Review

Rehabilitation of muscle after injury – the role of anti-inflammatory drugs

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Non-steroidal anti-inflammatory drugs (NSAIDs) are widely consumed among athletes worldwide in relation to muscle injury and soreness. This review aims to provide an overview of studies investigating their effects on skeletal muscle, in particular the repair processes in injured muscle. Muscle injury occurs in diverse situations and the nature of muscle injuries varies significantly, complicating extrapolations between experimental models and “real life.” Classical muscle strain injuries occur at the interphase between the muscle fibers and connective tissue, most often in the myotendinous junction, whereas contusion or overload injury can damage both myofibers and intramuscular connective tissue. The role of NSAIDs in muscle repair is complicated by differences in injury models used, variables evaluated, and time point(s) selected for evaluations.

While the temporal pattern of the influence of NSAIDs on muscle repair is difficult to settle on, it appears that a potential beneficial effect of NSAIDs in the early phase after injury is not maintained in the long term, or is even negated by a long-term repair deficit. At the cellular level, evidence exists for a negative influence of NSAIDs on the muscle stem cell population (satellite cells). At a structural level, it is known that muscle connective tissue undergoes significant remodeling during muscle regeneration, but the potential of NSAID exposure to alter this response in humans needs investigation.

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of analgesic medicines available over the counter worldwide and often employed in the early stages after muscle injury, despite a lack of clinical studies to evaluate their effectiveness. A growing awareness of the extent of NSAID consumption in the sporting world in particular has begun to emerge in the last decade, where reports now document widespread use among sports men and women from college to elite levels of performance, with youth players also being well represented (Warner et al., 2002; Alaranta et al., 2006; Tscholl et al., 2008, 2009). An interesting outcome of these reports is that the incidence of reported NSAID use generally exceeds the incidence of reported injury (Tscholl et al., 2009), leading to the conclusion that NSAIDs are not only consumed in the treatment of muscle injury, but also on a prophylactic basis (Warden, 2009; Warden, 2010). Despite this widespread use, whether NSAIDs are detrimental or beneficial for a muscle undergoing repair from injury, or indeed for muscle adaptation in general, remains unclear. The purpose of this review therefore is to provide an overview of the studies investigating the effects of NSAIDs on skeletal muscle, in particular how this medication may influence the repair processes in an injured muscle. Human studies have been cited, where available, and the relevant contributions in this context from animal and cell models are also included.

The nature of muscle injury

The treatment of muscle injury and the time it takes to repair varies according to the nature of the injury. Muscle injury can occur in many different situations, such as during explosive movement, direct impact to the muscle, and under controlled experimental conditions designed to study the mechanisms behind muscle injury and repair. Unfortunately, the nature of these types of injuries is not the same, and it is therefore often difficult to extrapolate findings from experimental studies on the role of NSAIDs in muscle repair to injuries sustained during more “real life” situations.

Strain and contusion injuries

Detailed descriptions of the types of muscle injury can be found elsewhere (Järvinen et al., 2007) so will only be
briefly mentioned here. The classic muscle rupture is the strain injury, occurring at the interphase between the muscle fibers and connective tissue components of the muscle. Such sites include the fiber-aponeurosis and the fiber–tendon (myotendinous junction) connections. Hence, the terms “strain” or “rupture” refer more strictly to the point of attachment of the muscle fibers to these connective tissue structures, rather than an actual disruption of the muscle fibers themselves. This type of injury typically occurs in the hamstring, quadriceps, or calf muscles as a result of explosive sprinting or kicking activity. Contusion injury, on the other hand, usually results from direct contact with another athlete, for example, during a tackle when the deep muscles of the quadriceps are compressed against the femur by the opponent’s knee. In this situation, the impact of the collision on the muscle can lead to vascular damage within the muscle, often resulting in a substantial hematoma. The extent of muscle fiber damage varies and the length of recovery time depends on how quickly the hematoma can be cleared (anything from 2 to 10 weeks). Muscle strain injuries are slower to heal (typically 8–12 weeks), due to the required reconstruction of the intricate muscle–matrix interphase (see Fig. 1) and susceptibility to re-injury before healing is fully complete. The extent of injury (see Fig. 2) and repair progress can be followed by ultrasound (Thorsson et al., 1993).

Myofiber injury

Damage or rupture of individual muscle fibers can occur following unaccustomed exercise, especially when the muscle performs lengthening (eccentric) contractions, as in the case of the quadriceps muscles during the downward phase of the squat exercise. Delivery of a high level (pain threshold limit) of neuromuscular electrical stimulation to the muscle in a controlled experimental setup, with or without eccentric contractions, can also induce myofiber damage (Crameri et al., 2007; Mackey et al., 2008). Damage to muscle fibers as a result of these human models has been repeatedly documented by light and electron microscopy analysis of muscle biopsy specimens obtained from the affected muscle at varying time points after the activity (Newham et al., 1983; Jones et al., 1986; Crameri et al., 2007; Mackey et al., 2008; Lauritzen et al., 2009), and complete regeneration from such damage is known to occur in healthy individuals, although this may take longer than 3–4 weeks (Paulsen et al., 2010; Mackey et al., 2011). In experimentally induced muscle damage, a significant drop (40–60% is not uncommon) in the force-producing capacity of the

![Fig. 1. Transmission electron micrograph of human myotendinous junction (MTJ) where the interdigitations at the contact surface between the muscle and tendon are clearly visible.](image1)

![Fig. 2. Ultrasonography picture of an acute muscle strain injury in a young female judo athlete who experienced sudden pain in the right calf after landing. The ultrasonography picture is taken at day 7 after injury and demonstrates a rupture in the myotendinous transition from m. gastrocnemius and the Achilles tendon, as well as a defect between m. gastrocnemius and m. soleus. On the left picture, regions in the injured right side and the healthy left side are displayed, and in the right picture, the injured region is shown in a more complete view. Note that the muscle itself on ultrasonography appears relatively intact.](image2)
Delayed-onset muscle soreness

The development of muscle soreness is also a common outcome of performing unaccustomed exercise (Clarkson et al., 1986; Mackey et al., 2004; Crameri et al., 2007), and can occur in the presence or absence of actual damage to the muscle fibers (Crameri et al., 2007). The delay in onset, typically not reaching its peak until 2–3 days after the activity (Child et al., 1998; Crameri et al., 2007; Mackey et al., 2008), has given rise to the term delayed-onset muscle soreness (DOMS), the extent of which can range from minor irritation to being quite debilitating in severe cases, resulting in acute pain during lengthening actions of the affected muscles. Investigations into the potential of NSAIDs to alleviate DOMS in exercised muscles are numerous, and the outcomes are inconsistent, with roughly equal numbers finding no effect of NSAIDs on DOMS (Kuipers et al., 1985; Donnelly et al., 1990; Bourgeois et al., 1999; Trappe et al., 2002; Nieman et al., 2006; Arendt-Nielsen et al., 2007; Mikkelsen et al., 2009) or a significant attenuation of DOMS (Donnelly et al., 1988; Hasson et al., 1993; Dudley et al., 1997; O’Grady et al., 2000; Baldwin et al., 2001; Sayers et al., 2001; Tokmakidis et al., 2003; Paulsen et al., 2010). It is possible that differences in the experimental model, extent of damage and timing or dosage of medication contribute to these divergent outcomes. However, since DOMS is not necessarily indicative of true muscle injury, combined with the fact that DOMS only occurs with unaccustomed exercise and not following repeated bouts of the same exercise (Byrnes et al., 1985; Nosaka et al., 2001), it can be argued that the issue of whether NSAIDs are effective in treating DOMS is of lesser importance than their effect on repair of injury.

Evidence for the potential of NSAIDs to influence the repair of injured skeletal muscle

Comparison of the many reports in the literature examining the role of NSAIDs in muscle repair is difficult due to differences in the model of muscle injury and the type of medication used, the variables on which evaluation is based, and, most importantly, the time point(s) selected for these evaluations. For example, it is not possible to draw conclusions on the long term outcome if only one early time point is included. (In general in this review, we define “early” as a few days, and “long term” as up to 1 or 2 months.) While some investigations have not found any effect of NSAID administration on muscle recovery (Donnelly et al., 1990; Tokmakidis et al., 2003; Paulsen et al., 2010), there are several reports supporting a protective effect of NSAID medication, typically characterized by a lesser degree of muscle damage and function deficit in the early period after injury (Hasson et al., 1993; Mishra et al., 1995; Dudley et al., 1997; Bourgeois et al., 1999; O’Grady et al., 2000; Baldwin et al., 2001; Sayers et al., 2001; Cheung & Tidball, 2003; Lapointe et al., 2003). However, the few studies that have followed the repair process over a longer period of time suggest that any apparent benefit of NSAID treatment in the short term is not maintained in the long term (Almekinders & Gilbert, 1986; Vignaud et al., 2005; Mikkelsen et al., 2009; Paulsen et al., 2010), or even negated by a long-term deficit (Obremsky et al., 1994; Mishra et al., 1995; Shen et al., 2005) in force production and muscle repair. It should be noted though that the distinction made here with regard to the short- and long-term outcomes is based on a broad mixture of different experimental models from human and animal studies. While the relevance of the experimental models used in these studies is low for strain injuries (where the site of rupture is the myotendinous junction or aponeurosis rather than the muscle fibers themselves), they nonetheless indirectly provide insight into the influence of NSAID treatment on the intramuscular structures and cells involved in the repair process.

NSAID effects on cells responsible for muscle repair

A population of muscle stem cells, known as satellite cells, is well recognized as being indispensable for the repair of skeletal muscle (Lepper et al., 2011; Sambasivan et al., 2011). The interplay between satellite cells and other cell types, such as macrophages (Sonnet et al., 2006; Arnold et al., 2007), endothelial cells (Christov et al., 2007), and fibroblasts (Murphy et al., 2011), is currently a growing field in muscle regeneration research. Taken together, there is accumulating evidence from human and animal studies for an inhibitory effect of NSAID action on expansion of satellite cell and macrophage numbers (Bondesen et al., 2004, 2006; Shen et al., 2005; Mackey et al., 2007; Mikkelsen et al., 2009; Monda et al., 2009), underlining the potency of NSAIDs to influence the behavior of cells playing a key role in muscle repair. In contrast to this, however, there is one study reporting increased numbers of ED2 macrophages (cells associated with muscle repair) in rat muscle subjected to unloading followed by reloading, when ibuprofen was administered (Cheung & Tidball, 2003). Support for no effect of NSAID administration on satellite cell or fibroblast proliferation, or capillarization, has also been reported in rat muscle recovering from contusion injury (Thorsson et al., 1998). While the literature is not entirely consistent, it does appear that the evidence for a negative influence of NSAIDs on cellular activity during muscle repair outweighs evidence for a beneficial effect and thus warrants further study of how
NSAID action could affect the interaction between inflammatory and regenerative processes in injured skeletal muscle (see Fig. 3).

NSAID effects on connective tissue healing

In addition to the cells involved in muscle repair, it has also been shown that the connective tissue surrounding individual fibers (endomysium) and fiber bundles (perimysium) undergoes significant remodeling during damage and regeneration in humans and likely plays an important role in providing protection against re-injury (Mackey et al., 2004, 2011). While there are as yet no studies examining the effects of NSAIDs on the endo- and perimysium specifically, other connective tissues of the body have received some attention. The influence of NSAIDs on bone, ligament and tendon has been reviewed (Radi & Khan, 2005; Magra & Maffulli, 2006; Ziltener et al., 2010), where it appears that healing of these tissues is not improved by NSAID treatment. Furthermore, inhibitory effects of NSAID treatment have been observed on the long-term healing of rat ligaments (Dahners et al., 1988; Elder et al., 2001), human joint sprains (Slatyer et al., 1997), and rat bone fractures (Endo et al., 2002). Interpretation of these outcomes however is clouded by the possibility that the medication may indirectly have facilitated a premature return to physical activity, rather than a direct effect of NSAID on the tissue.

NSAID effects on connective tissue adaptation to exercise

It was recently demonstrated that 12 weeks of resistance training in older persons increased the stiffness and modulus of the patellar tendon while cross-sectional area was unaltered. Interestingly, over-the-counter doses of ibuprofen did not influence this resistance training response, while acetaminophen yielded an increased tendon cross-sectional area, but an unchanged stiffness and modulus (Carroll et al., 2011). With regard to short-term responses, an inhibitory effect of NSAID exposure on the acute exercise-induced increase in collagen synthesis of healthy human tendons has been reported (Christensen et al., 2011). While this study only examines the outcome of the tendon response to a single bout of exercise, it raises the possibility that NSAID ingestion could also suppress the adaptive response of skeletal muscle connective tissue to exercise. This could take the form of hampering optimal regeneration of the complex myotendinous junction structure during recovery from a strain injury. Another possibility exists, however; that prolonged NSAID consumption could prevent an ongoing strengthening of the myotendinous junction during long-term training, making this site more susceptible to strain injury. A recent study analyzing homogenate of human muscle biopsies collected 8 days after a bout of unaccustomed high force lengthening contractions, however, did not find any effect of local infusion of NSAID into the working muscle on gene expression levels or fractional synthetic rate of collagen synthesis (Mikkelsen et al., 2011), despite an inhibitory effect of NSAID exposure on satellite cell proliferation in the same subjects (Mikkelsen et al., 2009). This study would appear to be in contrast to the tendon data mentioned above (Christensen et al., 2011), although collagen from two different tissues was investigated in these two studies. The adaptation of muscle connective tissue is known to be a multi-phase process, with a strong anabolic response of the muscle extracellular matrix not occurring until relatively late in the regeneration process, preceded by an early phase where de-adhesion and disassembly of the matrix are prioritized (Mackey et al., 2011). Furthermore, muscle extracellular matrix is a complex structure, not only responsible for force transmission, but also capable of actively regulating cells in its environment (Gillies & Lieber, 2011; Kragstrup et al., 2011), and therefore represents an important, but so far relatively neglected area of study. Further investigations are clearly required to elucidate the time course and role

![Fig. 3. Potential sites of nonsteroidal anti-inflammatory drug (NSAID) action in repair of muscle strain injury. Schematic (compare with Fig. 1) illustrating the potential sites of NSAID action with relevance for the repair of muscle strain injury.](image-url)
of the muscle connective tissue response during muscle repair following injury, and indeed the potential of NSAID exposure to alter this response, both in the context of acute muscle injury and in the ongoing training-induced fortification of muscle–matrix contact structures, such as the myotendinous junction (see Fig. 3).

NSAIDs and muscle adaptation without injury

While studies uncovering an effect of NSAID action at the cellular level are valuable in the overall understanding of how this medication may affect skeletal muscle, it can be argued that the cumulative outcome in terms of function is the most important variable to consider. Further evidence for the potency of NSAID treatment to influence muscle adaptation can be found in investigations into the development of muscle hypertrophy in response to long-term overload or resistance training. A 50–75% blunting of the muscle hypertrophy response to overloading has been reported in animals treated with NSAIDs (Soltow et al., 2006; Novak et al., 2009). While NSAID ingestion has been reported to suppress the protein synthesis response in young individuals to a single bout of exercise (Trappe et al., 2002), the outcome from human studies exploring the potential of NSAIDs to limit the hypertrophy response to 3 months of resistance training is not as clear (Petersen et al., 2011; Trappe et al., 2011). NSAID treatment was observed to have no effect on gains in muscle size in elderly patients with osteoarthritis (Petersen et al., 2011), although maximal muscle strength increased slightly, but significantly, more in the NSAID group compared with the placebo group (Petersen et al., 2011). Another human study demonstrated a clear positive influence of NSAID consumption on hypertrophy in healthy elderly individuals, with the ibuprofen group demonstrating a significantly greater increase in quadriceps muscle volume, combined with superior increases in strength, when compared with the placebo group (Trappe et al., 2011). While these findings may appear out of line with the animal studies presented here, it is possible that an age-associated elevation in systemic levels of inflammatory cytokines may explain the discrepancy. Indeed, it has been shown in old rats that ibuprofen ingestion lowered the naturally occurring age-associated systemic inflammation and resulted in a reduced loss of muscle mass, compared with control rats (Rieu et al., 2009). This explanation may also be behind the positive findings of NSAID treatment on recovery of force production in elderly individuals after a single bout of eccentric contractions (Baldwin et al., 2001). While this area of research is still in its infancy and requires further investigation, it can be speculated that NSAID treatment may have a positive effect on muscle injury in individuals with elevated circulating levels of inflammatory cytokines, such as might be the case in some elderly individuals. Further study is also required to evaluate potential differences between young and elderly in acute and chronic responses to exercise stimuli.

Perspectives

While there is evidence for and against a beneficial role of NSAIDs in muscle repair after injury, it appears on balance that reports favoring NSAID treatment may be outweighed by evidence pointing to a long-term negative influence of NSAIDs on muscle recovery from injury and adaptation of muscle and connective tissue to exercise training. An exception to this may be certain individuals with elevated systemic levels of inflammatory cytokines. However, in light of the adverse side effects and health risks associated with consumption of this medication, the risk–benefit ratio needs to be carefully evaluated when considering NSAID ingestion. Given the importance of muscle connective tissue as the main site of strain injuries and its role in cell signaling, it is clear that studies investigating the time course and the role of the muscle connective tissue response during muscle repair following injury, and the potential of NSAIDs to alter this response could contribute valuable knowledge to our understanding of how the repair of injured muscle could be optimized.

Key words: non-steroidal anti-inflammatory drugs (NSAIDs), muscle damage, eccentric exercise, muscle regeneration, connective tissue, DOMS.

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