Short-term sprint interval training increases insulin sensitivity in healthy adults but does not affect the thermogenic response to β-adrenergic stimulation

Jennifer C. Richards, Tyler K. Johnson, Jessica N. Kuzma, Mark C. Lonac, Melani M. Schweder, Wyatt F. Voyles and Christopher Bell

Department of Health and Exercise Science, Colorado State University, Fort Collins, CO, USA

Sprint interval training (SIT) and traditional endurance training elicit similar physiological adaptations. From the perspective of metabolic function, superior glucose regulation is a common characteristic of endurance-trained adults. Accordingly, we have investigated the hypothesis that short-term SIT will increase insulin sensitivity in sedentary/recreationally active humans. Thirty one healthy adults were randomly assigned to one of three conditions: (1) SIT ($n = 12$): six sessions of repeated (4–7) 30 s bouts of very high-intensity cycle ergometer exercise over 14 days; (2) sedentary control ($n = 10$); (3) single-bout SIT ($n = 9$): one session of 4 × 30 s cycle ergometer sprints. Insulin sensitivity was determined (hyperinsulinaemic euglycaemic clamp) prior to and 72 h following each intervention. Compared with baseline, and sedentary and single-bout controls, SIT increased insulin sensitivity (glucose infusion rate: 6.3 ± 0.6 *vs.* 8.0 ± 0.8 mg kg^{-1} min^{-1}; mean ± S.E.M.; $P = 0.04$). In a separate study, we investigated the effect of SIT on the thermogenic response to beta-adrenergic receptor (β-AR) stimulation, an important determinant of energy balance. Compared with baseline, and sedentary and single-bout control groups, SIT did not affect resting energy expenditure (EE: ventilated hood technique; 6274 ± 226 *vs.* 6079 ± 297 kJ day^{-1}; $P = 0.51$) or the thermogenic response to isoproterenol (6, 12 and 24 ng (kg fat-free mass)$^{-1}$ min^{-1}: %ΔEE 11 ± 2, 14 ± 3, 23 ± 2 *vs.* 11 ± 1, 16 ± 2, 25 ± 3; $P = 0.79$). Combined data from both studies revealed no effect of SIT on fasted circulating concentrations of glucose, insulin, adiponectin, pigment epithelial-derived factor, non-esterified fatty acids or noradrenaline (all $P > 0.05$). Sixteen minutes of high-intensity exercise over 14 days augments insulin sensitivity but does not affect the thermogenic response to β-AR stimulation.

(Received 11 March 2010; accepted after revision 11 June 2010; first published online 14 June 2010)
Corresponding author C. Bell: Department of Health and Exercise Science, 205E Moby B Complex, Colorado State University, Fort Collins, CO 80523-1582, USA. Email: cbell@cahs.colostate.edu

Abbreviations β-AR, beta-adrenergic receptor; EE, energy expenditure; FFM, fat-free mass; GLUT4, glucose transporter 4; NEFA, non-esterified fatty acids; PEDF, pigment epithelial-derived factor; RER, respiratory exchange ratio; SIT, sprint interval training; $\dot{V}_{O_2,peak}$, peak oxygen uptake.

Introduction

Habitual endurance exercise training is associated with superior metabolic regulation in adult humans. Two important examples include increased insulin sensitivity, the principal determinant of blood glucose control (Mikines *et al.* 1989; Hardin *et al.* 1995; Takala *et al.* 1999; Goodpaster *et al.* 2001; Frosig *et al.* 2007; Wadley *et al.* 2007; Dube *et al.* 2008) and augmented thermogenic response to beta-adrenergic receptor (β-AR) stimulation (Bell *et al.* 2006*a*; Stob *et al.* 2007*a*,*b*), a physiologically significant determinant of energy expenditure and thus a major regulator of energy balance and body mass/composition (van Baak, 2001). Despite the enormous potential health benefits of endurance exercise training, many adults choose not to participate, citing insufficient time as a perceived overriding obstacle (Stutts, 2002). Thus, an alternative program of exercise that may elicit similar favourable metabolic adaptations without requiring such an appreciable time commitment is highly attractive and worthy of investigation. Short-term sprint interval exercise training represents a very time-efficient

 DOI: 10.1113/jphysiol.2010.189886

Table 1. Selected subject characteristics from Study 1: sprint interval training and insulin sensitivity

	Sprint interval training	Single bout control	Sedentary control	*P* value
Male/female	5/7	2/7	2/8	—
Age (years)	29 ± 3	24 ± 1	23 ± 1	0.14
Body mass (kg)	75.8 ± 5.8	72.4 ± 5.1	80.3 ± 6.7	0.67
Height (m)	1.69 ± 0.03	1.66 ± 0.04	1.70 ± 0.04	0.75
BMI (kg m^{-2})	26.2 ± 1.3	26.0 ± 1.3	27.6 ± 1.7	0.70
% Body fat	29.6 ± 1.8	28.3 ± 2.5	31.0 ± 2.5	0.72
Fat mass (kg)	22.7 ± 2.8	20.8 ± 2.8	24.7 ± 3.2	0.67
Fat-free mass (kg)	52.8 ± 4.2	49.5 ± 4.3	53.9 ± 4.8	0.79
$\dot{V}_{O_2,peak}$ (ml kg^{-1} min^{-1})	32.7 ± 2.1	38.0 ± 3.9	35.1 ± 3.0	0.45
HR_{peak} (beats min^{-1})	188 ± 3	188 ± 4	192 ± 2	0.59
RER_{peak}	1.16 ± 0.03	1.16 ± 0.03	1.16 ± 0.04	0.99

Data are mean ± S.E.M. BMI, body mass index; HR_{peak}, peak heart rate; $\dot{V}_{O_2,peak}$, peak oxygen uptake; RER_{peak}, peak respiratory exchange ratio.

Table 2. Selected subject characteristics from Study 2: sprint interval training and thermogenic response to beta-adrenergic receptor stimulation

	Sprint interval training	Single bout control	Sedentary control	*P* value
Male/female	3/8	5/3	6/3	—
Age (years)	25 ± 3	28 ± 2	28 ± 2	0.75
Body mass (kg)	66.0 ± 3.3	74.3 ± 2.9	73.9 ± 3.5	0.14
Height (m)	1.68 ± 0.03	1.74 ± 0.02	1.71 ± 0.03	0.30
BMI (kg m^{-2})	23.2 ± 0.8	24.5 ± 1.0	25.3 ± 1.2	0.32
% Body fat	27.6 ± 2.2	21.7 ± 3.9	19.6 ± 2.6	0.13
Fat mass (kg)	18.9 ± 2.1	15.7 ± 3.0	14.2 ± 2.1	0.36
Fat-free mass (kg)	47.2 ± 2.9	56.9 ± 3.7*	58.5 ± 3.6*	0.05
REE_{FFM} (kJ day^{-1})	6274 ± 226	6414 ± 256	6289 ± 285	0.51
$\dot{V}_{O_2,peak}$ (ml kg^{-1} min^{-1})	34.8 ± 3.1	42.7 ± 4.6	42.4 ± 5.0	0.25
HR_{peak} (beats min^{-1})	187 ± 3	185 ± 3	187 ± 4	0.87
RER_{peak}	1.17 ± 0.03	1.19 ± 0.04	1.20 ± 0.04	0.87

Data are mean ± S.E.M. BMI, body mass index; REE_{FFM}, resting energy expenditure adjusted for fat-free mass; HR_{peak}, peak heart rate; $\dot{V}_{O_2,peak}$, peak oxygen uptake; RER_{peak}, peak respiratory exchange ratio. *denotes different to sprint interval training group ($P = 0.05$).

mode of exercise training and stimulates many similar metabolic adaptations to regular endurance exercise training (Burgomaster *et al.* 2005, 2006, 2007, 2008; Gibala *et al.* 2006; Rakobowchuk *et al.* 2008; Babraj *et al.* 2009; Whyte *et al.* 2010). Accordingly, we have completed two separate studies to investigate the hypotheses that short-term sprint interval training will increase insulin sensitivity (Study 1) and augment β-AR metabolic function (Study 2).

Methods

Subjects – Studies 1 and 2

We studied 59 adult males and females. Selected characteristics from participating subjects are presented in Tables 1 and 2 (Studies 1 and 2, respectively). Inclusion criteria for both studies consisted of a sedentary or recreationally active lifestyle (less than 3 days per week of regular moderate-intensity exercise over the previous year), normal fasting blood glucose concentration (<5.5 mmol l^{-1} (<100 mg dl^{-1})), and normal blood pressure ($<140/90$ mmHg). Exclusion criteria included regular use of tobacco products or medications that might confound the interpretation of data, and contraindications to vigorous exercise (as determined by 12-lead beat-by-beat electrocardiogram and blood pressure measurements at rest and during incremental exercise). Consequently, subjects demonstrated physiological attributes typical of young sedentary/recreationally active adults. That is, on average they were normal to slightly overweight (based on body mass index and body composition), of low to average aerobic capacity (based on peak oxygen uptake ($\dot{V}_{O_2,peak}$)), but otherwise healthy. The experimental protocol conformed to the standards set by the *Declaration of Helsinki* of 1975, as revised in 1983, and was approved by the Institutional Review Board at Colorado State University. The nature, purpose and risks

of the study were explained to each subject before written informed consent was obtained.

Overall experimental design (Studies 1 and 2)

All hypotheses were addressed using a repeated-measures design with two control groups (single bout sprint interval training and sedentary control). Briefly, following pre-screening and habituation procedures, and initial determination of primary dependent variables, subjects completed an intervention: short-term sprint interval training, single bout sprint interval training, or sedentary control. Primary dependent variables were re-determined 72 h after completion of the assigned intervention in all subjects. Data collection occurred in the morning following a 12 h fast, 24 h abstention from vigorous exercise, 12 h abstention from caffeine, and 2 h abstention from water. Subjects were studied under quiet resting conditions in the semi-recumbent position. Measurements were performed in a dimly lit room at a comfortable temperature (∼23°C).

Short-term sprint interval training

Sprint interval training, as previously described (Burgomaster *et al.* 2005), entailed six sprint interval training sessions consisting of 4–7 × 30 s maximal efforts on a stationary cycle ergometer (Monark Ergomedic 874 E, Monark, Sweden) performed against a resistance equivalent to 0.075 kg (kg body mass)$^{-1}$. Each 30 s bout was separated by 4 min; to facilitate recovery between training sessions, each session was separated by 1–2 days. Performance parameters during each training session (e.g. peak work rate, mean work rate, etc.) were measured/computed online via a hard-wire connection between the cycle ergometer and a personal computer, and using task-specific software (SMI Power 5.2.8, Delray Beach, FL, USA).

Single-bout sprint interval training (acute-effect control)

In order to determine whether changes in the primary dependent variables were due to an adaptation to short-term sprint interval training or an acute response to the most recent exercise bout, a subgroup of research participants were assigned to a single-bout of sprint interval training performed 72 h prior to 'post-tests'. This single bout consisted of 4 × 30 s maximal efforts on a stationary cycle ergometer against a resistance equivalent to 0.075 kg (kg body mass)$^{-1}$, and was identical to the final bout completed by the sprint interval training group. Each 30 s bout was separated by 4 min.

Sedentary control

To determine the day-to-day reliability of our measurements, the primary dependent variables were determined on two separate occasions in a subgroup of subjects separated by a minimum of 14 days; the subjects maintained their normal habitual physical activity and refrained from sprint interval training.

Study 1 – insulin sensitivity

Insulin sensitivity was determined using the hyperinsulinaemic euglycaemic clamp technique (DeFronzo *et al.* 1979; Rattarasarn *et al.* 2004); this is considered by many to be the gold-standard measurement of insulin sensitivity (Bloomgarden, 2006). Briefly, intravenous catheters were inserted into an antecubital vein for infusion of insulin and glucose, and into a contralateral dorsal hand vein, warmed via a heated blanket for arterialized-venous blood sampling. A descending dose (127–40 mU (m body surface area)$^{-2}$ min^{-1}) of regular insulin (Humulin, Eli Lilly and Co., Indianapolis, IN, USA) was administered over the first 10 min, followed by a continuous infusion (40 mU (m body surface area)$^{-2}$ min^{-1}) from 10 to 180 min. Administration of a 20% dextrose solution was initiated at 4 min (2 mg (kg body mass)$^{-1}$ min^{-1}) and adjusted as necessary to maintain blood glucose at a concentration of 5 mmol l^{-1} (90 mg dl^{-1}) throughout the clamp period. Arterialized-venous blood samples (∼1 ml) were obtained every 5 min and blood glucose concentration was analysed immediately using an automated device (2300 STAT Plus Glucose Lactate Analyzer, YSI Inc., Yellow Springs, OH, USA). Insulin sensitivity was determined from the mean rate of glucose infusion during the last 30 min of the clamp and expressed as milligrams of glucose per kilogram body weight per minute.

Metabolic flexibility

Metabolic flexibility (the ability to transition between lipid and carbohydrate as a primary fuel source) is typically expressed as the increase in respiratory exchange ratio (RER: CO_2 production/O_2 uptake ($\dot{V}_{CO_2}/\dot{V}_{O_2}$)) measured immediately prior to and during the final 5 min of a hyperinsulinaemic euglycaemic clamp. Compared with healthy lean adults the increase in RER during a clamp is attenuated in adults who are obese and/or insulin resistant (Kelley *et al.* 1999; Kelley & Mandarino, 2000; Storlien *et al.* 2004). To investigate the influence of sprint interval training on metabolic flexibility, breath-by-breath $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ data were collected at the mouth using a respiratory mass spectrometer (Perkin Elmer MGA 1100, MA Tech Services, St Louis, MO, USA) and an ultrasonic flow

sensor (ndd Medizintechnik AG, Zürich, Switzerland) and averaged over 5 min.

Study 2 – thermogenic response to β-AR stimulation

Resting energy expenditure was measured over 45 min. The first 15 min were considered a habituation period. $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were averaged each minute for 30 min using a custom-built ventilated hood indirect calorimetry system (Nighthawk Design, Boulder, CO, USA). The system was calibrated daily with precision-mixed gases (Airgas, Denver, CO, USA). Energy expenditure was calculated using the Weir formula (Weir, 1949). In our laboratory the measurement of resting energy expenditure has a coefficient of variation of 3.3% and a test re-test r^2 of 0.93 (Newsom *et al.* 2008).

Immediately following determination of resting energy expenditure the thermogenic response to β-AR stimulation was quantified as the percentage increase in energy expenditure above rest during continuous and incremental intravenous (antecubital or dorsal hand) administration of the non-selective β-AR agonist isoproterenol (6, 12 and 24 ng (kg fat-free mass)$^{-1}$ min^{-1}), as previously described (Bell *et al.* 2006*a*,*b*; Stob *et al.* 2007*a*,*b*). Each dose was administered over 30 min. Energy expenditure was calculated from the average of the final 25 min of each 30 min collection. Beat-by-beat heart rate (3-lead electrocardiogram) and blood pressure were determined throughout via an automated physiological monitor (Cardiocap 5, GE Datex-Ohmeda, Madison, WI, USA).

Procedures common to both studies

Fasting basal venous blood samples collected during Studies 1 and 2 (representing identical interventions) were combined and analysed for circulating concentrations of factors previously associated with insulin sensitivity and/or β-AR thermogenic function. Blood (∼20 ml preserved with K_3 ethylenediaminetetraacetic acid, plus ∼5 ml preserved with ethylene glycol tetraacetic acid/glutathione) was collected in chilled tubes, placed immediately on ice and centrifuged within 60 min of collection to isolate plasma. Plasma samples were stored at –80°C until analysis. Plasma catecholamine concentrations were analysed in duplicate using high-performance liquid chromatography. Enzyme-linked immunosorbent assays (ELISA) were used to measure, in duplicate, plasma concentrations of insulin, adiponectin and PEDF (all Millipore Corporation, Billerica, MA, USA), and non-esterified fatty acids (NEFA; Wako Diagnostics, Richmond, VA, USA).

Fat mass and fat-free mass were measured using dual-energy x-ray absorptiometry (DXA-IQ; Lunar Radiation Corp., Madison, WI, USA; software version 4.1). $\dot{V}_{O_2,peak}$ was determined with a metabolic cart (Parvo Medics, Sandy, UT, USA) during incremental cycle ergometer exercise (20–25 W min^{-1}) to volitional fatigue, as previously described (Bell *et al.* 1999*a*,*b*, 2003*a*).

Statistical analysis

These were controlled, repeated measures studies. Accordingly, in Study 1 the influence of sprint interval training on insulin sensitivity (glucose infusion rate) was examined via two-way (sprint training *vs.* single bout *vs.* sedentary control) repeated measures (before *vs.* after) analysis of variance (ANOVA). Similarly, in Study 2 the influence of sprint interval training on the thermogenic response to β-AR stimulation (% increase in energy expenditure above rest) was also examined by two-way repeated measures ANOVA. Resting energy expenditure was positively associated with fat-free mass ($r = 0.95$, $P < 0.0001$) thus, differences in resting energy expenditure were examined using analysis of co-variance (ANCOVA) with fat-free mass as the co-variant. Multiple comparisons of factor means were performed using the Newman–Keuls test. The level of statistical significance was set at $P < 0.05$. Data are expressed as mean ± S.E.M.

Results

Study 1 – sprint interval training and insulin sensitivity

Sprint interval training. Twelve subjects were prescribed 32 sprints over 2 weeks, equaling 384 sprints in total; 380 were successfully completed (>98%). No subject completed <30 sprints. Subjects who failed to complete the prescribed number of sprints in a given session attributed their failure to nausea; no injuries were sustained as a result of sprint interval training. The first and final sprint interval sessions each comprised four sprints. Peak and mean power outputs during these sessions are presented in Supplementary Table S1. There was a session–interval interaction for peak power ($P = 0.03$) in that peak power was greater in the final session for the 3rd and 4th intervals. The session–interval interaction for mean power failed to attain statistical significance ($P = 0.08$).

Insulin sensitivity. Insulin sensitivity, as indicated by the glucose infusion rate required to maintain a blood glucose concentration of 5 mmol l^{-1} during administration of insulin, was increased ($P = 0.04$) following sprint interval training (mean change: +1.66 ± 0.61 mg kg^{-1} min^{-1}) compared with the single-bout (+0.82 ± 0.93 mg kg^{-1} min^{-1}) and sedentary

($+0.34 \pm 0.40$ mg kg^{-1} min^{-1}) controls (Fig. 1). Sprint interval training increased insulin sensitivity in 10 subjects, decreased it in 1 (from 7.1 to 6.5 mg kg^{-1} min^{-1}) and left it unchanged in another. Due to technical reasons, we were unable to determine plasma insulin concentration at the end of the hyperinsulinaemic euglycaemic clamp in all subjects. However, in a sub-sample of subjects, the end-clamp insulin concentrations appeared to be relatively constant between trials (sprint interval training ($n = 5$): 457 ± 40 *vs.* 403 ± 25 pmol l^{-1}; single-bout ($n = 6$): 389 ± 83 *vs.* 397 ± 41 pmol l^{-1} sedentary control ($n = 9$): 462 ± 142 *vs.* 401 ± 167 pmol l^{-1}). Although not a primary focus of this investigation, there was no sprint interval training/insulin sensitivity/sex interaction ($P = 0.20$).

Unexpectedly, basal insulin sensitivity appeared to be greater in the single bout relative to the sprint interval training group; however, this difference did not attain statistical significance ($P = 0.059$). Moreover, the change in insulin sensitivity between interventions was unrelated to basal insulin sensitivity in any of the groups (sprint interval: $r = -0.26$, $P = 0.42$; single-bout: $r = -0.55$, $P = 0.26$; or sedentary: $r = 0.18$, $P = 0.61$).

Neither fasting nor end-clamp blood glucose concentrations were different between or within groups (all $P > 0.64$). Similarly, body mass did not differ between or within groups ($P > 0.37$).

RER increased in all subjects, in all groups and in all conditions during the final 5 min of the clamp compared with the pre-clamp measurement (Supplementary Data Fig. S1; $P < 0.0001$). However, there were no group/condition interactions ($P = 0.45$) indicating that metabolic flexibility was unaffected by sprint interval training relative to the control conditions.

In all subjects combined, basal insulin sensitivity was inversely associated with body mass index ($r = -0.54$, $P = 0.002$), %body fat ($r = -0.40$, $P = 0.03$) and fat mass ($r = -0.53$, $P = 0.003$), and was positively associated with $\dot{V}_{O_2,peak}$ ($r = 0.37$, $P = 0.045$).

Study 2 – sprint interval training and thermogenic response to β-AR stimulation

Subjects. Unexpectedly, fat-free mass was slightly greater in the single bout and sedentary control groups compared with the sprint interval group (Table 2; $P = 0.05$). There were no other between group differences (all $P > 0.12$).

Sprint interval training. Over 98% (347/352) sprints were successfully completed. No subject completed <30 sprints. Peak and mean power outputs during these sessions are presented in Supplementary Table S2.

Basal data and responses to β-AR stimulation. Resting energy expenditure, adjusted for fat-free mass (Table 2), was unaffected by short-term sprint interval training relative to the control conditions (Supplementary data: Fig. S2; $P = 0.51$). Similarly, there was no impact of sprint-interval training on respiratory exchange ratio (Supplementary Table S3; $P = 0.85$). β-AR stimulation increased energy expenditure in all subjects ($P < 0.001$); however, there were no group-intervention interactions ($P = 0.79$), indicating that short-term sprint interval training did not affect the thermogenic response to β-AR stimulation (Fig. 2). Similarly, there were no sprint interval training/thermogenic response/sex interactions ($P = 0.83$). Furthermore, sprint interval training did not affect the cardiovascular (heart rate and blood pressure) responses to β-AR stimulation (Supplementary Table S3; all $P > 0.43$). Heart rate was unexpectedly greater in the sprint interval group at all doses of isoproterenol ($P = 0.009$) compared with the other groups; however, the magnitude of increase in heart rate above baseline during β-AR stimulation was not different between groups ($P = 0.99$).

Combined blood/plasma data (Study 1 and Study 2)

Fasting plasma concentrations of glucose, insulin, noradrenaline, NEFA, adiponectin and PEDF are displayed in Table 3. Relative to the single-bout and sedentary control conditions, none of these variables were influenced by short-term sprint interval training (all $P > 0.05$).

Baseline plasma PEDF concentration was inversely associated with insulin sensitivity ($r = -0.51$; $P = 0.02$), and metabolic flexibility ($r = -0.72$; $P = 0.001$). Plasma

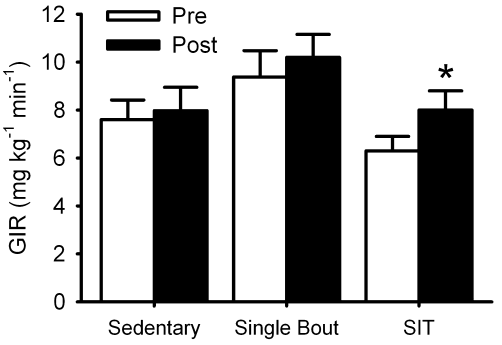

Figure 1. Short-term sprint interval training increases insulin sensitivity
Short-term sprint interval training increases insulin sensitivity, as described by the intravenous glucose infusion rate required to maintain blood glucose concentration at 5 mmol l^{-1} (90 mg dl^{-1}) during a standardized administration of insulin (hyperinsulinaemic euglycaemic clamp). Data are mean ± S.E.M. SIT, short-term sprint interval training. GIR, glucose infusion rate. * denotes difference between pre- and post-intervention ($P = 0.04$).

Table 3. Influence of short-term sprint interval training on selected blood parameters

	Sprint interval training		Single bout		Sedentary	
	Pre	Post	Pre	Post	Pre	Post
Glucose (mmol l^{-1})	4.44 ± 0.14	4.44 ± 0.11	4.05 ± 0.08	4.16 ± 0.06	4.22 ± 0.08	4.27 ± 0.06
Insulin (pmol l^{-1})	37.3 ± 7.9	32.1 ± 6.0	25.0 ± 4.8	22.8 ± 3.5	33.5 ± 8.1	33.1 ± 5.1
NEFA (mmol l^{-1})	0.51 ± 0.03	0.46 ± 0.04	0.50 ± 0.04	0.46 ± 0.04	0.45 ± 0.03	0.42 ± 0.03
Noradrenaline (nmol l^{-1})	0.97 ± 0.12	0.91 ± 0.09	0.86 ± 0.12	0.94 ± 0.12	0.94 ± 0.13	0.98 ± 0.10
Adiponectin (μg ml^{-1})	8.68 ± 0.97	8.72 ± 0.93	8.49 ± 0.62	8.52 ± 0.76	9.01 ± 0.47	8.59 ± 0.59
PEDF (μg ml^{-1})	4.28 ± 0.47	4.44 ± 0.62	4.32 ± 0.60	3.86 ± 0.48	4.74 ± 0.72	4.60 ± 0.74

Data are mean ± S.E.M. NEFA, non-esterified fatty acids; PEDF, pigment epithelial-derived factor.

PEDF concentration was decreased during β-AR stimulation (Fig. 3; $P = 0.014$).

Discussion

The novel findings of this investigation are: (1) short-term sprint interval training increased insulin sensitivity, as assessed using the gold-standard hyperinsulinaemic euglycaemic clamp technique. This improvement was not due to the acute effects of the most recent exercise bout, nor can it be attributed to changes in circulating concentrations of NEFA, adiponectin, PEDF or catecholamines; and (2) short-term sprint interval training did not affect resting energy expenditure or the thermogenic response to β-AR stimulation. We also report for the first time in humans on the inverse association between circulating PEDF concentration and a direct measure of insulin sensitivity, and on the decrease in circulating PEDF during β-AR stimulation, providing novel preliminary evidence for a role of the sympathetic nervous system in the regulation of PEDF in humans.

Based on several recent studies short-term sprint interval training appears to be a very time-efficient mode of exercise training that shares many of the same metabolic adaptations associated with traditional endurance exercise training (Burgomaster *et al.* 2005, 2006, 2007, 2008; Gibala *et al.* 2006; Rakobowchuk *et al.* 2008; Babraj *et al.* 2009; Whyte *et al.* 2010). In light of these observations, our hypotheses pertaining to increased insulin sensitivity and augmented β-AR thermogenic function are well supported. Increased aerobic enzyme capacities, mitochondrial biogenesis and

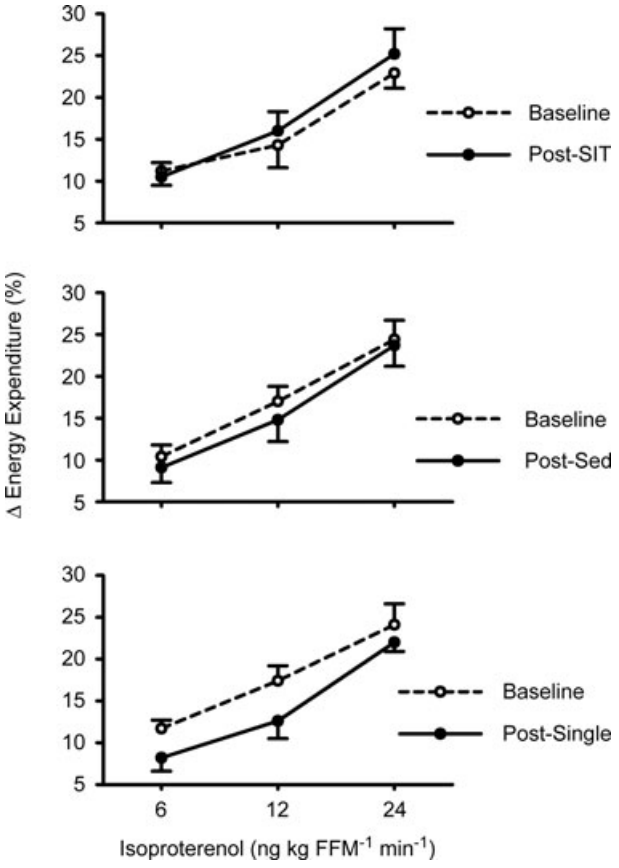

Figure 2. Short-term sprint interval training does not affect the thermogenic response to intravenous beta-adrenergic receptor (β-AR) stimulation

β-AR stimulation increased energy expenditure in all subjects ($P < 0.001$); however, there were no group-intervention interactions ($P = 0.79$). Data are mean ± S.E.M. SIT, short-term sprint interval training. SED, sedentary control. Single, single-bout of sprint interval training. FFM, fat-free mass.

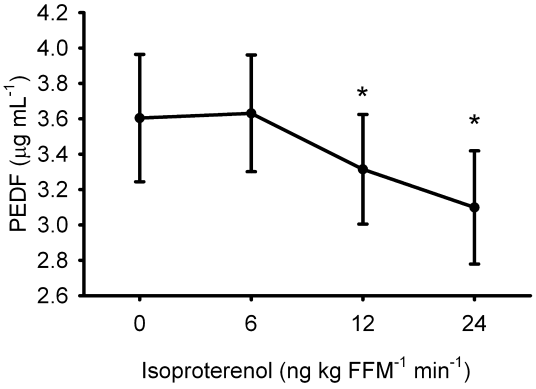

Figure 3. During acute, intravenous beta-adrenergic receptor stimulation circulating concentration of pigment epithelial-derived factor (PEDF) is decreased

* denotes difference to baseline (0 ng kg FFM^{-1} min^{-1}) value ($P < 0.05$). Data are mean ± S.E.M. FFM, fat-free mass.

increased glucose transporter 4 (GLUT4) expression have all been independently associated with improved insulin sensitivity (Hughes *et al.* 1993; Simoneau *et al.* 1995; Heilbronn *et al.* 2007) and short-term sprint interval training (Burgomaster *et al.* 2005, 2006, 2007, 2008; Gibala *et al.* 2006; Rakobowchuk *et al.* 2008; Babraj *et al.* 2009). Further, sprint interval training has been shown to decrease the magnitude and duration of the blood glucose response to oral consumption of a glucose-enriched beverage, providing indirect evidence of improved insulin sensitivity (Babraj *et al.* 2009).

In order to provide further insight into the influence of short-term sprint interval training on insulin sensitivity, we measured several circulating factors previously shown to be associated with insulin action. The link between plasma NEFA concentration and insulin sensitivity is clearly established (Steiner *et al.* 1980; Reaven *et al.* 1988; Byrne *et al.* 1994; Franks *et al.* 2002; Qvigstad *et al.* 2003; Gormsen *et al.* 2007; Schenk & Horowitz, 2007). In the current study, plasma NEFA was unaffected by short-term sprint interval training. This observation is supported by two previous studies demonstrating an unappreciable influence of identical programs of sprint interval training on circulating NEFA in young men (Babraj *et al.* 2009; Whyte *et al.* 2010).

Another circulating blood marker of potential significance to the current study is adiponectin; its insulin-sensitizing effects have been well described (Yamauchi *et al.* 2001; Wang *et al.* 2008). In the current study the relation between basal plasma adiponectin and insulin sensitivity did not attain statistical significance ($r = 0.43$, $P = 0.095$), nor did plasma adiponectin increase following short-term sprint interval training. The influence of exercise on plasma adiponectin concentration is unclear as some authors have reported an increase (Christiansen *et al.* 2010*a*; Okamoto *et al.* 2009), while others have either reported no change (Christiansen *et al.* 2010*b*; Ando *et al.* 2009) or a decrease (Moran *et al.* 2010; Van Berendoncks *et al.* 2010). These discrepancies may be attributed to differences in exercise intensity, duration and modality, and the pre-exercise training metabolic characteristics of the research participants.

PEDF is emerging as an important determinant of oxidative stress (Zhang *et al.* 2008; Banumathi *et al.* 2010); inflammation and angiogenesis (Jenkins *et al.* 2007; Zhang *et al.* 2008) is high in adults with diabetes (Jenkins *et al.* 2007; Ogata *et al.* 2007), and is positively associated with characteristics of the metabolic syndrome (Yamagishi *et al.* 2006). In the current investigation, basal plasma PEDF concentration was inversely associated with insulin sensitivity and metabolic flexibility; however, it was unaffected by short-term sprint interval training. We are unaware of any other study that has examined the influence of exercise training on PEDF in humans.

Other relevant, but not measured, circulating factors that may have contributed to the increased insulin sensitivity include, but are not limited to, tumour necrosis factor α (Hotamisligil *et al.* 1993, 1994; Plomgaard *et al.* 2005; Lambert *et al.* 2008), interleukin-6 (Carey *et al.* 2006; Lambert *et al.* 2008; Croft *et al.* 2009) and resistin (Pravenec *et al.* 2003; Singhal *et al.* 2007; Jones *et al.* 2009). Alternatively, it may be that the increase in insulin sensitivity was due to changes in the metabolic characteristics of skeletal muscle. This explanation is intuitively appealing as the hyperinsulinaemic euglycaemic clamp technique is thought to reflect skeletal muscle insulin sensitivity (Muniyappa *et al.* 2008). Potential skeletal muscle characteristics driving this response include, but are not limited to, increased GLUT 4, upregulated aerobic enzyme activity, increased mitochondrial biogenesis (all previously observed following short-term sprint interval training (Burgomaster *et al.* 2005, 2006, 2007, 2008; Gibala *et al.* 2006; Rakobowchuk *et al.* 2008; Babraj *et al.* 2009; Little *et al.* 2010)), and increased endogenous antioxidant defenses in response to exercise-induced production of reactive oxygen species (Marzatico *et al.* 1997; Ristow *et al.* 2009).

One potentially very important question pertinent to studies of exercise training and the resultant effects on insulin sensitivity is whether any change in insulin sensitivity is due to training, or to the most recent exercise bout. Effects of an acute exercise bout are detectable for up to 48 h (Cartee *et al.* 1989; Holloszy, 2005). In a recent investigation, insulin sensitivity (determined via an oral glucose tolerance test) was improved in overweight/obese men 24 h, but not 72 h, following short-term sprint interval training (Whyte *et al.* 2010). Differences between this and the current investigation include the technique for measurement of insulin sensitivity, subject characteristics (overweight/obese men *vs.* sedentary/recreationally active men and women) and the incorporation of control conditions (none *vs.* sedentary and single bout). We report that a single bout of sprint interval training, identical to the final bout of short-term sprint interval training, did not influence insulin sensitivity. Accordingly, we conclude that increased insulin sensitivity following short-term sprint interval training was indeed a training effect and not simply attributable to the acute influence of the final exercise bout.

Another important consideration, before prescribing short-term sprint interval training to improve insulin sensitivity, is the possibility that the insulin sensitizing effects of this type of exercise may be different, or even absent, in obese and/or insulin-resistant adults. A recent study showed that while sprint interval training may provide some health benefits to overweight/obese men, the improvement in insulin sensitivity was relatively short lasting (Whyte *et al.* 2010). Alternatively, exercise

training has been shown to induce similar mitochondrial adaptations in adults with type II diabetes compared with healthy controls (Phielix *et al.* 2010).

The second hypothesis of the current investigation (Study 2) pertained to the thermogenic response to β-AR stimulation. Tonic stimulation of β-ARs by the sympathoadrenal system is an important neuro-endocrine determinant of total daily energy expenditure and hence energy balance in humans (Tappy, 1996; Bell *et al.* 2001, 2003*b*, 2004; Monroe *et al.* 2001;van Baak, 2001). Further, habitual endurance exercise training is highly associated with augmented sympathoadrenal regulation of energy expenditure (Bell *et al.* 2001, 2004, 2006*a*; Jones *et al.* 2004; Stob *et al.* 2007*b*) and several studies have demonstrated favourable β-AR-mediated metabolic functioning in overweight and obese adults following endurance exercise training (van Aggel-Leijssen *et al.* 2001). In light of many of the metabolic adaptations common to both endurance and sprint interval training, we hypothesized that short-term sprint interval training would augment the magnitude of increase in energy expenditure during β-AR stimulation. Contrary to our hypothesis, we report that short-term sprint interval training does not affect resting energy expenditure or the thermogenic response to β-AR stimulation. Potential explanations for these observations include the perhaps trivial energetic cost of sprint interval exercise ($\sim$600 kJ; Gibala *et al.* 2006) and the lack of influence of sprint interval training on basal sympathoadrenal tone, as reflected by plasma catecholamine concentration, and indirectly by resting heart rate and blood pressure.

An additional observation in Study 2 pertained to sympathoadrenal regulation of PEDF. Contrary to animal and cell culture data showing decreased PEDF following surgical sympatholysis, and increased PEDF following isoproterenol/noradrenaline administration (Lashbrook & Steinle, 2005; Steinle *et al.* 2008), we have demonstrated that β-AR stimulation decreased circulating PEDF. One caveat to this conclusion is that our data were collected without an acute control condition (e.g. vehicle administration). In light of multiple and strong associations in humans between PEDF and metabolic and cardiovascular disease risk factors, (Yamagishi *et al.* 2006; Crowe *et al.* 2009; Klaus *et al.* 2009), identification of the physiological mechanism responsible for the regulation of PEDF should be a high priority. Our preliminary data provide impetus for future studies of a regulatory role for β-ARs.

On first inspection, our two primary dependent variables from Studies 1 and 2 seem unrelated; however, a recent study in rats modified by selective breeding for poor aerobic capacity demonstrated an association between insulin resistance and attenuated lipolytic response to β-AR stimulation (Lessard *et al.* 2009). The rationale for the study pertained to the role of β-ARs in the regulation of skeletal muscle lipid storage: briefly, impaired ability of β-ARs to activate hormone-sensitive lipase and subsequently mobilize diacyglycerol and triacyglycerol may contribute to disrupted insulin signaling in skeletal muscle. Rats with a low aerobic exercise capacity demonstrated low insulin sensitivity and an unappreciable response to β-AR stimulation (Lessard *et al.* 2009). In the current investigation, we have provided indirect, dissociative data (albeit in separate populations) as short-term sprint interval training increased insulin sensitivity but did not affect β-AR metabolic function.

There are several potential limitations in the current investigation that warrant discussion. First, unexpectedly, the research participants assigned to the single-bout control group appeared to have greater basal insulin sensitivity than the short-term sprint interval group. A potential implication of this difference, and an alternative interpretation of our data, is that insulin sensitivity was already high in the single-bout group, thus the likelihood of an additional increase was low compared with the sprint interval participants. While plausible, we do not believe this to be the case as the difference in basal insulin sensitivity between the groups was not statistically significant ($P = 0.06$), and, more importantly, based on data from previous studies employing a similar hyperinsulinaemic euglycaemic clamp protocol to that utilized in the current investigation, our single-bout participants were far from an upper limit of insulin sensitivity (Goodpaster *et al.* 2001; Bruce *et al.* 2003; Bergman *et al.* 2007; Dube *et al.* 2008).

Another potential limitation was the absence of a measurement of body composition following short-term sprint interval training. The primary outcome variables of the current investigation are all influenced by fat-free mass, thus it is plausible that any changes (or lack thereof) in insulin sensitivity, resting energy expenditure and the thermogenic response to β-AR stimulation may be due in part to changes in fat-free mass. Given that body mass did not change following sprint interval training in the current and in previous studies (Babraj *et al.* 2009) we speculate, but cannot definitively state, that body composition is not affected by short-term sprint interval training.

The inclusion of both male and female study participants may be viewed as a strength of the current investigation, although the potential for sex differences in responses to exercise training with respect to insulin sensitivity (Hickey *et al.* 1997; Potteiger *et al.* 2003) and sympathetic/β-AR function (Crampes *et al.* 1989; Bell *et al.* 2001; Scott *et al.* 2007) may have introduced additional variability to our data. We did not observe an influence of sex on the response to sprint interval training for either of our primary outcomes, although our experimental design was not statistically powered *a priori* to address this issue.

Finally, in Study 1 we were unable to report plasma insulin concentration at the end of the hyperinsulinaemic

euglycaemic clamp in all subjects. This limits our ability to rule out, with absolute certainty, the possibility that differences in glucose disposal were due to differences in end-clamp insulin concentration pre- and post-interventions. However, in the subset of subjects in whom we were able perform this analysis, the end-clamp insulin concentrations appeared to be relatively constant, thus rendering this potential alternative explanation as unlikely.

The perceived exertion associated with sprint interval training is extremely high and reports of nausea and light-headedness are not uncommon. Accordingly, successful completion of sprint interval training requires a high degree of motivation. In the current investigation, all sprint interval sessions were supervised and research participants received substantial verbal encouragement. While this combination of supervision and encouragement undoubtedly contributed to the high compliance rate, it raises the questions as to the feasibility of sprint interval training as a realistic alternative to traditional endurance exercise training. Future studies need to address whether similar benefits might be obtained from lower intensity exercise, and whether it is the absolute or relative load that determines the impact of short-term sprint interval training. For instance, a recent study has demonstrated that improvements in endurance performance and mitochondrial function are obtainable from low-volume (∼1 h per week), high relative-intensity (∼100% peak power) training (Little *et al.* 2010).

In summary, 16 min of very high-intensity, sprint interval exercise training distributed over 2 weeks, increased insulin sensitivity but did not impact resting energy expenditure or the thermogenic response to β-AR stimulation. The increased insulin sensitivity cannot be attributed to changes in plasma concentrations of NEFA, adiponectin and/or PEDF, nor can it be attributed to changes in body mass, and is unlikely to be due to changes in body composition. This implies that the increased insulin sensitivity may be due to adaptations within skeletal muscle. We also report for the first time in humans on the relation between plasma PEDF and a direct measure of insulin sensitivity, and on the potential regulatory role of β-ARs on plasma PEDF.

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Author contributions

J.C.R., T.K.J., M.C.L. and C.B. were involved with the conception and design of the study. J.C.R., T.K.J., J.N.K., M.C.L., M.M.S. and C.B. were involved with analysis and interpretation of data. All authors were involved with drafting the article or revising it critically for important intellectual content and providing final approval of the version to be published. Experiments were performed in the Department of Health and Exercise Science, at Colorado State University, Fort Collins, CO, USA.

Acknowledgements

This study was supported by an award from the American Diabetes Association's Amaranth Diabetes Fund.