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Effect of ibuprofen and acetaminophen on postexercise muscle protein synthesis

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Trappe, T. A., F. White, C. P. Lambert, D. Cesar, M. Hellerstein, and W. J. Evans. Effect of ibuprofen and acetaminophen on postexercise muscle protein synthesis. *Am J Physiol Endocrinol Metab* 282: E551–E556, 2002. First published October 30, 2001; 10.1152/ajpendo.00352.2001.—We examined the effect of two commonly consumed over-the-counter analgesics, ibuprofen and acetaminophen, on muscle protein synthesis and soreness after high-intensity eccentric resistance exercise. Twenty-four males (25 ± 3 yr, 180 ± 6 cm, 81 ± 6 kg, and 17 ± 8% body fat) were assigned to one of three groups that received either the maximal over-the-counter dose of ibuprofen (IBU; 1,200 mg/day), acetaminophen (ACET; 4,000 mg/day), or a placebo (PLA) after 10–14 sets of 10 eccentric repetitions at 120% of concentric one-repetition maximum with the knee extensors. Postexercise (24 h) skeletal muscle fractional synthesis rate (FSR) was increased 76 ± 19% ($P < 0.05$) in PLA (0.058 ± 0.012%/h) and was unchanged ($P > 0.05$) in IBU (35 ± 21%; 0.021 ± 0.014%/h) and ACET (22 ± 23%; 0.010 ± 0.019%/h). Neither drug had any influence on whole body protein breakdown, as measured by rate of phenylalanine appearance, on serum creatine kinase, or on rating of perceived muscle soreness compared with PLA. These results suggest that over-the-counter doses of both ibuprofen and acetaminophen suppress the protein synthesis response in skeletal muscle after eccentric resistance exercise. Thus these two analgesics may work through a common mechanism to influence protein metabolism in skeletal muscle.

paracetamol; analgesics; nonsteroidal anti-inflammatory agents; delayed-onset muscle soreness

ANALGESIC DRUGS ARE COMMONLY CONSUMED to reduce or prevent the pain and soreness encountered after completion of unaccustomed exercise. This is especially true when the exercise contains eccentric (muscle lengthening) contractions, which have been demonstrated to result in relatively large amounts of muscle damage and soreness (13). Ibuprofen and acetaminophen are two popular over-the-counter analgesics consumed for muscle soreness. In fact, it has been reported that ~5.5 million people in the United States consume an analgesic, antipyretic, or nonsteroidal anti-inflammatory drug (NSAID) each day (20).

Ibuprofen and acetaminophen are purported to relieve muscle soreness and pain through separate mechanisms. Ibuprofen is known to block cyclooxgenase (EC 1.14.99.1), which then reduces metabolites produced by this enzyme, such as prostaglandins, that are at least partially responsible for inflammation and algesia (14, 35, 36). However, prostaglandins have also been shown to regulate protein metabolism, and NSAIDs similar to ibuprofen have been shown to blunt protein metabolism in animal skeletal muscle (24, 30). Therefore, skeletal muscle protein metabolism may be influenced in individuals who consume ibuprofen after unaccustomed exercise. The mechanism of analgesic action of acetaminophen, also known as paracetamol, is less clear; however, it is believed to have its analgesic action within the central nervous system (8, 11, 15, 32, 36). Thus acetaminophen would not be expected to interfere with muscle protein metabolism after exercise.

An important question is whether or not these drugs, when consumed at nonprescription levels, have any influence on metabolism and pain in humans after unaccustomed exercise. Therefore, we studied the influence of ibuprofen and acetaminophen, at their maximal over-the-counter daily dose, on skeletal muscle protein fractional synthesis rate (FSR) and muscle soreness after high-intensity eccentric resistance exercise. This type of exercise has been shown to cause muscle soreness and damage and to stimulate a protein metabolism response (13, 26). We hypothesized that a group that consumed no drug (placebo) or acetaminophen would elicit a large increase in FSR, whereas the ibuprofen group would respond with a blunted protein turnover response. We also hypothesized that both drugs would have an equal effect on reducing muscle soreness compared with placebo.

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Table 1. *Subject characteristics*

Group	Age, yr	Height, cm	Weight, kg	Body Fat, %	Eccentric Load,* N/m
ACET	26 ± 4	179 ± 5	78 ± 5	16 ± 9	208 ± 50
IBU	24 ± 3	181 ± 5	78 ± 10	14 ± 6	216 ± 58
PLA	25 ± 3	181 ± 8	87 ± 23	20 ± 9	203 ± 52

Values are means ± SD. *Nondominant leg. ACET, acetaminophen; IBU, ibuprofen; PLA, placebo.

METHODS

Subjects. Twenty-four males were recruited and randomly divided into three groups of eight: placebo (PLA), ibuprofen (IBU), or acetaminophen (ACET) (Table 1). All subjects were accepted into the study after giving informed consent and after a screening for any metabolic abnormalities via a blood draw, urinalysis, and medical history questionnaire. Subjects were sedentary or recreationally active and were not completing any formal exercise during the study or any resistance exercise for ≥6 mo before the investigation. None of the subjects was chronically consuming ibuprofen, acetaminophen, or any analgesic or anti-inflammatory drug before the study. This investigation was approved by the Institutional Review Board of the University of Arkansas for Medical Sciences.

Overall experimental protocol. After enrollment in the study, each subject completed a 16-day protocol (Fig. 1). To standardize protein intake, all of the subjects' meals were prepared and provided by the metabolic kitchen of the Nutrition, Metabolism, and Exercise Laboratory (NMEL) during the 16 days. Total caloric content of the meals was determined by estimating the daily energy expenditure from the Harris-Benedict equation (17) multiplied by an activity factor of 1.5. Each diet was composed of 1.2 g protein·kg body $wt^{-1}\cdot day^{-1}$, with the remaining calories coming from carbohydrate (~55%) and fat (~25%). Body weight was measured each morning and, if necessary to maintain body weight, the carbohydrate and fat content of the diet was altered.

In the morning on *days 5* and *8,* each subject underwent a stable isotope infusion protocol (see *Isotope infusion protocol*) for the measurement of skeletal muscle protein FSR before and after (24 h) a bout of high-intensity eccentric exercise (*day 7*, see *Eccentric exercise protocol*). The evening before each infusion protocol, the subjects spent the night in the NMEL and were instructed to eat their evening meal so as to provide a fast of 10 h before the beginning of the FSR measurements.

Before and each morning after the exercise bout, each subject came to the laboratory in the fasted state for a resting blood draw for creatine kinase (CK) determination and a rating of perceived soreness (see *Measurement of perceived muscle soreness*). The blood draw and soreness rating were completed in the supine position after ~10 min of supine rest.

Isotope infusion protocol. On the morning of the infusions (Fig. 1), each subject had an 18-gauge catheter placed in an antecubital vein for the infusion of a stable, isotopically labeled amino acid ([$^2H_5$]phenylalanine; Mass Trace, Woburn, MA) for the measurement of skeletal muscle protein FSR. A 20-gauge catheter was placed in retrograde fashion in a dorsal vein of the hand, which was heated to provide an arterialized blood sample (1). [$^2H_5$]phenylalanine was dissolved in sterile 0.9% saline, filtered through a 0.2-μm filter before infusion, and infused with a calibrated infusion pump (PHD 2000, Harvard Apparatus, Natick, MA) at a rate of 0.05 $\mu mol\cdot kg^{-1}\cdot min^{-1}$ after a priming dose of 2.0 μmol/kg as previously described (26). This protocol has been shown to result in steady-state [$^2H_5$]phenylalanine enrichments in the blood and muscle intracellular free amino acid pool within 120 min (6, 26, 37). Before and during each infusion, blood samples were drawn (t = 0, 120, 180, 210, 240, 260, 280, and 300 min) for the measurement of plasma enrichment of [$^2H_5$]phenylalanine. Muscle biopsies were taken from the vastus lateralis muscle of the dominant leg before and from

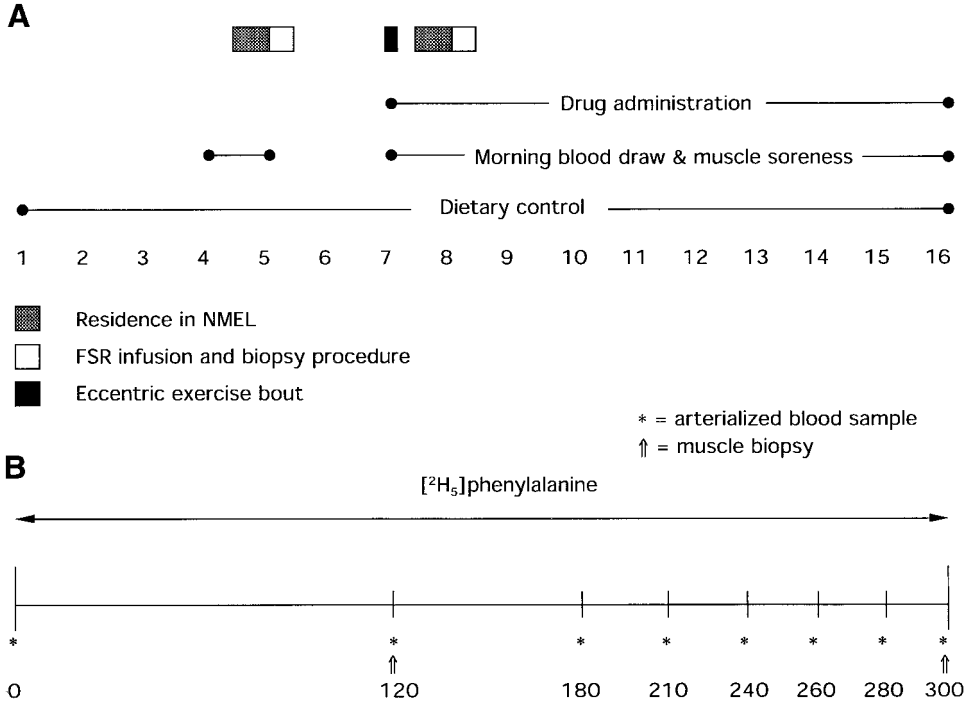

Fig. 1. *A*: overall experimental protocol. Nos. represent days of the protocol. NMEL, Nutrition, Metabolism, and Exercise Laboratory; FSR, fractional synthesis rate. Nos. represent time in days. *B*: isotope infusion schematic. Nos. represent time in minutes.

the nondominant leg after the eccentric exercise protocol (t = 120 and 300 min). Each muscle biopsy was taken through a new incision proximal to the previous biopsy. Tissue was obtained after local anesthetic (lidocaine HCl 1%) with the use of a 6-mm Bergstrom needle with suction (5). The muscle was cleansed of excess blood, connective tissue, and fat and immediately frozen in liquid nitrogen. The tissue was stored in liquid nitrogen (−190°C) until analysis.

Eccentric exercise protocol. On *day 7*, each subject completed a bout of unilateral high-intensity eccentric exercise with each leg. The maximal load that each subject could lift concentrically with his knee extensors (i.e., one repetition maximum, 1RM) was first determined and the eccentric workload set to 120% of 1RM. The eccentric exercise consisted of 10–14 sets of 10 repetitions with a 60-s rest between sets of knee extensor exercise on a muscle dynamometer in the isotonic mode (Cybex Norm, Lumenex, Ronkonkoma, NY). The range of 10–14 sets was achieved as a result of the variation in fatigue of the muscles of each subject. When the weight was lowered in less than 0.5 s, the subject completed that set, was deemed fatigued, and the protocol was stopped.

Drug dose and administration. Drugs were administered in a double-blind placebo-controlled fashion. Each drug was administered in three doses each day (8 AM, 2 PM, and 8 PM) corresponding to the maximal over-the-counter daily dose (ibuprofen: 400 mg per dose, total of 1,200 mg; acetaminophen: 1,500, 1,500, and 1,000 mg, total of 4,000 mg). The placebo group was given the same number of pills, which were indistinguishable from the drug doses. The first dose was given at the start of the eccentric exercise protocol (~8 AM on *day 7*). On the day of the postexercise infusion protocol, the 8 AM dose was given at the start of the [$^2H_5$]phenylalanine infusion. The times of dosing were chosen to divide the maximal over-the-counter dose evenly over the day and as a result of the pharmacokinetic studies that had previously been completed on these drugs (2, 11, 19). When single doses at or near those used in the current study are consumed, ibuprofen and acetaminophen have similar pharmacokinetic parameters. Both drugs appear in the plasma within 10 min; peak levels in plasma occur within 0.5–2.0 h; and the half-life of both drugs is ~2 h (2, 11, 19). The subjects were asked not to consume any other prescription or nonprescription drug during the study.

Measurement of perceived muscle soreness. A subjective measure of muscle soreness was obtained from each subject before the eccentric exercise protocol and each morning throughout the protocol. Each subject was presented a scale from 1 to 9, with 1 being the absence of soreness and 9 being unbearable soreness, and was asked to rate the level of soreness after the application of 40 N of force using a force transducer with a 2-cm-diameter tip (22, 23). Rating of perceived soreness was measured two times in random order over nine sites over the four heads of the quadriceps femoris. Each site was maintained over the study period by re-marking with a permanent marker. The average of the two measurements and all nine sites was taken to represent the average level of perceived soreness. The highest average value of the nine sites was taken to represent the maximal level of perceived soreness.

Measurement of isotope enrichment. Blood samples were analyzed for [$^2H_5$]phenylalanine enrichment, and muscle samples were analyzed for free intracellular and protein-bound [$^2H_5$]phenylalanine enrichment by mass spectrometry as previously described (6, 26), by use of the *N*-acetyl-*n*-butyl ester (NABE) derivative of phenylalanine. Derivatives were analyzed by gas chromatography-mass spectrometry (Hewlett-Packard 5973, series II) using electron impact ionization and selected ion monitoring of mass-to-charge ratios (m/z) 264, 267, 269, and 272 for the $m+0$, $m+3$, $m+5$, and $m+8$ ions, respectively. Protein-bound enrichment was determined by monitoring m/z 267 and 269, which are the $m+3$ and $m+5$ enrichments, respectively, where $m+0$ is the lowest mass isotopomer in the ion envelope. Enrichment of the protein-bound samples was determined using a linear standard curve from mixtures of known $m+5$-to-$m+3$ ratios. Precursor enrichment for calculation of FSR was determined from intracellular [$^2H_5$]phenylalanine by monitoring the $m+5$-to-$m+0$ ratio (mass 269 and 264 amu) enrichment of the NABE-phenylalanine. Plasma [$^2H_5$]phenylalanine enrichments were measured from the $m+5$-to-$m+0$ ratio.

Calculations. FSR was calculated as the rate of [$^2H_5$]phenylalanine tracer incorporation into muscle protein, using the muscle intracellular free phenylalanine enrichment as the precursor and the following equation

$$\text{FSR (\%/h)} = \{(Et_1 - Et_0)/[E_p \cdot (t_1 - t_0)]\} \cdot 100$$

where Et_0 is the enrichment in the protein-bound phenylalanine tracer from the t = 120-min biopsy, Et_1 is the enrichment in the protein-bound phenylalanine tracer from t = 300-min biopsy, $(t_1 - t_0)$ is the phenylalanine tracer incorporation time, and E_p is the mean intracellular free [$^2H_5$]phenylalanine enrichment from both biopsies (t = 120 and 300 min) (26).

Whole body phenylalanine appearance, taken as a measure of whole body protein breakdown, was calculated using the formula

$$R_a = F/E_p$$

where R_a is the rate of appearance ($\mu mol \cdot kg^{-1} \cdot min^{-1}$), F is the infusion rate ($\mu mol \cdot kg^{-1} \cdot min^{-1}$), and E_p is the arterialized blood [$^2H_5$]phenylalanine enrichment.

CK measurement. Serum CK activity was measured using a commercial assay kit (Sigma Chemical, St. Louis, MO).

Statistics. Subject characteristics (height, weight, age, %body fat, and eccentric load) among the groups were compared using a one-way analysis of variance (ANOVA). FSR, phenylalanine R_a, CK, and muscle soreness before and after exercise among the groups were compared using a two-way ANOVA with repeated measures over time. A two-way ANOVA with repeated measures over time was also used to compare blood and muscle intracellular free [$^2H_5$]phenylalanine enrichments over the blood draw and muscle biopsy time points, respectively, for both trials. Because of sample loss during mass spectrometry processing, FSR data include n = 7 (IBU), 6 (PLA), and 4 (ACET); all other data are represented by n = 8 per group. When a significant difference was obtained, a Tukey's post hoc analysis was used to find the location of the differences. Significance was accepted at a level of $P < 0.05$.

RESULTS

There were no differences in any of the subject characteristics among the three groups (Table 1). Body weight was maintained ($P > 0.05$) in all three groups over the study (PLA: 86.5 ± 22.7 vs. 85.6 ± 23.0; IBU: 78.2 ± 10.5 vs. 78.5 ± 10.2; ACET: 77.6 ± 14.9 vs. 77.2 ± 15.4 kg).

Blood and muscle intracellular free [$^2H_5$]phenylalanine enrichments did not change significantly over the time course (120–300 min) of both infusions (data not shown), which has been shown previously (6, 26, 37). Postexercise (24 h) skeletal muscle FSR was increased

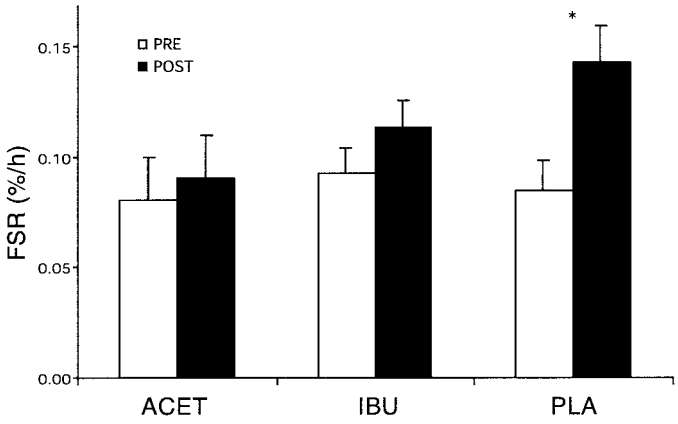

Fig. 2. FSR (%/h) of mixed skeletal muscle protein before and after the eccentric exercise bout. ACET, acetaminophen group (n = 4); IBU, ibuprofen group (n = 7); PLA, placebo group (n = 6). *$P < 0.05$ from preexercise.

76 ± 19% ($P < 0.05$) in PLA (0.058 ± 0.012%/h), and was unchanged ($P > 0.05$) in IBU (35 ± 21%; 0.021 ± 0.014%/h) and ACET (22 ± 23%; 0.010 ± 0.019%/h) (Fig. 2). Whole body phenylalanine turnover (R_a phenylalanine) was unchanged ($P > 0.05$) in response to exercise (PLA: 0.67 ± 0.05 vs. 0.63 ± 0.05 $\mu mol \cdot kg^{-1} \cdot min^{-1}$) or either drug (IBU: 0.67 ± 0.04 vs. 0.63 ± 0.03; ACET: 0.66 ± 0.05 vs. 0.62 ± 0.03 $\mu mol \cdot kg^{-1} \cdot min^{-1}$).

The CK response to the exercise was large and highly variable among the three groups. CK was significantly elevated in all three groups after the exercise, but the overall response was not different among the groups (Table 2). Because some of the nine sites did not elicit a soreness response, the average level of perceived muscle soreness underrepresented the amount of soreness that the subjects experienced. However, average and maximal ratings of perceived muscle soreness were elevated in a similar fashion after the exercise, and there was no difference among the three groups at any time point in either average or maximal soreness. Both average and maximal perceived soreness for the three groups combined increased within 1 day postexercise (4 ± 1 and 6 ± 1), peaked at 2 days postexercise (5 ± 1 and 7 ± 1), and returned to baseline by *days 6* and *7* postexercise.

DISCUSSION

Given the mechanisms of action and the widespread use of ibuprofen and acetaminophen, we believed it was necessary to better understand the potential metabolic implications of consuming these over-the-counter drugs after eccentric resistance exercise. The primary findings of this study were that ibuprofen blunted the protein synthesis response that is normally seen after the type of exercise used in this study; surprisingly, acetaminophen also had a similar effect on protein metabolism.

From our data, it appears that the mechanism of blunting protein metabolism in skeletal muscle by cyclooxygenase inhibition outlined by Rodemann and Goldberg (30) nearly 20 yr ago in rats may also be intact in humans. These authors showed an inhibition of protein synthesis in isolated rat skeletal muscle with three different cyclooxygenase inhibitors (aspirin, indomethacin, and meclofenamate). In the current study, we hypothesized that ibuprofen would also block cyclooxygenase and have a similar effect on muscle protein metabolism. However, it is difficult to determine how the amount of inhibitors (drugs) used in the previous studies that showed this effect in isolated muscles (24, 25, 30, 34) compare with the levels in human muscle after consumption of maximal over-the-counter doses of ibuprofen. Nonetheless, from our data, it is clear that the 1.2 g/day maximal over-the-counter dose of ibuprofen is potent enough to blunt the protein synthesis response to resistance exercise.

What is less clear is why acetaminophen also inhibited the increase in FSR after the resistance exercise bout. The most logical hypothesis is that acetaminophen also inhibits cyclooxygenase in skeletal muscle; however, to our knowledge, no other studies have examined the influence of acetaminophen on skeletal muscle metabolism. In addition, all of the previous data and the resultant nonperipheral effect of acetaminophen hypothesis are derived from studies of the central nervous system and other nonskeletal muscle organ studies (8, 11, 15, 32, 36).

The small sample size of the FSR values for the ACET group may appear to limit the interpretation of the findings. However, in an attempt to determine an underlying mechanism for the drug-induced blunting of the postexercise increase in FSR, we measured prostaglandin (PG)$F_{2\alpha}$ in the same muscle samples analyzed for the measurement of FSR taken during the pre- and postexercise infusions (33). $PGF_{2\alpha}$ is a product of the cyclooxygenase enzyme and has been shown to stimulate skeletal muscle protein synthesis (24, 30). Similar to the FSR results, $PGF_{2\alpha}$ after exercise was significantly increased (77%) in the PLA group, whereas it was unchanged in the ACET and IBU groups (33). Thus it appears that both ACET and IBU attenuate the postresistance exercise increase in FSR by blocking the production of $PGF_{2\alpha}$ via the cyclooxy-

Table 2. *Serum creatine kinase levels before and after the eccentric exercise bout*

Group	Pre	Post 1	Post 2	Post 3	Post 4	Post 5	Post 6	Post 7	Post 8	Post 9
ACET	74 ± 13	227 ± 52	828 ± 485	2,568 ± 1,568	4,143 ± 2,857	5,209 ± 3,052	4,837 ± 2,934	2,192 ± 1,118	1,460 ± 919	1,034 ± 647
IBU	78 ± 12	222 ± 56	200 ± 59	744 ± 352	859 ± 475	972 ± 498	819 ± 292	383 ± 142	285 ± 65	158 ± 20
PLA	76 ± 13	183 ± 78	276 ± 101	782 ± 519	1,751 ± 1,449	2,246 ± 1,965	1,697 ± 1,416	961 ± 604	575 ± 323	270 ± 163

Values are means ± SE and expressed as units per liter. Pre, preexercise; Post, hours after exercise. There were no differences ($P > 0.05$) in the responses among the 3 groups.

genase enzyme. These results, coupled with the fact that the $PGF_{2\alpha}$ measurements were completed on all eight subjects from each group, suggest that the effect of ACET on postexercise FSR is valid.

The implications of our data are important for those individuals that chronically consume either ibuprofen or acetaminophen during a period in which muscle hypertrophy is expected (i.e., resistance training). Although we did not measure the long-term effects of consumption of either of these drugs on muscle hypertrophy during resistance training, we speculate that the continued attenuation of the normal increase in protein synthesis after each resistance training bout would result in a blunting of the hypertrophic response. Our speculation assumes that the muscle protein breakdown response coincides with the protein synthesis response. This assumption seems appropriate, since the resting and postresistance exercise skeletal muscle FSR and fractional breakdown rate have been shown to be significantly correlated (26), suggesting that these two processes are linked.

Our resting (preexercise) protein synthesis (FSR) results are comparable to previous studies of young to middle-aged men in the postabsorptive state that have examined mixed muscle protein from the vastus lateralis (7, 29). The increase in FSR of the PLA group in the current study (76%) also compares favorably with previous studies when training status, dietary state, muscle studied, and the amount of exercise are considered (12, 26, 39).

In this study, we used the R_a of phenylalanine as a measure of whole body protein breakdown. Our data suggest, as others have found (26), that whole body protein breakdown is unchanged 24 h after resistance exercise. Our data also suggest that neither ibuprofen nor acetaminophen had any influence on protein breakdown at the whole body level. To this end, Gann et al. (16) have shown that chronic consumption of the NSAID indomethacin does not affect whole body protein synthesis or nitrogen retention in elderly subjects. This finding is consistent with the fact that the action of the drugs in the current study appears to be at the level of the skeletal muscle, and muscle protein metabolism constitutes only about one-third of whole body protein metabolism (21).

The exercise bout resulted in large increases in serum CK activity and ratings of perceived muscle soreness, which have been shown in previous studies (3, 13). The lack of effect of either drug on CK response to this type of exercise has also been reported (3, 9, 18), although higher prophylactic doses of ibuprofen (5 days before; 2.4 mg/day) have been shown to reduce circulating CK compared with placebo after eccentric muscular activity (28). The lack of effect of similar over-the-counter analgesic drugs on ratings of perceived muscle soreness has also been shown previously (3, 4, 9). However, Hasson et al. (18) reported that prophylactic and therapeutic doses of ibuprofen similar to those used in the current study do reduce levels of perceived muscle soreness 24 or 48 h after exercise with the use of a protocol that was less intense than the one used in the present study. It may appear somewhat surprising that neither of these drugs provided any level of analgesia compared with placebo, given the aforementioned study and the proven pain-reducing benefits of acetaminophen and ibuprofen for individuals with arthritis, headaches, and other symptoms (10, 11). However, the level of pain, soreness, and edema was high enough to severely inhibit the gait of the subjects in our study during the days after the exercise bout. It is quite possible that the level of soreness and pain was too severe for the dose of these drugs to be effective. It is also possible that the scale used for the measurement of perceived soreness among the groups was not able to discern small differences in soreness that were physiologically relevant.

We included only males in our study population, and it is unclear whether these same responses would hold in a similar group of females. However, there are no data to suggest that the metabolism of ibuprofen or acetaminophen or the mechanism of action of these two drugs is different between men and women. Furthermore, several studies of muscle protein metabolism at rest and after resistance exercise have not shown a difference between women and men (26, 27, 31, 38).

In conclusion, the increased rate of muscle protein synthesis normally seen 24 h after high-intensity eccentric resistance exercise was attenuated by consumption of ibuprofen and acetaminophen at over-the-counter levels. The long-term influence of this acute response after resistance exercise for individuals who chronically consume these (or similar) drugs cannot be determined from this study. However, long-term use of these drugs may inhibit the normal hypertrophic response to resistance training. Future studies on the impact of chronic consumption of over-the-counter doses of these drugs on skeletal muscle are warranted.

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