Exercise can be pyrogenic in humans

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Exercise can be pyrogenic in humans. Am J Physiol Regul Integr Comp Physiol 292: R143–R149, 2007. First published August 3, 2006; doi:10.1152/ajpregu.00926.2005.—Exercise increases mean body temperature (Tbody) and cytokine concentrations in plasma. Cytokines facilitate PG production via cyclooxygenase (COX) enzymes, and PGE2 can mediate fever. Therefore, we used a COX-2 inhibitor to test the hypothesis that PG-mediated pyrogenicity may contribute to the raised Tbody in exercising humans. In a double-blind, cross-over design, 10 males [age: 23 yr (SD 5), V˙O2 max: 5 3m l(e-mail: jcotter@otago.ac.nz).

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the purpose of this study was to use COX inhibition to determine whether a PG-mediated pathway is involved in exercising thermoregulation in humans. We used a COX-2-selective NSAID for the reasons indicated above. We hypothesized that a feverlike response would develop in exercise, as evidenced by higher exercising body temperature and thresholds for heat loss activity, following the administration of placebo compared with the NSAID. We used recreationally active rather than highly fit individuals because they are overly represented in exertional heat stroke casualties, and, similarly, higher fitness was shown to cause insensitivity to NSAID (indomethacin)-mediated reductions in the core temperature of passively heat-stressed sheep (47).

METHODS

A double-blind cross-over design was used. After fitness and familiarization sessions, participants consumed a course of COX-2 specific NSAID (rofecoxib) or a placebo (PLAC; ascorbic acid), on the 6th day of which they undertook an exercising stress test. Drug consumption periods were separated by a 2-wk washout period. The NSAIDs were consumed as a standard, orally administered pill, 25 mg twice a day, with the placebo taken likewise. The study was ethically approved by the University of Otago Human Ethics Committee in March 2003. Participants were first enrolled at that time, and data collection was completed in March 2004.

Participants

Ten recreationally active males provided their written, voluntary consent of participation. Their mean age was 23 yr (SD 5), mass was 78.22 kg (SD 7.95), and maximal oxygen consumption (\(V_{\text{O2 max}}\)) was 53.1 ml·kg\(^{-1}\)·min\(^{-1}\) (SD 5.3). Participants were screened via questionnaire for cardiovascular, musculoskeletal, and heat intolerance risks. None were heat acclimated.

Procedures

Fitness and familiarization. Participants’ \(V_{\text{O2 max}}\) was measured in an incremental treadmill test to exhaustion, with verbal support to encourage maximal exertion. The \(V_{\text{O2 max}}\) was calculated in real time from respiratory gases measured for \(O_2\) and \(CO_2\) content and for volume using calibrated transducers (Sensormedics 2900Z BXB, Sensormedics, Yorba Linda, CA). The \(V_{\text{O2 max}}\) (highest 20-s mean) and the highest running speed were recorded and used to estimate an appropriate intensity that would elicit \(\sim\)75% \(V_{\text{O2 max}}\) on the treadmill during the exercising stress test. These intensities were subsequently confirmed during a familiarization session, which exposed participants to the full experimental protocol, measurements, and exercise requirements.

Exercise stress test. This test was performed on day 6 of drug ingestion, and at least 1 wk after familiarization. The 6-day protocol was to permit time for attainment of steady-state COX-2 inhibition (days 1–3) before first undertaking a preliminary assessment of resting thermoregulation (days 4–5; data not reported). Participants arrived at 7 AM in a fasted state and without alcohol, caffeine, or strenuous exercise during the preceding 24 h. Their last drug ingestion was at 6:30 AM. Participants had been instructed to drink before coming into the lab and were also required to consume 500 ml of a carbohydrate and electrolyte beverage (8% carbohydrate, 20 mmol/l Na\(^+\)) prior to instrumentation. Participants were then weighed (to accuracy of 20 g; Digi D1-10, Teraoka, Seiko, Tokyo, Japan) before they inserted a rectal thermometer 10 cm beyond the anus, to provide an index of core temperature (\(T_{\text{core}}\)). Participants then rested while they were instrumented for measurement of cardiac frequency, skin temperature, sweat rate, and forearm perfusion. Resting data, including a resting venous sample (~5 ml, without stasis, 30 min before exercise), were collected. Participants then entered a climatic chamber set at temperature conditions (28°C, 50% relative humidity and 1.5 m/s air velocity) and rested for ~10 min, while further resting measurements were taken. They then ran for 45 min on a treadmill (Q65 series 90, Quinton Instrument, Seattle, WA) at ~75% \(V_{\text{O2 max}}\), followed by 45 min of cycling on an electromagnetically braked cycle ergometer (Rodby Elektronik AB, Södertälje, Sweden). The two exercise modes were separated by a 5-min transition period to set the participant up on the cycle and draw a midexercise blood sample (5 ml). Cycling intensity was established for each participant during familiarization to equate with their perceived exertion during the previous running and to facilitate completion of the 45 min. The purpose of using this dual-mode exercise protocol was to elicit substantial strain using running (i.e., orthostatically and mechanically stressful), then maintain it with a mode of exercise that facilitated 1) measurement of forearm perfusion and blood pressure, 2) continued exercise tolerance, and 3) additional time for fever effects to become evident. Participants were partially rehydrated with 200 ml after 30 min running and 500 ml after 15 min cycling, with the carbohydrate and electrolyte beverage described above. This was done to minimize influences of hyperosmolality and hypovolemia on thermoregulatory control and exercising body temperature, to aid participant tolerance to the exercise regime and to simulate common practice during prolonged exercise in warm conditions. The trial was stopped if participants requested termination or \(T_{\text{core}}\) exceeded 39.5°C. Following the 90 min of exercise, participants rested in an upright seated position for 60 min while recovery data were collected. A further blood sample (~5 ml) was taken 30 min into this recovery period.

Data Acquisition

Metabolic rate. \(V_{\text{O2}}\) and \(V_{\text{CO2}}\) were measured (Metalyser 3B, Cortex, Biophysik GmbH, Leipzig, Germany) for 2–3 min at 10 and 25 min of both running and cycling.

Temperatures. Rectal temperature was measured from a flexible, sterile, and disposable thermistor (Mallinckrodt 400 general purpose, Mallinckrodt Medical St Louis, MO). Factory calibration (SD 0.1°C) was accepted, although participants used the same thermistor in both stress tests. Skin temperatures were measured using insulated skin thermistors (Type EU, Grant Instruments, Cambridge, England) at nine right-side sites, from which mean skin temperature (\(T_{\text{sk}}\)) was calculated from standard area weighings (22) as 0.07· forehead + 0.0875· chest + 0.0875· abdomen + 0.175· scapula + 0.14· dorsal forearm + 0.05· fifth finger + 0.19· anterior thigh + 0.15· calf + 0.05· dorsi foot. Temperatures were logged at 15-s intervals (resolution 0.05°C; Grant 1200 series, Grant Instruments) and subsequently downloaded to a PC computer for analysis.

Sweat rate. Sweat rate kinetics were measured using a ventilated capsule system, from two capsules (19 mm ID) glued to the forehead and lateral arm. Capsules were ventilated at a known rate (flow sensor; Honeywell AWM5101, Freeport, IL) of ~0.5 l/min from bottled dry air. Using a custom-built system, we sampled the postcapsular air stream for humidity (resistance hygrometer; Honeywell HH 3605) and temperature (National Semiconductors LM35CAH, Hong Kong). Digital outputs from this system were obtained (PowerLab hardware 8e, ADI Instruments, Chain Hills, NSW, Australia) and recorded on a PC computer via data acquisition software (Chart 4.20, ADI Instruments). Sweat rates were calculated at 15-s intervals from standard equations, then represented as the mean from both capsules. Humidity sensor calibration was via saturated salt solutions. The 50 and 90% response times to an upward, full-scale (0 to 100%) humidity step were 22 and 174 s, respectively.

Forearm perfusion. Venous occlusion plethysmography was used to measure forearm perfusion (\(Q_{\text{forearm}}\)) following standard procedures, thus providing a validated index of cutaneous vasomotor activity in the absence of arm exercise (27). Briefly, arterial blood flow to the hand is occluded at the wrist with a blood pressure cuff
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\[ \text{gguanias (7), and heat stress in four unfit sheep (47), and to an exercising stress in seven participants, with the remaining one showing no difference.} \]

\[ \text{Mean skin temperature remained equivalent between drug conditions (} F_{3,27} = 0.92; P = 0.44; \phi = 0.23) \text{ (Fig. 1B), so the differential Tbody response was attributable to a differential Tcore response to exercise between drug conditions (} F_{1,7,15,1} = 16.91; P < 0.01; \text{ Fig. 1A).} \]

Cytokines. Venous samples were analyzed for plasma concentrations of TNF-\( \alpha \) and IL-10, as markers of proinflammatory and anti-inflammatory cytokine responses, respectively. Fresh venous samples were first transferred into tubes containing EDTA-anti-coagulant and immediately centrifuged at 4°C and 3,000 rpm for 10 min. The plasma was subsequently removed and stored in 1-ml aliquots at −80°C until determination of cytokine concentrations using commercially available ELISA immunoassays (Quantikine High Sensitivity, R&D Systems, Minneapolis, MN).

### Data Analysis

#### Calculations.

Mean body temperature (Tbody) was calculated from Tcore and Tskin using a ratio of 4:1 (12). Thus Tbody was used in the determination of sudomotor and vasomotor control because it more closely reflects their control than does Tcore alone. The sweating onset and offset thresholds were calculated by plotting mean sweat rate against Tbody for each participant and visually identifying the Tbody at which sweating increased and continued to rise from baseline (onset), and the Tbody at which the sweating trace returned to baseline and showed no subsequent rises (offset). This was completed by two investigators, both of whom are familiar with these determinations. Forearm vascular conductance (FVC) was calculated as Q˙forearm/mean arterial pressure (MAP).

#### Statistics.

We are unaware of previous research examining this issue in humans, but we used a sample size of 10 because 1) a within-subjects design was used, 2) previous research showed statistically supported effects of NSAID on Tcore responses to a passive heat stress in four unfit sheep (47), and to an exercising stress in seven iguanas (7), and 3) we had previously obtained statistically supported effects of COX-2-specific inhibitors on renal function using 12 participants (1). Fully repeated two-way ANOVA were used to examine the effects of NSAID administration on the relevant dependent variables. Specifically, there were two drugs (PLAC and NSAID) and either two time points (sweat onset and offset; metabolic rate in running and cycling; cytokines pre- and postexercise) or four periods (rest, run, cycle, and recovery: Tbody, Tcore, fatigue). Degrees of freedom were corrected using a Huynh-Feldt adjustment, and a Bonferroni correction was used to control Type I error during the post hoc analyses of significant ANOVAs (SPSS 11.0 for Windows, SPSS Inc, Chicago, IL). A paired \( t \)-test was performed on simple comparisons between experimental conditions (i.e., ambient conditions and FVC/Tbody relationship). Statistical power (\( \phi \)) is reported for nonsignificant results. The family-wise \( \alpha \) was 0.05. Data are reported as means with SD for \( n = 10 \), unless otherwise stated.

### RESULTS

All participants reported adhering to the drug ingestion protocol and dietary standardization, and they completed both stress tests. Dry-bulb temperature was equivalent (\( P = 0.86 \)) between PLAC (28.13°C, SD 0.17) and NSAID (28.15°C, SD 0.20).

#### Body temperatures.

The Tbody response to exercise differed between drug conditions (\( F_{2.2,19.6} = 11.67; P < 0.01 \)), in that it was similar during the 45-min run (\( P = 0.33 \)) but became higher in PLAC during cycling (by 0.33°C, SD 0.26; \( P = 0.03 \)) and remained this much higher during recovery (0.34°C, SD 0.26; \( P < 0.01 \); Fig. 1C). This response was observed in nine participants, with the remaining one showing no difference. Mean skin temperature remained equivalent between drug conditions (\( F_{3,27} = 0.92; P = 0.44; \phi = 0.23 \) (Fig. 1B), so the differential Tbody response was attributable to a differential Tcore response to exercise between drug conditions (\( F_{1,7,15,1} = 16.91; P < 0.01 \); Fig. 1A).

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**Fig. 1.** Rectal temperature (A), mean skin temperature (B), and mean body temperature (C) during 90-min exercise and 60-min recovery, following 6-day administration of a COX-2 selective inhibitor (NSAID; ⋄) or placebo (PLAC, □). Data are means ± SD for 10 males. *\( P < 0.05 \), significantly different between NSAID and PLAC. To aid visual interpretation, symbols are illustrated intermittently with respect to data and are horizontally offset.
**Thermoeffectors.** No sweat rate response differences were observed at the forehead or arm between drug conditions, thus the unweighted mean of both sites was used. The $T_{body}$ thresholds for sweating responded differently between the two drug conditions ($F_{1.8} = 7.24; P = 0.03; n = 9$). Whereas sweating was initiated at a similar $T_{body}$ in both drug conditions, the elevation in sweating cessation was 0.19°C (SD 0.22) greater in PLAC than in NSAID (Fig. 2A). That is, the postexercise $T_{body}$ threshold for sweating cessation was elevated above the onset threshold, as expected, but the administration of NSAID reduced this effect. This attenuation by NSAID was evident in seven of the nine participants for whom sweating data were obtained (Fig. 2B). Similar thresholds for FVC were not calculated because the running exercise prevented $Q_{forearm}$ measurement during the initial heat stress period. Therefore, the change in FVC from rest to cycling exercise was used and normalized to the change in $T_{body}$. The FVC response was significantly higher in NSAID than in PLAC (0.13 vs. 0.10 ml·100 ml tissue$^{-1}$·min$^{-1}$·mmHg$^{-1}$·°C$^{-1}$, both SD 0.05; $P = 0.01$). This indication of higher FVC sensitivity in NSAID was evident in all eight participants for whom data were available.

**Cytokines.** The plasma TNF-α and IL-10 responses to exercise indicated a mild cytokinemia that was equivalent between drug conditions. Specifically, the TNF-α concentration increased by an average of 41% (SD 36; $F_{1.9} = 6.23; P = 0.03$) from pre- to postexercise (2.96 to 4.17 pg/ml, SD 2.07 and 3.25), with no statistical interaction ($F_{1.0} = 0.47; P = 0.51$). The IL-10 concentration increased by 110% (SD 112, 2.43 to 5.10 pg/ml, SD 2.17 and 4.45; $F_{1.7} = 6.97; P = 0.03; n = 8$), also with no statistical interaction ($F_{1.7} = 0.97; P = 0.36$).

**Cardiac frequency.** In a similar manner to $T_{body}$, the progression of cardiac frequency in exercise differed between drug conditions ($F_{1.27} = 3.26; P = 0.04$; Fig. 3), and although it appeared to become progressively lower in NSAID relative to PLAC, the source of significant difference was not identifiable from post hoc testing. A main effect of drug was evident, with cardiac frequency being 6 min$^{-1}$ (SD 3) higher in PLAC than in NSAID (124 vs. 119 min, both SD 14; $F_{1.9} = 36.52; P < 0.01$). This effect was observed in all 10 participants.

**Metabolic rate.** Metabolic rate was similar between drug conditions ($F_{1.4} = 0.00; P = 0.99; n = 5; \varphi=0.05$), averaging 547 W·m$^{-2}$ (SD 72) in PLAC and 549 W·m$^{-2}$ (SD 102) in NSAID during running ($P = 0.88$), which was 75% (SD 6) of $V_{O2\, max}$. Metabolic rate was lower during cycling (64% of $V_{O2\, max}$, SD 4) but was also similar between drug conditions: 463 W·m$^{-2}$ (SD 56) and 465 W·m$^{-2}$ (SD 62).

**Body mass.** There was a tendency for baseline body mass to be slightly lower in PLAC (77.82 kg, SD 7.84) than in NSAID (78.49 kg, SD 7.95; $P = 0.14$). The net mass loss was similar between drug conditions [1.62 kg (SD 0.36) and 1.61 kg (SD 0.34), respectively; $P = 0.93$], thereby indicating that sweat losses were equivalent and caused dehydration of 2% of body mass.

**DISCUSSION**

To the best of our knowledge, this study provides the first direct evidence that a supplemental feverlike elevation in body temperature can occur during nonexhaustive exercise in humans. Administration of a COX-2-selective inhibitor lowered core and mean body temperatures during exercise and ensuing recovery, relative to the temperatures obtained after administration of a placebo. This was independent of endogenous heat stress or thermal environment. More importantly, in relation to the notion of an exercise-induced fever, administration of a
COX-2-specific inhibitor was associated with an unchanged T_{body} at which sweating was initiated but a relative lowering of the T_{body} at which sweating ceased in recovery from exercise and a greater increase in FVC relative to T_{body} in the latter portion of exercise. The postexercise elevation in the T_{body} threshold for sweating cessation observed in both conditions was expected due to effects of nonthermal factors, particularly the baroreceptor unloading due to residual vasodilation of skeletal muscle (28). These data therefore support our hypothesis and confirm, in humans, the work using animal models (7, 8, 47) that a pyrogenic effect can develop during exercise.

The inhibition of COX-2 enzymes in this study served our aim of identifying a feverlike effect during exercise, but the intervention has limitations. Fever is complex, likely inducible via numerous pyrogens and pathways, some of which remain unknown (3, 31, 52). Of those proposed, PGE_{2} has been suggested as a common mediator in raising the thermoregulatory set point (61). However, even though COX-2 enzymes have been repeatedly associated with the production of PGE_{2} largely responsible for fever and inflammation (23, 33, 49, 55), there is evidence for COX-1 having a regulatory role and for non-COX pathways (2, 58). Thus we are unaware whether the difference of 0.3°C (~20% of end exercise elevation in T_{core}) seen between the two groups was the entire pyrogenic response. These issues could be addressed using nonselective NSAIDs (COX-1 and 2 inhibition) or other antipyretic drugs, such as sodium salicylate or acetaminophen (paracetamol), which have antipyretic actions independent of COX inhibition. Equally, whether any feverlike effect would develop in non-exhaustive exercise of similar duration and intensity in endurance trained individuals is unknown.

This has been examined in sheep exposed to passive heat stress (47). The ~0.3°C attenuation in a 1.7°C hyperthermia in the present study (Fig. 1A) was of similar magnitude to that observed in unfit sheep exposed to passive heat stress (~0.3°C in 1.3°C; [47]). In that study, no decrease in T_{core} was seen in fit sheep, which possessed a higher splanchnic perfusion during heat stress that matched the baseline perfusion of the unfit sheep. Whether aerobically conditioned humans would similarly show no effect is unclear, but several factors indicate that such effects might occur. In most exercise settings, humans undergo higher absolute volumes of stress in accordance with their higher fitness. They can also suffer heat stroke. They have an anti-LPS IgG elevation that is proportional to their training volume and is diminished during exhaustive, competitive exercise (5, 25). Despite their larger splanchnic vessels (13) and perfusion (47), a pronounced splanchnic vasoconstriction still develops at exercise intensities similar to that used in this study (42). The regional competition for perfusion becomes especially pronounced during upright, dehydrating exercise in the heat (16, 17).

Fever appears to have two major pathways: neural and humoral. Neural pathways such as vagal or cutaneous sensory nerves have been implicated in the rapid transport of a febrile message to the central nervous system (CNS) causing initiation of the fever response (38, 46). For instance, rats injected with 10–100 μg/kg LPS showed a T_{core} rise within 10–20 min, peaking initially by 45–60 min (44, 45), apparently preceding LPS-induced changes in circulating cytokines (2). The humoral pathway, involving transport of cytokines or PGs to the brain to elevate the thermoregulatory set point, seems more likely to be responsible for the maintenance of a fever response (2). The extent to which cytokines can cross the blood-brain barrier and act directly or indirectly on thermoregulatory neurons is unclear, but endurance exercise seems to impair the integrity of this barrier, at least in hot conditions (59). It should also be considered that NSAIDs readily cross this barrier; thus local COX inhibition may attenuate PG production in response to stimuli of local, humoral, or afferent neural origin. The time course of a NSAID-associated attenuation of T_{core} in the present study (Fig. 1A) unfortunately coincided with changing of exercise mode and the slight reduction in metabolic heat production. Nonetheless, the time course seemed to be more indicative of a humorally mediated fever (44, 45), which would also be consistent with the mechanism of intervention, that is, COX-2 inhibition of PG production.

Endurance exercise may be capable of inducing a subclinical pyrogenic response, which, acting in concert with other fatigue processes, is usually self-limiting before the development of exertional heat stroke (19–21). The source and identity of pyrogenic factors could potentially include proinflammatory cytokines (e.g., IL-1, TNF-α, IL-6), mainly from muscle, liver, leukocytes, adipose tissue, or the central nervous system (CNS) itself, LPS leaking across the gut wall, and/or cellular constituents from within muscle or other stressed tissue. These factors might act humorally, via cytokines, or neurally. A probable source of a pyrogenic response is increased LPS from the GI tract in response to prolonged splanchnic vasoconstriction and elevated tissue temperature (4, 8, 14, 15, 18–21, 47). LPS leakage is normally low enough for hepatic detoxification and anti-LPS antibodies to keep pace. However, epithelial permeability and LPS leakage increase with a variety of factors, including local temperature (36, 50) and ischemia (14, 15). Increased LPS leakage can deplete antibodies and saturate hepatic clearance, increasing the LPS load and activating mediators of the nonspecific immune system (cytokines, interferon), vascular reactivity (PGEs), and coagulation (Factor XII), initially causing inflammatory and fever-producing effects. In advanced stages, this appears to underlie exertional heat stroke (20). However, data obtained from animal models indicate that even lower (i.e., sublethal) endotoxic loads may reduce heat tolerance (19), particularly if endurance fitness is limited (47).

IL-6 release, which is stimulated by TNF-α, also inhibits production of TNF-α, and in this respect has been proposed to have an important anti-inflammatory role, as well as a proinflammatory role. It is now known to be released mostly from inflammatory factors of the nonspecific immune system (cytokines, interferon), vascular reactivity (PGEs), and coagulation (Factor XII), initially causing inflammatory and fever-producing effects. In advanced stages, this appears to underlie exertional heat stroke (20). However, data obtained from animal models indicate that even lower (i.e., sublethal) endotoxic loads may reduce heat tolerance (19), particularly if endurance fitness is limited (47).

AJP-Regul Integr Comp Physiol • VOL 292 • JANUARY 2007 • www.ajpregu.org
to exhaustion, and none of the subjects reported difficulty or injury as a consequence of the exercise schedules. Even so, this study design does not allow us to exclude a potential acute effect of muscle damage on the pyrogenic response observed.

Recent studies using passively induced hyperthermia have demonstrated that heat-related impairment of force development is attributable to both central and peripheral effects (35, 54). Thus high body temperature itself can impair exercise tolerance independently of its effects in elevating cardiovascular, metabolic, and neuroendocrine strain. Minimizing the fever component of any such hyperthermia would therefore seem beneficial.

The use of NSAIDs during exercise, presumably for musculoskeletal injuries, appears to be widespread. Seventy-two percent of runners in an ultradurance race reported consuming NSAIDs, and, interestingly, the inflammatory cytokine profile of those runners was higher than that of nonusers after the 100-mile race (37). Also widespread is the belief that COX-2-selective NSAIDs avoid some dangers of nonselective NSAIDs, such as hyponatremia. However, COX-2 selective inhibition has been found to reduce free water clearance during and after endurance exercise to an extent similar to nonselective COX inhibition (1), along with the potential for a significant reduction in renal blood flow and glomerular filtration rate. Thus, even if attenuation of hyperthermia were known to be useful in a given athletic or occupational endeavor and COX-2 selective inhibition were shown effective in that setting, the effect of −0.3°C magnitude reduction in Tcore would be realistically achieved by a strategy focusing on adequate hydration, aerobic training, heat acclimatization, weight control, cooling, and possibly dietary modification, rather than the use of COX-2 inhibitors. In at-risk individuals, COX-2 inhibition, as well as nonselective COX inhibition, may carry an increased risk of cardiovascular events (26). The potential risk of a COX-2 inhibitor-associated cardiovascular event in athletes is unknown, but in light of the above discussion, we would recommend caution in the use of these agents in moderate to severe exercise.

Another limitation of using the COX-2 selective inhibitor to examine whether exercise can induce a fever response is that the drug may have a confounding influence on exercise thermoregulation. Although we believe that our hypothesis is supported primarily by virtue of the lower sweat offset threshold for NSAID compared with PLAC in the absence of a shift in MAP, the reduction of cardiovascular strain that was evident with NSAID usage in this study (cardiac frequency lower by −6/min; Fig. 3) is harder to explain. A direct Q10 effect chronotropically should only drop the frequency by −2/min, and although circulating catecholamine levels might further contribute, that should have been evident in measures such as the respiratory exchange ratio and MAP (both of which were equivalent). However, there may also be a direct effect of prostanoids on cardiac frequency (53), as evidenced from mice lacking receptors for the prostanoids thromboxane A2 and prostaglandin F2α. Relative to wild-type mice, the gene-deleted mice showed inhibition of inflammatory tachycardia, apparently via direct action of these prostanoids on cardiac pacemaker cells rather than effects on sympathetic activity. Thus use of a COX-2 inhibitor in our study could possibly have attenuated PGF2α production and exerted a direct negative chronotropic effect despite the low dosage we used.

Regarding other possible cardiovascular effects, inhibition of COX-2-mediated PGF2 production has been found, with higher drug dosages, to attenuate exercise hyperemia in endurance-exercised connective tissue (32), and prostacyclin (PGI2) has been shown to impact on maintenance of resting forearm blood flow (11). In contrast, nonselective COX inhibition with aspirin had no effect on resting forearm blood flow but did reduce vasodilation following isometric contraction of the forearm muscles at 60% MVC (60). Whether such effects could have impacted on cutaneous perfusion in this study is unknown, but we also note that there seems to be considerable redundancy among vasodilatory pathways (e.g., involving prostaglandins and prostanolcyns, ACH, nitrous oxide, and potassium; [9, 11, 32, 60]), such that nonthermoregulatory effects on exercise hyperemia might have been negligible. Finally, since we used a 5-day ingestion protocol (to attain steady-state COX-2 inhibition before first assessing resting thermoregulation), we cannot preclude the possibility of a short-term adaptive response to COX-2 inhibition.

In conclusion, submaximal endurance exercise can induce a feverlike response in humans which causes a supplementary increase in mean body temperature, possibly via the effects of COX-2-mediated PGF2 production on the thermoregulatory set point.

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