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Modulation of brainstem-reflexes by experimental/clinical craniofacial pain and gender/age in humans

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MODULATION OF BRAINSTEM-REFLEXES BY

EXPERIMENTAL/CLINICAL

CRANIOFACIAL PAIN AND GENDER/AGE IN HUMANS

Ph.D.-thesis

by

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2008

PREFACE

This Ph.D. thesis consists of a literature review and four research papers. The present studies have all been accomplished at Center for Sensory-Motor Interaction, Orofacial Pain Laboratory, Aalborg University, Denmark, during the period of 2002 - 2005.

I.   Peddireddy A, Wang K, Svensson P, Arendt-Nielsen L. Effect of experimental posterior temporalis muscle pain on human brainstem reflexes. Clinical Neurophysiol 2005;116:1611-1620 (DOI-10.1016/j.clinph.2005.02.022).

II.   Peddireddy A, Wang K, Svensson P, Arendt-Nielsen L. Influence of age and gender on the jaw-stretch and blink reflexes. Exp Brain Res 2006;171:530-540 (DOI- 10-1007/s00221-005-0300-y).

III. Peddireddy A, Wang K, Svensson P, Arendt-Nielsen L. Stretch reflex and pressure pain thresholds in chronic tention-type headache patients and healthy controls. Cephalalgia (accepted 9th September, 2008; DOI – 10.1111/j.1468-2982.2008.01772.x).

IV. Peddireddy A, Wang K, Svensson P, Arendt-Nielsen L. Blink reflexes in chronic tension-type headache patients and healthy controls. Clin Neuropyhsiol (revised October, 2008).

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1. INTRODUCTION

1.1. Background

Pain is the number one reason people seek health care; it is deemed the "fifth vital sign", to mark its importance as health status indicator (Lanser and Gesell, 2001). The most widely used definition of pain is an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (International association for the study of pain, 1979; Merskey and Bogduk, 1994).

Craniofacial pain refers to a large group of disorders, including temporomandibular disorders (TMDs), headaches, neuralgia, pain arising from dental or mucosal origins, and idiopathic pain (Madland et al., 2001; Agostoni et al., 2005). Tension-type headache (TTH) was defined as an ache or sensation of tightness, pressure, or constriction, widely varied in intensity, frequency, and duration; it is long-lasting, commonly occipital, and associated with sustained contraction of skeletal muscles, usually as a part of the patient's reaction during life stress (Ad Hoc Committee on classification of headache, 1962). TTH is extremely prevalent and represents a major health problem (Rasmussen et al., 1991, 1992; Bendtsen and Jensen, 2006; Stovner et al., 2007). Nevertheless its pathogenic mechanisms are largely unknown. Nociceptive processes in craniofacial muscles are believed to play a role in development and maintenance of TTH (Jensen et al., 1999; Mense et al., 2001; Jensen and Olesen, 1996). In recent years, however, central mechanisms (sensitization of neurons in the central nervous system) have been favoured (Schoenen et al., 1991a, b, c; Jensen, 2003; Bendtsen et al., 1996a, Bendsen, 2000, 2002; Ashina et al., 1999a, b; 2004, 2006; Leistad et al., 2006; Fumal and Schoenen, 2008).

For several reasons, standard neurophysiological techniques (such as cortical evoked potentials and nerve conduction studies) cannot be applied in the trigeminal territory. Not only are the nerve branches in a deep position but the superficial nerve terminals are very short and intermingle with those of the facial motor nerves (Ongerboer de Visser and Cruccu, 1993; Truini and Barbanti, 2004; Cruccu and Truini, 2006). Stimulation to the trigeminal area unavoidably elicits several reflex responses that contaminate or hide the genuine neural signals (Ongerboer de Visser and Cruccu, 1993; Truini and

Barbanti, 2004; Cruccu and Truini, 2006). For these reasons, neurophysiological testing of the trigeminal territory relies mainly on trigeminal reflexes (blink reflex (BR), masseter inhibitory reflex and jaw jerk reflex) (Galeotti et al., 2006).Acute and chronic pain in the trigeminal system presumably modulates the pattern of the brain stem reflexes in a facilitating or inhibiting manner (Hopf, 1994). As there are no structural abnormalities in TTH, only physiological studies can provide insight into the underlying mechanisms (Nardone and Tezzon, 2003).

One way to study the physiology of muscle pain is to use human experimental models in which time and location variables can be standardised (Graven-Nielsen et al., 1997a,b; Graven-Nielsen, 2006). There is a long history of a hypothesized association between excessive levels of muscle tension in the head and neck and TTH (Martin, 1972; Scott and Lundeen, 1980; Boureau et al., 1991, Oksanen et al., 2007a,b). Previous studies have consistently shown that the jaw stretch reflex is facilitated by experimental muscle pain (Svensson et al., 2000; Wang et al., 2000, 2001, 2002, 2004), but whether TTH itself influences the jaw- stretch reflex has not been tested.

Blink reflex (BR) studies have suggested a primary dysfunction of the nociceptive control central system in patients affected by TTH, migraine, cervicogenic headache (Sand and Zwart, 1994; Aktekin et al., 2001; Sand et al., 2006) and cluster headache (Lozza et al., 1997; Matharu and Goadsby, 2002). BR abnormality may be caused by brainstem lesions in various neurological diseases (Kimura, 1989; Cruccu and Deuschl, 2000) and it may reflect possible brainstem dysfunction or excitability changes in headache (Sand and Zwart, 1994).

Increased tenderness of pericranial muscles has been reported in patients with TTH (Drummond, 1987; Langemark et al., 1989; Jensen, 1996). However, when more specific measures are used, conflicting results appear. For instance, the least amount of force or pressure necessary to elicit a report of pain (PPT) has been reported as lower in chronic tension-type headache (CTTH) (Bendtsen et al., 1996b; Schoenen et al., 1991c; Schmidt-Hansen et al., 2007), but other reports indicate that there are no differences in TTH or migraine (Jensen, 1996; Bovim, 1992; Jensen et al., 1993; Neufeld et al., 2000; de

Tommaso et al., 2003). The studies mentioned do not discriminate if the sensitivity changes are inherent to the person, if they are secondary to the headache, or if they simply accompany the headache.

It is generally recognized that reflex action is impaired with increasing age; in particular complex reflexes tend to have longer delays, although the reason for this is uncertain (Corden and Lippold, 1996). Our understanding how the nervous system controls oral motor behavior is limited and even less is known about the effect of age on neuromuscular control of brainstem reflexes (Kossioni and Karkazis, 1998). TTH seems to be higher in women, and declines with age in both sexes (Lyngberg et al., 2005). There is a much higher prevalence of TTH among women of reproductive age (Friedman, 1979; Rasmussen et al., 1991; Jensen et al., 1993; Marcus, 2001; Lyngberg et al., 2005; Schmidt-Hansen et al., 2007), which suggests that sex-related factors may play a role in the pathophysiology of these conditions. However, review of the literature demonstrates a scarcity of published data on the impact of gender on the various components of brainstem reflexes.

This thesis is an attempt to understand the modulation of brainstem reflexes during experimental craniofacial pain in healthy volunteers and clinical craniofacial pain in CTTH patients.

1.2. Aim of the Ph.D. project

The recording of brainstem reflexes provides valuable information on the functional integrity of the brainstem and allows the afferent and efferent pathways of these reflexes to be assessed. The aims of the present studies were to test the overall hypothesis that the brainstem reflexes and PPT may be influenced by painful inputs from the craniofacial tissues (experimental/clinical craniofacial pain) and that the study of these simple reflex activities in different age- and sex-groups can reflect on differences in the neuromuscular circuits.

2. CRANIOFACIAL PAIN

2.1. Nociceptive mechanisms in craniofacial muscles

Free nerve endings typically located in the wall of arterioles and connective tissues (Stacey, 1969) are assumed to mediate muscle nociception (Mense, 1993). The muscle fibre proper is not supplied with free nerve endings (Reinert et al., 1998). Group IV afferents terminate exclusively in free nerve endings whereas group III units end predominantly in free nerve endings (Stacey, 1969; Heppelmann et al., 1990; Messlinger et al., 1996) but also in other muscle receptors, such as paciniform corpuscle (Stacey, 1969). Free nerve endings are unmyelinated axon terminals surrounded by a single layer of Schwann cell covering, except for the receptive areas, which are free of Schwann cell processes (Heppelmann et al., 1995; Messlinger et al., 1996) and have direct contact with the interstitial fluid. The endings have axonal expansions that contain neuropeptides and probably other endogenous substances (Reinert et al., 1998). The primary afferent fibers responsible for the sensation of pain can be classified as A-delta (group III) or C-polymodal fibers (group IV) (Schmidt, 1986). Histologically, the afferent fibers are either thin myelinated (group III) or non-myelinated (group IV) fibers (for a review see Mense, 1993, 1996). Group III and group IV fibers are both slowly conducting afferent fibers. In human microneurography studies, muscle nociceptors have been found with conduction velocities in the range 0.6–1.2 m/s for group IV and 3.1–13.5 m/s for group III (Martin and Jessell, 1991; Simone et al., 1994; Marchettini et al., 1996).

The nociceptive afferents from the jaw-muscles pass through the trigeminal ganglion to synapse on second-order neurones in the trigeminal (V) brain stem sensory complex. These neurones in the V brain stem sensory nuclear complex are excited by the incoming information and may by the process of synaptic transmission project to neurones at higher levels, i.e. the thalamus and the cerebral cortex, or to neurones in the brain stem region such as the reticular formation. Some neurones may also project to the upper cervical segments of the spinal cord or to neurones in other subnuclei of the V brain stem complex (Sessle, 1993). The fibres of second-order neurones proceed mainly via the spinothalamic or trigeminothalamic tracts (Craig and Kniffki, 1985). Other ascending tracts may also be involved (Kniffki et al., 1977; Hong et al., 1979). Commonly reported brain areas with haemodynamic responses to cutaneous pain are the primary and secondary somatosensory, posterior parietal, prefrontal, anterior cingulate, and insular cortices (Peyron et al., 2000). These brain areas are with some deviations also

found in experimental muscle pain studies (Svensson et al., 1997; Niddam et al., 2002; Kupers et al., 2004), although exceptions are described (Kupers et al., 2004; Korotkov et al., 2002; Schreckenberger et al., 2005; Thunberg et al., 2005).

The V sensory complex can be subdivided into the principle sensory nucleus and the spinal tract nucleus, which comprises three subnuclei; the rostral subnucleus oralis, the middle subnucleus interpolaris, and the caudal subnucleus caudalis that extends into the cervical spinal cord and merges with the spinal dorsal horn. Most of the nociceptive fibers make synaptic connections in the subnucleus caudalis (Sessle, 1987; 2000). Some nociceptive afferents from the cranial nerves VII, IV, and X may also synapse in the trigeminal complex (Sessle, 1993).

Thus, the main nociceptive transmission pathway related to craniofacial muscle pain involves the trigeminal nerve and its peripheral receptors, the trigeminal ganglion, and brain stem nuclei with sensory relay to the thalamus and cerebral cortex. Furthermore, the peripheral and central nervous systems may continuously modulate nociception and assist in shaping the individual behavioral and emotional responses to pain.

2.2. Experimental craniofacial pain

Several methods of inducing muscle pain have been reported. The infusion of hypertonic saline and the subsequent saline-induced jaw muscle pain has proved useful in studies on sensory-motor interaction (Svensson et al., 2000, 2001; Wang et al., 2000, 2001, 2002, 2004; Capra and Ro, 2000, 2004; Ro et al., 2007). In humans, intramuscular infusion of hypertonic saline can produce pain and the pain is similar in intensity and quality to clinical muscle pain (Capra and Ro, 2000; Svensson et al., 2001). This technique provides a temporal profile of pain so that the map of the spatial distribution of local and referred pain can be recorded (Graven-Nielsen et al., 1997a, b; 1998, 2002a, b, 2003; Graven-Nielsen and Arendt-Nielsen, 2002, 2003; Graven-Nielsen, 2006).

In animal studies, hypertonic saline is shown to excite group III and group IV muscle afferents (Kumazawa and Mizumura 1977; Capra and Ro, 2000; Ro et al., 2003; Cairns et al., 2003a; Hoheisel et

al., 2005). But other afferents (e.g. related to muscle spindles) may occasionally be activated by hypertonic saline as afferents responding to muscle stretch show an increased or decreased activity after hypertonic saline (Iggo 1961; Kumazawa and Mizumura 1977), although no specific details were given. Recordings from group III and IV afferents reveal that application of hypertonic saline directly onto the afferent cause excitation in 50% of the afferents tested (Orchardson 1978). In animal experiment, about 70 % of wide dynamic range (WDR) neurons and nociceptive specific (NS) neurons in the trigeminal subnucleus caudalis do respond to injection of hypertonic saline into small arteries supplying the jaw and tongue muscles, whereas relatively few (25%) low-threshold mechanoreceptive (LTM) neurons do (Amano et al., 1986; Carstens et al., 1998). It has been recently reported that injection of hypertonic saline (5%) into the masseter muscle strongly activates neurons of the subnucleus interpolaris that receives inputs from group III muscle afferents (Ro and Capra 1999; Ro et al., 2003).

Noxious chemical stimulation of the masseter muscle activates central trigeminal neurons in the ipsilateral subnucleaus caudalis, in the dorsal and ventral areas of the subnucleaus caudalis/interpolaris transition region bilaterally, and in the paratrigeminal nucleus, bilaterally (Imbe et al., 1999; Ro et al., 2003, 2004, 2007). The receptor type involved in saline-induced muscle pain is still not apparent but the stretch-inactivated ion channel is a potential candidate. The stretch-inactivated channel (a subtype of the transient receptor potential vanilloid receptor 1, TRPV1) is expressed in small-diameter sensory neurones and found to elicit an inward current in response to cell shrinkage following exposure to hypertonic solutions (Schumacher et al., 2000). Alternatively, the somatosensory receptors have a relatively high resting conductance for sodium and a drastic elevation of the extracellular sodium concentration by injections of hypertonic saline leads to sodium influx and cell depolarization (Graven-Nielsen et al., 1997a; Graven-Nielsen and Arendt-Nielsen, 2003; Graven-Nielsen 2006).

Hence hypertonic saline is a potent chemical stimulus for excitation of group III and IV muscle afferents and neurons encoding nociceptive information in the central nervous system. Due to the safety of the technique (Graven-Nielsen and Arendt-Nielsen, 2003; Svendsen et al., 2005) the similarities to clinical muscle pain, and the easy application to any specific muscle, intramuscular infusion of hypertonic

saline into the posterior temporalis muscle offers a useful model to study basic consequences of standardised muscle pain on trigeminal motor consequences of TTH.

In study I, the experimental muscle pain was induced by the infusion of hypertonic saline in the left posterior temporalis muscle. A standardized infusion paradigm was used with 0.2 ml saline infused over 20 s followed by a steady infusion rate of 6 ml/h for the next 440 s and finally 9 ml/h for the next 440 s (Svensson et al., 1998). Tonic infusion of hypertonic saline with the use of a computer-controlled pump has the advantage that the muscle pain can be maintained for longer periods (up to 15 min) compared to the bolus (3-5 min), with an average pain level within the ranges of pain levels reported by patients with persistent jaw-muscle pain (Stohler and Kowalski, 1999; Graven-Nielsen et al., 1997a; 1997b; 1998, 2002a,b, 2003, 2006).

2.3. Clinical craniofacial pain

TTH is the term designated to describe what previously was called tension headache, muscle contraction headache, psychomyogenic headache and stress headache (Mathew, 2006).

The former headache classification, from 1962, described the quality of pain in TTH as dull, aching, pressure-like, constricting, or giving a sense of fullness. This has been confirmed in a detailed analysis of 1420 cases by Friedman (1979). In the IHS classification from 1988 and 2004 defines pain quality as simply pressing or tightening. This pressing pain quality was confirmed by 83% of CTTH sufferers from a general population (Rasmussen et al., 1991) and in 95 of 100 patients with daily or almost daily headache from a specialized headache clinic (Solomon et al., 1992). The pain in TTH is similar to myofascial pain elicited from other parts of the body, but whether it is strictly localized to muscle tissues or to other deep tissues is still uncertain. In addition, although the pain clinically resembles pain from the myofascial tissues, components of both peripheral and central origin may contribute (Jensen, 1999). This leads to the second question, i.e., whether the pain in TTH is due to peripheral or to central factors, and no clear answer has been given. The nociceptive flexor reflex, a spinally organized reflex, was reported to be decreased in patients with CTTH (Langemark et al., 1993). As this reflex is

influenced by the endogenous modulating system, a defect either in the opioid system or in the production of neurotransmitters (Le Bars et al., 1979; Hole and Berge, 1981; Langemark et al., 1995) was suspected. Furthermore, the findings of increased metenkephalin levels in the cerebrospinal fluid from these patients (Langemark et al., 1995) support this, although the β-endorphin concentration was normal (Bach et al., 1992). These various abnormalities may, however, result in a disturbance of the balance between peripheral input and the central modulation, as discussed by Sandrini et al. (1991) and by Langemark et al. (1995), but the primary eliciting cause and the evolution of pain are still unknown. As the most frequently reported precipitating factors leading to TTH are stress, mental tension, and tiredness (Rasmussen, 1993; Clark et al., 1995; Ulrich et al., 1996), central supraspinal factors are undoubtedly involved too.

The level of electromyograph activity in the pericranial muscle is, on average, higher in patients with CTTH than in healthy controls (Schoenen et al., 1991a). As seen in a recent MRI study (Fernandez-de-las-Penas et al., 2007a), the relative crosssectional area (rCSA) of the minor and major rectus capitis posterior muscles were reduced in patients with CTTH, whereas the rCSA of the semispinalis and splenius capitis muscles was normal. The reduction in rCSA was negatively associated with the intensity, duration, and frequency of headache. Whether the atrophy of deep neck muscles that is seen in patients with CTTH is primary or secondary to the headache remains to be determined. Taken together, these studies do not favor increased activity, muscular inflammation, or disturbed metabolism of the pericranial muscles as important pathogenic factors in CTTH (Fumal and Schoenen, 2008).

The hypothesis of central sensitization in TTH is supported by clinical pharmacologic studies (Bendtsen, 2002). The only prophylactic treatment with proven efficacy is the tricyclic anti depressant amitriptyline (Holroyd et al., 2001; Bendtsen, 2003). It was assumed previously that the analgesic effect of amitriptyline could be ascribed to the blockade of serotonin reuptake in the central nervous system (CNS). This was questioned first by animal studies and later by human studies showing that selective serotonin reuptake inhibitors have little or no clinical effects in patients with CTTH (Bendtsen, 2003). Several of the other actions of the tricyclic anti depressents (e.g. inhibition of noradrenaline reuptake)

may contribute to their analgesic effect (Bendtsen and Jensen, 2000). It has been demonstrated that amitryptiline may act as an N-methyl-D-aspertate (NMDA) receptor antagonist (Watanabe et al., 1993), and it has been suggested that the analgesic effects of amitryptiline in chronic pain may result primarily from this action (Eisenach and Gebhart, 1995). The activation of NMDA receptors plays a prominent role in the development of sensitization in the dorsal horn, which is in agreement with the hypothesis of central sensitization in patients with CTTH.

Animal studies have shown that sentitization of pain pathways may be caused by or associated with activation of nitric oxide synthase (NOS) and the generation of nitric oxide (NO), and that NOS inhibitors reduce central sensitization in animal models of persistent pain. Based on these findings and the hypothesis of central sensitization in CTTH, Ashina et al. (1999a) investigated the analgesic effect of the NOS inhibitor NG-monomethyl-L-arginine hydrochloride. This drug significantly reduced headache (Ashina et al., 1999b) and pericranialmyofacial tenderness and hardness (Ashina et al., 1999b) in patients with CTTH. In addition, it has been demonstrated that infusion of the NO donor glyceryl trinitrate induces TTH in these patients (Ashina et al., 2000a). The immediate headache is not accompanied by an increase in pericranial tenderness (Ashina et al., 2000b) but it might be associated with endogenous production of nitric oxide and sensitization of perivascular sensory afferent nerves. (Ashina et al., 2004) These interesting studies support the theory that central sensitization is involved in the pathophysiology of CTTH. Moreover, these findings suggested that inhibition of NO and thus central sensitization may become a novel means of future treatment of CTTH.

Growth hormone and prolactin secretion was blunted in patients with CTTH in response to subcutaneous injections of sumatriptan (Rainero et al., 2002), which was thought to indicate reduced sensitivity of the hypothalamic 5-HT1_D serotonin receptors. The results of two independent studies suggest that sumatriptan, the $5\text{-HT1}_{B/D}$ serotonin agonist that is highly effective for acute migraine attacks, might also be effective in patients with TTH (Cady et al., 2000; Miner et al., 2007). Moreover, the results of a large study of migraineurs showed that mild headaches, which phenotypically resembled TTH, responded to oral sumatriptan (Cady et al., 2000).

Schmidt-Wilcke and co-workers (2005) found significant decreases in tissue mass, using MRI voxel-based morphometry, in several brain areas in the pain matrix in patients with CTTH. The decrease was not seen in patients with medication-overuse headache. Although CTTH and medication-overuse headache share a common clinical feature - frequent, almost daily, head pain - the underlying pathophysiology can differ substantially.

Sensitivity to electrical stimuli was investigated in a recent study (Ashina et al., 2006), which compared suprathreshold single and repetitive (2 Hz) stimulations of muscle and skin in cephalic (temporal and trapezius muscles) and extracephalic (anterior tibial muscle) regions. The results favored a generalised increase in pain sensitivity (generalised hyperalgesia) in patients with CTTH, which suggests that pain processing in the CNS is abnormal. The results also indicated that suprathreshold stimuli are more sensitive than pain thresholds for the evaluation of generalised pain perception. Thus, pain perception studies and pharmacological studies strongly suggested that the CNS is sensitized in patients with CTTH patients (Mathew, 2006).

The various pathophysiological abnormalities of TTH, and the differences between TTH types, led to the proposal of a model of TTH as a working hypothesis (Olesen and Schoenen, 1999; Bendtsen, 2000; Fumal and Schoenen, 2008). TTH might result from the interaction between changes in the descending control of second-order trigeminal brainstem nociceptors and interrelated peripheral changes, such as myofascial pain sensitivity and strain in the pericranial muscles. An acute episode of TTH (ETTH) can occur in people who are otherwise perfectly healthy, and episodes can be brought on by physical stress, usually combined with psychological stress, or by non-physiological working positions. In such cases, increased nociception from strained muscles might be the primary cause of the headache, possibly favored by a central temporary change in pain control due to stress. Emotional mechanisms increase muscle tension through the limbic system and, at the same time, reduce tone in the endogenous antinociceptive system. With more frequent episodes of headache, central changes become increasingly important. Long-term potentiation or sensitisation of nociceptive neurons and decreased activity in the antinociceptive system gradually lead to CTTH; these central changes probably predominate in frequent

ETTH and CTTH. The relative importance of peripheral and central factors might, however, vary between patients and over time in the same patient. Genetic components are likely to promote the psychological and central changes that lead to CTTH, whereas environmental factors are the main cause in ETTH (Olesen and Schoenen, 1999; Bendtsen, 2000; Fumal and Schoenen, 2008).

TTH is clinically and pathophysiologically heterogeneous. With regard to the pathogenesis, pericranial myofascial mechanisms are probably of importance in episodic TTH, whereas sensitisation of pain pathways in the CNS-due to prolonged nociceptive stimuli from pericranial myofascial tissues—and inadequate endogenous pain control seem to be responsible for the conversion from episodic to chronic TTH.

3. PRESSURE PAIN THRESHOLDS

3.1. Background

The pressure algometer was first described by Keele, 1954 and consists of a plunger mounted on a calibrated spring. Mechanical painful stimulation can be achieved with pressure algometers. The most widely used technique is manual pressure algometry (Graven-Nielsen et al., 1997a, b, 2002a, b, 2003, 2006; Jensen, et al., 1986, 1988; Fischer, 1998; Kosek et al., 1995, 1996, 1999). Methodological concerns such as short- and long-term reproducibility on pain thresholds (Jensen et al., 1986; Brennum et al., 1989; Kosek et al., 1993, 1999; Isselee et al., 1997, 1998, 2001, 2002; Persson et al., 2004; Rolke et al., 2005), influence of pressure rates, durations (List et al., 1991; Lavigne et al., 1994), muscle contraction levels (List et al., 1991; Lavigne et al., 1994; McMillan et al., 1994; Kosek and Ekholm, 1995; Kosek et al., 1996), and interexaminer variability or examiner expectancy (Reeves et al., 1986; Nussbaum and Downes, 1998; Antonaci et al., 1998; Ohrbach et al., 1998; Persson et al., 2004) have all been addressed.

PPT measurement has been used as a diagnostic procedure in different pain syndromes (Fisher, 1986) and the method has also been used to evaluate headache patients (Jensen et al., 1988; Langemark et al., 1989). Recordings of PPT are recommended as one of the diagnostic criteria for TTH associated with

disorders of pericranial muscles (Headache Classification Committee of the International Headache Society, 1988). Recently, the second edition of the Classification of Headache Disorders of the International Headache Society (IHS) has maintained former clinical criteria for the diagnosis of TTH (Headache Classification Committee of the International Headache Society, 1988, 2004). However, the second edition has withdrawn electromyography or pressure algometry from the diagnostic features for subdivision, as only tenderness on manual palpation has proved useful to distinguish different subtypes of TTH (Headache Classification Committee of the International Headache Society, 2004). Accordingly, the following subtypes of TTH are now considered: infrequent episodic TTH associated or not associated with pericranial tenderness; frequent episodic TTH associated or not associated with pericranial tenderness; CTTH associated or not associated with pericranial tenderness; and probable TTH (infrequent, frequent or CTTH). On the basis of these data, it seems plausible that pericranial tenderness may be relevant in the development of TTH. It is also possible that headache is causing muscle referred pain and in these referred pain areas there is tenderness (Graven-Nielsen et al., 1997b; Graven-Nielsen and Arendt- Nielsen, 2003). Nonetheless, increased tenderness of pericranial muscles has been reported in patients with TTH (Drummond, 1987; Langemark et al., 1989; Jensen, 1996). However, when more specific measures are used, conflicting results appear. For instance, the least amount of force or pressure necessary to elicit a report of pain (PPT) has been reported as lower in CTTH patients (Bendtsen et al., 1996b; Schoenen et al. 1991c; Schmidt-Hansen et al., 2007; Fernandez-de-las-penas et al., 2007b), but other reports indicate that there are no differences in TTH or migraine (Jensen, 1996; Bovim, 1992; Jensen et al., 1993; Neufeld et al., 2000; de Tommaso et al., 2003). The studies mentioned do not discriminate if the sensitivity changes are inherent to the person, if they are secondary to the headache, or if they simply accompany the headache.

Manually applied mechanical stimulation to induce pain from deep structures has been extensively used and validated. The pressure pain sensitivity is a combined measure of cutaneous and deep tissue mechanosensitivity (Graven-Nielsen et al., 2006). Several studies attempted to eliminate the contribution of skin sensations by using a eutectic mixture of local anaesthetic (EMLA) cream before assessing the

pressure pain sensitivity. Both decreased and unchanged pressure pain sensitivity after EMLA application has been reported (Graven-Nielsen et al., 1998; Kosek and Ekholm, 1995; Kosek et al., 1995; 1999; Laursen et al., 1997). In a recent study it was demonstrated that the pressure pain tolerance threshold was decreased (hyperalgesia) by EMLA cream, and after infiltration of the subcutaneous tissue with lidocaine the pain tolerance threshold increased (Graven-Nielsen et al., 2004). Moreover, the pressure pain threshold was not affected after EMLA cream and significantly increased after subcutaneous lidocaine. The brush sensation was still present after EMLA cream, in contrast to after lidocaine, whereas the pinprick sensation was significantly decreased after EMLA cream and further decreased after lidocaine. Thus, tissue sensitivity assessed by pressure is a combined measure of cutaneous and deep tissue mechanosensitivity. The lidocaine might block receptors in deeper subcutaneous layers (e.g. superficial parts of the fascia), accounting for the decreased pressure sensitivity after lidocaine. Before EMLA application, needle insertions typically caused pain before penetrating the fascia, in contrast to after EMLA cream, where the detection and pain sensations occurred after penetrating the fascia (Graven-Nielsen et al., 2004). This clearly demonstrated the mechanically elicited pain sensation from deep tissue. Interestingly, when blocking the thick afferent fibres from the muscle and simultaneously anaesthetizing the skin, subjects still have a non-painful and painful sensation to pressure (Graven-Nielsen et al., 2004).

The large proportion of group III and IV afferent fibres with low-mechanical thresholds (Mense and Meyer, 1985; Reinohl et al., 2003) might mediate the non-painful pressure sensation from muscle. PPT predominantly reflects muscle nociception, because it was not significantly influenced by cutaneous analgesia (Kosek et al., 1999).

3.2. Methodological parameters

PPT was determined with a hand-held electronic algometer (SomedicAB, Sweden, Range 0-2000 kPa with accuracy of +3% of reading) mounted with a 1-cm diameter circular rubber probe calibrated in kilopascals (kPa). The PPT was defined as the pressure at which, the subject's perceived sensation

changed from pressure to the first sensation of pain. To assess the PPT, the probe was held perpendicularly and pressure increased at a constant rate of approximately 30 kPa/s. In study III, a rate of approximately 30 kPa/s was chosen (Schoenen et al., 1991c; Farella et al., 2000; Prushansky et al., 2004), which was sufficiently slow to allow precise recording of subjects' reaction while preventing examiners hand fatigue and deviation from a constant rate of pressure increase (Prushansky et al., 2004). Algometric measurements were performed by a single examiner (by the author). The PPT was determined as the point at which the pressure stimulus applied to the skin changed from a sensation of pressure to pain. The subjects and patients indicated the PPT by pressing a push-button, which froze the current pressure value on the digital display. Before starting, the subjects were carefully instructed with regard to the whole procedure and a few test measurements were performed on their hands. The subjects sat in a chair and were asked to relax in the mandibular rest position during the recordings. While assessing the PPT, the subject's head was supported by counter-pressure from the opposite hand of the operator. During the measurements, the algometer was held perpendicular to the skin. Algometric measurements were performed on six points in all subjects. The masseter, anterior temporalis and splenius capitis muscles were tested. The most sensitive location for the assessment of PPT levels was the anterior and middle parts of the temporalis muscles within the CTTH patient group (Jensen et al., 1993, Silva et al., 2005; Fernandez-de-Las-Penas, 2007a). Muscular hyperalgesia has been detected mainly on the masticatory muscles or brachioradialis muscle, whereas hypoalgesia or unchanged sensitivity is found in studies on the larger tibialis anterior muscle. This could suggest that the development of muscular hyperalgesia depends on the size of the muscle and possibly the level of afferent barrage. This is supported by the PPTs being higher for a large muscle such as the tibialis anterior compared with a smaller muscle such as the brachioradialis. (Graven-Nielsen and Arendt-Nielsen, 2002). The cervical extensor musculature, particularly the suboccipital muscles, might play an important role in the genesis of TTH (Fernandez-de-las-Penas et al., 2007a).

The same order of testing was performed for all the patients and control subjects: left masseter, left anterior temporalis, left splenius capitis, right masseter, right anterior temporalis and right splenius

capitis muscles. The force was released immediately following the tone produced by pressing the handheld button. The single-point measurements of the muscles were done twice on both sides of the head for each individual. The average of the two different measurements was calculated and used in subsequent statistical calculations. Data from each muscle investigated were averaged in order to get a single estimate of PPT values.

3.3. Modulation by clinical muscle pain

Current knowledge of the nociceptive (pain receptor) system suggests that the derivative pain of TTH has a muscular origin. Muscular or myofascial pain tends to be dull and achy, poorly localized, and radiating, whereas pain originating from cutaneous structures is sharp, localized, and nonradiating. The supposition that the pain is muscular in origin and related to increased resting muscle tension corresponds with the current clinical understanding of TTH and derived treatment approaches (Millea and Brodie, 2002). TTH can last from 30 minutes to several days and can be continuous in severe cases. The pain is mild or moderately intense and is described as tightness, pressure, or a dull ache. The pain is usually experienced as a band extending bilaterally back from the forehead across the sides of the head to the occiput. Patients often report that this tension radiates from the occiput to the posterior neck muscles. In its most extensive form, the pain distribution is "cape like," radiating along the medial and lateral trapezius muscles covering the shoulders, scapular, and interscapular areas (Spira, 1998; Millea and Brodie, 2002). In addition to its characteristic distribution and intermittent nature, the history obtained from patients with TTH discloses an absence of signs of any serious underlying condition (Marks and Rapoport, 1997). Patients with TTH do not typically report any visual disturbance, constant generalized pain, fever, stiff neck, recent trauma, or bruxism (Millea and Brodie, 2002).

Our results in study III demonstrated that on average there is no significant difference in pericranial muscle PPT between the group of CTTH patients and healthy controls. This is consistent with the previous studies in which no significant differences in PPT between the time of headache attack and the pain-free interval in patients with migraine (Jensen et al., 1988) or between TTH and from that of

healthy subjects (Bovim, 1992; Göbel et al., 1992; Hyung-Suk et al., 1995; Neufeld et al., 2000; de Tommaso et al., 2003) was found. The PPTs at the anterior temporal region of 22 subjects with CTTH from the general population did not differ from the rest of the population or from the other headache groups (Jensen et al., 1993). Similarly, the pain thresholds and the pain tolerances in the temporal region of patients with CTTH were not different from those patients with episodic TTH (Brennum et al., 1989; Petersen et al., 1992) or in 30 age- and sex-matched healthy controls in the clinical study (Jensen et al., 1993; Jensen and Olesen, 1996). A decreased PPT indicates a state of allodynia, i.e. pain elicited by stimuli which normally are non-noxious. However, the findings of normal PPT indicate that the general pain sensitivity is not permanently disturbed, as previously suggested (Jensen and Olesen, 1996).

Ashina et al. (2000a) demonstrated that muscle hardness, myofascial tenderness and pressure-pain detection thresholds in the cranial (temporal) and extracranial (finger) regions are unchanged during nitric oxide (NO)-induced immediate headache either in CTTH patients or controls. These results seem to rule out sensitization of myofascial peripheral and central pathways as the mechanism of the immediate headache. Unchanged pressure-pain detection thresholds in the temporal region may also indicate no alteration in sensitivity of extracranial vasculature. Experimental studies in humans suggest that NO may directly activate or sensitize nociceptors around blood vessels. Intravenous infusion of glyceryl tri nitrate (GTN) (0.5 mg/kg per min over 20 min) induced dilatation of the middle cerebral artery which lasted until 1 h after stopping GTN infusion (Iversen et al., 1989). It is therefore more likely that immediate headache after GTN infusion in patients with CTTH may originate from NO-induced activation or sensitization of sensory nerves around intracranial arteries or from NO-induced arterial dilatation, or both.

3.4. Clinical implications

Palpatory tenderness of the muscle remains the essential element of diagnostic significance, whether we are dealing with persistent, localized or general muscle pain (Goulet and Clark, 1990). With tenderness to palpation a key component in the diagnostic process, the need for reliable clinical measurement is advocated. The diverse methods of manual palpation are difficult to quantify and standardize. Reliability

of muscle tenderness can be improved if, instead of using the finger, the examiner uses an instrument that applies pressure over a specific area at a constant uniform rate. Pressure algometers have been used to measure the PPT which is defined as the amount of applied pressure necessary for a subject to report the onset of pain. Pressure algometry has produced reliable and valid measures of PPT in patients with a variety of musculoskeletal pain syndromes (Reeves et al., 1986; Ohrbach and Gale, 1989a) and in asymptomatic subjects (Jensen et al., 1986; Fischer, 1987; Ohrbach and Gale, 1989b; Isselee et al., 1997), and is more objective than manual palpation. Algometers can improve reliability because of their constant area of skin contact and their ability to control the rate and direction of pressure application (List et al., 1991; Gracely and Kevin, 1995). Previous studies (Jensen et al., 1986; Fischer, 1987; Ohrbach and Gale, 1989a) suggest that pressure algometers allow a reliable and more objective quantification of muscle tenderness.

Among the various noxious stimuli, pain due to pressure is believed to assess deep tissue sensitivity. PPT measurements obtained using a pressure algometer are used for the evaluation and follow-up of various pain syndromes in which the main source of pain is myofascial (Prushansky et al., 2004). There is a growing evidence to support PPT's reproducibility and validity when measured with pressure algometer (Brennum et al., 1989; Ohrbach and Gale, 1989b; Jensen et al., 1986; Chung et al., 1992; Antonaci et al., 1998; Kosek et al., 1993; Sterling et al., 2002; Prushansky et al., 2004), which places it as an appealing device for clinical as well as research applications. Because tenderness is a clinical sign that may change with treatment, pressure algometry may provide a useful tool to quantify the clinical outcome of treatment modality (Prushansky et al., 2004).

PPT was used as a diagnostic and or evaluating tool in patients suffering from arthritis (McCarthy et al., 1965), temporomandibular joint disorders (Ohrbach and Gale, 1989b), ankylosis spondylitis (Incel et al., 2002), acute whiplash (Kasch et al., 2001), fibromyalgia (Kosek et al., 1995), trigger points (Kraus, 1981; Fischer, 1984, 1986; Reeves et al., 1986), and fibrositis (Moldovsky and Chester, 1970; Moldofsky et al., 1976; Campbell et al., 1983). PPT is also used to assess the course of development of these conditions and effectiveness of management techniques, eg, idocaine injections to trigger points (Jensen

et al., 1986). Measurement of deep visceral tenderness was used successfully in patients with abdominal pain due to pancreatitis, cholecystopathy and duodenal ulcer (Yamagata et al., 1976). It was established that pressure sensitivity varies over individual muscles and differs in upper and lower body. These variations in pressure sensitivity are evidently important for the clinical diagnosis of pathological local tenderness on palpation.

However, Farella et al. (2000) concluded that even though sensitivity and specificity of pressure algometry may reach acceptable values, because of the low positive predictive value, pressure algometry has limited diagnostic value.

Manually applied mechanical stimulation to induce pain from deep structures has been extensively used and validated. The pressure pain sensitivity is a combined measure of cutaneous and deep tissue mechanosensitivity. However, group III and IV afferent fibres from deep tissue are strongly involved in the sensation evoked by pressure stimulation.

4. BRAINSTEM REFLEXES

Since the 1950s the easiest neurophysiological method for assessing brainstem function has been established (Kugelberg, 1952; McIntyre and Robinson, 1959) and still is the electromyographic recording of brainstem reflexes (Ongerboer de Visser and Cruccu, 1993; Hopf, 1994; Kimura et al., 1994; Deuschl and Eisen, 1999).

Brainstem reflexes can be elicited and recorded with routine EMG equipment and exhibit distinct patterns of abnormality that have clinical, diagnostic and localizing value in various diseases, including cranial neuropathies, focal lesions within the cervical cord, brainstem, and brain, movement disorders, and during pain (Cruccu and Deuschl, 2000). The masseter stretch reflexes, and the blink reflexes are useful diagnostic tools for evaluation of brain stem disorders (Hopf, 1994). Monitoring jaw stretch reflex parameters makes it possible to look into the excitability of the trigeminal motoneuron pool. The level of this excitability may be modified by inputs from the orofacial area during function and dysfunction (Murray and Klineberg, 1984). Sudden stretches of the jaw-closing muscle can elicit short-latency

excitatory response in the muscles, so called jaw-jerk reflexes or stretch reflexes. One of the functions of the stretch reflex in the jaw-closing muscles is to maintain and restore the postural position of the mandible when it is perturbed during rapid head movements (Miles et al., 2003, 2007). The so-called "nociceptive specific" BR is an alternative, non-invasive and reliable electrophysiological technique to measure the nociceptive transmission state of the trigeminal system in humans (Ellrich, 2000; 2002; Katsarava et al., 2002; Romaniello et al., 2002; Giffin et al., 2004).

Brainstem reflexes along with clinical signs may be utilized to prove multitopic involvement of the central nervous system. Based upon the anatomy of the central loop of the individual reflex involved, one can determine whether associated clinical signs and reflex abnormalities are within the area of a single lesion (Hopf, 1994).

4.1. Blink reflex

In 1896, Overend was the first to describe a reflex of the orbicularis oculi muscles evoked by a gentle tap on the forehead: the BR (as quoted by Ellrich, 2000). An eyelid closure in response to some stimulus is a BR, which is normally isolated. In humans and primates, the closing is bilateral while in other animals, mostly those with eyes set laterally, the closure is frequently unilateral. Since Thomas Willis (1621-1672) this 'automatic', unwilling eyelid action has commonly been referred to as a typical example of 'reflex movement' (quoted by Esteban, 1999). In clinical practice, a BR is characteristically provoked by light corneal or eyelash touching or glabellar tapping. The BR is ubiquitously present in mammals and its electrophysiological characteristics have been studied in many common laboratory and domestic species (Shahani and Young, 1973; Evinger et al., 1993; Pellegrini et al., 1995; LeDoux et al., 1997; Gong et al., 2003; Zerari-Mailly et al., 2003; Smit et al., 2006; Dauvergne and Evinger 2007). In man, the BR provoked by an electrical shock has been studied repeatedly over the years (Kugelberg, 1952; Rushworth, 1962; Kimura et al., 1969; 1989 Ferrari and Messina, 1972; Shahani and Young, 1972a, b; Penders and Delwaide, 1973; ; Sand and Zwart, 1994; Ellrich and Hopf, 1996; Avramidis et al., 1998; Ellrich and

Treede,1998; Ellrich, 2000; Kaube et al., 2000; Cruccu and Deuschl, 2000; Drummond 2003, 2004; Cruccu et al., 1991, 2005; Baad-Hansen et al., 2006).

The BR consists of bilateral eyelid closure in response to a stimulus applied in the area innervated by the trigeminal nerve or directly on a branch of the trigeminal nerve. Other types of stimulation (e.g. light, acoustic stimulus) can also induce a BR response (Esteban, 1999).

EMG recordings from the orbicularis oculi muscle show that the BR evoked by mechanical or electrical stimulation of the supraorbital region comprises three components. The first or early reflex, R1, is an oligosynaptic, pontine, short EMG response (not visible clinically) that occurs at a 10-11 ms latency ipsilateral to the side of the stimulation. The second or late component R2 is a polysynaptic medullary bilateral response with onset latencies of 30-33 ms. (Figure 3). The last bilateral ultralate component is R3 (with onset latency around 84 ms) that probably follows the same central pathways as R2 (Kimura, 1989; Rossi et al., 1989; Ellrich and Hopf, 1996; Cruccu and Deuschl, 2000; Proietti Cecchini et al., 2003). Both R1 and R2 of BR responses are cutaneous and nociceptive in origin (Lindquist and Martensson, 1970; Shahani and Young, 1972a). The common afferent limb of the R1 and R2 reflex arcs is the ophthalmic nerve, usually the supraorbital branch, and the trigeminal sensory root. The common effererent limb is the facial nerve.

R3 was first described by Penders and Delwaide (1973), it was considered as a sporadic, irregular finding in the routine exploration of mostly young people. Studies by Rossi et al. (1989) and more recently by Ellrich and Hopf (1996) pointed out its systematic or nearly systematic appearance when an appropriate high electrical intensity is used. The R2 and, notably, R3 are considered nociceptive components of the BR (Esteban, 1999). However, very recently, Ellrich et al. (2001) showed that cutaneous A-β and A-δ, but not C fibers constitute the generators of the electrically evoked R3 component. As R2 and R3 components can also be evoked by acoustic stimuli (Ellrich et al., 1997), some authors consider the R3 component, which shows a marked tendency to habituate and tends to be systematically suppressed after an alerting prestimulus, to be part of a startle reflex (Rossi et al., 1993). The R3 response is bilateral and also obtainable from the infraorbital and mental nerve stimulation. It is

supposedly conducted mainly by nociceptive afferent fibers (Rossi et al., 1989). Upper cervical structures related to the spinal trigemial nucleus (subnucleus caudalis) have been claimed as a central part of the reflex arc (Rossi et al., 1989). However, the R3 has been found impaired in brainstem lesions, in parallel to the R2; thus, both components probably share the same central (or even peripheral) pathways (Ellrich and Hopf, 1996). Although now admittedly present in humans as part of the common BR, an equivalent R3 response has been exceptionally described in animals (Tamai et al., 1982). The nature of the R3 component of the blink reflex is still unclear and awaits further verifcation (Ellrich et al., 1999; 2001). Thus, it can not be assumed that the electrically evoked R3 is an adequate model to investigate nociceptive processing (Ellrich et al, 2001).

4.1.1. Neural circuits

The afferent impulses for the BR are conducted by medium-myelinated (A-β) fibers (Shahani, 1970; Cruccu et al., 1987) and relayed through a short oligosynaptic circuit (from 1 to 3 interneurons) to the facial motoneurons. The whole circuit lies in the pons. R1 is relayed by low threshold mechanoreceptive (LTM) neurones (Sessle et al., 1986; Ellrich and Treede, 1998; Ellrich et al., 1998). R1 is a `homotopical', strictly segmental response, best elicited by stimuli applied close to the eye, particularly at the supraorbital notch. In about 50% of normal subjects R1 can be elicited by stimulation of the maxillary division. It is seldom elicited by stimulation of the mandibular division (Kimura, 1983). In clinical practice, therefore, R1 is studied to investigate the afferents from the supraorbital region and the pons. It is diagnostically highly sensitive in extra-axial lesions, probably because it is supplied by a small number of afferents (Ongerboer de Visser and Cruccu, 1993; Kimura et al., 1994).

The R2 BR is mediated by low-threshold A-β afferents (Shahani, 1970; Cruccu et al., 1987). Nerve impulses responsible for R2 are conducted through the spinal tract in the dorsolateral region of the pons and medulla oblongata before they reach the most caudal area of the spinal trigeminal nucleus (Kimura and Lyon, 1972; Ongerboer de Visser and Kuypers, 1978). From there, impulses are further relayed through polysynaptic medullary pathways ascending both ipsilaterally and contralaterally to the stimulated side of the face, before connecting to the facial nuclei. Impulses cross the midline in the caudal

medullary region. The trigeminofacial connections ascend through the lateral tegmental field, lying medial to the spinal trigeminal nucleus (Aramideh et al., 1997). R1 and R2 share the same motoneurons (Dengler et al., 1982; Cruccu et al., 1991). Whereas R1 and R2 can be elicited by innocuous mechanical stimuli, only R2 but not R1 can also be elicited by selective activation of nociceptors using laser radiant heat stimuli suggesting an involvement of nociceptive neurones of the medullary dorsal horn in the mediation of R2 (Ellrich et al., 1997). The R2 was inhibited by remote painful heat stimuli and facilitated by homotopically applied painful heat demonstrating that R2 is mainly mediated via wide dynamic range (WDR) interneurones in the medullary dorsal horn. Schematic drawing of the blink reflex circuits and the nociceptive specific R2 of blink reflex in a single subject were shown in Figure 3 A, B respectively.

The brainstem interneurons that mediate reflex eyeblinking seem extremely sensitive to all sorts of sensory inputs. An R2-like reflex is elicited by sounds, flashes of light, radiant heat pulses (Ellrich et al., 1997), and electrical or mechanical stimuli delivered anywhere to the face or even to distant regions. Indeed, in response to startle, the orbicularis oculi muscle is far more excitable than any other muscle (Brown et al., 1991). Possibly because of the high number of synapses in the reflex circuit, R2 is relatively unstable, habituates rapidly to repetitive rhythmic stimulations, and is strongly modulated by suprasegmental influences, cortical and basal ganglia dysfunction, disorders of consciousness, and cognitive factors (Ongerboer de Visser and Cruccu, 1993; Kimura et al., 1994). Although R2 is less reliable than R1 in disclosing peripheral lesions, the simultaneous recording of the bilateral R2 allows differentiation between damage to the afferent (trigeminal) and efferent (facial) arcs of the reflex. Furthermore, R2 alone is usually abnormal in lateral medullary lesions (Cruccu and Deuschl, 2000).

The BR-R1 may be considered abnormal utilizing the following criteria (Kimura, 1989):

1. Unilateral loss of R1.

2. Unilateral delay by 1.4 ms or more.

3. Unilateral or bilateral delay above the age related mean + 2.5 SEM.

The criteria for considering the BR-R2 abnormal are (Kimura, 1989):

1. Latencies above 40 ms ipsilaterally and 41 ms contralaterally.

2. Side differences of 5 ms or more between the ipsilateral and contralateral responses obtained with unilateral stimulation.

3. Side differences of 7 ms or more between the R2 responses on a given side obtained with left and right side stimulation.

4.1.2. Methodological parameters

Recording and Stimulus parameters

Monopolar electrical square wave pulses of 0.5 ms duration and 0.6-1.5 mA (study I), 0.5-1.7 mA (in study II); 0.2 - 4.0 mA (in study IV) intensity were produced at an inter stimulus interval of 10-15 s by a constant current stimulator (Counterpoint MK2, Dantec, Denmark) controlled by a computerized system. Recording electrodes were placed infraorbitally (active) and at the outer canthus of the eye (indifferent), bilaterally, band width 1 Hz-1 kHz; sampling rate 2.5 kHz, sweep length 150 ms. A concentric electrode (CE) (stimulation area 22 mm^2) was placed on the left lower forehead close to the supraorbital foramen. Twelve blink reflex sweeps were evoked and recorded. The stimulus intensities to evoke individual sensory threshold (Is) and pin-prick pain sensation (Ip) were assessed. The current intensity was set at zero and increased at 0.1 mA increments and the subjects were asked to identify the first electric sensation, which was marked as individual sensory threshold and later to identify a sharper pin-prick like pain sensation with the increased current intensity, which was marked as pin-prick pain sensation. A fixed stimulation intensity of 1.5 times Ip was used to evoke the BR. The perceived pain intensity of the electrical stimulus (1.5 × Ip) was assessed by the subjects on a 0-10 cm VAS scale. How ever, since Ip is being established during the experiment, it is not possible to a priori state that this stimulus intensity preferentially activates A-δ fibers but not A-β and C-fibers (Kaube et al., 2000).

Stimulation electrode and Habituation

In the present studies, a special concentric planar stimulating electrode was used (Kaube et al., 2000). By virtue of its concentric design and small anode-cathode distance, a high current density is achieved that allows low current intensities to be used such that depolarisation is limited to the superficial layer of the

dermis containing mainly nociceptive fibers but does not reach the deeper, predominantly non-nociceptive fiber containing layers. The R2 response of this modified BR has been shown to be nociception specific (Kaube et al., 2000), although it can never be ruled out that non-nociceptive afferents are activated when an un-specific stimulus modality, such as electrical stimulation is used. Stimulation with the special concentric electrode and low current intensities in the territory of the supraorbital nerve is less invasive and aversive and therefore better tolerated (Kaube et al., 2000).

Repetitive stimulation often results in a progressive decrease in the elicited response. This pattern, termed habituation, is a prominent feature of the BR. The response reduction that results from exposure to repeated and constant stimuli is a ubiquitously expressed feature at the level of the CNS neural network. The rate and degree of the decrement are proportional to the number of stimulus presentations, to the stimulation frequency and to the stimulus intensity (Thomson and Spencer, 1966). To minimize reflex modulation by anticipatory behavior and prevent habituation, the subjects had no visual or auditory forewarning of the stimuli. All subjects were closing their eyes at the time of testing. The voluntary closing of eyes precludes or decreases the habituation of R2 (Esteban, 1999).

4.1.3. Modulation by experimental/clinical pain

R2 part of the BR component was inhibited during tonic jaw-muscle pain (Study I). In previous studies, it has been demonstrated that the electrically evoked BR could be suppressed by remote painful heat stimuli (Ellrich and Treede, 1998) and low frequency electrical peripheral stimulation (electro-acupuncture) (Boureau et al., 1991). The diffuse noxious inhibitory control system (DNIC), probably located in the medullary subnucleus reticularis dorsalis, was activated by remote painful heat, and suppressed the activity of WDR neurons in the medullary dorsal horn mediating the R2 blink reflex (Le Bars et al., 1992; Villanueva and Le Bars, 1995; Ellrich and Treede, 1998). General inhibitory mechanisms such as DNIC appear to suppress R2 during painful stimulation of the limbs (Pantaleo et al., 1988; Ellrich and Treede, 1998). In a previous study, it was reported that the R2 component of the blink reflex was strongly suppressed during and after painful conditioning stimulation (Drummond, 2003). The attenuation of R2

during and after painful conditioning stimulation of the ipsilateral temporalis muscle suggests that DNIC may also operate across different divisions of the trigeminal nerve. R2 suppression was greater for low- than high-intensity supraorbital nerve stimulation (Drummond 2003; Drummond 2004). This finding is consistent with the view that the major role of DNIC is to suppress background activity elicited by innocuous stimuli in WDR neurons (Villanueva and Le Bars, 1995). Painful infrared laser stimulation that selectively activates nociceptive A-δ fibers in the forehead evokes a bilateral BR at a latency corresponding to R2, but does not evoke an early ipsilateral R1 component (Ellrich et al., 1997). Thus, nociceptive A-δ fibers that project to the trigeminal nucleus caudalis apparently contribute to R2.

In study IV, we compared the R2 component of BR elicited by nociceptive electrical stimuli in CTTH patients and healthy controls. The results demonstrated significantly lower normalized RMS, AUC, average and duration for the left (ipsilatereal to stimulation) orbicularis oculi muscle in CTTH compared with control subjects. BR studies have suggested a primary dysfunction of the central nociceptive control system in patients suffering from TTH and migraine (Sand and Zwart, 1994; Aktekin et al., 2001). The trigemino-cervical response (short latency responses can be recorded in tonically active sternocleidomastoid muscle after stimulation of the infraorbital branch of the trigeminal nerve) was abnormal, in the size (reduced amplitude) or latency, in patients with CTTH compared with ETTH. This finding strongly suggests that only in the CTTH the underlying pathophysiology involves the trigeminal system (Nardone and Tezzon, 2003). Orthodromic conduction along the activated trigeminal fibers transmits information to central neurons in the trigeminal and other brainstem sensory nuclei that in turn relay the pain signal to higher cortical structures for registration and modulation of nociceptive information. It has been hypothesized that these central neurons may become sensitized as the headache attack progresses. Prolonged nociceptive stimuli from pericranial myofascial tissue may be of importance for the conversion of ETTH into CTTH (Nardone and Tezzon, 2003). It has been demonstrated that pericranial muscle tenderness is present early in the development of TTH, whilst the exteroceptive suppression of temporalis muscle activity emerges only later in the evolution of the disorder (Lipchik et al., 1996). The central neuroplastic changes may affect the regulation of peripheral mechanisms and

thereby lead to increased pericranial muscle activity or release of neurotransmitters in the myofascial tissues. By such mechanisms the central sensitization may be maintained even after the initial eliciting factors have been normalized, resulting in the conversion of ETTH into CTTH (Nardone and Tezzon, 2003). The main problem in CTTH seems to be the central sensitization at the level of the spinal dorsal horn/trigeminal nucleus because of prolonged nociceptive inputs and/or an impaired supraspinal modulation of incoming stimuli (Jensen, 1999).

Raudino (1990) reported lower R2 amplitude on the symptomatic side in cluster headache patients. Szmidt-Salkowska and Rowinska-Marcinska (2005) reported the presence of low amplitude of R2 responses in patients with amyotrophic lateral sclerosis (ALS) and suggested the loss of lower brainstem neurons connecting trigeminal and facial system, and probably also decreased facilitator effect of central nervous system on reticular formation in the brainstem.

4.1.4. Clinical implications

In clinical neurological practice, R1 is studied to investigate the afferents from the supraorbital region and the pons. R1 is a stable response and is uninfluenced by suprasegmental dysfunction, such as supratentorial lesions, disorders of consciousness and cognitive factors (Ongerboer de Visser and Cruccu, 1993). The R1 response is regarded as delayed if its latency exceeds 13.0 ms; a latency difference between the two sides exceeding 1.5 ms is also abnormal (Kimura et al. 1969). Possibly because it relays through a large number of synapses, R2 is a relatively unstable response and is strongly modulated by suprasegmental influences. Although R2 is less reliable than R1 in disclosing extra-axial lesions, it is crucial in diagnosing medullary lesions. The simultaneous recording of the bilateral R2 is useful in differentiating an afferent (trigeminal) and efferent (facial) pattern of lesion (Galeotti et al., 2006).

It has been reported that patients with headache may have various abnormalities in the orbicularis oculi reflexes. In patients with TTH, the latency of R1 increases significantly with the duration of headache; in patients with cervicogenic headache R1 latencies are shorter on the symptomatic side than on the non-symptomatic side (Sand and Zwart, 1994). The R2 blink reflex is delayed in migraine (Bank et al., 1992). In cluster headache the blink reflex has been found suppressed on the painful side (Raudino,

1990), whereas the corneal reflex has a lowered threshold (Sandrini et al., 1991). In patients with chronic paroxysmal hemicrania or hemicrania continua the blink reflex is normal; in chronic paroxysmal hemicrania the corneal reflex threshold, however, is significantly reduced bilaterally (Antonaci et al., 1994). Finally, blink reflex abnormalities have also been found in childhood headache (Puca and de Tommaso, 1999).

In a recent study, convergence of meningeal and facial input on the spinal trigeminal nucleus (STN), probably a condition for referred pain was demonstrated in healthy volunteers by facilitation of the R2 component of the BR by raising intracranial pressure (Ellrich et al., 1999). Acute and chronic pain in the trigeminal system presumably modulates the pattern of the brainstem reflexes in a facilitating or inhibiting manner.

BR abnormality may be caused by brainstem lesions in various neurological diseases (Kimura, 1989; Cruccu and Deuschl, 2000) and it may reflect possible brainstem dysfunction or excitability changes in headache (Sand and Zwart, 1994). The simultaneous recording of the bilateral R2 allows differentiation between damage to the afferent (trigeminal) and efferent (facial) arcs of the reflex (Cruccu and Deuschl, 2000). Several lines of evidence still suggest that R2 partly depends on nociceptive activation: R2 can be evoked by laser heat-pain stimuli (Romaniello et al., 2002), is inhibited by distant pain stimulation which activates the diffuse noxious inhibitory control system (DNIC) (Ellrich and Treede,1998; Drummond 2003, 2004), R2 abnormality is associated with facial pain in lateral medullary infarction (Fitzek et al., 2001), atypical odontalgia (Baad-Hansen et al., 2006) and R2 is partly suppressed by the opiate fentanyl, although to a lesser degree than the more pain-specific cornea reflex (Cruccu et al., 1991). R2 is probably mediated by medullar wide dynamic range (WDR) neurons (Ellrich and Treede, 1998) and the nociceptive contribution to R2 has recently been elucidated with a new concentric stimulation electrode (Kaube et al., 2000).

The strategic position of the neural structures of the BR, in an area involved in the gating of the various sensory-motor systems and the relative ease to its evaluation with common methodology used in

clinical neurophysiology, makes the BR an essential tool for the diagnosis and pathophysiological insight into an important number of human neurological disorders (Esteban, 1999).

4.2. Stretch reflex

Sudden stretches of the jaw-closing muscle can elicit short-latency excitatory response in the muscles, so-called jaw-jerk reflexes or stretch reflexes (see Figure 4). This was first described by Hoffman (1920) and has also been called "jaw jerk", "masseter reflex", "temporomasseter reflex", and "mandibular reflex" (Ongerboer de Visser, 1983). The stretch reflex in jaw-closing muscles is the trigeminal equivalent of the monosynaptic, myotatic spinal reflexes of limb muscles (Lund et al., 1983). One of the functions of the stretch reflex in the jaw-closing muscles is to maintain and restore the postural position of the mandible when it is perturbed during rapid head movements (Miles et al., 2003; Miles, 2007).

4.2.1. Anatomy and Physiology

The masseter reflex originates in the spindles of the masseter muscle (Hosokawa, 1961; Rokx et al., 1984). The afferent fibers follow the masticatory nerve as shown by horseradish peroxidase labeling (Nozaki et al., 1985; Chen et al., 1989). They probably cross over to the sensory root at the gasserian ganglion level via anastornoses (Gudmundsson et al., 1971), and run to the trigeminal mesencephalic tract and nucleus (TMesTN) (Fisher et al., 1976; Ferguson, 1978). In trigeminal neuralgia, the masseter reflex was abnormal postoperatively whenever the sensory impairment affected the mandibular division while the motor fibers were spared (Gudmundsson et al., 1971; Ongerboer de Visser, 1982; Saunders and Sachs, 1970). However, with gasserian ganglion coagulation or retrogasserian section, fibers of the motor or intermediate portions are frequently damaged (Saunders et al., 1971), which may result in a persistent masseter reflex abnormality despite recovery of masseter force (Cruccu et al., 1987).

The central loop, at its beginning within the midpons, is closely related to fibers mediating the BR-R1 component. This is apparent from combined changes of the two reflexes with lesions of the lateral midpontine tegmentum (Hopf et al., 1992). The loop then ascends with the trigeminal mesencephalic tract (Nomura and Mizuno, 1985) to the mesencephalic nucleus (Jaquin et al., 1983; Rokx et al., 1985), and

again descends to the trigeminal motor nucleus (TMotN) (Appenteng et al., 1978). The proprioceptive neurons are distributed along the trigeminal mesencephalic nucleus (Cody et al., 1972; Kubota et al., 1988). There are, however, morphologic indications that neurons belonging to spindles of individual muscles cluster within the nucleus (Capra et al., 1985; Nozaki et al., 1985; Chen et al., 1989). Electrophysiologically, stretch reflex involvement has been observed with rostra1 midbrain lesions (Ongerboer de Visser and Goor, 1976; Hopf and Gutmann, 1990;) but may be spared with midpontine lesion. Monosynaptic transmission takes place at the TMotN (Szentagothai, 1948; Appenteng et al., 1985; Nozaki et al., 1985). The stretch reflex efferents are the axons of the trigeminal motor portion and the masticatory nerve.

4.2.2. Neural circuits

Tapping of the chin by a hammer (Murray and Klineberg, 1984; Cruccu et al., 1992) or displacing the mandible by pressing the lower incisors downwards (Lamarre and Lund, 1975; Miles et al., 1993) or by pressing premolars and molars (Lobbezoo et al., 1996) during jaw-muscle contraction can usually evoke this reflex in normal subjects. The latency of the excitatory response has been described between 7 and 12 ms indicating a monosynaptic reflex (Lund et al., 1983). The amplitude of the short-latency response to stretch is highly variable and depends on the stimulus characteristics and background EMG activity (Murray and Klineberg, 1984).

In contrast to earlier studies that believed the jaw-closing muscle lacked a long-latency stretch reflex response, Poliakov and Miles (1994) showed that slower stretches of the jaw can elicit both short-latency, probably monosynaptic excitation, and long-latency, polysynaptic excitation, of stretch reflexes in the masseter surface EMG. From the recording of masseter motor units to stretch, Miles et al. (1995) also found that the majority of tonically active masseter motor units were excited in both short- and long-latency phases of the reflex. The short-latency response occurred 10-20 ms after the stimulus, and the long-latency response began at 35 ms and lasted until 100 ms (Miles et al., 1995; Miles, 1999). The long-latency component of the stretch reflex is believed to have greater functional significance in the co-

ordinated response to muscle stretch (Gielen et al., 1988). The neural circuit of the short-latency reflex has been described previously (Dubner et al., 1978; Ongerboer de Visser, 1983); however, the pathway of the long-latency response in masseter is still unclear (Miles et al., 1995). From studies on human hand muscles, it was suggested that the long-latency response is mediated via a polysynaptic, transcortical pathway (Matthews et al., 1990).

Muscle spindles are innervated by group I (large myelinated, 12-20 μm) and group II (small myelinated, 4-12 μm) afferent fibers (Dubner et al., 1978). The group I afferents innervating muscle spindles are called Ia afferents whereas those innervating tendon organs are referred to as Ib afferents. Group Ia afferents make monosynaptic connections to motoneurones whereas the main connection of group II and Ib afferents to motoneurones are polysynaptic (Gordon and Ghez, 1991). Afferent fibers from the jaw-muscle spindles probably pass through the mandibular division of the sensory root and trigeminal ganglion, entering the pons and ascending to their cell bodies in the trigeminal mesencephalic nucleus. The branches of these cells descend through the mesencephalic root to the trigeminal motor nucleus (Ongerboer de Visser, 1983). Muscle primary afferents also pass to other parts of the brain stem such as the supratrigeminal nucleus and connect with higher centre such as cerebellum and cerebral cortex (Dubner et al., 1978). Schematic drawing showing the reflex arc and the averaged reflex responses (20 sweeps for stretch) in the left temporalis evoked by fast jaw-stretches (1mm displacement, 10ms ramp time) in a single subject were shown in Figure 4 A, B respectively.

4.2.3. Methodological parameters

Stimulus parameters

Jaw-closing muscles of humans are richly endowed with muscle spindles, and the spindle afferents make excitatory connections to motoneurones of jaw-closing muscles (Hannam, 1972; Kubota and Masegi, 1977). Downward displacements of the mandible as small as 100 μm can elicit a large transient EMG response (Smith et al., 1985). Previously, stimuli were primarily applied with a hand held reflex hammer and were likely to result in a high degree of variability of magnitude and direction of force application

both within and between operators (Murray and Klineberg, 1984). It was also found that the stretch reflex, by tapping the chin, varies widely between subjects and between successive trials in the same individual (Cruccu et al., 1992). During isometric clenching, the amplitude of the monosynaptic jaw stretch reflex will be modulated by the displacement and speed of the stretch on the muscle spindles (Lobbezoo et al., 1993 a, b).

In order to evoke a reproducible stretch reflex, a standardised jaw-stretch machine was built based on the details described by Miles et al. (1993). In the present studies (I, II and III), the displacement of the lower jaw is moved by a standardized stretcher, by which the displacement and ramp time of the lower bar can be adjusted from 0.00-5.00 mm and 10-300 ms, respectively. Thus, the reflexes can be elicited more precisely with respect to distance, speed, and direction. In the present studies, the displacemant of 1 mm, and ramptime of 10ms were used.

The response may be considered abnormal utilizing one or more of the following criteria (Ferguson, 1978; Ongerboer de Visser, 1982; Sanders et al., 1985; Hopf et al., 1991; Fitzek et al., 2001; Koehler and Holker, 2004):

1. Unilateral or bilateral absence.

2. Side differences of 0.5 ms or more.

3. Unilateral or bilateral delay above the age related mean + 2.5 SEM.

Criteria indicating masseter reflex improvement are reappearance of the response, (or) shortening of the latency by > 0.8 ms.

Background activity

During isometric contractions, the stretch reflex response to a given stimulus is proportional to the pre-existing level of EMG activity, suggesting that it is proportional to the excitability of masseter motoneurones (Lund et al., 1983; Lobbezoo et al., 1993b; van der Bilt et al., 1997). This increase in reflex amplitude is related to a larger excitability of the alpha-motoneurones at a higher level of background muscle activity (Lund et al., 1983). To study the stretch reflex response of an individual muscle, the background EMG activity should be carefully controlled. To study different muscles in various

conditions, normalization of the EMG activity should be performed, which gives a comparable level of alpha-motoneurone excitability between different individuals, different muscles, and different pre-conditions. The normalization of the amplitude by its background EMG activity has the advantage that it standardises the pre-existing excitability of alpha-motoneurone across muscles, individuals, and conditions (Lobbezoo et al., 1996; Wang and Svensson, 2001). Under this controlled condition, the net effect of jaw-muscle pain on the stretch reflex could be investigated.

4.2.4. Modulation by experimental/clinical pain

The stretch reflex amplitude is affected not only by pre-motor adjustment from the output of the spindles to the alpha-motoneurone, but also by the amount of gamma drive to the muscle spindles, which adjusts the sensitivity of the spindle for different muscle lengths and various motor tasks (Gordon and Ghez, 1991). The velocity sensitivity of muscle spindles is increased by dynamic gamma-motoneurones firing and the length sensitivity mainly affected by static gamma- motoneurones (Lund et al., 1979; Larson et al., 1981). The stretch reflex sensitivity is also influenced by the properties of intrafusal muscle fibers and presynaptic mechanisms mediated by cutaneous, periodontal, mucosal, and temporomandibular joint receptors as well as higher centres (Capaday and Stein 1987, 1989).

Hypertonic saline infusion may predominantly activate nociceptive group III and IV afferents (Paintal, 1960; Kumazawa and Mizumura, 1977). Group III and IV afferents are believed to have excitatory action on gamma-motoneurones and thereby to increase the background firing of muscle spindles and to increase the sensitivity of the muscle spindle to stretch (Johansson and Sojka, 1991). Recent animal experiments have suggested that muscle pain can facilitate the gamma-system (Johansson and Sojka, 1991; Johansson et al., 1993). It was shown that muscle nociceptor activation leads to an increased firing by recording from hind limb gamma-afferents of the cat (Appelberg et al., 1983). Excitatory responses were also indicated by recording from triceps surae muscle spindle afferents in cats (Djüpsjöbacka et al., 1994, 1995). However, Mense and Skeppar (1991) reported a strong inhibition of extensor gamma-motoneurones following induction of muscle inflammation by carrageenan in cats. In the

trigeminal system, jaw-closing muscles are the physiological extensor because they maintain the posture of the mandible (Lund et al., 1991). They argued that non-nociceptive group III and IV afferents (low-threshold mechanosensitive) could be activated by pain-producing substances, which had stronger excitatory effects on the gamma-motoneurones. It was recently reported that intramuscular injections of hypertonic saline caused reflex activation of gamma-motoneurones innervating muscle spindles in homo- and heteronymous muscles. In most cases, the muscle spindle increased its static sensitivity (Hellström et al., 1999).

In human research, experimental muscle pain has been used to investigate the stretch reflex in the soleus and tibialis muscles (Matre et al., 1998), and in masseter mascle (Wang et al., 2000) in which the reflex response was facilitated significantly during pain. Since the stretch reflex was evoked by a fast stretch in that study, it was suggested that the increased reflex response was caused by an increased dynamic gamma-motor firing rather than static gamma-motor firing.

In study I, the infusion of hypertonic saline was employed to investigate the modulation of tonic jaw-muscle pain on the short-latency stretch reflex. The normalized peak-to-peak amplitude demonstrated facilitation in the presence of a painful input. Recently, human studies have provided evidence of facilitation of the early component of the stretch reflex during experimental muscle pain (Matre et al., 1998; Wang et al., 2000; 2001; 2002; 2004; Svensson et al., 2000; 2001). The fusimotor system was suggested to be involved in the increased muscle-spindle sensitivity as a result of muscle pain.

In study III, in our patients with strictly matched and controlled groups, the normalized peak-to-peak amplitude of the CTTH patients was higher compared to the control subjects in right and left temporalis muscles. Schoenen et al. (1991a) found that the EMG levels of pericranial muscles (temporalis, frontalis and trapezius muscles) were increased in CTTH patients compared to healthy volunteers. The finding that EMG level and pain sensitivity may vary independently at the same site, also suggests that pain is not directly linked to muscle contraction and concluded that EMG levels and pain thresholds would not necessarily vary simultaneously, but rather be peripheral "markers", which, in spite of being produced by a common central dysfunction, are expressed to varying degrees at the different

pericranial sites. Also, increased EMG values in the frontal, temporal or neck musculature in patients with TTH (Vaughn et al., 1977; Acosta et al., 1978¸ Andrasik and Holroyd, 1980; Hursey et al., 1985; Gannon et al., 1987; Gallai et al., 1989; Murphy et al., 1990; Hatch et al., 1992; Pritchard, 1995; Wittrock, 1997; Bansevicius et al., 1999; Harnphadungkit et al., 2001; Ong et al., 2003; Oksanen et al., 2007a,b) and in subjects with different orofacial conditions (Bodere et al., 2005) have been reported

A clinical consequence of the increased jaw-stretch reflex in the presence of muscle pain may be a protection of the painful (damaged) tissues due to reflex-mediated muscle stiffness. This results in a reduced mobility, thereby preventing further tissue damage (Matre and Svensson, 2004).

4.2.5. Clinical implications

Contradictory results emerge from jaw-jerk studies in TMD. Few have reported an increased side-asymmetry of the amplitude or latency (Murray and Klineberg, 1984; Buchner et al., 1989; Cruccu et al., 1997). Hence, testing of the jaw-jerk currently have uncertain diagnostic value and may yield false-positive diagnoses. In clinical practice the finding of a jaw-jerk asymmetry in a given patient by no means leads to a diagnosis of TMD. Jaw-jerk amplitudes and side asymmetries vary widely in normal subjects (Molin, 1972; Cruccu and Ongerboer de Visser, 1999; Koehler and Holker, 2004). Yet some TMD patients may even show a unilaterally absent jaw jerk. A useful diagnostic point to remember is that in a patient with no other trigeminal abnormality, unilaterally absent jaws jerk can be caused by a functional impairment. It does not necessarily imply damage to the nerve fibers or brainstem, and should warrant stomatognathic investigations before any MRI study.

The literature concerning electrical activity of pericranial muscles in primary headache disorders is inconclusive. No significant differences in EMG activity at rest were found between patients with TTH on the one hand and healthy individuals on the other (Philips, 1977; Boxtel van and Roozefeld van der Ven, 1978; Martin and Mathews, 1978; Drummond, 1987; Jensen et al., 1988). In contrast, increased EMG values in the frontal, temporal or neck musculature in patients with TTH (Vaughn et al. 1977; Acosta et al., 1978¸ Andrasik and Holroyd, 1980; Hursey et al., 1985; Gannon et al., 1987; Gallai et al.,

1989; Murphy et al., 1990; Hatch et al., 1992; Pritchard et al., 1995; Wittrock, 1997; Bansevicius et al., 1999; Harnphadungkit et al., 2001; Ong et al., 2003; Oksanen et al., 2007a,b) and in subjects with different orofacial conditions (Bodere et al., 2005) have been reported. In patients with symptomatic Chiari II malformation, significantly more abnormal masseter reflex recordings were documented compared with patients without brainstem dysfunction (Koehler et al., 2000, 2001).

The stretch reflex plays an essential role in motor control of muscular performance. Peripheral irritation of the trigeminal nerve due to entrapment of the motor branches in the infra-temporal fossa may cause involuntary movement and a disappearance of the masseteric jaw-jerk reflex (Schoenen et al., 1991a; Hatch et al., 1992; Jensen et al., 1994; Lipchik et al., 1996; Gross et al., 1999). The early detection and proper referral of these abnormal signs are possible when dentists record jaw reflex activity.

Nevertheless, monitoring jaw stretch reflex parameters makes it possible to look into the excitability of the trigeminal motoneurone pool. The level of this excitability may be modified by inputs from the orofacial area during function and dysfunction (Murray and Klineberg, 1984). Disorder of the peripheral trigeminal nerve causes impairment of the jaw-stretch reflexes; if the sensory root of the mandibular division, the respective parts of the trigeminal ganglion or the masticatory nerve are involved. Thus, electromyographic investigations of stretch reflexes in patients with different neurological disorders can provide important information about the pathophysiological mechanisms in both the spinal system (Toft et al., 1989) and the trigeminal system (De Laat, 1987a, b). EMG is the only reliable method available for the objective recording of a patient's muscular function. Because dysfunctional muscle activity may be the cause and/or the result of other factors of investigatory interest, the application of electromyography is appropriate in diagnosis and treatment (Widmalm et al., 2007).

The jaw reflexes, being trigemino-trigeminal reflexes, examine the sensory and motor trigeminal fibers, unlike the BR; they are not influenced by facial-nerve function and provide information on the maxillary and mandibular divisions. The jaw-jerk is unaffected by suprasegmental lesions. It is chiefly useful for disclosing unilateral lesions. It is most sensitive to focal-extra axial compression, for example from vascular anamolies or tumors in the posterior fossa, probably because it is supplied by a small

number of afferents and pressure damages the largest fibers first (Ongerboer de Visser and Cruccu, 1993). The jaw jerk also provides information on the rostral brain-stem. The jaw-jerk is also useful for differentiating axonopathies from neuropathies; in neuropathy it is the only reflex spared, possibly because the cell body of the primary afferents lies within the CNS rather than within the ganglion (Valls-Sole et al., 1990). Although an asymmetrical jaw jerk is a frequent finding in patients with temporo-mandibular disorders, it is by no means diagnostic (Cruccu et al., 1997).

4.3. Influence of gender and age on brainstem reflexes

TTH, which is often associated with a feeling of muscle strain or spasm in the neck/shoulder or temporalis muscles and are characterized by dull, aching, nonthrobbing pain that can be distributed unilaterally or bilaterally and referred to temporal, occipital, parietal, or frontal regions of the head occur at a 50% higher rate in women (Holroyd and Lipchik, 2000) .

Gender variation

In a cross-sectional population study, the increase in the prevalence of TTH between 1989 and 2001 was associated with an increase in sensitivity to pericranial pain, particularly in women (Anttila et al., 2002).

Chronic orofacial pain affects approximately 10% of adults and up to 50% of the elderly (Madland et al., 2001). There is evidence that sex differences in masticatory muscle pain and tenderness emerge as early as 19 years of age (Krogstad et al., 1992). Women of reproductive age, with a concentration of women in their 40s, seek treatment for orofacial pain more frequently compared to men by a 2:1 ratio (Dao and LeResche, 2000; Fillingim, 2000). Moreover, a greater proportion of women seek treatment for other pain conditions, such as TTH, migraine, fibromyalgia, autoimmune rheumatic disorders, chronic fatigue, orthopedic problems and irritable bowel syndrome (Fillingim, 2000; Rollman and Lautenbacher, 2001; Buckwalter and Lappin, 2003; LeResche et al., 2005; 2007).

There is a much higher prevalence of temporomandibular disorders (TMD) (Warren and Fried, 2001) and TTH (Marcus, 2001) among women of reproductive age, which suggests that sex-related

factors may play a role in the pathophysiology of these conditions. The importance of a diminished muscle mass to the age-related decline in muscle strength could be related to the sex of the individual (Young et al., 1984). Various factors may underlie this greater sensitivity, including cultural influences, social role expectations, psychological distress, reproductive hormones, as well as nociceptive integration in the central nervous system (Wise et al., 2002).

Animal research

A comprehensive meta-analysis by Mogil et al., (2000) found that female rats were more sensitive to electrical shock and chemically-induced inflammatory nociception (abdominal constriction, formalin tests) in most studies; however results using thermal assays were equivocal. Of the 23 studies reviewed, 17 reported no significant sex differences; in the remainder, females exhibited more sensitivity to hot plate test than did male rats. With regard to radiant heat and hot water immersion, most studies reported no sex differences, with 8 reporting increased sensitivity in male rats and 2 reporting increased sensitivity in female mice.

Recently it was shown that the glutamate-evoked masseter muscle afferent fiber activity was significantly greater in female rats than in male rats (Cairns et al., 2001). The value of testing female rodents at different stages of the estrous cycle is debatable. In rodents, an influence of estrous cycle stage is not necessarily indicated by larger observed variance (Mogil and Chanda, 2005); therefore, large samples are typically required to adequately power studies examining females in specific stages of the estrous cycle (Greenspan et al., 2007).

As noted in reviews, sex differences in acute pain models have been observed, but are often protocol-, species-, and strain-dependent (Mogil et al., 2000). Very few studies have investigated sex differences in chronic pain models such as nerve injury and persistent inflammation. This dearth of information makes it premature to suggest which protocols or animal species are most relevant to any particular human pain condition (Greenspan et al., 2007). One valuable approach involves parallel testing in the animal and human laboratory (e.g., Cairns et al., 2001a, b).

Two issues of terminology are important. First, the term ''sex'' refers to biologically based differences, while the term ''gender'' refers to socially based phenomena. Although biological sex exerts a major influence on one's gender identity, sex and gender are not equivalent, and the terms are not interchangeable. If subjects are categorized by anatomical features (chromosomes, reproductive organs), it is appropriate to describe the study as one of ''sex differences''. In contrast, if additional measures of masculinity/femininity or gender identity are used to describe subjects, then the term ''gender differences'' is appropriate (Hughes, 2003). Gender is often conceptualized as a dichotomous variable, yet individuals differ in the degree to which they conform to the norms for masculinity and femininity in their particular culture. Thus, gender is most accurately regarded as a continuous variable (ranging from exclusively feminine to exclusively masculine), with most individuals falling somewhere along the continuum of maleness to femaleness on a range of characteristics. Even within the same society, gender role expectations may differ for generations born at different times, and within an age-cohort, gender role expectations may change as a function of age. Finally, in any statistical analysis of human subjects, the dichotomous variable sex (male vs. female) is confounded with the social construct of gender. That is, in human studies in which the dependent measure is pain report, group differences are likely to be attributable to both sex and gender. Therefore, both constructs should be examined when possible in order to understand their relative contribution to differences in pain between men and women (Greenspan et al., 2007).

Although direct evidence of sex related differences in the properties of dural afferent fibers relevant to the development of headache has yet to be provided, there is evidence for such differences in afferent fibers that innervate other craniofacial tissues associated with sex-related differences in pain, such as the masseter muscle and TMJ. One such difference that has recently come to light is that the expression of calcitonin gene related peptide (CGRP), but not substance P or somatostatin, by trigeminal ganglion neurons that innervate the masseter muscle, is significantly higher in males than in females (Ambalavanar et al., 2003). The exact role of CGRP in the development and maintenance of vascular headaches remains a topic of debate; however, while evidence to support an association between the

release of CGRP by dural afferent fibers and the development of headache pain exists (O'Connor and van der Kooy, 1988; Juhasz et al., 2003; Goadsby, 2005), there is no evidence for a direct excitatory or sensitizing effect of CGRP on dural afferent fibers (Levy et al., 2005; Strassman and Levy, 2006).

Another sex-related difference in trigeminal afferent fiber response is seen when glutamate is used to excite Aδ and C fibers that innervate both the TMJ and masseter muscles. In this case, glutamate-evoked afferent discharge is significantly greater in females than in males (Cairns et al., 2001a). Glutamate-evoked afferent discharge is mediated through activation of peripheral N-methyl-D-aspartate (NMDA) receptors in these tissues (Cairns et al., 2003a; 2005) and recent evidence suggests that sex-related differences in afferent response may be mediated through alterations in peripheral NMDA receptor function and/or expression (Cairns et al., 2003a). A direct role for peripheral NMDA receptor mechanisms in the development of primary headaches has yet to be identified; however, cortical spreading depression, a central phenomenon thought to be associated with aura in migraine, appears to increase meningeal blood flow in part through peripheral NMDA receptor activation (Bolay and Moskowitz, 2005).

There is, however, again evidence for sex-related differences in the response properties of other trigeminal sensory neurons, such as those that respond to noxious stimulation of the TMJ. Inflammatory TMJ injury induces higher levels of the immediate early gene c-fos, an indicator of neuronal activation, in neurons in the caudal most part of the trigeminal sensory nucleus in female rats in proestrus (the estrous cycle stage associated with the highest levels of serumestrogen) than in male rats (Bereiter, 2001). Trigeminal sensory neurons that respond to noxious stimulation of the TMJ appear to have similar characteristics as those described above for dural activated trigeminal neurons, in particular a high degree of convergent cutaneous input from facial cutaneous receptive fields (Takeshita et al., 2001; Okamoto et al., 2003, 2005). The area of facial cutaneous receptive fields for TMJ-responsive neurons from proestrous females has been found to be greater than males, although this likely reflects previous findings that the receptive field area of cutaneous afferent fibers normally varies significantly over the estrous cycle (Bereiter and Barker, 1980). In addition, 65% of nociceptive trigeminal neurons recorded in

proestrous females respond to injection of glutamate into the TMJ, whereas only 27% of neurons recorded in males respond to this stimulus (Takeshita et al., 2001, Okamoto et al., 2003). These findings are consistent with the previously mentioned differences in glutamate-evoked TMJ afferent discharge and suggest that both peripheral and central mechanisms contribute to sex-related differences in response to noxious stimulation of certain craniofacial tissues.

In addition to altered sensory input there is also a well-described sex-related difference in response to opiate-induced analgesia, with males of many rat strains deriving significantly greater analgesia from morphine and other mu opioid receptor agonists than females (Mogil et al., 2000; Craft, 2003). In the craniofacial region, sex-related differences in the effectiveness of morphine to suppress noxious input from the TMJ have been reported and appear to result from both peripheral and central mechanisms. Morphine has been shown to cause a greater dose-related reduction in trigeminal sensory neuron activity after TMJ injury in neurons in males than in proestrous females (Okamoto et al., 2005). However, while it has been suggested that these effects of morphine may be limited to the central nervous system, it has been shown that local injection of morphine into the TMJ also suppressed nociceptive jaw muscle reflex responses in a dosedependent and naloxone-reversible manner in males to a greater extent than in females, which suggests that there are also alterations in the activity of peripheral mu opioid receptors (Cai et al., 2001). More recent work has found that activation of peripheral kappa opioid receptors results in a greater analgesia in females than in males after inflammatory injury of the TMJ (Clemente et al., 2004). These findings suggest that both the processing of ascending craniofacial nociceptive information and its modulation by opioidergic receptor mechanisms appear to be dependent on biological sex (Cairns, 2007).

Human research

Consistent with rodent research, there is considerable variability in the magnitude and direction of sex differences. A meta-analysis conducted by Riley and colleagues (1998) found that women generally show lower pain thresholds and tolerances than do men to a variety of noxious laboratory stimuli. Pressure pain

and electrical stimulation demonstrated the largest effects for the 22 studies reviewed, whereas thermal pain yielded inconsistent results.

Several studies have examined the laboratory models of orofacial pain. Karibe and colleagues (2003) noted that healthy female controls experienced more masticatory muscle pain during 6 minutes of gum chewing than men did, and had more pain (compared with pretest measures) an hour after chewing. Similarly Plesh and colleagues (1998) assessed jaw pain tolerance in healthy subjects during and after bite force tasks. Both sexes had increased pain during bite tasks; however, postclenching pain lasted longer for women. Notably women reported significantly more baseline pain upon jaw movement on the second day of testing, whereas men did not report an increase in baseline pain 24 hours later. The investigators ruled out muscular microtrauma because there were no significant differences in postexertion pressure pain tolerance or threshold. Instead, they suggested that neuronal hypersensitivity might play a role in postexertion hyperalgesia.

Injection of algesic substances into the facial and cervical muscles also has been used as an experimental model that mimics head and neck pain of muscular origin (Stohler and Kowalski, 1999). Injections of hypertonic saline or glutamate solutions into the trapezius muscle produced significantly more pain among women relative to men (Ge et al., 2004; 2005). Higher pain scores in female subjects compared to male subjects were reported by the glutamate-evoked experimental jaw-muscle pain (Cairns et al., 2001a, 2003a, b; Svensson et al., 2003a; 2003b).

Paulson et al (1998) recently observed sex differences in the patterns of cerebral activation during exposure to noxious stimulation. Using positron emission tomography, they demonstrated that women's report of greater pain during exposure to a 50^0 C thermode was accompanied by increased activation of the contralateral thalamus and anterior insula. These findings reflect differential central processing of nociceptive input in men and women, and suggest the possibility of differential activation of brain structures involved in descending modulation of spinal nociceptive transmission.

Intramuscular injections of hypertonic saline (Ge et al., 2004) or glutamate (Cairns et al., 2001a, 2003a, b; Svensson et al., 2003a; Ge et al., 2005) have been shown to evoke higher pain intensities in

females than in males. However, this is not consistent with recent study where no sex difference was reported after muscle pain induced by hypertonic saline injections (Ge et al., 2006). The pain thresholds to pressure stimulation are higher in males than in females (Chesterton et al., 2003; Maquet et al., 2004; Fillingim et al., 2004; Ge et al., 2004, 2005;), with a cyclic variation in thresholds depending on the menstrual cycle in women (Riley et al., 1999; Isselee et al., 2001). Exceptions with no demonstrable sex differences in PPT also exist (Jensen et al., 1986; Lee et al., 1994; Isselee et al., 1997, 1998; Svensson et al., 2003a; Ge et al., 2005; Nie et al., 2005), probably due to lack of statistical power.

However, in a meta-analytic review it was found that pressure stimulation evoked the largest gender difference compared to cutaneous modalities such as thermal or electrical skin stimulation (Riley et al., 1998). In general, it seems likely that nociceptive stimulation of deep tissue evokes a modest increased response in females compared to males, which is in line with the findings of sex-related differences in cutaneous pain sensitivity (Riley et al., 1998). Whether this is based on differences in transduction mechanisms, nociceptor density, central mechanisms, or hormonal levels is not clear. Cairns et al., (2001b) found that the response of afferent nociceptive nerve fibres after intramuscular injections of glutamate were greater in female than in male rats, indicating a peripheral mechanism. Central mechanisms, exemplified by facilitated temporal summation of cutaneous pain in females compared to males, have been reported (Fillingim et al., 1998; Sarlani and Greenspan et al., 2002) although not shown for pressure stimulation of muscle tissue (Nie et al., 2005).

Injection of certain noxious chemicals (glutamate, capsaicin, serotonin) either under the skin of the face or into the masseter muscle evokes pain which is reported as more intense by women than men (Cairns et al., 2001a, b; Svensson et al., 2003a; Gazerani et al., 2005, 2006). In healthy women and those suffering from TMDs there is some evidence that masseter muscle PPTs, which reflect sensitivity to noxious mechanical stimuli, are lowest during the perimenstrual phase when estrogen levels are at their lowest (Isselee et al., 2002; Sherman et al., 2005). Again, these results appear consistent with current animal data that indicate the mechanical threshold of masseter afferent fibers is positively correlated to estrogen levels (Mann et al., 2006). These findings also appear to support the suggestion that

physiological mechanisms account, at least in part, for the increased prevalence of conditions such as TMD and migraine headache in women and the reported increase in TMD-related pains and migraine headache perimenstrually (LeResche et al., 1997, 2003; Martin and Behbehani, 2006 a, b).

The stimulus intensities to evoke the three sensations; sensory thresholds (Is), pin-prick pain sensation (Ip) and electrical pain sensation (I), were lower in females than in males (Is, Ip and I sensations in study I; Is and Ip in study II; Is in Study IV) and the VAS scores for the electrical pain sensation were significantly higher in females compared to males in pain and post-pain conditions (study I). This is in agreement with the previous concept that women seem to show lower pain thresholds, a greater ability to discriminate painful sensations, higher pain ratings, and a lower tolerance for pain (Dao and LeResche, 2000; Svensson et al., 2003a).

However, study I and IV did not suggest gender-related differences in the effect of experimental/clinical muscle pain on jaw-stretch and BR. In study II, females have significantly higher normalized peak-to-peak amplitudes compared to males in the left temporalis. This finding is consistent with some previous studies, which have reported that the peak-to-peak amplitude of masseter and temporalis stretch reflexes is significantly larger in women than in men (Widmalm et al., 1979; Kossioni and Karkazis, 1994a; Cairns et al., 2003b). Thus, it is possible that there are sex-related differences that explain the present findings, such as differences in the number or sensitivity of spindle afferent fibers, the excitability of premotor interneurons, and/or the descending influences that can modulate the excitability of premotor interneurons and motoneuroons.

Significantly higher normalized peak-to-peak amplitudes for females compared to males in the right and left anterior temporalis muscles were found in study III, corresponding with the few other studies which have analyzed the sex variation in pericranial muscles (van Selms et al., 2005) as well as in extracephalic muscles (Passchier et al., 1984). Similarly, increased EMG amplitudes in the temporal and frontal muscles of subjects with CTTH in a clinical study of 32 female patients were found by Schoenen et al. (1991a).

In study III, PPTs from the left and right masseter, left anterior temporalis and splenius capitis muscles were lower in females than in males. This is consistent with the previous results (Buchanan and Midgley, 1987; Fischer, 1987; Ohrbach and Gale, 1989b; Bendtsen et al. 1995;; Lipchik et al. 1996; Jensen, 1999;   Farella et al., 2000; Buchgreitz et al., 2006; Schmidt-Hansen et al., 2007) indicating that the myofascial pain sensitivity is increased in females compared to males.

Age variations

In study II, the pre-stimulus EMG activity and the normalized peak-to-peak amplitude of older subjects were lower compared to the younger subjects. This indicates that the total number of motor units recruited for a specific reflex response is decreased with aging. The number of α-motoneurons has been shown gradually to decrease with age (Brown, 1972; Campbell et al., 1973). Similar results of decreased amplitude have been reported by Jensen et al. (1994) and Kossioni and Karkazis (1994a; 1998). The authors concluded that the age-related decrement in the monosynaptic reflex response is indicative of a generalized decline in the motor performance of the stomatognathic system and the decreased ability of the older patient to easily adapt to any dramatic changes in the sensory input. Ongerboer de Visser and Goor (1974) observed absence of the jaw-jerk reflex in five out of nine subjects over 70 years of age.

Lin and Sabbahi (1998) reported that the absolute amplitude of the short latency EMG (recorded from flexor carpi radialis) reflex response was significantly lower in the older group. If the data were normalized and expressed in percentage of the maximal voluntary EMG activity, however this group difference was not significant and the authors suggested based on these results that the number of motor units recruited during the stretch reflex activity declined with aging although the percentage of motor units recruited was not affected by aging and concluded that the central regulating mechanisms of the spinal motoneuron excitability are not compromised by aging.

The decline of efficiency of motor functions during ageing is due to reduction of number of muscle fibers as a result of random degeneration of some motor end-plates. The mechanism especially responsible for the disorder of the neuro-muscular system in old age is thought to be the impairment of intercellular neurotrophic relations (Gutmann et al., 1968). The effects of ageing and dental state on the

cross-sectional area and density of two jaw muscles, the masseter and medial pterygoid, were investigated by Newton et al. (1993) and reported that the cross-sectional area of both muscles showed a significant reduction with age; values for female subjects being found in the lower range of the distribution, and concluded that the results are consistent with a general age related change of muscle tissue in the body as a whole and may specifically indicate a reduction in the masticatory forces which can be or are being utilised by ageing patients. Much of the age associated muscle atrophy and declining strength may be explained by motor unit remodelling which appears to occur by selective denervation of muscle fibers with reinnervation by axonal sprouting from an adjacent innervated unit (Brooks and Faulkner, 1994). However, Kirkeby and Garbarsch (2000) reported that aging affects different human muscles in various ways. For example, type I fibers in the masseter became more circular while in the vastus lateralis muscle they decreased significantly in size. The type II fibers in the vastus became very small and deviated significantly from circularity whereas the type II fibers in the masseter only exhibited a decrease in the size of the fibers.

The results in study II showed a significantly lower RMS values for right and left orbicularis oculi muscle in the older compared with younger subjects and lower values in AUC and average for left orbicularis oculi muscle. Sun et al. (1997) reported that the mean amplitude and peak velocity of blinks decreased with age for spontaneous blinks and, to a lesser extent, for voluntary blinks. Some of this decline however, be attributed to a peripheral phenomenon, narrowed palpebral fissure width.

In humans, trigemino-facial blink reflex duration, latency and excitability increase after the age of 60 (Peshori et al., 2001). In study II, the duration of the BR was longer in older than the younger subjects. Even though the absolute latency is larger in older subjects, there was no significant difference between the groups. Because dopamine modulates trigemino-facial blink reflex duration (Basso et al., 1996), the normal age- related loss of substantia nigra dopamine neurons (McGeer et al. 1977; Gibb et al., 1990; Fearnley and Lees 1991; Itoh et al., 1996; Cruz-Sanhez et al., 1997) might explain the age-related increase in trigemino-facial blink duration. Rodent models of Parkinson's disease produced by dopamine depletion exhibit increased blink duration relative to control animals (Basso et al., 1996). Transiently

increasing dopamine levels decrease the duration of trigemino-facial blink reflex in rodents (Evinger et al., 1993). Similarly, increasing basal ganglia output, functionally equivalent to increasing dopamine levels, decreases blink duration in both rodents (Basso et al., 1996) and primates (Gnadt et al., 1997). Thus the normal age-related loss of dopamine-containing neurons can account for the age-related increase in blink duration.

Age-related change in the sensitivity to deep tissue pain is relatively unexplored compared to gender differences. A large population-based study showed increased PPT in older people, most pronounced in female subjects (Jensen et al., 1992). Another study showed decreased PPT in older males compared to young males but no age-related differences in females; in other words there was a gender difference in the young subjects but not in the older subjects (Pickering et al., 2002). Age- and gender-related differences in psychomotor parameters, such as reaction time (Pickering et al., 2002), need to be accounted for when comparing PPT across age and gender. Increased sensitivity to ischaemic muscle contractions were reported in older compared to young subjects; PPTs showed similar tendencies although non-significant (Edwards and Fillingim, 2001). The literature on age-related changes on cutaneous pain thresholds is equivocal; the main interpretation has been that older people are marginally insensitive to pain (Gibson and Farrell, 2004). However, this interpretation is likely only for the superficial and phasic nature of the nociceptive stimulus, but for tonic and deep tissue pain older people are probably more pain sensitive (Gibson and Farrell, 2004).

Sex- and age-related differences in muscle pain thresholds are modest and require a large statistical power to be elucidated. Lower muscle pain thresholds in young females compared to males is likely and for the older males the pain thresholds probably decrease compared to young males, eliminating the sex-related differences seen in the young subjects.

As seen in a recent MRI study (Fernandez-de-las-Penas et al., 2007a), the relative crosssectional area (rCSA) of the minor and major rectus capitis posterior muscles (RCPmin and RCPmaj) was reduced in patients with CTTH, whereas the rCSA of the semispinalis and splenius capitis muscles was normal in the age range of 24-56 years. The reduction in rCSA was negatively associated with the intensity,

duration, and frequency of headache. Whether the atrophy of deep neck muscles that is seen in patients with CTTH is primary or secondary to the headache remains to be determined. One possible explanation could be that muscles with a greater concentration of muscle spindles, such as the RCPmin and RCPmaj, might be more sensitive to muscle atrophy than muscles with lesser concentration of muscle spindles, i.e. semispinalis capitis and splenius capitis (Fernandez-de-las-Penas et al., 2007a).

Whether it represents a primary or secondary phenomenon, muscle atrophy could act as a perpetuating factor for chronic pain. McPartland et al. (1997) have reported that the atrophy of RCPmin and RCPmaj muscles is related to a comparative decrease in standing balance in patients with neck pain. Peck et al. (1984) found that the suboccipital muscles had greater concentration of muscle spindles (36 spindles/g for RCPmin; 30.5 spindles/g for RCPmaj) in comparison with other cervical extensor muscles (e.g. 7.6 spindles/g in the splenius capitis muscle). Such high density of muscle spindles in both rectus capitis posterior muscles suggests that they act as 'proprioceptive monitors' of the upper cervical spine. Proprioceptive signals stemming from the muscles conveyed by large-diameter Aβ-fibres may serve as a 'gate' that blocks nociceptive (C-fibre) transmission into the spinal cord and higher centres of the central nervous system (Wall, 2006). Muscle atrophy could account for a reduction of proprioceptive output from these muscles, and such reduced proprioceptive input may conceivably facilitate the transmission of impulses from wide dynamic range nociceptors (Wall, 2006; Bendtsen, 2000). In addition, a dysfunction of descending inhibitory pathways has been recently found in CTTH patients (Pielsticker et al., 2005). Both peripheral and central mechanisms, i.e. facilitation of impulses from peripheral nociceptors, and dysfunction of central inhibitory pathways, are probably involved in the maintenance of pain.

Female gender has been identified as an important risk factor for both migraine and TTH in the Danish epidemiological follow-up study (Lyngberg et al., 2005). The question is, what implications the gender differences might have on headache research. Firstly, it underlines the importance of controlling for age and gender, or using age- and gender-matched control groups (like we did in our studies) in clinical studies. Secondly, we must continue to research in gender differences in order to improve our understanding of the pathophysiology and treatment of pain disorders.

Considerable clinical and experimental evidence demonstrates gender and sex differences in the epidemiology, etiology, and manifestation of craniofacial pain. Experimental studies in humans consistently indicate greater pain sensitivity among women; although the magnitude of the sex difference varies across studies. Some evidence suggests sex differences in responses to pharmacologic and nonpharmacologic treatments for pain; however, conflicting findings abound. The mechanisms that underlie these sex differences in clinical and experimental pain responses are not understood fully; however, several biopsychosocial factors are believed to contribute, including gonadal hormones, genetics, cognitive/affective processes, and stereotypic gender roles.

5. SUMMARY AND CONCLUSIONS

TTH is extremely prevalent and represents a major health problem (Rasmussen et al., 1991, 1992; Bendtsen and Jensen, 2006; Stovner et al., 2007). Nevertheless its pathogenic mechanisms are largely unknown. Nociceptive processes in craniofacial muscles are believed to play a role in development and maintenance of TTH (Jensen and Olesen, 1996; Jensen et al., 1999; Mense and Simons, 2001). In recent years, however, central mechanisms (sensitization of neurons in the central nervous system) have been favoured (Schoenen et al., 1991a, b, c; Bendtsen et al., 1996a, 2000; Jensen, 2003; Ashina et al., 1999a, b, 2004, 2006; Leistad et al., 2006; Fumal and Schoenen, 2008). Substantial evidence for any of the suggested pathogenetic mechanisms is not yet available. Also review of the literature demonstrates a scarcity of published data on the impact of age and gender on the various components of brainstem reflexes. Brainstem reflexes help to indicate the topographical level of a putative brainstem lesion and/or the functional derangement of a brain structure. They may also serve as a valuable tool to establish the diagnostic, prognostic and evolution criteria in certain neurological disorders (Ellrich, 2000). The aim of the present studies was to investigate how the brainstem reflexes are modulated during experimental and clinical craniofacial pain and by age and gender.

In study I, surface EMG recordings examined the modulation of jaw-stretch and R2 BR by experimental posterior temporalis muscle pain in healthy volunteers. Short-latency stretch reflex

responses were evoked in the masseter and temporalis muscles by fast stretches (1 mm displacement, 10 ms ramp time) and the BR were evoked by painful electrical pulses (0.5 ms duration), delivered by a concentric electrode placed on the left lower forehead close to the supraorbital foramen before, during and 15 min after a period with experimentally induced muscle pain. The results indicated that experimental posterior temporalis muscle pain facilitates the jaw-stretch reflex, whereas the nociceptive specific blink reflex is inhibited.

In study II, the influence of age and gender on the EMG responses of jaw-stretch and R2 component of BR elicited by nociceptive electrical stimuli was studied. Significant effects of age and gender on these two brainstem reflexes was found. The results demonstrated that the normalized peak-to-peak amplitude of the stretch reflex in the older subjects was lower compared to the younger subjects and higher for females compared to males. The root mean square (RMS), area under curve (AUC) and average values of the BR R2 component were lower in old compared with younger subjects and in females compared with males. The results of study II demonstrated a significant affect of both age and gender on stretch and blink reflexes and suggest that these variables should be taken into consideration in the interpretation of brainstem reflexes.

Study III compared the jaw-stretch reflex and pressure pain thresholds (PPT) in chronic tension-type headache (CTTH) patients and healthy controls. The results indicated that normalized peak-to-peak amplitudes for CTTH patients were higher compared to healthy controls in the right and left anterior temporalis muscles; where as no significant differences in PPT measurements of pericranial musculature were found between healthy individuals and CTTH patients. Females showed higher normalized peak-to-peak amplitudes and lower PPT measurements compared to males indicating that the myofascial pain sensitivity is increased in females compared to males.

In study IV, R2 component of nociceptive specific BR was compared between CTTH patients and healthy controls. The results demonstrated altered R2 component of BR in CTTH patients compared with control subjects; thus, providing electrophysiological evidence that trigeminal afferents in brainstem may be altered in the CTTH. Therefore, the R2 of BR is a high sensitive method to evaluate the trigeminal

system involved in CTTH and their assessment may provide prognostic information and may have implication for a better prevention and treatment of the most prevalent type of headache. The present study did not suggest gender-related differences in BR between male and female subjects.

In conclusion, the present work on effects of experimental/clinical craniofacial pain on the brainstem reflexes and influence of age and gender on the same has provided new information on the sensory-motor interaction in the trigeminal system. The results might be helpful to improve the knowledge for diagnosis and treatment evaluation of CTTH and the usefulness of the brainstem reflexes in exploring the trigeminal pathways. Evaluation of pain sensitivity at asymptomatic body sites can reveal information about general pain-processing alterations, as has been shown for TTH (Schmidt-Hansen et al., 2007), and TMD (Sarlani et al., 2004) patients. Additionally, experimental provocation of a patient's clinical pain allows separate assessment of that pathological condition, for instance evaluating pressure pain sensitivity of symptomatic muscles of fibromyalgia patients (Staud et al., 2003).

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Abstract:

TTH is extremely prevalent and represents a major health problem. Nociceptive processes in craniofacial muscles are believed to play a role in development and maintenance of TTH, however, central mechanisms have been favoured. Brainstem reflexes may help to indicate the topographical level of a putative brainstem lesion and/or the functional derangement of a brain structure. They may also serve as a valuable tool to establish the diagnostic, prognostic and evolution criteria in certain neurological disorders. Review of the literature demonstrates the impact of age and gender on the various components of brainstem reflexes. The aim of the present studies was to investigate how the brainstem reflexes are modulated during experimental and clinical craniofacial pain and by age and gender.

The present work including four studies on effects of experimental/clinical craniofacial pain on the brainstem reflexes and influence of age and gender on the same has provided new information on the sensory-motor interaction in the trigeminal system. In study I, surface EMG recordings examined the modulation of jaw-stretch and blink reflex by experimental posterior temporalis muscle pain in healthy volunteers. The results indicated that experimental muscle pain facilitates the jaw-stretch reflex, whereas the nociceptive specific blink reflex is inhibited. In study II, the influence of age and gender on the EMG responses of jaw-stretch and blink reflex was studied. Significant effects of age and gender on these two brainstem reflexes was found. In Study III, the jaw-stretch reflex and pressure pain thresholds were compared between chronic tension-type headache (CTTH) patients and healthy controls. The results indicated that normalized peak-to-peak amplitudes for CTTH patients were higher compared to healthy controls in the anterior temporalis muscles. Females showed higher normalized peak-to-peak amplitudes and lower PPT measurements compared to males. In study IV, Blink reflex was compared between CTTH patients and healthy controls. The results demonstrated altered R2 component of blink reflex in CTTH patients compared with control subjects.

The results might be helpful to improve the knowledge for diagnosis and treatment evaluation of CTTH and the usefulness of the brainstem reflexes in exploring the trigeminal pathways.

Titel: Modulation af hjernestammereflekser i mennesker ved eksperimentel/klinisk kraniofacial smerte: Indflydelse af alder og køn

Resumé:

Tensionshovedpine (TTH) er stærkt udbredt og udgør et stort sundhedsproblem. Nociceptive processer i forbindelse med kraniofaciale muskler anses for at spille en rolle i udviklingen og opretholdelsen af TTH. Hjernestammereflekser kan anvendes til at bestemme hjernestammelæsioner og/eller funktionsforstyrrelser af hjernestrukturer. De kan også tjene som et værdifuldt værktøj til fastlæggelse af diagnostiske, prognostiske og udviklingsmæssige kriterier for visse neurologiske sygdomme. Gennemgang af litteraturen viser, at alder og køn har indflydelse på de forskellige komponenter af hjernestammereflekser. Målet med denne Ph D afhandling er at undersøge, hvordan hjernestammereflekser moduleres under eksperimentel og klinisk kraniofacial smerte som funktion af alder og køn..

Afhandlingen er baseret på fire studier der undersøger effekterne af eksperimentel/klinisk kraniofacial smerte på hjernestammereflekserne samt indflydelsen af alder og køn. Dette kan give ny viden om den sanse-motoriske interaktion i det trigeminale system. I delstudie I undersøgtes modulationen af kæbe- og blinkerefleksen ved eksperimentel posterior temporalis muskelsmerte i raske forsøgspersoner vha. overflade-EMG-registreringer. Resultaterne viste, at eksperimentel muskel-smerte fremmer kæberefleksen, hvorimod den nociceptiv-specifikke blinkerefleks hæmmes. I delstudie II blev indflydelsen fra alder og køn på EMG-reaktionerne på kæbe- og blinkerefleks undersøgt. Der blev fundet betydelige påvirkninger af alder og køn for disse to hjernestammereflekser. I delstudie III blev kæberefleksen og tærskelen for tryksmerte sammenlignet for patienter med kronisk TTH (CTTH) og en rask kontrolgruppe. Resultaterne viste, at normaliserede peak-to-peak amplituder for CTTH patienter var højere i temporalis anterior sammenlignet med den raske kontrolgruppe. Kvinder udviste højere peak-to-peak amplituder og lavere PPT-målinger sammenlignet med mænd. I delstudie IV, blev blinkerefleksen sammenlignet for CTTH-patienter og raske kontrolpersoner. Resultaterne udviser ændret R2-komponent af blinkerefleksen i CTTH-patienter sammenlignet med kontrolgruppen.

Resultaterne kan hjælpe til at forbedre kendskabet til diagnose og behandlingsevaluering af hovedpine og

hjernestammerefleksernes brugbarhed i forbindelse med undersøgelser af trigeminale mekanismer
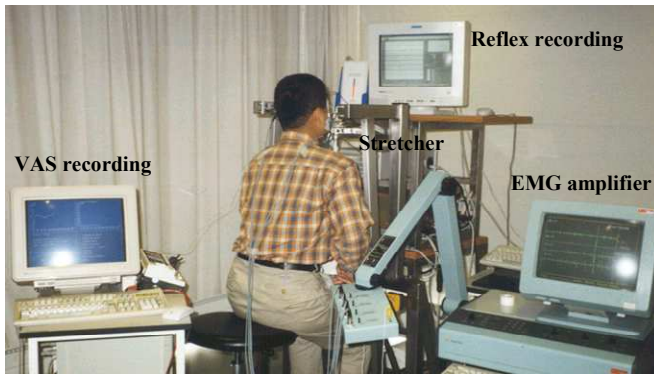
Figure 1. Experimental set up.

Figure 2. Schematic illustration of the brainstem reflexes investigated in the PhD.- thesis,
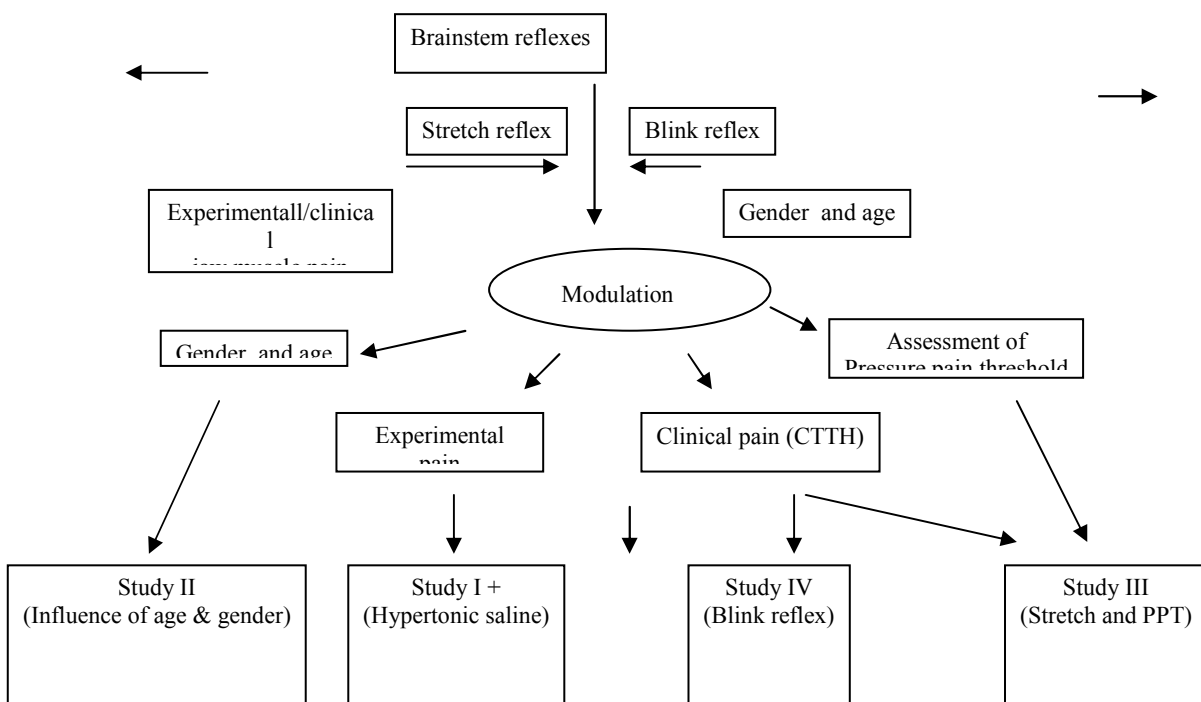and their modulation by experimental/clinical pain and gender/age.

Figure 3 .

Figure 3 B. Nociception specific R2 BR (11 sweeps rectified and averaged, 10 s inter-stimulus interval) in a single subject. Arrow shows the onset of the stimulus.
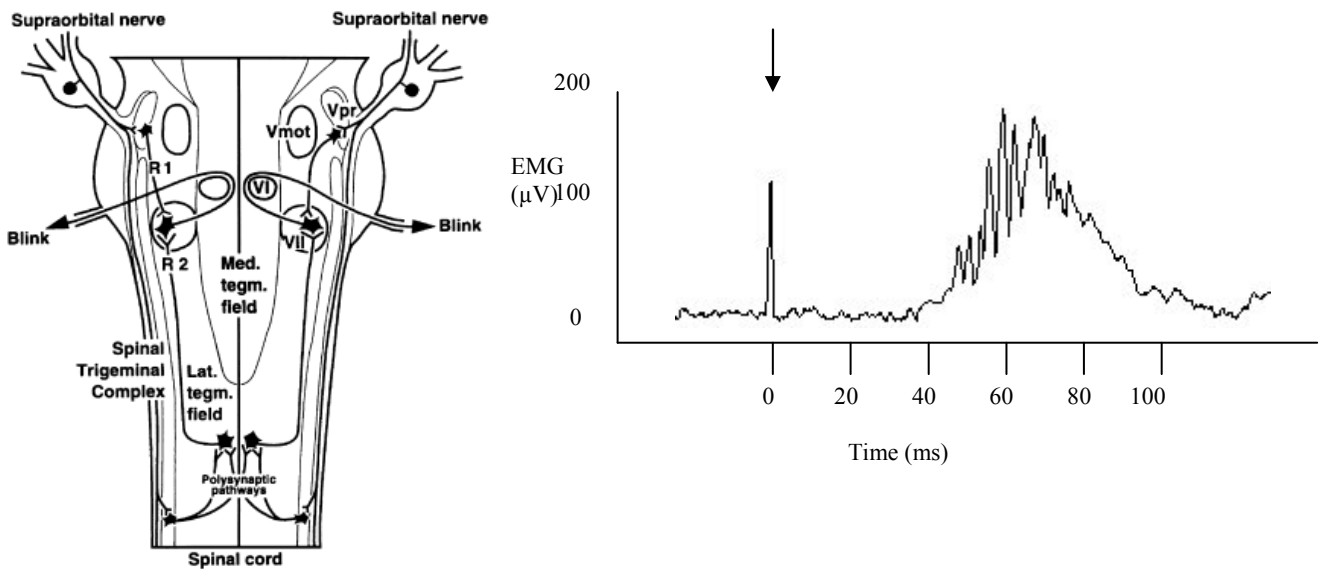
Figure 3 A. Schematic drawing of the blink reflex (BR) circuits. Afferents for the R1 BR connect with an oligosynaptic chain of interneurons located close to the ipsilateral trigeminal principal sensory nucleus (Vpr). The afferents for the R2 BR descend along the spinal trigeminal tract and connect with a polysynaptic chain of interneurons located in the lateral tegmental field of lower medulla. Vmot, trigeminal motor nucleus; VI, abducens nucleus; VII, facial nucleus. (Cruccu and Deuschl, 2000).

Figure 4.

Figure 4 B. Averaged reflex responses (20 sweeps for stretch) in the left temporalis evoked by fast jaw-stretches (1mm displacement, 10ms ramp time).
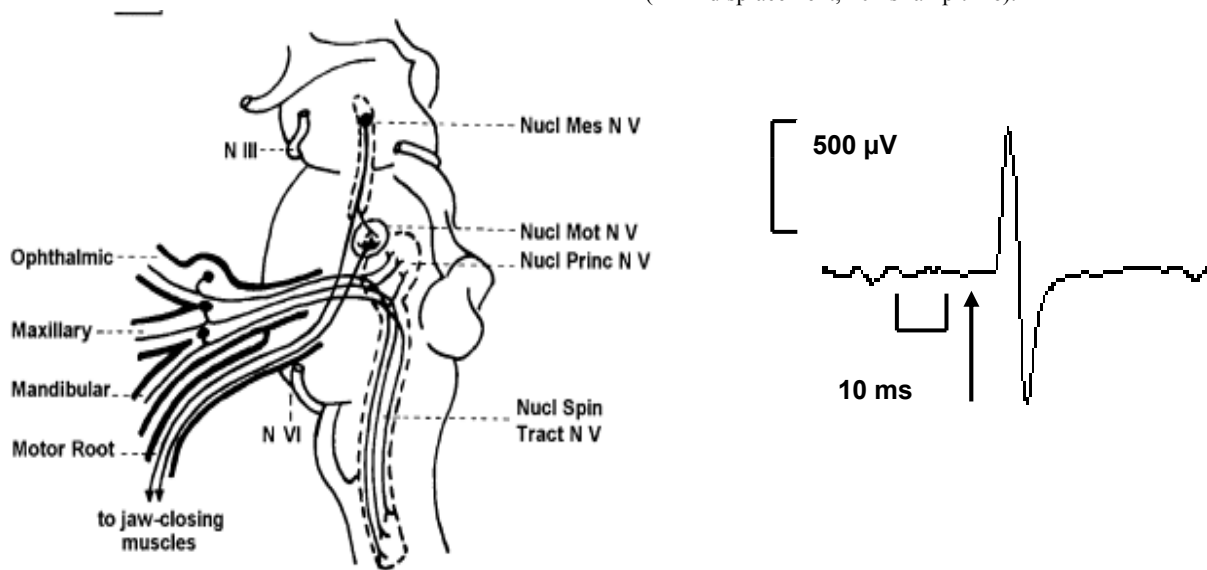
Figure 4A. Jaw-jerk and brainstem circuits. Schematic drawing showing the reflex arc. Note that primary afferents have their cell body in the mesencephalic nucleus. In animals these afferents travel in the motor root. In humans they might travel in the mandibular sensory root. Nucl, nucleus; Mes, mesencephalic; Princ, principalis; Spin, spinalis; N V, trigeminal nerve; N III, oculomotor nerve; N VI, abducens nerve. (from Cruccu and Ongerboer de Visser, 1999.)

Figure 5 . The main results and summary of the PhD studies

Studies:

| Study II (Influence of age & gender) | Study I (Hypertonic saline) | Study III (Stretch and PPT) | Study IV (Blink reflex [BR]) |

Recordings:

| Stretch and BR 30 young vs 30 old | Local muscle Pain Stretch and BR 15 male vs 15 femals | Stretch and PPTs 30 CTTH vs 30 controls | Blink reflex 30 CTTH vs 30 controls |

Results:

Stretch reflex:
pre-stimulus EMG: in older↓
Normalized peak-to-peak: in older↓
and in females▲

BR: R2 in older and females↓
Duration: in older and females▲

Local muscle pain:
Stretch reflex:
pre-stimulus EMG: ↓
Normalized peak-to-peak:▲
BR: R2 ↓

Isotonic saline: no
No sex differences

Stretch reflex:
pre-stimulus EMG: ↓
CTTH
and in females ▲
Normalized peak-to-peak:
in CTTH and females

PPT: CTTH: no
Females: ▼

CTTH:
pre-stimulus EMG: ▲
R2 BR:↓
Duration: ↓

Control: no
No sex differences