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

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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

COX-inhibiting drugs are one of the most commonly consumed classes of drugs in the world. In the United States, the top three consumed drugs of young, middle-aged, and older individuals, with ~50 million individuals using each of these drugs during any given week (52, 129). Interestingly, two of these drugs (acetaminophen and aspirin) have been used for over 100 yr, originating in the 1800s (4). Understanding the role of PGs in skeletal muscle adaptation to activity is important because of the widespread use and potential influence of COX-inhibiting drugs, for better or worse, and so we can understand more completely the mechanisms that control muscle adaptation.

The focus of this review will be on those studies that have used COX inhibition in human studies of skeletal muscle metabolism and adaptations to exercise. Distinction between studies using exercise paradigms that would be used for health benefits and those more focused on injury will be made when necessary and when appropriate animal and cell-culture studies will be discussed. A historical overview of the PG and COX pathway, with specific reference to skeletal muscle metabolism, will also be presented.
PGs, THE COX PATHWAY, AND SKELETAL MUSCLE

**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).

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**Fig. 1.** General schematic of the biosynthesis of the primary PGs in the PG/cyclooxygenase (COX) pathway and their associated receptors (53, 107, 108). The thicker arrows reflect conversions that are catalyzed by specific enzymes. Several other PGs are also made from the conversion (enzymatic or nonenzymatic) of those listed here: PGJ2, 15-deoxy-D12,14-PGJ2, and 11-epi-PGF2α are derived from PGD2; PGA2, PGB2, and PGC2 are derived from PGE2; 15-keto-PGF2α is derived from PGF2α; 6-keto-PGF1α, and 6-keto-PGF1 are derived from PGI2. PGs are lipid molecules with a general chemical formula of C20H28–34O3–6 and molecular weight range of 317–371 Da. See text for specific references related to the numerous aliases that exist for the variants and isoforms of the enzymes and receptors and for further understanding of the nomenclature. Although not a PG, thromboxane A2 is also derived from the enzymatic conversion of PGH2. This review focuses on the 2 primary PGs that influence skeletal muscle protein turnover (PGF2α and PGE2), which are discussed in the text and presented in further detail (see Fig. 2).

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**DP1–2, EP1–4, FP, and IP. PG receptors.**
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>Karim et al. (51)</td>
<td>1967</td>
<td>Humans</td>
<td>PGs are located in skeletal muscle.</td>
</tr>
<tr>
<td>Herbuzynska-Cedro and colleagues (41–43, 47)</td>
<td>1974, 1976</td>
<td>Dogs</td>
<td>Skeletal muscle PG release increased during and after simulated exercise; eliminated with COX inhibitor.</td>
</tr>
<tr>
<td>Kilborn and Wennmalm (54)</td>
<td>1976</td>
<td>Humans</td>
<td>Forearm skeletal muscle PG release increased during and after static and 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% 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 PGE2, PGE2, PGF2a, and PGF3 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 PGF2a and PGE2, which increased muscle protein synthesis and degradation, respectively; reduced or eliminated with COX inhibitors.</td>
</tr>
<tr>
<td>Palmer et al. (78)</td>
<td>1983</td>
<td>Rabbits</td>
<td>Simulated exercise (intermittent stretching) increased skeletal muscle PGF2a and protein synthesis; reduced or eliminated with COX inhibitors. PGF2a and protein synthesis levels correlated.</td>
</tr>
<tr>
<td>Gibson et al. (33)</td>
<td>1991</td>
<td>Humans</td>
<td>Reduced skeletal muscle PGF2a levels associated with reduced muscle protein synthesis and type I and II muscle fiber size.</td>
</tr>
<tr>
<td>Trappe et al. (126, 128)</td>
<td>2001, 2002</td>
<td>Humans</td>
<td>Increased skeletal muscle PGF2a, PGE2, and protein synthesis after resistance exercise; eliminated with over-the-counter, orally consumed COX inhibitors (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 increased workload.</td>
</tr>
<tr>
<td>Boushel et al. (15)</td>
<td>2002</td>
<td>Humans</td>
<td>Confirmed findings of Karamouzis et al. (49, 50) and showed that an oral dose of COX inhibitor (indomethacin) reduced intramuscular PGE2 during aerobic exercise by 90%.</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 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 PGF2a in the hours after resistance exercise; no apparent effect of age on resting or postexercise levels.</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 PGE2 production by nearly 95% during and after resistance exercise.</td>
</tr>
<tr>
<td>Burk et al. (18)</td>
<td>2010</td>
<td>Humans</td>
<td>COX-2-specific inhibitor (celecoxib) did not eliminate or reduce the increase 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 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 2 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 and muscle RING finger-1.</td>
</tr>
</tbody>
</table>

COX inhibitor effects on chronic exercise adaptations

Krentz et al. (56) | 2008 | Humans | Duration: 6 wk; Training: resistance exercise 2–3 days/wk; Drug dose: ibuprofen 400 mg, 2–3 days/wk (training days); Participants: 24 yr, men and women, resistance exercise trained (~6 yr); no effect on muscle mass or strength adaptations compared with placebo-consuming resistance exercise group. |
| Petersen et al. (81) | 2011 | Humans | Duration: 12 wk; Training: resistance exercise 3 days/wk; Drug dose: ibuprofen 1,200 mg/day; Participants: 50–70 yr, men and women, knee osteoarthritis patients; no effect on muscle mass, increased muscle strength compared with placebo-consuming resistance exercise group. |
| Trappe et al. (125, 127) | 2011, 2013 | Humans | Duration: 12 wk; Training: resistance exercise 3 days/wk; Drug dose: acetaminophen 4 g/day or ibuprofen 1,200 mg/day; Participants: 60–78 yr, men and women, healthy, untrained; enhanced muscle mass and strength gains 25–50% above placebo-consuming resistance exercise group. |
| Jankowski et al. (48) | 2012 | Humans | Duration: 16 wk; Training: resistance exercise ~3 days/wk; Drug dose: acetaminophen 1 g, 3 days/wk (training days); Participants: 64 yr, men, healthy, untrained; no effect on fat-free mass or muscle-strength adaptations compared with placebo-consuming resistance exercise group. |

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 PGF2a 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 PGF2a. At the same time, Palmer and colleagues (78, 106) showed that with simulated exercise in rabbit muscle, PGF2a 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...
natural text
et al. (45) showed that a single oral dose of 1,000 mg acetylsalicylic acid (aspirin), an irreversible inhibitor of COX, inhibits resting skeletal muscle PGE2 production by nearly 90% within 1 h. In addition, a single oral dose (100 mg) of indomethacin given to individuals, 16 h before exercise, eliminated 90% of the intramuscular PGE2 production during aerobic exercise (15). Clearly, doses typical for human consumption 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-inhibiting 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 considered 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 isoform 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 nonspecific 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 inhibitors (128). Similarly, Paulsen et al. (79) were unable to show an effect of the COX-2 inhibitor on intramuscular PGE2 levels, satellite cell activity, or autologous-radiolabeled leukocyte accumulation.

**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>
</thead>
<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: −1bα, −1bβ, −1bγ. 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></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>
</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...
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 eliciting 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.

REFERENCES

Review

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