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RESEARCH ARTICLE

Aspirin as a COX inhibitor and anti-inflammatory drug in human skeletal muscle

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Ratchford SM, Lavin KM, Perkins RK, Jemiolo B, Trappe SW, Trappe TA. Aspirin as a COX inhibitor and anti-inflammatory drug in human skeletal muscle. *J Appl Physiol* 123: 1610–1616, 2017. First published July 13, 2017; doi:10.1152/japplphysiol.01119.2016.—Although aspirin is one of the most common anti-inflammatory drugs in the world, the effect of aspirin on human skeletal muscle inflammation is almost completely unknown. This study examined the potential effects and related time course of an orally consumed aspirin dose on the inflammatory prostaglandin E_2 (PGE_2)/cyclooxygenase (COX) pathway in human skeletal muscle. Skeletal muscle biopsies were taken from the vastus lateralis of 10 healthy adults (5 male and 5 female, 25 ± 2 yr old) before (Pre) and 2, 4, and 24 h after (Post) a standard dose (975mg) of aspirin and partitioned for analysis of *1*) in vivo PGE_2 levels in resting skeletal muscle and *2*) ex vivo skeletal muscle PGE_2 production when stimulated with the COX substrate arachidonic acid (5 μM). PGE_2 levels in vivo and PGE_2 production ex vivo were generally unchanged at each time point after aspirin consumption. However, most individuals clearly showed suppression of PGE_2, but at varying time points after aspirin consumption. When the maximum suppression after aspirin consumption was examined for each individual, independent of time, PGE_2 levels in vivo (184 ± 17 and 104 ± 23pg/g wet wt at Pre and Post, respectively) and PGE_2 production ex vivo (2.74 ± 0.17 and 2.09 ± 0.11pg·mg wet wt^{-1}·min^{-1} at Pre and Post, respectively) were reduced ($P < 0.05$) by 44% and 24%, respectively. These results provide evidence that orally consumed aspirin can inhibit the COX pathway and reduce the inflammatory mediator PGE_2 in human skeletal muscle. Findings from this study highlight the need to expand our knowledge regarding the potential role for aspirin regulation of the deleterious influence of inflammation on skeletal muscle health in aging and exercising individuals.

NEW & NOTEWORTHY This study demonstrated that orally consumed aspirin can target the prostaglandin/cyclooxygenase pathway in human skeletal muscle. This pathway has been shown to regulate skeletal muscle metabolism and inflammation in aging and exercising individuals. Given the prevalence of aspirin consumption, these findings may have implications for skeletal muscle health in a large segment of the population.

aspirin; skeletal muscle; inflammation; prostaglandin E_2; cyclooxygenase

ASPIRIN (acetylsalicylic acid) is one of the oldest and most commonly consumed drugs in the world (17, 24, 42). In the United States, there are ~50 million regular users of aspirin, with a substantial increase in use over the last few decades (1, 17, 35, 73). Aspirin is well known for its analgesic, antipyretic, anti-inflammatory, and anti-platelet aggregation properties, working through the inhibition of the cyclooxygenase (COX) enzyme (17, 56). Aspirin may also be the most researched drug in history, with preclinical investigations leading to the Nobel Prize (67, 68) and scores of clinical trials on several hundred thousand individuals (11, 18, 69). These trials are providing evidence for the therapeutic benefits of aspirin against some of the most prevalent diseases (7, 17, 26, 49, 50). Unlike other COX-inhibiting drugs that only temporarily inhibit COX, aspirin irreversibly blocks COX through permanent acetylation of the enzyme (56). Thus, restoration of COX pathway activity is contingent on de novo synthesis of functional COX proteins, which can take up to several days (15). This unique inhibition mechanism underlies the benefits of regular aspirin use, which are likely conferred through the control of platelet activity and COX-regulated inflammation (7, 52, 56).

Although aspirin has been so extensively studied, it is surprising that almost no data exist regarding the influence of aspirin on human skeletal muscle metabolism and inflammation (22, 44). COX-derived prostaglandins (PGs) regulate skeletal muscle protein metabolism (62, 63, 65) and inflammation (29, 63). Furthermore, sarcopenia, the age-related loss of skeletal muscle mass and function, is associated with elevated levels of inflammation (3, 13, 16, 40, 53), and COX inhibitor consumption may lower the risk of sarcopenia (31). COX inhibitor consumption also enhances the antisarcopenic effects of resistance exercise through a reduction of COX-regulated inflammation (59, 61, 63, 64). Collectively, this information underscores the need for studies of aspirin as a COX inhibitor in human skeletal muscle.

Therefore, our goal was to examine the influence of aspirin on the inflammatory mediator and COX pathway product PGE_2 in healthy human skeletal muscle. To accomplish this, we examined the effects and related time course of an orally consumed aspirin dose on *1*) human skeletal muscle in vivo basal PGE_2 levels and *2*) ex vivo PGE_2 production when stimulated by the COX substrate arachidonic acid. The ex vivo measurements simulated conditions of myocellular stress similar to exercise or certain inflammatory states (9, 20, 62). The overarching hypothesis was that aspirin would inhibit the PGE_2/COX pathway in skeletal muscle relatively rapidly and for a prolonged period of time.

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MATERIALS AND METHODS

Subjects

Ten individuals (5 male and 5 female, 25 ± 1 yr old, 175 ± 4 cm, 71 ± 5 kg) were recruited to take part in the investigation and completed detailed medical history, exercise, and dietary habit questionnaires. All subjects were physically active (i.e., regular aerobic and/or resistance exercise 3–5 days/wk), nonobese, nonsmokers, and apparently healthy, with no known condition that would be a contraindication to aspirin consumption. None of the subjects chronically used any prescription or nonprescription analgesic or anti-inflammatory drug. Only 1 of the 10 subjects used aspirin as pain reliever of choice, albeit rarely. The subjects were advised of all study procedures, risks, and benefits before providing written consent to participate. The investigation was approved by the Institutional Review Board at Ball State University.

Experimental Design

Each subject completed an experimental trial (Fig. 1) with specific controls in place for COX inhibitor consumption, diet, and activity before and throughout the trial. A series of four muscle biopsies were obtained before and throughout a 24-h period following aspirin consumption to assess the time-course effects of aspirin on human skeletal muscle PGE_2 levels in vivo and PGE_2 production ex vivo.

COX inhibitor, diet, and activity controls. Subjects were instructed to refrain from consumption of aspirin and any other COX inhibitors (e.g., acetaminophen or ibuprofen) for 14 days before and throughout the experimental trial (2, 12, 15, 33). Subjects were asked to maintain normal dietary habits for the 3 days before the experimental trial and instructed to record the food type, portion size, and time food was consumed. The evening meal on *day 3* was supplied in liquid form (Ensure Plus, Abbott Laboratories, Columbus, OH; 57% carbohydrate, 15% protein, and 28% fat) and provided ~50% of their estimated daily calories [1.5 times the predicted resting metabolic rate (19)]. On the following day, subjects replicated their *day 3* dietary intake starting after the 4-h muscle biopsy (Fig. 1). This level of dietary control standardized the composition, amount, and timing (i.e., duration of fast, ~12 h) of the final meal consumed before the aspirin consumption and the morning muscle biopsies (8, 28). Subjects were also asked to abstain from alcohol and caffeine and refrain from exercise training or vigorous exercise for 3 days before and throughout the experimental trial. To control for potential menstrual cycle influences on aspirin pharmacokinetics (41, 43), all female subjects were studied between *days 3* and *7* of their menstrual cycle.

Aspirin consumption. Subjects consumed a single standard over-the-counter dose of aspirin [975 mg (three 325-mg tablets); Bayer Healthcare, Morristown, NJ] with 250 ml water in the morning after the first muscle biopsy (Fig. 1). A member of the investigative team observed the consumption of aspirin with water.

Muscle biopsy. After administration of local anesthetic (lidocaine HCl, 1%), subjects underwent a skeletal muscle biopsy of the vastus lateralis with a 5-mm Bergström needle (5) with suction before and 2, 4, and 24 h after aspirin consumption (Fig. 1). The pre-aspirin-consumption and 24-h biopsies were obtained after ≥30 min of supine rest. The 2- and 4-h biopsies were obtained while the subjects rested quietly in bed after aspirin consumption. Two biopsies were taken from each leg, with the second biopsy proximal to the first and through a new incision. After the biopsy, excess blood, visible fat, and connective tissue were removed and the muscle was divided for in vivo and ex vivo analyses. The muscle for in vivo analysis was immediately frozen and subsequently stored in liquid nitrogen for measurement of endogenous PGE_2 levels. For the ex vivo analysis, a single muscle strip was immediately processed for incubation and measurement of PGE_2 production in the presence of exogenous arachidonic acid.

Ex Vivo Skeletal Muscle Incubation

After the biopsy, each muscle strip was immediately weighed (12.1 ± 0.4 mg; model AE 200, Mettler, Highstown, NJ) in an incubation vial containing 2 ml of pregassed (95% O_2-5% CO_2) Krebs-Henseleit buffer (KHB; in mM: 118.5 NaCl, 1.2 $MgSO_4$, 4.7 KCl, 1.2 KH_2PO_4, 25 $NaHCO_3$, and 2.5 $CaCl_2$, pH 7.4) with 5 mM glucose and kept at room temperature for 10 min before incubation at 37°C with constant agitation for 20 min (total preincubation period of 30 min). The sample was then transferred to a new vial containing 2 ml of fresh pregassed KHB and 5 μM arachidonic acid (catalog no. BML-FA003, Enzo Life Sciences, Farmingdale, NY) and incubated for an additional 30 min at 37°C with constant agitation and gassing (95% O_2-5% CO_2). At the end of the 30-min incubation, the muscle sample was removed and the KHB medium was immediately frozen and stored at −80°C until PGE_2 analysis.

An arachidonic acid concentration of 5 μM was used for stimulation of PGE_2 production for several reasons: *1*) arachidonic acid concentrations for human (6, 45, 46) and animal (14, 37, 47, 57, 60)

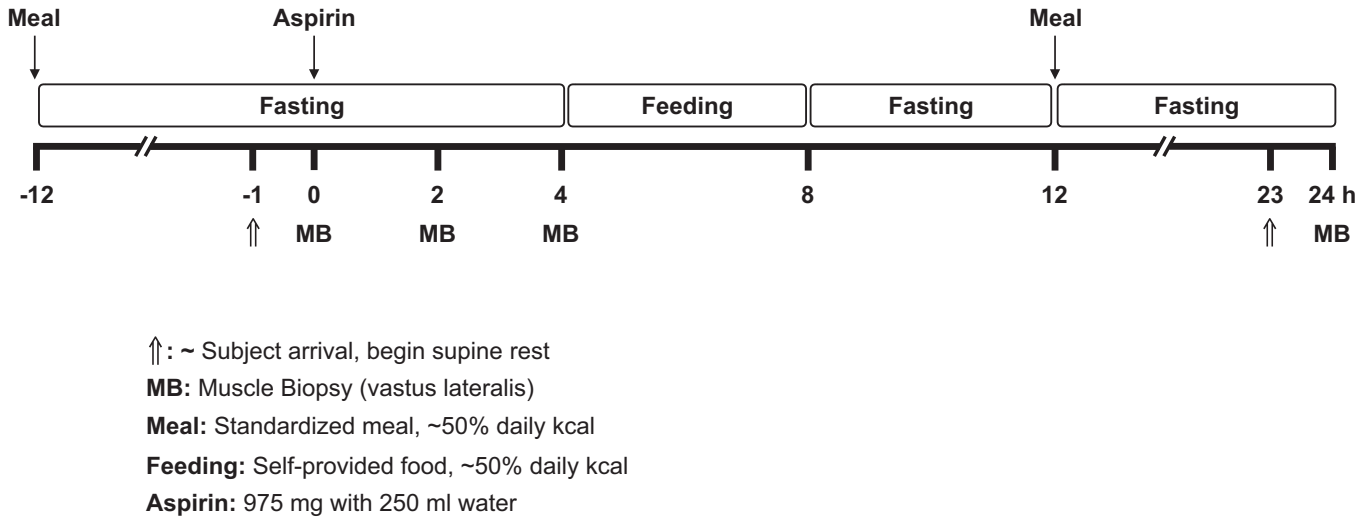

Fig. 1. Protocol schematic for muscle biopsy sampling and aspirin dosing. Subjects arrived ~1 h before aspirin dosing and rested quietly in the laboratory until the 4-h muscle biopsy was completed. All biopsies were taken in the fasted state after ≥30 min of supine rest. Specific drug, physical activity, and dietary controls were in place before and throughout the protocol. Muscle biopsies were used for in vivo and ex vivo PGE_2 measurements.

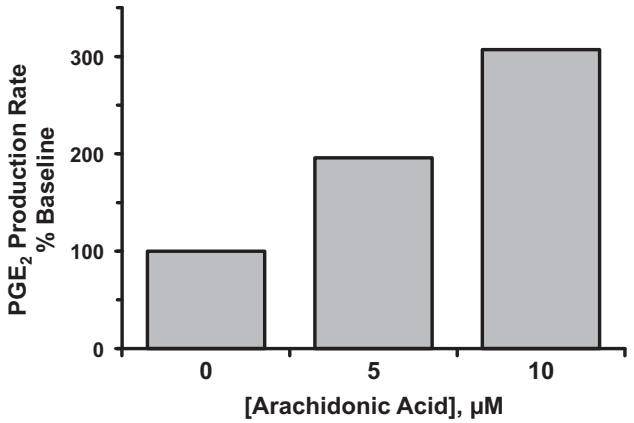

Fig. 2. Ex vivo PGE_2 production rate in human skeletal muscle (vastus lateralis) from 3 individuals (27 ± 3 yr old, 178 ± 4 cm, 81 ± 5 kg). Muscle samples were incubated for 30 min in Krebs-Henseleit buffer (gassed with 95% O_2-5% CO_2, 37°C) with a range of physiological arachidonic acid levels.

skeletal muscle incubation and cell culture studies primarily range from 0.2 to 25 μM, while 50–100 μM appears to be cytotoxic to skeletal muscle cells (37); *2*) 5 μM arachidonic acid should provide a linear PG production rate for ≥60 min (14); *3*) 5 μM arachidonic acid coincides with reported K_m values measured in isolated human COX enzyme experiments (58, 66); *4*) 5 μM arachidonic acid stimulates PGE_2 production and protein turnover in incubated animal muscle, and these responses can be blunted by aspirin and other COX-inhibiting drugs (47); and *5*) initial results from our laboratory show a linear increase in PGE_2 production rates when human vastus lateralis muscle is incubated in 0, 5, and 10 μM arachidonic acid (Fig. 2), suggesting that 5 μM arachidonic acid does not saturate the COX enzyme in human skeletal muscle. These findings also suggest that 5 μM arachidonic acid stimulates PGE_2 production in isolated human skeletal muscle by a magnitude that is observed in vivo in response to exercise (9, 62).

PGE_2 Analyses

The muscle samples for determination of in vivo PGE_2 concentrations were weighed (18.59 ± 0.42 mg) at −25°C (Cahn C-35, Orion Research, Beverly, MA) and homogenized (Powergen 700, Fisher Scientific) in 25 volumes of phosphate-buffered saline (in mM: 137 NaCl, 2.7 KCl, 10 Na_2HPO_4, and 2 KH_2PO_4) and 10 μg/ml meclofenamic acid to prevent further production of PGs from endogenous arachidonic acid. Homogenates were centrifuged at 4°C for 15 min at 14,000 *g* to pellet cellular debris, and the supernatant was removed and stored at −80°C until PGE_2 analysis. The supernatants were thawed and vacuum-dried (Savant ISS 110 SpeedVac) before reconstitution in a PGE_2 assay-specific buffer (catalog no. X067-55ML, Arbor Assays, Ann Arbor, MI). Samples were analyzed in duplicate in an enzyme immunoassay designed to quantitatively measure PGE_2 (catalog no. K051-H5, Arbor Assays). Sample concentrations were determined using a four-parameter logistic regression curve based on PGE_2 standards diluted in the assay-specific buffer.

The KHB media samples for determination of ex vivo PGE_2 production in the presence of 5 μM arachidonic acid were removed from −80°C storage and thawed at room temperature. Samples were analyzed for PGE_2 in duplicate (catalog no. K051-H5, Arbor Assays), and sample concentrations were determined using a four-parameter logistic regression curve based on PGE_2 standards diluted in KHB.

Statistical Analysis

Pre- vs. post-aspirin responses for all variables were compared using paired *t*-tests and corrected for multiple comparisons of the post-aspirin time points (i.e., Pre vs. 2, 4, and 24 h) using Bonferroni's correction. Significance was accepted at $P < 0.05$. In vivo data from one individual were deemed to be statistically outlying (6-13 SDs from the group mean); therefore, the in vivo data represent nine subjects. Values are means ± SE.

RESULTS

In Vivo Basal PGE_2 Responses

Intramuscular PGE_2 levels were generally unchanged ($P > 0.05$) at each time point following aspirin consumption (Table 1). However, most individuals showed suppressed PGE_2 levels at one or more time points following aspirin consumption. In several individuals, PGE_2 levels were suppressed by >50%, with 97% suppression in one individual at 2 h and 76% suppression in another at 4 h. This variability in the time course and magnitude of responsiveness is not uncommon for drugs in general (48, 51, 70) and aspirin specifically (4, 10). Therefore, the lowest intramuscular PGE_2 level for each individual, independent of time, after aspirin consumption was compared with pre-aspirin (Fig. 3). These data showed that intramuscular PGE_2 levels were significantly ($P < 0.05$) suppressed by 44% following the single dose of aspirin (Fig. 3).

Ex Vivo Stimulated PGE_2 Responses

Weights of the incubated vastus lateralis muscle strips were similar across all four time points (12.6 ± 0.7, 11.5 ± 0.7, 11.9 ± 0.7, and 12.4 ± 0.9 mg at Pre, 2 h, 4 h, and 24 h, respectively). Ex vivo stimulation of skeletal muscle PGE_2 production with 5 μM arachidonic acid was generally unchanged ($P > 0.05$) at each time point following aspirin consumption (Table 1). However, similar to the in vivo responses, most individuals showed suppressed ex vivo PGE_2 production at one or more time points following aspirin consumption, with 30–50% suppression in several individuals. Therefore, the lowest ex vivo arachidonic acid-stimulated PGE_2 production for each individual, independent of time, after aspirin consumption was compared with pre-aspirin (Fig. 4). These data showed significant ($P < 0.05$) suppression (by 24%) of ex vivo skeletal muscle PGE_2 production following the single dose of aspirin (Fig. 4).

DISCUSSION

The overarching aim of the current investigation was to examine the possible role of orally consumed aspirin in regulation of the PGE_2/COX pathway in human skeletal muscle. This aim was developed in the context of *1*) the known negative impact of COX-dependent inflammation on skeletal muscle health and exercise adaptations (29, 31, 63), *2*) the dearth of aspirin investigations that have directly examined

Table 1. *Skeletal muscle PGE_2 levels and production rates in vivo and ex vivo*

	In Vivo, pg/g muscle wet wt	Ex Vivo, pg·mg wet wt^{-1}·min^{-1}
Pre-aspirin	184 ± 17	2.74 ± 0.17
2 h	192 ± 41	2.50 ± 0.16
4 h	146 ± 28	2.72 ± 0.21
24 h	140 ± 15	2.33 ± 0.20

Values are means ± SE.

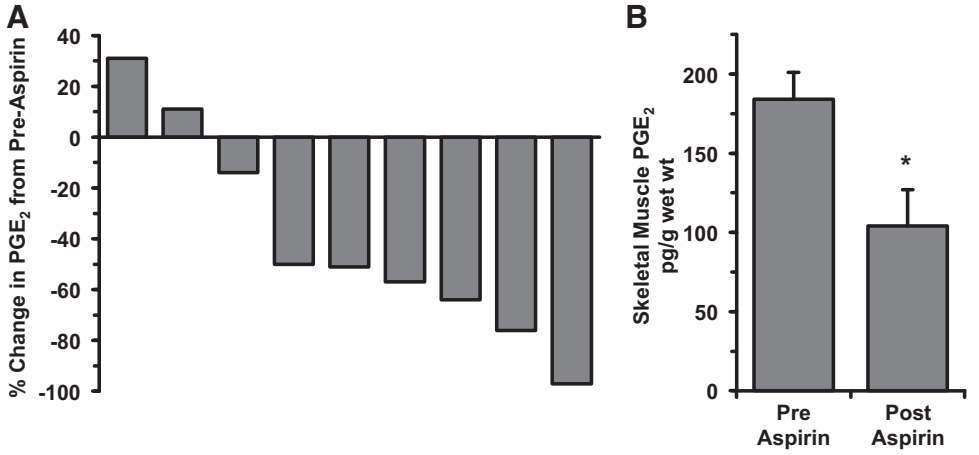

Fig. 3. In vivo skeletal muscle PGE_2 levels in response to a single 975-mg dose of aspirin. *A*: individual PGE_2 changes shown as percent change from pre-aspirin to the lowest PGE_2 level following aspirin consumption, independent of time (2, 4, or 24 h). Numbering subjects from *left* to *right*, bars correspond to male (M) or female (F) subjects as follows: F, M, M, F, M, F, M, F, and F. *B*: average PGE_2 levels, with post-aspirin data represented by the lowest PGE_2 level following aspirin consumption, independent of time (2, 4, or 24 h). $*P < 0.05$.

human skeletal muscle (22), and *3*) the recent findings that COX regulation by aspirin in other tissues may have significant health benefits (7, 26, 50, 52, 69). The focus of the investigation was on the inflammatory mediator and COX pathway product PGE_2, which has been shown to regulate skeletal muscle mass (59, 63). The main findings from the study suggest that an oral dose of aspirin sufficiently blocks the COX enzyme in human skeletal muscle, resulting in a significant reduction of skeletal muscle PGE_2 production in the basal and stimulated states.

The results from the in vivo portion of the study provide some interesting and novel insights into the interactions of orally consumed aspirin and skeletal muscle COX-related metabolism. It appears that a single standard over-the-counter dose of aspirin (975 mg) can have potent inhibitory effects on the PGE_2/COX pathway in skeletal muscle as early as 2 h, at which point PGE_2 levels in some subjects were reduced by 50–97% from baseline. These findings are in line with pharmacokinetic studies showing that aspirin appears in the peripheral circulation within a few minutes following a single dose, peaks within 15–45 min, and is removed from the circulation within 3–4 h (21, 27). Interestingly, in most of the individuals, suppression of intramuscular PGE_2 continued at 24 h, ~20 h after aspirin was likely no longer available from the circulation. Thus the prolonged PGE_2 suppression is likely explained by acetylation and permanent inhibition of COX enzymes, which occurred in the first few hours after aspirin consumption. These results suggest that resynthesis of the COX enzyme in resting human skeletal muscle following acetylation may be slow and may require several hours or days to return PGE_2 levels to baseline.

For the ex vivo experiments, we chose an integrative approach that allowed for in vivo acetylation of skeletal muscle COX by aspirin before the muscle biopsy and ex vivo incubation without further drug exposure. Similar to the in vivo findings, the ex vivo results demonstrated that a single, oral dose of aspirin was capable of suppressing PGE_2 production in some individuals as early as 2 h and for ≥24 h following

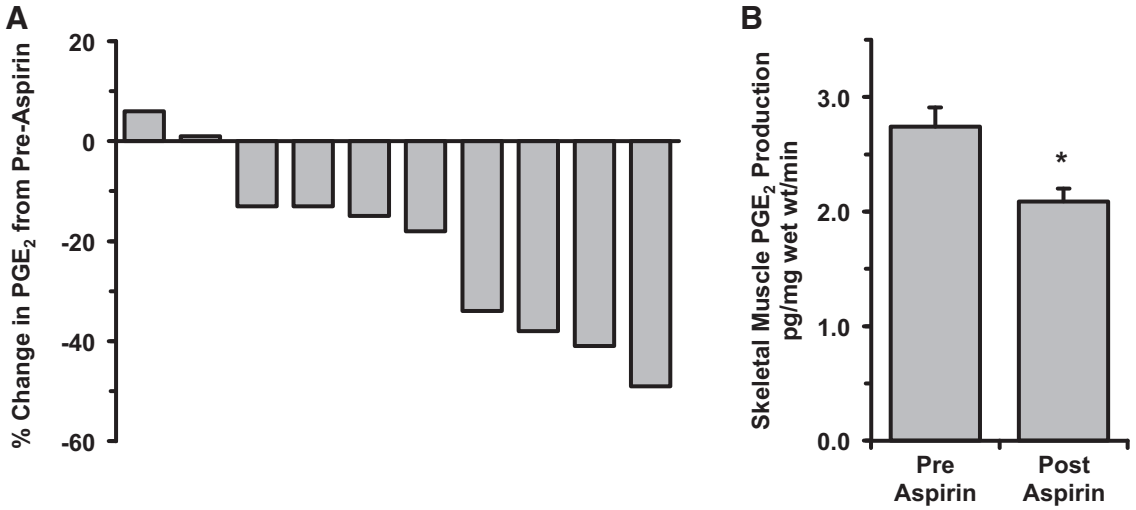

Fig. 4. Ex vivo skeletal muscle PGE_2 production after a single 975-mg dose of aspirin. Human biopsy samples (~12-mg muscle strips) were stimulated with 5 μM arachidonic acid in Krebs-Henseleit buffer. *A*: individual changes shown as percent change from pre-aspirin to the lowest PGE_2 production level following aspirin consumption, independent of time (2, 4, or 24 h). Corresponding with numbering and male (M) and female (F) labeling from Fig. 3, from *left* to *right*, bars correspond to subjects as follows: 3M, 9F, 6F, 4F, 1F, 10M, 5M, 7M, 8F, and 2M: *subject 3* (M); *subjects 9*, *6, 4*, and *1* (F); *subjects 10, 5*, and *7* (M); *subject 8* (F), and *subject 2* (M). *B*: average PGE_2 production rate, with post-aspirin data represented by the lowest PGE_2 production level following aspirin consumption, independent of time (2, 4, or 24 h). $*P < 0.05$.

aspirin consumption. However, the magnitude of the aspirin effect in the ex vivo experiments (−24%) was less than the in vivo responses (−44%). This difference is likely explained by a higher arachidonic acid substrate flux through the COX enzyme in the ex vivo condition, coupled with an incomplete acetylation of the skeletal muscle COX enzyme pool by the single oral aspirin dose.

It is interesting to speculate about the possibility of chronic acetylation of human skeletal muscle COX from chronic oral aspirin dosing. This concept is well understood in platelet biology, as chronic (low-dose) aspirin consumption has long-lasting effects on platelet COX and subsequent clotting due to the anucleated nature of platelets and their inability to synthesize new COX (42). In addition, peripheral tissues capable of generating COX enzymes, but at a relatively slow turnover rate, are subject to the chronic acetylation effects of aspirin. This is evident in the gastrointestinal mucosa and results in long-lasting PG-suppressive effects and related health consequences and benefits (7, 11, 15, 52). In skeletal muscle, chronic COX acetylation could have implications for inflammatory conditions such as sarcopenia (3, 13, 16, 40, 53). Landi et al. (31) recently showed that chronic COX inhibitor consumption was associated with a decreased prevalence of sarcopenia, suggesting that the COX pathway regulates skeletal muscle mass with age. Daily aspirin use in older individuals (1, 35, 73) may beneficially control the production of PGE_2, which may be upregulated in aging skeletal muscle due to an elevated level of the cytosolic PGE_2 synthase enzyme (32). This may also have implications for older exercising individuals, as other COX inhibitors have been shown to enhance the antisarcopenic effects of resistance exercise through a reduction of COX-regulated inflammation (59, 61, 63, 64).

The post-aspirin responses were examined independent of time because of the variation in individual responses and the substantial amount of PGE_2 suppression in most individuals (Figs. 3 and 4), which was not adequately reflected in the grouped time-point-specific data (Table 1). The basis for the variability in the time course and magnitude of responsiveness to drugs is highly complex and has been shown to be the result of a multitude of factors, including body size and composition, drug dilution space, gastrointestinal drug handling and absorption, portal circulation and hepatic metabolism, metabolism and transport in the circulation, tissue-specific blood flow, renal clearance, and numerous genetic factors (48, 51, 70). Indeed, variability in response to aspirin has been shown to be related to many of these factors (4, 10, 21, 71), including genetic polymorphisms of the COX pathway components (36, 72). In the current study, skeletal muscle-specific responses could have also been influenced by intramuscular levels of the enzymes in the COX pathway (29, 32, 63, 64).

Variability in response to aspirin treatment is well recognized and has led platelet biologists and clinicians to develop the concept of aspirin resistance. The platelet literature suggests that ~20–30% of the population may be resistant to the anticoagulation effects of aspirin (10, 23). Although this type of aspirin resistance has substantial clinical relevance, the basis of aspirin resistance is not universally understood and accepted. Even different laboratory tests have yielded varying levels of clotting suppression and claims of aspirin resistance (30, 34, 72). Interestingly, the data from the current study are consistent with this prevalence of aspirin resistance and assay-specific variability in defining aspirin resistance: two individuals appeared to be aspirin-resistant in either the in vivo or ex vivo experiments (Figs. 3 and 4), and they were not the same two individuals in both experiments. When the current in vivo responses are considered without the two individuals in whom PGE_2 levels were not reduced at any time point after aspirin consumption, the intramuscular PGE_2 levels trended downward from baseline and were significantly ($P < 0.05$) reduced by 35% at 24 h (189 ± 21, 174 ± 48, 128 ± 32, and 123 ± 11 pg/g muscle wet wt at Pre, 2 h, 4 h, and 24 h, respectively). Not surprisingly, the magnitude of the PGE_2 suppression was also greater (−59%) after aspirin consumption, independent of time, in this subgroup (189 ± 21 and 77 ± 19 pg/g muscle wet wt at Pre and Post, respectively). A similar, but smaller, effect was noted in the ex vivo stimulation responses when the subgroup of aspirin responders was examined. Higher and/or chronic dosing may provide a more uniform PGE_2 suppression across individuals, including those who appear to be relatively aspirin-insensitive.

Although the study was not specifically designed to address sex differences in response to aspirin, there were no notable differences between the male and female subjects in terms of the in vivo and ex vivo PGE_2 responses. This similarity in response is worth noting, as sex-based differences in aspirin pharmacokinetics have been reported and are related to differences in drug absorption and clearance, as well as circulating esterase levels (21, 25, 39, 41, 43). Our subject selection criteria and menstrual cycle control may have helped minimize these potential influences.

One relatively new area of aspirin science that should be considered in future studies of skeletal muscle inflammation relates to the aspirin-triggered production of lipid metabolites (38, 54, 55). Recent evidence in nonskeletal muscle tissues suggests that the interaction of aspirin with the COX-2 isoform results in production of anti-inflammatory proresolving mediators (e.g., lipoxins, resolvins, and protectins) (54, 55). While the role of COX-2 in adaptations of skeletal muscle along the continuum of health and disease is not yet clear (63), this emerging area of proresolving lipid mediators may have interesting implications for skeletal muscle (38).

In summary, this study focused on the effects of aspirin on the PGE_2/COX pathway in human skeletal muscle via an integrative approach of in vivo and ex vivo investigations. The results suggest that orally consumed aspirin has the potential to significantly inhibit COX and decrease the inflammatory and metabolic regulator PGE_2 in skeletal muscle. Further investigation of the acetylation and turnover of the COX enzyme in human skeletal muscle following oral aspirin consumption is needed. With millions of adults consuming aspirin on a regular basis, knowledge of how aspirin may influence skeletal muscle health through attenuation of COX-mediated inflammation could have implications for a large segment of the population.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

S.M.R., K.M.L., R.K.P., B.J., and T.A.T. conceived and designed research; S.M.R., K.M.L., R.K.P., B.J., and T.A.T. performed experiments; S.M.R., K.M.L., R.K.P., B.J., and T.A.T. analyzed data; S.M.R., K.M.L., R.K.P., B.J., S.W.T., and T.A.T. interpreted results of experiments; S.M.R. and T.A.T. prepared figures; S.M.R. and T.A.T. drafted manuscript; S.M.R., K.M.L., R.K.P., B.J., S.W.T., and T.A.T. edited and revised manuscript; S.M.R., K.M.L., R.K.P., B.J., S.W.T., and T.A.T. approved final version of manuscript.

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