# Effects of exercise on gut peptides, energy intake and appetite

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## Abstract

This study investigated the acute effects of exercise on the postprandial levels of appetite-related hormones and metabolites, energy intake (EI) and subjective measures of appetite. Ghrelin, polypeptide YY (PYY), glucagon-like peptide-1 (GLP-1) and pancreatic polypeptide (PP) were measured in the fasting state and postprandially in 12 healthy, normal-weight volunteers (six males and six females) using a randomised crossover design. One hour after a standardised breakfast, subjects either cycled for 60 min at 65% of their maximal heart rate or rested. Subjective appetite was assessed throughout the study using visual analogue scales and subsequent EI at a buffet meal was measured at the end (3-h post-breakfast and 1-h post-exercise). Exercise significantly increased mean PYY, GLP-1 and PP levels, and this effect was maintained during the post-exercise period for GLP-1 and PP. No significant effect of exercise was observed on postprandial levels of ghrelin. During the exercise period, hunger scores were significantly decreased; however, this effect disappeared in the post-exercise period. Exercise significantly increased subsequent absolute EI, but produced a significant decrease in relative EI after accounting for the energy expended during exercise. Hunger scores and PYY, GLP-1 and PP levels showed an inverse temporal pattern during the 1-h exercise/control intervention. In conclusion, acute exercise, of moderate intensity, temporarily decreased hunger sensations and was able to produce a short-term negative energy balance. This impact on appetite and subsequent energy homeostasis was not explained by changes in postprandial levels of ghrelin; however, 'exercise-induced anorexia' may potentially be linked to increased PYY, GLP-1 and PP levels.

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## Introduction

Obesity has become a global epidemic in developed countries (World Health Organization 2003) and UK is no exception with an almost threefold increase in obesity prevalence in the last two decades and present numbers indicating that over 60% of the population are overweight (National Audit Office 2001). This picture is undeniably linked to a decrease in physical activity (PA) over the past few decades, driven by dramatic changes in lifestyle (Varo *et al.* 2003, World Health Organization 2003).

Although the role of PA in preventing weight gain is widely accepted (Haapanen *et al.* 1997, Martinez-Gonzalez *et al.* 1999), its impact on weight loss in the absence of energy restriction seems to be only modest (Miller *et al.* 1997). The ability of exercise to create a negative energy balance (EB) relies not only directly on its impact on energy expenditure (EE), but also indirectly on its potential to modulate energy intake (EI) (King *et al.* 1997*b*). It has been suggested that the relative inefficacy of exercise on weight loss may originate from the energy deficit created by exercise being partially compensated for by an increase in EI (Blundell & King 1999).

Even though most studies show no impact of acute exercise on appetite (King *et al.* 1996, Imbeault *et al.* 1997, Hubert *et al.* 1998) or subsequent EI (King *et al.* 1996, 1997*a*, Imbeault

*et al.* 1997, Hubert *et al.* 1998, Blundell & King 1999), this is a rather controversial area (Blundell & King 1999).

Depending on the time frame of the response, different mechanisms operate in the complex system that regulates appetite and EB: long-term signals including leptin and insulin, intermediate signals including post-absorptive signals associated with macronutrient oxidation and, finally, short-term mechanisms involving post-ingestive signals including the gut peptides ghrelin, cholecystokinin (CKK), peptide YY (PYY), glucagon-like peptide-1 (GLP-1) and pancreatic polypeptide (PP) (Blundell 1991, King *et al.* 1997*b*). These metabolic and endocrine signals are then received and processed by specific areas in the hypothalamus and brainstem, resulting in a co-ordinated response targeting both EI and EE (Neary *et al.* 2004). As exercise is a major determinant in the EB equation, it is, therefore, of extreme importance to determine how these appetite-related hormones respond to exercise. However, research in this area is rather limited (Sullivan *et al.* 1984, Greenberg *et al.* 1986, Bailey *et al.* 2001, O'Connor *et al.* 2006). The purpose of this study was, therefore, to investigate the effects of an acute period of moderate intensity exercise, when performed in the fed-state, on postprandial levels of ghrelin, PYY, GLP-1 and PP in normal-weight subjects and to correlate potential

alterations with changes in subjective feelings of appetite/satiety and prospective food intake at a subsequent meal.

## Material and Methods

### Subjects

Twelve healthy volunteers (six males and six females) not currently dieting to lose weight were recruited for this study. Their mean age was $25 \cdot 9 \pm 4 \cdot 6$ years and mean scores for restrained, external and emotional eating based on the Dutch Eating Behaviour Questionnaire (DEBQ; van Strien et al. 1986) were $2 \cdot 4 \pm 0 \cdot 8$, $2 \cdot 7 \pm 0 \cdot 6$ and $2 \cdot 2 \pm 0 \cdot 6$ respectively. Mean body mass index was $22 \cdot 0 \pm 3 \cdot 2$ kg/m$^2$.

The exclusion criteria were as follows: a score of more than $3 \cdot 5$ in the restrained scale of the DEBQ, history of coronary heart disease, type 1 or type 2 diabetes, anaemia, gout, depression or other psychological disorders, eating disorders, drug or alcohol abuse within the last 2 years, current medication known to affect appetite or induce weight loss and hypertension. Smokers and those with a highly active lifestyle (performing more than 1 h of moderate to intense exercise per day, on every day of the week), based on a 3 months exercise history, were also excluded. The experimental protocol was approved by the University of Surrey Ethics Committee and subjects gave written informed consent.

### Study protocol

Subjective appetite sensations, EI and postprandial levels of hormones and metabolites in response to rest and exercise were investigated using a randomised crossover design. Subjects acted as their own controls and were assigned to the two experimental conditions (resting and exercise), 1 week apart, in a counter-balanced order.

To reduce the inherent variability, for 24 h prior to each investigation, subjects were instructed to refrain from moderate to heavy exercise and from consuming alcohol. They were required to complete 24-h dietary records, which were analysed for energy and macronutrients using WinDiets (Robert Gordons University, Aberdeen, UK). Participants were also provided with a standardised evening meal (pasta ready meal: 521 kcal, 22 g protein, 26 g fat and $50 \cdot 7$ g carbohydrates) and asked to eat it at around 2000 h on the day preceding each of the study days.

On each of the two study days, subjects arrived in a fasted state at the clinical investigation unit (CIU) at $\sim$0800 h. An i.v. cannula was inserted into an antecubital vein and two fasting blood samples were taken ($-30$ and 0 min). Serial blood samples (20 ml) were then taken at regular intervals for the following 3 h.

Subjects consumed a standard breakfast at time, $t=0$ h (hot chocolate drink: 500 kcal, $18 \cdot 9$ g protein, $21 \cdot 4$ g fat and $59 \cdot 4$ g carbohydrate; this meal has been used by us in the previous studies; Robertson et al. 2003) and were randomly allocated to a resting or exercise intervention which began at

$t = 1$ h. During the resting condition, participants remained seated, whilst allowed to read/write quietly. During the exercise condition, participants cycled on a cycle ergometer at 65% of their age estimated maximal heart rate (maxHR) for 60 min. Participants were provided with water available *ad libitum* throughout the study.

Visual analogue scores (VAS) for hunger, fullness and prospective food consumption were completed after each blood sample, as described previously (Hill et al. 1987, Flint et al. 2000). After the resting/exercise intervention ($t=$ 120–180 min), participants stayed in the CIU, but were free to write/read quietly. One hour after the end of the exercise/resting intervention ($t=180$ min), participants were placed at individual booths, presented with a buffet test meal and instructed to eat as much as or as little as they wanted until satisfied.

### Exercise bout

The exercise intervention consisted of intermittent cycling on a cycle ergometer at 65% of each subject's estimated maxHR for $\sim$60 min (2 min warming up $+$ 17 min exercise $+$ 3 min break $+$ 17 min exercise $+$ 3 min break $+$ 17 min exercise $+$ 2 min cooling down). HR was measured continuously using a HR monitor (Polar F1 – Polar Electro Oy, Kempele, Finland). Average heart rate during the 60-min cycling was $129 \pm 6$ bpm, corresponding to $66 \cdot 4 \pm 2 \cdot 5$% of maxHR.

The energy expended during the exercise and resting sessions (180 min) was calculated using metabolic equivalents (MET) as previously described (Ainsworth et al. 2000).

### Buffet meal

The buffet test meal consisted of a standardised buffet available *ad libitum*, in excess of expected consumption (4100 kcal, 85 g protein, 250 g fat and 373 g carbohydrates), with a variety of lunch-type foods (sandwiches, salad, fruit, cake, biscuits, crisps, yogurt, mayonnaise and mustard). The choice of a buffet instead of a homogeneous meal allowed the measurement of not only total energy, but also macronutrient selection.

In an attempt to avoid over- or under-consumption due to the presence of highly desirable foods or, conversely, no palatable foods, participants were asked before the start of the study to rank different food items by order of preference and eliminate those that they would not eat. Based on this questionnaire, the buffets were made up of the second or second and third preferences rated by each subject (Rogers 1993).

The buffet foods were weighed/counted before participants sat down to the meal and reweighed/recounted after each subject had finished eating, and energy and macronutrient intake calculated.

### Hormone and metabolites measurement

Venous blood was collected into potassium–oxalate tubes for analysis of glucose, lithium heparin tubes for lipids and insulin,
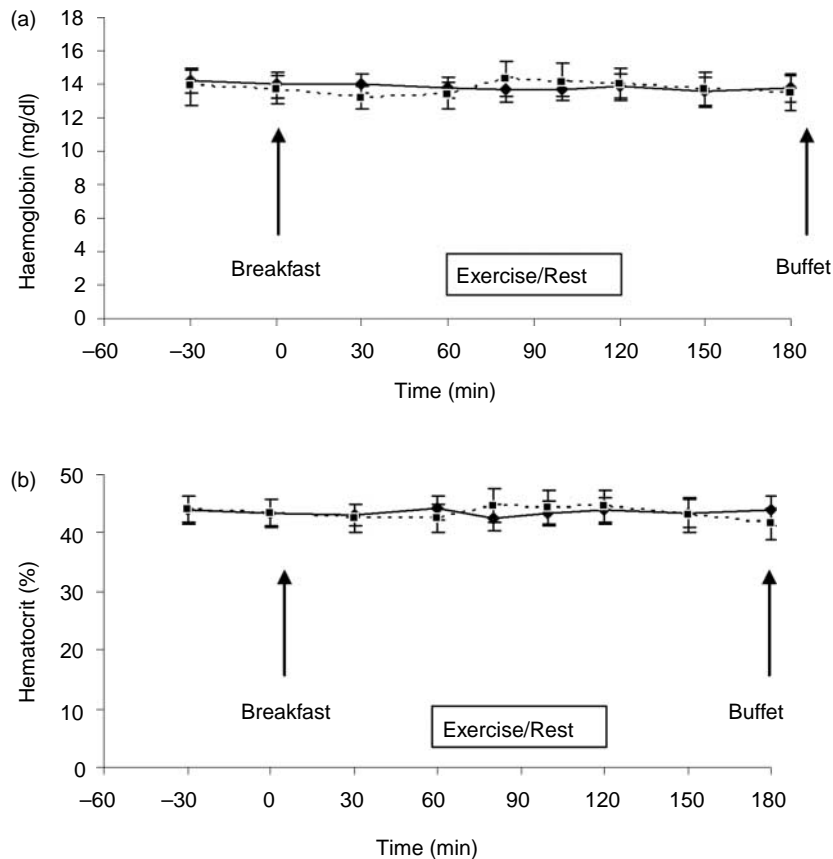
**Figure 1** (a) Haemoglobin levels (mg/dl) over time, 1 h after a 500 kcal breakfast, during the exercise (▪) and control (♦) trials. Values represent means±S.E.M. for 12 subjects. Repeated measures ANOVA showed no significant main effects of time, condition or time×condition interaction. (b) Hematocrit (%) over time, 1 h after a 500 kcal breakfast, during the exercise (▪) and control (♦) trials. Values represent means±S.E.M. for 12 subjects. Repeated measures ANOVA showed no significant main effects of time, condition or time×condition interaction.

and potassium EDTA-coated tubes, containing 200 kIU aprotinin/ml whole blood, for the measurement of gut peptides. Samples were then centrifuged at 1750 *g* for 10 min and the plasma stored at −20 °C. All samples were batch analysed at the end of the study to reduce interassay variability.

Plasma triacylglycerol (TAG) and non-esterified fatty acids (NEFA) were measured colorimetrically using an automated centrifugal analyser (Randox Space, Antrim, UK AlfaWasserMann) and glucose using an immobilised enzyme biosensor (YSI 2300 Stat Plus Glucose & Lactate Analyzer). Total ghrelin, PYY, GLP-1, PP and insulin were quantified using established RIAs (Adrian *et al.* 1976, 1985, Hampton 1984, Kreymann *et al.* 1987, Patterson *et al.* 2005). The sensitivity of the assays was 2·5 pmol/l for insulin and PP, 17 pmol/l for ghrelin, 2 pmol/l for PYY and 1 pmol/l for GLP-1. All samples were assayed in duplicate and in one assay to eliminate the effects of interassay variation. The interassay coefficient of variation can then be removed. All metabolites
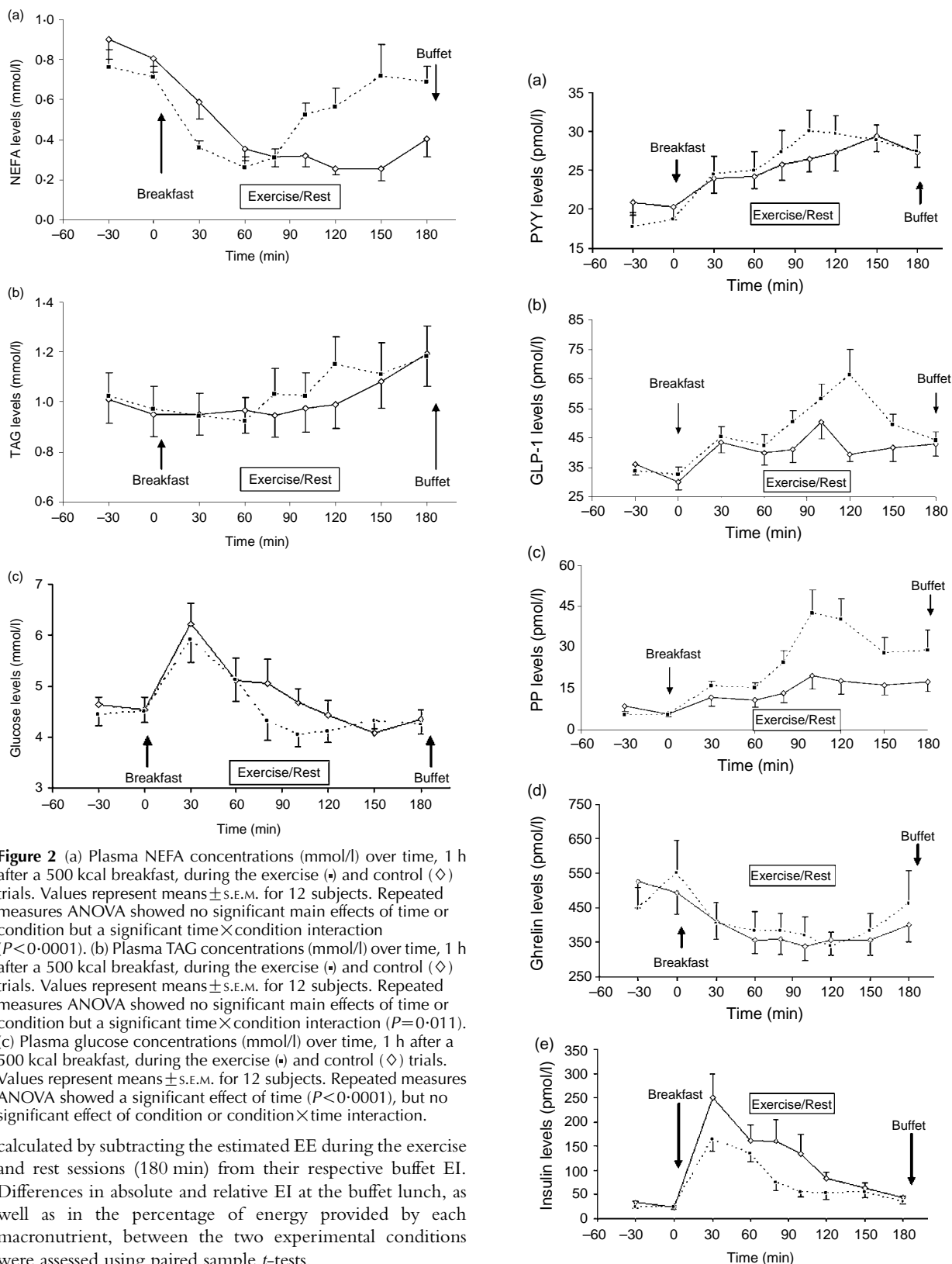
and hormones assayed exhibited an intra-assay coefficient of variation of <5 and 10% respectively.

Hematocrit (Hct) was measured in duplicate with a microHct centrifuge and haemoglobin (Hb) was measured using a co-oximeter (Instrumentation Laboratory, Warrington, UK).

### Statistical analysis and calculations

Statistical analysis was carried out using SPSS version 11.0 (SPSS, Inc., Chicago, IL, USA). All the variables were checked regarding their normal distribution using the Shapiro–Wilk test and data expressed as means±S.E.M., unless otherwise stated.

Differences in fasting/postprandial levels of metabolites and hormones and appetite/hunger sensations between the two conditions (control and exercise) were assessed by a two-way repeated measure ANOVA using treatment and time as independent variables. Relative energy intake (REI) was
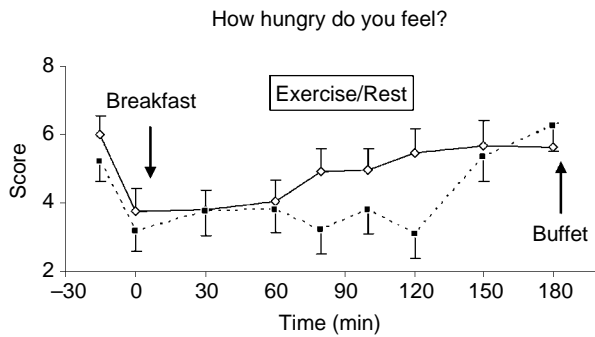
**Figure 2** (a) Plasma NEFA concentrations (mmol/l) over time, 1 h after a 500 kcal breakfast, during the exercise (∎) and control (◇) trials. Values represent means±s.e.m. for 12 subjects. Repeated measures ANOVA showed no significant main effects of time or condition but a significant time×condition interaction ($P<0.0001$). (b) Plasma TAG concentrations (mmol/l) over time, 1 h after a 500 kcal breakfast, during the exercise (∎) and control (◇) trials. Values represent means±s.e.m. for 12 subjects. Repeated measures ANOVA showed no significant main effects of time or condition but a significant time×condition interaction ($P=0.011$). (c) Plasma glucose concentrations (mmol/l) over time, 1 h after a 500 kcal breakfast, during the exercise (∎) and control (◇) trials. Values represent means±s.e.m. for 12 subjects. Repeated measures ANOVA showed a significant effect of time ($P<0.0001$), but no significant effect of condition or condition×time interaction.

calculated by subtracting the estimated EE during the exercise and rest sessions (180 min) from their respective buffet EI. Differences in absolute and relative EI at the buffet lunch, as well as in the percentage of energy provided by each macronutrient, between the two experimental conditions were assessed using paired sample *t*-tests.

## How hungry do you feel?



**Figure 4** VAS scores for hunger over time during the exercise (▪) and control (◇) trials. Values represent means±S.E.M. for 12 subjects. Repeated measures ANOVA showed a significant effect of time ($P < 0.0001$) and a condition×time interaction ($P = 0.004$).

## Results

No significant differences between study legs were observed in energy or macronutrient intake in the 24 h prior to each trial.

### Plasma metabolites and hormones

No significant changes in either Hct or Hb were observed over time during the exercise or the control leg (Fig. 1a and b). Therefore, as there was no evidence for haemoconcentration during the exercise leg of the study, all metabolites and hormones measured are expressed in pmol/l plasma instead of all blood volume.

Mean plasma levels of NEFA ($P < 0.0001$; Fig. 2a) and TAG ($P = 0.011$; Fig. 2b) became elevated during exercise, when compared with similar period of resting. Glucose plasma levels were not significantly affected by exercise

(Fig. 2c). Mean PYY, GLP-1 and PP levels were significantly increased ($P = 0.038$, 0.011 and 0.001 respectively) during the 1-h exercise (60–120 min), and this increase was maintained during the post-exercise period for GLP-1 and PP (Fig. 3a–c). No significant effects were observed in ghrelin levels (Fig. 3d). Despite a tendency for lower insulin levels during the 1-h exercise intervention, when compared with a similar period of resting, they did not reach statistical significance ($P = 0.066$; Fig. 3e).

No significant differences were observed in the plasma levels of any of the hormones and the metabolites immediately before buffet lunch ($t = 180$ min) between the two conditions, with the exception of NEFA levels that were significantly higher in the exercise when compared with the control leg ($0.69 \pm 0.28$ vs $0.40 \pm 0.31$ mmol/l, $P = 0.001$).

An inverse temporal pattern was observed, during the 1-h exercise/control intervention, between hunger and motivation to eat scores and PYY, GLP-1 and PP levels.

### Effects on self-reported appetite/satiety measures and subsequent food intake

Hunger scores ('How hungry do you feel?') were significantly decreased ($P = 0.004$) during the 1-h exercise period, but the effect was transient and disappeared post-exercise (Fig. 4). No significant changes were observed in fullness ('How full do you feel?') or motivation to eat ('How much do you feel you can eat?') in response to exercise (data not shown). The VAS scores taken at 180 min, immediately before the buffet meal, were not significantly different between the two conditions.

Absolute energy intake at the buffet meal was significantly higher in the exercise when compared with the control intervention ($P = 0.04$ and 0.035 respectively), with no significant differences being observed in the percentage of energy provided by either protein, fat or carbohydrates (Table 1). When absolute EI was adjusted for the energy expended during each condition, there was a significantly lower REI following the exercise period when compared with control ($P = 0.038$; Table 1).

**Figure 3** (a) Plasma PYY concentrations (pmol/L) over time, 1 h after a 500 kcal breakfast, during the exercise (▪) and control (◇) trials. Values represent means±S.E.M. for 12 subjects. Repeated measures ANOVA showed a significant effect of time ($P < 0.0001$) and a significant condition×time interaction ($P = 0.038$). (b) Plasma GLP-1 concentrations (pmol/l) over time, 1 h after a 500 kcal breakfast, during the exercise (▪) and control (◇) trials. Values represent means±S.E.M. for 12 subjects. Repeated measures ANOVA showed a significant effect of time ($P < 0.0001$), condition ($P = 0.011$) and condition×time interaction ($P = 0.001$). (c) Plasma PP concentrations (pmol/l) over time, 1 h after a 500 kcal breakfast, during the exercise (▪) and control (◇) trials. Values represent means±S.E.M. for 12 subjects. Repeated measures ANOVA showed a significant effect of time ($P < 0.0001$), condition ($P = 0.001$) and a condition×time interaction ($P < 0.0001$). (d) Plasma ghrelin concentrations (pmol/l) over time, 1 h after a 500 kcal breakfast, during the exercise (▪) and control (◇) trials. Values represent means±S.E.M. for 12 subjects. Repeated measures ANOVA showed a significant effect of time ($P < 0.0001$), but no effect of condition or time×condition interaction. (e) Plasma insulin concentrations (pmol/l) over time, 1 h after a 500 kcal breakfast, during the exercise (▪) and control (◇) trials. Values represent means±S.E.M. for 12 subjects. Repeated measures ANOVA showed no significant effect of time, and a trend towards a significant effects of condition ($P = 0.066$) and time×condition interaction ($P = 0.069$).

**Table 1** Absolute energy and macronutrient intake at the buffet lunch and 'relative' energy intake (REI) during the exercise and control trials. Values are means±S.D.

|  | Exercise | Control |
|---|---|---|
| **Absolute** | | |
| Energy (kcal) | 913±363* | 762±252* |
| Protein (%) | 14±2 | 15±3 |
| Fat (%) | 36±7 | 33±6 |
| Carbohydrates (%) | 51±6 | 53±5 |
| REI (kcal) | 421±302* | 565±226* |
| EE (kcal) | 492±92* | 197±37* |

EE, energy expenditure; REI, relative energy intake (EI after accounting for EE). Means sharing the same symbol denote significant differences between trials: *$P < 0.05$.

## Discussion

Our aim was to investigate whether acute exercise could affect the postprandial levels of ghrelin, PYY, GLP-1 and PP, thereby providing a potential mechanism for changes in appetite sensations and EI in response to exercise. For the first time, we have shown that an acute bout of moderate intensity exercise performed in the fed-state increases PYY, GLP-1 and PP plasma levels, in normal-weight subjects, with a concomitant reduction in self-reported hunger. The phenomenon of 'exercise-induced anorexia' although traditionally associated with intense exercise (King *et al.* 1994) has also been reported after moderate intensity exercise (Tsofliou *et al.* 2003), consistent with our findings.

One hour of moderate intensity exercise caused a significant increase in EI at the buffet meal. This is a rather surprising result since no significant differences in hunger scores or gut hormone concentrations immediately before food intake were observed between conditions. However, this apparent uncoupling between subjective feelings of hunger and food intake has been previously reported (Mattes 1990, Flint *et al.* 2000).

Surprisingly, once the energy expended during the 1-h exercise had been accounted for, a significant reduction in relative energy expenditure (REE) was observed, allowing the attainment of a short-term negative EB. We were able to reproduce this pattern. Even though the use of METs to estimate EE has some limitations, since it does not take into account subjects' fitness level or gender (two important predictors of EE), similar results were obtained when EE was estimated using an equation (Hilloskorpi *et al.* 2003) specific for each gender which incorporates HR, an accurate predictor of EE.

In response to feeding, PYY and GLP-1 are both secreted from endocrine L-cells of the distal ileum and colon (Bottcher *et al.* 1984) and PP, a member of the PP-fold peptide family, which also includes PYY and neuropeptide Y (NPY), is produced by endocrine type F-cells of the pancreatic islets (Adrian *et al.* 1976). These satiety hormones seem to inhibit food intake by altering central nervous system appetite circuits, within the arcuate nucleus of the hypothalamus or area postrema (Gutzwiller *et al.* 1999, Batterham & Bloom 2003). However, the inhibitory effect of PP on food consumption seems to be indirectly regulated through vagal nerves in part by decreasing gastric emptying (Katsuura *et al.* 2002).

This is the first study to address the effects of exercise on PYY levels in humans. A single study has previously demonstrated that running had no impact on postprandial GLP-1 levels when compared with a similar period of rest (O'Connor *et al.* 2006). However, this study involved high-intensity exercise and was performed in athletes. An increase in PP plasma levels has been reported, both in fasting (Hilsted *et al.* 1980, Sullivan *et al.* 1984) and in response to a meal (Greenberg *et al.* 1986), consistent with our results. However,

the role of PP on subjective hunger and EI in response to acute exercise is a novel aspect of this study.

We have now demonstrated that acute exercise increases PYY, GLP-1 and PP plasma levels, although the effect was short-lived for PYY. Interestingly, hunger scores and the plasma levels of these gut peptides showed an inverse temporal pattern during the 1-h exercise/control intervention; while mean levels of these satiety hormones increased, theoretically inducing a higher satiety effect, hunger scores were suppressed. Although several mechanisms have been proposed to explain 'exercise-induced anorexia' (King *et al.* 1997*b*, Westerterp-Plantenga *et al.* 1997), the reason for this phenomenon remains unknown. It needs to be addressed whether the inverse relationship observed between hunger scores and the plasma levels of these gut peptides (PYY, GLP-1 and PP) can be considered causal. A significant increase in the plasma levels of these gut peptides, together with a significant suppression in hunger scores (compared with infusion of saline) have been reported in studies where these hormones were infused to normal-weight healthy volunteers (Flint *et al.* 1998, Batterham *et al.* 2003, Degen *et al.* 2005). However, the satiety effects of these hormones are only seen at pharmacological rather than physiological levels. Even though the observed increase in PYY, GLP-1 and PP plasma levels with exercise was probably too small to have effects on hunger when considered in isolation, PYY and GLP-1 have already been shown to inhibit food intake additively when infused together (Neary *et al.* 2005) and the anorexic effects observed with PP infusion seem to be independent of changes in PYY, GLP-1 or indeed other gut peptides (Batterham *et al.* 2003). The concomitant increase in the plasma levels of these satiety peptides yields, therefore, a potential explanation for the phenomenon of 'exercise-induced anorexia'. However, the precise role of these gut peptides in this phenomenon can only be fully investigated when specific antagonists of these hormones, in humans, become available.

Ghrelin, in opposition, is the only peripheral hormone with orexigenic properties, and is probably involved in meal initiation (Cummings *et al.* 2001). Fasting ghrelin levels do not seem to respond to acute exercise, at least in normal-weight subjects (Schmidt *et al.* 2004). A single study reported a significant change, in overweight women, but found no effect when the same volume of exercise was performed in the fed-state (Borer *et al.* 2005). We were able to reproduce this latter finding in normal-weight subjects, by showing no significant changes in postprandial ghrelin plasma levels with 1-h moderate intensity exercise.

Although we showed that exercise in the fed-state induces compensatory neuroendocrine reflexes needed for the regulation of metabolic fuels (Coyle 2000), with increases in both NEFA and TAG levels, we were not able to show a similar compensatory response regarding ghrelin, PYY, GLP-1 and PP, GI hormones involved in appetite regulation, which would defend the body against a negative EB. There is no evidence that acute exercise triggers physiological adaptations that would lead to an increase in hunger

sensations or subsequent EI, with the exception of the Borer *et al.* (2005) study that was performed in overweight post-menopausal women. The significant increase in buffet EI observed with exercise (despite the attainment of a negative EB when REI was accounted for) was not explained by differences in hunger sensations or changes in any of the appetite-related hormones studied. We suggest that the increased EI in response to acute exercise may be the result of cognitive factors including attitudes and beliefs associated with exercise, such as 'food rewards for exercising' and the belief that 'exercise increases appetite' (King 1999).

Our findings that acute exercise, performed in the fed-state, significantly increases PYY, GLP-1 and PP levels but has no effect on ghrelin levels, together with the short-lived suppression of hunger and a significant reduction in REI, supports the hypothesis that acute exercise is able to produce a short-term negative EB and, if sustained in the long-term, may have an important role in weight mainten-ance. The phenomenon of 'exercise-induced anorexia' may be potentially linked to the increased PYY, GLP-1 and PP levels observed during exercise.

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