Chapter 69

Human Studies of Experimental Pain From Muscle

Peter Svensson and Messoud Ashina

Experimental pain studies in healthy subjects and patients with well-defined pain complaints represent one of many approaches to gaining more insight into the pathophysiologic mechanisms involved in headache as well as in other musculoskeletal pain conditions. In research on tension-type headache, special emphasis has been given to the function of the epicranial, temporomandibular, and neck muscles. This chapter describes human experimental models developed and used specifically to investigate pain originating from muscle tissue.

In general, experimental pain research involves a standardized induction of pain and the appropriate assessment of the responses (Fig. 69-1). The evoked pain responses can be recorded by multiple techniques ranging from simple measures of self-reported pain to advanced psychophysical and electrophysiologic testing, biological markers, and sophisticated imaging of nociceptive processing. The particular assessment technique depends on the specific aim of the experimental study; the reader is referred to recent reviews for more detailed descriptions (23). This chapter focuses on the models available to induce pain in the cervicotrigeminal system, including chemical, mechanical, and electric stimulation and exercise-induced activation of human muscle nociceptors and their contribution to the understanding of muscle pain mechanisms.

CHEMICAL STIMULATION

Hypertonic Saline

Injection of hypertonic saline (4 to 6%) has been by far the most frequently used chemical stimulus in human experimental muscle pain research and therefore is described in detail. A major reason for the popularity of hypertonic saline is the safety and reliability of this technique; no side effects after numerous intramuscular injections have been reported (71). Kellgren (35) was the first to use hypertonic saline to evoke pain in various muscles including the temporomandibular and suboccipital muscles. He noted a rapid increase in pain intensity shortly after a bolus injection of 0.1 mL of 6% saline into the masseter muscle associated with a spread of pain to adjacent regions of the face, including the teeth. The pain peaked after 1 to 2 minutes and faded over a period of 3 to 5 minutes. This preliminary description of one subject was later verified in larger study populations both with bolus injections into the temporalis muscle and masseter muscle (28,63,66–68). The bolus injection technique has also been refined so that a computer-controlled syringe pump can maintain a continuous slow infusion of hypertonic saline for up to 15 to 20 minutes with relatively constant pain in the temporomandibular muscles (72,79). This type of tonic experimental pain seems to have similar qualities to clinical pain conditions (62) and allows sufficient time for elaborate studies of sensory motor interactions or other physiologic effects of pain (33,71). The osmolarity of the hypertonic saline solution probably contributes to the pain responses by a direct mechanical effect on the terminal endings and sodium channels and/or a release of substance P (SP) (12). Recordings from nociceptive C-fiber afferents from the rat masseter muscle have indeed documented strong activity evoked by injection of hypertonic saline (12). Furthermore, the dominant sensation caused by injection of hypertonic saline is a deep, diffuse pain sensation (71). Interestingly, it has been shown that injection of hypertonic saline in the vicinity of motor end plate regions is associated with higher pain scores than injection in other muscle sites suggesting focal areas within the muscle with a higher density of nociceptors (52). This evidence indicates that hypertonic saline is a potent chemical stimulus for activation of muscle nociceptors.

A particularly interesting feature of intramuscular saline injection is the spread and referral of pain to adjacent regions. Pain induced in the suboccipital muscles

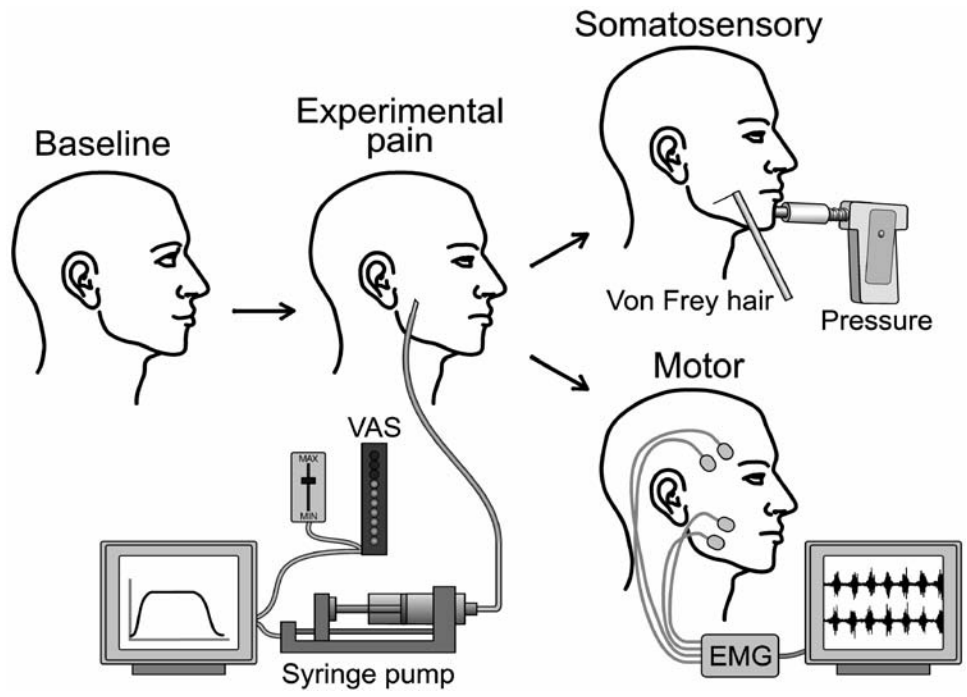

FIGURE 69-1. Overview of experimental design. A computer program can be used to control a syringe pump and sample the perceived pain intensity as indicated on an electronic visual analog scale and the infusion pressure. Healthy volunteers can be examined at baseline and during muscle pain caused by infusion of, for example, hypertonic saline. The effects of muscle pain on somatosensory (e.g., pressure pain thresholds, von Frey stimulation) and motor function (e.g., electromyogram [EMG]) can be determined.

of one subject was perceived as a headache (35), and repeated injections into the temporalis muscle of another single subject caused pain in the neck muscles (57). More recent studies in larger populations showed that pain from the temporalis muscle can be referred to both the upper and lower jaw, ear, and eye region (28,68) and that pain from the masseter muscle is described as being located above the temporomandibular joint, posterior teeth in the upper and lower jaw, and temple region (63,68,72) (Fig. 69-2). The available data do not suggest major differences in the quality or intensity of the pain from hypertonic saline injections into the anterior part of the temporalis or masseter muscles, and the localization of pain is partly overlapping (68). However, major differences in the pain patterns are clear when the posterior part of the temporalis muscle is injected with hypertonic saline because the pain spreads toward the neck, vertex, and temple but rarely toward the lower jaw region (54). Thus, pain patterns evoked by stimulation of the masseter muscle seem to resemble pain patterns reported by patients with temporomandibular disorders and pain patterns evoked by stimulation of the posterior temporalis muscle and neck muscles look similar to pain patterns from patients with tension-type headache (54).

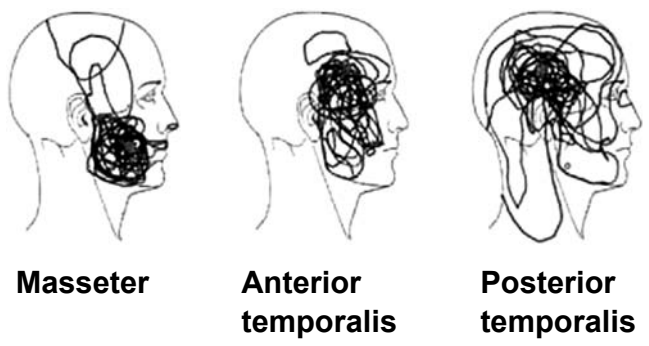

FIGURE 69-2. Spread of pain evoked by standardized injection (0.2 mL) of hypertonic saline into the masseter, anterior temporalis and posterior temporalis in healthy subjects ($n = 20$). Note the overlap between the two first figures. (From Schmidt-Hansen PT, Svensson P, Jensen TS, et al. Patterns of experimentally-induced pain in pericranial muscles. [Submitted].)

The neurophysiologic mechanisms responsible for the spread and referral of muscle pain are not entirely clear, but are likely to involve central convergence of peripheral afferents onto wide dynamic-range neurons in the dorsal horn and subnucleus caudalis (55). It has also been shown that intramuscular administration of hypertonic saline results in neuronal activity in convergent spinal dorsal horn neurons and in neurons encoding nociceptive information in the nucleus submedius in the thalamus (34). Central sensitization of wide dynamic-range and nociceptive specific neurons and unmasking of new receptive fields owing to the central sensitization are also likely to mediate referred pain (55).

In addition to standardized descriptions of somatosensory changes induced by experimental muscle pain (72), the model with hypertonic saline also can be used to examine the effects of pain on motor function. Muscle dysfunction has long been thought to be an important etiologic factor for the development and maintenance of

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myofascial pains. Thus, induction of pain in healthy subjects may provide insight into the cause-and-effect relationship between pain and muscle function, which is difficult to establish from clinical studies of patients with tension-type headache or temporomandibular disorders (71). Experimental pain from the masseter muscle has a profound effect on dynamic repetitive movements such as chewing; that is, the amplitude of the jaw movements are smaller, and there is less electromyographic (EMG) activity in the jaw-closing phase and more EMG activity in the jaw-opening phase, suggesting a guarding and protective effect (66). These experimental results are in accordance with the pain-adaptation model presented by Lund et al. (40). The model with hypertonic saline also shed light on the classic, yet still controversial, problem of increased or nonincreased postural EMG activity in patients with tension-type headache and temporomandibular disorders. Stohler et al. (64) showed a small increase (1 to 2 μV) in the temporalis and masseter muscles during a period of saline-induced pain from the masseter muscle in healthy subjects; however, these authors attributed the small EMG activity recorded by using surface electrodes to contamination from mimic muscles, because similar changes were observed in control experiments in which pain was "imagined." Svensson et al. (73) used intramuscular electrodes but could not show any relation between pain intensity and EMG changes. Interestingly, it has recently been shown that painful stimulation of the masseter muscle is associated with significant EMG increases in the cervical muscles pointing to functional relationships between pain in the trigeminal and cervical regions (75). Additionally, trigeminal reflex pathways and jaw tremor have been shown to be modulated by saline-evoked muscle pain (25,78), for example the short-latency jaw-stretch reflex is facilitated during jaw muscle pain, which could contribute to a reflex-mediated stiffness of the jaw. However, no experimental evidence has so far been found to suggest a long-lasting muscle hyperactivity induced by pain in temporomandibular muscles.

Brain imaging techniques have also been used to examine the central processing of pain from the temporomandibular muscles. A recent positron emission tomography study showed that saline-evoked masseter pain is associated with significant increases in regional cerebral blood flow (rCBF) in the dorsal-posterior insula, anterior cingulate and prefrontal cortices, right posterior parietal cortex, brainstem, cavernous sinus, and cerebellum, whereas no rCBF changes occurred in the primary (SI) or secondary somatosensory (SII) cortices (37) (Fig. 69-3). Nonpainful von Frey stimulation produced a significant rCBF increase in the contralateral SI face representation, whereas von Frey stimulation in combination with ongoing muscle pain produced mechanical hyperesthesia and significant rCBF increases in the subgenual cingulated and the ventroposteromedial and dorsomedial thalamus. These results suggest that mechanical hyperesthesia has a unique representation in the brain (37). Saline-evoked jaw muscle pain has also been shown to induce regional release of endogenous opioids and activation of μ-opioid receptor system in the ipsilateral amygdala and contralateral ventrolateral portion of the thalamus (81). Furthermore, activation of the μ-opioid system is linked to reductions in sensory

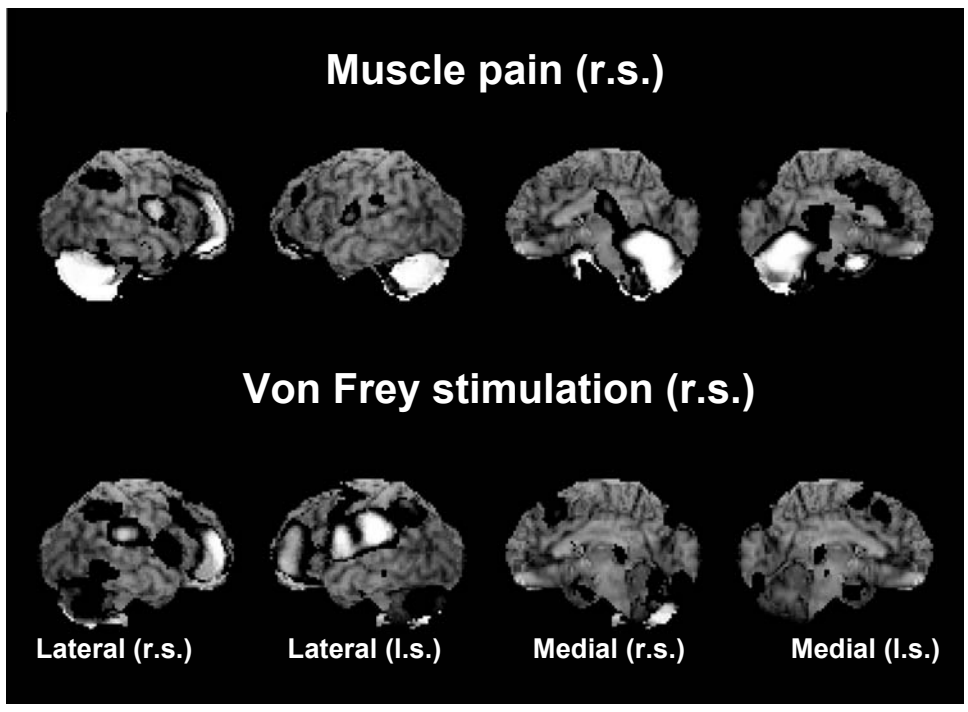

FIGURE 69-3. Positron emission tomography scans showing rCBF changes evoked by injection of hypertonic saline into the right masseter muscle (muscle pain) or by repetitive (0.5 Hz) tactile stimulation with a nonpainful von Frey filament ($n = 10$). Note that muscle pain is associated with marked activation of the contralateral (left) anterior cingulate, cerebellum and prefrontal cortices. Von Frey stimulation evokes pronounced activity in the contralateral primary somatosensory cortex. (From Kupers RC, Svensson P, Jensen TS. Cerebral processing of muscle pain and mechanical hyperesthesia in the orofacial region: a positron emission tomography study. *Pain.* 2004;108:284–293.).

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and affective ratings of the jaw muscle pain (81). Studies on the genetic polymorphism of the catechol-*O*-methyltransferase enzyme have revealed striking associations between genotypes, the endogenous μ-opioid system activation and phenotypic responses such as sensory and affective ratings of jaw muscle pain (80).

In conclusion, the model with hypertonic saline may help us to explore peripheral and central mechanisms in various chronic pain conditions including tension-type headache. Brain imaging studies used in combination with hypertonic saline model seem to be a fruitful avenue to study the complex neurobiology and psychophysiology related to muscle pain at a system level.

Endogenous Algogenic Substances

Intramuscular injections of numerous endogenous algogenic substances and neuropeptides also have been used for chemical activation of human muscle nociceptors (Table 69-1). Substantial evidence has been found from studies in animal models that bradykinin and 5-hydroxytryptamine (5-HT) can trigger action potentials in nociceptive group III and IV fibers (42). When injected into the human temporalis muscle, 5-HT does not induce significant levels of pain, and bradykinin induces only relatively low levels of pain (30). However, Ernberg et al. (19,20) have shown that injection of 5-HT into the human masseter causes a significant reduction in pressure–pain thresholds, that is, allodynia to mechanical stimuli. Injections of combinations of 5-HT and bradykinin cause significantly more pain than injections of isotonic saline and a significant reduction of pressure–pain thresholds, a finding that supports the importance of presensitization with 5-HT for bradykinin-induced neural activity (7,8,30). E-type prostaglandins also can sensitize muscle afferents to bradykinin, which releases prostaglandin E_2 (PGE_2) from tissue cells, thereby potentiating its own action (42). SP has been studied extensively in cutaneous pain, but it does not appear to sensitize muscle nociceptors to mechanical stimuli (42). In itself, SP does not produce pain when injected into the human temporalis muscle (31); however, in combination with calcitonin gene-related peptide (CGRP) and bradykinin, it does induce muscle pain and a significant reduction of pressure–pain thresholds in the temporal muscle (31,49). Recently, an extensive examination of various combinations and concentrations of 5-HT, bradykinin, histamine, PGE_2, and adenosine triphosphate (ATP) injected into the trapezius muscles was carried out and this "inflammatory soup" was shown to produce both pain and prolonged tenderness in healthy subjects (45). ATP (>18,000 nmol/mL) was associated with unacceptable side effects, but did not appear to be essential for the development of pain or tenderness; thus injections of 5-HT (156 nmol), bradykinin (92 nmol), histamine (140 nmol), and PGE_2 (1.95 nmol) were suggested to be valuable model for the study of myofascial pain mechanisms (45).

TABLE 69-1 Chemical Substances Used for Activation of Human Muscle Nociceptors

Hypertonic saline (4–20%/0.2–1.0 mL)
Hypotonic saline
Potassium chloride (100 mmol/0.2 mL)
Bradykinin (10 mmol/0.2 mL)
Serotonin (10 mmol/0.2 mL)
Substance P (1 mmol/0.2 mL)
Calcitonin gene-related peptide (1 mmol/0.2 mL)
ATP (9,000–36,000 nmol/L)
Neurokinin A (1 mmol/0.2 mL)
Capsaicin (0.01%, 1 mL)
Nerve growth factor (0.03–1.9 mg/kg)
Glutamate (0.5–1.0 mol/0.2 mL)

Other neuropeptides and excitatory amino acids have recently implicated in the modulation of muscle nociceptors, especially glutamate, and the NMDA receptors may play an important role in deep pain (43). Indeed, intramuscular injections of 1.0 mol glutamate in humans reliably evoke both muscle pain and mechanical sensitization, which may, in part, be mediated by activation of peripheral NMDA receptors (10–12,69). It has also been shown that intramuscular injection of glutamate in rats excites predominantly slowly conducting (<10 m/s) masseter afferent fibers thought to mediate nociceptive function and that activation of peripheral NMDA and non-NMDA receptors appears to be responsible for the glutamate-induced mechanical sensitization of masseter muscle afferent fibers (10,11). Peripheral administration of the NMDA receptor antagonist ketamine has recently been shown to have analgesic properties in the glutamate-evoked muscle pain model (12). These findings direct attention toward the peripheral levels of glutamate in myofascial pain conditions, although recent microdialysis studies have failed to identify increased levels of glutamate in tender points in the trapezius muscle of patients with chronic tension-type headache (6) or during experimental muscle pain induced by chemical mixture (5-HT, bradykinin, histamine, and PGE_2) (5).

Intramuscular injection of capsaicin (chili pepper extract) has also been used to elicit pain in the temporomandibular muscles (2,58,59). The evoked muscle pain is cramplike, severe, and has been shown to be associated with significant increases in neural activity of group III and IV muscle afferents in humans (41). The advantage of the capsaicin pain model is the extensive information on the receptor binding mechanisms through the TRPV receptors (13).

Finally, an intriguing finding is that systemic administration of human nerve growth factor (NGF) in 45 healthy

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subjects induced pain, particularly in the temporomandibular muscles. The pain was more pronounced in women than in men and tended to worsen during function (50). It has now been shown that injection of NGF into the human masseter muscle causes local signs of mechanical allodynia and hyperalgesia that persist for at least 7 days as well as pain during strenuous jaw movement (70). Estrogen and NGF may interact in the regulation of nociceptive processes, and this could be important to explaining the female preponderance in tension-type headache and temporomandibular disorders (61).

In conclusion, injection of endogenous algogenic substances and neuropeptides can be helpful in characterizing the neurobiological basis of human muscle pain, which in turn may be of clinical importance in headache conditions if intracranial changes can trigger the release of critical neuroactive substances by antidromic mechanisms influencing the peripheral conditions for myogenous nociception (26). Furthermore, this experimental approach will give insight into possible pharmacologic interventions and allow the testing of specific antagonists.

MECHANICAL STIMULATION

Few studies have applied mechanical stimuli to the temporomandibular muscles to induce pain. In contrast, mechanical stimuli delivered with pressure algometers have been used to assess the sensitivity of deep tissues. Intense mechanical stimuli activate nociceptors in the muscle but, unfortunately, also in the skin. Thus, the evoked pain sensation may have a component from both types of tissue. Anesthetizing the skin causes a significant elevation of the pressure–pain thresholds on temporomandibular muscles (53). Few studies have used mechanical stimulation of the epicranial muscles and tissues to evoke pain. An original, old study applied a head screw device in which the rubber-coated tips barely touched the scalp (57). Nevertheless, after 15 minutes, all the three of the tested subjects reported excruciating pain coming from the neck and scalp, which was associated with an increase in EMG activity of the neck muscles. Thus, the authors suggested that sustained painful mechanical stimulation of the epicranial muscles would lead to muscle hyperactivity of the neck muscles and that this was the cause of the developing neck pain. Many subsequent controlled EMG studies in headache patients, however, have been unable to demonstrate this muscle hyperactivity and interpretation of the results should be viewed with caution.

ELECTRIC STIMULATION

Direct stimulation of muscle afferents can be accomplished by using intramuscular electrodes (77). Thus, the elicited sensation is described as a cramplike pain, often in combination with a visible muscle contraction. One disadvantage of this technique is activation of non-nociceptive afferents, and it cannot be regarded a specific pain stimulus. Furthermore, the peripheral receptors are bypassed and the axons stimulated directly. Nevertheless, this model is able to elicit referred pain areas in a reliable fashion (39) and, in contrast to chemical stimuli, can start and terminate the pain immediately. Using intramuscular electrical stimulation Ashina et al. (4) compared pain sensitivity and temporal summation in the trapezius and anterior tibialis muscles. It was found that muscle pain sensitivity was higher in the trapezius than in the anterior tibialis muscle. Furthermore, temporal summation was more pronounced in muscle than in skin in the trapezius but not in the anterior tibialis region. These data may help to explain why chronic muscle pain most frequently is located in the shoulder and neck regions (4).

Intraneural microstimulation (INMS) is an advanced and powerful, but invasive, technique for selective stimulation of single human muscle afferents. The projected pain area increases as a function of stimulus duration (temporal summation) and as a function of a number of stimulated afferents (spatial summation) (41,56,76). So far, intramuscular electric stimulation of temporomandibular muscles or INMS of trigeminal nerves have not been attempted, but might be an interesting technique in headache research because of the easy control of the stimulus parameters and the possibility of eliciting referred pain areas.

EXERCISE-INDUCED STIMULATION

It is a common experience that heavy and unaccustomed physical exercise can lead to significant levels of muscle soreness and pain. Thus, many experimental studies have used various muscle exercises to test the development of head pain (71). Generally, two different approaches can be used. One technique is based on repeated or sustained concentric contractions of the temporomandibular, epicranial, or suboccipital muscles. The other method involves repeated eccentric contractions that cause forced lengthening of the muscle fibers.

Concentric Contraction Models

In conditions with overloading and insufficient resting periods, concentric dynamic and isometric contractions elicit muscle pain thought to share the same pathophysiologic mechanisms as ischemic pain (48). Ischemia alone is not sufficient to produce pain, but if it is combined with contractions, strong pain can develop. Accumulation of metabolites, such as lactate and potassium, or the lack of oxidation of metabolic products, in addition to mechanical determinants like the number of contractions, duration, and force may play a significant role (42). Furthermore,

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hypoxia and the release of bradykinin, PGE_2, and CGRP, in association with a reduced pH, can cause sensitization of muscle nociceptors, leading to pain evoked by mechanical stimulation during contractions (42).

In the cervicotrigeminal system, many studies have tried to establish an experimental model to induce head pain. A combination of dynamic concentric contractions (chewing) and ischemic block of the superficial temporal artery in healthy subjects causes a continuously increasing, bilateral dull frontal headache (22) with significantly more head pain and significantly shorter onset of pain than chewing without an ischemic block (44). In these models, the ischemia is achieved using scalp sphygmomanometers wrapped around the head, which not only reduce blood circulation but also cause activity in cutaneous and deep mechanoreceptors like the head screw device of Simons et al. (57).

Sustained or repeated static tooth clenching procedures have long been known to cause intense pain with a rapid onset (9,16). The pain quickly disappears, however, and most studies have failed to show any significant pain in the temporomandibular muscles the following days after exercise. A recent study showed that even with 5 days of repeated submaximal tooth clenching, it is difficult to elicit longer-lasting muscle pain and soreness in healthy subjects (65). Also, studies with sustained submaximal contraction of the frontalis muscles have failed to produce significant levels of head pain (38).

Thus, it can be concluded that pain in the temporomandibular muscles cannot be readily induced in healthy subjects using the concentric contraction models. The contraction levels and duration have generally been in excess of what is found in clinical populations, which seems to suggest that simple concentric contraction of muscles may be inadequate to explain the pathophysiology of tension-type headache and temporomandibular disorders.

Eccentric Contraction Models

In contrast to the immediate and short-lasting muscle pain evoked by concentric contractions, eccentric contractions are more effective to induce a delayed onset of muscle pain or soreness. The mechanisms underlying this kind of muscle pain seem to be different from that of ischemic muscle pain. Muscle injuries at the ultrastructural level or damages in the connective tissue have been implicated because histologic studies have shown disorganization of myofilaments and extensive disruption of muscle structures localized particularly in the regions of the Z-discs (48). An increased level of intracellular calcium may damage muscle tissues, probably by activating phospholipase A, which acts on membrane phospholipid components and increases the availability of arachidonic acid. Forced lengthening of tetanic-stimulated masticatory muscles in mice demonstrated decreased contractile tension and elevated levels of plasma creatine kinase as indices of muscle injury (24). Experimental tooth grinding for 30 minutes, presumably involving eccentric contractions, originally was reported to cause significant levels of facial pain lasting for several days in nine healthy subjects (14). In a recent study, 45 minutes of strong tooth grinding in 12 subjects caused only moderate levels of pain and tenderness during the following 3 days (1). The distribution of pain was quite similar to the experimental models with hypertonic saline infusion, and it was notable that the temporal region was involved less often than the masseter region.

These results from exercise-induced activation of human muscle nociceptors show that excessive and strong contractions of the muscles can cause pain in the head, but the pain is usually of rather short duration. No experimental evidence has been established showing that a self-perpetuating, vicious cycle can be initiated by muscle hyperactivity, leading to pain that again should lead to more muscle hyperactivity.

EXPERIMENTAL MODELS USED IN PATIENTS AND TO STUDY GENDER DIFFERENCES

An intriguing possibility is to use the experimental pain models in patients to obtain a better understanding of pain responses under controlled conditions. For example, patients with widespread muscle pain and a clinical diagnosis of fibromyalgia report significantly more pain and larger spread of pain induced by hypertonic saline into the anterior tibialis muscle than do healthy control subjects (60). Patients with chronic whiplash syndrome also show this kind of facilitation of pain responses, probably suggesting a state of hyperexcitability in the central nervous system (36). Injection of hypertonic saline into the jaw muscles of patients with temporomandibular disorders have shown a substantially larger spread of pain and higher pain ratings as compared with matched control subjects (74). Control injections in a leg muscle did not, however, show similar differences suggesting some regional differences in pain sensitivity in these patients, although other test modalities (e.g., pressure–pain) indicate a more generalized increase in pain sensitivity (74). Preliminary data from patients with tension-type headache have indicated similar exaggerated pain responses (54). Injection of an "inflammatory soup" in the trapezius muscle of patients with tension-type headache has also shown higher pain ratings and a tendency to increased tenderness (46,47). These findings have been interpreted as indications of peripheral sensitization, which would fit the observations from direct recordings of primary nociceptive afferents in animal models (10,12). Moreover, a recent study reported lower electrical pain thresholds in muscle and skin of the cephalic region, but not in lower limb muscle and skin in patients with chronic

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tension-type headache than in healthy controls (3). These findings indicate that increased sensitivity in nociceptive pathways from cephalic region may be of importance in the pathophysiology of chronic tension-type headache.

The exercise models have also been used to study the pain responses in tension-type headache patients. Thus, clenching the teeth for 30 minutes at about 10% of the maximum bite force evoked progressive increases in pain and a headache after 24 hours in 40 out of 58 patients (29). This may suggest a relationship between sustained muscle activity and development of headache in at least some patients, but also points out that modifying factor like activation of endogenous pain inhibitory pathways may play a role (29). Jensen et al. (27) used a sustained tooth clenching task to provoke migraine attacks in migraineurs, but they were unable to show any effect on pericranial tenderness, although patients reported pain in the temporomandibular muscles immediately after the exercise. Recently, Christensen et al. (15) investigated the impact of static contraction of the shoulder and neck muscles on muscle tenderness and headache in 20 patients with frequent episodic tension-type headache and 20 healthy age- and gender-matched controls. The subjects performed static contraction of the trapezius muscles (active procedure) or the anterior tibial muscles (placebo procedure) with 10% of maximal force for 30 minutes. Sixty percent of the patients and 20% of the healthy controls developed headache after the active procedure. Fifty percent of the patients and none of the controls developed headache after the placebo procedure. There was no significant difference in headache development between the active and the placebo procedure in either patients or controls. From that study it was concluded that some tension-type headache patients are more liable to develop shoulder and neck pain in response to static exercise than healthy controls. In a similar way, studies on chewing-evoked pain have shown that 50 to 80% of patients with temporomandibular disorders experience an increase in their pain after intense chewing, but also that 15 to 30% of the patients experience a significant relief of pain (18,21). These findings raise the possibility to use exercise models to classify subgroups of patients, which could be related to different underlying pathophysiologic mechanisms.

Experimental models have also been used extensively to address the question of gender differences in muscle pain responses and several reviews have concluded that there appears to be greater responses in women particularly to stimuli of longer duration (17). For example, injection of glutamate into the jaw muscles evokes significantly higher pain scores in women than in men; a finding mirrored by a greater glutamate-evoked muscle afferent discharge in female rats than male rats (11,69). Experimental pain models may be useful to screen for gender differences in, for example, analgesic response before large-scale clinical trials. Several studies have also documented gender differences in pain evoked by mastication, clenching, and other jaw functions (32,51) and it seems important to determine if such findings play a role in the pathophysiology of, for example, tension-type headache.

CONCLUSIONS

The experimental muscle pain models must be chosen after careful consideration of the aim of the planned study, because each model has a number of distinct advantages and also some potential disadvantages. It is important that some of the hypothesized etiologic factors for tension-type headache and temporomandibular disorders can be tested by using the experimental approach. Thus, muscle pain can be induced, and the sensory, motor, and autonomic effects can be described in standardized settings; it is also possible to induce putative painful motor tasks and then analyze the sensory outcome, which allows assumptions about the cause-and-effect relationship between pain and muscle (dys)function that are difficult to derive from basic animal studies and cross-sectional clinical studies. Finally, experimental muscle pain models can be applied to patients with well-defined pain conditions and used to study potential gender differences related to muscle pain.

REFERENCES

1. Arima T, Svensson P, Arendt-Nielsen L. Experimental grinding in healthy subjects: a model for postexercise jaw muscle soreness? *J Orofac Pain*. 1999;13:104–114.
2. Arima T, Svensson P, Arendt-Nielsen L. Capsaicin-induced muscle hyperalgesia in the exercised and non-exercised human masseter muscle. *J Orofac Pain*. 2000;14:213–223.
3. Ashina S, Babenko L, Jensen R, et al. Increased muscular and cutaneous pain sensitivity in cephalic region in patients with chronic tension-type headache. *Eur J Neurology*. 2005;12:543–544.
4. Ashina S, Jensen R, Bendtsen L. Pain sensitivity in pericranial and extracranial regions. *Cephalalgia*. 2003;23:456–462.
5. Ashina M, Jørgensen M, Stallknecht B, et al. No release of interstitial glutamate in experimental human model of muscle pain. *Eur J Pain*. 2005;9:337–343.
6. Ashina M, Stallknecht B, Bendtsen L, et al. Tender points are not sites of ongoing inflammation—in vivo evidence in patients with chronic tension-type headache. *Cephalalgia*. 2003;23:109–116.
7. Babenko V, Graven-Nielsen T, Svensson P, et al. Experimental human muscle pain and muscular hyperalgesia induced by combinations of serotonin and bradykinin. *Pain*. 1999;82:1–8.
8. Babenko V, Svensson P, Graven-Nielsen T, et al. Duration and distribution of experimental muscular hyperalgesia in humans following combined infusions of serotonin and bradykinin. *Brain Res*. 2000;853:275–281.
9. Bowley JF, Gale EN. Experimental masticatory muscle pain. *J Dent Res*. 1987;66:1765–1769.
10. Cairns BE, Gambarota G, Svensson P, et al. Glutamate-induced sensitization of rat masseter muscle fibers. *Neuroscience*. 2002;109:389–399.
11. Cairns BE, Hu JW, Arendt-Nielsen L, et al. Sex-related differences in human pain perception and rat afferent discharge evoked by injection of glutamate into the masseter muscle. *J Neurophysiol*. 2001;86:782–791.
12. Cairns BE, Svensson P, Wang K, et al. Activation of peripheral NMDA receptors contributes to human pain and rat afferent fiber discharge

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evoked by injection of glutamate into the masseter muscle. *J Neurophysiol*. 2003;90:2098–2105.
13. Caterina MJ, Schumacher MA, Tominaga M, et al. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature*. 1997;389:816–824.
14. Christensen LV. Facial pain and internal pressure of masseter muscle in experimental bruxism in man. *Arch Oral Biol*. 1971;16:1021–1031.
15. Christensen MB, Bendtsen L, Ashina M, et al. Experimental induction of muscle tenderness and headache in tension-type headache patients (in press).
16. Clark GT, Adler RC, Lee JJ. Jaw pain and tenderness levels during and after repeated sustained maximum voluntary protrusion. *Pain*. 1991;45:17–22.
17. Dao TT, LeResche L. Gender differences in pain. *J Orofac Pain*. 2000;14:169–184.
18. Dao TT, Lund JP, Lavigne GJ. Pain responses to experimental chewing in myofascial pain patients. *J Dent Res*. 1994;73:1163–1167.
19. Ernberg M, Lundeberg T, Kopp S. Effect of propranolol and granisetron on experimentally induced pain and allodynia/hyperalgesia by intramuscular injection of serotonin into the human masseter muscle. *Pain*. 2000;84:339–346.
20. Ernberg M, Lundeberg T, Kopp S. Pain and allodynia/hyperalgesia induced by intramuscular injection of serotonin in patients with fibromyalgia and healthy individuals. *Pain*. 2000;85:31–39.
21. Gavish A, Winocur E, Menashe S, et al. Experimental chewing in myofascial pain patients. *J Orofac Pain*. 2002;16:22–28.
22. Göbel H, Cordes P. Circadian variation of pain sensitivity in pericranial musculature. *Headache*. 1990;30:418–422.
23. Graven-Nielsen T, Arendt-Nielsen L. Induction and assessment of muscle pain, referred pain, and muscular hyperalgesia. *Curr Pain Headache Rep*. 2003;7:443–451.
24. Hutchins MO, Skjonsby HS, Brazeau GA, et al. Weakness in mouse masticatory muscles by repetitive contractions with forced lengthening. *J Dent Res*. 1995;74:642–648.
25. Jaberzadeh S, Svensson P, Nordstrom MA, et al. Differential modulation of tremor and pulsatile control of human jaw and finger by experimental muscle pain. *Exp Brain Res*. 2003;150:520–524
26. Jaeger B. Tension-type headache and myofascial pain. In: Fricton JR, Dubner R, eds. *Orofacial pain and temporomandibular disorders*. New York: Raven; 1995:205–213.
27. Jensen K, Bülow P, Hansen H. Experimental toothclenching in common migraine. *Cephalalgia*. 1985;5:245–251.
28. Jensen K, Norup M. Experimental pain in human temporal muscle induced by hypertonic saline, potassium and acidity. *Cephalalgia*. 1992;12:101–106.
29. Jensen R, Olesen J. Initiating mechanisms of experimentally induced tension-type headache. *Cephalalgia*. 1996;16:175–182.
30. Jensen K, Tuxen C, Pedersen-Bjergaard U, et al. Pain and tenderness in human temporal muscle induced by bradykinin and 5-hydroxytryptamine. *Peptides*. 1990;11:1127–1132.
31. Jensen K, Tuxen C, Pedersen-Bjergaard U, et al. Pain, tenderness, wheal and flare induced by substance-P, bradykinin and 5-hydroxytryptamine in humans. *Cephalalgia*. 1991;11:175–182.
32. Karibe H, Goddard G, Gear RW. Sex differences in masticatory muscle pain after chewing. *J Dent Res*. 2003;82:112–116.
33. Kato Y, Kowalski CJ, Stohler CS. Habituation of the early pain-specific respiratory response in sustained pain. *Pain*. 2001;91:57–63.
34. Kawakita K, Dostrovsky JO, Tang JS, et al. Responses of neurons in the rat thalamic nucleus submedius to cutaneous, muscle and visceral nociceptive stimuli. *Pain*. 1993;55:327–338.
35. Kellgren JH. Observations on referred pain arising from muscle. *Clin Sci*. 1938;3:175–190.
36. Koelbaek Johansen M, Graven-Nielsen T, et al. Generalised muscular hyperalgesia in chronic whiplash syndrome. *Pain*. 1999;83:229–234.
37. Kupers RC, Svensson P, Jensen TS. Cerebral processing of muscle pain and mechanical hyperesthesia in the orofacial region: a positron emission tomography study. *Pain*. 2004;108:284–293.
38. Lacroix JM, Corbett L. An experimental test of the muscle tension hypothesis of tension-type headache. *Int J Psychophysiol*. 1990;10:47–51.
39. Laursen RJ, Graven-Nielsen T, Jensen TS, et al. Quantification of local and referred pain in humans by intramuscular electrical stimulation. *Eur J Pain*. 1997;1:105–113.
40. Lund JP, Donga R, Widmer CG, et al. The pain-adaptation model: a discussion of the relationship between chronic musculoskeletal pain and motor activity. *Can J Physiol Pharmacol*. 1991;69:683–694.
41. Marchettini P, Simone DA, Caputi G, et al. Pain from excitation of identified muscle nociceptors in humans. *Brain Res*. 1996;740:109–116.
42. Mense S. Nociception from skeletal muscle in relation to clinical muscle pain. *Pain*. 1993;54:241–289.
43. Mense S, Hoheisel U, Kaske A, et al. Muscle pain: basic mechanisms and clinical correlates. In: Jensen TS, Turner JA, Wiesenfeld-Hallin Z, eds. *Proceedings of the 8th World Congress on Pain: progress in pain research and management,* vol 8. Seattle: IASP Press; 1997:479–496.
44. Meyers DE, McCall WD. Head pain as a result of experimental ischemic exercise of the temporalis muscle. *Headache*. 1983;23:113–116.
45. Mørk H, Ashina M, Bendtsen L, et al. Experimental muscle pain and tenderness following infusion of endogenous substances in humans. *Eur J Pain*. 2003;7:145–153.
46. Mørk H, Ashina M, Bendtsen L, et al. Induction of prolonged tenderness in patients with tension-type headache by means of a new experimental model of myofascial pain. *Eur J Neurol*. 2003;10:249–256.
47. Mørk H, Ashina M, Bendtsen L, et al. Possible mechanisms of pain perception in patients with episodic tension-type headache. A new experimental model of myofascial pain. *Cephalalgia*. 2004;24:466–475.
48. Newham DJ, Edwards RHT, Mills KR. Skeletal muscle pain. In: Wall PD, Melzack R, eds. *Textbook of pain*. Edinburgh: Churchill Livingstone; 1994:423–440.
49. Pedersen-Bjergaard U, Nielsen LB, Jensen K, et al. Calcitonin gene-related peptide, neurokinin A and substance P: effects on nociception and neurogenic inflammation in human skin and temporal muscle. *Peptides*. 1991;12:333–337.
50. Petty BG, Cornblath DR, Adornato BT, et al. The effects of systematically administered recombinant human nerve growth factor in healthy human subjects. *Ann Neurol*. 1994;36:244–246.
51. Plesh O, Curtis DA, Hall LJ, et al. Gender difference in jaw pain induced by clenching. *J Oral Rehabil*. 1998;25:258–263.
52. Qerama E, Fuglsang-Frederiksen A, Kasch H, et al. Evoked pain in the motor endplate region of the brachial biceps muscle: an experimental study. *Muscle Nerve*. 2004;29:393–400.
53. Reid KI, Carlson C, Rayens MK, et al. The influence of cutaneous tissue afferents on masticatory pain-pressure thresholds. *J Orofac Pain*. 1996;10:324–329.
54. Schmidt-Hansen PT, Svensson P, Jensen TS, et al. Patterns of experimentally-induced pain in pericranial muscles. (Submitted).
55. Sessle BJ. Acute and chronic craniofacial pain: brainstem mechanisms of nociceptive transmission and neuroplasticity, and their clinical correlates. *Crit Rev Oral Biol Med*. 2000;11:57–91.
56. Simone A, Marchettini P, Caputi G, et al. Identification of muscle afferents subserving sensation of deep pain in humans. *J Neurophysiol*. 1994;72:883–889.
57. Simons DJ, Day E, Goodell H, et al. Experimental studies on headache: muscles of the scalp and neck as sources of pain. *Assoc Res Nerv Ment Dis*. 1943;23:228–244.
58. Sohn MK, Graven-Nielsen T, Arendt-Nielsen L, et al. Inhibition of motor unit firing during experimental muscle pain in humans. *Muscle Nerve*. 2000;23:1219–1226.
59. Sohn MK, Graven-Nielsen T, Arendt-Nielsen L, et al. Effects of experimental muscle pain on mechanical properties of single motor units in human masseter. *Clin Neurophysiol*. 2004;115:76–84.
60. Sörensen J, Graven-Nielsen T, Henriksson KG, et al. Hyperexcitability in fibromyalgia. *J Rheumatol*. 1998;25:152–155.
61. Stohler CS. Masticatory myalgias: emphasis on the nerve growth factor-estrogen link. *Pain Forum*. 1997;6:176–180.
62. Stohler CS, Kowalski CJ. Spatial and temporal summation of sensory and affective dimensions of deep somatic pain. *Pain*. 1999;79:165–173.
63. Stohler CS, Lund JP. Effects of noxious stimulation of the jaw muscles on the sensory experience of volunteer human subjects. In: Stohler CS, Carlson DS, eds. *Biological and psychological aspects of orofacial pain: craniofacial growth series 29*. Ann Arbor: Center for Human Growth and Development, University of Michigan; 1994:55–73.

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64. Stohler CS, Zhang X, Lund JP. The effect of experimental jaw muscle pain on postural muscle activity. *Pain*. 1996;66:215–221.
65. Svensson P, Arendt-Nielsen L. Effects of 5 days repeated submaximal clenching on masticatory muscle pain and tenderness: an experimental study. *J Orofac Pain*. 1996;10:330–338.
66. Svensson P, Arendt-Nielsen L, Houe L. Sensory-motor interactions of human experimental unilateral jaw muscle pain: a quantitative analysis. *Pain*. 1996;64:241–249.
67. Svensson P, Arendt-Nielsen L, Nielsen H, et al. Effect of chronic and experimental jaw-muscle pain on pain-pressure thresholds and stimulus-response curves. *J Orofac Pain*. 1995;9:347–356.
68. Svensson P, Bak J, Troest T. Spread and referral of pain in different jaw-muscles. *J Orofac Pain*. 2003;17:214–223.
69. Svensson P, Cairns BE, Wang K, et al. Glutamate-induced sensitization of pressure pain thresholds in human masseter muscle. *Pain*. 2003;101:221–227.
70. Svensson P, Cairns B, Wang K, et al. Injection of nerve growth factor into human masseter muscle evokes long-lasting mechanical allodynia and hyperalgesia. *Pain*. 2003;104:241–247.
71. Svensson P, Graven-Nielsen T. Craniofacial muscle pain: review of mechanisms and clinical manifestations. *J Orofac Pain*. 2001;15:117–145.
72. Svensson P, Graven-Nielsen T, Arendt-Nielsen L. Mechanical hyperesthesia of human facial skin induced by tonic painful stimulation of jaw-muscles. *Pain*. 1998;74:93–100.
73. Svensson P, Graven-Nielsen T, Matre D, et al. Experimental muscle pain does not cause long-lasting increase in resting EMG activity. *Muscle Nerve*. 1998;21:1382–1389.
74. Svensson P, List T, Hector G. Analysis of stimulus-evoked pain in patients with myofascial temporomandibular pain disorders. *Pain*. 2001;92:399–409.
75. Svensson P, Wang K, Sessle BJ, et al. Association between pain and neuromuscular activity in the human jaw and neck muscles. *Pain*. 2004;109:225–232.
76. Torebjörk HE, Ochoa JL, Schady W. Referred pain from intraneural stimulation of muscle fascicles in the median nerve. *Pain*. 1984;18:145–156.
77. Vecchiet L, Dragani L, Bigontina P, et al. Experimental referred pain and hyperalgesia from muscles in humans. In: Vecchiet L, Albe-Fessard D, Lindblom U, eds. *New trends in referred pain and hyperalgesia*. Amsterdam: Elsevier; 1993:239–249.
78. Wang K, Svensson P, Arendt-Nielsen. Effect of tonic muscle pain on short-latency jaw-stretch reflexes in humans. *Pain*. 2000;88:189–197.
79. Zhang X, Ashton-Miller JA, Stohler CS. A closed-loop system for maintaining constant experimental muscle pain in man. *IEEE Trans Biomed Eng*. 1993;40:344–352.
80. Zubieta JK, Heitzeg MM, Smith YR, et al. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science*. 2003;299:1240–1243.
81. Zubieta JK, Smith YR, Bueller JA, et al. Regional mu opioid receptor regulation of sensory and affective dimensions of pain. *Science*. 2001;293:311–315.