Effects of prostaglandins and COX-inhibiting drugs on skeletal muscle adaptations to exercise
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Effects of prostaglandins and COX-inhibiting drugs on skeletal muscle adaptations to exercise

Todd A. Trappe and Sophia Z. Liu
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Trappe TA, Liu SZ. Effects of prostaglandins and COX-inhibiting drugs on skeletal muscle adaptations to exercise. J Appl Physiol 115: 909–919, 2013. First published March 28, 2013; doi:10.1152/japplphysiol.00061.2013.—It has been ~40 yr since the discovery that PGs are produced by exercising skeletal muscle and since the discovery that inhibition of PG synthesis is the mechanism of action of what are now known as cyclooxygenase (COX)-inhibiting drugs. Since that time, it has been established that PGs are made during and after aerobic and resistance exercise and have a potent paracrine and autocrine effect on muscle metabolism. Consequently, it has also been determined that orally consumed doses of COX inhibitors can profoundly influence muscle PG synthesis, muscle protein metabolism, and numerous other cellular processes that regulate muscle adaptations to exercise loading. Although data from acute human exercise studies, as well as animal and cell-culture data, would predict that regular consumption of a COX inhibitor during exercise training would dampen the typical muscle adaptations, the chronic data do not support this conjecture. From the studies in young and older individuals, lasting from 1.5 to 4 mo, no interfering effects of COX inhibitors on muscle adaptations to resistance-exercise training have been noted. In fact, in older individuals, a substantial enhancement of muscle mass and strength has been observed. The collective findings of the PG/COX-pathway regulation of skeletal muscle responses and adaptations to exercise are compelling. Considering the discoveries in other areas of COX regulation of health and disease, there is certainly an interesting future of investigation in this re-emerging area, especially as it pertains to older individuals and the condition of sarcopenia, as well as exercise training and performance of individuals of all ages.

PGE2; PGF2α; acetaminophen; ibuprofen; sarcopenia
Historical context. PGs were discovered in the 1930s from extracts of the prostate gland and named by von Euler (136). Subsequent studies, over the next 40 yr, elucidated many of the tenets of PG structural biology and physiology, resulting in the Nobel Prize being awarded to Bergström, Samuelsson, and Vane in 1982 (10, 97, 135). There are numerous PGs (e.g., PGA-J) that are produced from arachidonic acid (53), which is liberated from the membrane of cells by PLA2 (19, 32, 38) (Fig. 1). The enzyme PG G/H synthase, more commonly known as COX, is a dual-function enzyme that converts arachidonic acid to PGG2 and then PGH2 (105, 107), which is then rapidly converted to a specific PG (e.g., PGD2, PGE2, PGF2α, PGI2) by PG synthases (70, 107, 137). Additionally, there are two well-known isoforms of COX—COX-1 and COX-2 (44, 105, 107, 141)—and a possible third isoform (an intron-retaining variant of COX-1, referred to as COX-1b or COX-3) may exist in some tissues (22, 86, 101, 138).

PGs work in an autocrine and paracrine fashion through receptors specific to each PG, some of which have multiple isoforms (1, 17, 32, 62, 72, 112). PGs are relatively transient molecules with a half-life, typically, of only seconds to minutes (32). For example, ~90% of PGE2 and PGF2α is removed from the blood in one pass through the pulmonary circulation (85). PGs are also potent in relatively small amounts (9, 32). As a result, circulating PG levels are typically low, and in response to stimulation, tissue production can be increased tremendously [e.g., 10 times the total resting tissue content can be generated every minute (135)].

The first studies of PG production and release by skeletal muscle in response to muscular work were published by Herbaczynska-Cedro and colleagues (41–43, 47) in 1974 and 1976 (Table 1). These studies were focused on identifying muscle-produced vasodilators and blood flow regulation during simulated exercise in dogs and showed that more than one PG was produced by exercising skeletal muscle (suggested as at least PGE2 and PGF2α), which could be eliminated by the COX inhibitor indomethacin. These authors also speculated that the mechanism of the PG release was the distortion of the muscle cell membrane but showed that the PG release occurred during and after the exercise bouts. Soon thereafter, a study in humans using a static and dynamic exercise forearm model showed similar results (54). Subsequent arteriovenous studies by Nowak and Wennmalm (75) showed no net release or uptake of PGs across the leg at rest, but cycling exercise at ~75% maximal oxygen consumption substantially increased net release of PGs from the leg. Whereas PGs were reported to be in resting human skeletal muscle as early as 1967 (51), Berlin et al. (11) showed in 1979, with radiolabeled arachidonic acid added to homogenates of skeletal muscle biopsy samples, that skeletal muscle could produce PGD2, PGE2, PGF2α, and PGI2. PGE2 was the predominant PG produced (11), but this could be shifted to PGF2α if the assay environment was altered (74).
Table 1. Noteworthy studies of PGs, skeletal muscle, and exercise adaptations

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Species</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karim et al. (51)</td>
<td>1967</td>
<td>Humans</td>
<td>PGs are located in skeletal muscle.</td>
</tr>
<tr>
<td>Herbaczynska-Cedro and</td>
<td>1974</td>
<td>Dogs</td>
<td>Skeletal muscle PG release increased during and after simulated exercise;</td>
</tr>
<tr>
<td>colleagues</td>
<td>1976</td>
<td></td>
<td>eliminated with COX inhibitor.</td>
</tr>
<tr>
<td>Kilbom and Wennmalm (54)</td>
<td>1976</td>
<td>Humans</td>
<td>Forearm skeletal muscle PG release increased during and after static and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dynamic exercise; reduced with COX inhibitor (indomethacin).</td>
</tr>
<tr>
<td>Nowak and Wennmalm (75)</td>
<td>1978</td>
<td>Humans</td>
<td>Leg skeletal muscle PG release increased during cycling exercise at 75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>maximal oxygen consumption.</td>
</tr>
<tr>
<td>Berlin et al. (11)</td>
<td>1979</td>
<td>Humans</td>
<td>Skeletal muscle had the enzymatic capacity to produce PGD₂, PGE₂, PGF₂α,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>and PGI₂ from arachidonic acid.</td>
</tr>
<tr>
<td>Young et al. (142)</td>
<td>1981</td>
<td>Monkeys</td>
<td>Aging increased skeletal muscle PG production.</td>
</tr>
<tr>
<td>Rodemann and Goldberg (93)</td>
<td>1982</td>
<td>Rats</td>
<td>Arachidonic acid increased skeletal muscle PGF₂α and PGE₂, which increased</td>
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<tr>
<td></td>
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<td></td>
<td>muscle protein synthesis and degradation, respectively; reduced or</td>
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<td></td>
<td></td>
<td></td>
<td>eliminated with COX inhibitors.</td>
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<tr>
<td>Palmer et al. (78)</td>
<td>1983</td>
<td>Rabbits</td>
<td>Simulated exercise (intermittent stretching) increased skeletal muscle</td>
</tr>
<tr>
<td>Smith et al. (106)</td>
<td></td>
<td></td>
<td>PGF₂α and protein synthesis; reduced or eliminated with COX inhibitors.</td>
</tr>
<tr>
<td>Gibson et al. (33)</td>
<td>1991</td>
<td>Humans</td>
<td>Reduced skeletal muscle PGF₂α levels associated with reduced muscle protein</td>
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<td></td>
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<td>synthesis and type 1 and II muscle fiber size.</td>
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<tr>
<td>Contemporary studies</td>
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<tr>
<td>Trappe et al. (126, 128)</td>
<td>2001</td>
<td>Humans</td>
<td>Increased skeletal muscle PGF₂α, PGE₂, and protein synthesis after resistance</td>
</tr>
<tr>
<td></td>
<td>2002</td>
<td></td>
<td>exercise; eliminated with over-the-counter, orally consumed COX inhibitors</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(acetaminophen and ibuprofen).</td>
</tr>
<tr>
<td>Karamouzis et al. (49, 50)</td>
<td>2001</td>
<td>Humans</td>
<td>Aerobic exercise increased intramuscular PGE₂; increased production with</td>
</tr>
<tr>
<td>Boushel et al. (15)</td>
<td>2002</td>
<td>Humans</td>
<td>increased workload.</td>
</tr>
<tr>
<td>Höffner et al. (45)</td>
<td>2003</td>
<td>Humans</td>
<td>An oral dose of COX inhibitor (aspirin) reduced intramuscular PGE₂ production</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>at rest by nearly 90% within 1 h.</td>
</tr>
<tr>
<td>Trappe et al. (123)</td>
<td>2006</td>
<td>Humans</td>
<td>Both young and old individuals increased intramuscular PGF₂α in the hours</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>after resistance exercise; no apparent effect of age on resting or postexercise</td>
</tr>
<tr>
<td>Mikkelsen et al. (67)</td>
<td>2008</td>
<td>Humans</td>
<td>Local intramuscular low-dose COX inhibitor (indomethacin) delivery blocked</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PGE₂ production by ~85% during and after resistance exercise.</td>
</tr>
<tr>
<td>Burd et al. (18)</td>
<td>2010</td>
<td>Humans</td>
<td>COX-2-specific inhibitor (celecoxib) did not eliminate or reduce the increase</td>
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<td></td>
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<td>in skeletal muscle protein synthesis after resistance exercise.</td>
</tr>
<tr>
<td>Paulsen et al. (79)</td>
<td>2010</td>
<td>Humans</td>
<td>COX-2-specific inhibitor (celecoxib) did not influence intramuscular PGE₂</td>
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<td></td>
<td></td>
<td></td>
<td>levels or satellite cell activity after resistance exercise.</td>
</tr>
<tr>
<td>Petersen et al. (82)</td>
<td>2011</td>
<td>Humans</td>
<td>COX inhibitor (ibuprofen) did not influence skeletal muscle protein synthesis</td>
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<tr>
<td></td>
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<td></td>
<td>24 h after aerobic exercise in older osteoarthritic patients.</td>
</tr>
<tr>
<td>Kreiner and Galbo (55)</td>
<td>2011</td>
<td>Humans</td>
<td>Resting intramuscular PGE₂ levels 20 times higher than plasma.</td>
</tr>
<tr>
<td>Standley et al. (110)</td>
<td>2013</td>
<td>Humans</td>
<td>PGE₂ stimulated transcription of the skeletal muscle mass regulators IL-6</td>
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<td></td>
<td></td>
<td></td>
<td>and muscle RING finger-1.</td>
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<tr>
<td>Krentz et al. (56)</td>
<td>2008</td>
<td>Humans</td>
<td>Duration: 6 wk; Training: resistance exercise 2–3 days/wk; Drug dose:</td>
</tr>
<tr>
<td></td>
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<td>ibuprofen 400 mg, 2–3 days/wk (training days); Participants: 24 yr, men</td>
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<td>and women, resistance exercise trained (~6 yr); no effect on muscle mass or</td>
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<td>strength adaptations compared with placebo-consuming resistance exercise</td>
</tr>
<tr>
<td>Petersen et al. (81)</td>
<td>2011</td>
<td>Humans</td>
<td>Duration: 12 wk; Training: resistance exercise 3 days/wk; Drug dose:</td>
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<tr>
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<td></td>
<td>ibuprofen 1,200 mg/day; Participants: 50–70 yr, men and women, knee</td>
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<td></td>
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<td>osteoarthritis patients; no effect on muscle mass, increased muscle strength</td>
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<td>compared with placebo-consuming resistance exercise group</td>
</tr>
<tr>
<td>Trappe et al. (125, 127)</td>
<td>2011</td>
<td>Humans</td>
<td>Duration: 12 wk; Training: resistance exercise 3 days/wk; Drug dose:</td>
</tr>
<tr>
<td></td>
<td>2013</td>
<td></td>
<td>acetaminophen 4 g/day or ibuprofen 1,200 mg/day; Participants: 60–78 yr,</td>
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<td></td>
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<td>men and women, healthy, untrained; enhanced muscle mass and strength gains</td>
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<td></td>
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<td>25–50% above placebo-consuming resistance exercise group</td>
</tr>
<tr>
<td>Jankowski et al. (48)</td>
<td>2012</td>
<td>Humans</td>
<td>Duration: 16 wk; Training: resistance exercise ~3 days/wk; Drug dose:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>acetaminophen 1 g, 3 days/wk (training days); Participants: 64 yr, men,</td>
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<td></td>
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<td></td>
<td>healthy, untrained; no effect on fat-free mass or muscle-strength</td>
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<td></td>
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<td>adaptations compared with placebo-consuming resistance exercise group</td>
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</table>

COX, cyclooxygenase.

The initial reports of PG regulation of skeletal muscle protein turnover were in the early 1980s when Rodemann and Goldberg (93) showed that arachidonic acid supplementation to rat muscle in vitro increased muscle protein synthesis and degradation, which could be replicated with PGF₂α and PGE₂ supplementation, respectively, and reduced or eliminated with COX inhibition. Arachidonic acid supplementation increased muscle production of both PGs, but about twice as much PGE₂ was synthesized compared with PGF₂α. At the same time, Palmer and colleagues (78, 106) showed that with simulated exercise in rabbit muscle, PGF₂α was produced by intermittent muscle stretch (+105%), which in turn, stimulated muscle protein synthesis (+70%), both of which were reduced or eliminated by COX inhibition. In addition, the increase in...
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muscle PGF$_{2\alpha}$ production and protein synthesis was sustained following the cessation of simulated exercise.

Over the next 10–15 yr following these seminal studies, many investigations in animal and cell-culture models built on these findings (5, 7, 34, 35, 39, 40, 64, 65, 75, 77, 90, 94, 113, 132–134). Although the animal- and cell-culture data were compelling with regard to PG and COX-inhibitor regulation of skeletal muscle protein turnover, very few studies in humans were completed during this time, and none focused on exercise. Gibson et al. (33) showed that women (mean age of 58 yr) with rheumatoid arthritis receiving steroid treatment (which lowers PG production via COX-independent PLA$_2$ inhibition; mean treatment time: 8 yr) had reduced muscle PGF$_{2\alpha}$ levels, muscle protein-synthesis rates, and type I and II muscle fiber size compared with a group of controls (mean age of 70 yr). In addition, the rheumatoid arthritis patients had elevated intramuscular PGE$_2$, resulting in $>12$ times more PGE$_2$ than PGF$_{2\alpha}$ compared with approximately three times in the controls. McNurlan et al. (65) showed that a single dose of the COX inhibitor indomethacin was unable to influence whole-body protein synthesis in the fed and fasted states, but given that muscle protein turnover constitutes <30% of whole-body turnover (71), it is unclear if there was an influence on muscle protein turnover (as they had shown in rats).

Contemporary information. What is known about PG and COX-inhibiting drug regulation of muscle protein turnover with exercise in humans has been obtained since ~2000 (Table 1). Several studies using animal models of simulated exercise and muscle growth have also been completed during this time period and have provided additional insight. Also during this time frame, the amount of basic information about the PG/COX pathway has increased substantially, including characterization of the structure and enzymology of the PG synthases (107), leading the way for new drug development (8, 96). Much more has also been learned from continued investigation of the COX-specific inhibitors engineered in the 1990s and many of the “classic” COX inhibitors in other areas of health and disease.

Studies completed during the 1990s using isotopically labeled amino acids showed that muscle protein synthesis increased after resistance exercise for up to 48 h in humans (23, 58, 84), and the accumulation of these acute increases in muscle protein synthesis was generally understood to be, at least in part, the underlying basis of muscle hypertrophy. Perturbations (e.g., pharmaceutical, nutrition, a specific exercise regimen) that altered this response would alter the benefits of strength training. With the consideration of the aforementioned studies showing that PGF$_{2\alpha}$ was a regulator of muscle protein synthesis, it was realized that orally consumed COX inhibitors might interfere with the normal muscle protein-synthesis response to resistance exercise. This interfering effect might be particularly important after damaging exercise that caused muscle soreness, which is, at least in part, a result of increases in intramuscular PG$_E_2$ (3, 55, 66) and would further increase the likelihood of COX-inhibitor consumption. Indeed, this was shown to be the case when individuals consumed an over-the-counter dose of the COX inhibitor acetaminophen (4 g/day) or ibuprofen (1.2 g/day) in the 24 h following a single bout of excessive resistance exercise [10–14 sets of 10 eccentric (lowering) contractions; thus the work equivalent of $\sim$70 typical repetitions] that caused muscle soreness (126, 128). Muscle protein synthesis (+76%) and intramuscular PGF$_{2\alpha}$ (+77%) were increased significantly, 24 h after the exercise bout, and these increases were eliminated with the consumption of the COX-inhibiting drugs. Intramuscular PG$_E_2$ was also increased (+64%), 24 h after the exercise, and this increase was also eliminated with COX inhibition.

This study presented some interesting initial findings regarding PG and COX regulation of skeletal muscle responses to exercise and raised several interesting questions. First, the continued, increased production of intramuscular PGF$_{2\alpha}$ and PGE$_2$, 24 h after a single bout of resistance exercise, considering the short half-life of PGs, highlighted that it would be important to understand the typical PG levels in human skeletal muscle and how they are affected by exercise (i.e., time course, magnitude, type of exercise). Second, considering the pharmacokinetic and metabolic complexities of orally consumed COX inhibitors, it was interesting that doses of the most commonly consumed COX inhibitors could apparently produce intramuscular drug levels that inhibited intramuscular COX to the extent that PGF$_{2\alpha}$ and PGE$_2$ production and muscle protein metabolism after exercise were inhibited. Given the large number of COX-inhibiting drugs available for human consumption, it followed that knowledge regarding the efficacy of these drugs and doses in relation to the COX isoforms found in skeletal muscle at rest and after exercise would be necessary. Third, the obvious question from this investigation was: what are the impacts of chronic COX-inhibitor consumption on exercise-training adaptations? Whereas there is much yet to be discovered in this area, several studies have added to our understanding and started to address some of the key questions.

Intramuscular PGs and exercise. Muscle biopsy-derived measures of PGs that regulate protein turnover show PGE$_2$ to be the dominant PG in young and old human muscle (11, 33, 51, 74, 126). Intramuscular PG$_E_2$ levels are three to four times higher than PGF$_{2\alpha}$ at rest and after resistance exercise in young individuals, suggesting equivalent, relative increases in both PGs after exercise (126). This same ratio of PGE$_2$ to PGF$_{2\alpha}$ appears to hold in resting skeletal muscle of older individuals as well (33). However, studies in skeletal muscle of rhesus monkeys show that PG production is approximately twofold higher in older muscle compared with young (142). Several studies in humans using the microdialysis technique to sample the muscle interstitial fluid provide additional information on intramuscular levels of the PGs (primarily PGE$_2$). Few studies report both intramuscular and plasma levels of PGs, but it has been shown that resting vastus lateralis and trapezius intramuscular PG$_E_2$ levels are $\sim$20 times higher than plasma levels (55), albeit in older individuals. However, the intramuscular levels reported in that study are similar to those reported in middle-aged and younger individuals (29, 49, 50). In addition, low-level muscular work does not increase PG$_E_2$ levels (30, 50), whereas resistance and aerobic exercise stimulate the muscle to produce PGE$_2$ and/or PGF$_{2\alpha}$ during and/or after exercise (15, 49, 50, 67, 123, 126). Furthermore, increasing the workload during aerobic exercise increases the muscle production of PGE$_2$ (15, 49). Specifically, going from rest to cycling exercise at 100 W and 150 W increased intramuscular PG$_E_2$ levels by $\sim$400% and $\sim$600%, respectively (49). No information is available on the possible workload effects on PG production following resistance exercise; however, there does

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not appear to be an age effect on PGF_{2α} production during the
24 h following resistance exercise (123).

**COX inhibitors and skeletal muscle COX.** There are some-
what limited data on PG synthesis and muscle protein metab-
olism at rest or after exercise in response to oral consumption
of over-the-counter COX inhibitors (82, 126, 128). Mikkelsen
et al. (67) have shown that an intramuscular infusion of a
relatively low dose of the prescription COX inhibitor indo-
methacin reduced PGE_{2} levels in the muscle during and after
resistance exercise by ~85%. This same COX-inhibitor deliver-
ancy approach during and for a few hours after resistance
eriod did not influence muscle protein synthesis measured
near the infusion site 24 h later (69). Furthermore, numerous
studies of PG regulation of skeletal muscle blood flow at rest
and in response to exercise have used over-the-counter- and
prescription-strength COX inhibitors (15, 45, 100), and these
studies provide some additional insight. For example, Höfler
et al. (45) showed that a single oral dose of 1,000 mg acetyl-
salicylic acid (aspirin), an irreversible inhibitor of COX, inhib-
its resting skeletal muscle PGE_{2} production by nearly 90%
within 1 h. In addition, a single oral dose (100 mg) of
indomethacin given to individuals, 16 h before exercise, elim-
inated 90% of the intramuscular PGE_{2} production during
aerobic exercise (15). Clearly, doses typical for human con-
sumption can impact intramuscular PG production, but more
data are needed in this area and in the context of muscle protein
turnover.

The efficacy of these over-the-counter and prescription COX
inhibitors should also be considered in the context of the COX
enzymes found in skeletal muscle (Table 2). That is, COX-inhib-
iting drugs are commonly classified based on their specificity
toward the two main isoforms of COX—COX-1 and COX-2
(24, 105). The aforementioned drugs that have been shown to
reduce intramuscular PG production in humans (acetaminophen,
ibuprofen, indomethacin, aspirin) are all generally con-
sidered to be nonspecific COX inhibitors (i.e., they block both
COX-1 and COX-2 to some degree). Confusion can arise,
however, if this classification is considered to hold across all
tissues and physiological conditions. That is, different tissues
under different stresses express different levels of the COX
isoforms and have different cellular environments that appear
to affect drug efficacy. In healthy individuals at rest and
following exercise, human skeletal muscle expresses COX-1
almost exclusively at the transcript and protein level (18, 125,
138). Interestingly, there is a relatively ignored variant of the
COX-1 isof orm that is the most abundant transcript in human
skeletal muscle, and it is responsive to exercise (18, 125, 138).
COX-2 transcript levels in healthy human skeletal muscle at
rest or after exercise are very low, and similarly, the amount of
detectable, enzymatically active COX-2 protein is questionable
(18, 116, 125, 138). However, intramuscular COX-2 transcript
levels do increase in response to COX-2-specific and nonspec-
cific COX inhibitors (18, 69). The COX-3 (i.e., COX-1b)
isoform in human skeletal muscle has been ruled out as a
contributor to PG production (18, 125, 138). Animal models of
muscle adaptation (13, 14, 27, 73, 102–104, 109) suggest that
COX-2 plays a substantial role in PG production in skeletal
muscle, but these models appear to be more reflective of
muscle injury and not necessarily human exercise (18, 125).
Overall, the COX-2 isoform in skeletal muscle appears to be
more responsive to injury-related stimuli, which is consistent
with the large induction of skeletal muscle COX-2 protein
levels in humans with septic myopathy (87). Further support
for this notion comes from two separate studies showing that a
COX-2-specific inhibitor designed for human consumption did
not influence the skeletal muscle responses to a single bout of
eccentric resistance exercise (18, 79). Burd et al. (18) showed
that the COX-2 inhibitor was unable to block the normal
increase in muscle protein synthesis following exercise, as was
shown previously with two different, nonspecific COX inhib-
itors (128). Similarly, Paulsen et al. (79) were unable to show
an effect of the COX-2 inhibitor on intramuscular PGE_{2} levels,
satellite cell activity, or autologous-radiolabeled leukocyte ac-
cumulation.

**Chronic effects of COX inhibitors on exercise adaptations.**
Four recent studies (48, 56, 81, 125) provide the initial evi-
dence as to whether chronic consumption of commonly con-
sumed COX inhibitors negatively impacts chronic exercise
adaptations (Table 1).

Krentz et al. (56) showed in young men and women that 400
mg ibuprofen taken after six sets of biceps curls [three sets of
eight to 10 concentric repetitions at 70% one repetition maxi-
mum (1RM) and three sets of four to six eccentric repetitions
at 70% one repetition maximum (1RM)], 2–3 days/wk for 6 wk, did not influence muscle
growth or strength adaptations. The discrepancy between the
acute suppression of muscle protein synthesis in younger
individuals by ibuprofen (128) and these chronic findings is not
completely clear. The lower dose of ibuprofen (1,200 mg/day

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**Table 2. COX enzymes in healthy human skeletal muscle in relation to exercise and COX-inhibiting drugs**

<table>
<thead>
<tr>
<th>Isoform</th>
<th>Variant(s)</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>COX-1</td>
<td>Variant 1 (~1v1)</td>
<td>Relatively abundant at the transcript and protein level at rest and after acute and chronic exercise. The protein product commonly believed to interact with nonspecific COX-inhibiting drugs. Acute exercise increases transcript levels; chronic exercise training increases transcript and protein levels.</td>
</tr>
<tr>
<td>COX-1</td>
<td>Variant 2 (~1v2)</td>
<td>A truncated transcript of COX-1v1 (missing 111 bases from exon 9) that may not generate a functional protein product. Most abundant COX transcript but specific role in skeletal muscle unknown. Acute exercise and chronic exercise training increase transcript levels.</td>
</tr>
<tr>
<td>COX-1</td>
<td>Variant b (~1b)</td>
<td>Also known as COX-3. An intron-1-retaining version of COX-1 with 3 splice variants: ~1h, ~1b, ~1b. Apparently sensitive to common COX-inhibiting drugs in other tissues. Nondetectable or very low transcript levels at rest and nonresponsive to acute and chronic exercise. Unlikely involved in exercise adaptations or related COX-inhibitor effects.</td>
</tr>
<tr>
<td>COX-2</td>
<td>Very low or nondetectable transcript and enzymatically active protein levels at rest and after acute and chronic exercise. Although low, transcript levels increase with ingestion or infusion of COX-2-specific or nonspecific COX inhibitors after acute exercise, as well as with chronic exercise training.</td>
<td></td>
</tr>
</tbody>
</table>

See text and related studies (18, 69, 105, 116, 125, 138) for further discussion of skeletal muscle COX.
vs. 800–1,200 mg/wk); the somewhat short duration of training, limiting the time for the COX inhibitor to have an effect; and the possible influence on muscle protein breakdown are plausible explanations.

Petersen et al. (81) recently showed that older patients with osteoarthritis (mean age ~62 yr), taking ibuprofen (1,200 mg/day) and completing 12 wk of progressive resistance training, 3 days/wk (four to five sets of eight to 15 repetitions at 70–80% of 1RM), had no effect on muscle mass gains, but muscle strength was enhanced in those individuals consuming the COX inhibitor. The authors suggest that this effect on muscle function was related to the pain relief obtained from the drug consumption. These findings are corroborated by this same group’s data showing that ibuprofen (1,200 mg/day) does not influence the muscle protein-synthesis response to exercise in older osteoarthritis patients (mean age ~62 yr) (82). Interestingly, they also reported that 12 wk of training and taking ibuprofen did inhibit the increase in muscle satellite cell number induced with training in the placebo group (81). These results are in accordance with reports of COX-inhibiting drugs interfering with satellite cell activity after exercise, which is apparently mediated through COX-1 (61, 68, 79). These findings raise the question of whether satellite cells are necessary for muscle hypertrophy, at least the amount that is generally elicited with exercise-training paradigms used for health and wellness of older individuals and the treatment of sarcopenia. This general question has been debated recently (63, 76), and the answer is apparently not yet at hand (46, 60, 83).

With the use of doses of acetaminophen (4 g/day) or ibuprofen (1.2 g/day) in healthy, older men and women (60–78 yr) completing resistance-exercise training 3 days/wk (three sets of 10 repetitions at ~75% of 1RM/day) for 12 wk, Trappe et al. (125) unexpectedly showed an enhancement of muscle mass and strength gains of 25–50% over a placebo-consuming group. Follow-up studies on muscle biopsies obtained from these individuals (125, 127) and subsequent ex vivo studies (110) provide some mechanistic clarity about these unexpected COX-inhibitor effects (Fig. 2). It appears the COX inhibitors reduced the PGE2 production (126) and resultant stimulation of intramuscular IL-6 and muscle RING finger protein-1 (MuRF-1) production (57, 88, 111), which increased net protein balance in response to each exercise bout throughout the exercise program. This hypothesis is based on the data that show that low-level increases in IL-6 acutely inhibit muscle protein turnover (131), chronically promote muscle atrophy (12, 37), and are associated with a reduction in muscle mass and functional independence in older individuals (6, 25, 28, 99), as well as the proteolytic nature of the ubiquitin ligase MuRF-1 (20, 98). The COX-inhibitor consumption also promoted an upregulation of the PGF2α receptor in the muscle of the drug groups (127). This increase coupled with a general training increase in COX-1 and the PGF2α-producing enzymes (PGF2α synthase and PGE2-to-PGF2α reductase) (125, 127) would make the muscle less susceptible to the same, daily COX-inhibiting drug doses and more sensitive to any PGF2α that was produced following exercise. Whether these responses and muscle adaptations are specific to older individuals and any potential basal inflammatory state or exaggerated response following exercise (21, 26, 36, 80, 89, 117, 118, 124) is unclear and needs further investigation. Interestingly, COX-inhibitor consumption did not promote muscle growth in the nonexercising hamstring muscles, suggesting an exercise-loading and/or stretch-related mechanism. This nonexercise finding is somewhat in conflict with the data from Rieu et al. (92), showing that chronic consumption of ibuprofen limits sarcopenia through restoration of the muscle protein-synthesis response to feeding in older rats. The discrepancy between these studies is possibly due to the longer-term dosing of the animals (20% vs. 0.4% of the lifespan) and the higher dose of the drug (30 vs. 14 mg·kg body wt⁻¹·day⁻¹). However, these collective findings have implications, not only for use of COX inhibitors during resistance-exercise training for the treatment of sarcopenia but also for the potential chronic use of low-level, long-term, exercise-independent consumption of COX inhibitors for

**Fig. 2. Schematic of the portion of the PG/COX pathway involved in the regulation of skeletal muscle protein metabolism and adaptation.** See text for specific references related to the enzymes, intermediates, and receptors of the COX pathway, as well as the studies that have delineated the factors and cellular processes regulated by the PGE2 and PGF2α receptors that influence skeletal muscle mass. See Trappe et al. (127) for nomenclature related to the PG synthases, reductase, and receptors. MuRF-1, muscle RING finger protein-1; PI3K/ERK/mTOR, phosphoinositide 3-kinase/ERK/mammalian target of rapamycin (62).
the treatment of sarcopenia, as is promoted or contemplated for several other conditions, such as cardiovascular disease, dementia, and certain types of cancer (91, 95, 105, 130).

It is interesting to note that acetaminophen is not commonly considered a nonsteroidal, anti-inflammatory drug because of its relative lack of COX-inhibitory or anti-inflammatory effect in many peripheral tissues, yet it is a potent analgesic, fever reducer, and COX inhibitor within the central nervous system (22, 31). Nonetheless, acetaminophen clearly inhibits PG synthesis in human skeletal muscle (126). Chronic acetaminophen consumption in animals has also been shown to influence skeletal muscle fiber size and glucose metabolism (139, 140). The basis for this tissue specificity is not clear but may be related to the cellular environment (16, 138).

Finally, Jankowski et al. (48) showed recently that 16 wk of progressive resistance-exercise training, 3–5 days/wk (three sets of five to 12 repetitions at 60–80% 1RM coupled with stair-climbing and jumping exercises), combined with the COX-inhibitor acetaminophen (1,000 mg only on days of exercise, average of 3 days/wk) had no effect on fat-free mass or muscle-strength gains in older men (mean age 64 yr). The large difference in acetaminophen dosing (28 g/wk vs. 3 g/wk) likely explains the different responses in this study and those reported by Trappe et al. (125).

Collectively, these chronic studies, albeit of a limited number, highlight three main points: 1) chronic consumption of commonly consumed COX inhibitors at over-the-counter doses during exercise training does not appear to interfere with the muscle mass and strength gains expected from typical resistance-exercise-training regimens; 2) there appears to be a threshold of the amount of drug that is needed to influence skeletal muscle metabolism and adaptation; and 3) there may be differences between the acute and chronic COX-inhibitor effects on muscle metabolism between younger and older individuals.

It should also be noted that the animal studies in this area clearly show an interfering effect of COX inhibitors on muscle growth and adaptation (14, 59, 73, 109). The discrepancy between these studies and the aforementioned human exercise-training and COX-inhibitor studies is most likely due to the animal studies not necessarily reflecting typical human exercise stimuli, as eluded to previously (18). The consideration of the stress placed on the muscle in the different models is also important in understanding the potential role of COX isoforms, as well as PG and inflammatory regulation of muscle adaptation. For example, typical and highly effective resistance-exercise programs in humans only need to load the muscle for a few minutes every 2–3 days (2, 115, 119–122, 125), resulting in <10 min of muscle loading/wk. Whole muscle-growth rates typical for these types of training paradigms are ~0.5%/wk, and the highest reported muscle-growth rate reported in the literature is ~1%/wk (114). These rates are in contrast to the animal models of hypertrophy—some of which have almost constant loading and elicited edema—that result in muscle growth of 25–40%/wk. Considering the potential use of the animal studies and particularly, the PG/COX-pathway genetically modified animals, development of appropriate animal exercise models could facilitate significant advancements in this area.

CONCLUDING REMARKS

The research field of PG and COX-inhibitor regulation of health and disease has grown enormously over the last 80 yr of existence. That skeletal muscle responses and adaptations are regulated by PGs synthesized by the muscle that produced them is now firmly established. It is also clear that one of the most commonly consumed classes of drugs in the world—COX inhibitors—can alter several cellular processes that regulate skeletal muscle responses to acute exercise loading and chronic exercise training. There is much research yet to be done in this complex area to better understand the role of PGs and COX inhibitors, specifically as they pertain to older individuals and the condition of sarcopenia, as well as exercise training and performance of individuals of all ages. The PG/COX-pathway research being conducted in other areas of health and disease will no doubt continue to add significantly to our understanding of this research area in skeletal muscle.

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DISCLOSURES

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Author contributions: T.A.T. conception and design of research; T.A.T. and S.Z.L. analyzed data; T.A.T. and S.Z.L. interpreted results of experiments; T.A.T. and S.Z.L. prepared figures; T.A.T. and S.Z.L. drafted manuscript; T.A.T. and S.Z.L. edited and revised manuscript; T.A.T. and S.Z.L. approved final version of manuscript.

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