Recent Studies using an Overuse Animal Model Show that Signal Substances are Highly Involved in Muscle Derangement and Muscle Inflammation

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Abstract: Muscle overuse is a frequent condition accompanying sports-related activities. There is a lack of knowledge concerning the importance of signal substances in situations when overuse leads to markedly affected muscle structure and muscle inflammation. Recent observations on signal substance systems for the muscle tissue in situations with muscle overuse, noted via the use of a rabbit model, are therefore here focused on. The signal substance systems are the tachykinin system, the TNF-alpha system and the glutamate system. The studies have shown that all three systems are involved in the myositis/muscle derangement processes that occur. A central finding is the notion that signal substances in all three systems become locally produced in the muscle tissue and that there is a marked presence of receptors for these in the inflammatory/affected muscle tissue. The relevance of the findings in relation to what is known for the systems and possibilities in treatment regimens are discussed. The findings suggest that signal substances, more than what has been previously considered, should be taken into consideration as factors of relevance in situations when overuse leads to structural derangement and muscle inflammation.

1 INTRODUCTION

It is well-known that sports activities related to muscle overuse can lead to symptoms and disabilities for the muscles. It is thus frequently noted that overuse of muscles can lead structural abnormalities and inflammation as well as pain (Schoenfeld, 2012). We have in studies using an experimental model noted that pronounced overuse leads to a marked muscle derangement and inflammation (myositis) (Spang et al., 2012); (Song et al., 2012); (Forsgren et al., 2012).

Although there overall is certain knowledge concerning affected muscles in relation to overuse, there are still many questions to be answered concerning the pathophysiology and treatments of muscle derangement and myositis induced by overuse. These conditions, accompanied by chronic pain, can lead to the ending of sports-related activities and can even in the long run, due to unwanted physical inactivity, be related to development of metabolic disorders. Via the use of the animal model commented on above we have obtained new information on the features that occur within the muscle tissue during muscle derangement/myositis and which can be important backgrounds for the further understandings of these conditions for human beings.

Three signal substance systems were focused on; the tachykinin system [focus on substance P (SP)], the TNF-alpha system and the glutamate system. The reason for choosing the tachykinin system was that this system is involved in pain signaling, is upregulated in the form of increased peripheral SP-innervation in response to muscle inflammation ((Reinert et al.,1998) and the fact that SP is known to be pro-inflammatory (De Swert et al., 2009). The TNF-alpha system was chosen as TNF-alpha production has been noted for infiltrated white blood cells in muscle tissue of patients with inflammatory myopathies (De Bleeker et al., 1999) and in the inflammatory cells in crush-injured and transplanted muscle autografts in mice (Peterson et al., 2006). Based on the findings of TNF-alpha reactions in the muscle tissue of patients with inflammatory myopathies, it has been suggested that TNF-alpha may have a role in the pathogenesis of the myositis in these diseases (Efthimiou et al., 2006). The glutamate system was chosen as glutamate is known to be associated with pain symptoms and as

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increased glutamate concentrations have been noted for the trapezius muscle of persons with chronic muscle pain (Flodgren et al., 2005). It is furthermore well-known that glutamate in excess is toxic to neurons, an excessive release of glutamate leading to neuronal excitotoxicity and brain damage (Matsumoto et al., 1993). Effects on oversensitive glutamate receptors can lead to overexcitation. How the situation is for the three signal substance systems in response to marked muscle overuse has in principle been unknown.

2 OUR ANIMAL MODEL

An animal model in rabbits leading to marked overuse of the triceps surae muscle in one of the extremities has been used. It is related to the use of an apparatus ("kicking machine") that leads to passive repetitive flexions and extensions of the right ankle joint. A pneumatic piston being attached to the foot produces the movements. During the plantar flexion phase, an active contraction is furthermore induced by electrical stimulation via surface electrodes positioned over the triceps surae muscle. In order to obtain pronounced effects on the tissue, the exercise regimen was for certain of the animals coupled to local peritendinous injections leading to pronounced effects of tachykinins. The details of the procedures are previously published (Song et al., 2012); (Spang et al., 2012); (Forsgren et al., 2012).

We observed that the overuse emanating from this experimental model leads to muscle morphological changes that were marked and which conformed to a distinct muscle inflammation, i.e. an infiltration of white blood cells (a myositis process), an increase in connective tissue and muscle fiber changes such as fiber necrosis (Song et al., 2012). The morphological features show resemblances to features seen for overused muscles of humans (Hikida et al., 1983). The marked inflammatory cell infiltration and the fiber necrosis do to large extent resemble the situation seen in muscle tissue in inflammatory myopathies (De Bleeker et al., 1999). Information on the three signal substances described above can give hints of relevance for the situations of marked muscle damage/myositis in man. The advantage is that the features in very advanced myositis/muscle derangement can be evaluated, which is not easily done for muscle of man.

3 TACHYKININ, TNF-ALPHA AND GLUTAMATE SYSTEMS IN THE ANIMAL MODEL

3.1 There is an Involvement of the Tachykinin System in the Processes of Muscle Derangement/Myositis

The muscle derangement/myositis process was found to be accompanied by an involvement of the tachykinin system. There was an expression of both tachykinin (SP) and the neurokinin-1 receptor (NK-1R) in invading white blood cells, there was an increased expression of tachykinin in the blood vessel walls and an occurrence of NK-1R reactions in these (Song et al., 2013a; 2013b). We also found that there was an increase in tachykinin-like immunoreactive nerve fibers as well as in NK-1R immunoreactive nerve fibers in myositis areas. Interestingly, there were NK-1R expressions in muscle fibers which showed features of being in a regenerative stage. Furthermore, NK-1R immunoreactions and NK-1R mRNA reactions were noted for macrophages that had extensively infiltrated into necrotic muscle fibers (Song et al., 2013b).

The effects in the muscle tissue can be related to proinflammatory effects, effects which are frequently ascribed SP (De Swert et al., 2009), and vasoactive effects, including vasodilatory, angiogenetic and oedema-producing effects (Lembeck and Holzer, 1970). However, SP is also described to be involved in trophic and proliferative events (Pinto et al., 2010) and in healing processes (Schmassmann et al., 2004). The findings for the muscle fibers favour that tachykinins are involved in necrotic processes in the muscle tissue as well as in regenerative events. Thus, tachykinins can have double-edged effects in muscle derangement/myositis.

The findings show that tachykinins such as SP have a remarkable involvement in the processes that occur in response to muscle overuse. These are completely new findings and which underscore that tachykinins definitely not only are neuropeptides in the sense that they solely are confined to the sensory innervation but that they also are produced by cells locally in the tissues. As these cell types were equipped with NK-1 receptors (Song et al., 2013b), it is likely that tachykinins have autocrine/paracrine effects for the muscle tissue in myositis/muscle tissue derangement.

3.2 There is also an Involvement of the TNF-alpha System in the Process of Muscle Derangement/Myositis

We have noted that there is an involvement of the TNF-alpha system in the muscle derangement/myositis process in the animal model. This relates to TNF-alpha expression in invading white blood cells, namely macrophages (Forsgren et al., 2012). TNF-alpha mRNA was also seen for both necrotic muscle fibers and fibers being in a regenerative stage (Renström et al., 2013). Interestingly, NK-1 R reactions were noted in the same regenerating muscle fibers as those that showed TNF-alpha mRNA and white blood cell-related TNF-alpha mRNA and NK-1R immunoreaction were noted in the same necrotic muscle fibers (Renström et al., 2013). In preliminary studies, we have noted occurrence of TNF receptor reactions not only in infiltrated white blood cells and aberrant muscle fibers but also in nerve fascicles in myositis areas (unpublished observations).

Features evidencing TNF-alpha production has never before been shown for muscle tissue in response to marked overuse. TNF-alpha may actually be involved in detrimental effects for the musculature. In accordance with this suggestion, TNF-alpha has been considered to have a damaging role in myopathic conditions (Kondo et al., 2009) and to be involved in the immune responses after musculoskeletal trauma (Warren et al., 2002). It is, however, also suggested that TNF-alpha in certain situations can have a protective role (Echternacher et al., 1996), and that it can be involved in the recovery of muscle function and play a role in muscle regeneration (Tidball, 2005). It therefore appears as if, similarly as for tachykinins discussed above, TNF-alpha can have a dual role in muscle derangement.

A noteworthy feature was that there were TNF-alpha mRNA and NK-1R immunoreactions in the same muscle fibers, these being either necrotic or in a regenerative stage. It thus appears as if the TNF-alpa and tachykinin systems show interactions in the processes of degeneration/regeneration. In accordance with this assumption, an occurrence of an interrelationship between the tachykinin and TNF-alpha systems has previously been noted (Joachim et al., 2006).

3.3 Involvement of the Glutamate System in our Animal Model

We have also observed that the glutamate system is involved in the myositis/muscle derangement process. The invading white blood cells thus exhibited reactions, both at the protein and mRNA level, for the glutamate transporter VGluT2 (Spang et al., 2012). Furthermore, the cells also exhibted reactions for the glutamate receptor NMDAR1 (Spang et al., 2012). This is unexpected as the glutamate system is mainly related to the nervous system. Another unexpected feature previously noted by us concerning the glutamate system is that the tendon cells in the human Achilles tendon exhibit reactions for VGluT2, especially so in the tendinosis (tendinopathy) situation (Scott et al., 2008). Our observations show that the glutamate system is a factor to be considered for both in myositis/muscle derangement and for tendinosis. Ongoing studies indicate that the nerves in the myositis areas are under influence by glutamate (unpublished observations).

4 INTERPRETATIONS OF THE FINDINGS; IMPLICATIONS FOR TREATMENTS?

4.1 What do the Findings Imply for Overuse-induced Muscle Problems for Humans – What can we Learn, and do the Findings Give Options for New Treatments?

Although the animal model is not related to a physiological situation that mimics the situations when human beings get overuse-related problems in their muscles, there are findings that are noteworthy and that we can learn from. A main point is that the model leads to very marked alterations in the form of a pronounced myositis process, and marked alterations in the muscle structure, including both degenerative and regenerative features.

It was noteworthy that the signal substance systems that were here evaluated, signal substance systems which are known to have well established functional importance in various situations, indeed became involved in the muscle derangement processes. It was namely observed that the signal substances in these systems are locally produced within the affected areas of the muscle tissue. This means that there is a local supply of tachykinin, TNF-alpha and glutamate in the muscle tissue in these areas. The findings of receptors for all three substances also show that they have effects in the ongoing processes.

4.2 The Good and Bad Sides of the Systems

As is commented on above, all three systems are related to the inflammatory process in the muscle tissue in the sense that tachykinin, TNF-alpha and the glutamate transporter VGluT2 all are expressed by the invading white blood cells and that these cells show expressions of NK-1R, TNF receptors and glutamate receptors. It is noteworthy that there is a large amount of evidence clarifying that tachykinins as well as TNF-alpha can have pro-inflammatory and deleterious effects but actually also trophic and healing effects. How the situation is for glutamate in this regard is more uncertain. Glutamate is mainly considered to act as a central pain-mediating factor, being present together with SP in primary afferents (De Felipe et al., 1998).

It should be stressed that the inflammation as such within muscle tissue must not in the long run be deleterious but instead be a primary stage in the response of the tissue, initiating the healing process. If the inflammation is chronic and very long-lasting there may be deficits in this restoration.

It is evident that the tachykinin system and the TNF-alpha system both are related to fiber necrotic as well as fiber regenerative events. This shows further that the two systems are related to both sides of muscle reorganization and suggests that the two systems show interactive effects in the reorganization.

4.3 Should Treatments that Interfere with TNF-alpha Effects be given?

The effectiveness of antiTNF treatment is nowadays well established not only for rheumatoid arthritis but also for other inflammmatory disorders (Feldman and Maini, 2003). It has also been suggested that TNF-alpha may be a target for interfering with myositis development (Baer, 2006). The use of antiTNF treatment (etanercept) has actually been shown to reduce the tissue breakdown in dystrophic mdx mice, a model for Duchenne Muscular Dystrophy (Hodgetts et al., 2006). Nevertheless, it is obvious that the experience of antiTNF treatments still is very limited concerning myositis and muscle derangement and that more research is needed in order to clarify if this type of treatment indeed is beneficial in these conditions (Mastaglia, 2008).

It is evident that the question concerning the possibility that TNF-alpha blocking could be used in the situations of muscle derangement and myositis can at present not be answered. A central aspect is, as commented on above, that TNF-alpha is not only related to deleterious effects but also trophic and healing effects. An interesting recent finding is that blocking of TNF-alpha primarily has effects on nociceptive brain activity. The nociceptive CNS activity in several brain regions, as seen via functional MRI, was thus blocked after infusion of a monoclonal antibody to TNFalpha (Hess et al., 2011). This was found at an early stage, namely before the effects on joint swelling and acute phase reactants were noted. It is our hope that we in further studies using our animal model can evaluate the effects of TNF-alpha interference treatments on the development of the myositis processes.

4.4 Should NK-1R Blockers be given?

NK-1R blockers have since long time been tested experimentally for various conditions. They have e.g. been found to have good effects in situations like dextran sulfate-induced colitis in rats (Stucchi et al., 2000). The results of more recently performed experiments have indicated that blockade of NK-1R signaling may be of importance in treatments of colitis (Gad et al., 2009), oedema after traumatic brain damage (Donkin et al., 2009) and lung injury after smoke inhalation and burn injury (Jacob et al., 2010). However, results obtained in clinical trials for different conditions have to a large extent not been convincing. A noteworthy fact is that NK-1R blocking has not been found to induce pain reduction. The most clear indication for which NK-1 R blocking is functioning is for the prevention of postoperative nausea and vomiting and for inhibiting chemotherapy-induced nausea and vomiting (Huang and Korlipara, 2010).

It seems far-fetched at the moment to suggest that NK-1R blocking might be effective in myositis. As we have observed that NK-1R expression is occurring in parallel with presence of TNF-alpha mRNA in regenerating muscle fibers, it would really be strange to suggest NK-1R antagonism as an optional treatment model. If NK-1R interference should be considered, it should probably be in the very early stages of the derangement/inflammation processes, remembering that SP has distinct pro-inflammatory effects (De Swert et al., 2009). In parallel with the plans for evaluating the effectiveness of treatments that interfer with TNF-alpha effects using our animal model, it is also our intention to evaluate for the effectiveness of NK-1R blocking in early stages of the muscle overuse. Information we have obtained so far is that local treatments with neutral endopeptidase and ACE

inhibitors, leading to more pronounced tachykinin effects, leads to an aggravation of the muscle derangement/myositis processes in the model (unpublished observations).

Another possibility to reduce the effects of tachykinin would be to use capsaicin. It is thus well-known that capsaicin reduces the levels of SP and that it can be used clinically as an analgetic and anti-inflammatory agent. It is, however, unclear whether it can be used in a condition like myositis.

4.5 Should Instead Tachykinin Agonist Treatment be given?

It is frequently documented that SP can have wound-healing and restorative effects. SP is e.g. shown to accelerate intestinal regeneration after gamma-irradiation induced damage (Kang et al., 2009). Exogenous administration of SP is described to enhance wound healing in a skin-injury model in rats (Delgado et al., 2005) and SP is proposed to promote early tissue proliferation and regulation of nerve ingrowth in repair responses after experimental Achilles tendon rupture in rats (Carlsson et al., 2011). SP is also reported to be a mechanoresponsive and autocrine regulator of human tenocyte proliferation (Backman et al., 2011). It is on the whole evident that the effects of tachykinin can be double-edged. Our findings of NK-1R in regenerating muscle fibers show that tachykinins are related to restoration processes. On the other hand, the injections of ACE and endopeptidase inhibitors, leading to increased tachykinin effects in the tissue, aggravated the muscle derangement process.

4.6 Should Interference with Glutamat Effects be Made?

Glutamate receptors have since long been looked upon as novel targets for drugs (Knoepfel et al., 1995). It is possible to interfer with glutamate effects via medication. This has especially been discussed for diseases like ALS, Huntington´s disease and Alzheimer´s disease. Two examples of medications that are used are Memantine and Remacemide, both being NMDA receptor antagonists. NMDA receptor antagonists are also used as anesthetics for animals and are known to have psychotomimetic effects. However, many clinical trials invloving NMDA receptor antagonists have failed due to unwanted side effects. Interestingly, NFkB antagonists have been suggested to be therapeutic agents in inflammatory situations with increased levels of glutamate and/or TNFalpha (Zou and Crews, 2005). Furthermore, injections with glutamate receptor antagonist have in experimental studies on mice been found to reduce responses to both SP and TNF-alpha (Jesse et al., 2008).

4.7 Currently used Medications for Overused/Painful Muscles and Exercise-induced Positive Effects for the Muscle Tissue

Some comments on currently used mediations are here given. Non-steroidal anti-inflammatory drugs (NSAIDs) are much used for sports active persons when trying to cope with muscle pain and injury. That includes situations with muscle overuse. It, however, appears as if the potential beneficial effects of NSAIDs in the early stages is not followed by positive features in the long run. These drugs have profound side effects (Stovitz and Johnson, 2013), and have detrimental effects on muscle regeneration and can lead to an impairment on satellite cell activity (Schoenfeld, 2012).

Besides these facts concerning medications it is obvious that exercise as such can have positive effects for muscle tissue. Exercise is known to have anti-inflammatory effects. That is not least related to effects on the systems here focused on. It is thus e.g. shown that exercise leads to a suppression of TNF-alpha production (Petersen and Pedersen, 2005). Exercise-induced mechanical loading has in experimental studies been found to involve a function of SP in initial stages for initializing bone formation (Ytterborg et al., 2013). Exercise has also been shown to be effective in the induction of ischemic tolerance for the brain via a reduction of the mRNA levels for certain glutamatergic receptors (Zhang et al., 2010). Physical exercise is also associated with a release of neurotransmitters within the brain, leading to alleviation of the pain, and a release of endorphins from the pituitary gland. Exercise can also lead to the creation of new neurons as well. Exercise is on the whole known to improve muscle strength and performance as well as oxygen capacity (Nagaraju et al., 2000). It is suggested that physical exercise should be prescribed as part of the treatment

5 FURTHER USE OF THE ANIMAL MODEL; FINAL CONCLUSIONS

There has been a lack of a model for which marked overuse leads to affected muscle structure and pronounced muscle inflammation. Our currently used animal model can be used in order to further evaluate if interference with tachykinin, TNF-alpha and glutamate effects can limit the affection in the muscle tissue in a situation with overuse.

A main finding in the rabbit model studies is that there is a pronounced signal substance production locally in the muscle tissue in response to the muscle overuse. This fact, together with the findings of marked occurrence of receptors for the signal substances in the tissue, show that these substances, more than what has been considered so far, should be taken into consideration as factors of relevance when overuse leads to structural affection and marked muscle inflammation. It is hoped that discussions at the International Congress on Sports Science Research and Technology Support will give new insight into the questions of the tissue changes in muscle overuse in relation to the effects of locally produced signal substances.

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