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Acute Inactivity Impairs Glycemic Control but Not Blood Flow to Glucose Ingestion

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Abstract

Purpose—Insulin-stimulated increases in skeletal muscle blood flow play a role in glucose disposal. Indeed, 7 days of aerobic exercise in type 2 diabetes patients increased blood flow responses to an oral glucose tolerance test (OGTT) and improved glucose tolerance. More recent work suggests that reduced daily physical activity impairs glycemic control (GC) in healthy individuals. Herein, we sought to determine if an acute reduction in daily activity (from >10,000 to <5,000 steps/day) for 5 days (RA5) in healthy individuals reduced insulin-stimulated blood flow and GC in parallel and if a 1 day return to activity (RTA1) improved these outcomes.

Methods—OGTTs were performed as a stimulus to increase insulin in 14 healthy, recreationally active men (24±1.1 yrs) at baseline, RA5, and RTA1. Measures of insulin sensitivity (Matsuda index) and femoral and brachial artery blood flow were made during the OGTT. Free living measures of GC including peak postprandial glucose (peak PPG) were also made via continuous glucose monitoring.

Results—Femoral and brachial artery blood flow increased during the OGTT but neither was significantly impacted by changes in physical activity ($p>0.05$). However, insulin sensitivity was decreased by RA5 (11.3±1.5 to 8.0±1.0; $p<0.05$). Likewise, free living GC measures of peak post prandial blood glucose (113±3 to 123±5 mg/dL; $p<0.05$) was significantly increased at RA5. Interestingly, insulin sensitivity and GC as assessed by peak PPG were not restored after RTA1 ($p>0.05$).

Conclusions—Thus, acute reductions in physical activity impaired GC and insulin sensitivity; however blood flow responses to an OGTT were not affected. Further, a 1 day return to activity was not sufficient to normalize GC following 5 days of reduced daily physical activity.

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Conflicts of Interest

The authors have no conflicts of interest.

Keywords

inactivity; blood glucose; insulin; conduit artery flow

Introduction

By the year 2050, 1 in 3 individuals will be diagnosed with type 2 diabetes (4), a disease characterized by skeletal muscle insulin resistance (30). Skeletal muscle is the largest site for glucose disposal which in part is regulated by insulin (10). Insulin mediated skeletal muscle glucose disposal is also regulated by the vasculature (2, 9, 38). Insulin in muscle and endothelial cells stimulates the insulin receptor to activate phosphatidylinositide 3-kinase and protein kinase B/AKT (13). In muscle this results in the translocation of glut-4 to the plasma membrane to uptake glucose (17). In endothelial cells activation of AKT stimulates the production of nitric oxide (NO), a vasodilator (13) as well as endothelin-1 (ET-1), a vasoconstrictor (13). In normal healthy subjects, the stimulation of insulin on the endothelial cell results in vasodilation. However, with reductions in insulin sensitivity, an imbalance in the production of NO and ET-1 occurs favoring vasoconstriction of blood vessels (14). Insulin stimulated blood flow has been shown to account for up to 40% of glucose uptake (2), thus reducing the blood flow response to insulin may also reduce the ability of the muscle to uptake glucose.

We have previously shown that short term reductions in physical activity in healthy individuals leads to increased post prandial blood glucose responses (PPG) (25). This alteration is important as previous studies show that an elevated PPG is associated with increased cardiovascular disease morbidity and mortality (26). Our lab also, recently demonstrated that short term reductions in daily physical activity impairs endothelial function (5). Given the importance of the endothelium for insulin stimulated blood flow responses, this finding may be related to impaired glycemic control with physical inactivity. However, it is unclear if blood flow responses to insulin are impaired following reduced physical activity and occur in parallel with reductions in glycemic control and insulin sensitivity. In addition, although it is known that a single bout of exercise can improve insulin sensitivity (11) and glycemic control in sedentary individuals (27) it is unkown if one bout of exercise can restore free living glycemic control and insulin sensitivity in subjects who were acutely transitioned to reduced daily activity or if these changes will track with insulin stimulated blood flow responses.

The purpose of this study was to determine if an acute transition to reduced daily physical activity (from >10,000 to <5,000 steps/day) for 5 days (RA5) in healthy, recreationally active men, reduced skeletal muscle blood flow responses following glucose ingestion and glycemic control in parallel. We also examined if a 1 day return to physical activity (>10,000 steps/day) (RTA1) improved these outcomes. An oral glucose tolerance test (OGTT) was used to increase plasma insulin levels, while femoral and brachial artery blood flow were measured. Insulin sensitivity was assessed via the Matsuda index. In addition, in order to assess the post prandial blood glucose response in free living conditions, we utilized continuous glucose monitoring systems (CGMS) and standardized meals across the study

intervention. We hypothesized that blood flow responses to an OGTT would be reduced with 5 days of physical inactivity concurrently with reduced glycemic control and a 1 day return to physical activity would improve these outcomes.

Methods

Subjects

Protocols were approved by the University of Missouri Health Sciences Institutional Review board and written informed consent was obtained from all subjects. Healthy, recreationally active, young (24±1.1yrs) men (n=14) were recruited for the study. Completing at least 90 min of primarily aerobic lower body exercise ≥3 days per week (self-reported) and taking greater than 10,000 steps per day (verified by pedometers) defined recreationally active for this study. Exclusion criteria included: smoking, recent (<2 mo.) change in body weight, or training for competitive endurance events. A subset of data examining endothelial function following 5 days of reduced activity from 12 subjects recruited for this study have been previously published (5).

Experimental Design

Pre Intervention Testing—Prior to the study intervention body composition was assessed by DEXA (Hologic) and fitness by a graded maximal treadmill test to elicit maximal oxygen uptake (VO_{2max}). Subjects were provided with breakfast, lunch, dinner, and snacks for three consecutive days prior to testing to determine daily energy intake. Specifically, due to the habitual eating patterns of young adult Americans (37) the breakfast meal was standardized to 15% of daily energy (~450 kcal) and lunch was standardized to 24% of daily energy intake (~850 kcal). A morning and afternoon snack was also provided (~200 kcal/snack). Lastly, an ad libitum dinner was provided to allow the participants to adjust their intake according to their habitual dietary pattern. All meals were comprised of 57% carbohydrate, 28% fat, and 15% protein. Daily energy intake over the 3-days was then determined. Subjects were asked to fill out a questionnaire to assess compliance to the diet and were also asked to return any uneaten food in packed out containers back to the laboratory. Subjects also monitored daily steps for 3 days via a pedometer and average daily energy expenditure above 3 METS (kilojoules) via a physical activity monitor (Body Media). Kilojoules were then converted to kilocalories by the following equation: $\text{kilocalories} = (\text{kilojoules} \times 0.239)$. Average daily energy expenditure was not calculated in 2 subjects due to software malfunction of the physical activity monitor. The activity monitor also recorded wear time so that compliance could be verified.

Intervention (5 Days of Reduced Physical Activity and 1 Day Return to Activity)—Figure 1 shows the timeline of the overall study design. Subjects began the 5 days of reduced daily physical activity intervention (<5,000 steps/day) following baseline testing, as previously described by our lab (5). In order to achieve this, subjects were instructed to refrain from structured exercise, take the elevator instead of stairs and/or park closer to the door entrance. Following the 5 day inactivity intervention testing, subjects immediately began a 1 day return to physical activity. During this phase subjects resumed normal physical activity levels in addition to performing a supervised bout of aerobic

exercise that was of similar duration and magnitude as baseline testing. The exercise bout was performed in the morning (~7 am) prior to breakfast at both baseline and during the 1 day return to activity visits. This intervention was chosen for the return to physical activity because one bout of exercise in previously sedentary individuals has been shown to improve insulin sensitivity and glycemic control (27, 35). Pedometers were worn for subjects to quantitatively assess daily steps.

Experimental Protocol

Subjects wore a pedometer and physical activity monitor for 3 days before baseline testing and were instructed to follow normal physical activity patterns. A continuous glucose monitor was inserted subcutaneously in the abdomen of each subject for recording of interstitial blood glucose (24, 25). During the 2 days prior to baseline testing and throughout the entire study intervention, the subjects received eucaloric meals and snacks based on their respective measured intake determined during the pre-intervention testing. A 45 minute supervised treadmill exercise session at 60% of heart rate reserve was performed 24 hours prior to baseline testing to control for the amount and time of day when the subjects received their last bout of structured physical activity. This was done to control for exercise-induced hyperemia on the vasculature (21, 29) as well as exercise induced increases in insulin sensitivity. Additional exercise was avoided following this exercise bout.

Study visits were conducted between 7:00am and 10:00am in a temperature controlled room kept at 21–22°C. Height and weight were obtained via standard methods. After resting in a supine position an intravenous catheter was placed. After a 15 minute rest period, baseline blood samples were obtained for measurement of glucose and insulin. Blood flow and vascular conductance were measured via Doppler ultrasound in two limbs; one which underwent large alterations in physical activity with the study intervention (femoral artery) and one in which physical activity changes were likely minimized during the reduced daily steps intervention (brachial artery) (5, 32). An oral glucose tolerance test (OGTT) was performed as previously described by our lab (23). Briefly, subjects drank a 75g glucose drink within 1 minute and blood samples were drawn every 30mins for 2 hours. Blood flow through the femoral and brachial artery was measured every 30 minutes for the duration of the OGTT. Brachial and femoral blood flows during the OGTT were performed at baseline, following 5 days of inactivity (RA5), and following a 1 day return to physical activity (RTA1).

Experimental Measures

Blood Flow Measures

Blood flow to the femoral (Logiq P5, GE Medical Systems, Milwaukee, WI) and brachial (Logiq7, GE Medical Systems, Milwaukee, WI) artery were measured simultaneously using duplex Doppler ultrasound with a linear array transducer (10–12 Mhz), as previously described by our lab (5, 23, 32). Blood velocity was obtained simultaneously with diameter in pulsed-wave mode at an insonation angle of 60° and operating at a frequency of 5 MHz with the velocity cursor set mid-vessel. Sample volume was maximized to encompass the entire vessel lumen without extending beyond it. Limbs were secured and transducer

stabilized using a custom designed clamp. Baseline blood flows in the femoral and brachial arteries were recorded for 5 minutes prior to glucose ingestion and every 30 minutes for 2 hours following ingestion of glucose. The same Doppler ultrasound unit (Logiq P5 and Logiq 7) and ultrasonographer were used to measure blood flow in each limb across the 3 study visits. Blood flow measurements were not performed in 1 subject due to technical difficulties. A custom-designed edge-detection and wall tracking software measured diameter and velocity (Labview; National Instruments) as previously described in detail (15, 28, 32). Blood flow (mL/min) was calculated as:

$\text{blood flow} = \pi \times (\text{diameter}/2)^2 \times \text{V}_{\text{mean}} \times 60$, where V_{mean}= mean velocity. Peak blood flow was determined as the maximum blood flow response following the OGTT for each subject. Conductance was calculated as peak blood flow divided by mean arterial pressure. Finger photoplethysmography was used to measure beat-to-beat blood pressure (Finometer; Finapres Medical Systems, Amsterdam, The Netherlands). Return to flow calibrations were performed before each Finometer recording.

Continuous Glucose Monitoring

Glycemic control was assessed for a 48 hour period at baseline and for two separate 24 hour periods during RA5 and RTA1 using a continuous blood glucose monitoring system (CGMS: iPro CGM, Medtronic Diabetes, Minneapolis, MN), as previously described by our laboratory (24, 25). A glucose sensor was inserted subcutaneously into the abdomen of each subject and the CGMS was connected to the sensor. The CGMS measures interstitial blood glucose every 5 mins over the 24 hour period. Study food logs containing the start times of each meal and at least 4 blood glucose recordings from finger sticks (Accu-check Compact Plus, Roche Diagnostics Peak) were collected from subjects and the CGMS data was analyzed using Solutions Software for CGMS iPro (Medtronic Diabetes). Blood glucose responses over 48 hours were analyzed for baseline and 24 hours for RA5 and RTA1. Peak PPG was measured by averaging the largest blood glucose response during the 2 hour period following breakfast, lunch, and dinner. Continuous overlapping net glycemic action (CONGA-2), a measure of blood glucose variability, was measured by assessing the standard deviation of PPG for 2 hours following each meal. The 2 h glucose area under curve (AUC) was calculated from the averaged glucose AUC response from each meal consumed during the different phases of the study. Glycemic control was not assessed in 2 subjects during RTA1 due to software malfunction of the CGMS.

Blood sample analysis from OGTT

Serum blood glucose measures were made using the glucose oxidase method (Sigma, St. Louis, MO). Insulin was measured via enzyme-linked immunosorbent assays (Immulite 1000 Analyzer, Siemens, Deerfield, IL). Insulin sensitivity was assessed using the Matsuda index as previously described by our lab and others (22, 23). Insulin and glucose measurements were not performed in 1 subject due to problems obtaining an IV.

Statistical Analysis

Data was analyzed using Sigma Stat. A one way repeated measures ANOVA was used to analyze the Matsuda index, peak PPG, CONGA-2, and PPG AUC across the 3 study visits;

as well as average daily steps and kilocalories per day across the study intervention. Rank order testing was applied where necessary. A two way repeated measures ANOVA was used to assess the glucose and insulin response to the OGTT, the brachial and femoral artery blood flow and conductance responses from baseline to peak response across the 3 study visits. Least Significant Difference post hoc testing was applied where significant main effects were found. Significance was set at $p<0.05$. All data are presented as means±SEM.

Results

Baseline subject characteristics of the male subjects were: age: 24±1.1yrs, BMI: 24.4±0.8kg/m^2, body fat: 19.2±0.9%, and VO_{2max}: 52.6±2.5ml/kg/min.

Physical Activity Measures and Diet

Steps/day and kilocalories expended above 3 METS per day were significantly decreased following 5 days of reduced activity (Figure 2) ($p<0.05$ from baseline). Further, all were significantly elevated back to baseline values following the 1 day return to activity ($p>0.05$ from baseline). The physical activity monitor recorded that subjects wore the monitor approximately 18 hours per day (minus bathing and sleep time). For the standardized diet, subjects were compliant in eating all of the packed out food as recorded by questionnaire and the return of empty food containers.

Insulin Stimulated Blood Flow and Vascular Conductance

Femoral (Figure 3 A) and brachial artery (Figure 3 B) blood flow increased during the OGTT (both $p<0.05$ from 0 min of OGTT). However, no significant differences occurred in the femoral or brachial artery blood flow responses across the study interventions ($p>0.05$ from baseline). Similar results were obtained for peak femoral and brachial artery conductance with increases during the OGTT that were unaffected by changes in physical activity ($p>0.05$ from baseline).

Insulin Sensitivity

The glucose response to the OGTT across the phases of the study was not significantly different ($p>0.05$ from baseline) (Figure 4A). However, the insulin response to the OGTT displayed a significant main effect for the study interventions without an interaction (Figure 4B). Furthermore, insulin sensitivity, measured by the Matsuda index, was significantly reduced following RA5 and remained suppressed during RTA1 compared to baseline ($p<0.05$) (Figure 4C).

Glycemic Control

Peak PPG (a marker of free-living postprandial glycemic control) and CONGA-2 response (a marker of free-living glycemic variability) were significantly elevated following RA5 (Figure 5A and C) ($p<0.05$ from baseline) compared to baseline. Peak PPG remained significantly elevated following RTA1 (Figure 5A) ($p<0.05$). The 2 h area under the curve response averaged across meals trended to be different between the 3 study interventions ($P=0.067$) (Figure 5B). Upon further investigation with paired t-tests, RA5 and RTA1 were elevated above baseline ($p<0.05$). In line with this finding, the impairments in free-living

glycemic control with the physical inactivity intervention can be readily appreciated from the visual inspection of the minute by minute blood glucose measures obtained between 7am and 8pm across study interventions (Figure 6).

Discussion

The major novel findings of this study are that 1) impairments in glycemic control following changes in physical activity are not paralleled by reductions in blood flow responses following an OGTT and 2) a 1 day return to daily ambulatory activity following 5 days of reduced daily physical activity did not restore free-living glycemic control or insulin sensitivity measured by an OGTT. Overall, these data demonstrate that acute physical inactivity reduces insulin sensitivity and glycemic control, but this occurs without changes in blood flow responses to an OGTT.

Previous studies have examined the effects of insulin to increase blood flow to skeletal muscle (2, 6, 19, 20). These studies establish an important link in the role of insulin-stimulated blood flow to regulate glucose disposal into skeletal muscle. However, whether reducing insulin sensitivity via reductions in physical activity impairs the blood flow response to an OGTT has not been examined extensively. One study found that detraining in endurance trained subjects reduced the blood flow response to an OGTT (1). However, the subjects in this study were high fit (VO_{2max}= 63 ml · kg^{-1} · min^{-1}), which does not describe the majority of individuals. Further, the study examined detraining and not reductions in daily ambulatory activity. In contrast, our subjects were recreationally active men (>10,000 steps day) who reduced their total physical activity slightly below that of the average, sedentary US citizen (<5,000 steps/day) (5, 36).

In the present study we demonstrate that the blood flow response to the OGTT is not related to decreased insulin sensitivity and glycemic control following 5 days of physical inactivity and a 1 day return to activity in young healthy previously active men. In a previous study we found that adding physical activity, through 7 days of aerobic exercise (1 hour · day^{-1}), increased blood flow responses to an OGTT in subjects with type 2 diabetes, responses that tracked with improved glycemic control and insulin sensitivity (23, 24). Previous evidence showed that impairing insulin stimulated blood flow through eNOS inhibition reduced skeletal muscle glucose disposal by 40% (2), leading us to posit that the increase in insulin sensitivity and blood flow responses to an OGTT were linked. However, we did not find the same relationship with reduced activity in the current study. Certainly exercise and increased physical activity are not necessarily the inverse of reduced activity (34). Moreover, this data suggests that factors other than blood flow are driving the decline in glycemic control and insulin sensitivity observed after acute reductions in physical activity. Nevertheless, it is possible that longer term reductions in physical activity (greater than 5 days) would impair the blood flow response to an OGTT, further reducing glycemic control and insulin sensitivity. This warrants further study.

Previous studies have shown that 6 days of detraining reduces the glucose transporter protein, Glut-4, in skeletal muscle (39). Both insulin and exercise stimulate increases in glucose uptake via Glut-4 translocation in muscle (12) and it is generally recognized that

Glut-4 content tracks with insulin sensitivity. Rodent studies using an analogous method to reduce daily physical activity, the wheel lock model, show that insulin signaling proteins and insulin stimulated skeletal muscle glucose uptake are both reduced during a transition to lower daily activity (18). Interestingly, there is strong evidence that one bout of exercise may increase Glut-4 protein expression (31) and repeatedly increases insulin sensitivity in healthy and diseased subjects (35) but the one day return to activity in the present study did not restore insulin sensitivity or glycemic control. The exact reason for these disparate responses is unclear. However, most studies that have examined one bout of exercise and the effect on insulin sensitivity used techniques that focused on skeletal muscle insulin sensitivity via a hyperinsulinemic-euglycemic clamp or insulin exposure to skeletal muscle, whereas this study utilized an OGTT which relies upon various tissue responses including but not limited to muscle, liver, and pancreas. Also, in general agreement with our findings, Heath et al. (16) reported that cessation of exercise training for 10 days in endurance athletes led to higher insulin and glucose responses to an OGTT, and although 1 exercise bout tended to return glucose and insulin responses back toward pre-detraining values, it did not completely restore responses. Nevertheless, it should be noted that “exercise training cessation” and “imposing physical inactivity” where daily ambulation is lowered are two different stimuli and may not evoke similar results. This is similar to the concept that bed rest studies do not accurately reflect the physical inactivity most people experience in their daily life where they maintain some level of ambulation.

Although the primary reason for the lack of a change in blood flow during the OGTT following reductions in physical activity is unknown, several possibilities warrant discussion. First, we measured conduit artery blood flow. While the assumption is that changes in conduit artery blood flow are representative of alterations in downstream arteriolar and capillary beds of skeletal muscle, this might not always be the case. It is possible that changes within the skeletal muscle microcirculation occurred with a lack of change in conduit artery blood flow. In this regard, skeletal muscle microcirculation blood flow is increased with lower levels of circulating plasma insulin compared to conduit artery blood flow (9). Thus, in the present study, it is possible that alterations in microvascular blood flow tracked with alterations in glycemic control and insulin sensitivity which were not demonstrated with conduit artery blood flow. The concept of nutritive and non-nutritive blood flow is important to consider when examining the links between insulin stimulated-blood flow and -glucose disposal (3, 8, 9). Non-nutritive blood flow is considered microvascular blood flow which perfuses tissue with relatively low metabolic demand (i.e. connective tissue), while nutritive blood flow perfuses skeletal muscle microvasculature with high metabolic demand and glucose transport (8, 9). Non-nutritive blood flow is thought to serve as a reservoir for nutritive capillaries such that when meal induced insulin stimulation occurs, blood flow carrying glucose and insulin is shunted towards nutritive capillaries in skeletal muscle (9). Thus, via a redistribution of blood flow from non-nutritive capillaries to nutritive capillaries during insulin stimulation it is possible to recruit skeletal muscle capillaries without increasing conduit artery or bulk flow.

Further, it must be acknowledged that the lack of change in femoral and brachial artery blood flow to reductions in daily physical activity may be due to a compensatory increase in plasma insulin following changes in physical activity (see Figure 4). Given that the 2 hr

glucose curves during the OGTT are overlaid on top of each other from baseline to reduced daily physical activity, increased plasma insulin to the OGTT following inactivity, must be accounting for reduced insulin sensitivity as assessed by the Matsuda index. Thus, increased plasma insulin during reduced daily activity may be providing for a normal conduit artery blood flow response. While it is tempting to speculate that a similar plasma insulin level to baseline (active phase) would result in a reduced blood flow response to the OGTT following reduced activity, this would require future studies. It is also possible that blood flow to the OGTT in the current study would be decreased following a longer term reduced physical activity/insulin sensitivity intervention, given that individuals with chronic insulin resistance display blunted blood flow responses to insulin stimulation (19, 23).

A potential limitation of this study is that it was a single group, time series design, without a randomized control comparison group (or condition). Therefore, it is possible that habituation or decreased stress levels with repeated laboratory visits may have influenced responses to the testing procedures rather than the imposed physical inactivity. However, all subjects visited the laboratory several times before the study began and were familiarized with the procedures prior to any measures. Also, using a similar study design, we previously reported that a measure of vascular function, flow mediated dilation, was not altered from baseline with repeat visits during 5 days of maintaining normal physical activity giving us some assurance that this was likely not a problem in the outcomes of our study (5). We also employed a standardized diet throughout to control for fluctuations in diet and their potential impact on study outcomes.

In summary, our data suggest impaired insulin sensitivity and glycemic control to reductions in daily physical activity do not occur in parallel with alterations in the blood flow response to an OGTT. Further, our data suggest that 1 day return to physical activity following 5 days of reduced daily activity in previously active individuals is not sufficient to restore insulin sensitivity or glycemic control. Further, these data build upon our previous findings that daily physical activity is important in regulating glycemic control (24, 25) and suggests that inactivity may play a permissive role in the development of conditions like type 2 diabetes where glycemic control is impaired. More specifically, our data show that acute reductions in ambulatory activity leads to greater variability in blood glucose throughout the day (CONGA) and greater postprandial swings in blood glucose, both of which are increasingly being linked to cardiovascular risk (7, 33). Collectively, our results suggest that acute inactivity leads to deleterious impairments in insulin sensitivity and glycemic control, but that these changes are not due to postprandial blood flow impairments.

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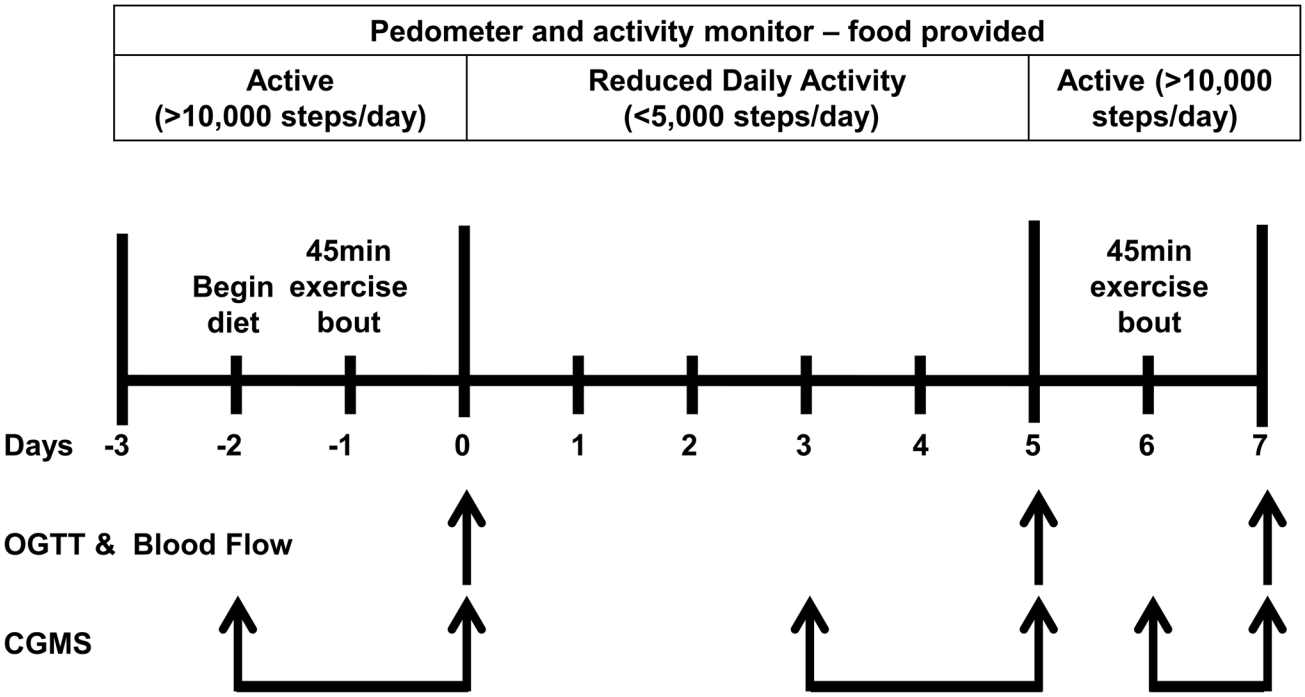

Figure 1.
Timeline of study interventions and measurements. Oral glucose tolerance test (OGTT); continuous glucose monitoring (CGMS)

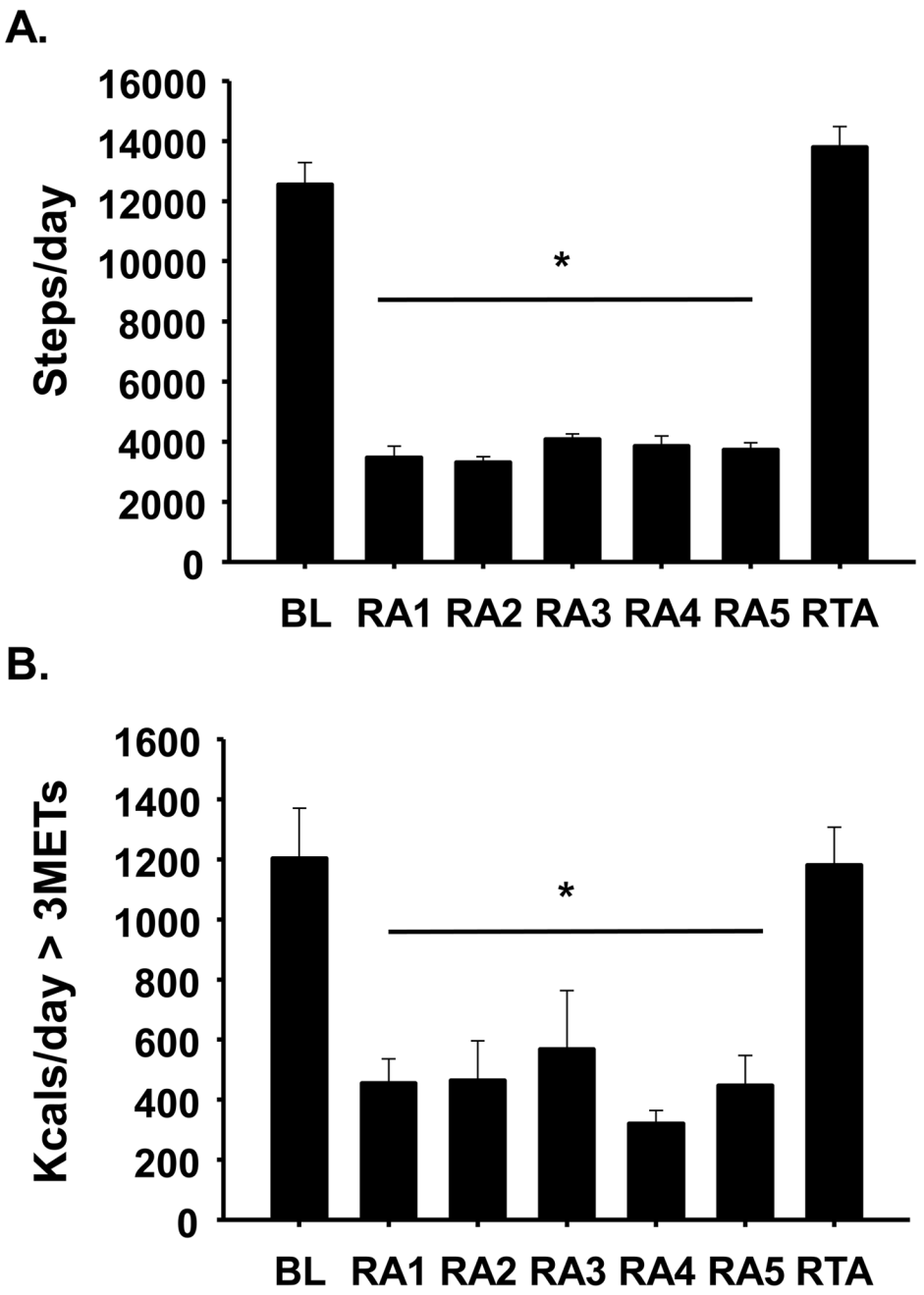

Figure 2.

Average daily steps taken per day during the 5 days of inactivity (RA) and the 1 day return to activity (RTA1; Panel A). Average daily kilocalories expended above 3 METs across the study intervention (Panel B). *$p<0.05$ from baseline (BL). Data are shown as means±SEM.

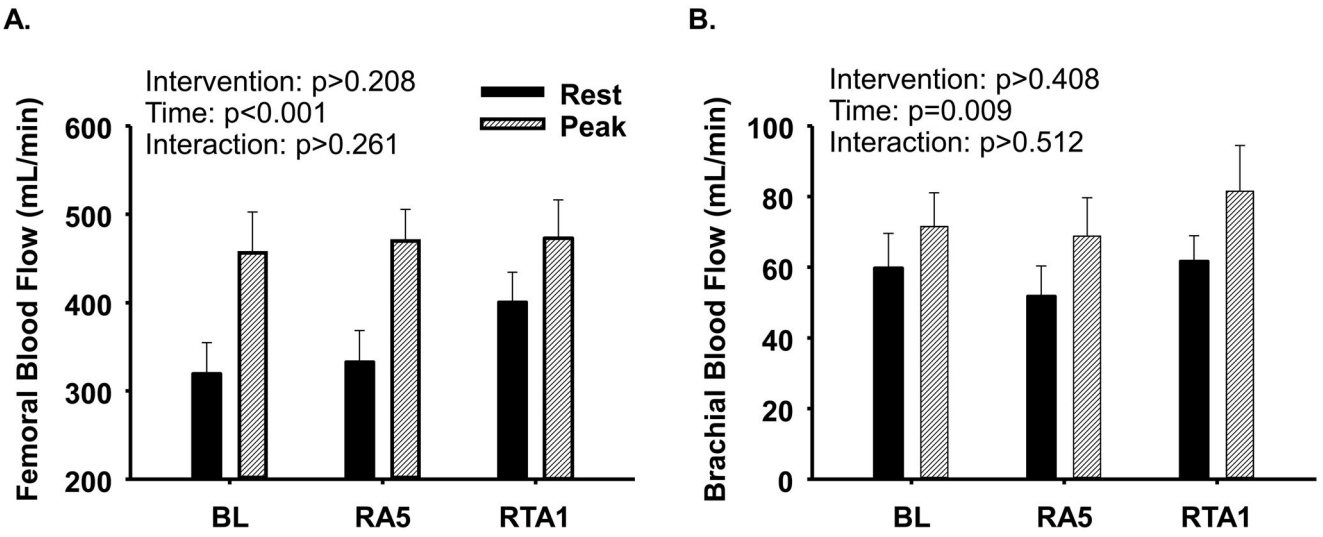

Figure 3.

Resting and peak femoral (A) and brachial (B) artery blood flow responses during the oral glucose tolerance test performed at baseline (BL) and following 5 days of inactivity (RA5) and a 1 day return to activity (RTA1). Data are shown as means±SEM.

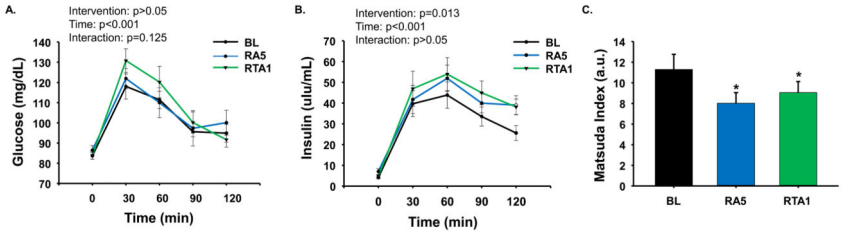

Figure 4.

Glucose (Panel A) and insulin (Panel B) responses and insulin sensitivity (Matsuda index) (Panel C) during the oral glucose tolerance test at baseline (BL) and following 5 days of inactivity (RA5) and a 1 day return to activity (RTA1). Data are shown as means±SEM.

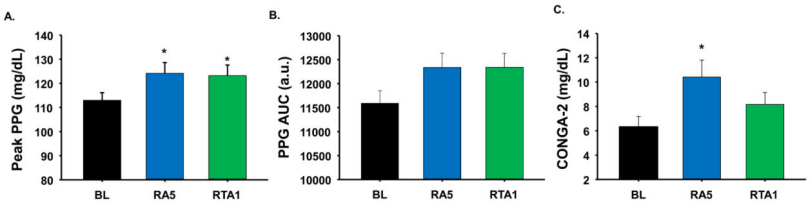

Figure 5.

Summary data for continuous glucose monitoring measures in free living conditions at baseline (BL) and following 5 days of inactivity (RA5) and a 1 day return to activity (RTA1). Data are shown for peak post prandial blood glucose (PPG) over 2 hours following each meal (Panel A); glucose Area Under the Curve (AUC) over 2 hours following each meal (Panel B), and continuous overlapping net glycemic action over 2 hours following each meal (CONGA-2) (Panel C). *$p<0.05$ from BL. Data are shown as means±SEM.

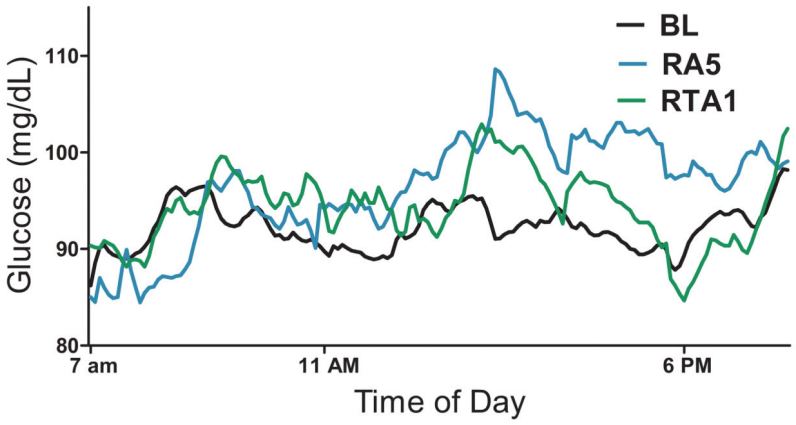

Figure 6.

Minute by minute blood glucose from 7am to 8pm across the study interventions. Baseline (BL); 5 days of inactivity (RA5) and 1 day return to activity (RTA1).