatigue evoked by low levels of tooth clenching effects on descending inhibition not only to orofacial but also to more distal region such as PPT at finger'

F, female; M, male; MVOF, maximal voluntary occlusal force; PI, pain intensity; VAS, visual analog scale; PDT, pain detection threshold; MPQ, McGill Pain Questionnaire; ↑, increase; ↓, decrease.

of four repeated sustained voluntary contraction of 25%, 50%, 75% and 100% of maximum effort at a protrusive position in eight subjects, and this study was the first to follow the subjects for several days after the experimental tooth clenching. Although maximum intensity of the immediate pain was quite high (approximately 75 mm on VAS of pain intensity), the pain resolved quickly within a few minutes, and there was no significant masticatory muscle pain in the volunteers during the days after concentric exercises. One study showed that even with repeated submaximal tooth-clenching at 25% of maximum voluntary contraction (MVC) for 5 days, it is extremely difficult to elicit longer-lasting jaw-muscle pain and soreness in healthy female subjects (141). In fact, there was a significant decrease in pain reports during the 5 days, indicating an adaptation or 'training' effect. These results from the jaw-closing muscles are in accordance with data on sustained submaximal contraction of the frontalis muscles, which have failed to produce significant levels of headache (142). However, patients with tension-type headache and migraine will more frequently develop headache following sustained tooth-clenching (<30% MVC) than healthy control subjects (143, 144). It has been suggested that patients with headache have an increased sensitivity to afferent stimuli, which could be related to impaired endogenous inhibitory control mechanisms and sensitization of primary afferent nerve fibres or higher-order neurones in the nociceptive system (145, 146).

Thus, acute jaw-muscle pain and soreness can reliably be induced in healthy subjects in concentric contraction models, but the level of the symptoms is generally low (Table 3). This suggests that simple concentric contraction of jaw muscles may be inadequate to explain the entire pathophysiology of persistent craniofacial pain. There is so far no evidence that a deep nociceptive input applied to an exercised jaw muscle has a stronger impact on the perceived pain intensity than the same stimulus applied to a non-exercised jaw-muscle (147–149). However, injection of hypertonic saline into spinal muscles or repetitive pressure stimuli causes higher levels of pain when the muscles are exercised (150, 151). The latter studies are in line with the observation of increased sensitivity to afferent stimuli in patients with headache (143, 144), but further research is needed to clarify the complex interaction between nociceptive activity and jaw muscle fatigue and pain.

In contrast to the immediate and rather short-lasting muscle pain evoked by concentric contractions, eccentric contractions (i.e. lengthening of the muscle fibres despite an attempt to contract the muscle) are more effective in inducing a delayed onset of muscle pain or soreness in healthy subjects (152–157). One example is downhill walking where the contracting quadriceps muscle controls the rate of knee flexion against the force of gravity and in the process the muscle undergoes an eccentric contraction during each step (158). In these cases, there is usually no or only little pain immediately after the exercise but significant pain, soreness and stiffness can persist in the spinal muscles on the following day and up to 4–5 days after such exercise. This condition is usually referred to as delayed onset muscle soreness (DOMS) and it has been suggested that this type of pain is related to bruxism (159). The prevailing theory is that unaccustomed eccentric exercise leads to localized areas of damage in the muscle, which will be associated with inflammatory changes (156, 157). This inflammation will trigger some of the mechanisms as described above with peripheral sensitization of the primary afferent nerve fibres. Some of the clinical characteristics of DOMS are quite different from other myofascial pain conditions (158). For example, there is no spontaneous pain but only pain on movement of the exercised limb or part of body. Stretch, and muscle contraction will increase the pain. An intriguing finding is that vibratory stimuli may increase the pain and soreness in DOMS rather than relieve it (49, 50). The suggestion has been made that large-diameter muscle afferents could be involved in DOMS and that similar mechanisms as secondary hyperalgesia and allodynia could be features in DOMS, a phenomenon coined 'proprioceptive allodynia' (50, 51). The injuries to the muscle may include both contractile and cytoskeletal components of the myofibrils. Thus, the mechanisms underlying this kind of muscle pain are probably related to muscle injuries at the ultrastructural level or damages to the connective tissue (160–163). Histological studies have demonstrated disorganization of myofilaments and extensive disruption of muscle structures localized particularly in the regions of the Z-discs (123, 164, 165). Two possible initial events are discussed as responsible for the subsequent damage (158). One possibility is damage to excitation-contraction coupling system and the second is the disruption at the level of the sarcomeres; most evidence favours the latter suggestion (158). It is

interesting to note, that the magnitude of tissue damage induced by the eccentric exercise does not correlate with perceived intensity of DOMS (166), again substantiating the claim that there is no one-to-one relationship between tissue injury and pain.

Another characteristic feature of DOMS is the 'training' effect, i.e. 1 week after the first eccentric exercise, a second exercise will cause much less damage and symptoms such as pain and soreness (158, 167). It has been proposed that this adaptation process is based on an increase in sarcomere number in the muscle fibres that leads to a shift in the muscle's optimum length for active tension, and it has in fact been suggested to use mild eccentric exercises in the clinic as a training or protection of muscles against major injuries (158). The concept of an exercise-induced pain followed by an exercise-mediated adaptation or training effect could potentially explain some of the characteristics observed in relation to bruxers and craniofacial pain: on one hand a single bout of bruxism would be able to trigger painful symptoms but on the other hand repeated 'exercises' would tend to diminish the symptoms. There may, however, be several obstacles to this explanatory model, for example, DOMS has been shown to be associated with lower pain scores in women than in men (168, 169), which also has been shown for exercise-induced pain in jaw muscles (149). This is in striking contrast to the majority of both experimental and clinical studies demonstrating that women in general are more sensitive to painful stimulation of the muscles and outnumber the men in the pain clinics (26, 170).

Forced lengthening of tetanically stimulated jaw muscles in mice has shown to decrease contractile tension and elevate levels of plasma creatine kinase as indices of muscle injury (171, 172). Experimental tooth-grinding for 30 min, presumably also involving eccentric contractions, was originally reported to cause significant levels of jaw-muscle pain lasting for several days in nine healthy subjects (173); however, no detailed information on pain intensity was provided for the days following tooth-grinding. Bowley and Gale (135) reproduced Christensen's short-term findings but unfortunately did not follow their subjects on the days after the exercise. In a more recent study, it was demonstrated that 45 min with strong tooth-grinding activity at 50% of maximum effort in 12 healthy subjects caused only low levels of pain and soreness the following 3 days (174). The results from exercise-

induced activation of human muscle nociceptors show that excessive and strong contractions of the muscles can cause pain in jaw muscles but the pain is usually short-lasting and self-limiting (Table 3).

Generally, muscles, tendons and bones will adapt to repetitive loading by appropriate remodelling (175). Highly repetitious low forces are, however, sufficient to trigger local responses in musculoskeletal tissues (176). The role of the local changes in musculoskeletal tissues in generating pain in the so-called repetitive strain injuries (RSI) is far from being established. Local tissue level changes involving components of inflammation have not been considered the major source of continuing pain as seen in RSI because there are no visible clinical signs of inflammation. The intriguing view has been developed that parallel changes may occur in peripheral nerves. For example, the median nerve has been shown to swell by 10% following only 5 min of hand activity (177). Reduced nerve movements because of low grade and subclinical inflammation in the environment around the nerve could therefore be one possibility (175). Furthermore, full extension of the upper limbs causes the median nerve path to increase by 3 cm or more (corresponding to approximately 8–18%) which may be sufficient to reduce nerve blood flow and slow nerve conduction (175). So far there is no direct evidence to support such mechanisms in relation to bruxism, although the thickness of the masseter muscle as assessed by ultrasonography is temporarily increased by 14% after static contractions at 15% of maximum effort until endurance in healthy subjects (178). Exercise-evoked swelling of the medial and lateral pterygoid muscles could therefore theoretically lead to compression of the mandibular nerve. There is good evidence that the lateral pterygoid muscle is involved in the force production during horizontal jaw movements, for example during protrusive or side-to-side movements in the presence of jaw-closing muscle activity (179). However, there is no evidence to link the lateral pterygoid muscle specifically to bruxism-induced muscle pain and there are significant concerns about the reliability of manual palpation of this muscle (180) and the sensitivity and representation of pain does not seem to vary from other jaw muscles (181).

In summary, experimental bruxism studies with tooth-clenching or tooth-grinding in healthy human subjects have consistently shown low grades of painful symptoms which quickly resolves and no studies have so far been able to match the characteristics of DOMS in

limb muscles. There may nevertheless still be merit in trying to understand the neurobiology and physiology of exercised jaw muscles but it seems unlikely that transient or tissue injury-based pain alone can explain the clinical characteristics and manifestations of persistent craniofacial pain. Changes in central nociceptive mechanisms and endogenous pain control systems undoubtedly are also involved.

Potential insights from clinical studies

Another possible way to examine the relationship between bruxism and craniofacial pain is to examine the studies, which have attempted to modify bruxism, i.e. to reduce the loading and strain on the jaw muscles and TMJ and to analyse the outcome on craniofacial pain.

Indeed, a wide range of intervention or treatment methods have been proposed over the last several decades to modify or decrease the level of bruxism (2, 15, 182). These methods include hypnosis, occlusal adjustment, night-guards, physiotherapy and muscle relaxation exercises, acupuncture and biofeedback (e.g. 107, 183–191). The most common treatment of bruxism involves protection of the teeth by occlusal splints (192). Although occlusal splints may be beneficial in protecting the dentition, the efficacy of intra-oral appliances in reducing nocturnal jaw muscle activity and the report of craniofacial pain upon awakening is unclear (2). When the efficacy of occlusal splints in the management of sleep bruxism is considered at the individual level, some authors have shown a decrease, no effect at all, or even an increase in muscle activity. Recently, Van der Zaag *et al.* (193) used polysomnography to examine the effects of occlusal splints on patients with sleep bruxism and found that approximately 66% of the subjects treated with appliances demonstrated either no change or an increase in masticatory muscle EMG activity. Dube *et al.* (194) showed in their polysomnographic study that occlusal splints reduced the muscle activity associated with sleep bruxism in tooth-grinding subjects 2 weeks after the insertion. However, their study evaluated the short-term effect of occlusal splints on sleep bruxism with a onetime measurement. Another recent study reported that occlusal splints reduced muscle activity associated with sleep bruxism but this effect was only temporary (195). Also the NTI (Nociceptive Trigeminal Inhibitory) splint has in a recent short-term study been shown to

reduce the EMG activity during sleep but without significant effects on TMD pain complaints (226). It has previously been highlighted that 'mono-therapy' with occlusal appliances in order to reduce the muscle activity associated with bruxism may not result in predictable improvement of symptoms (196, 197). Comprehensive reviews by Dao and Lavigne (198) and Kato *et al.* (199) concluded that occlusal splints are useful adjuncts in the management of sleep bruxism, but are not definitive treatment. So far no definitive conclusions can be given in relation to the effects of occlusal splints on craniofacial pain because either the included patients in the above cited studies were free of pain or there were no specific information on this important outcome parameter.

Biofeedback techniques appear to be promising treatment options for patients with sleep bruxism. For example, EMG-activated alarms have been tested (200). Although the EMG suppression induced by auditory stimulation is interesting, a consistent return to pre-treatment bruxism levels has been reported in all studies that have monitored bruxism after stopping the feedback (190). Another disadvantage of auditory feedback is that it significantly interferes with sleep stage and quality. Watanabe *et al.* (201) reported results from a single subject who used contingent vibratory stimulation delivered to the maxillary teeth via an occlusal splint. The subject also exhibited a significant decrease in the number of events/hour (25% reduction) and the duration of each event (44% reduction). One potentially stronger form of afferent biofeedback is low-level electrical stimulation of the trigeminal nerve. Recently, a study reported the use of contingent electrical stimulation of the perioral region in seven subjects and showed a decrease in the EMG activity by 37% over five nights (190). Interestingly, Jadidi *et al.* (191) reported that the effect of conditioning electrical stimulation during sleep was a significant change in the EMG events/hour sleep, with a reduction of approximately 53% in sessions with stimulation in contrast to a minor decrease in EMG activity of approximately 31% in the last session without stimulation. These results raise the question whether learning or conditioning effects could take place over time. However, further studies are required to determine the long-term effect and any possible learning effects of biofeedback on patients with sleep bruxism will require further studies. In the Jadidi *et al.* (191) study, there were however, no significant effects on craniofacial pain parameters; this

could be due to low levels of painful problems at the time of inclusion, lack of statistical power because of a relatively low number of studied patients or a dissociation between levels of muscle activity and craniofacial pain.

In summary, the reviewed studies have shown that different therapeutical interventions have at least a temporary effect on muscle activity; however, these changes are not directly translated into changes in craniofacial symptoms, i.e. pain and unpleasantness. Pharmacology may be another way to modify the muscle activity associated with bruxism. The possible relationship between bruxism and different pharmacological drugs has unfortunately not been systematically and extensively examined, although some drugs are believed to influence this condition (2, 115). In the literature there are some case reports and small studies, which suggest that some drugs, which are related to the dopaminergic, serotonergic and adrenergic systems may either suppress or exacerbate bruxism (202).

Dopamine agonists and antagonists have been shown to influence rhythmic jaw movements in animals (203–206). For example in cats, dopamine D1 receptors within the ventral pallidal area take part in the mediation of orofacial dyskinesia (206). It should be kept in mind, although, that these drug effects on jaw movements in animals may be more closely related to oral tardive dyskinesia than to bruxism (202). In humans, reports of the effects of dopamine agonists on bruxism are limited. In one case report, levodopa exacerbated bruxism (207) but later studies could not support this finding. On the contrary, Lobbezoo *et al.* (208) found an inhibitory effect of levodopa on the number of bruxism episodes and the level of EMG activity per bruxism burst in a double-blind, placebo-controlled, crossover study. In a further study, the effect of a dopamine D2 agonist bromocriptin on bruxism was examined in a double-blind, placebo-controlled, polysomnographic and neuroimaging study (209). Unfortunately, four of six patients in this study dropped out due to intolerable side effects but the two patients who finished the study showed a reduction in the number of bruxism periods per hour of sleep. Later, the study was repeated with the co-administration of domperidone, a peripheral D2 receptor antagonist to reduce side effects, but the authors found no effect of bromocriptin on bruxism in this study, possibly due to the domperidone (210). There are some case reports available on the effects of dopamine antagonists on

bruxism but they are inconclusive due to a limited number of patients (211, 212). A dose of 25 mg day⁻¹ dose of amitriptyline, a tricyclic antidepressant, has no effect on bruxism-related EMG activity or craniofacial pain over a period of 4 weeks (213–215). Venlafaxine, a heterocyclic antidepressant, has been reported to cause bruxism in case reports (216, 217) but there are no controlled studies to support this. The selective serotonin reuptake inhibitors (SSRI) are generally believed to be associated with exacerbation of bruxism habits (202) but this has never been documented in controlled studies. However, several case reports point in the same direction (e.g. 218, 219) and this matter should be investigated further. Sedative and anxiolytic drugs have been suggested as a treatment for bruxism. One mg of the benzodiazepine clonazepam reduced bruxism EMG activity and improved sleep quality in a single-blind, non-randomized polysomnography study on 10 patients (220). Otherwise, the literature on this matter consists of numerous case reports describing the effect of buspirone (an anxiolytic drug with affinity for the 5HT-1a receptor) in the treatment of drug-induced bruxism (202). Buspirone is thought to relieve anxiety without hypnotic, anticonvulsant, or muscle relaxant actions.

Finally, botulinum toxin (BTX) is a potent biological toxin, which acts paralytic because of inhibition of the release of acetylcholine at the neuromuscular junction. BTX is administered by intramuscular injection and the paralytic effect usually lasts 3–6 months (221). In an open study, 18 bruxism patients were treated with a total of 123 BTX treatment sessions (221). The authors reported a mean duration of response of 19 weeks but the criteria for 'response' was not clear. Furthermore, a high percentage of the patients in this study were patients with dystonia and other movement disorders and hence very severe bruxism patients. Some case reports also state that BTX may be useful in the treatment of bruxism but, to date, no double-blind, placebo-controlled studies have examined this.

In conclusion, most of the cited pharmacological studies indicate that different classes of drugs may, indeed, influence the muscle activity related to bruxism but do not report the effect of the pharmacological treatment on craniofacial pain parameters. A further potential problem with this approach is that drugs that influence the regulation of bruxism, potentially also could have a direct effect on the nociceptive transmission (e.g. serotonergic or adrenergic pathways) and

therefore bias the assumption that changes in muscle activity have an effect on the development or maintenance of craniofacial pain.

Conclusions and future directions

This review has attempted to highlight some of the problems related to the understanding of the relationship between bruxism and craniofacial pain. While it is clear that there are associations, one has to be cautious inferring direct and simplistic cause–effect relationships. One reason is the problems with operationalized definitions of bruxism. In research settings and advanced university-based clinics it may be possible to use polysomnographic recordings, which will be the gold standard because EMG activity, jaw movements and noises can be recorded and detected. However, this is also the bottle-neck because the majority of clinical research will be unable to apply such sophisticated and resource-demanding techniques. Furthermore, there may be reasons to differentiate between sleep bruxism and awake bruxism and these potentially different entities may have different associations with TMD pain. Another important issue to consider is whether the intensity and frequency of bruxism is mainly dependent on patient-based measures (self-report of perceived tension, awareness of tooth-grinding or clenching habits, bed-partner reports of noises etc) or objective measures of jaw movements and jaw-muscle EMG activity. A better characteristic of the temporal aspects (e.g. infrequent, intermittent, or frequent types of bruxers) in addition to a grading of the diagnostic probability (definite, probable, possible and unlikely bruxers) might be useful to further advance the field.

Few studies have actually tried to characterize pain associated with bruxism, i.e. to examine the neurobiological and physiological features of jaw muscles. Animal as well as human experimental models to examine these features are needed. For example, one way to investigate the underlying mechanisms of pain related to bruxism could be to use the recent observations on ‘proprioceptive allodynia’, i.e. to test for changes in vibratory sensation as well as other somatosensory modalities. Another approach would be to use microdialysis and get an insight into potential inflammatory mediators in muscles of bruxers. Simple provocation tests like ‘clenching on a tooth’ should also be more systematically examined in patient populations and may be able to provide important diagnostic

information. Careful analyses of the phenotypes of bruxers may together with advances in genotyping also hold promise for a better understanding of the relationships between bruxism and craniofacial pain. For the clinicians, it may be important to understand the concept of ‘nonlinear’ relationships between bruxism and craniofacial pain to avoid oversimplification of diagnosis and management. Rather, pain and bruxism should be managed as separate problems in the individual patients.

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