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REVIEW ARTICLE

Influence of sympathetic nervous system on sensorimotor function: whiplash associated disorders (WAD) as a model

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Abstract There is increasing interest about the possible involvement of the sympathetic nervous system (SNS) in initiation and maintenance of chronic muscle pain syndromes of different aetiology. Epidemiological data show that stresses of different nature, e.g. work-related, psychosocial, etc., typically characterised by SNS activation, may be a co-factor in the development of the pain syndrome and/or negatively affect its time course. In spite of their clear traumatic origin, whiplash associated disorders (WAD) appear to share many common features with other chronic pain syndromes affecting the musculo-skeletal system. These features do not only include symptoms, like type of pain or sensory and motor dysfunctions, but possibly also some of the pathophysiological mechanisms that may concur to establish the chronic pain syndrome. This review focuses on WAD, particular emphasis being devoted to sensorimotor symptoms, and on the actions exerted by the sympathetic system at muscle level. Besides its well-known action on muscle blood flow, the SNS is able to affect the contractility of muscle fibres, to modulate the proprioceptive information arising from the muscle spindle receptors and, under certain conditions, to modulate nociceptive information. Furthermore, the activity of the SNS itself is in turn affected by muscle conditions, such as its current state of activity, fatigue and pain signals originating in the muscle. The possible involvement of the SNS in the development of WAD is discussed in light of the several positive feedback loops in which it is implicated.

Keywords Whiplash-related disorders (WAD) · Sympathetic nervous system (SNS) · Pain · Stress · Sensorimotor system

Introduction

Whiplash neck injuries are induced mainly by rear-end motor vehicle collisions and by front- or side-impact, which produce sudden acceleration–deceleration forces acting on head and neck, causing a swift neck flexion-hyperextension involving compression and/or torsions of the cervical spine. This may result in bone or soft-tissue injuries, which produce a large variety of clinical manifestations, grouped under the term of whiplash-associated disorders (WAD) or WAD syndrome (Spitzer et al. 1995)[1].

With increasing traffic, the occurrence of this illness is progressively increasing. Statistics indicate that a whiplash injury occurs in every second car accident (e.g., Ottosson 2005); the estimated incidence in the population is 3.8 per thousand (Barnsley et al. 1994). Most individuals suffering from whiplash recover within a few weeks, but a significant proportion of them develop chronic symptoms that require medical treatment. According to different studies, their proportion ranges from 10 to 25% (Lovell and Galasko 2002), from 14 to 42% (Barnsley et al. 1994; Spitzer et al.

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[1] The Quebec task force suggested for whiplash the term whiplash-associated disorders that includes a wide range of symptoms in one clinical syndrome, and classified with a grading system

1995; Rodriquez et al. 2004). Most studies report that 6–18% of the patients are left with permanent severe pain and disability, whereas higher figures are reported by others (see reviews by Barnsley et al. 1994; Lovell and Galasko 2002; Rodriquez et al. 2004). The causes of such long-term disability are unknown. Whiplash-associated disorders are a common cause of acute and chronic pain and musculoskeletal impairments, a significant health problem in the Western world. The prolonged or persistent symptoms are responsible not only for the inflicted subjects' suffering but also for the formidable financial burden associated with this condition, in terms of sick leave, medical and rehabilitative treatments and early retirement.

Soon after injury, whiplash-injured subjects present with a broad range of systemic physical and cognitive symptoms, which vary widely irrespective of the degree of recovery. Among these symptoms are stiffness and pain in neck and shoulder area, sensory deficits, motor dysfunction, muscle fatigue, local cervical mechanical hyperalgesia, temporo-mandibular dysfunction, often associated with dizziness, tinnitus, intermittent headache, signs of autonomic dysfunction, cognitive dysfunctions such as memory and concentration disturbances and psychological distress, depression and anxiety, and sleep disturbances (for review and refs, see Gimse et al. 1997; Eck et al. 2001; Horner 2003; Bergholm et al. 2004; Rodriquez et al. 2004; Ferrari et al. 2005; Sterling et al. 2005). The Quebec task force classification of WAD (Spitzer et al. 1995) is based on the type and severity of signs and symptoms observed shortly after injury, rather than on the specific type of lesion produced. In fact, lesions are often difficult to identify and/or evaluate as to their magnitude, and may be quite diversified in different patients (Volle and Montazem 2001; reviewed by Lovell and Galaxo 2002; Bergholm et al. 2004; Ferrari et al. 2005). As a result, WAD is a heterogeneous group. The numerous injuries occurring at the same time are responsible for a variety of pathogenetic mechanisms that may account for such diversity in symptoms and evolution of the disorder. The pathological processes underlying the wide spectrum of symptoms of WAD are still controversial and debated. Computer tomography and magnetic resonance imaging of the brain and cervical spine do not usually evidence abnormalities and do not usually correlate well with clinical and subjective symptoms, neither are there reliable and generally accepted tests that allow an objective diagnosis of WAD (for review and refs see Lovell and Galaxo 2002; Bergholm et al. 2004; Rodriguez et al. 2004; Ferrari et al. 2005; Kaale et al. 2005). However, most patients suffering from chronic pain in the neck region, irrespective of the anatomical injury, present with the above symptoms, most of which seem to be the expression of dysfunctional behaviour of the central nervous system (CNS). In addition, symptoms may develop a long time after the accident, so that the relation of cause and effect is not always obvious. Symptoms may change in the different stages of the illness and are often intermittent. As a consequence, the credibility of these patients may be frequently and greatly underestimated by their doctors and insurance companies, leading to incorrect diagnostic labels of psychosomatic disease, psychogenic disease, or malingering, and subsequent referral to psychiatric specialists. While these patients often experience psychological depression, it has been debated in the literature whether depression/psychiatric symptoms are causes or effects of their pain. More recent studies seem to qualify depression as a consequence of pain and not vice versa, i.e., the symptoms arise from the injury, and are modulated by psychological conditions and psychosocial environment (e.g., Wallis et al 1996, 1997; Peebles et al. 2001; Ferrari et al. 2005). This still supports the need for judiciously applied, adjunctive psychiatric intervention to address the psychiatric component of a given patient's nociceptive or central experience of pain. However, psychiatric labelling and referral should not be dismissive of the patient. It does not absolve the health care community from investigating and addressing what may be the primary issue propagating and sustaining the patient's true experience of a nociceptive neuromusculoskeletal problem.

In this review, we intend to investigate the role that the sympathetic nervous system (SNS) might play in the

Footnote 1 continued
from 0 to IV (Spitzer et al. 1995). Grade 0 designates no symptoms; grade I neck pain, stiffness and tenderness, with no objective physical signs; grade II neck complaints and musculoskeletal signs (point tenderness, decreased range of movements); grade III: neck pain or stiffness associated with neurological signs (weakness, paresthesias into the arm, reflexes decreased or absent due, e.g., to nerve root compression by a disk protrusion); grade IV: neck pain or stiffness associated with cervical fracture and/or dislocation. All the other numerous physical and psychological problems of a diffuse nature listed below in this introduction may be present in all grades. Patients included in grades I and II represent more than 90% of "whiplash injury claims" (Holm et al. 1999; Hartling et al. 2001; Ferrari et al. 2005). As compared to grades III and IV in which the cause of the injury is more obvious, grade I and II are the most controversial cases, in terms of pathophysiology, diagnosis and prognosis, and therefore also for the insurance compensation system, because of the absence of clearly detectable anatomic injuries and of specific and generally accepted pathological signs. For these reasons most of the studies presented in the literature, and quoted in the present article, refer to this group of patients, some of them also include grade III. Grade IV patients (neck problems due to fracture or dislocations) are excluded.

development of WAD syndromes. Its involvement in this syndrome is suggested by epidemiological data that report the frequent association between WAD and physical and psychosocial stress (e.g., Sterling 2004; Sterling et al. 2005; Tomlinson et al. 2005; Hendriks et al. 2005; Holm et al. 2006), i.e., a condition that implies sympathetic nervous system activation. In addition, there is evidence to show that, besides physical factors, psychological factors play a role in the recovery, and that psychological distress and post-traumatic stress reaction are psychological predictors of poor outcome (e.g., Nederhand et al. 2004; Hendriks et al. 2005; Sterling et al. 2005, 2006). While a number of different mechanisms have been identified and suggested to mediate the sympathetic maintenance of chronic pain, little information is available to explain a role for the SNS in the development of a chronic muscle pain syndromes. However, the SNS exerts several actions at the muscle level that affect sensorimotor functions: besides controlling muscle blood flow, catecholamines modulate contractility of skeletal muscle fibres and sensory activity of muscle-spindle receptors thereby potentially affecting proprioception and motor control. These notions, mainly provided by basic research work performed on animal experimental models, appear to be largely neglected in the current literature. The mechanisms of sympatho-motor interaction are here reconsidered and their possible involvement in positive feedback loops underlying the development/maintenance of muscle pain syndromes is discussed and put forward as working hypothesis.

Before dealing with the known and hypothesized interactions between the sympathetic nervous system and sensorimotor functions, we will first summarize some general signs and symptoms of WAD, with a focus on sensorimotor dysfunction.

Disturbances in WAD patients

Pain

Most of the recent clinical studies on chronic cervical pain carefully group patients according to the origin and onset of pain (e.g., traumatic, post-traumatic, non-traumatic). However, the different groups may, in fact, share common features as to alterations in conduction and processing of nociceptive information. In this context, it is noteworthy that symptoms and pain extension to near and often distant territories observed in WAD patients may be common to several other types of chronic pain of non-traumatic origin (see below, Pain processing).

In WAD patients, pain is the predominant symptom and mostly, but not always, the onset symptom. When pain appears, it is often initiated by exercise or stress, may initially migrate for a while, then generalise throughout the body and is often intermittent (e.g., Bergholm et al. 2004; Ferrari et al. 2005).

Origin

Pain may originate from acute lesions in various structures in the occipito-atlanto-axial segments, such as ligaments, capsules, facet joints (Volle and Montazem 2001; Bergholm et al. 2004; Kaale et al. 2005). Lesions or their consequences (swelling, inflammatory processes), can affect nociceptors, afferent and efferent pathways and pain processing mechanisms, thus producing symptoms of different severity.

The cervical facet joints are reported to be the most common source of neck pain in WAD patients (Barnsley et al. 1994; Hartling et al. 2001). The strain on these structures increases during flexion-extension loading when a pre-torque is applied. That would explain why position/pre-rotation of the head at the time of impact is a risk factor and cause of increased symptom severity and persistence among persons with whiplash injury (e.g., Sturzenegger et al. 1995; Winkelstein et al. 2000; Vibert et al. 2001; Kumar et al. 2005). The presence of both mechanoreceptors and nociceptors in the human cervical facet capsules suggests that neural input from these structures is able to elicit proprioceptive reflexes aimed at increasing joint stability.

In addition, other receptors/pathways conveying proprioceptive information, usually responsible for correct motor control, may be affected. The consequent malfunction or misuse of the affected muscles, maintained over time, may in turn enhance and/or maintain the pain. In addition, in the acute stage of injury, the "pain-related fear" and "avoidance" behaviours are common automatic reactions, aimed at minimizing the probability of pain and further injury, and, at the same time, enabling healing of the damaged tissues. In a number of injured subjects, this avoidance pattern persists after the initial injury has apparently healed, leading to a "disuse syndrome" that causes detrimental changes in musculoskeletal and cardiovascular systems, with impairment of muscle coordination This condition is also believed to play a role in the development and exacerbation of chronic pain (for review and refs see Vlayen and Linton 2000; Asmundson et al. 2004). These alterations in motor control will be further discussed in the next section.

Pain processing

Nociceptive processes are qualitatively altered in patients suffering from pain of different aetiology

(Banic et al. 2004; for review and refs see Woolf and Salter 2000; Blair et al. 2003; Windhorst 2003a, b; Kehlet et al. 2006), and this also applies to WAD-patients (Curatolo et al. 2001, 2004; Nederhand et al. 2002). Due to aberrant signal processing at peripheral and central levels, pain sensation may be largely independent of the magnitude of the actual nociceptive stimulus, and/or the generation of pain may occur in response to a low mechanical stimulus. Behavioural models indicate that a persistent small afferent input, as generated by tissue injury, may result in chronic alteration in sensory processing, i.e., hyperalgesia at the injury site and tactile allodynia in adjacent areas. Hyperalgesia is based on both peripheral and central sensitisation, while allodynia is due to central facilitation. Each of the mechanisms involved in hyperalgesia is subjected to, or is the expression of, neuronal plasticity, i.e., the capacity of neurons to change their function, chemical profile, structure, as well as synaptic circuitry and connectivity in the spinal cord. A condition of "*central hypersensitivity*" may explain, at least in part, the presence of pain in the absence of detectable tissue damage, as is often the case in whiplash injury, idiopathic neck pain and fibromyalgia (Banic et al. 2004; Scott et al. 2005). A generalized sensitisation of the nociceptive system is suggested by the presence of widespread hyperalgesia to stimulation of the painful muscles (Koelbaek Johansen et al. 1999), as well as generalized hypersensitivity to mechanical and thermal stimuli over the cervical spine sites (Sterling et al. 2003a, 2005). While the above findings are common to WAD and idiopathic neck pain patients, chronic WAD subjects may exhibit additional hypersensitivity in distant areas, such as in legs (Scott et al. 2005). In addition, the higher prevalence of temporomandibular pain disorder in patients with WAD than in chronic neck pain patients (Haggman-Henrikson et al. 2004; Klobas et al. 2004; Visscher et al. 2005) led Visscher et al. (2005) to suggest that the temporomandibular disorder in WAD is part of a more widespread chronic pain disorder.

Unfortunately a standardized animal model of whiplash is not available; current evidence for plastic changes in central pathways processing nociceptive information comes from investigations carried out on several different simplified animal models of chronic pain. In an experimental rat model, cervical facet injury is associated with phenotypic changes in neurons innervating C5/6 (labelled in the dorsal root ganglion: DRG) and pain sensations in the cervical spine (Ohtori et al. 2001, 2003). In particular, the facet joint capsules contain small unmyelinated nerve fibres immunoreactive to calcitonin gene-related peptide (CGRP), a marker of sensory neurons involved mainly in pain perception. After cervical facet lesions, a subpopulation of large myelinated DRG neurons, usually sensitive to mechanical stimuli (not to pain) and not normally producing CGRP, start to generate it. Another important piece of information comes from experiments first performed by Woolf and colleagues in the lumbar territory, which revealed what is now considered to be a ubiquitous mechanism (Woolf et al. 1995; review and refs in Woolf and Salter 2000). They showed that, after peripheral nerve injury, phenotypic changes occur in sensory A-fibres, which are the morphological correlate of a central reorganization and altered sensory processing. Terminals of A-fibres sprout from their deep dorsal horn laminar location, (laminae III–IV, where non-nociceptive inputs are processed), to the area where usually small nociceptive C fibres terminate (laminae I-II), and make functional synaptic contacts with the C-fibres. As Woolf and Salter point out, "the resultant change in connectivity might be a factor in the intractable nature of many neuropathic pains". The above-mentioned *phenotypic change* in large neurons, at the level of dorsal horn neurons (Windhorst 2003b), may provide the pathophysiological basis for the diffuse neck and shoulder pain, as well as for the headache, experienced by patients with cervical facet lesions.

Different mechanisms have different time courses

The study of sensitisation processes not only shows the functional complexity of the events that occur secondary to a focal injury, but also suggests that chronic pain depends on a cascade of events that is initiated, but not necessarily sustained, by the injury stimulus. In addition, *emotional and stress-related influences* (see Stress) may have a powerful modulating action on the evolution of the sensitisation process and pain perception via an imbalance of supraspinal and descending pain-modulating neuronal circuits (Fields 1992; for review and refs see Mense 1997; Baron et al. 1999; Windhorst 2003b; Curatolo et al. 2004). The multiple mechanisms potentially involved in the sensitisation process exhibit different time courses, and the symptoms exhibit a great inter-individual variability (see below), which makes it difficult to identify the stage of the illness and to compare the data collected from different patients.

In view of the chain reactions induced by the persistence of pain of different origin, the suggestion of Cousins (2002) and Sterling et al. (2003a) that "an early management of WAD patients at risk with appropriate expeditious treatment might help to prevent the transition from acute to persistent pain" (Sterling et al.

p. 516), seems theoretically appropriate and is supported by observations of the time course of the pain symptoms. These symptoms as well as motor dysfunctions often stabilize within 3 months, then increase again after 6 months (Sterling et al. 2003a, b), and fluctuate in severity (Tomlinson et al. 2005) (see Modulation of nociceptive activity).

Possible neuroanatomical regional differences

In this context, we wish to mention that a number of studies performed on experimental animals (reviewed by Neuhuber 1998) indicate that the innervation of the head and neck muscles differs from that of other regions of the body. For instance, unlike the arrangement seen in hind limb muscles, a relevant number of thick-calibre neck muscle afferents, mostly from the C2–C3 segments, project directly to the vestibular nuclear complex, while thin-calibre fibres, mainly nociceptive afferents from cervical segments, are channelled to limbic structures different from the targets of thoracolumbar afferents. Neuhuber (1998) comments "it is tempting to consider these neuroanatomical peculiarities relevant for the pathogenesis of the puzzling symptoms after whiplash injury".

Individual pain sensitivity

Evaluation of pain level is not only important for the treatment of patients but also, as mentioned in Introduction for WADX, in connection with the financial costs related to working environment and insurance claims. In this context we wish to briefly remind that sensitivity to pain exhibits, in general, a wide inter-individual, as well as intra-individual variability. Cognitive and emotional states such as fear of pain or of (re)injury, uncertain expectations, anxiety (e.g., Ploghaus et al. 2003; Asmundson et al. 2004), as well as environmental (Chesler et al. 2002) and genetic factors play relevant roles in the development and exacerbation of chronic pain of different aetiology. As for cognitive and emotional states, the possible mechanisms were briefly commented above. As for genetic factors, studies performed on animal models, particularly on mice inbred for nociceptive traits, have shown that hypersensitivity pain responses to thermal, chemical and mechanical stimuli are distinct and genetically dissociable phenomena (Lariviere et al. 2002; Wilson et al. 2003), and the relevant genes are being identified on the DNA sequence level in such models. To date we know only a few examples of single gene mutations or polymorphism associated with specific pain conditions in humans (Mogil et al. 2000; Zubieta et al. 2003; Fischer et al. 2005; Diatchenko et al. 2005, 2006). In the context of myalgias, the most common metabolic disorder of human skeletal muscles is the myoadenylate deaminase deficiency that is associated with exercise-induced myalgia (Fischer et al. 2005; refs in Gross et al. 2002). It is observed in approximately 2% of the Caucasian population and in African-Americans, even though most of the deficient subjects are asymptomatic. Exercise-induced myalgia is also the most frequent symptom of muscle carnitine palmitoyltransferase II deficiency, an autosomal recessive disorder of fatty acid oxidation characterized by attacks of myalgia and myoglobinuria (Deschauer et al. 2005). Recently a single nucleotide polymorphism of the gene that codes for catecholamine-*O*-methyltransferase (COMT), an enzyme that metabolizes catecholamines and catechol-substances and which is known to play a crucial role in mediating physiological and psychological responses to environmental stressors, is reported to substantially affect pain sensitivity in human population (Zubieta et al. 2003; Diatchenko et al. 2005, 2006). In particular it contributes to developing a chronic musculoskeletal pain condition, i.e., temporomandibular joint disorder (Diatchenko et al. 2005), and possibly other chronic pain conditions. One of the hypothesized mechanisms by which COMT activity inversely correlates with pain sensitivity is the following. Reduced COMT activity entails elevated levels of catecholamines that, by stimulating beta2-adrenergic receptors in the peripheral and central nervous system, may produce persistent pain states (Khasar et al. 2003; Diatchenko et al. 2005, 2006).

The possibility is being investigated that complex qualitative pain traits, as well as susceptibility to pain, may depend on alterations in the expression of the numerous genes that code for proteins involved in the complex neurochemical mechanisms processing nociceptive messages in the spinal cord and in the brain stem.

Motor control

It is generally accepted that movements and posture are altered in WAD patients. All these patients exhibit a reduction of different extent in the range of active cervical movement (range of motion), in movement precision and coordination, in head–neck balance, and show jerky and disharmonic movement patterns. The few studies that have compared motor disturbances in subjects suffering from chronic neck pain of traumatic and non-traumatic aetiology could not evidence clear-cut characteristics that are peculiar or specific to WAD patients, which suggests that musculoskeletal disturbances in

chronic neck pain syndromes share common pathophysiological mechanisms, irrespective of the aetiology.

Postural control

Postural control appears to be impaired in both WAD patients and chronic neck pain patients, as indicated by the larger postural trunk sway before the balance is reached, both in stance tasks and more complex gait tasks (Sjöstrom et al. 2003; Michaelson et al. 2003; Madeleine et al. 2004). Head stability also appears to be reduced, as observed by Michaelson et al. (2003) who specifically monitored head and trunk postural adjustments in response to unexpected or self-administered perturbation, the postural deficits being more pronounced in WAD as compared to work-related chronic pain patients.

Possible alterations in muscle activity and motor patterns have been investigated in many studies by means of surface electromyography (EMG).

In superficial neck muscles such as the sternocleidomastoid and upper trapezius muscles, the magnitude of EMG activity is reported to be increased in patients as compared to healthy subjects when performing different tasks (Sterling et al. 2004; Jull et al. 2004; Nederhand et al. 2000; Falla et al. 2004a) the extent of increase being related to the severity of symptoms. Electromyographic activity of the superficial neck flexor muscles is increased during the cranio-cervical flexion test, the increase persisting for 3 months in all groups, i.e., from mild to severe pain and disability (Sterling et al. 2003b). Stronger co-activation of antagonist muscles during physical exercise and a decreased ability to relax muscles after physical exercise are common traits in patients suffering from chronic pain, as observed in patients suffering from WAD (Nederhand et al. 2000; Elert et al. 2001), as well as fibromyalgia (Elert et al. 2001). Indeed, a decreased ability to relax the trapezius muscles after exercise has been suggested to identify patients with WAD (Nederhand et al. 2000). However the picture is not as simple, heterogeneity within groups of patients with the same chronic pain disorder is a frequent finding (Elert et al. 2001) and EMG levels have also been reported to inversely correlate with the "neck pain disability" (Nederhand et al. 2003).

Models linking muscle activity and pain

Whether muscle hyperactivity occurs and possibly plays a role in development or maintenance of chronic muscle pain syndromes has long been debated and two major hypotheses have been put forward.

A vicious circle hypothesis was initially advanced by Travell et al. (1942) and later reconsidered by Schmidt et al. (1981) and Johansson and Sojka (1991). In this latter formulation the model states that activation of group III and IV muscle afferents (high threshold mechano-chemical and pain receptors) increases muscle activity by exciting alpha motoneurons through an action exerted on muscle spindles via gamma motoneurons. The increase of muscle activity will in turn increase muscle fatigue and pain thereby further exciting muscle group III and IV receptors, giving rise to a vicious circle that maintains muscle hyperactivity and pain (Travell et al. 1942; Johansson and Sojka 1991).

Conversely, the "*pain-adaptation model*" (Lund et al. 1991), which in cognitive behavioural term is often formulated as the "fear-avoidance model", predicts decreased activity in painful muscles, resulting from a learned protective behaviour aimed at reducing amplitude and speed of movement in order to minimize the use of the painful muscles and joints (for review and refs, see Lund et al. 1991; Graven-Nielsen et al. 2003; Asmundson et al. 2004).

The hypothesis about the development of a vicious circle, along with its possible extensions and variants (Johansson et al. 2003, see later Feedback loops) is attractive and, although mainly supported by results from animal experiments performed on several territories (Johansson et al. 1993; Djupsjöbacka et al. 1994, 1995a, b; Pedersen et al. 1997; Thunberg et al. 2001; Hellström et al. 2002; but see also, in humans, Svensson et al. 2004), it would account for the frequent clinical observation of contractures and muscle spasms in chronic muscle pain patients (Rivner 2001; Simons 2004). However, a longitudinal study, in which a group of WAD patients was followed from 1 week to 6 months after injury, failed to evidence any change in trapezius muscle activity during static and dynamic tasks as well as in response to exercise (Nederhand et al. 2003), i.e., detecting no initiation of muscle hyperactivity in the transition from acute to chronic muscle pain. On the contrary EMG levels appeared to be inversely related to a "disability index" obtained from subject reports; on this basis the authors suggested the presence of an altered motor strategy in these patients, compatible with the pain adaptation model.

Altered motor strategies

Evidence for a change in motor strategies also comes from several recent studies that investigated the activation patterns of specific muscle groups in response to rapid arm movements, based on sophisticated EMG

recording techniques (Falla et al. 2004a, b, c; Jull et al. 2004). The results show that, as compared with healthy controls, patients suffering from neck pain (of both traumatic and not traumatic origin) exhibit altered spatio-temporal patterns of activation in several neck muscles (Falla et al. 2004d). Reduced and delayed activations of the deep cervical muscles (Falla et al. 2004b, c) and increased activations of superficial accessory neck muscles (Falla et al. 2004a; Jull et al. 2004) have been reported. Anticipatory activation of neck muscles during rapid arm movement is known to take place in order to ensure stability of the head during voluntary movements (Gurfinkel et al. 1988). The delayed activation of deep cervical muscles during voluntary arm movements suggests an altered feedforward control of the cervical spine (Falla et al 2004c; Gurfinkel et al. 1988).

Another example of reorganization of motor patterns in WAD patients has been reported by Kelders et al. (2005). They found the *cervico-ocular reflex* increased over a wide range of peak velocities of head rotation. This reflex, which operates in conjunction with vestibulo-ocular and optokinetic reflexes in stabilizing the eyes in space following neck movements, exhibits long-term and short-term plasticity depending on subject age and training (Kelders et al. 2003; Rijkaart et al. 2004). The increase in the cervico-ocular reflex in WAD-patients may indicate a central adjustment of reflex gains as part of a modified motor strategy aiming at avoiding neck pain in the end-range of motion. Given the consistency of their observations, Kelders et al. (2005) suggest that testing the cervico-ocular reflex might be an appropriate and objective technique to assess cervical injury. However, its specificity as a test suitable for the diagnosis, prognosis, and possibly monitoring therapeutic effects in WAD-patients requires further study.

The reorganization of motor strategies in the presence of pain is a rather quick process to the extent that it could be observed in healthy subjects under experimental pain or threat of pain in different body areas (Lund et al. 1991; Arendt-Nielsen et al. 1996; Graven-Nielsen et al. 1997; Moseley et al. 2004; Moseley and Hodges 2005). The general picture supports the *pain adaptation model* in that in activity of painful muscles is reduced as well as movement of threaten or painful joints. This may imply the recruitment of antagonist and/or accessory muscles aimed at reducing the extent of movement and stiffening the threatened joint. Initially, the modulation of the motor performance was attributed to a "direct" (reflex) action of nociceptive afferents (*pain interference*) (Lund et al 1991; Graven-Nielsen et al. 1997). However, Moseley and Hodges (2005) recently observed that repeated nociceptive stimuli did not produce habituation of the response, and removal of the nociceptive stimulus did not immediately restore the original motor strategy. On this basis they suggested that the switch to a protective motor strategy during pain is mediated at a higher level in the CNS.

In conclusion, many studies have demonstrated that in pain conditions an alteration of the motor strategy takes place, in agreement with the *pain adaptation model*. However, if such protective motor strategy is maintained for long time, a *vicious cycle* of pain and motor dysfunction may secondarily be promoted by the abnormal activity requested to accessory (auxiliary, antagonists) muscles as well as by the increased compressive load of cervico-spinal segments (Panjabi et al. 1989; Moseley and Hodges 2005).

A glance to proprioception

An interesting hypothesis followed by a number of investigators is that the postural symptoms that characterize WAD patients may also be partly attributed to a proprioceptive deficit.

Proprioception is based on afferent signals emanating from mechanosensory receptors in ligaments, joints and muscles, to some extent also in skin. Proprioceptive information, particularly from muscle spindles, has an important role in motor control for movement coordination and joint stability, and contributes to moment-to-moment reflex corrections of the ongoing movement (feedback control of movement). In addition, this information subserves higher level functions, such as the construction and updating of the body schema, the provision of initial conditions for motor acts, the planning of motor programs (feedforward control of movement), the learning of motor tasks and the calibration of other sensory systems (for review and ref see Prochazka 1996; Lackner and DiZio 2000; Roatta and Passatore 2006). Distortion of this information may thus disrupt the normal perception of the own body and the control and coordination of movements by acting at several levels of the CNS.

Only few studies specifically addressed the proprioceptive issue in WAD as well as in other chronic neck pain patients. Cervical proprioception, generally assessed through tasks requiring postural corrections and head repositioning, was found to be consistently reduced, as compared to control subjects (Revel et al. 1991; Michaelson et al. 2003; Kristjansson et al. 2003; Treleaven et al. 2003, 2005).

In addition, impaired proprioception has also been implicated in dizziness. In fact, postural control

involves the interaction between visual, vestibular and somatosensory information, in which proprioceptive inputs from the cervical segments play a major role. If information on motion coming from these different sensory systems is incongruent, the resulting "sensory mismatch", if powerful enough, produces a sensation of *spatial disorientation and dizziness*. This leads to less stable postural control and unsteadiness (Karlberg et al. 1995; Magnusson and Karlberg 2003), often associated with episodes of loss of balance, which are frequent complaints in patients suffering from persistent WAD. WAD-patients reporting high neck pain and dizziness also exhibit greater joint position errors in head-repositioning tasks than do subjects reporting mild or low pain (Treleaven et al. 2003, 2005). An interesting model suggesting a hypothetical vicious circle in cervical dizziness was recently presented by Magnusson and Karlberg (2003): dizziness per se is a strongly alarming and alerting sensation that, together with pain, may cause anxiety and consequent enhancement in sympathetic drive. This in turn may disturb proprioceptive information (Roatta et al. 2002b, see also below), thereby further worsening the above-mentioned condition of sensory mismatch and dizziness. Such a model may also apply to WAD-patients.

A possible mechanism underlying the disturbance of proprioception in WAD, as well as in chronic neck pain patients, has been suggested by Michaelson et al. (2003) on the basis of results from animal experiments. Namely activation of chemo- and nociceptive sensory afferents from muscles and joints, elicited by injecting inflammatory substances in limb (Johansson et al. 1993; Djupsjöbacka et al. 1994, 1995a, b) and neck muscles (Pedersen et al. 1997; Thunberg et al. 2001; Hellström et al. 2002), strongly affects proprioceptive activity of muscle spindle afferents via involvement of gamma-motoneurons (Jovanovic et al. 1990). Likewise, chemoreceptors and nociceptors could be stimulated by injury/inflammation following the whiplash and thereby reflexly change (and derange) muscle spindle behaviour.

Another possible mechanism accounting for impaired proprioception involves whiplash-induced stretch/damage to cervical ligaments. In fact, ligament mechanoreceptors have a role in muscle coordination and reflex regulation of joint stability, through their action on muscle spindle afferent activity via gamma motoneurons (Sjolander et al. 2002).

Finally, proprioception may be impaired by the action exerted by the sympathetic nervous system on muscle spindle receptors. This possibility will be discussed more thoroughly in the next sections.

The emphasis on proprioceptive deficits is here justified by the fact that it may produce similar modification of motor strategies as described for the *pain adaptation model* and give rise to similar possible consequences. In fact, a proprioceptive deficit may result in inaccurate perception of head or limb position. To overcome the ensuing loss of movement accuracy and precision, the system may adopt a different *motor strategy* in performing a given movement, in terms of the muscles or groups of muscles or motor units activated, the time of onset and the sequence in their individual patterns of activation and relaxation, the co-activation of antagonist muscles *(co-contraction)* (Ghez and Sainburg 1995; Gribble et al. 2003). In general, a sub-optimal strategy will be adopted, such as stiffening and stabilizing the affected structures, which may lead to a less efficient and, in a long run, possibly harmful muscle function. In particular, the presence of long-lasting static contractions (like stabilizing co-contractions) is a well-known risk factor for chronic muscle pain (Veiersted et al. 1993; Veiersted 1996; Sjögaard et al. 2000). These mechanisms will be further discussed below (see Positive feedback loops).

As a final consideration, it should be pointed out that plastic changes might occur in the brain due chronic pain conditions that may distort the body image and body schema (Birklein and Rowbotham 2005; Moseley 2005; Moseley et al. 2005). This in turn may be one of themechanisms that cause a change in the motor program.

Systemic dysfunctions

Disturbances in cardiovascular function, such as heart rate and arterial blood pressure instability, disturbance in temperature regulation, blushing, are often reported in WAD-patients (Bergholm et al. 2004; Ferrari et al. 2005). These disturbances suggest an impaired autonomic control whose mechanism has been and is being investigated. One of the proposed possibilities is that the trauma-induced deformation might induce a long-lasting or permanent alteration of the mechanical properties of ligaments and capsules of the upper cervical spine segment, i.e., the structures aimed at mechanically limiting head movement and thus exerting a protective function on the spinal cord. This condition may affect the structural behaviour and stability of the upper cervical spine, thus altering the complex kinematics of the craniocervical region (Brolin and Halldin 2004). The instability of the craniocervical junction may in turn produce, during particular head movements, compression of the cervical spinal cord and medullary areas, as it could be evidenced in a number

of these patients, through magnetic resonance, during head rotations (Volle and Montazem 2001).

Disturbances in cardiovascular function are reported not only in grade IV and grade III WAD patients, in whom cervical fracture and/or dislocation may produce a visible compression of spinal-medullary areas (Spitzer et al. 1995), but also in WAD lower grades in which injuries are not easily identifiable. Recent clinical work points out that disturbances in the vertebrobasilar circulation are frequently occurring in WAD-patients, creating ischemic problems that could justify the reported occurrence of apparently unrelated pathologies. In a large number of WAD patients presenting no X-ray evidence of bone lesion, Seric et al. (2000) recorded blood flow in vertebral and basilar arteries, through transcranial Doppler sonography. They report the presence of significant disturbances attributed to spasm that, in a large percentage of patients, persisted throughout the 6 months following the accident, and correlated well with the severity of clinical picture. Mayor and minor neurological symptoms were reported, attributed to ischemia in the territories innervated by vertebrobasilar arteries, as a result of even minor trauma inducing lesions of the vertebrobasilar system (review and refs in De Decker et al. 2003).

Finally, Ferrari et al. (2005), in a recent re-examination of a large population of patients, also suggest the systemic nature of WAD: "Neck pain was only one of many diffuse and intense symptoms, including, often, low back pain. The range of symptoms including concentration problems, fatigue, dizziness, paresthesiae, headache, spinal pain, nausea, and jaw pain could be interpreted as a systemic disorder that cannot be explained by a single anatomic region of injury and extends well beyond what can be labelled as a neck injury" (p. 1,337). It may be added that many of the above mentioned symptoms would be justified by the presence of an ischemic condition of medullary areas (see also Seric et al. 2000; De Decker et al. 2003; Syme 2005). In this context, we wish to mention a provocative recent hypothesis (Syme 2005) linking three syndromes characterised by altered pain appreciation and autonomic imbalance: cardiac syndrome X, irritable bowel syndrome and reflex sympathetic dystrophy. Syme (2005) proposes that microvascular ischaemia of the caudal lateral/posterior medullary region of the brain stem, due to minor injury of the vertebral artery inducing abnormality or occlusion at microvascular level, is responsible for these (all three) syndromes. According to Syme, the patients suffering from such pathologies "present in their thirties, with no vascular risk factors and without florid neurological signs, often have a previous history of significant whiplash or head injury" (p. 146). He comments that the vertebral artery may be especially vulnerable to whiplash injury, due to its long transforaminal course, and that the frequency of these lesions after trauma is probably underestimated.

Involvement of the sympathetic nervous system in WAD

It is generally accepted that sympathetic activation is largely aimed at supporting motor function by exerting a number of generalized preparatory actions on vegetative functions to meet the varying metabolic requirement of the active muscle. These actions are centrally programmed to be appropriate for each particular motor task and are realized by central commands that activate sympathetic preganglionic neurons parallel to the motoneurons innervating the exercising muscles (Goodwin et al. 1972; McCloskey 1981; Seals and Victor 1991; Suzuki et al. 1999; Mano 1999). However, in modern life, stressful situations often produce activation of the sympathetic system that for different reason (e.g. social constraints) may not be accompanied by its motor counterpart. The increased sympatho-adrenal outflow will then result to be excessive and inappropriate to serve an organism during quite or sedentary activity. Such unbalance is one important component of the stress response and has been implicated in various diseases not exclusively related to the cardiovascular system but concerning virtually all body functions, including immune system (e.g., Boscarino 2004; Connor et al. 2005; Elzinga and Roelofs 2005; and see, for review and refs, Habib et al. 2001; Thayer and Brosschot 2005).

Epidemiological data report the frequent association between chronic musculoskeletal pain in the neck–back areas, including WAD, and psychosocial stress, (e.g., Skov et al. 1996; Eriksen 2004; McLean and Clauw 2004). In a recent prospective study, Sterling et al. (2005) maintain that both physical factors and psychological distress play a role in the recovery or non-recovery from whiplash injury. According to several studies (e.g., Wallis et al. 1996, 1997; Richter et al. 2004; Miettinen et al. 2004; Nederhand et al. 2004; Ferrari et al. 2005; Hendriks et al. 2005; Guez et al. 2005), socio-demographic, cultural and psychological factors add to physical factors in affecting the short- and long-term outcome after whiplash injury, and are listed among the predictive factors for the subjects to develop chronic neck pain disability (see Pain).

There are several levels at which excessive sympatho-adrenal outflow may be involved in producing

skeleto-motor disturbances and pain. Sympathetic activation exerts a number of actions at muscular level, such as vasoconstriction in skeletal muscles (see Vascular control), modulation of skeletal muscle contractility (see Modulation of skeletal muscle contractility), modulation of the discharge of numerous receptors (in particular muscle spindles which carry key-information for motor control: see Modulation of proprioceptive activity) and, in chronic pain states, modification in the excitability of pain receptors (see A debated issue). In turn, sympathetic outflow is affected by what is going on in the muscle, i.e., by intramuscular chemistry (Roatta et al. 2002a; see also somato-sympathetic reflexes: reviewed by Sato et al. 1997).

After a brief introduction about stress, the above listed different actions will be detailed and discussed in terms of their possible role in the chronic pain and motor dysfunctions reported in WAD.

Stress

There is no universally accepted definition of stress (for review and refs see Habib et al. 2001; Kalezic et al. 2003). It may be defined as that particular state in which the brain interprets the quantity of stimulations as excessive or its quality as threatening, thus responding in a generalized way (Chrousos 1998). These stimuli or "stressors" may be physical, psychological or psychosocial. They produce adaptive responses whose magnitude is related to the stress stimulus as well as to the individual's perception of it. Such responses are very finely tuned, ranging from very localized reactions to a generalized and systemic state. In this condition, the brain can influence virtually any organ or body system through the activation of the hypothalamic-pituitary-adrenal axis and of the sympatho-adrenal system, accompanying the behavioural/motor responses. The generalized response to stress classically consists of mobilising body resources to acutely prepare the organism for a powerful motor reaction, the so-called "fight or flight" reaction, taking place within seconds. Stored energy is mobilized, and the relevant transport systems are activated, resulting in increases in respiration, blood pressure and heart rate, redistribution of blood to relevant organs, mobilization and enhanced delivery of energy substrates to brain and muscles, as well as deactivating systems not acutely needed, such as alimentary tract, kidney, sexual function, immune system etc. Cannon (1929) defined fear and anxiety as being the "emotional manifestation" of the "fight or flight" response, characterized by activation of the sympathetic nervous system and parasympathetic withdrawal. Another important effect of stress concerns sensory perception, in particular perception of pain, which may range from stress-induced short-lasting analgesia (e.g., soldiers wounded in battle, athletes injured during sport events), to development and maintenance of chronic pain states and hyperalgesia (e.g., sympathetically-maintained pain), determined by the activation of endogenous antinociceptive pathways and facilitatory modulatory systems (Fields 1992; reviewed by Mense 1997; Baron et al. 1999; Windhorst 2003b).

The reactions listed above are usually beneficial in the acute state of stress, in that they support the increased motor activity and realize efficient adaptive adjustments that help organisms to cope with changing environmental conditions and re-obtain homeostasis, thus promoting health and survival. In our modern life, however, the motor component of the stress response is most often suppressed by social constraints; this leaves an "unbalanced" autonomic (sympathetic) activation that is no longer appropriate and beneficial to the organism. In fact, whenever the stress is excessive and prolonged, i.e., it becomes a chronic state that keeps the above-mentioned actions going, it generally impacts negatively on physiological homeostasis, being the recognized cause, or the possible con-cause, of a variety of diseases (for review and refs see Damasio 1998; Selkowitz 1992; Habib et al. 2001; Kalezic et al. 2003; Asmundson et al. 2004; Boscarino 2004; Thayer and Brosschot 2005).

Human subjects vary widely as to their response to the same stressor, and strong heterogeneity of responses is also reported in animals (Cohen and Zohar 2004). Genetic as well as environmental influences, such as bringing up, cultural differences, motivation, previous traumas etc., contribute to the psychological make-up characteristics of every individual, and to his/her response to both stress and pain (e.g., Chrousos 1998; Habib et al. 2001; Nederhand et al. 2004; Asmundson et al. 2004; Richter et al. 2004; De Kloet and Derijk 2004). Recent studies suggest that genetic polymorphisms and alterations in the expression of genes, e.g., the one encoding the alpha$_2$-adrenergic receptors (Finley et al. 2004), as well as the one encoding beta2-adrenergic receptors (see Individual pain sensitivity), are involved in the regulation of magnitude of autonomic response to stress, thus in the individual's susceptibility to stressors.

It merits emphasis that pain is one of the most powerful stressors; therefore the presence of pain per se may enhance the sympathetic outflow.

Vascular control

The blood supply to skeletal muscles is regulated by two competing mechanisms. As in all sympathetically

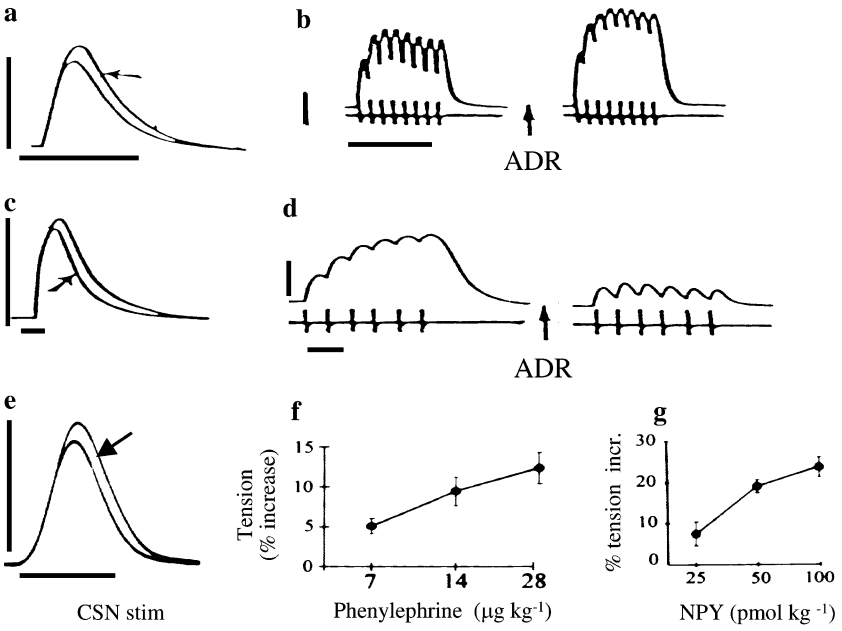

Fig. 1 Effect of catecholamines on the contractile force of fast- and slow-contracting muscles in various territories, in mammals. Intravenous injection of adrenaline (ADR) increases amplitude and duration of the twitch response in fast-contracting tibialis muscle of rabbit as indicated by the *arrow* (**a**) and increases force developed by sub-tetanic contraction (**b** control and after ADR). Conversely, reductions are observed in slow-contracting muscles, such as soleus m. in cat (**c**, **d**). Amount of adrenaline injected: **a** 10 μ/kg, **b** 8 μg/kg, **c** 1 μg/kg, **d** 2 μg/kg. (modified from Bowman 1981, with kind permission of Springer Science and Business Media) Co-operation between noradrenaline and NPY in enhancing the force developed by a fast-contracting muscle, rabbit digastric, is shown in **e**–**g**. Cervical sympathetic nerve (CSN) stimulation at 10 imp s^{-1} (**e**) increases amplitude and duration of maximal twitches. In this territory/species the effect of CSN stimulation is reproduced by close arterial injection of both α1-adrenoceptor agonist phenylephrine, and neuropeptide Y (NPY) with a dose-response relationship (**f**, **g**, respectively), (modified from Grassi et al. 1996, with permission). For all twitches, control and effect of ADR administration/ CSN stimulation (indicated by *arrows*) are superimposed. Calibrations: *vertical lines* correspond to 5 *N* in **a**–**d**, to 1 *N* in (**e**); *horizontal lines* under single twitches to 50 ms (**a**, **c**, **e**); *horizontal lines* under subtetanic contractions to 0.25 s (**b**, **d**)

innervated organs, activation of the sympathetic system, via central command or reflex actions, induces a generalized tonic constriction.[2] of arterioles and precapillary sphincters. In active tissues and organs, the blood flow may increase, provided that the neurogenic vasoconstriction is antagonized and overridden by metabolite-induced vasodilatation, which also occurs in working skeletal muscles (for review and refs see Thomas and Segal 2004). An imbalance between these two actions toward insufficient flow, either due to "excessive" sympathetic vasoconstriction or to insufficient metabolic dilatation, produces hypoxia and toxic effects for inadequate washout of metabolites. Under this condition, free radicals are produced, which change the intracellular oxidation-reduction balance toward oxidation. The ensuing oxidative stress may be responsible for the exercise-induced muscle inflammation, damage and chronic pain (Sjögaard and Sögaard 1998; Jenkins 2000). A persistent condition of oxidative stress is held responsible for deposition of connective tissue undergoing fibrotic degeneration in numerous tissues and organs, among which are muscles (fibromyalgia). In the context of muscle hypoxia, an additional factor should be evaluated, i.e., the intramuscular pressure produced by the contractile activity that may reduce or arrest blood flow. This occurs in all muscles for contractions that constitute small percentages of the maximal voluntary effort and varies in relation to mass and shape of muscle, type of contraction, limb position and external loads (Møller et al. 1979; Järvholm et al. 1988; see for review and refs Sjögaard et al. 2000). This factor becomes particularly relevant in long-lasting contractions such as the static contractions/co-contractions required for the maintenance of posture.

[2] Besides vasoconstrictor sympathetic supply to blood vessels, which is largely predominant, sympathetic cholinergic fibres producing vasodilatation have been reported in experimental animals. However the existence of neurogenic dilatation is still doubtful in human skeletal muscles since morphological and functional data were unable to prove its presence (for review and refs see Joyner and Halliwill 2000; Joiner and Dietz 2003; Passatore and Roatta 2003). Therefore we are not dealing with neurogenic vasodilatation in this article.

Clinical and experimental data from animal models are accumulating in the literature, which suggest a cause–effect relation between hypoxic/ischaemic conditions and chronic myalgia. However, the matter is still unsettled. Even though data on muscular blood flow or morphological changes occurring in subjects affected by WAD are not available, data coming from myalgias of different aetiology may be relevant. Larsson et al. (1988, 1998, 1999), who recorded microcirculation in patients suffering from chronic trapezius myalgia (cervico-brachial pain syndrome), found muscle blood flow to be significantly lower on the more painful side and muscle tension to be somewhat elevated. In addition, morphological data relevant in this context come from studies performed by Thornell's group (Kadi et al. 1998; Henriksson et al. 1993) on muscle biopsies of patients suffering from chronic work-related trapezius myalgia. These data indicate the occurrence of structural changes in this muscle. These changes concern an imbalance between the capillary supply and the cross-sectional area of both type I (slow oxidative) and type IIa (fast, non-fatigable) muscle fibres. In particular, there are indications of: (a) presence of "ragged red" and "moth-eaten" fibres, typically associated with mitochondrial myopaties, which is similar to the picture emerging in animal models of ischaemic muscles; (b) a correlation between pain scores and low capillary-to-fibre-area ratio for both I and II fibre type. The above findings suggest disturbances in microcirculation. The consequence is an impairment of the diffusion of nutrients, of O_2 delivery and washout of metabolic inflammatory substances and CO_2, a condition that, if prolonged, is likely to develop degenerative processes and induce and/or maintain muscle pain (Sjögaard et al. 2000).

The altered metabolite concentration in the intercellular muscle interstitium may activate chemosensitive group III and IV muscle afferents (which include muscle nociceptors) that are known to exert complex reflex actions on spinal neurons, thus starting a number of vicious circles or "positive feedback" loops, which in turn may lead to less efficient intramuscular and intermuscular coordination, as well as to changes in the central processing of nociception (discussed in Positive feedback loops).

In summary, impaired regulation of intramuscular microcirculation, regardless of whether it is due to excessive sympathetic outflow or to damage in the mechanisms involved in metabolic dilatation, may be a causal factor of deterioration of motor coordination and of inducing or maintaining muscle pain. Interestingly, not all muscles behave the same way during stress. In healthy humans undergoing a mental stress task, the sympathetically induced haemodynamic response is reported to vary widely among different jaw muscles (Hidaka et al. 2004a, b). If this variability in the sympathetic influence on different muscles is confirmed in other muscles, this factor is likely to have important implications in the susceptibility of the different muscles to myalgia.

Modulation of skeletal muscle contractility

It has been known for a long time that catecholamines affect the force developed by muscle fibre contraction. The effect is classically described through the modification exhibited by the muscle twitch (muscle response to single-pulse electrical stimulation): the developed force is increased and longer lasting in fast contracting muscle fibres (Fig. 1a, b), while it is decreased and shorter lasting in slow-contracting fibres (Fig. 1c, d) (for review and ref see Bowman 1981). The potentiating effect on fast-contracting fibres, that in the masticatory muscle was shown to be partly mediated by the noradrenaline co-transmitter NPY (Fig. 1e–g) was generally observed in limb muscles at relatively high doses of injected adrenaline or at relatively high frequencies of splanchnic sympathetic stimulation, casting doubts on its actual physiological significance. On the contrary, the inhibitory effect on slow-twitch muscle fibres could be evoked with much lower doses of injected adrenaline (Bowman and Zaimis 1958) as well as thorough reflex sympathetic activation obtained with hypoxic stimulus (Bowman 1981) and is therefore expected to have an impact in physiological conditions.

Few more recent experiments performed on in vitro preparations from different muscles, i.e., isolated muscles or muscle fibre bundles, confirm the above mentioned effects of catecholamines on muscle contractility observed in in vivo, except that increases in twitch amplitude are occasionally reported also for slow-twitch muscle fibres. This discrepancy was attributed to the difference between the in vivo and in vitro experimental models, namely, possible effects of anaesthetics and of circulating hormones and different basal levels of the involved intracellular mediators (Cairns and Dulhunty 1993; Ha et al. 1999). As for the receptors responsible, there seems to be some variability in different muscles and species. Beta2-adrenoceptors are mainly involved and the mechanism responsible has been recently elucidated. These receptors are diffusely present on the sarcolemma, particularly of slow contracting muscle fibres (Elfellah and Reid 1987; Jensen et al. 2002). The increase in muscle force is related to increased Ca^{++} release by the sarcoplasmatic reticulum, while the decreased

twitch duration (slow fibres only) is attributed to accelerated Ca^{++} re-uptake. These effects would be achieved by phosphorylation of both ryanodine receptors and the sarcoplasmic pump regulatory protein phospholamban, respectively, via the cAMP-PKA pathway (Cairns and Dulhunty 1993; Ha et al. 1999). In addition, beta2-adrenoceptors also stimulate the Na/K pump. Due to the ensuing hyperpolarizing effect, activation of beta2 receptors potentiate muscle force during hyperkalemia-induced muscle weakness (e.g., Clausen et al. 1993; Hansen et al. 2005), a mechanism that is considered to mediate the "anti-fatigue" or Orbeli effect (Orbeli 1923).

Adrenergic modulation of muscle contractility was largely investigated in the past but appears to be mostly neglected by the recent literature. Our opinion is that these mechanisms deserve to be reconsidered. In particular, it is relevant in this context the twitch-duration shortening effect in slow-contracting fibres, the relevant fibre type in antigravity muscles, such as neck muscles, the long muscles of the back and the leg extensors. Shorter twitch duration implies a reduction in the force developed by subtetanic contractions, the usual working mode of skeletal muscles. Hence, as a consequence of sympathetic activation, the motor commands to alpha-motoneurons innervating slow-contracting muscle units (essentially postural antigravity muscles) should be enhanced in order that the muscle produces the same force and thus maintains the correct posture/upright position. In other words, during an increase in sympathetic outflow, antigravity muscles may need a different activation pattern, e.g., increase in the number of active motor units or the discharge frequency of individual motor units or both. For any motor action involving muscles with a "mixed" motor-unit composition, motor units are recruited in a certain order, based on the "size principle" of Henneman (1957). In general, the small type I motor units are recruited first (at low forces) and are therefore involved in virtually all motor acts, irrespectively of the strength of the contraction, thus remaining active for a long time and having less time to rest ("Cinderella" fibres: Hägg 1991). The weakening effect of sympathetic activity on type I fibres worsens their working condition and performance. To this effect that has been described in animal models, has been attributed the sensation of muscle weakness that humans experience in antigravity muscles under conditions of stress and fear, as well as in patients suffering from phaeochromocytoma (Bowman and Nott 1969). It remains to be established whether the sensation of muscle weakness often experienced by WAD patients may have the same origin.

Modulation of proprioceptive activity

There is an abundant literature showing that SNS activation and sympathomimetic drugs are able to modulate the discharge of numerous mechanical and chemical receptors, through an action exerted on the receptors themselves or on their first neurons (reviewed by Akoev 1981; Koltzenburg 1997; Roatta et al. 2003), thereby affecting reflex actions mediated by these receptors.

For skeletomotor functions, sensory afferents from muscle spindles are the most relevant ones since they provide information on muscle length and its changes, and possibly contraction parameters (e.g., Prochazka 1996). As discussed above, such proprioceptive information is widely employed in motor reflexes as well as in higher functions connected with motor control. In a number of experimental animal models, e.g., rats, rabbits and cats, activation of the SNS has been shown to affect sensory information from spindles in jaw, neck and limb muscles (Hunt 1960; Hunt et al. 1982; Matsuo et al. 1995; Roatta et al. 2002b; Hellström et al. 2005). This action that is particularly pronounced in jaw and neck muscles, is generally characterized by a depression of the sensitivity to muscle length changes (Fig. 2), while the basal discharge shows reductions or enhancements, as shown in Fig. 2a, b, respectively. The reduction in spindle sensitivity may explain the sympathetically induced decrease in the magnitude of both jaw jerk and tonic vibration reflex in jaw muscles shown in Fig. 3 (Grassi et al 1993a, b). This means that the *quality of proprioceptive information* on muscle length changes is worsened, which should negatively impact on feedback correction of movements, i.e., on the ability of the motor system to correct perturbations. The latter effect was recently confirmed by Roatta et al. (2005) in an experimental rabbit model, in which rhythmical jaw movements were induced by electrical stimulation of the cortical masticatory area. In these experiments, the sympathetic stimulation induced: (a) a powerful reduction in the excursion of the mandibular movements, preceded by a transient enhancement (Fig. 4), this effect reproducing the sign and time course of the effects exerted by sympathetic activity on the jaw-closing spindle afferent discharge, and (b) a considerable change in the characteristics of the rhythmic movements in response to ramp-and-hold force pulses delivered to jaw-closing muscles, which shows a sympathetically induced reduction in the ability to correct perturbations.

As mentioned above, sympathetic activation also affects the basal discharge rate of the spindle afferents, inducing reductions or enhancements (Roatta et al. 2002b; Hellström et al. 2005). Even though the origin

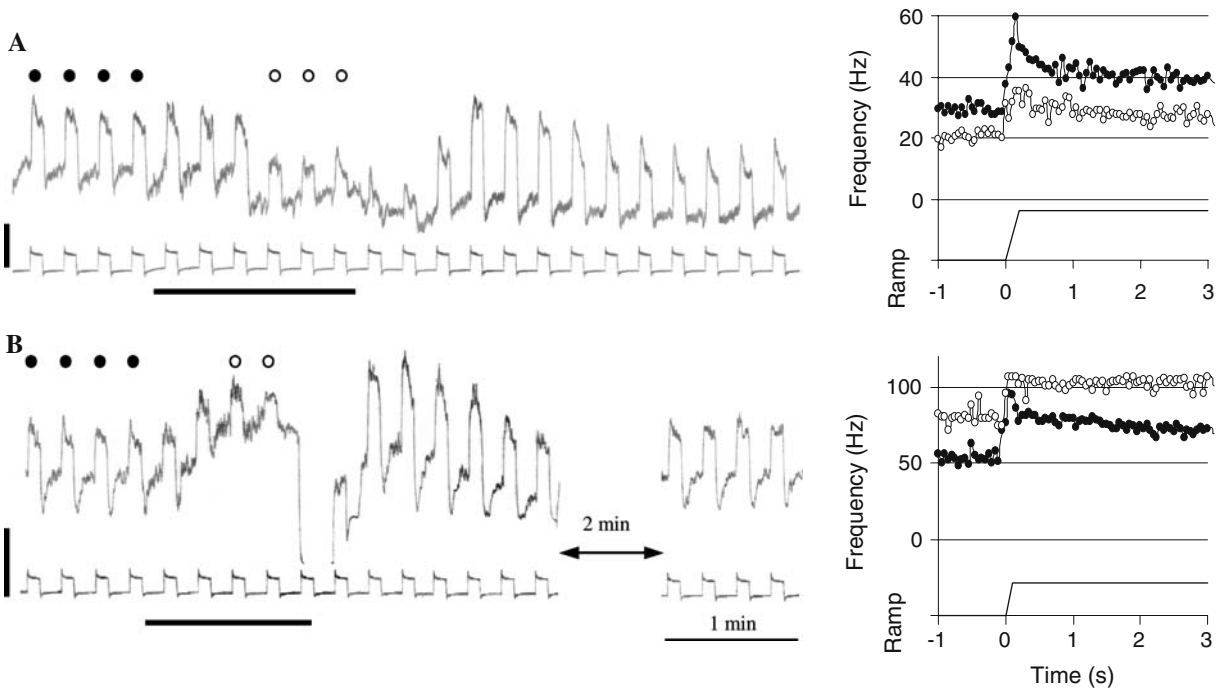

Fig. 2. Changes in sensitivity of muscle spindle afferents (MSA) induced by sympathetic stimulation. Typical examples of the effect of sympathetic stimulation at 10 imp s^{-1} on a group Ia (**a**) and a group II (**b**). MSA located in the masseter muscle, while trapezoidal stretches were delivered by lowering the mandible. The *left* side shows records of integrated afferent activity (upper traces in **a** and **b**) and the tension signal detected by the puller (lower traces; calibration: 2 *N*), providing a reference of the stretch stimulus. The heavy *horizontal bars* indicate CSN stimulation. On the *right* side are shown averages of MSA responses to a number of consecutive trapezoidal stretches, selected before (control: *close circles*) and during sympathetic stimulation (*open circles*); the traces below are the corresponding length signals: 2 mm for **a**, 1 mm for **b**. The stretch responses selected for averaging are marked with the same symbols on the left records (from Roatta et al. 2002, with permission)

of this difference is not clear as yet, this effect is of obvious importance since the baseline activity of spindle afferents, through its support to alpha-motoneurons, contributes to muscle tone. Moreover, the observation that effects on stretch sensitivity and basal discharge rate also have different time courses suggest that more than one mechanism mediates the response; different sites on the muscle spindles may be the target of sympathetic transmitters, in particular extra-junctional regions of intrafusal muscle fibres, sensory endings of group I and II spindle afferents and the encoding site have been hypothesized (Roatta et al. 2002b).

A debated issue

The issue of sympathetic modulation of muscle spindle afferent activity is being debated since many years for different reasons, namely: sympathetic innervation of muscle spindles was thought to concern only a percentage of muscle spindles ranging between 8 and 65% in different muscles (Barker and Saito 1981) and the 10 Hz stimulation frequency of sympathetic pathways employed in several studies (e.g., Grassi et al. 1993a, b; Hunt el al. 1982; Matsuo et al. 1995; Roatta et al. 2002a, b, 2005; Hellström et al. 2005) is considered to be beyond physiological limits. A number of investigators therefore considered the sympathetically induced effects as being secondary to the concomitant reduction in blood flow, and devoid of any physiological meaning (Hunt et al. 1982). On the other hand, the effects of sympathetic stimulation on MSAs (a) were not appreciably affected by occlusion of the blood supply to the relevant muscles (Roatta et al. 2002b; Hellström et al. 2005), (b) were often produced also by 3–5 Hz stimulation frequencies. Incidentally, a large amount of studies based on microneurography have indicated surprisingly low firing rates (<1 Hz) in postganglionic sympathetic fibres, particularly in human subjects (Macefield and Wallin 1999; Macefield et al. 2002). However the preganglionic fibres in the cervical sympathetic trunk appear to have rather high firing frequencies 1.4–2.9 Hz (Mannard and Polosa 1973; Jänig and Schmidt 1970; refs in Jänig 1985) in resting conditions while, in response to sympathetic activation stimuli, firing frequency in sympathetic fibres has, in some case, been reported to exceed 10 Hz on average

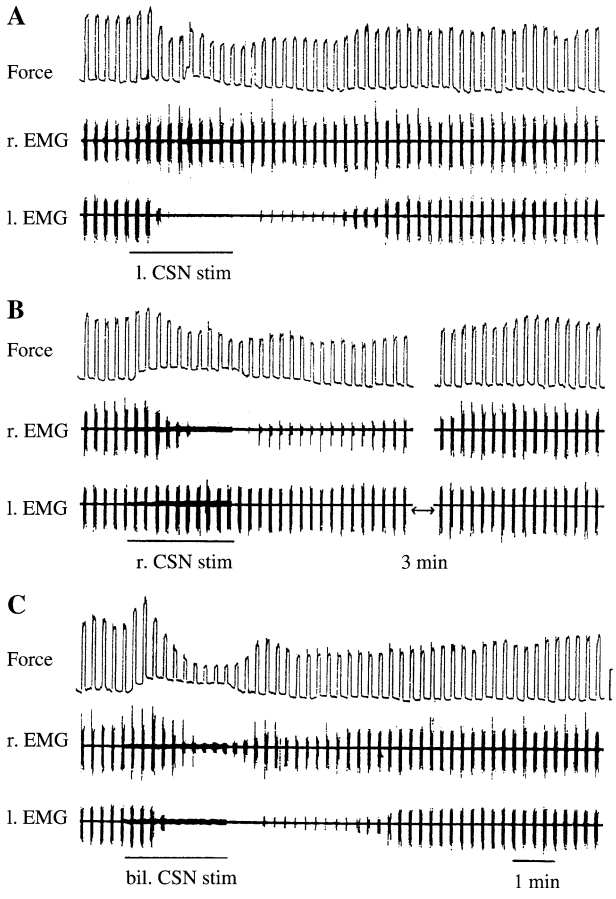

Fig. 3 Effects of CSN stimulation on tonic vibration reflex (TVR) in jaw elevator muscles. TVRs are elicited by 5 s-lasting vibrations repeated every 15 s (170 Hz, 30 μs peak-to-peak amplitude). Stimulations at 10 imp s^{-1} are performed on left (**a**), right CSN (**b**) and bilaterally (**c**). In each trial, traces from top to bottom: tension developed by each reflex contraction, EMG records from right and left masseter muscles. Tension calibration: 0.5 *N*

(Dorward et al. 1987). As a final methodological consideration, it should be reminded that, the electrical supramaximal stimulation at constant frequency remains a rather different pattern of activation as compared to the selective recruitment of sympathetic fibres, firing asynchronously and in "bursts", as occurs in physiological conditions. Therefore the physiological MSA response to sympathetic activation is likely to be different to the one observed experimentally.

A conclusive support for a direct control operated by the sympathetic innervation on muscle spindle is provided by the recently reported presence of adrenergic receptors on the surface of the large majority of intrafusal muscle fibres (Bombardi et al. 2006), in rabbit masticatory muscles. Bombardi et al.(2006) confirm the presence of sympathetic fibres, visualized by immunofluorescent labelling of the noradrenaline-synthesizing enzymes tyrosine hydroxylase and dopamine beta-hydroxylase, along the entire length of the spindles, within the capsule lamellar layers or within the periaxial fluid space and in close apposition to intrafusal fibres. In addition a high density of α_{1a}-adrenoreceptors is revealed by immunohistochemical fluorescent method, at the polar region of both bag and chain intrafusal fibres, in 88.1% of the muscle spindles tested. Localization of the α_{1a}-adrenoreceptors in the polar regions of the spindles suggests that the sympathetic mediator modulates the spindle afferent discharge by altering the mechanics of both types of intrafusal fibres. Along the same lines are preliminary observations suggesting the presence of NPY release sites and receptors in a large number of muscle spindle fibres, both bag and chain, in human lumbrical muscles (L-E. Thornell, personal communication).

Human studies

Although sympathetic modulation of muscle spindle afferent activity is well documented in animal studies, its relevance for human beings has been debated in the recent literature. Several research groups have investigated possible alterations in proprioception or in motor control in healthy humans, in whom acute increases in sympathetic activity were provoked by stimuli of different type. Matre and Knardahl (2003) showed that proprioceptive acuity at the ankle joint was not reduced by sympathetic activation induced either by a cold-pressor test or glucose ingestion. A similar conclusion was reached by Macefield et al. (2003) who stated that inspiratory capacity apnoea and maximal expiratory apnoea, i.e., manoeuvres increasing muscle sympathetic nerve activity, did not affect MSA activity as assessed by microneurography from relaxed ankle extensor muscles. On the contrary, Christou et al. (2004) reported an increase in the fluctuations of the pinch-grip force, i.e., a decreased control of muscle force, when stressing the subject with painful electrical stimuli. In the last study, the effectiveness of the stressor was evidenced by both the results of cognitive assessment and by the significant increase in the plasma concentrations of stress hormones (epinephrine, norepinephrine, ACTH). In another study, handgrip, post-handgrip ischemia and mental stress were shown to increase the stretch reflex in soleus muscle (Hjortskov et al. 2005). In other studies, stressors of various qualities and intensities have been shown to impair motor performances in humans, with the same stressor eliciting different effects, depending on the intensity as well as basal conditions of anxiety of the subjects (e.g., Noteboom et al. 2001; Sade et al. 1990). The variability of results in human studies may depend on three main reasons: (a) the adopted stimuli may

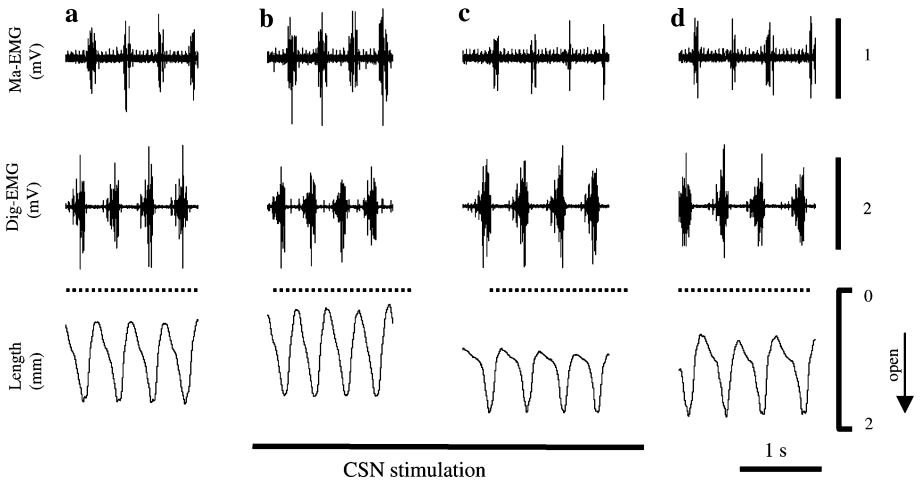

Fig. 4 Effect of CSN stimulation on a sequence of rhythmic jaw movements induced by electrical stimulation of the masticatory cortex, in a rabbit detail of masticatory cycles collected before starting CSN stimulation (**a**), at the initial transient excitatory phase induced by the stimulation (**b**), during full effect of the stimulation (**c**), and return to control pattern (**d**). From top to bottom: EMG from masseter muscle (*Ma-EMG*), from digastric m. (*Dig-EMG*) and mandibular displacements: downward movement indicating jaw opening (*arrow*) and *dotted line* indicating full mouth closure (tooth contact). CSN stimulation at 10 imp s^{-1} (from Roatta et al. 2002b, with permission)

produce changes in the central sensory-motor circuitry, including changes in gamma fusimotor activity, which is difficult to control in awake humans; (b) it may be difficult to effectively stress enrolled volunteers, (c) SNS is known to differentially affect different target depending on the different stressors (for review and refs see Jänig and Habler 2000a) and it is not known as yet which is the adequate stressor that activates sympathetic pathways to muscle spindles.

Implications

Provided that results from animal studies will be confirmed in humans, the possible implications may be hypothesized on the basis of what is known about the role of this proprioceptive information in body function (see above, Motor control). In particular, the powerful inhibition exerted by the sympathetic nervous system on proprioceptive information could contribute to explain several disorders in sensorimotor functions observed in subjects suffering from WAD, such as impairments of position sense and postural performance during perturbations (Michaelson et al. 2003; Treleaven et al. 2003, 2005; Madeleine et al. 2004). As already discussed, the reduced quality of proprioceptive information might be responsible for the reduction of the efficiency and precision of movements, which, if maintained over time, may produce a reorganization in the activation of neck-shoulder muscles. Such re-adjustments of the motor strategy often consist in additional co-contraction of accessory muscles aimed at stabilizing the joints, thus reducing the degrees of freedom of moving structure (Messier et al. 2003; Laursen et al. 1998; Ghez and Sainburg 1995; Gribble et al. 2003). In turn, in the long run, static contractions such as co-contractions may progressively activate a number of vicious circles (also discussed below) leading to musculoskeletal problems and to the development and/or maintenance of myalgias (Veiersted et al. 1993; Björklund et al. 2000; Van Dieën et al. 2003).

The above-described action of the sympathetic system on muscle spindles has also been implicated in the mechanisms behind myofascial trigger points (TrPs). TrPs are generally defined as "hyper-irritable nodules of spot tenderness in a palpable taut band of skeletal muscles" (Simons 2004). They are the main manifestation of the myofascial pain syndrome (Rivner 2001; Simons 2004) but are also reported in many other musculoskeletal disorders including WAD (Dommerholt 2005; Packard 2002; Friedman and Weisberg 2000). Hubbard and Berkoff (1993) first hypothesized that a hyperactive muscle spindle excited by the sympathetic system lay at the TrP site: Electrical activity (detected by needle EMG) of presumed intrafusal muscle fibres was seen to increase with stress and to cease with alpha-adrenergic blockade, and a muscle spindle was found in a biopsy performed at a TrP in one patient (Hubbard and Berkoff 1993; McNulty et al. 1994; Hubbard 1996). Treatment with local injections of the alpha-blocker phenoxybenzamine proved effective in reducing muscle pain in the long term (4 months). This attractive hypothesis, although accounting for a number of clinical and experimental observations, is still

debated and competes with alternative explanations (Rivner 2001; Simons 2004).

Modulation of nociceptive activity

The sympathetic nervous system is able to modulate sensory information through actions exerted both at the receptor level and along the transmission pathways (for review and refs see Koltzenburg 1997; Roatta et al. 2003; Windhorst 2003b). These actions, even though reported for a number of receptors, are not considered relevant in modifying nociceptive information under physiological conditions. However, they may become powerful under pathological conditions, when some "precipitating factor" intervenes, such as peripheral nerve lesions resulting from injury or compression, trauma of soft tissues, inflammatory processes or previous sensitisation of the relevant receptors. Whiplash trauma, which implies most of the above conditions, is certainly one possible "precipitating factor". Moreover, there are several forms of chronic regional pain syndromes that manifest autonomic symptoms, such as sweating and temperature dysregulation in the affected area. In these syndromes, pain is maintained by sympathetic efferent innervation or by circulating catecholamines, and is relieved by sympathetic blockade (Bonica 1979; Nathan 1983; Merskey and Bogduk 1994; Schwartzman and Popescu (2002): a symptom defined sympathetically-maintained pain (SMP, see also footnote 3). Moreover, acute stress was shown to induce/increase pain in patients affected by various chronic pain syndromes, the effect being generally independent of changes in EMG activity in the relevant muscles (Bansevicius et al 2001; Ge et al. 2006). As suggested by Koltzenburg (1997) and summarized in Fig. 5A, a, SMP may be a symptom of several diseases. Also, the intensities of SMP and sympathetically independent pain may vary in the different diseases, as well as in different stages of the same disease, as exemplified by the points X and Y in Fig. 5A, b.

The sympathetic action is exerted particularly on scarcely myelinated or unmyelinated fibres, type III and IV, respectively, which convey information on pain as well as on the chemical–metabolic status of the muscle.

Some of the mechanisms through which the sympathetic system may change nociceptive transmission, that have been identified in animal experimental models, are illustrated in Fig. 5B, a–c (for review and refs see Koltzenburg 1997; Baron et al. 1999; Windhorst 2003a, b). In particular, at peripheral level, a nerve lesion may induce loss of normal electrical insulation in the afferent fibres, which makes these neurons more accessible to diffusible substances and may trigger the

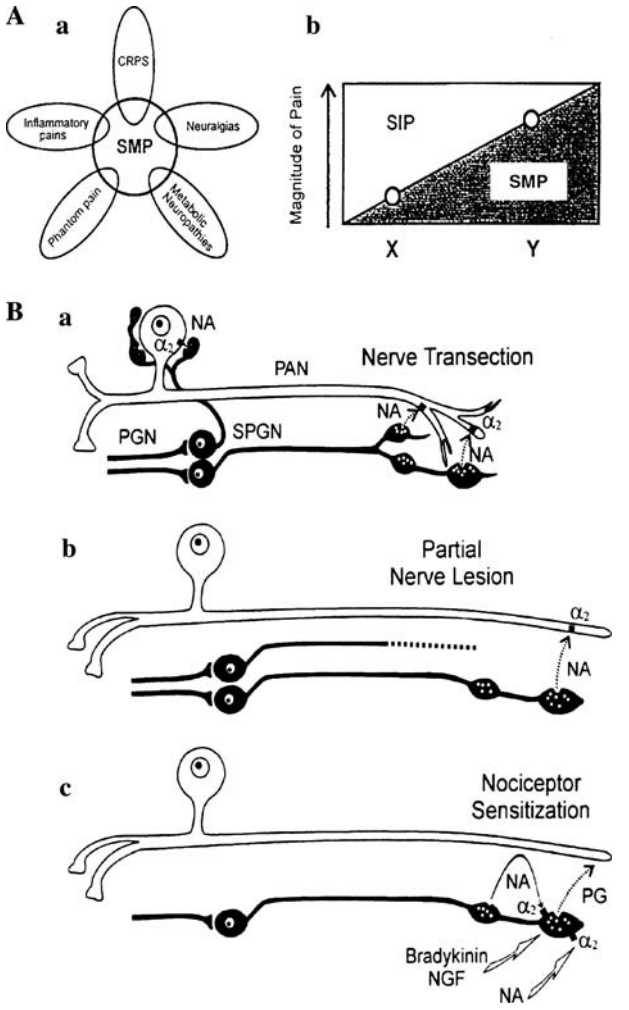

Fig. 5 Modulation of nociception by the sympathetic outflow. Sympathetically-maintained pain (*SMP*) may be a symptom in many chronic pain syndromes (**A**, **a**). The relative proportion between SMP and sympathetically-independent pain (*SIP*) may vary widely in the different diseases, as well as in the different stages of the same disease, as exemplified by the points X and Y (From Koltzenburg 1997, with permission). Possible mechanisms underlying SMP in disease states of different aetiology, which involve nerve injuries or inflammation (**B**, **a**–**c**). *CRPS* complex regional pain syndrome, *PAN* primary afferent neuron, *PGN* sympathetic preganglionic neuron, *SPGN* sympathetic postganglionic neuron, *NA* noradrenaline, *NGF* nerve growth factor, *PG* prostaglandins (from Baron et al. 1999, with permission)

production of alpha-adrenoceptors on the membrane of primary afferent neurons. In this condition, noradrenaline released by sympathetic terminals as well as circulating catecholamines released by the adrenal glands can evoke pain by producing excitation of a number of skin nociceptors and/or enhancing their responsiveness to nociceptive stimuli. The injured fibres may develop abnormal electrogenic membrane properties that accompany the loss of normal electric insulation. This may lead to non-synaptic communication

between different classes of neurons ("ephaptic transmission", i.e., a type of electric coupling between contiguous neurons entailing a direct transfer of current). This mechanism may lead to the production of pain and aberrant sensations such as mechano-hyperalgesia and allodynia (Shyu et al. 1989a, b for review and refs see Baron et al. 1999). In addition, morphological changes are reported, such as sprouting of sympathetic postganglionic fibres around cell bodies in dorsal root ganglia to form "basket-like" structures (Fig. 5B, a). These close contacts with sensory neurons would enhance their excitability, increase their spontaneous activity and/or evoke activity in silent neurons (Chung et al. 1996, 1997; McLachlan et al. 1993). In a rat model of sciatic nerve lesion, these catecholaminergic baskets start to appear 4 weeks after the lesion and increase in number up to 8 months afterwards (for review see Jänig and Häbler 2000b). However, it is not yet established to what extent the pain symptom in this model follows the time course of these morphological changes. In addition, varicosities may be generated in efferent sympathetic fibres and alpha-adrenoceptors be produced at the plasma membrane of axotomized afferent neurons (Fig. 5B, b). In recent work on chronic constriction injury to innervation of rat lower lip (Grelik et al. 2005) and hind paw (Yen et al. 2006), a significant sympathetic sprouting is reported, temporary and permanent, respectively, to areas of the upper dermis usually not containing sympathetic fibres. The observation that such ectopic sympathetic fibres do not innervate blood vessels but form a novel fibre arrangement, being wrapped around sprouted peptidergic nociceptive fibres, induce Yen et al. to suggest that this novel fibre arrangement after nerve lesion may play an important role in the development and persistence of sympathetically maintained neuropathic pain after partial nerve lesions.

Sensitivity to noradrenaline may also develop in non-injured (intact) primary afferents as a consequence of *tissue inflammation.* Levine et al. (1986) suggested that such sensitisation is not due to the direct action of noradrenaline on the sensory fibre, but is mediated by the release of prostaglandins from α_2-adrenergic receptors at the sympathetic terminals (Fig. 5B, c). Sympathetic terminals seem to be involved in bradykinin- and NGF-induced nociceptor sensitisation, both substances being released upon tissue injury and inflammation. Incidentally, the same mechanism may contribute to synovial plasma extravasation, which is dependent on the presence of intact postganglionic sympathetic neurons, even when they are not active (Miao et al. 1996).

In chronic pain conditions, the picture may be complicated by the intrinsic plastic properties of the sympathetic nervous system and by the influence it exerts on trophism and phenotype of neighbouring cells.

In the sympathetically-dependent pain states, chemical or surgical sympathectomy usually alleviates pain and mechanical allodynia in a number of human and animal models, while the symptoms may be reproduced in asymptomatic subjects by local administration of catecholamines (Procacci et al. 1975; Price et al. 1998; Baron et al. 1999; Jänig and Häbler 2000b) even though this does not occur in all stages of the illness (e.g., Fig. 5A, a, from Koltzenburg 1997).

It clearly emerges from the above that a stress-induced increase in sympathetic activity may, in the presence of a "precipitating factor", influence the generation, maintenance and perception of pain.

The experimental data reviewed above do not tell what happens in WAD patients following a lesion in nervous structures, such as fibres innervating facet joints, dorsal root ganglia, etc. (e.g., Taylor et al. 1998; Hartling et al. 2001). However, provided the concepts can be extrapolated to WAD, the important point is that, among the numerous mechanisms contributing in neuropathic pain, some act very fast since they rely on physiological changes at existing structures, while others, which require the development of new anatomical structures (new nerve fibres or connections, new blood vessels) may appear much later.

In more general terms, the knowledge of the multifarious mechanisms involved in pain, as well as the time course of each of them and the relationship between them, would be obviously of great importance to intervene with therapeutic measures at the right time, with the aim, as pointed out by Woolf (2004), to move from symptom control toward mechanism-specific pharmacological management of pain.

Positive feedback loops

Above, the interactions between the sympathetic nervous system and the somatosensory system have been dealt with separately in order to detail the underlying mechanisms. In this section, we intend to provide a more integrated and global view. The emphasis is now on the potential vicious circles that may develop and reinforce each other, sustained by the individual processes discussed above, as well as by others mechanisms not involving the sympathetic nervous system.

The concept is schematised in Fig. 6, in which the main sympathetic action at muscle level are reproduced; note that group III and IV muscle afferents provide one possible positive feedback pathway. These afferents may in fact be activated in response to

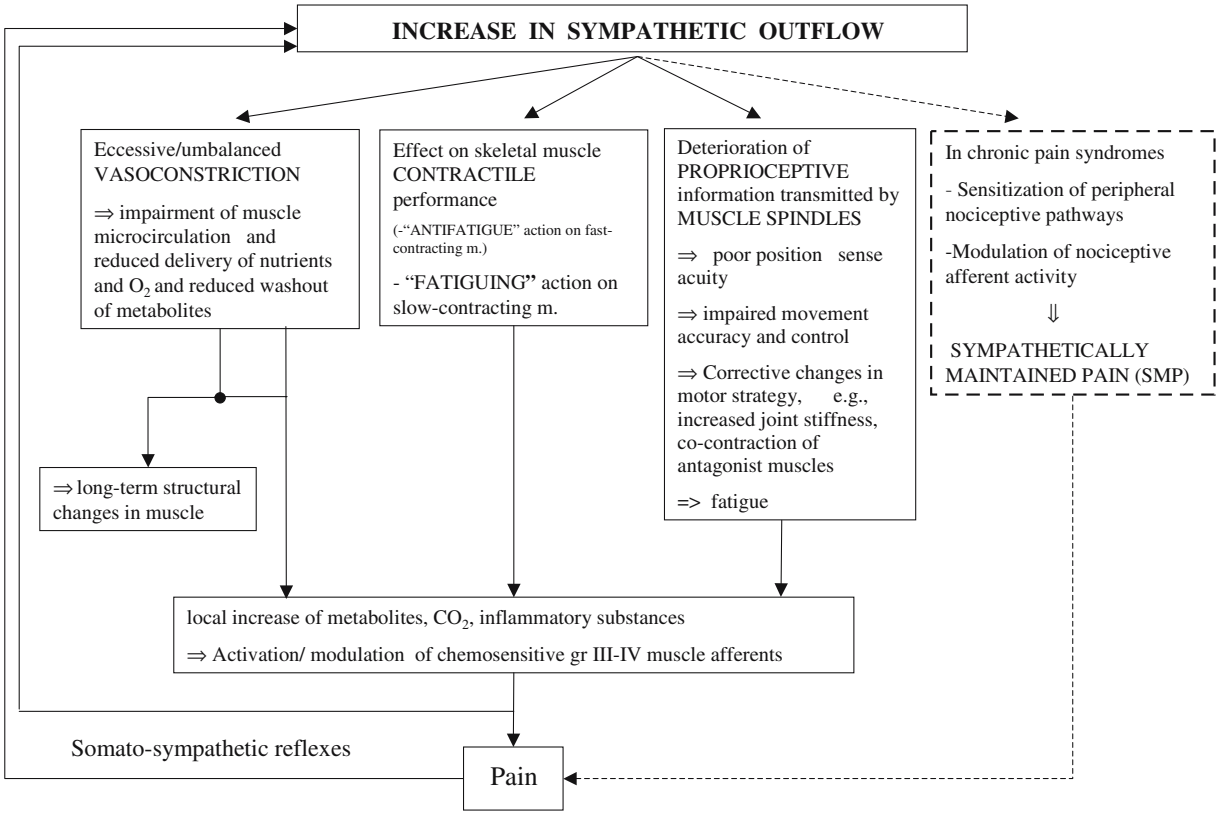

Fig. 6 Actions of the sympathetic system on muscle function, which may play a role in the development and maintenance of chronic muscle pain states (see text). From the left, continuous *line boxes* list physiological actions that may account for the "development" phase. All of them contribute to increase the local concentration of metabolites thus activating group III and IV afferents; these, in turn, further activate the sympathetic system (somato-sympathetic reflexes), thus potentially establishing multiple positive feedback loops, which may maintain the pain state. On the right, *dashed box*, sympathetic action in chronic pain states may increase pain sensation and, consequently, further increase sympathetic activity (pain-mediated vicious circle)

local increase in metabolite concentration provoked/enhanced by excessive sympathetic activation, acting through various mechanisms. From left to right in the figure, an increased metabolite concentration can be expected from (a) reduced interstitial washout resulting from reduced blood flow secondary to vasoconstriction; (b) increased muscle metabolism due to increased activity in type I muscle fibres, consequent to their reduced contractility; (c) increased activity of accessory muscles, as it may occur when motor strategies are altered with the aim of coping with impaired proprioception. Activation of group III and IV afferents may thus further excite the sympathetic system through the so-called somato-sympathetic reflexes (reviewed by Sato et al. 1997) thus giving rise to a vicious cycle. The final global effect will of course result from the integration of these actions with many other plausible mechanisms. For instance, type I muscle fibres are also involved in the already mentioned Cinderella hypothesis (Hägg 1991), stating that these low-threshold fibres are subjected to overwork and little rest and are thereby likely to be the first to develop signs of fatigue, derangement or inflammation (Larsson et al. 1988; Kadefors et al. 1999). As for the change in motor strategy, it was previously shown that the fear-avoidance model predicts, just like the compensation for reduced proprioception, recruitment of accessory muscles, joint stiffening, static (stabilizing) co-contraction of antagonist muscles, a working mode recognised as being a risk factor for development of chronic myalgias (Veiersted et al. 1993; Veiersted 1996; Sjögaard et al. 2000).

All these mechanisms, some of them largely acknowledged and some still debated, may take part in the development of muscle pain, and in particular to the transition from acute to chronic pain. Sympathetic system activation is in fact one of the recognized factors involved in pain maintenance (see syndromes labelled "sympathetically maintained pain"), and the presence of pain itself is a stress condition that may in turn further activate the SNS, giving rise to an additional positive feedback pathway (Fig. 6, right).

Many other positive feedback loops can be envisaged and have been proposed based on different mechanisms, in most cases the afferent branch still being group III and IV muscle afferents, the major/unique "voice" of the suffering muscle. These afferents have in fact been shown to affect many spinal neural targets involved in motor control, such as gamma-motoneurons, Renshaw cells, alpha-motoneurons, as well as to project to supraspinal centres involved in pain control (for review and refs see Windhorst 2003a, b; Johansson et al. 2003). Given this "final common output", all vicious cycles would reinforce each other; thus a multitude of mechanisms may be involved in the pathogenesis of WAD, and this may apply as well to other chronic muscle pain syndromes of non-traumatic origin.

The possibility that chronic muscle pain may be a pathological state sustained by multiple positive feedback loops is attractive and may explain the effectiveness of different treatments targeted at interrupting one or more of the loops involved. In fact, breaking any of the vicious circles at any peripheral or central point, even for a short time, may diminish the insidious stimuli (e.g., the concentration of metabolites in the muscle) and make the system shift towards its "normal" state, below the "threshold" that triggers the positive feedback reactions.

This mechanism may account, for instance, for the therapeutic effect of the temporary blockade of sympathetic ganglia in CRPS.[3] In I and II patients, the relief from pain was shown to outlast by an order of magnitude the duration of the anaesthetic blockade (Procacci et al. 1975; Price el al. 1998; De Monte et al. 2003; Schattschneider et al. 2006; see also Jänig and Häbler 2000b). It may be observed that the temporary interruption of the loop does not per se prevent a subsequent re-establishment of the vicious circle, along with its pathologic symptoms. However, temporary suppression of the vicious circle and the ensuing tissue relief could, for example, allow for some desensitisation of muscle afferents, which would decrease the gain of the loop thus stabilizing the physiological status (as stated by control theory a positive feedback loop does not produce instability as far as its "open loop gain" remains below 1). If this interpretation is correct the efficacy of the treatment should increase with duration of the blockade or repetition of the treatment. This mechanism may account for the reported complete and "long lasting" remission of pain, which may occur after repeated anaesthetic ganglion blockades, as reported in several types of SMP (e.g., Linson et al. 1983; Rho et al. 2002; for review and refs see Baron et al. 1999; Jänig and Häbler 2000b), as well as in WAD patients (De Monte et al. 2003).

[3] The term complex regional pain syndrome, subdivided in Type I and II (CRPS I, CPRS II) was recommended by the taxonomic Committee of the International Association for the Study of Pain (Mersky and Bogduk 1994). In CRPS I minor injuries precede onset of symptoms while CRPS II develops after major peripheral nerve injury (for rev and ref, and diagnostic criteria, see Mersky and Bogduk 1994; Blair 2003). Sympathetically maintained pain (SMP) is a pain that is maintained by sympathetic afferent innervation or by circulating catecholamines; it may occur in several conditions and is not limited to CRPS I or II (see, for review and refs, Mersky and Bogduk 1994; Blair 2003, see also Fig. 5a).

Final considerations

In this paper we reviewed the main actions exerted by the sympathetic nervous system on motor function, with a focus on their possible involvement in the mechanisms underlying the onset and maintenance of chronic muscle pain in general, and WAD in particular. Sympathetic pathways are involved in a number of positive feedback loops that, under certain conditions, may destabilize homeostasis and lead to pathological states. On this basis, it is suggested that stress may facilitate the development of chronic pain states, irrespective of their non-traumatic (e.g., work-related) or traumatic (WAD) origin.

Many of the experimental data reported above have been collected under conditions of "acute" activation of sympathetic pathways in animal models and healthy humans, and are therefore not directly applicable to chronic pain and/or chronic stress conditions. In fact, the former produces plastic changes in the relevant tissues and sensitisation of peripheral and central nociceptive pathways while the latter also involves activation of the hypothalamic-pituitary-adrenal axis affecting virtually all body functions. Thus, even though the results obtained in "acute" experiments should be interpreted with caution, they suggest the existence of the positive feedback loops outlined in Fig. 6 (the first three from the left), which may be triggered by acute sympathetic activation in an initially healthy tissue. Activation of a positive feedback loop may induce a healthy condition to degenerate into a pathological one by activating a cascade of events, possibly including other vicious circles, so that the final chronic pain condition may be maintained even if the original triggering event has faded away. It is tempting to speculate that the mechanisms and vicious circles involved in this chronicization process could be triggered by different stimuli/conditions (e.g., stress, muscle fatigue, injury/inflammation, etc.) and thereby underlie the pathophysiological process of many

chronic pain syndromes of different aetiology. Each vicious circle in principle leads to an alteration of the physiological states that, if maintained "long enough", may produce plastic, i.e., permanent, changes in the system. The identification of these mechanisms and the characterization of their *time course* would be of great relevance for advances in prevention, treatment and successful rehabilitation.

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