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# Potential Muscle Biomarkers of Chronic Myalgia in Humans – A Systematic Review of Microdialysis Studies

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## 1. Introduction

### 1.1 Epidemiology

Approximately 20% of the European population report severe chronic pain (Breivik et al., 2006), with higher prevalences in women and in lower income groups (Gerdle et al., 2004; Larsson et al., 2007). Common chronic pain conditions are localized neck-shoulder pain including trapezius myalgia (prevalence in population 10-20%) (Lidgren, 2008), chronic whiplash associated disorders (WAD) (prevalence in the population 1.5%) (Guez et al., 2002), and chronic widespread pain (CWSP) (prevalence in population 5-10%) (Gerdle et al., 2008a). Chronic pain is associated with disability, low quality of life, and substantial socioeconomic costs (Breivik et al., 2006; Phillips, 2006; SBU, 2006).

### 1.2 Development of chronic myalgia – Chronic trapezius myalgia as an example

There is a connection between physical demands, psychosocial demands, and the risk of persistent muscle pain (Bernard, 1997; Punnett & Wegman, 2004); however, the mechanisms behind chronic myalgia are poorly understood. Myalgia usually starts with a feeling of tiredness and stiffness. At the beginning, the initial intermittent stage, pain can be alleviated for short or long periods. Chronic regional myalgia (CRM) in the neck-shoulder area often gradually becomes more easily triggered and more diffuse and can be spread to include most of the body (CWSP). CWSP includes fibromyalgia, a subgroup characterized by widespread hyperalgesia. The risk factors for the transition from a local/regional pain condition to CWSP are poorly understood (Larsson et al., in press). The diagnoses CRM (e.g., chronic trapezius myalgia) and CWSP are settled by careful anamnesis and clinical examinations that reveal tender muscle at palpation corresponding to the reported painful areas.

### 1.3 Neurobiological alterations in chronic pain

Acute pain results from a complex integrated series of events at peripheral and central levels. In healthy subjects, mechanisms related to acute pain might not necessarily be valid in subjects with subchronic, intermittent, or chronic pain.

Pace et al. suggested two types of persistent chronic pain: 1) nociceptive/inflammatory pain and 2) neuropathic pain (Pace et al., 2006). The present study mainly discusses nociceptive/inflammatory pain. Chronic pain is more complex than acute pain as extensive short-term and long-term plastic and sometimes permanent changes (including peripheral and/or central hyperexcitability/sensitization) of the pain transmission system can occur at different levels (Kuner, 2010; Reichling & Levine, 2009) and by the modification of psychological (e.g., attentional, emotional, and anticipation status) and context factors (Grachev et al., 2000; Hunt & Mantyh, 2002; Petersen-Felix & Curatolo, 2002; Schmidt-Wilcke, 2008; Wilder-Smith et al., 2002; Woolf & Salter, 2000). Different structures in the brain – vaguely labelled as the pain matrix (Iannetti & Mouraux, 2010; Lee & Tracey, 2010; Legrain et al., 2011) – are dynamically involved in processing of nociception and pain (including emotions, cognitions, and motivation) (Ossipov et al., 2010). In patients with chronic pain conditions, a pain matrix shows different types of alterations including morphological changes (Apkarian, 2008; Schweinhardt & Bushnell, 2010), indicating that different chronic pain conditions exhibit unique anatomical “brain signatures” (Baliki et al., 2011).

Descending supraspinal control of spinal nociception originates from many brain regions (Heinricher et al., 2009; Ossipov et al., 2010). The descending supraspinal control includes a dynamic balance between inhibiting and facilitating mechanisms that can be altered due to behavioural, emotional, and pathological states (Heinricher et al., 2009; Ossipov et al., 2010). When the system shifts towards inhibition, hyposensitivity or lack of pain in spite of inputs from peripheral tissue may result (Heinricher et al., 2009; Kuner, 2010; Porreca et al., 2002; Ren & Dubner, 2002; Robinson & Zhuo, 2002; Wilder-Smith et al., 2002). The evolutionary value of this is that the organism can ignore pain during critical situations, e.g., flight or fight scenarios (Kuner, 2010). A facilitating shift of the descending system has been reported for different groups of patients with persistent pain (Heinricher et al., 2009; Julien et al., 2005; Kuner, 2010; Porreca et al., 2002; Ren & Dubner, 2002; Robinson & Zhuo, 2002; Wilder-Smith et al., 2002).

Decreased production of substances such as endorphins or gamma-aminobutyric acid (GABA), the most common inhibitory neurotransmitter in the central nervous system, may contribute to disturbances in pain inhibition. Animal and human studies have confirmed that the endogenous opioid system and GABA play a role in the modulation of pain. However, the understanding of the mechanisms, including the peripheral balances between nociceptive and antinociceptive processes, behind chronic myalgia is incomplete. The analgesic properties of *exogenous* cannabinoids have been recognized for many years. Data clearly implicate endocannabinoids as endogenous tonic pain controlling molecules (Agarwal et al., 2007; Richardson et al., 1998; Walker & Huang, 2002), but little is known as to whether *peripheral* endocannabinoid signalling is disturbed in human pain.

#### 1.4 Muscle nociception and peripheral sensitization

Neurophysiological studies have indicated that small-diameter, slowly conducting afferent nerve fibres from skeletal muscle – free nerve endings of group III (A $\delta$ ) and IV afferent (C) fibres – have to be excited to elicit pain (Mense, 2003). The nociceptor is specialized to respond to noxious stimuli and communicate this information to the CNS. Nociceptors or noxious stimulus detectors (Woolf & Ma, 2007) are sensitive to chemical substances released from damaged or overloaded cells and excessive tissue deformation (Coutaux et al., 2005; Mense, 1993). Nociceptors respond to single or combinations of stimuli: noxious mechanical

stimuli, temperature, and chemical substances such as serotonin  $H^+$ , (5-HT), bradykinin (BKN), glutamate, prostaglandin  $E_2$  ( $PGE_2$ ), substance P, nerve growth factor (NGF), ATP, and potassium (Coutaux et al., 2005; Mense, 1993; 2009). Administration of any of these substances, alone or in combination, results in excitation of nociceptors (Mense, 1993). The relative effectiveness of these substances is unknown. In a pathophysiological situation due to trauma or inflammation, a combination of substances acts on the nociceptors (the inflammatory “soup” or “cocktail”)(Mense, 2009). The nociceptor is not a static detector as plastic changes can occur such as peripheral sensitization (Woolf & Ma, 2007). A sensitized nociceptor has a lowered threshold for activation and can thus be activated by stimuli that are normally innocuous (Coutaux et al., 2005; Mense, 1993). Several substances – e.g.,  $H^+$ , NO,  $K^+$ , ATP, bradykinin (BKN),  $PGE_2$ , NGF, TNF- $\alpha$ , IL-6, and glutamate – are known to cause peripheral sensitization (Coutaux et al., 2005; Mense, 2009; Momin & McNaughton, 2009). The action of these substances is mediated by their specific receptors mainly found in three classes: 1) G protein coupled receptors; 2) receptor tyrosine kinases; and 3) ionotropic receptors/ion channels (Linley et al., 2010). Sensitization is often accompanied by an increase in the sensitive area (Mense, 1993). In addition, other alterations of the nociceptors, including activation of silent nociceptors, have been found as the result of injury or inflammation (Schaible et al., 2009). When persistent alterations in the nociceptors as the result of induced gene transcription and protein synthesis drive pain in the absence of noxious stimuli these alterations represent a pathological condition (Woolf & Ma, 2007).

### 1.5 The bio-psycho-social model of chronic pain

The net result of the above mentioned and other alterations are clinically registered as pain hypersensitivity – an increased responsiveness to nociception and sometimes to innocuous stimuli. In clinical management of chronic pain, a bio-psycho-social model (Gatchel et al., 2007) is preferred since the above mentioned complex blend of factors – neurobiological, psychological (e.g., depression, catastrophizing, and anxiety), coping styles, and contextual factors – contribute to the development and maintenance of chronic pain (Alonso et al., 2004; Asmundson & Katz, 2009; Börsbo et al., 2008; Dersh et al., 2001; Ericsson et al., 2002; Means-Christensen et al., 2008; Ocañez et al., 2010; Sofat et al., 2011; Sullivan et al., 2001).

### 1.6 Central versus peripheral causes for chronic pain

One of the consequences of the discovery of central sensitization is that CNS can change pain –e.g., amplification, duration, degree, and spatial extent – so that pain no longer directly reflects the peripheral noxious situation (Woolf, 2011). It is unknown whether a chronic pain condition can be driven by established central alterations such as central hyperexcitability, alterations in pain matrix, and alterations in descending mechanisms (facilitation) with very little or no peripheral stimuli or nociception. However, there are several indications that central alterations in nociceptive processing are driven by peripheral tissue alterations (Gerdle et al., 2008c) and peripheral nociceptive input (Schneider et al., 2010; Staud, 2010; Staud et al., 2009; Woolf, 2011).

### 1.7 The microdialysis technique

Concerns have been expressed at the lack of success in translating basic science data using animals into clinical analgesics (Lascalles & Flecknell, 2010). Microdialysis may be able to

replace animal experiments (Langley et al., 2008). The microdialysis technique offers a well-established *in vivo* method for studying the local biochemistry of individual tissues in the body (Ungerstedt, 1991), e.g., nociceptive and metabolic mechanisms. This technique has been used in neuroscience to monitor neurotransmitter release, but has also found application in monitoring the biochemistry of peripheral tissues in both animals and humans (Ungerstedt, 1991).

Microdialysis mimics the function of a capillary blood vessel by perfusing a thin dialysis tube (catheter) implanted into the tissue with a physiological saline solution. Through simple diffusion, substances can move across the dialysis membrane along the concentration gradient. The chemical analysis of the dialysate reveals the composition of the extracellular fluid. Thus microdialysis allows for continuous sampling of compounds in the interstitial space of the muscle, where nociceptor free nerve endings terminate close to the muscle fibres, providing accurate information on regional biochemical changes before such compounds are diluted and cleared by the circulatory system. The trapezius muscle has been used as a *human model muscle* for chronic myalgia both due to its clinical importance and to its accessibility for invasive investigations. Some studies use the masseter, vastus lateralis, and gastrocnemius muscles to examine myalgia.

To determine the concentrations of small molecules such as lactate, pyruvate, glutamate, and glucose, a catheter with a 20 kDa cut-off is usually used (Waelgaard et al., 2006). To determine the concentrations of larger molecules such as cytokines, a catheter with a 100 kDa cut-off is usually used (Waelgaard et al., 2006).

A crucial parameter in microdialysis is relative recovery (RR): the ratio between substance concentrations in the dialysate to that in the perfusate (Afinowi et al., 2009; Dahlin et al., 2010 ; Ungerstedt, 1991). RR is used to determine the true concentration of extracellular fluid. Because the perfusate constantly flows across the membrane, a state of equilibrium will never be achieved and as a result the dialysate will only represent a certain percentage of the actual concentration of the extracellular fluid (Afinowi et al., 2009; Hamrin et al., 2002). Therefore, the final concentration in the dialysate partially depends on the flow rate of the perfusate. Low flow rate results in higher RR; high flow rates, result in lower RR. At a very low flow (i.e.,  $\leq 0.3 \mu\text{l}/\text{min}$ ), the recovery is near 100%, but factors such as alterations in the osmotic pressure, temperature, weight cut-off, area of the membrane, concentration gradient, and composition of the perfusate can influence RR (Dahlin et al., 2010 ; Hamrin et al., 2002 ; Plock & Kloft, 2005 ). Between cytokines have been reported marked variation in RR; molecular weight correlated negatively with RR (Helmy et al., 2009).

## 1.8 Aim

Microdialysis has several important advantages, but studies with patients are expensive and time consuming. Hence a systematic review of the literature is needed. Systematic knowledge of the results of such studies might help provide new assessment approaches of patients with chronic myalgia, new treatments, and new rehabilitation techniques for patients with chronic myalgia. Most research on muscle pain has been conducted on animals; however, this review will primarily focus on human studies of neck and shoulder myalgia, for which the frequently affected trapezius muscle often serves as a model muscle. This study systematically reviews studies in the literature that have investigated alterations



in metabolic substances, pain-related substances (algesics), and anti-analgesics in different chronic muscle pain conditions (mainly myalgia) in humans using microdialysis. This systematic review was done to identify potential biomarkers – an objectively measured and evaluated indicator of, e.g., normal pathogenic processes (Ptolemy & Rifai, 2010).

## 2. Methods

### 2.1 Inclusion and exclusion criteria

Studies that focused on chronic pain conditions affecting human muscles (myalgias) were included. To be included, the studies had to use microdialysis and had to use a patient group and a healthy control group, so articles concerning only healthy subjects have been excluded.

### 2.2 Search strategy

This review identified the studies fulfilling the above criteria in the systematic review of Larsson et al. (Larsson et al., 2007). Furthermore, we modified their search strategy in the following ways: ((muscle OR pain) AND microdialysis) OR (muscle AND pain AND induced) AND (Humans[Mesh] AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Review[ptyp]) AND English[lang] AND adult[MeSH] AND "last 10 years"[PDat]).

Using this strategy, PubMed was searched. From this search, the titles and abstracts were scrutinized. If the articles were relevant and necessary, they were read for further evaluation. We also checked reference lists of these articles. If the article was relevant according to our aim and inclusion criteria, we listed the results in tables. The tables of the different conditions reported the statistics concerning comparisons between the patient group and control group with respect to baseline data or corresponding data for all investigated substances. Moreover, we listed gender, flow rate, number of subjects in each group, and if and how the authors handled RR.

### 2.3 Positive outcome with respect to potential biomarker

A specific substance was classified as a potential biomarker if the majority of studies (including the majority of subjects) showed significantly lower or significantly higher concentrations in the patient group compared to the controls.

## 3. Results

Using the modified search strategy, we had 441 hits after searching PubMed. After screening, we identified 17 articles that fulfilled our inclusion criteria. Thirteen of these were not mentioned by Larsson et al. (Larsson et al., 2007). After scrutinizing these 13 articles and the articles selected by Larsson et al., we found 22 articles concerning different chronic pain conditions involving muscle. These articles are summarized in **Tables 1-7**. Moreover, we identified three articles concerning chronic tendinosis (**Table 8**).

### 3.1 Chronic trapezius myalgia

For chronic trapezius myalgia, we identified seven groups of patients reported in ten studies (**Table 1**). The majority of the studies reported increases in the interstitial concentrations of

lactate (Flodgren et al., 2010; Flodgren et al., 2006; Larsson et al., 2008; Rosendal et al., 2004b; Sjogaard et al., 2010). However, the studies conducted by Flodgren et al. (Flodgren et al., 2010; Flodgren et al., 2006) did not compensate for relative recovery despite the fact that the flow rate was relatively high (2µl/min) compared to a flow rate associated with full recovery (0.3µ l/min).

Study	Condition Number of Subjects, % women (W) Muscles	Substances investigated Flow rate	Results (Comparisons between patients and HC; p-values)	Comments (Compensated for RR (Y/N) or low flow rate* (NA or Y/N)
Flodgren et al. (Flodgren et al., 2005)	Chronic shoulder pain (CSP; n=9), 100% W HC (n=9), 100%W Trapezius	Glutamate PGE <sub>2</sub>  0.3µl/ min	Glutamate-trapezius: ns PGE <sub>2</sub> -trapezius: ns	Compensated for RR: N Low flow: Y
Flodgren et al. (Flodgren et al., 2010)	Chronic trapezius myalgia (MYA; n=14), 100% W HC (compared with healthy subjects (n=20) in (Flodgren et al., 2006)), 100% W Trapezius	Lactate Pyruvate Glutamate PGE <sub>2</sub>  2µl/ min	Lactate-trapezius: ns Pyruvate-trapezius: Glutamate-trapezius: MYA<HC, significant PGE <sub>2</sub> -trapezius: not reported.	Compensated for RR: N Low flow: N
Rosendal et al. (Rosendal et al., 2004b)	Chronic trapezius myalgia (MYA; n=19), 100%W HC (n=20), 100%W Trapezius	Lactate Pyruvate Glutamate 5-HT  5µl/ min	Lactate-trapezius: MYA > HC; P=0.001 Pyruvate-trapezius: MYA > HC; P=0.001 Glutamate-trapezius: MYA > HC; P=0.05 5-HT-trapezius: MYA > HC; P=0.01	Compensated for RR: Y Low flow: NA
Rosendal et al. (Rosendal et al., 2005)	Chronic trapezius myalgia (MYA; n=19), 100%W HC (n=20), 100%W Trapezius	K <sup>+</sup> LDH IL-6 Collagen turnover  5µl/ min	K <sup>+</sup> -trapezius: MYA > HC; P=significant LDH-trapezius: ns IL-6-trapezius: ns Collagen turnover- trapezius: ns	Compensated for RR: Y Low flow: NA

Study	Condition Number of Subjects, % women (W) Muscles	Substances investigated Flow rate	Results (Comparisons between patients and HC; p-values)	Comments (Compensated for RR (Y/N) or low flow rate* (NA or Y/N)
Gerdle et al. (Gerdle et al., 2008b)	Chronic trapezius myalgia (MYA; n=19), 100%W Chronic whiplash associated disorders (WAD; n=22), 100%W HC (n=20), 100%W  Trapezius	BKN Kallidin 5µl/ min	BKN-trapezius: No group differences. Kallidin-trapezius: MYA>HC; P=0.018 No other group differences for this substance.	Compensated for RR: Y Low flow: NA
Larsson et al. (Larsson et al., 2008)	Chronic trapezius myalgia (MYA; n=20), 100%W HC (n=20), 100%W  Trapezius	Lactate Pyruvate Glutamate 5-HT K <sup>+</sup> BKN GM-CSF IL-1β IL-6 IL-8 TNF-α IL-2 IL-4 IL-5 IL-10  5µl/ min	Lactate-trapezius: ns Pyruvate-trapezius: MYA > HC; P=0.032 Glutamate-trapezius: MYA > HC; P=0.005 5-HT-trapezius: MYA > HC; P=0.023 K <sup>+</sup> -trapezius: ns BKN- trapezius: ns GM-CSF- trapezius: ns IL-1β-trapezius: ns IL-6-trapezius: ns IL-8-trapezius: ns TNF-α-trapezius: ns IL-2-trapezius: ns IL-4-trapezius: ns IL-5-trapezius: ns IL-10-trapezius: ns	Compensated for RR: Y Low flow: NA
Ghafouri et al. (Ghafouri et al., 2010)	Chronic trapezius myalgia, (MYA; n=18), 100%W HC (n=30), 100%W  Trapezius	5-HT  5µl/ min	5-HT- trapezius: MYA>HC, P=0.044	Compensated for RR: Y Low flow: NA



Study	Condition Number of Subjects, % women (W) Muscles	Substances investigated Flow rate	Results (Comparisons between patients and HC; p-values)	Comments (Compensated for RR (Y/N) or low flow rate* (NA or Y/N)
Ghafouri et al. (Ghafouri et al., 2011)	Chronic trapezius myalgia, (MYA; n=11), 100%W HC (n=11), 100%W Trapezius	PEA SEA 5µl/ min	PEA-trapezius: MYA>HC, P=0.011 SEA-trapezius: MYA>HC, P=0.002 (The statistics are for dialysate concentrations, but significant differences were found when compensated for RR)	Compensated for RR: Y Low flow: NA
Sjøgaard et al (Sjogaard et al., 2010)	Chronic trapezius myalgia (MYA; n=43), 100%W HC (n=19), 100%W Trapezius	Lactate Pyruvate Glucose K <sup>+</sup> 5µl/ min	Lactate-trapezius: MYA>HC, significant Pyruvate-trapezius: MYA>HC, significant Glucose-trapezius: ns K <sup>+</sup> -trapezius: ns	Compensated for RR: Y Low flow: NA
Shah et al (Shah et al., 2005)	Myofascial trapezius pain with active trigger point (MFActive; n=3) HC with latent trigger point (HClatent; n=3) HC without trigger point (HC;n=3) Trigger points of Trapezius	BKN CGRP Substance P IL-1β TNF-α 5-HT Norepineph rine H <sup>+</sup> 1and 2 µl/ min	BKN-trapezius: MFActive>two other groups; P<0.01 CGRP-trapezius: MFActive>two other groups; P<0.01 Substance P- trapezius: MFActive>two other groups; P<0.01 IL-1β-trapezius: MFActive>two other groups; P<0.01 TNF-α-trapezius: MFActive>two other groups; P<0.01 5-HT-trapezius: MFActive>two other groups; P<0.01 Norepinephrine-trapezius: MFActive>two other groups; P<0.01 H <sup>+</sup> -trapezius: MFActive>two other groups; P<0.01	Compensated for RR: Y Low flow: NA

Study	Condition Number of Subjects, % women (W) Muscles	Substances investigated Flow rate	Results (Comparisons between patients and HC; p-values)	Comments (Compensated for RR (Y/N) or low flow rate* (NA or Y/N)
Shah et al. (Shah et al., 2008)	Myofascial trapezius pain with active trigger point (MActive; n=3) HC with latent trigger point (HClatent; n=3) HC without trigger point (HC; n=3) Trigger points of Trapezius Gastrocnemius medialis without trigger points	BKN CGRP Substance P IL-1β TNF-α IL-6 IL-8 5-HT Norepinephrine H <sup>+</sup> 1 and 2μl/min	BKN-gastrocnemius: MActive>2 other groups; Sign CGRP-gastrocnemius: MActive>2 other groups; Sign Substance P-gastrocnemius: MActive>2 other groups; Sign IL-1β-gastrocnemius: MActive>2 other groups; Sign TNF-α-gastrocnemius: MActive>2 other groups; Sign 5-HT-gastrocnemius: MActive>2 other groups; Sign Norepinephrine-trapezius: MActive>2 other groups; Sign H <sup>+</sup> -gastrocnemius: MActive>2 other groups; Sign Comparisons between trapezius (T) and gastrocnemius (G) in MActive: BKN: T>G; Sign CGRP: T>G; Sign Substance P: T>G; Sign IL-1β: T>G; Sign TNF-α: T>G; Sign IL-6: T>G; Sign IL-8: T>G; Sign 5-HT: T>G; Sign Norepinephrine: T>G; Sign H <sup>+</sup> :ns Comparisons between trapezius (T) and gastrocnemius (G) in MFlatent: BKN, IL-1β, IL-6, IL-8, 5-HT, Norepinephrine, H <sup>+</sup> : ns CGRP: T>G; Sign	Compensated for RR: Y Low flow: NA

Study	Condition Number of Subjects, % women (W) Muscles	Substances investigated Flow rate	Results (Comparisons between patients and HC; p-values)	Comments (Compensated for RR (Y/N) or low flow rate* (NA or Y/N)
			Substance P: T>G; Sign TNF- $\alpha$ : T>G; Sign Comparisons between trapezius (T) and gastrocnemius (G) in HC: BKN: T>G; Sign Other substances: ns	

\*Low flow rate associated with 100% relative recovery was defined as 0.3 $\mu$ l/min.

Table 1. Studies of chronic trapezius myalgia. The results of the different substances are baseline data. Healthy controls are abbreviated as HC. The bold horizontal lines indicate different patient groups.

A similar pattern was noted for the majority of studies reporting increased interstitial concentrations of pyruvate (Flodgren et al., 2010; Flodgren et al., 2006; Larsson et al., 2008; Rosendal et al., 2004b; Sjogaard et al., 2010). Flodgren et al. did not show any significant differences for pyruvate (Flodgren et al., 2010; Flodgren et al., 2006).

Three studies that focused on chronic trapezius myalgia investigated the interstitial muscle concentration of glutamate (Flodgren et al., 2005; Larsson et al., 2008; Rosendal et al., 2004b). In two of these studies (Larsson et al., 2008; Rosendal et al., 2004b), which were markedly larger than the third study (Flodgren et al., 2005), revealed significant increases in the interstitial concentrations of glutamate. In all the studies investigating glutamate, the interstitial muscle concentration of 5-HT was significantly increased (Ghafouri et al., 2010; Larsson et al., 2008; Rosendal et al., 2004b; Shah et al., 2008; Shah et al., 2005). Furthermore, glutamate was also increased in patients with chronic WAD (**Table 2**) (Gerdle et al., 2008c).

Four studies examined the interstitial concentrations of BKN and/or Kallidin (Gerdle et al., 2008b; Larsson et al., 2008; Shah et al., 2008; Shah et al., 2005). Shah et al. (Shah et al., 2008; Shah et al., 2005) found increased levels of BKN in subjects with active trigger points and the levels were higher in the trapezius (with pain) than in a pain-free distant muscle. In contrast, two studies - a field study and a laboratory study - found no differences between patients and controls (Gerdle et al., 2008b; Larsson et al., 2008). Kallidin was only investigated in one study and this study reported significantly higher interstitial levels in patients with chronic trapezius myalgia (Gerdle et al., 2008b).

Several studies have investigated cytokines, but only Shah et al. found significant differences for active trigger points (Shah et al., 2008; Shah et al., 2005). These authors also have compared the levels of cytokines in the myalgic trapezius (trigger points) with a muscle without pain and found higher levels in the aching muscle. These studies, however, are limited because their sample size was small. Larger studies have not found elevated levels of cytokines (Larsson et al., 2008; Rosendal et al., 2005). In three relatively large

studies, potassium revealed no consistent pattern (Larsson et al., 2008; Rosendal et al., 2005; Sjogaard et al., 2010). PGE<sub>2</sub> was not increased in two groups of patients (Flodgren et al., 2005; Flodgren et al., 2010; Flodgren et al., 2006), but the first of these groups was relatively small (Flodgren et al., 2005) and the other had possible methodological drawbacks related to RR (Flodgren et al., 2010; Flodgren et al., 2006).

Study	Condition Number of Subjects, % women (W) Muscles	Substances investigated Flow rate	Results (Comparisons between patients and HC; p-values)	Comments (Compensated for RR (Y/N) or low flow rate* (NA or Y/N))
Gerdle et al. (Gerdle et al., 2008c)	Chronic whiplash associated disorders (WAD; n=22), 100% W HC (n=20), 100% W  Trapezius	Lactate Pyruvate Glutamate K <sup>+</sup> 5-HT IL-6  5µl/min	Lactate-trapezius: ns Pyruvate-trapezius: ns Glutamate-trapezius: ns K <sup>+</sup> - trapezius: ns 5-HT-trapezius: WAD>HC; P=0.05 IL-6-trapezius: WAD>HC; P=0.008	Compensated for RR: Y Low flow: NA
Gerdle et al. (Gerdle et al., 2008b)	Chronic trapezius myalgia (MYA; n=19), 100% W Chronic whiplash associated disorders (WAD; n=22), 100% W HC (n=20), 100%W  Trapezius	BKN Kallidin  5µl/min	BKN- trapezius: No group differences. Kallidin-trapezius: MYA>HC; P=0.018 No other group differences for this substance.	Compensated for RR: Y Low flow: NA

\*Low flow rate associated with 100% relative recovery was defined as 0.3µl/min.

Table 2. Studies of chronic WAD. The results of the different substances are baseline data. Healthy controls are abbreviated as HC.

In two studies, Shah et al. investigated P and CGRP (Shah et al., 2008; Shah et al., 2005). They found significant increases in active trigger points in the trapezius and found that these levels were higher in the aching trapezius than in a distant pain-free muscle.

Substances only reported in single studies/patient groups were glucose (no difference) (Sjogaard et al., 2010), norepinephrine (significant difference) (Shah et al., 2008; Shah et al., 2005), and H<sup>+</sup> (significant difference) (Shah et al., 2008; Shah et al., 2005).

3.2 Chronic WAD

We identified two studies (Table 2) using the same material concerning patients with chronic WAD (Gerdle et al., 2008b; Gerdle et al., 2008c), and 5-HT and IL-6 were significantly higher in WAD than in HC. No differences were found in the concentrations of investigated metabolites, potassium, glutamate, BKN, or kallidin compared with healthy controls.

3.3 Fibromyalgia

Two studies investigated fibromyalgia patients (Table 3). In the larger study investigating the painful trapezius muscle of fibromyalgia patients, significantly higher interstitial concentrations of lactate and pyruvate were found compared to healthy controls (Gerdle et al., 2010). In the other study, the vastus lateralis muscle was investigated in eight patients with fibromyalgia and the authors reported no differences in concentrations of lactate compared to controls (McIver et al., 2006). It is unclear from this study if the vastus lateralis was habitually painful and/or painful at palpation (e.g., tender point examination). Moreover, no compensation for RR was done despite a relatively high flow rate.

Study	Condition Number of Subjects, % women (W) Muscles	Substances investigated Flow rate	Results (Comparisons between patients and HC; p-values)	Comments (Compensated for RR (Y/N) or low flow rate* (NA or Y/N))
Gerdle et al. (Gerdle et al., 2010)	Fibromyalgia (FM; n=19), 100% W HC (n=19), 100% W  Trapezius	Lactate Pyruvate Glutamate  0.3µl/min	Lactate-trapezius: FM>HC; P=0.039 Pyruvate-trapezius: FM>HC; P=0.001 Glutamate-trapezius: ns.	Compensated for RR: N Low flow: Y
McIver et al (McIver et al., 2006)	Fibromyalgia (FM; n=8), 100%W HC (n=8), 100% W Vastus lateralis	Lactate  2µl/min	Lactate-vastus: ns	Compensated for RR: N Low flow: N

\*Low flow rate associated with 100% relative recovery was defined as 0.3µl/min

Table 3. Studies of fibromyalgia. The results of the different substances are baseline data. Healthy controls are abbreviated as HC.

3.4 Temporomandibular pain disorders

Compared to the healthy controls, fibromyalgia patients had increased 5-HT in the masseter muscle (Ernberg et al., 1999). Compared to the healthy controls, myofascial temporomandibular disorder patients had significantly higher glutamate levels (Castrillon et al., 2010) (Table 4).

Study	Condition Number of Subjects, % women (W) Muscles	Substances investigated Flow rate	Results (Comparisons between patients and HC; p-values)	Comments (Compensated for RR (Y/N) or low flow rate* (NA or Y/N)
Ernberg et al (Ernberg et al., 1999)	Fibromyalgia (FM; n=18), 100%W Localized myalgia of the temporomandibular system (LM; n=17), 76% W HC (n=10), 60%W Masseter	5-HT (corrected for S-5-HT)  7µl/ min	5-HT (corrected for S-5- HT)-trauma- masseter: FM>HC: P=0.05 5-HT (corrected for S-5- HT)-baseline- masseter: no group differences	Compensated for RR: N, but corrected for S- 5-HT Low flow:N
Hedenberg- Magnusson et al (Hedenberg- Magnusson et al., 2001)	Fibromyalgia (FM; n=19), 89%W Localized myalgia of the temporomandibular system (LM; n=19), 74%W HC (n=11), 64% W Masseter	PGE <sub>2</sub> Leukotriene B <sub>4</sub> (LTB <sub>4</sub> )  7µl/ min	PGE <sub>2</sub> -masseter: ns LTB <sub>4</sub> -masseter: FM>LM; P=0.05	Compensated for RR: N Low flow: N
Castrillon (Castrillon et al., 2010)	Myofascial temporomandibular disorder pain (TMD; n=13), 77%W HC (n=10), 80%W Masseter	Glutamate  2µl/ min	Glutamate- masseter: TMD> HC; P=0.023	Compensated for RR: Low flow:

\*Low flow rate associated with 100% relative recovery was defined as 0.3µl/ min.

Table 4. Studies of temporomandibular pain disorders. The results of the different substances are baseline data. Healthy controls are abbreviated as HC.

3.5 Chronic tension type headaches

In two studies of one group of patients (Ashina et al., 2002; Ashina et al., 2003) with chronic tension headaches, no differences were found in metabolites and some algescic substances (e.g., BKN and PGE2) in the trapezius muscle (Table 5).

3.6 Polymyalgia rheumatica

We found two studies of polymyalgia rheumatica based on the same groups of subjects (Kreiner & Galbo, 2011; Kreiner et al., 2010) (Table 6). These two studies reported marked



alterations in cytokines but also to some extent in algescic substances such as glutamate in two muscles. These two studies also reported 5-HT in one muscle and in BKN in one muscle. Interestingly, all alterations were normalized after prednisolone treatment.

Study	Condition Number of Subjects, % women (W) Muscles	Substances investigated Flow rate	Results (Comparisons between patients and HC; p-values)	Comments (Compensated for RR (Y/N) or low flow rate* (NA or Y/N)
Ashina et al. (Ashina et al., 2003)	Chronic tension-type Headache (CTTH; n=16), 63% W HC (n=17), 71% W Trapezius	Pyruvate Glucose Urea Glutamate K <sup>+</sup> BKN PGE <sub>2</sub> ATP 2μl/min	Pyruvate-trapezius: ns Glucose-trapezius: ns Urea-trapezius: ns Glutamate- trapezius: ns K <sup>+</sup> -trapezius: ns BKN-trapezius: ns PGE <sub>2</sub> -trapezius: ns ATP-trapezius: ns	Compensated for RR: Y Low flow: NA
Ashina et al. (Ashina et al., 2002)	Chronic tension-type Headache (CTTH; n=16), 63% W HC (n=17), 71% W Trapezius	Lactate  2μl/min	Lactate- trapezius: ns	Compensated for RR: Y Low flow: NA

\*Low flow rate associated with 100% relative recovery was defined as 0.3μl/min.

Table 5. Studies of chronic tension type headaches. The results of the different substances are baseline data. Healthy controls are abbreviated as HC.

3.7 Mitochondrial myopathy

In a study of mitochondrial myopathy that included four patients, no significant differences were found for metabolites, glutamate, hypoxanthine, urate, and aspartate (Table 7).

3.8 Chronic tendinosis

We also found three studies that focused on chronic tendinosis (Table 8). These three studies are small and have investigated different tendons with pain. The interstitial concentrations of glutamate, PGE<sub>2</sub>, and lactate were investigated, but no consistent pattern with respect to these substances was found.

Study	Condition Number of Subjects, % women(W) Muscles	Substances investigated Flow rate	Results (comparisons between patients and HC; p-values)	Comments (Compensated for RR (Y/N) or low flow rate* (NA or Y/N)
Kreiner & Galbo (Kreiner & Galbo, 2011)	Polymyalgia rheumatica (PMR)(n=20), 60%W Healthy controls (HC) (n=20), 65%W Trapezius Vastus lateralis	Lactate Pyruvate Glutamate 5-HT BKN PGE2 K+ ATP 3µl/min	Lactate -trapezius: PMR >HC; P=0.05 Pyruvate -trapezius: ns Glutamate-trapezius: PMR >HC; P=0.05 5-HT-trapezius: ns BKN-trapezius: ns PGE2-trapezius: ns K+-trapezius: ns ATP-trapezius: ns Lactate-vastus: ns Pyruvate-vastus: ns Glutamate-vastus: PMR >HC; P=0.05 5-HT-vastus: PMR >HC; P=0.05 BKN-vastus: ns PGE2-vastus: PMR >HC; P=0.05 K+-vastus: ns ATP-vastus: ns	Compensated for RR: Y Low flow: NA
Kreiner et al. (Kreiner et al., 2010)	Polymyalgia rheumatica (PMR)(n=20), 60%W Healthy controls (HC) (n=20), 65% W Trapezius Vastus lateralis	IL-1α/β IL-1 receptor antagonist (IL-1Ra) IL-6 IL-8 TNF-α Monocyte chemoattract ant protein 1(MCP-1) 3µl/min	IL-1α-trapezius: PMR >HC; P=0.001 IL-1β-trapezius: PMR >HC; P=0.01 IL-1Ra-trapezius: PMR >HC; P=0.01 IL-6-trapezius: PMR >HC; P=0.01 IL-8-trapezius: PMR >HC; P=0.05 TNF-α-trapezius: PMR >HC; P=0.05 MCP-1-trapezius: PMR >HC; P=0.05 IL-1α-vastus: PMR >HC; P=0.01 IL-1β-vastus: PMR >HC; P=0.05 IL-1Ra-vastus: PMR >HC; P=0.05 IL-6-vastus: PMR >HC; P=0.05 IL-8-vastus: PMR >HC; P=0.05 TNF-α-vastus: PMR >HC; P=ns MCP-1-vastus: PMR >HC; P=0.05	Compensated for RR: Y Low flow: NA

\*Low flow rate associated with 100% relative recovery was defined as 0.3µl/min.

Table 6. Studies of Polymyalgia rheumatica. The results of the different substances are baseline data. Healthy controls are abbreviated as HC.

Study	Condition Number of Subjects, % women(W) Muscles	Substances investigated Flow rate	Results (Comparisons between patients and HC; p-values)	Comments (Compensated for RR (Y/N) or low flow rate* (NA or Y/N))
Axelson et al (Axelson et al., 2002)	Mitochondrial Myopathy (MM; n=4); 50% W HC (n=11), 36% W Tibialis anterior	Lactate Pyruvate Glutamate Hypoxanthine Urate Aspartate 0.3µl/min	Lactate-tibialis: ns Pyruvate-tibialis: ns Glutamate-tibialis: ns Hypoxanthine- tibialis: ns Urate-tibialis: ns Aspartate-tibialis: ns	Compensated for RR: N Low flow: Y

\*Low flow rate associated with 100% relative recovery was defined as 0.3µl/min.

Table 7. Studies of mitochondrial myopathy. The results of the different substances are baseline data. Healthy controls are abbreviated as HC.

Study	Condition Number of Subjects, % women(W) Tendon	Substances investigated	Results (Comparisons between patients and HC; p-values)	Comments (Compensated for RR (Y/N) or low flow* (NA or Y/N))
Alfredson et al (Alfredson et al., 2000)	Tennis Elbow (TE; n=4), 25% W HC (n=4), 50%W Extensor carpi radialis brevis tendon	Glutamate PGE <sub>2</sub>	Glutamate: ns PGE <sub>2</sub> :TE>HC;P< 0.001	Compensated for RR: N Low flow: Y
Alfredson et al (Alfredson et al., 2001)	Jumpers' knee (JK; n=5), 20%W HC (n=5), 20%W Patellar tendon	Glutamate PGE <sub>2</sub>	Glutamate: JK>HC; P=0.01 PGE <sub>2</sub> : ns	Compensated for RR: N Low flow: Y
Alfredson et al (Alfredson, 2005)	Chronic Achilles tendinosis (CAT; n=4), 0%W HC (n=5), 0%W Achilles tendon	Lactate	Lactate: CAT>HC; P=0.05	Compensated for RR: N Low flow: Y

\*Low flow was defined as 0.3µl/min.

Table 8. Studies of tendons with chronic pain. The results of the different substances are baseline data. Healthy controls are abbreviated as HC.

## **4. Discussion**

### **4.1 Metabolites**

The majority of studies concerning the trapezius in chronic trapezius myalgia have reported increases in the interstitial concentrations of lactate and pyruvate (Flodgren et al., 2010; Flodgren et al., 2006; Larsson et al., 2008; Rosendal et al., 2004b; Sjogaard et al., 2010). However, Flodgren et al. (Flodgren et al., 2010; Flodgren et al., 2006) did not compensate for RR and their results might be biased.

There are several possible explanations for the generally higher interstitial levels of pyruvate levels in chronic trapezius myalgia and in the trapezius of patients with FMS. For example, changes in the lactate-pyruvate metabolism via lactate dehydrogenase isoforms may result in higher pyruvate levels (Philip et al., 2005). Another explanation is a reduction in tissue oxygenation in FMS (Bengtsson, 2002) and chronic trapezius myalgia (Larsson et al., 2004), reductions that may result in higher pyruvate and higher lactate concentrations due to a shift towards an anaerobic state. A lower fitness level is a third explanation as a low fitness level means more frequent reliance on anaerobic metabolism. However, it is unknown if a general deconditioning in these two pain conditions involves the postural trapezius. The aerobic capacity of a muscle is largely governed by the number of mitochondria and their enzymes (Weibel & Hoppeler, 2005). The mitochondrial density increases as result of exercise and this increased density affects the level of metabolites (i.e., enhanced aerobic capacity) (Norrbom, 2008). Lower capillary density and/or enzymes associated with aerobic metabolism have been reported in FMS and in chronic trapezius myalgia (Larsson et al., 2004; Lindh et al., 1995). For FMS and chronic trapezius myalgia, the trapezius muscle fibres can appear with alterations in mitochondrial content and distribution, e.g., moth-eaten fibres and ragged red-fibres (Bengtsson, 2002; Bengtsson et al., 1986; Larsson et al., 2000; Larsson et al., 2004).

The role of lactate is complex. Lactate may assist in the detection of exercise stress before tissue damage occurs and can be exchanged rapidly among tissue compartments where it may be oxidized as a fuel or reconverted to form pyruvate or glucose (Gladden, 2004; Kim et al., 2007; Philip et al., 2005; Robergs et al., 2004). Lactate is also involved in peripheral nociception and it appears to facilitate the response of the acid-sensing ion channel 3 (ASIC-3) to low pH (Kim et al., 2007). Such ASIC channels are considered to be molecular transducers for nociception and mechanosensation (Kim et al., 2007).

To summarize, most studies of myalgic trapezius muscles show significant increases in interstitial levels of lactate and pyruvate. These results might be explained by decreased fitness level, reduced tissue oxygenation, increased muscle activation, and/or damaged mitochondria.

### **4.2 Pain-related substances**

#### **4.2.1 Glutamate**

Two of the studies of chronic trapezius myalgia (Larsson et al., 2008; Rosendal et al., 2004b), which are markedly larger than the third study (Flodgren et al., 2005), found significant increases in the interstitial concentrations of glutamate. A possible difference between subjects of these studies may contribute to the inconsistent glutamate finding. The myalgic

subjects studied by Larsson et al. and Rosendal et al. (Larsson et al., 2008; Rosendal et al., 2004b) comprised subjects reporting considerable pain and had distinct current muscular signs confirmed at clinical examination. The pain history, the present pain, and clinical muscular neck status of the subjects are very sparsely presented in the Flodgren study (Flodgren et al., 2005). Moreover, one study found the painful masseter was significantly associated with increased glutamate (Castrillon et al., 2010).

Glutamate, a pain modulator in the human central nervous system, acts via the N-methyl-D-aspartate (NMDA) receptor (Coggeshall & Carlton, 1997) (Hudspith, 1997) and influences peripheral pain processing (Carlton, 2001; Varney & Gereau, 2002), e.g., muscle inflammation and delayed onset muscle soreness (Cairns et al., 2001a; Cairns et al., 2001b; Cairns et al., 2003; Svensson et al., 2003; Svensson et al., 2005; Tegeder et al., 2002). Glutamate is released from peripheral afferent nerve terminals (Miller et al., 2011). Studies of animals have shown that glutamate receptors are located on the peripheral ends of small-diameter primary afferents in several tissues such as muscle (Coggeshall & Carlton, 1998). Inflammatory animal models reveal increased levels of glutamate in peripheral tissues and nociceptive behaviours (Miller et al., 2011). Several studies have demonstrated that injections of glutamate increase pain intensity (Cairns et al., 2003; Gazerani et al., 2006). A review from 2008 concluded that elevation of interstitial glutamate in skeletal muscle alters pain sensitivity in healthy humans and is associated with pain symptoms in some chronic non-inflammatory muscle pain conditions (Cairns & Dong, 2008), which are probably mediated through activation of peripheral excitatory amino acid receptors located on the terminal ends of nociceptors. The present review mainly supports the conclusions of that review. However, the interstitial concentrations of glutamate were not increased in the trapezius of patients with chronic WAD (Gerdle et al., 2008c) or in patients with fibromyalgia (Gerdle et al., 2010). One difference between chronic trapezius myalgia and the two other conditions might be the more widespread (spatial) hyperalgesia in the two latter conditions (Arendt-Nielsen & Graven-Nielsen, 2003; Wallin et al., 2011).

#### 4.2.2 Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) is involved in the central and peripheral modulation of nociceptive pain and hyperalgesia (Sommer, 2004). 5-HT is synthesized in brain neurons from the essential amino acid tryptophan and released from platelets and mast cells in the periphery due to tissue damage (Mense, 1993). Whether 5-HT has an analgesic or hyperalgesic action depends on the cell type and type of receptor it targets. Currently, seven receptor families have been identified. These receptors are cell-surface proteins that bind 5-HT and trigger intracellular changes that influence the behaviour of cells and explain the broad physiological actions and distribution of this biochemical mediator. According to animal studies, the 5-HT receptor classes currently identified, the 5-HT<sub>1</sub> and the 5-HT<sub>2</sub>, may be involved in mainly chemical and thermal hyperalgesia (Ernberg, 2008). 5-HT activates the descending endogenous pain system and this inhibits centrally mediated pain transduction (Sommer, 2006; Suzuki et al., 2004). In the periphery, 5-HT sensitizes afferent nerve fibres, contributing to hyperalgesia in inflammation and nerve injury (Giordano & Rogers, 1989; Sommer, 2004; Taiwo & Levine, 1992). Intramuscular administration of 5-HT into the human masseter muscle has been demonstrated to induce pain (Ernberg et al., 2006). The studies identified in this systematic review concerning chronic trapezius myalgia (**Table 1**) clearly



indicate significantly increased levels of 5-HT in the whole spectrum of severity of chronic trapezius myalgia and these findings agree with other studies of muscle pain conditions such as myalgic masseter muscle (Ernberg et al., 1999) (**Table 4**) and chronic whiplash associated pain including trapezius pain (Gerdle et al., 2008c) (**Table 2**). The finding that there are higher interstitial levels of 5-HT in chronic trapezius myalgia than in controls at rest agrees with other studies that also found that 5-HT is a peripheral pro-nociceptive substance activated by afferents and by the release of other substances (Saria et al., 1990; Sommer, 2004). The results of the present systematic review clearly indicate that 5-HT can be a potential biomarker of different types and severity of chronic myalgia.

#### 4.2.3 Bradykinin (BKN) and Kallidin (KAL)

BKN and KAL are kinins – a group of structurally related 9-11 amino acid peptides that are produced by kallikrein-mediated enzymatic cleavage of kininogen (Coutaux et al., 2005; Riedel & Neeck, 2001; Wang et al., 2006). Kinins mediate their effects via two different G protein coupled receptors, B<sub>1</sub> and B<sub>2</sub>, that provoke an increase in intracellular Ca<sup>2+</sup> (Meyer et al., 2006; Zubakova et al., 2008). In normal tissue in the acute situation, BKN and KAL act via the B<sub>2</sub> receptor. In the chronic phase of the response of tissue injury and infection, B<sub>1</sub> receptors are expressed by BKN and KAL via this receptor (Calixto et al., 2004; Coutaux et al., 2005; Couture et al., 2001; Graven-Nielsen & Mense, 2001; McMahon et al., 2006). Interstitial muscle BKN and KAL have been suggested as algescic kinins involved in muscle pain. BKN was the first inflammatory mediator recognized to have potent hyperalgesic properties (Levine & Reichling, 1999). BKN induces pain and modifies the receptive fields of dorsal horn neurons to noxious stimuli in humans when administered in different ways (Boix et al., 2005; Meyer et al., 2006). BKN and cytokines are central factors in the link between tissue damage and inflammatory responses (Coutaux et al., 2005). Moreover, BKN is a potent vasodilator and is increased in the interstitium of muscle during exercise (Clifford & Hellsten, 2004; Schmelz et al., 2003; Stewart & Rittweger, 2006). Animal studies have shown that BKN can both excite (i.e., algogenic) and sensitize nociceptors (Levine & Reichling, 1999; Wang et al., 2006). The present review identified four studies investigating the interstitial concentrations of BKN and/or Kallidin (Gerdle et al., 2008b; Larsson et al., 2008; Shah et al., 2008; Shah et al., 2005). The relatively small studies conducted by Shah et al. (Shah et al., 2008; Shah et al., 2005) clearly indicated that BKN was involved since increased levels of BKN in subjects with active trigger points and the levels were higher in the trapezius (with pain) than in a pain-free distant muscle. In contrast no significant differences in BKN were found between patients and controls in a field study and a laboratory study, (Gerdle et al., 2008b; Larsson et al., 2008). The difference in results between the above mentioned studies could be due to the fact that alterations in BKN might be very localized (i.e., in the trigger points) and not generally found in the aching trapezius muscle. KAL was only investigated in one study and increased in chronic trapezius myalgia but not in the trapezius of chronic WAD compared to controls (Gerdle et al., 2008b). Clearly, more pathophysiological *in vivo* studies are necessary in order to understand the roles of BKN and KAL for nociception and pain in patients with chronic pain.

#### 4.2.4 Potassium

Increased interstitial potassium levels may be related to muscle pain (Graven-Nielsen et al., 1997). Green et al., however, did not find potassium related to acute ischaemic myalgia in



healthy subjects (Green et al., 2000). Repetitive work in healthy subjects may increase potassium levels (Rosendal et al., 2004a), although in the present systematic review no consistent pattern of increased potassium was found in patients with chronic trapezius myalgia (Larsson et al., 2008; Rosendal et al., 2005; Sjogaard et al., 2010) (**Table 1**) or with chronic WAD (**Table 2**).

#### 4.2.5 Cytokines

There are several direct and indirect pathways that link cytokines with nociception or hyperalgesia (Coutaux et al., 2005; Sommer & Kress, 2004; Uceyler et al., 2009). Four studies investigated cytokines in chronic trapezius myalgia, but significant differences were only found for active trigger points (Shah et al., 2008; Shah et al., 2005). These studies, however, used very few subjects, an obvious limitation. Larger studies have not found elevated levels of cytokines (Larsson et al., 2008; Rosendal et al., 2005). On the other hand, these studies might have had some technical problems due to the catheters used, also a limitation. However, the chronic WAD study found increased IL-6 (Gerdle et al., 2008c).

#### 4.3 Anti-analgesic substances

As is obvious from the above, most studies concern metabolites and algesic substances. Little is known about changes in the pain-inhibitory signalling molecules. One interesting group of such molecules is the *N*-acylethanolamines (NAEs), which is a family of endogenous lipid mediators that have several roles including the regulation of inflammation and pain (Pacher et al., 2006). Examples of NAEs are *N*-palmitoylethanolamine (PEA), *N*-stearoylethanolamine (SEA), *N*-oleoylethanolamine (OEA), and *N*-arachidonoyl ethanolamine (anandamide, AEA). The most thoroughly studied of the NAEs is AEA, which interacts with cannabinoid receptors. At higher concentrations, AEA also targets transient receptor potential (vanilloid-1) receptors and has been shown to have anti-nociceptive actions in a number of animal models of pain (Calignano et al., 1998). The present review also includes one study of SEA and PEA (Ghafouri et al., 2011), which reported significantly increased levels of two NAEs.

#### 4.4 Other pain conditions identified

According to our review, microdialysis of painful muscles have also been investigated, but these studies have only been based on one group of patients of each condition: polymyalgia rheumatic, chronic tension-type headache, and mitochondrial myopathy. Hence no definite conclusions concerning potential biomarkers can be drawn for these conditions. The results concerning polymyalgia rheumatic were prominent for several algesics including cytokines. Kreiner et al. investigated the presence of muscle alterations (Kreiner & Galbo, 2011; Kreiner et al., 2010), and they found that the biochemical alterations were normalized after treatment with prednisolone. Although more studies are needed, their results suggest that intramuscular mechanisms are important.

In the studies of different chronic tendinosis, the number of patients was low and no consistent patterns were seen. Larger studies are needed to identify biochemical alterations.

#### 4.5 Suggestions with respect to future studies

The fact that most studies of chronic trapezius myalgia, chronic WAD, and temporomandibular pain disorders included women is expected, as the prevalence of these conditions are higher in women. Future studies should also include groups of men with chronic muscle pain conditions. In addition, it is important to describe the patient group in detail with respect to clinically relevant examination parameters. Furthermore, systematic descriptions of the patient groups are needed that reflect pain intensity and psychological distress as well as consequences such as work participation and sick leave. A systematic description will allow a more accurate characterization of pain severity in a broad context. Most studies rely on bivariate correlations between pain descriptors such as pain intensity or pressure pain thresholds and the concentration of a certain substance. Multivariate correlation analyses and regression analyses are methods that can be used to investigate how groups of clinical examination variables, several simultaneous symptoms, and the concentrations of several biochemical substances intercorrelate. To better understand the potentially complex biochemical situation of the muscle in chronic pain conditions, it is necessary to also investigate the multivariate interrelationships between the concentrations of the investigated substances. According to ICD, the clinically used pain diagnoses are symptom diagnoses based on temporal and anatomical characteristics (e.g., chronic lumbago). Hence a certain diagnosis may include patients with different activated pathophysiological mechanisms. To identify subgroups of patients with identical pathophysiological mechanisms, it is important to use large patient groups and appropriate statistical methods (e.g., cluster analysis and principal component analysis).

#### 5. Conclusion

This systematic review found that most of the studies focused on trapezius myalgia (seven patient groups reported in ten studies), temporomandibular pain syndromes (two patient groups reported in three studies), and fibromyalgia (two patient groups but different muscles). Relatively strong scientific support identifies 5-HT as a potential biomarker in chronic myalgia. Moderately strong scientific support identifies glutamate, pyruvate, and lactate as potential biomarkers in chronic trapezius myalgia. There is a need for larger studies of well-characterized patient groups with respect to perceived situations, symptoms, and signs so as to investigate several substances simultaneously in order to improve the understanding of peripheral nociceptive processes in myalgia.

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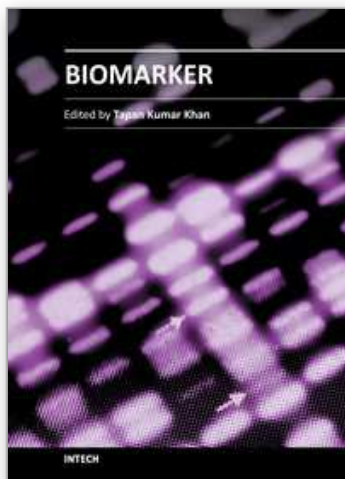
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## **Biomarker**

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Clinicians, scientists, and health care professionals use biomarkers or biological markers as a measure of a person's present health condition or response to interventions. An ideal -biomarker should have the following criteria: (I) ability to detect fundamental features of the disease, (II) ability to differentiate from other closely related diseases, (III) ability to detect early stages and stages of progression, (IV) the method should be highly reliable, easy to perform and inexpensive, and (V) sample sources should be easily accessible from body. Most of the chapters in this book follow the basic principle of biomarkers.

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