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Research Article

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Mechanisms of myofascial pain in the context of metabolism, redox stress and inflammation: a narrative review

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Abstract

Pain syndromes usually progress spatially in a stepwise fashion. Myofascial trigger points, a best-studied feature of myofascial pain syndrome and a very common finding on clinical examination of people with various chronic pain syndromes, occur in an active or latent form, consistent with the clinical features of myofascial pain syndrome, and progress from a less painful state to a more painful one. The clinical presentation apparently encompasses a continuum from barely detectable clinical phenomena of latent trigger points to a complex chronic pain syndrome with currently unsatisfactory treatment options. The mechanisms of trigger point development, transition, and maintenance are not well understood. This review discusses the existing mechanistic evidence and proposes a new conceptualization based on disruption of growth/repair/energy utilisation in the neuromuscular system as one of the possible mechanistic backgrounds of the MPS phenomenon. Accordingly, research opportunities that should be explored in the future are discussed.

Keywords: Myofascial Pain, Latent Trigger Points, Active Trigger Points, Redox Stress, Metabolic Flexibility

Introduction

Myofascial pain syndrome (MPS) is a pain syndrome originating from muscles and muscle fascia characterized by spontaneous or provoked pain of varying degrees, local and referred pain, mechanical hyperalgesia or allodynia, limited range of motion and/or weakness, possibly accompanied by other sensory and autonomic symptoms [1]. The estimated prevalence of MPS is 46% [2]. The lack of universally accepted diagnostic criteria based solely on clinical examination makes it difficult to estimate the true impact of the MPS phenomenon on health and societal costs [3]. MPS may present as a primary condition, but there is increasing evidence that it is a common comorbidity associated with various painful and non-painful medical conditions [4].

Myofascial trigger points (MTrPs) are key findings on clinical examination that are recognised to be related to underlying pathophysiology [1]. MTrPs manifest as focal areas of hypercontracted muscle that are stiff and painful on palpation and may reproduce patients' local and distant symptoms. MTrPs occur in active or latent forms, which refers to the observation that an existing trigger point may be transitioning from a less painful state to a more painful one. In its latent form, it causes symptoms such as stiffness, weakness, or paresthesias, whereas in its active form, it results in more or less debilitating spontaneous pain. The clinical presentation apparently encompasses a continuum from barely detectable clinical phenomena of latent trigger points to a complex chronic pain syndrome with currently unsatisfactory treatment options [2]. The mechanisms of trigger point development, transition, and maintenance are not well understood, which in itself contributes to limited treatment options because of the lack of a solid mechanistic basis. On the other hand, the observation that MPS is a comorbidity with so many other painful or non painful medical condition (such as primary headache, complex regional pain syndrome, radiculopathies, endometriosis, oncologic diseases, stroke, inflammatory and infectious diseases, mental illness, and others) [4] raises the possibility of common underlying mechanisms that ultimately contribute to the clinical presentation of the various conditions or clinical phenomena, MPS being one of them. This review discusses the existing mechanistic evidence and proposes a new conceptualization based on disruption of growth/repair/energy utilisation in the neuromuscular system as one of the possible mechanistic backgrounds of the MPS phenomenon. Accordingly, research opportunities that should be explored in the future are discussed.

Mechanisms of Myofascial Trigger Point Development

Myofascial trigger points are found clinically in muscle areas with tender palpable areas with stiff bands and are histologically associated with contracted sarcomeres with activated muscle

contraction signaling [5]. Studies examining spontaneous muscle activity at MTrP localizations of active or latent trigger points have yielded mixed results, but experimental findings suggest the presence of sustained spontaneous EMG activity in active MTrPs (endplate noise, spikes), possibly caused by symapthetically activated intrafusal muscle fibers [6-9]. Pathologically sustained hypercontraction/activity could contribute to decreased blood flow, ATP depletion, and metabolic stress, leading to downstream effects of increased release of cytokines, myokines, and neurotransmitters, documented in experiments by Shah et al [10]. The latter does not prove the inflammatory nature of MPS, as no infiltration of inflammatory cells has been documented in human MTrP tissue from patients with MPS [5], but argues for changes in the secretion profile of skeletal muscle under conditions that promote the development and maintenance of MTrP. It appears that contracted sarcomeres are not pathognomonic of the pain symptoms described by chronic pain patients, but represent one of the predilection conditions at the level of body structure and function that predispose to the development of the (myofascial) pain syndrome as it presents in clinical practice.

The presence of latent trigger points therefore raises the question of the mechanistic relationship between the development of trigger points and the development of pain. Even less is known about the symptomatology of latent trigger points and their significance in clinical practice. Existing studies support a continuum of myofascial pain syndrome ranging from the latent to the manifest state, with the latent form possibly already present in completely asymptomatic individuals [11]. Latent MTrPs in asymptomatic individuals are more common in women and in lower extremity muscles [11]. In one study, the number of latent MTrPs was generally associated with depression symptoms [12]; in contrast, Hasuo et al. found no association with depression but with alexythymia and especially alexisomia [13,14]. On the other hand, there are some interesting data, albeit from an animal model, on a possible role of diet (especially hypercaloric diet) in spontaneous neurotransmission favoring the development of MTrPs [15]. The present data clearly suggest heterogeneous underlying conditions. The scientific literature on the clinical features of latent MTrPs is mainly sparse, and well-designed clinical trials are needed to gain a better understanding of the clinical development of MPS. In addition, treatment of latent MTrP with dry needling appears to offer some benefit for patients without spontaneous pain, particularly in terms of contractile properties and pressure pain threshold in the affected muscles [16,17], the latter possibly reflecting changes in nociceptive priming. Thus, treatment of latent MTrP (by definition, a nonpainful condition) could prevent the unfolding of downstream mechanisms leading to peripheral and central sensitization processes and the development of a chronic pain syndrome.

Transition from Regional to Widespread Pain and Pain Development Trajectory

Pain propagation is a clinical marker of deterioration and progression of a chronic pain syndrome [18,19]. Pain syndromes often progress spatially in people with previous vitality problems [18]. The dynamics between fatigue and pain, as explored in clinical practise through history and examination, may also be important for understanding the underlying mechanisms of latent trigger point development, transition to active trigger point states, and development of chronic pain syndrome. The observation of latent trigger points which are related to increased intramuscular activity but not surface muscle activity of latent MTrP during synergistic muscle activation leading to incoherent muscle activation with possible overload of muscle fibres speaks to the importance of the role of latent trigger points in excessive muscle activity and possible spatial spread of pain symptoms themselves [20]. In addition to excessive activity and possible muscle overload from increased strain, there may be other factors associated with the spatial spread of pain. Shah et al. observed shifts in the chemical milieu of local muscles with active MTrPs as well as distant unaffected muscles in both the active and latent MTrp groups, although greater in the active MTrP group than in the latent, but significantly greater than in healthy control subjects [12]. The observed systemic perturbations in body functions, already noted in subjects with latent MTrPs and without spontaneous pain, might be related to priming and the risk of spatial spread of pain.

Myofascial Pain Syndrome Is A Manifestation of Regeneration/Repair Processes under Low-Energy Conditions Overlaid by Pathological (Potential Tissue Damage) Pain Signalling

The development of MTrPs has been associated with muscle damage or overuse [21]. The causes of overuse/overload/(micro) damage in muscles that develop MTrPs range from overt trauma to the effects of invisible chronic psychological stress and phenomena described as repetitive strain injuries [21,22]. Muscle overactivation may be associated with a consequence of musculoskeletal trauma or various neurological disorders that impair motor functions. MTrPs occur in well-trained professional athletes and can impair athletic performance [23]. They are found (unexpectedly) in the abdominal wall of women with endometriosis and are related to their underlying simpotmatology, which is generally perceived as visceral pain [24]. The muscle fibres may therefore be in a state of stress in relation to various circumstances, which is a well-known clinical observation.

Under optimal conditions, muscle fibres regenerate well. Here, a concept is purposed, of adverse conditions impeding adequate muscle tissue repair/regeneration/myogenesis in MPS and examine the existing mechanistic data. The objective findings, such as contraction knots are a tissue disorder indicative of muscle fibres in a state of hypercontraction (a dysfunction), and represent an adaptation process of muscle fibres under (relatively) low cellular energy conditions, and as such are a precondition for the development of chronic pain syndrome, but are not a pathognomonic feature of chronic pain syndrome. Pain itself develops in the context of protective tissue healing; in the case of MPS, the healing and regeneration process may become stuck. Under adverse (systemic) conditions, pain signalling therefore gets stuck in a pathological form, with clinical features ranging from

regional to widespread pain, depending on the (non) resolution of the adverse conditions. Peripheral and/or central mechanisms may be involved, and neuropathic pain features may also occur.

A study by Ye et al. on an animal model of MPS revealed problems at the level of mitochondrial biogenesis [25]. Downregulation of the AMPK-PGC -1alpha-SIRT3 axis may underlie the link between mitochondrial dysfunction and MPS. The degree of AMPK phosphorilation was negatively correlated with the reduction in ATP production. The experiment revealed a persistent depression of mitochondrial biogenesis and a vicious cycle of energy crisis mediated by a decrease in intracellular phosphorylation potential that accompanies the decrease in ATP generation. Sustained muscle contraction and concomitant vasoconstriction with hypoperfusion is considered to be the main cause of the energy crisis, as originally proposed by Simons in the integrated trigger point hypothesis and later extended by others [26]. In the development of MTrP, the energy status of the muscle cell is not maintained in homeostasis, and the decrease in ATP availability is a net effect of higher demand (hypercontraction, sympathetic stimulation, increased neurotransmission) and apparent decreased ATP production capacity, leading to cellular, organelle and systemic adaptations that gradually create an MPS phenotype.

The AMPK suppression in MPS animal model observed in the study by Ye et al, if also confirmed in human studies, could be related to the genetic background. A genome- wide association study identified a novel genetic risk locus, Ring Finger Protein 123, which was surprisingly associated with the chronic widespread pain (CWP) phenotype, in addition to a higher risk of obesity and depression [27]. The E3 ubiquitin ligase MG53, a protein encoded by the identified genetic risk locus, mediates AMPKα degradation and deactivation [28]. Hyperglycemia induced reactive oxygen species (ROS) signals AKT to phosphorylate AMPKα at S485/491, which facilitates recruitment of MG53 and subsequent ubiquitination and degradation of AMPKα [28]. This suggests a genetic susceptibility of certain individuals to a hypercaloric diet that leads to both obesity and the development of CWP. Obesity is a risk factor for chronicity of regional low back pain and for the development of CWP [18,29]. There are other possibilities leading to hyperglycemia, such as postprandial hyperglycemia after eucaloric meals and in potentially lean individuals [30], the mechanisms of which should also be explored in the future in relation to risk factors for chronic pain.

AMPK supression may not be the only cause of SIRT3 downregulation. In one study, in cardiac muscle SIRT activity is attenuated by a low ratio of NAD+ to NADH due to complex I deficiency, and the attenuated function of SIRT3 results in less deacetylation of proteins in mitochondria [31]. It is well known that increased mitochondrial protein acetylation impairs the response to cardiac stress. In this study, a decreased NAD+/NADH ratio and increased mitochondrial protein acetylation were shown to be causally related to increased sensitivity of mPTP during calcium stress, implying a decrease in tolerance to mechanical stress. Hyperacetylated malate-aspartate shuttle proteins that transport NADH from the cytosol to the mitochondrion and NAD+ in the opposite direction may also be impaired. The capacity for oxidative phosphorilation could thus be further impaired, leading to an even more reductive environment and metabolic reprogramming to a glycolic phenotype, another "low-energy state". One might speculate that similar mechanisms operate at the level of skeletal muscle and could be behind the observation of high pyruvate levels in certain (overworked?) muscles of patients with fibromyalgia [32]. Metabolic reprogramming to glycolysis could also be the result of an inflammatory environment in muscle that also prevents the transport of pyruvate to mitochondria and interferes with efficient ATP production in the mitochondrion.

Regeneration of skeletal muscle, affected by damage or overuse requires activation, migration, proliferation, and fusion of muscle stem cells to generate fully functional muscle fibres. The process of myogenesis in an adult requires a finely tuned inflammatory response [33]. AMPK activation promotes the reduction of the inflammatory response [34,35]. AMPKα1 in macrophages is critical for the transition from damage-associated to restorative phenotype, and impaired resolution of inflammation impairs muscle regeneration [36]. The upstream AMPK regulator Lkb1 plays a critical role in muscle stem cell homeostasis through AMPK mTOR for proliferation and GSK-3beta for differentiation [37].

Pain as a protective mechanism could also function to protect muscle healing, repair, and regeneration. The study by Jin et al. demonstrated upregulation of 15 RTK family proteins in MPS, particularly EphB1/EphB2 and RhoA and Rac1, but not Cdc42 [5]. The development of MTrPs and the upregulation of RTK proteins are closely related, and there is ample evidence that activation of the RTK family with downstream signalling pathways promotes the development of peripheral sensitization [38,39]. Eph receptors are also expressed in muscle tissue. They are involved in actin filament cross-linking and actin cytoskeleton remodelling, which may play a role in continuous contraction at the site of MTrPs [40,41], modulated by RhoA activity, which is known for its influence on actin filament polymerization, transport, and degradation dynamics [42]. Eph/ephrin is involved in signal transduction between muscle stem cells and differentiated myofibers and modulates motility and patterning of muscle satellite cells [43]. Actin depolymerization and consequently muscle relaxation can also be induced by AMPK, which has been demonstrated in vascular smooth muscle cells [44]. It would be interesting to investigate whether such AMPK- driven and Ca2+-independent control of muscle tone also exists in skeletal muscle.

A cell under compression (a mechanical stress) or oxidative stress uses mitochondrial fission as a survival mechanism, which is in the case of cardiomyocytes under oxidative stress expressed by the activation of RhoA [45,46]. It appears that a moderate level of RhoA activation provides cardioprotection through mitochondrial fission [46]. In contrast, chronic β-adrenergic receptor activation may cause not only enhanced mitochondrial fission but also mitochondrial depolarization leading to apoptosis. Mitochondrial

fission and SIRT3 downregulation go hand in hand, and some degree of SIRT3 downregulation would be expected in affected cells. However, the processes observed in animal models of MPS may in part reflect cellular homeostasis and survival regulation in myofascial tissue that, under optimal basal conditions (including no chronic adrenergic stimulation), may serve survival and regeneration after threat.

A deficiency in AMPK signalling is not only associated with problems in muscle energy production, inflammation, or actin filament remodelling, but also with the development of "neuropathy-like" pain due to peripheral and/or central sensitization processes. In an animal model, obese rats with or without nerve injury were shown to have increased mechanical pain sensitivity after a high-fat diet, which was inhibited by AMPK activation [47]. High-fat fed obese rats exhibited decreased levels of phosphorylated AMPK independent of nerve injury, which correlated with higher expression of CGRP in the spinal cord and DRGs. CGRP is known to increase MEPP amplitude in a dose-dependent manner via an increase in acetylcholine quantum size [48]. In another animal model, a hypercaloric diet led to an increase in MEPP frequency, which may contribute to the generation of MTrPs [15].

Muscle Function in the Context of Redox Stress, Insulin Resistance, Metabolic Inflexibility, Inflammation and Behavioural Factors

In addition to the well-described influence of oxidative stress on muscle function and possibly on MPS [49], not much attention has been paid to the influence of reductive stress on muscle function and structure [50]. Reductive stress generally refers to lower reactive oxygen species availability (ROS), an excess of reducing equivalents and higher NADH/NAD+ or lactate/pyruvate or GSH/GSSG ratios. It is increasingly recognised that an optimal rate of ROS bursts is required for many cellular processes, e.g., insulin signalling, activation of certain enzymes that enable cellular homeostasis related to growth and repair, energy production, or autophagy. Reductive stress occurs under various stress conditions (hypoxia, hyperglycemia) and results in, among other things, reserve energy production through glycolysis and an overall low energy state. Conditions associated with reductive stress include activation of polyol pathway to combat high glucose levels associated with hyperglycemia, low-grade inflammation, and others [50,51]. Further knowledge is needed about muscle functioning under reductive stress conditions and also in relation to trigger point developement. Reductive stress is known to impair myogenesis [52], which may be related to sarcopenia. In association with muscle atrophy, there is the possibility of the development of MPS under chronic overload of the remaining atrophic muscle fibres.

Loss of SIRT3 function in muscle was studied in an animal model [53]. Mice lacking SIRT3 show increased insulin resistance in muscle due to defects in glucose uptake in skeletal muscle. The extreme version of SIRT3 dysfunction associated with a high-fat diet results in decreased trigliceride content in muscle, decreased TCA cycle substrate-based respiration, and increased fatty acid-based respiration, resulting in fuel switching from glucose to fatty acids and loss of metabolic flexibility. Decreased glucose uptake in muscle was consistent with decreased hexokinase activity II and formation of mPTP, a pore that allows exchange of ADP and ATP across the mitochondrial membrane, resulting in lower rates of glycolysis, insulin-stimulated glycogen synthesis rate, and ultimately lower ATP production. The experiment proves the role of SIRT3 as a master regulator of glucose fluxes in overfed states, as insulin action was not impaired in lean SIRT3 KO mice because it does not affect GLUT4 translocation [53]. SIRT3, as an important mitochondrial deacetylase, is crucial in the context of overeating for the regulation of protein hyperacetylation; in the context of caloric restriction, it is involved in metabolic reprogramming and fuel switch to fat utilisation. As mentioned above, in MPS there seems to be a problem with SIRT3 protein activity (at the post-transcriptional level), which in the long term may affect not only ATP production at the cellular level, but also glycemic control at the whole organism level. In fibromyalgia, which is associated with the formation of widespread MTrPs [54], there is some evidence of higher glycosylated haemoglobin A1c (HbA1c) levels, which may both precede and be a consequence of the pain disorder [55]. In addition, poor glycemic control with frequent hyperglycemic episodes, even in the so-called "euglycemic" population, could underlie all of the aforementioned disorders: polyol pathway activation, higher NADH/NAD+ levels, higher lactate/pyruvate levels, RNT123 gene expression, all of which are directly or indirectly related to AMPK function.

Lipid concentrations in skeletal muscle may also increase in association with insulin resistance. In an animal model, long-term denervation has been shown to result in persistent insulin resistance in oxidative skeletal muscle, but increased insulin sensitivity in glycolic muscle [56], mediated by a change in GLUT4 expression. Further studies are needed to investigate possible links between muscle denervation, insulin resistance, fatty transformation of muscle, and also in relation to the development of MPS. Certain orthopaedic conditions (e.g., lumbar spinal stenosis) and muscle disuse lead to fatty transformation of muscles, which is mainly related to poorer physical function rather than to pain itself [57,58]. It would be interesting to investigate MPS comorbidity in patients with spinal stenosis in relation to muscle fatty degeneration because of the possibility of trunk muscles overuse to compensate for multifidus muscle fatty infiltration dysfunction. It would be expected that myofascial dysfunction (and pain) would not correlate specifically with muscle fatty transformation per se, but with functional adaptation to loss of function of muscles with fatty infiltration.

Currently, there are no experimental data to support that MPS is an inflammatory condition [5]. As mentioned previously, there may be a problem in muscle regeneration related to the transition from a damage-associated to a restorative phenotype in a proinflammatory environment [40]. With respect to MPS, proinflammatory muscle states occur most frequently in obesity or inflammatory rheumatic diseases [51,59]. An association between chronic pain and obesity is well established [18], but much less so between the occurrence of MTrPs and obesity [60]. Future research should examine the

interactions between obesity, trigger point occurance and MPS in human longitudinal studies.

There is very little literature on the behavioural aspects of MPS. Based on the literature presented in this nerrative review, the behavioural aspect should be explored in more detail in the future. Behaviour, connected to any type of motor or even mental intense activity, for whatever reason, might be connected to higher sympathetic activation, muscle activity and acetylcholin neurotransmission [21,22]. The relationship between latent trigger points and mood disorders [12], connection of the imbalance between excitatory and inhibitory descending corticospinal influences with anxiety trait in chronic MPS [61], and the phenomena described as alexithymia or alexisomia in realtion to latent MTrPs [13, 14] require further research. MPS as a common phenomenon in patients with any type of chronic pain [4] should be further investigated in the context of behavioural risk factors for obesity and metabolic disorders. On the other hand, physical hypoactivity and sleep hygene habits, which are also due to the predominant sedentary lifestyle and other cultural influences, could be another behavioural risk factor for the development of MTrPs.

Conclusion

Myofascial pain is a common condition in people suffering from chronic pain. The concept presented in this article aims to understand MPS as a regenerative problem in low-energy states that do not eliminate pathological pain syngnalization due to systemic influences mainly related to commonly preventable factors (nutrition, under or overactivity, psychophysical stress regulation). Future studies are needed to gain insight into the conditions related to latent MTrPs, nutrition, and MPS; the relationship between muscle fatty transformation, MTrPs, pain, and functional status in certain orthopaedic conditions; and, most importantly, the behavioural factors related to physiological dysregulation (psychological and/or physical overactivity/hypoactivity, eating behaviours, sleep habits) that promote nonresolution of MTrPs and chronification of pain.

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