The Use of NSAID's for Exercise-Induced Muscle Damage: Implications for Skeletal Muscle Development

Brad Schoenfeld, MSc, CSCS
Department of Health Sciences
Program of Exercise Science
APEX Building, Room # 265
Lehman College, CUNY
250 Bedford Park Blv. West
Lehman College
Bronx, NY 10468
Phone: 914-391-9357
Email: brad@workout911.com

Word Count: 3602

Abstract

Exercise-induced muscle damage (EIMD) is a common condition resulting from a bout of vigorous exercise, particularly if the individual is unaccustomed to performance of the given movement. Symptoms of EIMD include delayed-onset muscle soreness (DOMS) and a loss of physical function. Non-steroidal anti-inflammatory drugs (NSAIDs) are routinely prescribed post-exercise to alleviate these symptoms and restore normal physical function. Of potential concern for those who use NSAIDs to treat EIMD is the possibility that they may impair the adaptive response to exercise. Specifically, there is emerging evidence that the action of cyclooxygenase (COX) enzymes, and COX-2 in particular, are important and even necessary to achieve maximal skeletal muscle hypertrophy in response to functional overload. Given that NSAIDs exert their actions by blocking COX and thus suppressing prostaglandin production, a theoretical rationale exists whereby these drugs may have detrimental effects on muscle regeneration and supercompensation. Therefore, the purpose of this paper is to extensively review the literature and evaluate the effects of NSAIDs on muscle growth and development. Based on current evidence, there is little reason to believe that the occasional use of NSAIDs will negatively affect muscle growth, although the efficacy for their use in alleviating inflammatory symptoms remains questionable. Evidence on the hypertrophic effects of the chronic use of NSAIDs is less clear. In those who are untrained, it does not appear that regular NSAID will impede growth in the short-term, and at least one study indicates that it may in fact have a positive impact. Given their reported impairment of satellite cell activity, however, longer-term NSAID use may well be detrimental, particularly in those who possess greater growth potential.

Key Words: cyclooxygenase inhibitor, anti-inflammatory drug, muscle hypertrophy, muscle growth, muscle damage

Acknowledgements

This review was not funded by any outside organization. Brad Schoenfeld is the sole author of this work. There are no conflicts of interest present.

Introduction

Exercise-induced muscle damage (EIMD) is a common condition resulting from a bout of vigorous exercise, particularly if the individual is unaccustomed to performance of the given movement. Damage can be specific to just a few macromolecules of tissue or manifest as large tears in the sarcolemma, basal lamina, and supportive connective tissue, as well as altering the function of contractile elements and the cytoskeleton (1). While concentric and isometric actions can cause EIMD (2, 3), damage is increased by the performance of eccentric exercise whereby muscles are forcibly lengthened (4). For an in depth review of the topic, see the paper by Clarkson and Hubal (4).

Muscle soreness is a frequently reported consequence of EIMD. This phenomenon has been termed delayed-onset muscle soreness (DOMS), as the associated symptoms of pain and tenderness generally peak 24-48 hours post-exercise. DOMS is believed to be the result of a sensitization of nociceptors by tissue breakdown products and noxious chemicals such as histamines, bradykinins, prostaglandins, and free radicals (4, 5). Soreness also may involve mechanoreceptors, including muscle spindle afferents, which are able to access the pain pathway at the level of the spinal cord (5). In addition, biochemical changes due to structural disruption of the extracellular matrix (ECM) has been implicated with playing a role in the process (6). It has been postulated that damage to myofibers facilitates the escape and entrance of intracellular and extracellular proteins respectively, while disturbance of the ECM mediates the inflammatory response (6). Symptoms can be exacerbated by swelling within muscle fibers, which exerts pressure on nociceptors and thus increases the sensation of pain (4).

EIMD can also decrease physical function, with the degree of impairment modulated by the type, intensity, and/or duration of training (7). Functional post-exercise decrements have been

attributed to damage to the excitation-contraction coupling system and disruption of the sarcomere (5). Swelling and stiffness can also contribute to the process by limiting range of motion.

Non-steroidal anti-inflammatory drugs (NSAIDs) are routinely prescribed to alleviate EIMD-related symptoms and restore normal physical function. This class of drugs can be obtained either by prescription or purchased over-the-counter. It is estimated that 30 million people worldwide use NSAIDS on a daily basis (8), and their consumption is particularly prevalent among athletes and others who engage in vigorous physical activity (9).

A primary way in which NSAIDs are believed to exert their pain-reducing effects is by inhibiting the activity of cyclooxygenase (COX), a family of enzymes that catalyze the conversion of arachidonic acid to proinflammatory prostanoids (10, 11). Although the exact details have not been fully elucidated, it is believed that damage to skeletal muscle leads to activation of Phospholipase A2, which cleaves arachidonic acid (AA) from the cell membrane, ultimately resulting in COX mediated production of prostaglandins (12) (see Figure 1). Prostanoids are subsequently released outside the cell, influencing biological functions by interacting with G protein–coupled cell surface receptors in an autocrine/paracrine manner (12). In addition to their role in promoting pain and edema, specific prostanoid receptors are theorized to induce anabolic signaling, conceivably via stimulation of upstream protein synthetic regulators that include PI3K and extracellular signal-regulated kinases (13). It also has been shown that prostanoid-mediated signaling through calcium-dependent pathways influences satellite-cell derived myonuclear accretion, directly leading to increased myofiber growth (14). These data strongly suggest that COX activity is necessary to achieve maximal skeletal muscle hypertrophy in response to functional overload (15).

Three COX isoforms have been identified: COX-1, COX-2, and COX-3. Of these isoforms, only COX-1 and COX-2 are expressed in skeletal muscle (16, 17) and appear to be upregulated in response to physical exercise (16, 18, 19). It has been proposed that COX-2 provides the primary impetus for the inflammatory response following EIMD, although emerging data seem to support an important role for COX-1 in the process (18, 20). Interestingly, recent studies seem to show that certain NSAIDs may upregulate COX-2 production, possibly as a means to compensate for the anti-inflammatory blockade (18, 21). Other mechanisms of action have been attributed to NSAIDs including activation of descending serotonergic pathways, upregulation of cannabinoid receptors, and inhibition of leukocyte adhesion pathways (22-24).

Despite their immense popularity as an analgesic and anti-inflammatory agent, the ability of NSAIDs to relieve symptoms associated with EIMD remains dubious. Although several researchers have shown that NSAID administration facilitates recovery of muscle function following EIMD (25-27), others have failed to note improvements in comparison with placebo (28-31). Similarly, while some studies have reported reductions in ratings of perceived soreness with post-exercise NSAID consumption (27, 28), a review by Connelly et al. (32) found that the preponderance of evidence reveals no therapeutic effect from their use.

Of potential concern for those who use NSAIDs to treat EIMD is the possibility that they may impair the adaptive response to exercise. Specifically, there is emerging evidence that COX enzymes are important and even necessary to achieve maximal skeletal muscle hypertrophy in response to functional overload (15). The hypertrophic effects of COX appear to be related to the synthesis of various prostaglandins, which have been shown to stimulate satellite cell proliferation, differentiation, and fusion (19) and increase muscle protein synthesis (33, 34). Given that NSAIDs supposedly exert their actions by blocking COX and thus suppressing

prostaglandin production, a theoretical rationale exists whereby these drugs may have detrimental effects on muscle regeneration and supercompensation. Therefore, the purpose of this paper is to extensively review the literature and evaluate the effects of NSAIDs on muscle growth and development. To carry out this review, English-language literature searches of the PubMed and EBSCO databases were conducted for all time periods up to December 2011. Combinations of the following keywords were used as search terms: "NSAID", "anti-inflammatory drug", "cyclooxygenase inhibitor", "exercise", "muscle" "hypertrophy", "growth", "satellite cell", "myoblast", "protein synthesis". The reference lists of articles retrieved in the search were then screened for any additional articles that had relevance to the topic. All applicable studies were included for discussion, with a focus on the results of in vivo protocols, particularly those involving human subjects.

Effects of NSAIDS on Muscle Protein Synthesis

The maintenance of skeletal muscle tissue involves the dynamic balance between muscle protein synthesis and degradation (35, 36). Muscle hypertrophy occurs when protein synthesis exceeds proteolysis. Protein synthetic rates are markedly increased following resistance exercise in both young and old individuals alike, facilitating adaptation to imposed demands (37, 38). The post-exercise accretion of muscle proteins is carried out via a complex cascade of anabolic signaling pathways, although the exact mechanisms and interplay between these pathways are not clearly understood at this time (36).

Early studies in animal models demonstrated that NSAIDs impaired protein metabolism (33, 34, 39). These findings were attributed to an attenuation of prostaglandin production via COX inhibition. A suppression of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), in particular, was purported to play a primary role in blunting the muscle protein synthetic rate.

To date, 4 trials have investigated the effects of NSAID administration on post-exercise muscle protein synthesis in humans (see Table 1). The first of these studies was conducted by Trappe et al., (40). Twenty-four sedentary or recreationally active males (25 ± 3 years) were randomly assigned to receive either 1200 mg. of ibuprofen, 4000 mg. of acetaminophen, or placebo following a bout of supramaximal eccentric exercise. Exercise consisted of 10 to 14 sets of 10 lengthening actions for the knee extensors at a workload set to 120% of concentric 1 repetition maximum (RM). Compared with pre-exercise levels, skeletal muscle fractional synthetic rate (FSR) was significantly greater in those receiving placebo compared to ibuprofen or acetaminophen (76 ± 19% versus 35 ± 21% versus 22 ± 23%, respectively) at 24-hours post-exercise. In addition, levels of $PGF_{2\alpha}$ were significantly increased (77%) in the placebo group but remained unchanged in the treatment groups. Based on this data, it was concluded that NSAIDs blunt post-exercise protein synthesis by suppressing production of $PGF_{2\alpha}$ via the COX enzyme. A limitation of the study was that researchers only analyzed mixed muscle protein synthesis. Therefore, it is not clear what percentage of the FSR represented myofibrillar versus non-contractile proteins such as collagen.

In contrast to these findings, Burd et al., (18) employed a similar study design but found that NSAID consumption did not impair mixed muscle protein FSR following performance of 10 sets of 10 lengthening contractions for the knee extensors at a workload equating to 120% of concentric 1RM. Subjects were 16 recreationally-active males (23 ± 1 yr) randomly assigned to receive either 600 mgs of Celecoxib or placebo in double-blind fashion. The primary difference between this study and that of Trappe et al., (40) was the use of a selective COX-2 inhibitor (celecoxib) rather than a non-selective COX inhibitor (ibuprofen). Results suggest that the COX-1 enzyme may play a primary role in mediating post-exercise muscle protein synthesis and that

COX-2 may be more reactive to injury-related stimuli. As with the study by Trappe et al. (40), however, results were limited by an inability to isolate the contractile component of muscle protein synthesis.

Petersen et al., (41) was the first to evaluate the effects of NSAIDs on post-exercise contractile muscle protein synthesis. In a double blind fashion, 20 elderly subjects (50 to 70 years of age) with knee osteoarthritis were divided into either a treatment group (n = 9) who received 1200 mg of ibuprofen or placebo group (n = 11). Exercise consisted of 60 minutes of one-legged kicking at 55% of maximal workload while the contralateral leg did not exercise. At 24 hours post-exercise, plasma levels of $PGF_{2\alpha}$ were significantly lower in the NSAID compared to placebo but myofibrillar FSR was not different between groups. It is difficult to justify these seemingly contradictory results. Moreover, considering the injury history and age of the subjects as well as the endurance-oriented nature of the exercise protocol, the generalizability of findings to healthy individuals who perform resistance exercise is questionable.

Most recently, Mikkelsen et al. (21) studied the effects of NSAID on post-exercise protein synthesis in 8 healthy male volunteers (23 ± 3 years) who were experienced in endurance exercise but not lower body resistance training. Forty-five mg of indomethacin was locally infused for 7.5 hours via catheter into the vastus lateralis muscle of one leg before, during, and after exercise while the contralateral leg was infused with placebo. Exercise consisted of 200 unilateral maximal isokinetic lengthening contractions for the knee extensors. Muscle biopsies taken 24 to 28 hours after training revealed no significant differences in either myofibrillar or collagen mean muscle FSR between the NSAID infused leg compared to placebo at 24 to 28 hours post-exercise.

Effects of NSAIDS on Satellite Cell Activity

Satellite cells are myogenic stem cells that reside between the basal lamina and sarcolemma of muscle fibers. At rest, the satellite cell pool remains quiescent until aroused by mechanical stimuli. Once activated, they (1) generate precursor cells (myoblasts) that proliferate and ultimately fuse to existing cells, providing agents needed for repair and subsequent growth of new muscle tissue (42). Satellite cells also help to retain the mitotic capability of muscles by donating their nuclei to existing muscle fibers, thereby increasing the capacity to synthesize new contractile proteins (43, 44). Since a muscle's nuclear-content-to-fiber-mass ratio remains constant during hypertrophy, the satellite cell-derived addition of new myonuclei is believed to be essential for realizing long-term increases in muscle mass (45). This is consistent with the concept of myonuclear domain, which proposes that the myonucleus regulates mRNA production for a finite sarcoplasmic volume and any increases in fiber size must be accompanied by a proportional increase in myonuclei (46). Moreover, satellite cells co-express various myogenic regulatory factors such as Myf5, MyoD, myogenin, and myogenic regulatory factor (MRF)4 (47), which bind to sequence specific DNA elements present in the promoter of muscle genes to aid in the hypertrophic process (48, 49).

Although somewhat controversial, current theory suggests that satellite cells are crucial for the regulation of muscular growth (50). In support of this view, a recent cluster analysis by Petrella et al., (46) demonstrated that subjects who experienced extreme increases in mean myofiber cross sectional area of the vastus lateralis (>50%) possessed a much greater ability to expand the satellite cell pool compared to those who experienced moderate or negligible increases in hypertrophy. Further support for the theory comes from studies showing that muscle hypertrophy is significantly attenuated when satellite cells are obliterated by gamma-irradiation (51). It should be noted that some researchers dispute the importance of satellite cells in exercise-

induced muscle hypertrophy. A complete discussion of the topic is beyond the scope of this paper and those interested are referred to the point/counterpoint articles by O'Connor and Pavlath (50) and McCarthy and Esser (52).

Evidence that NSAIDs might have a negative impact on satellite cell activity was initially documented in animal cell culture. Zalin (53) displayed a marked suppression of fusion of chick myoblasts when they were subjected to non-selective COX inhibitors. Subsequently, Santini et al. (54) found that that differentiation into myotubes was impaired when myoblasts were maintained in indomethacin. Follow up in vitro studies have confirmed these results for both the COX-1 and COX-2 enzymes independently (55, 56). In vivo research on rodents has similarly demonstrated that selective COX-2 suppression reduced satellite cell activation, proliferation, and differentiation, as well as inhibiting myonuclear incorporation into muscle (19, 57). Interestingly, COX-1 was not found to play a significant role in these studies, leading to the supposition that COX-1 and COX-2 pathways have distinct roles during muscle repair.

More recently, researchers have conducted human trials to investigate the topic (see Table 2). Mackey et al., (58) examined the influence of NSAID use on satellite cell activity following a single bout of intense exercise in 14 healthy, well-trained male endurance athletes. Subjects were divided into two groups, receiving either a 100 mg. daily dose of the non-specific COX inhibitor indomethacin for 12 days or placebo. Exercise for both groups consisted of a 36-km run, with muscle biopsies collected 1, 3 and 8 days post-exercise. Compared with pre-exercise levels, results showed a 27% increase in the number of neural cell adhesion molecule-positive cells on day 8 post-exercise in placebo, while levels remained unchanged at all time points for the NSAID group.

Mikkelsen et al., (59) investigated the effects of NSAID administration on the satellite cell response to a bout of eccentric exercise. Eight healthy male volunteers (age 23 ± 3 years)

performed 200 unilateral maximal isokinetic lengthening contractions for both legs. Subjects were considered well-trained but had not performed resistance training of the lower limbs for at least one year. On the day of the exercise bout, 45 mg of indomethacin was locally infused for 7.5 hours via catheter into the vastus lateralis muscle of one leg before, during, and after exercise. The control leg was infused with placebo. Results showed that the number of Pax7(+) cells per myofiber was significantly increased by 96% in the control leg 8 days post-exercise but remained unchanged in the muscles infused with indomethacin, indicating a decidedly detrimental effect of NSAID administration on satellite cell activity. A noteworthy aspect of the study was that these findings were seen with a single infusion of NSAID, suggesting that COX blockage in the early post-exercise period may interfere with pathways necessary for satellite cell proliferation.

In a double-blind, placebo-controlled experiment, Paulsen et al., (31) evaluated the effects of a selective COX-2 inhibitor on muscle recovery following damaging exercise. Thirty-three young, physically active volunteers (22 males; 11 females) performed 2 bouts of maximal lengthening actions of the elbow flexors. The bouts were separated by 3 weeks and only one arm was trained per session with the other arm serving as a non-exercise control. Participants were randomized to either an NSAID group or a placebo group. Those in the NSAID group received 400 mg of Celecoxib daily for 9 days, with the first dose administered approximately 45 minutes prior to each exercise bout. The placebo group received lactose pills over the same time periods. In contrast to the findings of Mackey et al., (58) and Mikkelsen et al., (59), results showed no significant differences in the number of satellite cells/myoblasts per myofiber between groups following either exercise bout at any of the time points studied. No significant differences were found in the number of macrophages, although the 5 highest peak values were all found in

samples from those in the placebo group. Whether the discrepancy between this study and those reporting a negative effect on satellite cell activity are due to the use of a selective COX-2 inhibitor versus a non-selective COX inhibitor are not clear at this time.

Interestingly, Mikkelsen et al., (21) found that non-selective NSAID use down-regulated insulin-like growth factor (IGF)-1Ea expression at 5 hours post-exercise. IGF-IEa has been shown to enhance fusion of satellite cells with existing muscle fibers, facilitating the donation of myonuclei and helping to maintain optimal DNA to protein ratios in muscle tissue (35, 51). Levels of the muscle specific IGF-1E-c isoform (i.e. MGF), however, were unaffected by NSAID administration. This is intriguing because the initial pulse of IGF-1Ec has been shown to activate satellite cells and mediate their proliferation and differentiation (60, 61). The implications of these findings require further study.

Effects of NSAIDs on Muscle Hypertrophy

Studies on rodents have consistently shown that treatment with both selective and non-selective NSAIDs following chronic overload have a profoundly detrimental effect on muscle growth. Soltow et al. (15) demonstrated that ibuprofen administration in Sprague-Dawley rats resulted in a 50% decrease in hypertrophy of the plantaris muscle 14 days post-surgical removal of the gastrocnemius and soleus. Similar impairments in compensatory hypertrophic increases have been reported from the use of selective COX-2 inhibitors following synergist ablation of the triceps surae (62) and chronic hindlimb suspension in mice (57).

In contrast to the aforementioned animal studies, the 3 human trials conducted to date have failed to demonstrate a negative impact of NSAIDS on hypertrophy (see Table 3). Krentz et al. (63) examined the impact of a moderate dose of NSAID on hypertrophy in 18 young volunteers (12 males, 6 females; ~24 years of age). Employing a counter-balanced, double-blind

design, subjects were randomly assigned to receive a daily dose of 400 mg of ibuprofen following resistance exercise for the elbow flexors of one arm and placebo after working the other arm the next day. Training consisted of 6 sets of 4-10 repetitions, and was performed 5 days a week. After 6 weeks of training, no differences in muscle thickness were noted between arms (~0.29 cm. change in muscle thickness for NSAID arm versus ~0.28 cm for placebo). The study was limited by its short duration and thus it is not clear whether differences may have manifested had a longer-term protocol been employed. It also should be noted that the dosage (400 mg of ibuprofen) was substantially less than that used in the other studies, making it difficult to draw relevant conclusions.

Trappe et al. (64) conducted a double-blind study whereby 36 healthy, elderly adults (60-85 years of age; 24 males, 12 females) were randomly assigned to receive a daily dose of either 4000 mg/day of acetaminophen (n = 11), 1200 mg/day of Ibuprofen (n = 13), or placebo (n = 12). Subjects performed 3 sets of 10 repetitions of progressive resistance exercise for the knee extensors. Training was carried out 3 days a week on non-consecutive days. After 12 weeks, subjects who consumed anti-inflammatory drugs displayed a significantly greater increase in muscle volume compared to control (placebo: 69 ±12; acetaminophen: 109±14; ibuprofen: 84±10 cm^3). These results suggest that chronic NSAID use may in some way promote adaptations that ultimately lead to greater long-term skeletal muscle protein accretion. Findings were limited to untrained, elderly subjects, however, and thus it remains unknown whether similar results would be seen in a young, athletic population.

Most recently, Petersen et al. (65) investigated the effects of NSAID administration on muscle hypertrophy in elderly subjects (20 women, 16 men; age range, 50-70 years) with a history of bilateral tibiofemoral knee osteoarthritis. Participants were randomly divided to

receive either 1200 mg of ibuprofen, 1500 mg glucosamine, or placebo. Training consisted of unilateral knee extension and leg press for both legs, with intensity increasing from 4 sets of 15 RM in the first week to 4 sets of 8 RM by week 7 and onward. Training was carried out on 3, non-consecutive days per week. After 12 weeks, results failed to show any differences in muscle cross sectional area between groups. Interestingly, however, consumption of NSAID resulted in greater gains in maximal isometric strength, maximal eccentric strength,and eccentric work compared to placebo. This suggests that the alleviation of pain in this population may allow individuals to exert greater force during resistance training efforts and thereby enhance strength capacity. That said, the effect size of the reported gains was rather small, calling into question whether costs of treatment outweigh the benefits.

Contradictions in Findings

Based on the body of current literature, evidence is lacking that COX inhibitors have a detrimental acute effect on post-exercise protein synthesis. Although animal studies have shown an impaired response when either selective or non-selective NSAIDs were given following chronic overload, the majority of human trials fail to support this finding. Possible reasons explaining these discrepancies are differences in methodologies between studies, physiological differences between species, and/or differences in the mechanisms of the various drugs used (i.e. selective versus non-selective COX inhibitors).

Longer-term effects of NSAIDs on exercise-induced muscle hypertrophy are equivocal at this time. There is strong evidence that satellite cell activity is impaired by the use of non-selective COX inhibitors in both animal and human trials, although further study is warranted to determine if such effects persist with the administration of drugs selective to the COX-2 enzyme. It seems logical to infer from these data that NSAID consumption would limit a person's

hypertrophic potential by restricting the satellite cell pool. Some researchers have proposed that a myonuclear domain ceiling of ~2,000 μm^2 exists beyond which further hypertrophy cannot occur unless there is satellite cell-mediated incorporation of additional myonuclei (66). If true, NSAIDs would most certainly be detrimental to those who aspire to maximize muscle development. Emerging data, however, suggests this might only have relevance to a certain segment of the population. As previously noted, Petrella et al. (46) showed that hypertrophic "responders" to resistance training had a robust capacity to increase satellite cell activity while "non-responders" did not. Thus, it may be that any negative effects of NSAID administration on muscle growth may be specific to those with an increased potential to add lean mass and have a minimal impact on the rest of the population.

Direct studies on the topic are contradictory. The preponderance of data in animal models shows a marked reduction in exercise-induced hypertrophy following NSAID administration. These results are consistent with the use of both selective and non-selective COX inhibitors. On the other hand, the limited number of human studies conducted to date do not indicate that NSAIDs blunt the hypertrophic response, and one recent study (64) actually found up to a 50% increase in muscle mass over 12 weeks in subjects consuming either ibuprofen or acetaminophen. These conflicting findings are difficult to reconcile. A possible explanation is that NSAID-mediated reductions in proteolysis may be greater than any suppression of protein synthesis, thereby leading to an overall positive nitrogen balance. In support of this contention, Rodemann et al., (33) displayed that COX inhibition of incubated rat soleus muscle resulted in a 39% increase in net protein balance, which was attributed to an attenuation of protein breakdown that exceeded impairments in protein synthetic rate. However, this would not explain the marked NSAID-induced impairment in hypertrophy found in vivo in animal studies.

Another possibility is that the degree of myofiber hypertrophy experienced by subjects in the human trials did not reach their myonuclear domain ceiling. This would conceivably account for the significant blunting of hypertrophy in animal models, where the techniques employed (i.e. chronic stretching, synergist ablation) result in extreme rates of weekly hypertrophy not seen in traditional human exercise programs (~40% versus 1%, respectively) (18) and thus would seemingly require a robust satellite cell pool. Further research is needed to assess this prospect.

Conclusion

In summary, there is little reason to believe that the occasional use of NSAIDs will negatively affect muscle growth, although the efficacy for their use in alleviating inflammatory symptoms remains questionable. Evidence on the hypertrophic effects of the chronic use of NSAIDs is less clear. In those who are untrained, it does not appear that regular NSAID use will impede growth in the short-term, and at least one study indicates that it may in fact have a positive impact. Given their reported impairment of satellite cell activity, however, longer-term use may well be detrimental, particularly in those who possess greater growth potential. Future research should seek to clarify inconsistencies between studies, as well as investigating the effects of NSAIDs on muscle hypertrophy in trained subjects and athletes, who are known to be frequent consumers of these drugs.

Table 1

Summary of human studies investigating the effect of NSAID consumption on post-exercise protein synthesis

Study	Subjects	Subject Age	Exercise Protocol	NSAID/Dosage	Measurement Timepoints	Results
Trappe et al., 2002 (40)	24 healthy sedentary or recreationally active males	25 ± 3 yrs	10–14 sets of 10 repetitions of unilateral knee extensor exercise at 120% 1RM separated by 60 second rest intervals	Ibuprofen/1200 mg/day: n=8, or Acetaminophen /4000 mg/day: n=8, or placebo: n=8	Baseline and 24-hours post-exercise	Increase in mixed muscle FSR significantly greater in placebo group compared to NSAID 24 hours post-exercise
Burd et al., 2010 (18)	16 healthy recreationally active males	23 ± 1 yrs	10 sets of 10 repetitions of unilateral knee extensor exercise at 120% 1RM separated by 60 second rest intervals.	Celecoxib/600 mg/day: n=8, or placebo: n=8	Baseline and 24-hours post-exercise	No significant difference in mixed muscle protein FSR between groups 24 hours post-exercise
Petersen et al., 2011 (41)	20 sedentary or recreationally active males (n=11) and females (n=9) with knee osteoarthritis	50 to 70 yrs	60 min of one-legged kicking at 55% of workload maximum	Ibuprofen/1200 mg/day: n=9, or placebo: n=11	Baseline and 24-hours post-exercise	No significant difference in myofibrillar FSR between groups 24 hours post-exercise
Mikkelsen et al., 2011 (21)	8 healthy endurance-trained males	23 ± 3 yrs	200 unilateral maximal eccentric knee extensor contractions	Indomethacin/45 mg/day: n=8 (within-subject design)	Baseline and 24- to 28-hours post-exercise	No significant differences in either myofibrillar or collagen mean muscle FSR between groups 24-28 hours post-exercise

Table 2

Summary of human studies investigating the effect of NSAID consumption on satellite cell activity

Study	Subjects	Subject Age	Exercise Protocol	NSAID/Dosage	Measurement Timepoints	Results
Mackey et al., 2007 (58)	14 healthy male endurance athletes	25 ± 3 yrs	Running 36 km	Indomethacin/100 mg/day: n=7, or placebo: n=7	Baseline, and 1, 3, and 8 days post-exercise	Significant increase in number of NCAM+ cells on day 8 post-exercise in placebo group versus no change in the NSAID
Mikkelsen et al., 2010 (59)	8 healthy endurance-trained males	23 ± 3 yrs	200 unilateral maximal eccentric knee extensor contractions	Indomethacin/45 mg/day: n=8 (within-subject design)	Baseline and 8 days post-exercise	Significant blunting of satellite cell number in NSAID group compared to placebo 8 days post-exercise
Paulsen et al., 2011 (31)	33 healthy recreationally active males (n=22) and females (n=11)	~25 yrs	2 bouts of 70 maximal unilateral eccentric actions of the elbow flexors separated by 3 weeks	Celecoxib/400 mg/day: n=15, or placebo: n=18	Baseline and 1, 2, 4, and 7 days post-exercise	No significant differences in satellite cell activity between groups at 1, 2, 4 and 7 days post-exercise

Table 3

Summary of human studies investigating the effect of NSAID consumption on muscle hypertrophy

Study	Subjects	Subject Age	Exercise Protocol	Study Duration	NSAID/Dosage	Measurement Instrument	Results
Krentz et al., 2008 (63)	18 healthy males (n=12) and females (n=6) experienced in resistance training	~24 yrs	3 sets of 8–10 concentric repetitions at 70% of 1 RM, and 3 sets of 4–6 eccentric repetitions at 100% of 1 RM for the elbow flexors with 1 min rest interval performed on alternate days for each arm for 5 days/wk	6 weeks	Ibuprofen/400 mg/day: n=18 (within-subject design)	B-mode ultrasound	No differences in muscle thickness of the upper arm between groups after 6 weeks
Trappe et al., 2011 (64)	36 healthy untrained males (n=24) and females (n=12)	60 to 85 yrs	2sets of 5 knee extensions at a light weight, followed by 3 sets of 10 repetitions with 2 min rest interval performed 3 days a week on non-consecutive days	12 weeks	Acetaminophen/ 4000 mg/day: n=11, or Ibuprofen/1200 mg/day: n=13, or placebo: n=12	Magnetic resonance imaging	Significantly greater increase in muscle hypertrophy in NSAID group compared to control after 12 weeks
Petersen et al., 2011 (65)	20 sedentary or recreationally active males (n=16) and females (n=20) with knee osteoarthritis	50 to 70 yrs	4 sets of 15 RM in the first week progressively increasing to 4 sets of 8 RM by week 7 and onward of the knee extension and leg press performed 3 non-consecutive days per week.	12 weeks	Ibuprofen/1200 mg/day: n=12 , glucosamine/1500 mg/day: n=12, or placebo: n=11	Magnetic resonance imaging	No differences in muscle cross sectional area of quadriceps between groups after 12 weeks

References

1. Vierck J, O'Reilly B, Hossner K, Antonio J, Byrne K, Bucci L, et al. Satellite cell regulation following myotrauma caused by resistance exercise. Cell Biol Int. 2000;24(5):263-72.

2. Clarkson PM, Byrnes WC, McCormick KM, Turcotte LP, White JS. Muscle soreness and serum creatine kinase activity following isometric, eccentric, and concentric exercise. Int J Sports Med. 1986 06;7(3):152-5.

3. Gibala MJ, MacDougall JD, Tarnopolsky MA, Stauber WT, Elorriaga A. Changes in human skeletal muscle ultrastructure and force production after acute resistance exercise. J Appl Physiol. 1995 Feb;78(2):702-8.

4. Clarkson PM, Hubal MJ. Exercise-induced muscle damage in humans. Am J Phys Med Rehabil. 2002 11;81(11):52-69.

5. Proske U, Morgan DL. Muscle damage from eccentric exercise: Mechanism, mechanical signs, adaptation and clinical applications. J Physiol. 2001 Dec 1;537(Pt 2):333-45.

6. Stauber WT, Clarkson PM, Fritz VK, Evans WJ. Extracellular matrix disruption and pain after eccentric muscle action. J Appl Physiol. 1990 Sep;69(3):868-74.

7. Malm C. Exercise-induced muscle damage and inflammation: Fact or fiction? Acta Physiol Scand. 2001 03;171(3):233-9.

8. Baum C, Kennedy DL, Forbes MB. Utilization of nonsteroidal antiinflammatory drugs. Arthritis Rheum. 1985 Jun;28(6):686-92.

9. Warner DC, Schnepf G, Barrett MS, Dian D, Swigonski NL. Prevalence, attitudes, and behaviors related to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in student athletes. J Adolesc Health. 2002 Mar;30(3):150-3.

10. Vane JR, Botting RM. Anti-inflammatory drugs and their mechanism of action. Inflamm Res. 1998 Oct;47 Suppl 2:S78-87.

11. Burian M, Geisslinger G. COX-dependent mechanisms involved in the antinociceptive action of NSAIDs at central and peripheral sites. Pharmacol Ther. 2005 Aug;107(2):139-54.

12. Dey I, Lejeune M, Chadee K. Prostaglandin E2 receptor distribution and function in the gastrointestinal tract. Br J Pharmacol. 2006 Nov;149(6):611-23.

13. Fujino H, Xu W, Regan JW. Prostaglandin E2 induced functional expression of early growth response factor-1 by EP4, but not EP2, prostanoid receptors via the phosphatidylinositol 3-kinase and extracellular signal-regulated kinases. J Biol Chem. 2003 Apr 4;278(14):12151-6.

14. Horsley V, Pavlath GK. Prostaglandin F2(alpha) stimulates growth of skeletal muscle cells via an NFATC2-dependent pathway. J Cell Biol. 2003 04/14;161(1):111-8.

15. Soltow QA, Betters JL, Sellman JE, Lira VA, Long JH, Criswell DS. Ibuprofen inhibits skeletal muscle hypertrophy in rats. Med Sci Sports Exerc. 2006 May;38(5):840-6.

16. Weinheimer EM, Jemiolo B, Carroll CC, Harber MP, Haus JM, Burd NA, et al. Resistance exercise and cyclooxygenase (COX) expression in human skeletal muscle: Implications for COX-inhibiting drugs and protein synthesis. Am J Physiol Regul Integr Comp Physiol. 2007 Jun;292(6):R2241-8.

17. Peterson JM, Trappe TA, Mylona E, White F, Lambert CP, Evans WJ, et al. Ibuprofen and acetaminophen: Effect on muscle inflammation after eccentric exercise. Med Sci Sports Exerc. 2003 Jun;35(6):892-6.

18. Burd NA, Dickinson JM, Lemoine JK, Carroll CC, Sullivan BE, Haus JM, et al. Effect of a cyclooxygenase-2 inhibitor on postexercise muscle protein synthesis in humans. Am J Physiol Endocrinol Metab. 2010 Feb;298(2):E354-61.

19. Bondesen BA, Mills ST, Kegley KM, Pavlath GK. The COX-2 pathway is essential during early stages of skeletal muscle regeneration. Am J Physiol Cell Physiol. 2004 Aug;287(2):C475-83.

20. Prisk V, Huard J. Muscle injuries and repair: The role of prostaglandins and inflammation. Histol Histopathol. 2003 Oct;18(4):1243-56.

21. Mikkelsen UR, Schjerling P, Helmark IC, Reitelseder S, Holm L, Skovgaard D, et al. Local NSAID infusion does not affect protein synthesis and gene expression in human muscle after eccentric exercise. Scand J Med Sci Sports. 2011 Oct;21(5):630-44.

22. Anderson BJ. Paracetamol (acetaminophen): Mechanisms of action. Paediatr Anaesth. 2008 Oct;18(10):915-21.

23. Botting RM. Mechanism of action of acetaminophen: Is there a cyclooxygenase 3? Clin Infect Dis. 2000 Oct;31 Suppl 5:S202-10.

24. Diaz-Gonzalez F, Sanchez-Madrid F. Inhibition of leukocyte adhesion: An alternative mechanism of action for anti-inflammatory drugs. Immunol Today. 1998 Apr;19(4):169-72.

25. Dudley GA, Czerkawski J, Meinrod A, Gillis G, Baldwin A, Scarpone M. Efficacy of naproxen sodium for exercise-induced dysfunction muscle injury and soreness. Clin J Sport Med. 1997 Jan;7(1):3-10.

26. Bourgeois J, MacDougall D, MacDonald J, Tarnopolsky M. Naproxen does not alter indices of muscle damage in resistance-exercise trained men. Med Sci Sports Exerc. 1999 Jan;31(1):4-9.

27. Sayers SP, Knight CA, Clarkson PM, Van Wegen EH, Kamen G. Effect of ketoprofen on muscle function and sEMG activity after eccentric exercise. Med Sci Sports Exerc. 2001 May;33(5):702-10.

28. Tokmakidis SP, Kokkinidis EA, Smilios I, Douda H. The effects of ibuprofen on delayed muscle soreness and muscular performance after eccentric exercise. J Strength Cond Res. 2003 Feb;17(1):53-9.

29. Howell J, Conatser R, Chleboun G, Chila A. The effect of nonsteroidal anti-inflammatory drugs on recovery from exerciseinduced muscle injury 1. flurbiprofen. J Muscoskel Pain. 1998;6:59-68.

30. Stone MB, Merrick MA, Ingersoll CD, Edwards JE. Preliminary comparison of bromelain and ibuprofen for delayed onset muscle soreness management. Clin J Sport Med. 2002 Nov;12(6):373-8.

31. Paulsen G, Egner IM, Drange M, Langberg H, Benestad HB, Fjeld JG, et al. A COX-2 inhibitor reduces muscle soreness, but does not influence recovery and adaptation after eccentric exercise. Scand J Med Sci Sports. 2010 Feb;20(1):e195-207.

32. Connolly DA, Sayers SP, McHugh MP. Treatment and prevention of delayed onset muscle soreness. J Strength Cond Res. 2003 Feb;17(1):197-208.

33. Rodemann HP, Goldberg AL. Arachidonic acid, prostaglandin E2 and F2 alpha influence rates of protein turnover in skeletal and cardiac muscle. J Biol Chem. 1982 Feb 25;257(4):1632-8.

34. Palmer RM. Prostaglandins and the control of muscle protein synthesis and degradation. Prostaglandins Leukot Essent Fatty Acids. 1990 Feb;39(2):95-104.

35. Toigo M, Boutellier U. New fundamental resistance exercise determinants of molecular and cellular muscle adaptations. Eur J Appl Physiol. 2006 08;97(6):643-63.

36. Schoenfeld BJ. The mechanisms of muscle hypertrophy and their application to resistance training. J Strength Cond Res. 2010 Oct;24(10):2857-72.

37. Phillips SM, Tipton KD, Aarsland A, Wolf SE, Wolfe RR. Mixed muscle protein synthesis and breakdown after resistance exercise in humans. Am J Physiol. 1997 Jul;273(1 Pt 1):E99-107.

38. Drummond MJ, Dreyer HC, Pennings B, Fry CS, Dhanani S, Dillon EL, et al. Skeletal muscle protein anabolic response to resistance exercise and essential amino acids is delayed with aging. J Appl Physiol. 2008 May;104(5):1452-61.

39. Vandenburgh HH, Hatfaludy S, Sohar I, Shansky J. Stretch-induced prostaglandins and protein turnover in cultured skeletal muscle. Am J Physiol. 1990 Aug;259(2 Pt 1):C232-40.

40. Trappe TA, White F, Lambert CP, Cesar D, Hellerstein M, Evans WJ. Effect of ibuprofen and acetaminophen on postexercise muscle protein synthesis. Am J Physiol Endocrinol Metab. 2002 Mar;282(3):E551-6.

41. Petersen SG, Miller BF, Hansen M, Kjaer M, Holm L. Exercise and NSAIDs: Effect on muscle protein synthesis in patients with knee osteoarthritis. Med Sci Sports Exerc. 2011 Mar;43(3):425-31.

42. Zammit PS. All muscle satellite cells are equal, but are some more equal than others? J Cell Sci. 2008 Sep 15;121(Pt 18):2975-82.

43. Moss FP, Leblond CP. Satellite cells as the source of nuclei in muscles of growing rats. Anat Rec. 1971 Aug;170(4):421-35.

44. Barton-Davis ER, Shoturma DI, Sweeney HL. Contribution of satellite cells to IGF-I induced hypertrophy of skeletal muscle. Acta Physiol Scand. 1999 12;167(4):301-5.

45. Timmons JA. Variability in training-induced skeletal muscle adaptation. J Appl Physiol. 2011 Mar;110(3):846-53.

46. Petrella JK, Kim J, Mayhew DL, Cross JM, Bamman MM. Potent myofiber hypertrophy during resistance training in humans is associated with satellite cell-mediated myonuclear addition: A cluster analysis. J Appl Physiol. 2008 06;104(6):1736-42.

47. Cornelison DD, Wold BJ. Single-cell analysis of regulatory gene expression in quiescent and activated mouse skeletal muscle satellite cells. Dev Biol. 1997 Nov 15;191(2):270-83.

48. Sinha-Hikim I, Cornford M, Gaytan H, Lee ML, Bhasin S. Effects of testosterone supplementation on skeletal muscle fiber hypertrophy and satellite cells in community-dwelling older men. J Clin Endocrinol Metab. 2006 08;91(8):3024-33.

49. Sabourin LA, Rudnicki MA. The molecular regulation of myogenesis. Clin Genet. 2000 01;57(1):16-25.

50. O'Connor RS, Pavlath GK. Point:Counterpoint: Satellite cell addition is/is not obligatory for skeletal muscle hypertrophy. J Appl Physiol. 2007 Sep;103(3):1099-100.

51. Velloso CP. Regulation of muscle mass by growth hormone and IGF-I. Br J Pharmacol. 2008 06;154(3):557-68.

52. McCarthy JJ, Esser KA. Counterpoint: Satellite cell addition is not obligatory for skeletal muscle hypertrophy. J Appl Physiol. 2007;103:1100-2.

53. Zalin RJ. Prostaglandins and myoblast fusion. Dev Biol. 1977 09;59(2):241-8.

54. Santini MT, Indovina PL, Hausman RE. Prostaglandin dependence of membrane order changes during myogenesis in vitro. Biochim Biophys Acta. 1988 Mar 3;938(3):489-92.

55. Otis JS, Burkholder TJ, Pavlath GK. Stretch-induced myoblast proliferation is dependent on the COX2 pathway. Exp Cell Res. 2005 11/01;310(2):417-25.

56. Mendias CL, Tatsumi R, Allen RE. Role of cyclooxygenase-1 and -2 in satellite cell proliferation, differentiation, and fusion. Muscle Nerve. 2004 10;30(4):497-500.

57. Bondesen BA, Mills ST, Pavlath GK. The COX-2 pathway regulates growth of atrophied muscle via multiple mechanisms. Am J Physiol , Cell Physiol. 2006 06;290(6):1651-9.

58. Mackey AL, Kjaer M, Dandanell S, Mikkelsen KH, Holm L, Dossing S, et al. The influence of anti-inflammatory medication on exercise-induced myogenic precursor cell responses in humans. J Appl Physiol. 2007 Aug;103(2):425-31.

59. Mikkelsen UR, Langberg H, Helmark IC, Skovgaard D, Andersen LL, Kjaer M, et al. Local NSAID infusion inhibits satellite cell proliferation in human skeletal muscle after eccentric exercise. J Appl Physiol. 2009 Nov;107(5):1600-11.

60. Yang SY, Goldspink G. Different roles of the IGF-I ec peptide (MGF) and mature IGF-I in myoblast proliferation and differentiation. FEBS Lett. 2002 07/03;522(1-3):156-60.

61. Hill M, Wernig A, Goldspink G. Muscle satellite (stem) cell activation during local tissue injury and repair. J Anat. 2003 07;203(1):89-99.

62. Novak ML, Billich W, Smith SM, Sukhija KB, McLoughlin TJ, Hornberger TA, et al. COX-2 inhibitor reduces skeletal muscle hypertrophy in mice. Am J Physiol Regul Integr Comp Physiol. 2009 Apr;296(4):R1132-9.

63. Krentz JR, Quest B, Farthing JP, Quest DW, Chilibeck PD. The effects of ibuprofen on muscle hypertrophy, strength, and soreness during resistance training. Appl Physiol Nutr Metab. 2008 Jun;33(3):470-5.

64. Trappe TA, Carroll CC, Dickinson JM, LeMoine JK, Haus JM, Sullivan BE, et al. Influence of acetaminophen and ibuprofen on skeletal muscle adaptations to resistance exercise in older adults. Am J Physiol Regul Integr Comp Physiol. 2011 Mar;300(3):R655-62.

65. Petersen SG, Beyer N, Hansen M, Holm L, Aagaard P, Mackey AL, et al. Nonsteroidal anti-inflammatory drug or glucosamine reduced pain and improved muscle strength with resistance training in a randomized controlled trial of knee osteoarthritis patients. Arch Phys Med Rehabil. 2011 Aug;92(8):1185-93.

66. Petrella JK, Kim JS, Cross JM, Kosek DJ, Bamman MM. Efficacy of myonuclear addition may explain differential myofiber growth among resistance-trained young and older men and women. Am J Physiol Endocrinol Metab. 2006 Nov;291(5):E937-46.