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Nonsteroidal Anti-Inflammatory Therapy After Eccentric Exercise in Healthy Older Individuals

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Background. Aging is associated with greater susceptibility to muscle injury and soreness after exercise. Although elderly persons regularly consume nonsteroidal anti-inflammatory drugs (NSAIDs), it is not clear that NSAIDs alleviate muscle dysfunction and/or inflammation following injurious exercise.

Methods. In this double-blind crossover study, 10 men and 5 women (aged 60 ± 2 years, mean ± *SE*) consumed naproxen sodium or placebo for 10 days after performing 64 unilateral eccentric (ECC) knee extensions using 75% of the ECC 1-repetition maximum. Strength was measured before, 3 days after, and 10 days after each bout. Injury and soreness were assessed using magnetic resonance images of m. quadriceps femoris (QF) and a visual analog scale.

Results. Three days after exercise, concentric strength loss was greater for placebo (−32 ± 9%) than NSAID (−6 ± 8%; $p = .0064$). Likewise, isometric strength declined less for NSAID than placebo (−12 ± 7% vs −24 ± 4%; $p = .0213$), and thigh soreness while rising from a chair was greater for placebo ($p \leq .0393$) than NSAID (43 ± 7 mm vs 26 ± 7 mm). QF cross-sectional area (cm^2) showing elevated T_2 was 27% and 35% greater ($p \leq .0096$) for placebo on Days 3 and 10, respectively.

Conclusions. Naproxen sodium attenuated muscle injury, strength loss, and soreness following ECC exercise in older individuals and may be beneficial during the early stages of increased physical activity.

DELAYED-ONSET soreness arises from eccentric (ECC) muscle actions (1,2). Walking down stairs, sitting down in a chair, and gardening, for example, involve ECC actions (3). Many older individuals experience disuse and weakness, due to their sedentary lifestyle, or hospitalization that may predispose them to muscle dysfunction, injury, and soreness upon remobilization or increased physical activity (4,5). Older individuals are also increasingly encouraged to become physically active or to become mobile as soon as possible following inactivity. However, older adults recover strength slower (6) and show equivalent or greater fiber damage (7–9) than young adults following ECC exercise. Older individuals also often consume over-the-counter (OCT) nonsteroidal anti-inflammatory drugs (NSAIDs) for soreness. It is not known, however, if NSAIDs protect against exercise-induced muscle injury and dysfunction in this population. We recently found that an OCT NSAID attenuated exercise-induced inflammation, strength loss, and soreness in young adult males (10). This study examined the efficacy of naproxen sodium for exercise-induced muscle strength loss, injury, and soreness in older adults.

Methods

General Design

A double-blind crossover design was used in this study (10,11). Unilateral exercise (a different limb for each trial) was performed to avoid the protective effect of ECC exercise (12,13). After 1 month of familiarization to unilateral concentric actions using each m. quadriceps femoris (QF) (4 sessions), the concentric one-repetition maximum (1-RM) and maximal isometric force were determined, and resting magnetic resonance (MR) images of both thighs were obtained (5,10,14). One week after familiarization, novel ECC exercise with the right or left QF was performed. Drug or placebo was administered over the next 10 days, beginning immediately after exercise. MR images of each QF, maximal isometric force, and 1-RM were measured on Days 3 and 10 of recovery. Perceived QF soreness was recorded on these days using a visual analog scale. After a 3-week washout, ECC exercise and outcome measurements were repeated with the contralateral QF and the drug or placebo crossed over.

Participants

Fifteen healthy, but not resistance-trained, men ($n = 10$) and women ($n = 5$) participated in this study (aged 60 ± 2 years, height 176 ± 2 cm, and weight 80 ± 4 kg; mean ± *SE*). Procedures, risks, and benefits of the study were explained, and informed written consent was obtained from each subject after approval from the Institutional Review Board of The University of Georgia. No subjects reported taking NSAIDs during the month prior to the study. During the study, participants were told to take only the prescribed NSAID or placebo.

Testing and Exercise Procedures

Unilateral QF concentric 1-RM tests and ECC exercise were performed on a knee extension machine (Badger-Magnum; Milwaukee, WI) after familiarization (5,10,13) that consisted of two 1-RM's per week for 4 weeks. The 1-RM increased about 20% over the four sessions, mainly from Week 1 to Week 2 (Table 1). The load for the ECC bout

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Table 1. Knee Extension Concentric 1-Repetition Maximum (1-RM) During Familiarization Over Four Weekly Sessions

	Week			
QF	1	2	3	4
Left	32 ± 2	37 ± 3	37 ± 4	38 ± 4
Right	33 ± 3	36 ± 4	39 ± 4	39 ± 4

Notes: Values are mean ± *SE*; $n = 15$. QF = m. quadriceps femoris. 1-RM did not differ for either QF among Weeks 2, 3, and 4 ($p \geq .3766$).

(75% of the ECC 1-RM) was estimated from the CON 1-RM for two reasons: (i) the ECC 1-RM can be estimated from the CON 1-RM and it is approximately 40% greater (15), and (ii) we did not expose subjects to ECC exercise before their ECC bout to avoid a "protective effect" (12,13). The goal of the ECC bout was to perform 8 sets of 7 to 10 ECC repetitions with 90 seconds rest between sets (5,10,13,14). The load was reduced to allow completion of 7 to 10 repetitions.

During each familiarization session, at least five maximal isometric contractions of the QF were performed on a KinCom dynamometer (Chattanooga Group, Inc., Chattanooga, TN) (13). On the day of testing, the best of five efforts (1-minute rest between efforts) was used for analysis.

Pharmacology

Participants consumed one capsule of naproxen sodium (220 mg) or placebo (sucrose) three times a day (every 8 hours) for 10 days, beginning immediately after the ECC bout. The total daily dosage (660 mg) is the maximum recommended OCT. After a 3-week washout, subjects performed the second ECC bout (using the contralateral QF) before undergoing the crossed-over treatment for 10 days. Capsules were prepackaged such that neither the investigator nor the participants knew condition of the capsules. All capsule containers returned to the investigator after the study were empty, suggesting 100% compliance.

Magnetic Resonance Imaging

Muscle injury was assessed with MR imaging (5,10,14). Transaxial images (TR/TE 2000/30 60, 256 by 256 matrix, 40 cm FOV, 1 NEX) 1.0-cm thick with a 0.5-cm gap between slices were obtained from the knee joint to the head of the femur. MR images were transferred to a Macintosh (Cupertino, CA) computer for determination of muscle cross-sectional area (CSA) and T_2 using NIH Image (National Institutes of Health, Bethesda, MD; 5,10,14). For each participant, data were averaged over the 12 contiguous images immediately inferior to the m. gluteus maximus. The reliability (squared intraclass correlation coefficient [R^2]) of a CSA measure on different days was .98.

Soreness Ratings

Subjects rated soreness in each QF on a visual analog scale when seated with the hips and knees at approximately 90° and while standing up without upper body assistance (16). The 100-mm visual analog scale was anchored with "no pain" and "extremely painful."

Statistical Analyses

Variables were analyzed with a two-way repeated measures (treatment × time) ANOVA. If the sphericity assumption was not met, the Huyne-Feldt adjustment was made to the level of probability so that the *F* ratio was not positively biased (17). Specific differences were analyzed by the least squares means test. The level of statistical significance was set at $p < .05$. All data are presented as mean ± *SE*.

RESULTS

Muscle Strength After ECC Exercise

The 1-RM showed a treatment-by-time interaction ($p = .0064$) due to a greater loss for placebo (−32 ± 9%) than NSAID (−6 ± 8%) 3 days after exercise (Table 2). By Day 10, 1-RM returned to baseline under both conditions. The placebo trial also resulted in a greater loss ($p = .0213$) of maximal isometric force (−24 ± 4%) than NSAID (−12 ± 7%) 3 days after exercise (Table 2). Additionally, isometric strength during the placebo trial was depressed 9 ± 5% below baseline 10 days after the ECC bout ($p = .0226$) but had recovered fully with NSAID.

Muscle Soreness

Seated QF soreness did not show a main effect for treatment or treatment-by-time interaction ($p \geq .3816$). However, upon standing, less soreness was reported with the drug than with placebo 3 days after the ECC bout ($p \leq .0393$) (Table 2).

Muscle Injury

The relative CSA with an elevated T_2 was 27% and 35% greater ($p \leq .0096$) for placebo than NSAID on Days 3 and

Table 2. Strength, Soreness, and Magnetic Resonance Image Data of M. Quadriceps Femoris Before and 3 and 10 Days After Eccentric Exercise With (NSAID) or Without (placebo) Naproxen Sodium

		Time		
Variable	Group	Before Exercise	3 Days After Exercise	10 Days After Exercise
1-RM, kg	NSAID	39 ± 2	37 ± 1	38 ± 1
	Placebo	40 ± 1	27 ± 1	36 ± 1
Isometric force, N	NSAID	474 ± 25	417 ± 35	458 ± 31
	Placebo	489 ± 31	374 ± 31	447 ± 33
QF CSA, cm^2	NSAID	54 ± 3	59 ± 3	58 ± 3
	Placebo	53 ± 3	60 ± 4	61 ± 4
QF %CSA	NSAID	8 ± 4	27 ± 4	18 ± 4
	Placebo	9 ± 1	38 ± 5	29 ± 4
QF T_2, ms	NSAID	32 ± 1	36 ± 1	35 ± 1
	Placebo	32 ± 1	37 ± 2	36 ± 1
Soreness, mm	NSAID	0 ± 0	26 ± 7	2 ± 4
	Placebo	0 ± 0	43 ± 7	1 ± 1

Notes: Values are mean ± *SE*; $n = 15$. NSAID = nonsteroidal anti-inflammatory drug; QF = m. quadriceps femoris; CSA = cross-sectional area; QF %CSA = relative CSA of QF with elevated T_2. Soreness = soreness of the QF when rising from a chair rated on a 100-mm visual analog scale. One-repetition maximum, isometric force, QF %CSA, and soreness showed significant group-by-time interaction, with lesser responses for NSAID 3 days after exercise. QF CSA and QF T_2 showed time effects. See Results for *p* values.

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10 of recovery, respectively (Table 2). Neither CSA of the QF nor whole muscle T_2 showed a main effect for treatment or treatment-by-time interaction ($p \geq .7951$) (Table 2). Following novel ECC exercise, the time effect for CSA (cm^2) of the QF ($p = .0001$) was reflected in the 11 ± 2% increase on Day 3 that had not recovered by Day 10 (Table 2). Whole-muscle T_2 increased ($p = .0001$) from 32.01 ± 0.30 milliseconds to 36.47 ± 0.94 milliseconds, pre-exercise to Day 3, and remained elevated on Day 10 ($p = 0.0007$) (Table 2).

Discussion

This study examined the efficacy of an OCT NSAID for exercise-induced muscle dysfunction, damage, and soreness in 55- to 64-year-old subjects. Our subjects, methods, and experimental design were selected for several reasons. Older individuals are encouraged to exercise to prevent a decline of physical function. However, older individuals show equivalent or greater muscle fiber damage and soreness and slower strength recovery after novel exercise than younger individuals (6–9). Strength decrements may be especially precarious for older individuals because weakness is strongly associated with falls, the most common cause of accidental injury in the older persons (4). Although the participants in this study were not frail, members of this age group are at increased risk of falls and have an increased fear of falling and reduced physical activity (18). Age-associated changes in neuromuscular function and mobility have been noted in 60-year-old subjects (19). Also, many persons beyond this age (>70 years) have a history of chronic NSAID use that might confound the examination of a drug's efficacy and/or increase the risk of gastrointestinal bleeding or other side effects. The QF was studied because knee extension strength is important for activities requiring mobility, such as rising from a chair (20). Tokuhiro and colleagues (21) also observed increased electromyographic activity of knee extensors during downhill walking, presumably to stabilize the knee. The unilateral exercise regime we employed isolates the QF from other muscle groups (5,10,14) and induces muscle injury, soreness, and strength loss (1,5,10,13,14). Likewise, transverse (spin-spin) relaxation time (T_2) in MR images of muscle are increased following ECC exercise-induced muscle injury (22–29). Additionally, acute increases (5–10%) in muscle CSA in MR images following ECC exercise reflect edema (22–29).

The 1-RM and isometric strength were reduced 32% and 24%, respectively, 3 days after ECC exercise. This compares well with responses in younger groups (5,10,13,14). Also, the QF showed increases in CSA and T_2 on Day 3 of recovery; these increases were comparable to previous research in young adults (10). The placebo group experienced injury in approximately 40% of the muscle as reflected by T_2 contrast shifts. This agrees with other studies that indicate that ECC exercise may damage ≥50% of the fibers in the involved muscle (1,7) but is greater than the values reported more recently (8,9).

The primary finding of this study was that naproxen sodium attenuates the loss of muscle function following ECC exercise. This was mostly likely mediated by the anti-inflammatory actions of the drug on the exercised muscle tissue. Naproxen sodium is both an analgesic and an anti-inflammatory that competitively inhibits the cyclooxygenase enzyme, thereby reducing prostaglandin E_2 (PGE_2) synthesis. By reducing the perfusion and/or muscle protein degradation triggered by PGE_2, naproxen may also reduce muscle edema following injurious exercise (30). Naproxen may also relieve soreness by desensitizing type IV afferent nerve endings, which transmit dull, aching pain to higher centers via PGE_2 (30). We have suggested that NSAIDs reduce exercise-induced muscle injury and dysfunction by attenuating the inflammatory response (10). As in that report, drug treatment was initiated in this study following exercise. Hence, naproxen could only have affected events subsequent to the ECC bout, rather than those that caused the initial injury.

The present observations agree with our strength and muscle injury data from younger participants who exercised with 85% of the ECC 1-RM (10). The younger volunteers also reported less muscle soreness during naproxen sodium treatment (10). However, the younger subjects reported mean values ≥75 mm on the analog scales, whereas the older participants of the present study averaged 42 mm on Day 3 of recovery (Table 2). The older participants also did not report soreness under either condition during seated rest, perhaps because type IV muscle afferent (nociceptor) nerve endings were not stimulated in the quiescent QF. Although PGE_2 release may increase in with aging (31), type IV free nerve endings may also become less sensitive to prostaglandins. Regardless of the mechanism, a deficit in soreness perception may have significance for older individuals during activities that could exacerbate injury and weakness and/or put them at a greater risk of falling. In this regard, it should be noted that naproxen reduced muscle soreness during activity (Table 2) but did not completely abolish muscle injury or weakness. This suggests that older individuals using NSAIDs should be reminded that function may be compromised despite soreness relief.

Although neither CSA nor T_2 differed by trial, the relative area of the QF with elevated T_2 (i.e., damaged muscle) was less with naproxen. These results are similar to those reported for young adults (10), suggesting that NSAIDs attenuate the expression of the inflammatory response to exercise-induced muscle fiber injury, thereby limiting secondary injury.

Although NSAIDs are commonly used, only a few studies have evaluated their efficacy in younger individuals (10,11,32–37). The investigations that have failed to substantiate the anti-inflammatory properties of NSAIDs after muscle injury have used unreliable markers of muscle injury (plasma creatine phosphokinase) (35), exercised the same musculature repeatedly (35,36)—likely protecting the tissue against further injury after the initial bout (12,13)—and/or examined trained subjects (36,37) who are less susceptible to muscle injury. Conversely, Hasson and colleagues (33) found that administering ibuprofen 24 hours before or immediately after exercise and for 3 days thereafter attenuated strength decrements and blunted muscle soreness.

Our data strongly suggest that NSAIDs ameliorate muscle injury and dysfunction following novel ECC actions in older persons, although further evaluation of these drugs is

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necessary. For example, Mishra and colleagues (38) showed that NSAIDs attenuated force decrements in isolated rabbit muscle early after ECC actions but exacerbated the force deficit 1 month after injury. They cautioned against the liberal use of NSAIDs, which is common among elderly persons. On the other hand, approximately 1 month following NSAID therapy in the present study, muscle strength and MR images indicated full recovery from the ECC bout (unpublished results). Nonetheless, the side effects of NSAIDs (e.g., gastrointestinal and hepatic stress) mandate proper medical supervision during prolonged use.

In summary, naproxen sodium administered for 10 days immediately after novel ECC exercise attenuated muscle injury and soreness and improved strength recovery in older individuals. These results suggest that NSAIDs might benefit older individuals embarking on a novel program of physical activity that might induce muscle injury and soreness and/or compromise function during everyday activities.

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