HIGHLIGHTED TOPIC | Role of Inflammation in Skeletal Muscle, Connective Tissue, and Exertional Injuries: To Block or Not to Block?

Does an NSAID a day keep satellite cells at bay?

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SATELLITE CELLS (see Figs. 1 and 2) are a population of cells resident in adult skeletal muscle and have been proven to be essential for muscle repair (33, 67). The cycle of satellite cell activity (see Fig. 3) has been most widely studied in models of muscle injury or overload where the satellite cells are awoken from their dormant state. Briefly, the main steps involved include 1) activation to enter the cell cycle, and 2) proliferation, after which the cells either 3) undergo differentiation and fuse with a myofiber, or 4) return to quiescence (24, 50, 68, 95). With the capacity to perform these two functions, namely repairing damaged tissue and replenishing their own cell pool, satellite cells have been ascribed the status of the muscle stem cell. While it appears that satellite cells in the muscle of elderly individuals are not as easily activated as in younger individuals (11), triggering activation and proliferation in vivo appears to be relatively easy, and many factors are now recognized as being capable of this. For example, mechanical stimuli in the form of stretch or forceful contractions, damage to the muscle, pharmacological agents, and inflammatory conditions are strong activators of satellite cells. It appears from the literature that nonsteroidal anti-inflammatory drugs (NSAIDs) can influence satellite cell activity, both directly and indirectly. This minireview will consider how NSAIDs can influence satellite cells at any of the separate and overlapping stages of muscle adaptation to various intervention stimuli.

NSAIDs act by inhibiting the activity of cyclooxygenase (COX), the key enzyme in the synthesis of prostaglandin (PG) from arachidonic acid (AA) (83, 84). It should be noted that AA can also be metabolized through the lipoxygenase and epoxygenase pathways, reviewed elsewhere (4), and, importantly, that NSAIDs do not block these pathways. In fact, blocking COX metabolism of AA could redirect AA down these alternative pathways and could even explain some of the negative effects of NSAID action on various tissues (10). The main focus of this review is on NSAID action through the COX/PG pathways due to the lack of literature on the influence of the lipoxygenase and epoxygenase pathways on skeletal muscle. The COX-1 isoform is known to be constitutively expressed while COX-2 is induced, for example in response to trauma (84), and both isoforms have been detected in human skeletal muscle at the gene and protein levels (75). It is thought that the potential for a cell to respond to PG activity is dependent on the expression of at least one of the four known E-prostanoid (EP) receptors (EP1, EP2, EP3, and EP4) (73). All of these receptors have
been detected in mouse skeletal muscle at the gene level and EP3 at the protein level (89), but at the time of writing, very little evidence could be found for the presence of EP receptors in human skeletal muscle. EP3 mRNA has been detected in homogenate of human skeletal muscle (29) and mRNA for EP2, EP3 and EP4, but not EP1, in cultured myoblasts isolated from human fetal muscle diagnosed with myotonic dystrophy type I (6). Two recent studies of human skeletal muscle have reported abundant gene expression levels of EP4, which were observed to increase further with 12 wk of resistance training, while only infrequent or low gene expression levels of EP1, EP2, and EP3 were detected (62, 78). Interestingly, the PGF2α receptor was also detected at the gene level and observed to be upregulated in elderly individuals who performed resistance training for 12 wk in conjunction with ingestion of the NSAID ibuprofen or acetaminophen, while no change was detected in the placebo group (78). Shown in Fig. 4 are EP1+ cells on a regenerating adult human muscle fiber; these cells were not Pax7+ and no EP1+ cells were observed in resting muscle examined before exercise. It is possible that EP1 is expressed on some infiltrating cells, such as inflammatory cells, in connection with muscle regeneration. EP2, EP3, and EP4 were not detectable by this method on this material. Taken together, there is a good base of evidence for COX/PG activity in skeletal muscle, but the presence of EP receptors in human skeletal muscle and their localization to a specific cell type or structure is new ground for future investigations.

A wide range of NSAIDs has emerged on the market since the discovery of aspirin in the late-nineteenth century. While pain relief in disease conditions is the principal reason for use, athletes have also taken advantage of the analgesic properties of NSAIDs, with many taking NSAIDs on a prophylactic basis (90, 91). The great extent of NSAID consumption among athletes is beginning to become clear where reports document widespread use through self-administration and physician-prescribed, as well as coaches playing an active role. Widespread use of NSAIDs has been documented for elite athletes, especially speed and power athletes (2), male and female footballers participating in FIFA tournaments (81, 82), and youth age groups are also well represented (81, 92). This is despite the paucity of evidence for any benefit of NSAID intake to the physiological response of muscle to exercise. On the contrary, it appears that, at least in young healthy individuals, ingesting

Fig. 1. Human satellite cells. Microscope image of a single muscle fiber obtained from the vastus lateralis muscle of a healthy young male. Two satellite cells are visible (pink), detected by immunofluorescence staining with an antibody against Pax7. Myonuclei are stained blue with DAPI. Scale bar, 50 μm. The studies performed for Figs. 1, 2, and 4 were approved by The Research Ethics Committees of the Capital Region of Denmark and conformed to the standards set by the Declaration of Helsinki. All volunteers gave written informed consent before inclusion.

Fig. 2. Satellite cell environment. Microscope image of a cross section of a vastus lateralis sample obtained from a young healthy individual. Image X is a higher magnification of the indicated region of the merged image. One satellite cell (sc) is visible, situated between the myofiber plasmalemma (detected by dystrophin staining, red) and the basement membrane (detected by laminin staining, green). Note the different location of the myonucleus (mn), situated inside the myofiber plasmalemma. A capillary (cap) is visible in green in close proximity to the satellite cell. Nuclei are stained blue with DAPI.
NSAIDs may result in a negative outcome for muscle adaptation.

EFFECTS OF NSAIDs ON SATELLITE CELLS

**Acute loading in humans.** There are very few studies investigating the potential of NSAIDs to alter the satellite cell response in humans. In one study of young healthy individuals, oral ingestion of a COX-2-specific inhibitor, celecoxib, beginning ~45 min before exercise and continuing twice daily for 9 days, was not observed to have any detectable effects on the response of satellite cells to a single or repeated bout of eccentric contractions, despite a significant amelioration of muscle soreness postexercise with celecoxib treatment (55). In another study of young healthy male volunteers consuming placebo or NSAID (indomethacin) daily from 4 days before the exercise until completion of the study, a significant increase in the satellite cell content of muscle biopsies collected from the vastus lateralis muscle 8 days after running a 36-km race was reported for the placebo group, while no increase was observed in the NSAID group (41). In this study, no significant time × drug interaction was detected, but the lack of increase in the NSAID group suggests that NSAID may exert a negative effect on the satellite cell response to exercise. This hypothesis was tested further, again in young healthy male volunteers, by a different approach, where NSAID was infused directly into the working muscle (46, 47). In studies where NSAID is consumed orally, PG release is blocked systemically at the whole body level. Inserting microdialysis catheters into the muscle allows the infusion of NSAID directly into the muscle to exert effects locally, which was confirmed by detection of reduced levels of PGE2 in dialysate collected from catheters inserted at distances of 1 cm and 4 cm, respectively, away from the infusion catheter (46). It is not possible to compare the concentration of NSAID infused in this study directly with doses administered orally in other studies, but the PG levels appeared to be similar (47). The exercise model employed using this method was a single bout of maximal eccentric contractions, and muscle biopsies were collected from the infused leg and the noninfused leg 8 days after exercise. Analysis of these muscle biopsies revealed a

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**Fig. 3.** Influence of nonsteroidal anti-inflammatory drugs (NSAIDs) on the cycle of satellite cell activity. Satellite cells are activated to proliferate and either undergo fusion or return to quiescence to renew the satellite cell pool. Many growth factors (GF) have been shown to be capable of activating satellite cells following an appropriate stimulus, such as exercise, and are potential targets of NSAID action. The synthesis of prostaglandins (PG), which are important for fusion of myoblasts, is inhibited by NSAIDs and thus represents the main target of NSAID action in skeletal muscle. How NSAIDs could affect satellite cell renewal has not been investigated.

**Fig. 4.** EP1 receptors on a human skeletal muscle fiber. Microscope images of a regenerating muscle fiber obtained from the vastus lateralis muscle of a healthy young male 7 days after a damaging exercise intervention. This fiber has been double stained with an antibody against Pax7 (red) and the EP1 receptor (green), and nuclei are stained blue with DAPI. **Row B** is a higher magnification of **A** for better visualization of the EP1 staining pattern. Two EP1+ cells are indicated by arrows, detected by immunofluorescent staining with an antibody against EP1 (101740, Cayman Chemical). These cells are not Pax7+ satellite cells. Note the 2 regions (encircled) in **A** with a high density of Pax7+ cells, typical of regenerating muscle. Scale bars, 100 μm.
doubling of the satellite cell content of the noninfused muscle compared with preexercise values, while no increase was observed in the muscle that had been exposed to NSAIDs (47). These data provide further support for the hypothesis that NSAIDs can block the satellite cell response to exercise and, importantly, given that NSAID was only perfused for 7.5 h on the day of exercise, that this inhibition occurs in the short time during and immediately after exercise. Thus it appears there are satellite cell-activating signals that are present transiently in the muscle during and in the hours after exercise that can be suppressed if the muscle is exposed to NSAID during this period. One such potential signal is insulin-like growth factor (IGF)-1, since a tendency toward a downregulation of IGF-1 mRNA levels by NSAID was detected 5 h postexercise in the same muscle samples (48), which may have altered the satellite cell response over the following days. While it appears that IGF-1 alone cannot induce muscle hypertrophy, but requires a concurrent growth stimulus (69), IGF-1 has been shown to act very potently on satellite cells in vitro by enhancing their proliferative potential (13) as well as stimulating proliferation and differentiation through induction of members of the myogenic regulatory family of proteins (22).

Resistance training in humans. In a study on the effects of NSAIDs in patients with osteoarthritis performing 12 wk of resistance training, a significant increase in the satellite cell content of the trained muscle was observed in the placebo group, when compared with pretraining levels (57). While there was no significant difference between groups in the change in satellite cell content with training, the group consuming the NSAID ibuprofen (beginning ingestion 1 wk before starting the training and continuing twice daily until completion of the study) did not demonstrate any change in satellite cell content (57), again suggestive of a potential for NSAIDs to suppress the satellite cell response to exercise. The increase in the placebo group is in line with previous studies following the potential of long-term resistance training to induce an enhancement of the satellite cell pool in ageing individuals (38, 64, 85, 87), although some studies have reported no change with training (26, 60). Of course it is difficult to draw comparisons between these studies of a long-term training period and the single bouts of exercise referred to in the previous paragraph, since damage may be present following a single bout of unaccustomed exercise, which would place a different demand on the satellite cells, i.e., to repair the muscle, compared with following 3–4 mo of resistance training, where it is likely that the muscle has adapted to its loading and damage is not evident. Although it has been shown that satellite cells are not required for hypertrophy (42), reports of enhanced numbers of satellite cells with training in the absence of hypertrophy (39) would indicate that expansion of the satellite cell pool is a basic physiological adaptation to loading, and blocking this by NSAID ingestion is therefore likely to be unfavorable for the muscle. However, the mechanisms at play in this scenario remain to be elucidated.

Methodological limitations of human studies. A methodological limitation of the studies exploring the potential of NSAIDs to affect satellite cells in human skeletal muscle is the lack of satellite cell assessment specific to type I and II fibers. An uneven distribution of satellite cells between fiber types has been reported for healthy elderly men (86, 87) and women diagnosed with trapezius myalgia women (36), but not young healthy individuals (28). It has been shown repeatedly that type II fibers contain a lower satellite cell content in the untrained state and demonstrate a greater relative increase in satellite cell content with resistance training than type I fibers (35, 85, 87), highlighting the importance of assessing satellite cells relative to specific fiber types. As of yet, however, there are no studies investigating the effects of NSAIDs on the fiber-type distribution of satellite cells in muscle recovering from exercise or injury. It would be valuable to investigate how young and elderly individuals might differ in the response of type II fiber-associated satellite cells to NSAIDs, given the age-related reduction in satellite cell content and the marked atrophy of type II fibers with ageing (32, 34, 61), together with recent findings of a positive effect of NSAIDs on hypertrophy in elderly individuals performing strength training (76).

Animal studies. Animal studies examining the effects of NSAID treatment on satellite cells are limited, but one study of overloaded rat soleus demonstrated a reduced satellite cell response (number of cells positive for MyoD and or m-cadherin) in rats exposed to NSAID (ketoprofen injected post-surgery for 3 days) compared with saline-injected rats (49). A series of studies by Shen and colleagues (70, 71) evaluated the role of COX in the muscle response to the severe muscle laceration injury model. Using a COX-2-specific inhibitor, administered by injection after surgery for 3–5 days, a delayed regeneration response was observed on days 7 and 14 post-injury (70). This was evaluated from sections of muscle stained for hematoxylin and eosin by calculating 1) the percentage of fibers containing centrally located nuclei (an indicator of muscle regeneration), and 2) the diameter of fibers, where fibers of small diameter were considered new regenerating fibers (70). A greater area of the muscle cross-sections was observed to be occupied by fibrous tissue, as assessed by trichrome staining, in the treated mice on day 7, compared with the untreated mice, suggesting that fibrosis is upregulated in healing skeletal muscle subjected to COX-2 inhibition (70). These authors then compared the muscle regeneration response in wild-type and COX-2 gene-deficient mice, where they observed a lower number of small fibers and fibers containing central nuclei in the COX-2 gene-deficient mice compared with wild-type mice (71), confirming their earlier findings indicating an important role for COX activity in muscle regeneration.

In vitro studies. In vitro studies have also demonstrated a role for COX activity in the response of myogenic cells. For example, in an early study by Zalin (93), low concentrations of PGE2 were observed to provoke fusion of primary chick myoblasts faster than under conditions without PG. In the same study, indomethacin and aspirin were shown to inhibit fusion, which could be reversed by the addition of PGE2 (93), confirming that the action of NSAID on cell fusion is through its inhibitory action on PG rather than a direct effect on the fusion process itself. The same author was later able to show a similar response in fetal human myoblasts, with higher levels of fusion at an earlier time point in the presence of PGE2 when compared with controls (94). Again, indomethacin and aspirin were shown to inhibit fusion, which could be reversed by the addition of PGF2α (94). Together these studies suggest that PGs are produced by the myogenic cultures themselves. Later investigation into the role of PGF2α in cell fusion revealed that it exerts its action not in the initial fusion of muscle cells that forms myotubes but in the second stage of muscle cell fusion
where cells are recruited to fuse with the preexisting multinucleated cells (27). In the study of COX-2 gene-deficient mice (71), cells isolated from the gastrocnemius muscles of these mice were reported to exhibit a poorer fusion ability than cells isolated from wild-type mice (71), providing further support for an important role for COX and PG activity in the fusion of myogenic cells.

**Potential implications of inhibiting satellite cell proliferation and fusion.** Poor fusion in vivo would theoretically leave the muscle with an inferior content of myonuclei, which could explain the animal findings of delayed or poorer muscle regeneration after injury when exposed to NSAID. Similarly, the consequences of a suppressed proliferation of satellite cells due to NSAID ingestion in recovering muscle are not clear since no studies on the long-term effects have been carried out, but it is possible that negative effects would only become apparent at the functional level with chronic NSAID use, and perhaps only in individuals who exercise at a high level, pushing their muscles to the limit with regard to muscle hypertrophy. Alternatively, it can be speculated that negative consequences of long-term NSAID use as a youth might not become manifest until old age, where it can be argued that an inferior reservoir of satellite cells and myonuclei might lead to a faster progression of sarcopenia. In support of this, it has been suggested that myonuclei are not easily added to the muscle fibers of older animals, but rather that the incorporation of myonuclei into fibers occurs more readily in younger muscle and that these myonuclei are not lost during periods of muscle atrophy but are preserved (8). This would imply that blocking satellite cell proliferation, as the source of new myonuclei, could prevent myonuclear accretion, which cannot be rectified later in life. However, it is not clear whether this hypothetical scenario would have any functional implications for the muscle in healthy individuals.

**EFFECTS OF NSAIDs ON FACTORS INFLUENCING SATELLITE CELLS**

**Inflammatory cells.** With regard to the time course of satellite cell proliferation following exercise, actively dividing satellite cells have been observed in muscle biopsies 48 h after a single bout of electrical stimulation (40), and a greater satellite cell content of the muscle can be detected on days 4 and 8 postexercise (18, 19, 43, 47, 53), although some groups have reported increases in satellite cell number as early as 24 or 48 h postexercise (21, 43–45, 53). It seems, thus, that proliferation of satellite cells after exercise is not instant, but rather an event that requires some initial signaling. Potential candidates with the capacity to activate satellite cells are inflammatory cells, since macrophages in pro- or anti-inflammatory states have been shown to affect myogenic progression and tissue repair (5, 65). Similarly, activated satellite cells demonstrate a strong affinity for macrophages, initiating monocyte chemotaxis (15). However, in a study of the effect of the NSAID ibuprofen on the increase in macrophage content of muscle biopsies collected 24 h after a single bout of eccentric contractions in young healthy males, no effect of NSAID (regular oral administration from the onset of exercise protocol until 5 h before the postexercise biopsy was collected) was observed (59). In contrast to this, in regenerating mouse muscle, a COX-2 inhibitor (delivered in the drinking water from 3 days before injury until the end of the regeneration period) was observed to result in a lower number of macrophages (Mac-1+) as well as myoblasts (MyoD+) 3 days after injury, compared with controls (7). Reconciling this discrepancy is difficult given the nature of the different animal vs. human models of injury used and the different sampling time points, and further highlights the need for additional study of this aspect of muscle adaptation to exercise.

**Growth factors.** In addition to macrophages, endothelial cells are close geographical neighbors of satellite cells (17) and have been demonstrated to act on myogenesis through the release of a host of growth factors, including IGF-1, vascular endothelial growth factor (VEGF), hepatocyte growth factor, and basic fibroblast growth factor (bFGF) (17). This action is reciprocal with myogenic cells influencing endothelial cell activity by promoting angiogenesis (1, 17), illustrated in Fig. 5. In support of the potential for NSAIDs to alter this signaling, a study of COX-1 signaling in cervical carcinomas uncovered enhanced expression of angiogenic factors, including bFGF and VEGF, under COX-1 overexpression (66). Interestingly, this upregulation of angiogenic factor expression was blocked by the NSAID indomethacin (66). Given that bFGF and VEGF are potent promoters of satellite cell activity (12, 17), it can be hypothesized that the inhibitory action of NSAIDs on satellite cells is through its suppression of these growth factors. With regard to IGF-1, the indication that NSAIDs could downregulate IGF-1 in human muscle recovering from exercise (48), together with the finding of a greater content of satellite cells in muscle with elevated levels of growth hormone and IGF-1 (25), provides a theoretical basis for the potential of NSAIDs to alter satellite cell activity through the IGF-1 pathway. This remains to be investigated, however.

**Connective tissue.** The highly organized arrangement of proteins making up the connective tissue network of skeletal muscle is capable, through mechanotransduction, of initiating signaling pathways in cells located in its environment (88) and undergoes extensive remodeling during regeneration and ageing (23, 30). The adaptation of muscle connective tissue to exercise is a complex process and consists of an early phase of

![Fig. 5. Signaling in the satellite cell niche. Schematic based on Fig. 2, illustrating the location of different receptors (red and blue circles) on the extracellular matrix (ECM, green lines) and myofiber (red line) sides of the satellite cell (s) envelope. It is believed that these receptors exert different signaling to direct the fate of the new satellite cells to either fuse with the fiber or to remain as a satellite cell to maintain the satellite cell pool. This schematic also depicts the bidirectional release of growth factors that has been demonstrated to exist between satellite cells and endothelial cells making up the capillaries (cap). A myonucleus (m) is also shown, situated under the sarcolemma (red line).](http://jap.physiology.org/)
deadhesion and disassembly of the matrix, followed by a strong matrix anabolic phase that occurs late in the regeneration process (37). Interestingly, the delayed anabolic matrix activity was associated with a persistent elevation in the satellite cell content of the regenerating muscle 30 days after muscle damage was induced, compared with a biopsy collected from the control leg at the same time point (37), raising the possibility that cross talk between satellite cells and the muscle connective tissue matrix exists. Indeed it has been proposed that the fate of the satellite cell, in contact with the myofiber on one side and the basement membrane on the other side, is determined by the different receptors present on the two sides (see Fig. 5), such that, after division, the cell in contact with the fiber differentiates and is incorporated into the fiber as a new myonucleus while the cell in contact with the basement membrane remains as a satellite cell and thereby replenishes the satellite cell pool (31). Alterations to the composition of the niche could thus have consequences for satellite cell asymmetric division and ultimately the maintenance of the satellite cell pool. Studies of the adaptation of connective tissue to exercise under the influence of NSAIDs are, however, sparse. In a study of the same human muscle biopsies collected 8 days after a single bout of eccentric contractions, where an inhibitory effect of NSAID exposure on satellite cell proliferation was observed (47), no influence of NSAIDs was detected on collagen gene expression levels or the fractional synthetic rate of collagen synthesis (48). With regard to other tissues, NSAID ingestion (beginning 3 days before exercise and continuing until the end of the study) has been reported to suppress the collagen synthesis response to exercise around human tendon tissue (16), in contrast to a study of rat Achilles tendon cells exposed to ibuprofen, which demonstrated an upregulation of genes for collagens compared with untreated cells, while no effect on collagen types I or III was observed (80). In a rat osteoarthritis model, long-term NSAID ingestion has been reported to upregulate the protein levels of collagen types I and III in articular cartilage (54). In addition to this, a study of the composition of rat mammary extracellular matrix undergoing remodeling revealed a modulation of matricellular and laminin proteins by NSAID treatment (52). Together these studies underline the potential of NSAIDs to alter the extracellular matrix of various tissues in different ways, possibly due to the dissimilar composition, the nature of loading, and the state of remodeling. With regard to potential growth factors at play in NSAID signaling in connective tissue, IGF-1 is a candidate; since elevated local and systemic levels of IGF-1 through 2 wk of growth hormone administration were observed to result in enhanced collagen type I gene expression and collagen protein synthesis in the muscle and tendon of young healthy men (20). An alternative candidate is hepatocyte growth factor (HGF), since this has been reported to be a potent activator of satellite cells (3) and is located in the muscle extracellular matrix (74). A study of stomach tissues of mice exposed to NSAID in the drinking water revealed an inhibitory effect of NSAID on HGF protein levels (14). However, it has been reported in humans that HGF gene expression levels during recovery are not influenced by NSAID exposure to the working muscle at the time of exercise (48). This, together with the previously mentioned indication of a potential inhibitory action of NSAIDs on IGF-1 gene expression levels in human muscle recovering from exercise (48), indicates that further investigations are required to elucidate the pathways by which NSAIDs may alter the growth factor response of muscle connective tissue to loading.

EFFECTS OF NSAIDs ON HYPTERTROPHY AND PROTEIN SYNTHESIS

The development of muscle hypertrophy in response to overload has been studied in rodents subjected to a synergistic-ablation model of muscle loading, where the plantaris muscle is subjected to overload through surgical removal of the synergistic soleus and gastrocnemius muscles of a hindlimb. Normal walking after this operation exerts a substantial overload on the plantaris as it now has to bear the full load previously shared with its neighboring muscles, and increases in muscle size of 60% (72) and 80% (51) have been reported after 14 days of such loading. Daily injection with the NSAID ibuprofen or daily intake of a COX-2-specific inhibitor via drinking water was observed to blunt this hypertrophy by 50% and 75%, respectively (51, 72), supporting an important role for COX activity in the muscle hypertrophy adaptation to loading. The outcome of studies on humans performing resistance training is not so clear, with no effect of NSAID ingestion observed on muscle hypertrophy in patients with osteoarthritis (57), and yet a clear positive influence of NSAID ingestion on muscle hypertrophy reported for healthy elderly individuals (76). This issue is further clouded by the possibility that in the study of osteoarthritis patients (57), NSAID ingestion may have reduced pain and thereby allowed the patients to train harder than without pain-relieving medication. Since an increase in the rate of muscle protein synthesis is required for an increase in muscle mass, studies examining the effect of NSAIDs on the anabolic response to training will also be considered here. In a group of young healthy males, daily NSAID ingestion beginning at the onset of an exercise bout has been reported to blunt protein synthesis 24 h postexercise, as assessed by determining the fractional synthetic rate of mixed muscle homogenate (79). The blunted synthesis response was accompanied by an attenuation of the exercise-induced increase in PGE2 in the NSAID group (77), indicating a role for this PG in muscle protein synthesis. Such an effect on the muscle anabolic response to exercise was not observed when NSAID was infused locally into the working muscle (48) or when a COX-2-specific inhibitor was consumed (9). In the study of patients with osteoarthritis, NSAID ingestion was not observed to affect muscle contractile protein synthesis, although NSAIDs may have exerted a minor inhibitory effect on the sarcoplasmic proteins (58). The apparent discrepancies arising out of these studies are difficult to reconcile, but it is possible that the muscle of young and old individuals responds differently to exercise when subjected to the influence of NSAID, highlighting an area for future study.

Young vs. old. One potential explanation for the discrepancy in the response of young and old individuals may be the impact of NSAID on systemic inflammation, which has been reported to increase with ageing. Elevated levels of inflammatory cytokines have been detected in the circulation of older individuals compared with younger controls (56). The addition of NSAID to the drinking water of old rats with low-grade inflammation has been reported to not only reduce circulating levels of inflammatory markers but also attenuate the loss in muscle.
mass seen in the control rats over the same 5-mo period (63). This study suggests that the positive action of NSAIDs on muscle in the elderly could be through the lowering of a constantly elevated systemic level of inflammatory activity. Indeed NSAID ingestion by healthy elderly individuals performing a 12-wk program of resistance training has been shown to eliminate the increase in the muscle gene expression levels of the cytokines interleukin-6 and -10 observed in the placebo group (78). Further studies in humans are required, however.

SUMMARY AND AREAS FOR FUTURE RESEARCH

Evidence for a positive or negative influence of NSAIDs on the muscle response to exercise or injury has been reported. On balance, however, it appears that there is more evidence pointing toward a negative effect, at least in young healthy individuals, warranting caution against athletes using NSAIDs. Several studies indicate that the elderly respond differently, potentially indicating a positive influence of NSAID exposure on muscle adaptation. Further work is required to explain the mechanisms behind this discrepancy. In particular studies should focus on the role of inflammation in muscle adaptation to exercise and whether the balance shift from too little to too much might explain the apparent beneficial effects of NSAIDs on ageing muscle. The long-term consequences for the muscle of the apparent inhibitory effect of NSAIDs on satellite cells are not known and may first become apparent with chronic use in high-level athletes or with age. It is possible however that any negative influence of NSAIDs on satellite cells is irrelevant for muscle adaptation to low-level recreational physical activity. Reports of the potential for NSAIDs to alter PG and growth factor signaling provide a basis for further study of the mechanism of NSAID action on satellite cells. In addition, there is a lack of information on the location of EP receptors in mature human skeletal muscle and any changes in their concentration and distribution with muscle injury, regeneration, and ageing. Finally, when the COX pathway has been inhibited by NSAIDs, the consequences of a stimulation of the lipoxygenase pathways, for satellite cells and skeletal muscle should be investigated to establish a broader understanding of the influence of NSAIDs.

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