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Acute ibuprofen ingestion does not attenuate fatigue during maximal intermittent knee extensor or all-out cycling exercise

Original investigation

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ABSTRACT

Purpose: Recent research suggests that acute consumption of pharmacological analgesics can improve exercise performance, but the ergogenic potential of ibuprofen (IBP) administration is poorly understood. This study tested the hypothesis that IBP administration would enhance maximal exercise performance. **Methods:** In one study, 13 physically active males completed 60×3 -s maximum voluntary contractions (MVC) of the knee extensors interspersed with a 2-s passive recovery period, on two occasions, with the critical torque (CT) estimated as the mean torque over the last 12 contractions (part A). In another study, 16 active males completed two 3-min all-out tests against a fixed resistance on an electrically-braked cycle ergometer with the critical power (CP) estimated from the mean power output over the final 30-s of the test (part B). All tests were completed 60 min after ingesting maltodextrin (placebo, PL) or 400 mg of IBP. Peripheral nerve stimulation was administered at regular intervals and electromyography was measured throughout. **Results:** For part A, mean torque (IBP: 60 ± 12 vs. PL: $58 \pm 14\%$ of pre-exercise MVC) and CT (IBP: 40 ± 15 vs. PL: $41 \pm 16\%$ of pre-exercise MVC) were not different between conditions ($P > 0.05$). For part B, end-test power output (IBP: 292 ± 28 W vs PL: 288 ± 31 W) and work done (IBP: 65.9 ± 5.9 kJ vs PL: 65.4 ± 6.4 kJ) during the 3-min all-out cycling tests were not different between conditions (all $P > 0.05$). For both studies, neuromuscular fatigue declined at a similar rate in both conditions ($P > 0.05$). **Conclusion:** Acute ingestion of 400 mg IBP does not improve single-leg or maximal cycling performance in healthy humans.

Key words: Electromyography; neuromuscular fatigue; non-steroidal anti-inflammatory drugs; single leg exercise; whole-body cycling exercise

INTRODUCTION

Ibuprofen (IBP), a non-steroidal anti-inflammatory drug (NSAID) predominantly used to treat pain and reduce inflammation and fever, is considered safe for oral ingestion within healthy populations at the standard therapeutic dose (Albert & Gernaat, 1984; García-Martín et al. 2004). Consequently, utilisation of analgesic (i.e., pain relieving) and anti-inflammatory medication, such as IBP, has emerged as a popular pre-competition strategy in elite athletes attempting to enhance athletic performance (Alaranta et al. 2008; Corrigan & Kazlauskas, 2003; Da Silva et al. 2015; Gorski et al. 2011; Huang et al. 2006). It is believed that NSAIDs act centrally and peripherally to reduce the perception of pain and tissue inflammation, respectively (Friden & Lieber, 1992). The therapeutic effect of NSAIDs in treating inflammation and pain has largely been ascribed to inhibited synthesis of prostaglandins (i.e. PGE₂, Friden & Lieber, 1992). Specifically, IBP limits the metabolism of arachidonic acid, a precursor for the synthesis of prostaglandins, by inhibiting the enzyme, cyclooxygenase (Albert & Gernaat, 1984).

Following the onset of muscle contractions, changes in contraction-induced mechanical stimuli and noxious chemicals (**including an increased PGE₂ release**) activate and/or sensitise molecular receptors located on the terminal end of group III and IV nerve fibers, contributing to an increased sensation of muscle pain during exercise (O'Connor & Cook, 1999; McCord & Kaufmann, 2010; Pollak et al. 2014). The activation of these receptors appears to play a role in neuromuscular fatigue development through modulating both central and peripheral fatigue. Indeed, when the ascending projection of group III and IV muscle afferents is attenuated via intrathecal fentanyl administration, central motor drive is increased (as inferred via electromyography, EMG) and peripheral fatigue development is expedited (Amann et al. 2009, 2011; Blain et al. 2016). Therefore, it is possible that an intervention that is able to

reduce the magnitude of afferent feedback, such as NSAID administration, may attenuate the decline in skeletal muscle activation during intense exercise and thus improve exercise performance (Amann & Calbet, 2008; Morgan et al. 2018a; Morgan et al. 2018b). Indeed, elevating the magnitude of muscle afferent feedback is known to impair endurance exercise capacity (i.e. Amann et al. 2013).

Acute consumption of analgesics (e.g. **acetaminophen, ACT**) has been shown to improve exercise performance (Foster et al. 2014; Mauger et al. 2010; Morgan et al 2018a; Morgan et al. 2018b). Mauger et al. (2010) administered an acute dose of 1.5 g ACT to trained cyclists and reported a 2% improvement in 16.1-km time-trial (TT) performance. Moreover, an acute dose of ACT has been shown to improve exercise tolerance in the heat (Mauger et al. 2014), repeated sprint performance (Foster et al. 2014), repeated maximal voluntary contraction (MVC) performance of the knee extensors (Morgan et al. 2018a) and maximal cycling performance (Morgan et al. 2018b). However, while these studies suggest that oral administration of a commercially-available pharmaceutical analgesic can delay fatigue development and improve exercise performance (Foster et al. 2014; Mauger et al. 2010; Morgan et al 2018a, b), the ergogenic effects of IBP are unclear despite widespread use of IBP as a putative performance aid (Cleak, & Eston. 1992; Nosaka & Clarkson, 1996).

In contrast to the effects of ACT consumption on exercise performance, there is currently very limited published research on NSAID and NSAID-like compounds during exercise when muscle damage is not present. Despite the prevalence of its use amongst athletic populations, it is unclear whether IBP will provide an ergogenic benefit to performance in a ‘fresh’ state. Other NSAID-like compounds have elicited no ergogenic effect on endurance performance (e.g., aspirin, Cook et al. 1997; ginger, Black & O’Connor, 2008). In contrast,

enhanced aerobic exercise performance following caffeine ingestion has been related, at least in part, to altered pain perception and enhanced endurance performance (e.g., Gonclach et al. 2016). In addition, whilst exercise has been shown to increase PGE₂ release (Trappe et al. 2001; Novak & Wennmalm, 1979; Wilson & Kapoor, 1993; Vinikka et al. 1984), the extent to which it plays an important role, especially following interventions aimed at reducing PGE₂ synthesis, during endurance exercise in the absence of muscle damage is unclear.

The purpose of this study was to test the hypotheses that, compared to a placebo, acute consumption of 400 mg IBP would increase total work done, and reduce the rate of fatigue development by enabling a better maintenance of muscle activation during exercise. Two studies are presented using two different types of exercise: a 5-min single-leg intermittent MVC test and a 3-min maximal whole body cycling test to provide a more comprehensive understanding of the ergogenic potential of IBP.

MATERIALS AND METHODS

Participants

Two independent groups of thirteen recreationally-active males (mean $\pm$ SD: age 31 ± 7 years, height 1.76 ± 0.08 m, body mass 75 ± 11 kg), and sixteen recreationally-active males (mean $\pm$ SD: age 29 ± 9 years, height 1.79 ± 0.07 m, body mass 77 ± 8 kg, $\dot{V}O_{2peak}$ 60.8 ± 7.8 ml·kg⁻¹·min⁻¹), volunteered for the first (A) and second (B) part of this study, respectively. All participants provided written, informed consent to participate in this study, which was approved by the Sport and Health Sciences Ethics Committee at the University of Exeter. After being informed of the experimental procedures and associated risks, all participants completed a medical health questionnaire to ensure it was safe for them to consume IBP prior to performing exhaustive exercise, due to the potential contraindications associated with IBP

99 **ingestion.** Participants were not consumers of any ‘pain relief’ or anti-inflammatory
100 medication (prescription or non-prescription) over the course of the study. None of the
101 participants had a history of motor or neurological disorders. Participants were instructed to
102 arrive at the laboratory in a rested and fully hydrated state, at least 3 h post-prandial, and to
103 avoid strenuous exercise and refrain from consuming caffeine and alcohol in the 24 h
104 preceding each testing session. **Participants were also instructed to consume their habitual**
105 **diet and continue normal training activities for the experimental period. For part A and B,**
106 **participants recorded their diet and physical activity for 7 d prior to the first experimental**
107 **visit and then replicated this for all remaining experimental visits.**

109 *Experimental Design*

110 Both protocols (part A and B) followed identical experimental designs to previous research
111 conducted within our laboratory (Morgan et al. 2018a, 2018b). For part A (Morgan et al.
112 2018a), participants visited the laboratory on three occasions over a 3-4 week period with
113 tests being conducted on an isokinetic dynamometer (Biodex System 3, Shirley, NY, USA).
114 For part B (Morgan et al. 2018b), participants visited the laboratory on five occasions over a
115 5-6 week period and tests were conducted on an electronically braked cycle ergometer (Lode
116 Excalibur Sport, Groningen, the Netherlands). **Experimental tests were separated by at least**
117 **7, but no more than 9, days (part A) and for at least 72 h (part B),** and were completed at a
118 similar time of day ($\pm$ 90 mins). The first laboratory visits for each study were used to
119 familiarise participants to the measurements and experimental protocols described below.
120 Subsequently, participants performed the fatiguing protocol (s) under two conditions (*see*
121 *‘Experimental Protocol’*): placebo (PL) and IBP.

123 *Experimental Protocol A (60 MVC protocol)*

The isokinetic dynamometer was initially adjusted so that the axis of rotation of the lever arm was in line with the lateral epicondyle of the right femur. Participants were seated with the hip and knee joints at relative angles of 155° and 90°, respectively. The remainder of the chair settings were recorded (during familiarisation) and replicated in all subsequent tests to ensure identical body position throughout the experimental trials. Inelastic padded Velcro straps were fastened at the ankle, quadriceps, hip and shoulders to maintain a stable body position.

Following the familiarisation trial, visits 2 and 3 were completed in a double-blind, randomised fashion using a cross-over experimental design. 1000 mg of maltodextrin (placebo) or 400 mg IBP (combined with 600 mg maltodextrin) was ingested orally, 60 minutes prior to the exercise bout such that the start of the exercise trial was expected to coincide with peak plasma [ibuprofen] concentration (Janssen & Venema, 1985). For IBU, 2 identical capsules containing 200 mg ibuprofen and 300 mg maltodextrin each were ingested. The placebo was made from dextrose powder inserted into 2 gelatine capsules (500 mg in each capsule) designed to have a similar appearance and the weight to IBU capsules. The trials started with a standardised isometric warm-up routine (10 isometric contractions for 3 s at 50% of pre-exercise MVC as measured during familiarisation testing) and testing of the optimal EMG electrode, anode, and cathode placement and stimulation intensity for peripheral nerve stimulation. The experimental protocol consisted of 60 brief MVCs (3 s contraction, 2 s rest), in response to a visual prompt to ‘go’ and ‘relax’, accompanied by the same verbal instructions from the experimenter. Every 6th contraction was accompanied by peripheral nerve stimulation during and 1 s post MVC (as described for pre-trial measurements below). Participants were not made aware of the time or the number of MVCs

that had elapsed during the protocol and were instructed to continue to perform maximal contractions throughout.

Experimental protocol B (3-min cycling test)

For the 3-min cycling protocol, participants initially completed an incremental ramp test to exhaustion for the determination of gas exchange threshold (GET), linear factor, peak aerobic power output and peak oxygen uptake $\dot{V}O_{2peak}$ as previously described (Black et al. 2014; Morgan et al. 2018b). The fixed resistance for the 3-min cycling protocol was set using the linear mode (i.e. linear factor) of the ergometer such that on reaching their preferred cadence, the participants would achieve a power output equivalent to 50% of the difference between GET and $\dot{V}O_{2peak}$ (linear factor = $50\% \Delta$ peak aerobic power output/preferred cadence²). During this visit, the seat and handlebar positions were adjusted for comfort and replicated for all tests. During the second and third laboratory visits, participants completed a 3-min all-out test with these serving as familiarization trials to the experimental protocol as described below and to ensure the coefficient of variation for work done and critical power (CP) between visits was <1%. Participants then performed the 3-min all-out cycling test under two conditions: placebo (PL) and IBP.

The experimental protocol consisted of a 3-min period of unloaded pedalling at each participant's preferred cadence (85-100 rpm), followed by a 3-min all-out sprint, 60 min following ingestion of either placebo (1000 mg maltodextrin) or 400 mg of IBP. The order of trials on visits 4 and 5 were administered in a double-blind, randomised fashion using a cross-over experimental design. The 3-min all-out cycling protocol used in this study replicated the procedures described previously by Vanhatalo et al. (2007, 2008).

Neuromuscular function (Parts A and B)

For part A and B, neuromuscular function was assessed pre-, during- and post-trial (< 10 s). Single peripheral nerve stimulation pulses were manually triggered at rest to determine pre-exercise neuromuscular function, namely the characteristics of the M-wave response (M-wave amplitude; $M_{\max}$) to supra-maximal nerve stimulation, voluntary activation (for part A only) and potentiated twitch torque (pTw, for part A only). During MVCs, peripheral nerve stimulation pulses were triggered to occur as soon as a peak torque was achieved (typically 1.5 s into a 3 s contraction) and were each separated by a 45 s rest period. The stimuli were also delivered 1-s after the cessation of the contraction to provide a resting pTw. Identical measurements were repeated as soon as possible (< 10s) after the fatiguing exercise to determine post-exercise neuromuscular function (see figure 1).

Torque (Part A)

For part A, knee-extensor torque from the Biodex isokinetic dynamometer was sampled at 1000 Hz and low-pass filtered at 40 Hz, before being displayed on a wide screen monitor using Spike2 (CED, Cambridge, UK). Torque was expressed throughout as a percentage (%) of initial pre-exercise MVC.

Breath-by-breath pulmonary gas exchange (Part B)

For the 3-min maximal cycling protocol, participants wore a face mask connected to an impeller turbine transducer assembly (Cortex Metalyzer, Cortex, Leipzig, Germany). Inspired and expired gas volume and concentration signals were continuously sampled at 100 Hz. The analyser was calibrated before each test with gases of known concentration, and a calibration syringe of known volume (3-L; Hans Rudolph, KS).

Electromyography (Parts A and B)

For parts A and B, surface EMG activity was recorded from *m.vastus lateralis*, *m.vastus medialis* and *m.rectus femoris* of the quadriceps and *m.biceps femoris* of the hamstring of the right leg using active bipolar bar electrodes in a single differential configuration (DE2.1, DelSys Inc, Boston, MA, USA). The electrodes were placed over the respective muscle bellies (SENIAM guidelines). Double-sided adhesive tape and a hypoallergenic medical tape were used to ensure the EMG sensor stability. The skin area underneath each EMG electrode was shaved, then exfoliated and cleaned with alcohol to minimise the skin impedance. The EMG and torque signals were pre-amplified (1,000 x), band-pass filtered (20–450 Hz, Bagnoli-8, DelSys Inc, Boston, MA, USA), and then transferred to a computer with a sampling frequency of 2 kHz and high-pass filtered at 10 Hz. EMG and torque data were recorded continuously and digitised synchronously with 16 bit resolution via an A/D converter (± 5 V range, CED 1401 power, Cambridge, UK). EMG was average rectified using the root mean square method (EMG_{RMS}). EMG_{RMS} was then normalised to the pre-exercise maximum (or maximal EMG signal) and the local M-wave amplitude (closest time point measure of the M-wave) in order to exclude any changes to the EMG trace to changes in local excitability. The ground electrode was placed over the patella of the right leg.

Peripheral Nerve Stimulation (Parts A and B)

Electrical stimulation was applied with a constant current stimulator (Digitimer Stimulator DS7A, Digitimer, UK) for the assessment of M-waves (parts A and B) and potentiated twitch force (part B). M-waves were elicited by supramaximal percutaneous electrical stimulation of the femoral nerve (200 μ s duration). The cathode was placed over the femoral nerve in the inguinal fossa, approximately 3–5 cm below the inguinal ligament in the femoral triangle. The cathode was systematically moved vertically and horizontally and the amplitude of the

muscle action potential (i.e. M-wave) was monitored to identify the optimal position of the cathode for attaining maximal peak-to-peak M-wave amplitude. Once the M-wave was elicited, the maximum amplitude (peak-to-peak) of the M-wave was determined ($M_{\max}$) for the vastus lateralis and vastus medialis. To determine the stimulation intensity, single stimuli were delivered in 20 mA step-wise increments from 100 mA until a plateau in quadriceps pTw (part A only) and M-wave were observed. To ensure a supramaximal response, the current was increased by an additional 30% (mean $\pm$ SD current = 214 ± 66 mA; 251 ± 46 mA, part A and B, respectively). The average $M_{\max}$ was obtained from 3 stimuli, with ~8-10 s separating each pulse at rest. For the 3-min maximal cycling protocol, single peripheral nerve stimulation pulses were manually triggered at 'rest' (defined as 80 rpm at 20 W) to determine pre-exercise neuromuscular function. Initially, the crank angle at which peripheral nerve stimulation was to be delivered during the trials was determined for each subject as described by Black et al. (2014) and as performed by Sidhu et al. (2012). Peripheral nerve stimulation pulses were triggered to coincide with maximal muscle activation around the crank cycle (typically around 50-60° from top-dead centre) 3 times, randomly, during a 10 s period using a custom written sequencer script. Identical measurements were repeated every 30 s in the all-out sprint.

Data Analyses

Data were analysed using a custom written script developed in Spike2 software (CED, Cambridge, UK). For part A, mean torque for each 3 s contraction during the 60 MVC protocol was determined as the mean value over a 1-s period which approximated the plateau level of the highest torque (i.e. 500 ms before and after the peak torque). The pTw was calculated as the peak torque achieved following the single pulse delivered 1-s post-MVC. The twitch torque superimposed onto the peak force production of the MVC (sTw) was

calculated as the increment in torque immediately following the pulse during MVCs. The end-test torque (i.e. critical torque, CT) during the 60 MVC test was defined as the mean of the last 12 contractions (i.e., the last 60 s; Burnley, 2009; Morgan et al. 2018a). The torque-impulse was calculated as the area under the torque-time curve by accumulating the time integral of each MVC (3 s).

Voluntary activation (VA, %) was calculated using the interpolated twitch method from peripheral nerve stimulation (Merton, 1954; Goodall et al. 2010). Specifically, the increment in torque evoked during the MVCs was expressed as a fraction of the amplitude of the potentiated twitch produced with the same stimulus in the relaxed muscle post-MVC. The level of voluntary drive was then quantified as a percentage: $[1 - \text{evoked torque (superimposed on voluntary torque, sTw)} / (\text{mean control evoked response, pTw}) \times 100]$ (i.e., Allen et al. 1998). The changes in voluntary torque and pTw, were used to assess global fatigue and peripheral fatigue, respectively with VA, M_{Max} and EMG_{RMS} used to assess central fatigue. The maximal EMG was taken from the first MVC during the 60 MVC task and compared to the last MVC at task end. The neuromuscular parameters extracted from the three sets of maximal contractions completed post-exercise were tested for statistical differences between sets of contractions and then compared to the first set of MVCs completed pre-exercise (Froyd et al. 2013; Pageaux et al. 2015; Doyle-Baker et al. 2017). Neuromuscular function was also measured for each of the stimulated contractions during the exercise and normalised to the corresponding pre-exercise values at 100% MVC.

For the 3-min cycling protocol (part B), the end-test power (i.e. CP) during the 3-min test was defined as the mean of the last 30 s (Vanhatalo et al. 2007; 2008). The W' was calculated as the area above the CP from the power-time curve. Power output was recorded second-by-

second, and the peak power was determined as the highest 1-s value. The changes in power output, M_{Max} and EMG_{RMS} , were used to quantify neuromuscular fatigue development and changes in muscle activation. Peak $\dot{V}O_2$ was determined as the highest value recorded in a 15-s interval. The achievement of $\dot{V}O_{2peak}$ was an essential criterion for a valid 3-min test. All neuromuscular parameters and torque were averaged across the protocol using 30-s bin averages.

Statistics

Paired-samples *t*-tests were used to compare the mean torque, total work done, CT, W' and pTw between IBP and PL in part A. In addition, paired-samples *t*-tests were used to compare the total work done, CP, W' and cardiorespiratory responses between IBP and PL obtained from the 3-minute maximal cycling test. For the 60 MVC test, the profiles of VA and M-wave amplitude were analysed using two-way ANOVAs with repeated measures (using 12 contraction averages; i.e. 6 time points). In addition, a two-way ANOVA with repeated measures (condition $\times$ work rate) was used to assess differences in end exercise $\dot{V}O_2$ and the profiles of EMG and M-wave amplitude. Normalised EMG_{RMS} were analysed using two-way ANOVAs with repeated measures using 30-s means (i.e. 10 time points). Where sphericity was violated, Greenhouse-Geisser correction factor was used. For all tests, results were considered statistically significant when $P < 0.05$. Data are presented as means $\pm$ SD unless otherwise indicated. All statistical analyses were conducted using IBM SPSS Statistics version 23.

RESULTS

Part A (60 MVC test)

The mean MVC torque achieved prior to the 60 MVC protocol was 232 ± 47 and 230 ± 55 N.m for PL and IBU, respectively. VA of the knee extensors achieved during the preliminary MVCs was 88 ± 7 and $89 \pm 6\%$ for PL and IBU, respectively. Baseline MVC and VA were not different between conditions ($P>0.05$). The profile for mean torque during each contraction across all participants for the 60 MVC protocol is illustrated in figure 2a. During the PL trial, torque declined from a peak of $99 \pm 3\%$ MVC (relative to pre-exercise MVC) during the first contraction to $40 \pm 15\%$ MVC during the last 12 contractions ($P<0.01$, Table 1, figure 2a). During the IBP trial torque declined from a peak of $99 \pm 3\%$ to $41 \pm 16\%$ MVC. The mean torque (relative to pre-exercise MVC) achieved across the 60 MVCs not different with IBP ($60 \pm 13\%$, 87.1 ± 22.2 N.m,) compared to PL ($58 \pm 14\%$, 83.8 ± 22.7 N.m, $P=0.39$). There was no difference in CT (PL: $40 \pm 15\%$ vs. IBP: $41 \pm 16\%$, $P=0.74$), W' (PL: 6.97 ± 2.43 vs. IBP: 7.23 ± 3.57 N.m.s; $P=0.69$) or total impulse, the surrogate measure of total work done (PL: $22,055 \pm 3,885$ vs. IBP: $22,919 \pm 3,394$ N.m.s; $P=0.26$) between the PL and IBP conditions.

Part A (Neuromuscular Function)

Alongside the decline in voluntary force (figure 2a), pTw (figure 3a), VA (figure 3b), EMG_{RMS} (figure 3c) and M_{Max} (figure 3d) were also reduced as protocol A progressed (main effect of time, all $P<0.01$). There were no differences between PL and IBP in pTw, VA, EMG amplitude or M-wave amplitude at any time point (all $P>0.05$). pTw declined from 63 ± 14 to 30 ± 21 N.m and from 68 ± 17 to 31 ± 23 N.m, VA declined from 89 ± 8 to $59 \pm 19\%$ and from 88 ± 7 to $60 \pm 18\%$, EMG declined from 99 ± 4 to $59 \pm 17\%$ and 100 ± 2 to $64 \pm 20\%$ (from first 6 to last 6 contractions) and M-wave amplitude declined from 100 ± 1 to $96 \pm 14\%$ and 100 ± 1 to $95 \pm 12\%$ in the PL and IBP conditions, respectively ($P<0.05$), with no differences between PL and IPB for any of these variables ($P>0.05$).

Part B (3-min cycling test)

The mean power output profile for all participants during the 3-min all-out cycling test is shown in figure 2b for the PL and IBP conditions. During the PL trial, power output declined from 820 ± 139 W to 288 ± 31 W during the last 30 s of the 3-min test ($P < 0.01$; table 1, figure 2b). During the IBP trial, power output declined from 816 ± 131 W to 292 ± 28 W during the last 30 s of the 3-min test. There were no differences in CP (PL: 288 ± 31 vs. IBP: 292 ± 28 W, $P = 0.11$), total work done (PL: 65.4 ± 6.4 vs. IBP: 65.9 ± 5.9 kJ, $P = 0.11$) or W' (PL: 13.6 ± 2.4 vs. IBP: 13.7 ± 2.8 kJ, $P = 0.84$) between conditions.

Part B (Neuromuscular Function)

Similar to the 60 MVC protocol, alongside the decline in power output, there was a progressive decline in M-wave ($P < 0.01$, figure 4b) and EMG amplitudes ($P < 0.01$, figure 4a). The profiles of the M-wave and EMG amplitudes were not altered following IBP ingestion at any time point (both $P > 0.05$). Using 30 s mean values, EMG decreased from 94 ± 4 to $54 \pm 17\%$ and from 96 ± 6 to $57 \pm 14\%$ (figure 4b) in PL and IBP, respectively.

DISCUSSION

Contrary to our experimental hypotheses, the principal findings of this study were that acute ingestion of 400 mg of IBP in a 'fresh' state had no effect on fatigue development or neuromuscular function during either a 5-min single-leg intermittent MVC test or a 3-min maximal cycling test. Across both protocols, power output and torque declined, and neuromuscular fatigue was evident in both the IBP and PL conditions. However, there were no differences in CT or CP, total work done or neuromuscular fatigue markers between the

IBP and PL conditions. These findings do not support the acute ingestion of IBP as a strategy to blunt fatigue development during exercise in healthy, recreationally active adults.

Effects of acute IBP ingestion on exercise performance

In contrast with our previous findings of improved CT and CP following the acute ingestion of ACT (Morgan et al. 2018a; Morgan et al. 2018b), these variables were not improved in the current study following the acute ingestion of IBP. However, our findings in the current study are in line with some previous observations that IBP ingestion does not improve performance during whole body exercise in humans (e.g., Cleak, & Eston. 1992; Da Silva et al. 2015; Nosaka & Clarkson, 1996; Tokmakdis et al. 2003). Previous studies that have reported improved exercise performance following IBP administration have typically assessed exercise performance following muscle damage. Nonetheless, while there is some evidence to suggest that the increases in muscle soreness, pain, damage and contractile dysfunction after contraction-induced muscle damage can be attenuated following NSAID administration (Ebbeling & Clarkson, 1989; Hasson et al. 1993; Pizza et al. 1999; Tokmakdis et al. 2003), there is also evidence that NSAID administration does not impact these variables after muscle damage is induced (Da Silva et al. 2015; Tokmakdis et al. 2003). Taken together, these observations suggest that the ergogenic potential of administering IBP, a purported analgesic and anti-inflammatory agent (Friden & Lieber, 1992), is limited without prior induction of muscle damage, and even when muscle damage is induced, and inflammation and pain sensation are correspondingly increased, the effect of IBP ingestion on exercise performance is equivocal.

One explanation for the lack of performance improvement following IBP ingestion in our study may be the reduced ability to regulate the distribution of effort (i.e., pacing strategy) in

the maximal protocols employed in response to a potential modulation of pain. For example, Mauger et al. (2010) reported that pain` sensation was reduced (i.e., a greater power output was possible for the same pain sensation) and cycling time trial performance was enhanced following ingestion of ACT. Similarly, Gonglach et al. (2016) reported that manipulating pain perception via caffeine ingestion lead to higher power outputs when participants were asked to pace their effort based upon pain perception. Therefore, we cannot exclude the possibility that IBP consumption could be ergogenic in situations wherein pacing strategy is self-selected such as during longer duration endurance exercise.

Another possible explanation for the absence of an ergogenic effect of IBP in our study is that inhibiting cyclooxygenase may induce secondary effects that may limit the cardiopulmonary response to exercise (Takayama et al. 2002) including a reduction in exercise-induced hyperaemia (Bradford et al. 2007; Scharage et al. 2004). If skeletal muscle perfusion was impaired following IBP ingestion as a function of cyclooxygenase inhibition (Albert & Gernaat, 1984), this could have negated any potential ergogenic effects following IBP ingestion. However, given that performance was not enhanced during either smaller (single-leg exercise) or larger (double leg cycling) muscle mass exercise following acute IBP ingestion in the current study, and that skeletal muscle perfusion is less likely to be a limiting factor for performance in a single leg model (Joyner & Casey, 2015), this seems unlikely.

Effects of acute IBP ingestion on neuromuscular function

The ingestion of 400 mg of IBP was not associated with attenuation of neuromuscular fatigue development as estimated with peripheral muscle excitability (part A and B), voluntary activation (part A), potentiated twitch (part A) or EMG amplitude (part A and B), consistent with the lack of change in exercise performance. We previously investigated the influence of

acute ingestion of 1 g of ACT on neuromuscular function during exercise and reported that, whilst EMG declined across the 3-min cycling protocol in both conditions, EMG declined to a lesser extent in the ACT (~72 %) compared to the PL (~54 %) condition (Morgan et al. 2018b). The magnitude of this effect was remarkably similar to the results we obtained during a 60 MVC protocol completed in a single leg exercise model (ACT: 87% vs. PL: 59 %, Morgan et al. 2018a). This observation suggests that improved maintenance of muscle activation contributed to the ergogenic effect of ACT (Morgan et al. 2018a). It is of interest, therefore, that similar effects were not evident following IBP ingestion. We are not aware of any research to suggest that ACT acts as a more potent stimulus to reduce pain sensation or alter muscle activation. However, it is possible that a combination of the higher ACT dose administered (1000 mg vs 400 mg for IBU), ACT's potential as an antipyretic (Foster et al. 2014) and differences in pharmacokinetics (Anderson, 2008; Albert & Gernaat, 1984) may have contributed to the disparate effects of IBP in our current study and ACT in our previous studies (Morgan et al. 2018a; Morgan et al. 2018b) on exercise performance and neuromuscular fatigue development. It is also pertinent to note that ACT ingestion has been reported to increase corticospinal excitability at rest, a factor which may contribute to its ergogenic potential (Mauger & Hopker, 2013).

Experimental considerations

Whilst our study contributes to a further understanding of the effect of IBP on exercise-induced fatigue and some of its underlying mechanisms, there are some limitations that require consideration. Firstly, it is acknowledged that we did not measure pain sensation or biomarkers of inflammation. Pain was not assessed due to the protocols requiring the completion of maximal exercise. Asking participants to rate pain sensation may have compromised their ability to focus on the exercise task and to provide a true maximal effort.

The effect of IBP on exercise performance when pacing is permitted, and the individual can adjust their pacing strategy in response to potential differences in pain sensation, warrants further investigation. In addition, the extent to which prostaglandin synthesis during endurance exercise plays a role in pain perception in the absence of muscle damage requires further consideration. It is also important to point out that individuals intending to ingest IBP need to consider its potential side effects and be aware that it could impair the adaptive response to exercise (Schoenfield, 2012) and aspects of the beneficial remodelling of skeletal muscle to exercise training (Mikkelsen, 2009). Therefore, individuals wishing to explore the use of pain relievers to enhance exercise performance should do so infrequently, with caution, and at the recommended therapeutic doses.

Conclusion

Acute ingestion of IBP did not attenuate the decline in neuromuscular function or improve CT or CP during a 60 MVC protocol of the knee extensors or a 3-min maximal cycling test. Therefore, our results indicate that IBP ingestion does not attenuate neuromuscular fatigue development, during either single-limb or whole-body cycling exercise, and do not support IBP ingestion as an ergogenic aid.

Conflict of interest

The author declares that there is no conflict of interest regarding the publication of this article.

Author contribution

P.T. Morgan, A. Vanhatalo, A.M. Jones and S.J. Bailey conceived and designed the research. P.T. Morgan conducted all experiments. J.L. Bowtell provided assistance with pilot testing prior to experimental data collection as well supporting data analysis. P.T. Morgan wrote the manuscript. J.L. Bowtell, A. Vanhatalo, A.M. Jones and S.J. Bailey helped supervise the project throughout. All authors contributed to the interpretation of results and read, edited and approved the manuscript.

References

- Albert, K.S., and Gernaat, C.M. 1984. Pharmacokinetics of Ibuprofen. *American Journal of Medicine*. **77**: 40–46.
- Alaranta, A., Alaranta, H., and Helenius, I. 2008. Use of prescription drugs in athletes. *Sports Medicine*. **38**: 449–463.
- Allen, G.M., McKenzie, D.K., and Gandevia, S.C. 1998. Twitch interpolation of the elbow flexor muscles at high forces. *Muscle Nerve*. **21**(3): 318-28.
- Amann, M., and Calbet, J.A.L. 2008. Convective oxygen transport and fatigue. *Journal of Applied Physiology*. **104**: 861–870.
- Amann, M., Blain, G.M., Proctor, L.T., Sebranek, J.J., Pegelow, D.F., and Dempsey, J.A. 2011. Implications of group III and IV muscle afferents for high-intensity endurance exercise performance in humans. *Journal of Physiology*. **589**: 5299-5309.
- Amann, M., Proctor, L.T., Sebranek, J.J., Pegelow, D.F., and Dempsey, J.A. 2009. Opioid-mediated muscle afferents inhibit central motor drive and limit peripheral muscle fatigue development in humans. *Journal of Physiology*. **587**: 271-283.
- Amann, M., Venturelli, M., Ives, S.J., McDaniel, J., Layec, G., Rossman, M.J., and Richardson, R.S. 2013. Peripheral fatigue limits endurance exercise via a sensory feedback-mediated reduction in spinal motoneuronal output. *Journal of Applied Physiology*. **115**: 55–364.

474

475 Anderson, B.J. 2008. Paracetamol (Acetaminophen): mechanisms of action. Paediatric
476 Anaesthesia. **18**: 915-921.

477

478 Armstrong, R.B. 1984. Mechanisms of exercise-induced delayed onset muscular soreness.
479 Medicine & Science in Sports & Exercise. **16**: 529-538.

480

481 Black, M.I., Durant, J., Jones, A.M., and Vanhatalo, A. 2014. Critical power derived from a
482 3-min all-out test predicts 16.1-km road time-trial performance. European Journal of Sport
483 Science. **14**: 217-223.

484

485 Black, C.D., and O'Connor, P.J. 2008. Acute effects of dietary ginger on quadriceps muscle
486 pain during moderate-intensity cycling exercise. International Journal of Sport Nutrition and
487 Exercise Metabolism. **18**: 653–664.

488

489 Blain, G.M., Mangum, T.S., Sidhu, S.K., Weavil, J.C., Hureau, T.J., Jessop, J.E., Bledsoe,
490 A.D., Richardson, R.S., and Amann, M. 2016. Group III/IV muscle afferents limit the
491 intramuscular metabolic perturbation during whole body exercise in humans. Journal of
492 Physiology. **594**: 5303–5315.

493

494 Bradford, C.D., Cotter, J.D., Thorburn, M.S., Walker, R.J., and Gerrard, D.F. 2007. Exercise
495 can be pyrogenic in humans. American Journal of Physiology. Regulatory, Integrative and
496 Comparative Physiology **292**: R143-9.

497

498 Burnley, M. 2009. Estimation of critical torque using intermittent isometric maximal
 499 voluntary contractions of the quadriceps in humans. *Journal of Applied Physiology*. **106**:
 500 975-983.
 501
 502 Cleak, M.J., and Eston, R.G. 1992. Muscle soreness, swelling, stiffness and strength loss after
 503 intense eccentric exercise. *British Journal of Sports Medicine*. **26**: 267–272.
 504
 505 Cook, D.B., O'Connor, P.J., Eubanks, S.A., Smith, J.C., and Lee, M. 1997. Naturally
 506 occurring muscle pain during exercise: assessment and experimental evidence. *Medicine and*
 507 *Science in Sports and Exercise*. **29**: 999–1012.
 508
 509 Corrigan, B., and Kazlauskas, R. 2003. Medication use in athletes selected for doping control
 510 at the Sydney Olympics (2000). *Clinical Journal of Sport Medicine*. **13**: 33–40.
 511
 512 Da Silva, E., Pinto, R.S., Cadore, E.L., and Kruel, L.F. 2015. Nonsteroidal anti-inflammatory
 513 drug use and endurance during running in male long-distance runners. *Journal of Athletic*
 514 *Training*. **50**: 295–302.
 515
 516 Donnelly, A.E., Maughan, R.J., and Whiting, P.H. 1990. Effects of ibuprofen on exercise-
 517 induced muscle soreness and indices of muscle damage. *British Journal of Sports Medicine*.
 518 **24**: 191–195.
 519
 520 Doyle-Baker, D., Temesi, J., Medysky, M.E., Holash, R.J., and Millet, G.Y. 2017. An
 521 Innovative Ergometer to Measure Neuromuscular Fatigue Immediately after Cycling.
 522 *Medicine & Science in Sports & Exercise*. **50**(2): 375-387.

523

524 Ebbeling, C.B., and Clarkson, P.M. 1989. Exercise-Induced Muscle Damage and Adaptation.

525 Sports Medicine. **7**: 207–234.

526

527 Foster, J., Taylor, L., Christmas, B.C., Watkins, S.L., and Mauger, A.R. (2014). The influence

528 of acetaminophen on repeated sprint cycling performance. European Journal of Applied

529 Physiology. **114**: 41-48.

530

531 Fridén, J., and Lieber, R.L. 1992. Structural and mechanical basis of exercise-induced muscle

532 injury. Medicine and Science in Sports and Exercise. **24**: 521–530.

533

534 Froyd, C., Millet, G.Y., and Noakes, T.D. 2013. The development of peripheral fatigue and

535 short-term recovery during self-paced high-intensity exercise. Journal of Physiology. **591**:

536 1339–1346.

537

538 García-Martín, E., Martínez, C., Tabarés, B., Frías, J., and Agúndez, J.A.G. 2004.

539 Interindividual variability in ibuprofen pharmacokinetics is related to interaction of

540 cytochrome P450 2C8 and 2C9 amino acid polymorphisms. Clinical Pharmacology and

541 Therapeutics. **76**: 119–127.

542

543 Goodall, S., Ross, E.Z., and Romer, L.M. 2010. Effect of graded hypoxia on supraspinal

544 contributions to fatigue with unilateral knee-extensor contractions. Journal of Applied

545 Physiology. **109**: 1842–1851.

546

547 Gonglach, A.R., Ade, C.J., Bemben, M.G., Larson, R.D., and Black, C.D. 2016. Muscle pain
548 as a regulator of cycling intensity: Effect of caffeine ingestion. *Medicine and Science in*
549 *Sports and Exercise*. **48**: 287–296.

550

551 Gorski, T., Lusa Cadore, E., Santana Pinto, S., Marczwski Da Silva, E., Silva Correa, C.,
552 Gabe Beltrami, F., and Martins Kruehl, L.F. 2011. Use of NSAIDs in triathletes: Prevalence,
553 level of awareness and reasons for use. *British Journal of Sports Medicine*. **45**: 85–90.

554

555 Grossman, J.M., Arnold, B.L., Perrin, D.H., and Kahler, D.M. 1995. Effect of Ibuprofen Use
556 on Delayed Onset Muscle Soreness of the Elbow Flexors. *Journal of Sport Rehabilitation*. **4**:
557 253–263.

558

559 Hasson, S.M., Daniels, J.C., Divine, J.G., Niebuhr, B.R., Richmond, S., Stein, P.G., and
560 Williams, J.H. 1993. Effect of ibuprofen use on muscle soreness, damage, and performance: a
561 preliminary investigation. *Medicine & Science in Sports & Exercise*. **25**: 9–17.

562

563 Huang, S.H., Johnson, K., and Pipe, A.L. 2006. The use of dietary supplements and
564 medications by Canadian athletes at the Atlanta and Sydney olympic games. *Clinical Journal*
565 *of Sport Medicine*. **16**: 27–33.

566

567 Jankowski, C.M., Shea, K., Barry, D.W., Linnebur, S.A., Wolfe, P., Kittelson, J., Schwartz,
568 R.S., and Kohrt, W.M. 2015. Timing of ibuprofen use and musculoskeletal adaptations to
569 exercise training in older adults. *Bone Reports*. **1**: 1–8.

570

571 Janssen, G.M.E., and Venema, J.F. 1985. Ibuprofen: Plasma Concentrations in Man. Journal
572 of International Medical Research. **13**: 68–73.

573

574 Joyner, M.J., and Casey, D.P. 2015. Regulation of Increased Blood Flow (Hyperemia) to
575 Muscles During Exercise: A Hierarchy of Competing Physiological Needs. Physiological
576 Reviews. **95**: 549–601.

577

578 Leadbetter, W.B. 1995. Anti-inflammatory therapy in sports injury. The role of nonsteroidal
579 drugs and corticosteroid injection. Clinics in Sports Medicine. **14**: 353–410.

580

581 Mauger, A.R., and Hopker, J.G. 2013 The effect of acetaminophen ingestion on cortico-
582 spinal excitability. Canadian Journal of Physiology and Pharmacology. **91**: 187–189.

583

584 Mauger, A.R., Jones, A.M., and Williams, C.A. 2010. Influence of acetaminophen on
585 performance during time trial cycling. Journal of Applied Physiology. **108**: 98-104.

586

587 Mauger, A.R., Taylor, L., Harding, C., Wright, B., Foster, J., and Castle, P.C. 2014. Acute
588 acetaminophen (paracetamol) ingestion improves time to exhaustion during exercise in the
589 heat. Experimental Physiology. **99**: 164-171.

590

591 McCord, J.L., and Kaufman, M.P. 2010. Reflex Autonomic Responses Evoked by Group III
592 and IV Muscle Afferents. In: L. Kruger & A.R. Light (eds). Translational Pain Research:
593 From Mouse to Man, Chapter 12, pp 283-300. CRC Press/Taylor & Francis, Boca Raton, FL.

594

595 Merton, P.A. 1954. Voluntary strength and fatigue. *The Journal of Physiology*. **123**: 553–
 596 564.

597

598 Mikkelsen, U.R., Langberg, H., Helmark, I.C., Skovgaard, D., Andersen, L.L., Kjaer, M., and
 599 Mackey, a L. 2009. Local NSAID infusion inhibits satellite cell proliferation in human
 600 skeletal muscle after eccentric exercise. *Journal of Applied Physiology*. **107**: 1600–1611.

601

602 Morgan, P.T., Bowtell, J.L., Vanhatalo, A., Jones, A.M., and Bailey, S.J. 2018a. Acute
 603 acetaminophen ingestion improves performance and muscle activation during maximal
 604 intermittent knee extensor exercise. *European Journal of Applied Physiology*. **118**: 595–605.

605

606 Morgan, P.T., Bowtell, J.L., Vanhatalo, A., Jones, A.M., and Bailey, S.J. 2018b.
 607 Acetaminophen improves muscle activation and performance during 3-min all-out cycling.
 608 *Applied Physiology, Nutrition, and Metabolism* (under review).

609

610 Nosaka, K., and Clarkson, P.M. 1996. Changes in indicators of inflammation after eccentric
 611 exercise of the elbow flexors. *Medicine and Science in Sports and Exercise*. **28**: 953–961.

612

613 Novak, J., and Wennmalm, A. 1979. Effect of exercise on human arterial regional venous
 614 plasma concentrations of prostaglandin E. *Prostaglandins and Medicine*. **1**: 489-497.

615

616 O'Connor, P.J., and Cook, D.B. 1999. Exercise and pain: the neurobiology, measurement, and
 617 laboratory study of pain in relation to exercise in humans. *Exercise and Sport Sciences*
 618 *Reviews*. **27**: 119-66.

619

620 Pageaux, B., Angius, L., Hopker, J.G., Lepers, R., and Marcora, S.M. 2015. Central
 621 alterations of neuromuscular function and feedback from group III-IV muscle afferents
 622 following exhaustive high-intensity one-leg dynamic exercise. *American Journal of*
 623 *Physiology - Regulatory, Integrative and Comparative Physiology*. **308**: R1008–R1020.
 624
 625 Pizza, F., Calende, D., Stockard, A., Baylies, H., and Beighle, A. 1999. Anti-Inflammatory
 626 Doses of Ibuprofen: Effect on Neutrophils and Exercise-Induced Muscle Injury. *International*
 627 *Journal of Sports Medicine*. **20**: 98–102.
 628
 629 Pollak, K.A., Swenson, J.D., Vanhaitsma, T.A., Huguen, R.W., Jo, D., White, A.T., Light,
 630 K.C., Schweinhardt, P., Amann, M., and Light, A.R. 2014. Exogenously applied muscle
 631 metabolites synergistically evoke sensations of muscle fatigue and pain in human subjects.
 632 *Experimental Physiology*. **99**: 368-380.
 633
 634 Schrage, W.G., Joyner, M.J., and Dinunno, F.A. 2004. Local inhibition of nitric oxide and
 635 prostaglandins independently reduces forearm exercise hyperaemia in humans. *Journal of*
 636 *Physiology*. **557**: 599–611.
 637
 638 Schoenfeld, B.J. 2012. The use of nonsteroidal anti-inflammatory drugs for exercise-induced
 639 muscle damage: Implications for skeletal muscle development. *Sports Medicine*. **42**: 1017–
 640 1028.
 641
 642 Tokmakidis, S.P., Kokkinidis, E.A., Smilios, I., and Douda, H. 2003. The effects of ibuprofen
 643 on delayed muscle soreness and muscular performance after eccentric exercise. *Journal of*
 644 *Strength and Conditioning Research*. **17**: 53–59.

645

646 Trappe, T.A., Fluckey, J.D., White, F., Lambert, C.P., and Evans, W.J. 2001. Skeletal muscle
647 $\text{PGF2}\alpha$ and PGE2 in response to eccentric resistance exercise: Influence of ibuprofen and
648 acetaminophen. *Journal of Clinical Endocrinology and Metabolism*. **86**: 5067–5070.

649

650 Vane, J.R. 2000. Aspirin and other anti-inflammatory drugs. *Thorax*. **231**(25): 232–235.

651

652 Vane, J.R., and Botting, R.M. 2003. The mechanism of action of aspirin. In *Thrombosis*
653 *Research*, (Elsevier Ltd). 255–258.

654

655 Vanhatalo, A., Doust, J.H., and Burnley, M. 2007. Determination of critical power using a 3-
656 min all-out cycling test. *Medicine and Science in Sports and Exercise*. **39**: 548–555.

657

658 Vanhatalo, A., Doust, J. H., and Burnley, M. 2008. A 3-min all-out cycling test is sensitive to
659 a change in critical power. *Medicine and Science in Sports and Exercise*. **40**(9): 1693–1699.

660

661 VanHeest, J., Stoppani, J., TP, S., Collins, V., Roti, M., Anderson, J., ... CM, M. 2002.
662 Effects of ibuprofen and Vicoprofen on physical performance after exercise-induced muscle
663 damage. *Journal of Sport Rehabilitation*. **11**: 224–234.

664

665 Vinikka, L., Vuori, J., and Ylikorkala, O. 1984. Lipid peroxidases, prostacyclin, and
666 thromboxane A₂ in runners during acute exercise. *Medicine & Science in Sports & Exercise*.
667 **16**: 275-277.

Table 1: Performance and neuromuscular function parameters of the 60 MVC (protocol A) and 3-min all-out cycling (protocol B) tests following placebo and ibuprofen ingestion.

	Placebo (PL)	Ibuprofen (IBU)
<i>Protocol A</i>		
Performance		
Peak MVC (N.m)	232 ± 47	230 ± 55
Mean torque (% MVC)	58 ± 14	60 ± 13
Total Impulse (N.m.s)	22055 ± 3885	22919 ± 3394
Critical torque, CT (% MVC)	40 ± 15	41 ± 16
W' (N.m.s ⁻¹)	6971 ± 2432	7231 ± 3570
Neuromuscular function		
Change in pTw (N.m)	44 ± 27	43 ± 25
End-exercise pTw (N.m)	30 ± 21	31 ± 23
End-exercise VA (%)	59 ± 19	60 ± 18
End-exercise M-wave amplitude (%)	96 ± 14	95 ± 12
End-exercise EMG amplitude (%)	59 ± 17	64 ± 20
<i>Protocol B</i>		
Performance		
Peak power output (W)	820 ± 139	816 ± 131
Total Work Done (kJ)	65.4 ± 6.4	65.9 ± 5.9
Critical power, CP (W)	288 ± 31	292 ± 28
W' (kJ)	13.6 ± 2.4	13.7 ± 2.8
Neuromuscular function		
End-exercise M-wave amplitude (%)	84 ± 21	83 ± 18
End-exercise EMG amplitude (%)	54 ± 17	57 ± 14

MVC, maximal voluntary contraction; CT, critical torque measured in the last 6 contractions; CP, critical power measured in the last 30 s of the 3-minute maximal cycling test; pTw, potentiated twitch force; VA, voluntary activation measured using the interpolated twitch method technique; EMG, electromyography; N.m, newton metres; N.m.s⁻¹, newton metres per second; ms, milliseconds.

Figure captions

Figure 1

Schematic of the procedures used prior to (panel a), during (panel b) and within 10 s following (panel c) the 60 maximal isometric voluntary contraction (MVC) protocol. 10 s separated each single pulse stimulation administered at rest (small dashed arrows). A, C 45 s rest period separated maximal efforts (MVCs). Single pulse stimuli were administered during peak force production of MVCs (large solid arrow) and immediately (<1-s) post MVCs (small grey arrows). B: 60 MVC protocol of the knee extensors. The figure presents a period of 30 s which is repeated sequentially for 5 min. Each MVC was held for 3 s and interspersed by a 2 s passive recovery period. Every 6th MVC was accompanied by single pulse stimuli administered during peak force production (large solid arrow) and immediately following (>1 s) post MVCs (small grey arrows). This cycle was repeated 10 times such that the protocol spanned 5 minutes requiring the completion of 60 MVCs. Surface electromyography (EMG) was measured throughout.

Figure 2

The torque profile during the 60 maximal contractions for placebo (PL, clear circles) and ibuprofen (IBU, filled circles) trials in protocol (a) is demonstrated in panel A. The torque during all contractions was normalized to a control maximal voluntary contraction (MVC) performed before the test commenced. Note that torque falls over the first ~150 s before reaching stable values between 240 and 300 s (the end-test torque; last 12 MVCs). Panel B illustrates the mean $\pm$ SE power output profile during the 3-min maximal cycling protocol for placebo (clear circles) and ibuprofen (filled circles) trials. Note that power output falls over the first ~120-150 s before reaching stable values (the end-test power output; i.e. CP).

694 *Figure 3*

695 Mean $\pm$ SE potentiated twitch (A), voluntary activation (B), and EMG amplitude (C) and M-
696 wave amplitude (D) responses during the 60 MVC test for placebo (clear circles) and
697 ibuprofen (filled circles) trials for protocol a.

698

699 *Figure 4*

700 Mean $\pm$ SE M-wave amplitude (A) and EMG amplitude (B) responses during the 3-minute
701 maximal cycling exercise for placebo (clear circles) and ibuprofen (filled circles) trials for
702 protocol b.