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ORIGINAL ARTICLE

Oxyntomodulin increases energy expenditure in addition to decreasing energy intake in overweight and obese humans: a randomised controlled trial

K Wynne[1,3], AJ Park[1,3], CJ Small[1], K Meeran[1], MA Ghatei[1], GS Frost[2] and SR Bloom[1]

[1]*Department of Metabolic Medicine, Imperial College London, Hammersmith Hospital, London, UK and* [2]*Department of Dietetics, Imperial College London, Hammersmith Hospital, London, UK*

Background: Oxyntomodulin has recently been found to decrease body-weight in obese humans and may be a potential anti-obesity therapy.
Objective: To determine whether oxyntomodulin alters energy expenditure, in addition to reducing energy intake, in 'free-living' overweight and obese volunteers.
Design: Randomized double-blind controlled cross-over trial.
Setting: Community and hospital-based.
Participants: Fifteen healthy overweight and obese men and women (age: 23–49 years, BMI: 25.1–39.0 kg/m^2). All volunteers completed the study protocol.
Interventions: Four-day subcutaneous self-administration of pre-prandial oxyntomodulin, three times daily. Participants were advised to maintain their normal dietary and exercise regimen.
Measurements: (1) Energy expenditure, measured by indirect calorimetry and combined heart rate and movement monitoring; (2) energy intake, measured during a study meal.
Results: Oxyntomodulin administration reduced energy intake at the study meal by 128 ± 29 kcal ($P = 0.0006$) or 17.3 ± 5.5% ($P = 0.0071$), with no change in meal palatability. Oxyntomodulin did not alter resting energy expenditure; but increased activity-related energy expenditure by 143 ± 109 kcal/day or 26.2 ± 9.9% ($P = 0.0221$); total energy expenditure by 9.4 ± 4.8% ($P = 0.0454$) and physical activity level by 9.5 ± 4.6% ($P = 0.0495$). A reduction in body weight of 0.5 ± 0.2% was observed during the oxyntomodulin administration period ($P = 0.0232$).
Conclusion: Oxyntomodulin increases energy expenditure while reducing energy intake resulting in negative energy balance. This data supports the role of oxyntomodulin as a potential anti-obesity therapy.
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Keywords: energy expenditure; activity; appetite; oxyntomodulin; proglucagon

Introduction

The rapidly increasing prevalence of obesity[1] is the result of an interaction between environmental factors such as highly palatable energy-dense food and little requirement for physical activity, and genetic factors which pre-dispose to weight gain.[2,3] Current interventions and therapies have not abated the mounting obesity crisis.[4] However, manipulation of the gut–brain axis offers potential strategies for the development of novel anti-obesity therapies.

The 37 amino-acid peptide, oxyntomodulin, is a product of the proglucagon gene released post-prandially from the L-cells of the small intestine in proportion to calorie intake.[5] It is a satiety signal, which has been shown to reduce energy intake when administered to rodents and humans.[6–9]

We have recently demonstrated that repeated pre-prandial self-administration of oxyntomodulin results in significant weight loss of 2.3 ± 0.4 kg (2.4 ± 0.4% body-weight) in overweight and obese study participants over a 4-week period.[9] One mechanism of this weight loss in humans is a decrease in energy intake; it has been observed that oxyntomodulin significantly suppresses energy intake by 19 ± 6% when administered intravenously at a dose of 3.0 pmol/kg min[6]

Correspondence: Professor SR Bloom, Department of Metabolic Medicine, Imperial College London, 6th Floor Commonwealth Building, Hammersmith Hospital, Du Cane Road, London W12 ONN, UK.
E-mail: s.bloom@imperial.ac.uk
[3]These authors contributed equally to the project.
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and by 25±5 to 35±9% when administered subcutaneously at a dose of 400 nmols.[9] However, rodent studies have suggested that increased energy expenditure, as well as reduced energy intake, is responsible for the decrease in body weight observed after administration of oxyntomodulin.[7,8] Rats, which received twice-daily intraperitoneal injections of oxyntomodulin (50 nmol/kg) for seven days demonstrated lower adiposity and body weight than pair-fed animals, despite identical calorie intake.[8] It has been hypothesised that a positive effect of oxyntomodulin on energy expenditure in rodents may occur as a consequence of a change in the thyroid axis.[7]

Increased sedentary behaviour is an important factor in the development of human obesity.[10] Whilst low-resting energy expenditure may contribute to obesity,[11,12] recent research has indicated it has minimal impact on weight gain[13,14] and activity-related energy expenditure may be much more important.[15] It has been reported that low physical activity accounted for 77% of weight gain over a year in one prospective study[16] and inactivity is a major determinant of increased adiposity during overfeeding.[17] Indeed, the variability of response to an obesigenic environment may be explained by inter-individual differences in non-exercise physical activity, which vary over 30-fold.[3] An anti-obesity treatment which both increases activity and reduces energy intake is more likely to be a successful long-term therapy for obesity.

The effect of oxyntomodulin on energy expenditure in humans has not been investigated. We hypothesised that subcutaneous oxyntomodulin self-administered before meals would increase energy expenditure in addition to reducing energy intake in overweight and obese volunteers.

Methods (experimental)

Volunteers

Healthy male and female volunteers, aged 18–55 years, with a stable body-mass index (BMI) 25–40 kg/m^2, were recruited by advertisement and completed the study between February and May 2005 at the Sir John McMichael Centre for research study, Hammersmith Hospital (London, UK). The subjects had stable body weight over the preceding 3 months and were not on calorie-restricting diets or weight-loss medications. All subjects were non-smokers with normal physical examination, routine blood tests and electrocardiograms. Subjects were excluded if they demonstrated abnormal eating patterns as measured by questionnaire.[18,19] Food preferences were assessed using a nine-point hedonistic scale to ensure the study meal was acceptable. Women of child-bearing age were advised to use adequate contraception and provided regular urine samples to ensure they were not pregnant.

A power calculation was used in order to estimate the minimum number of subjects required to detect a significant effect of oxyntomodulin on participant's energy intake. Based on our previous data,[9] assuming a difference of 170±45 kcal to be clinically significant, using a significance level of $P<0.05$ and 90% power, it was calculated that a minimum of 11 subjects were required to complete the protocol. Fifteen volunteers were recruited and all participants completed the entire study protocol.

Ethical approval was obtained from the Medical Ethics Committee (04/Q0401/136). All subjects gave informed written consent and the study was performed in accordance with the Declaration of Helsinki.

Materials

Human sequence oxyntomodulin peptide was synthesized (Bachem, UK), and confirmed as sterile on culture and pyrogen free (Cape Cod Ltd, Liverpool, UK). Individual doses of freeze-dried oxyntomodulin and sodium chloride were prepared in vials indistinguishable from each other. A dose of 400 nmol of oxyntomodulin was chosen as it successfully decreased body weight in our previous study.[9] Study participants prepared all injections by the addition of 0.25 ml sterile water to the vials and self-administered the dissolved substance subcutaneously into their abdomen using a 27 gauge needle.

Protocol

The study was a randomised controlled double-blind cross-over study designed to investigate the effect of oxyntomodulin on energy expenditure and energy intake. Fifteen subjects completed three 4-day study sessions, separated by at least 72 h. Each study session protocol was identical (Figure 1) and was scheduled on the same calendar days of the week. During the initial study session, all subjects self-administered saline in order to habituate to the procedures. During the second and third study periods subjects self-administered saline and oxyntomodulin in random order, as allocated by an independent investigator. All participants were advised to continue their usual exercise and dietary regimen throughout the study period.

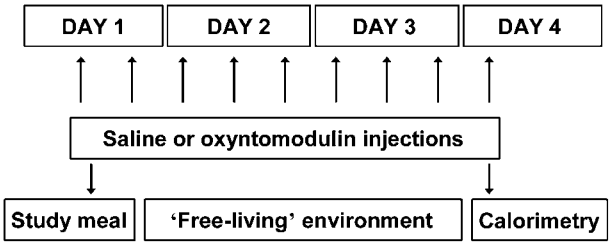

Figure 1 Participants injected saline and 400 nmol oxyntomodulin pre-prandially, three times daily, over a four day period. The interventions were performed in random order, separated by at least 72 h. Energy expenditure was monitored over the study period. A study meal to measure energy intake was completed on day 1 and indirect calorimetry was performed on day 4.

Participants self-administered injections subcutaneously, three times daily, 30 min before their meal. Each subject administered nine injections over a study session, commencing at lunchtime on day 1 and terminating at breakfast on day 4. On days 2 and 3 subjects were 'free-living' and injections were self-administered in their own environment. Compliance with injections was 99.25% during both the saline and oxyntomodulin administration periods, estimated by counting returned empty vials and confirmed by checking cutaneous sites of injection and inspecting accumulated used needles.

Energy intake was measured at a study meal in the research unit. For 24 h before commencement of each study session, subjects avoided alcohol and strenuous exercise and then fasted overnight from 2100. On day 1, participants attended the research unit and self-administered their injection. A meal of known energy content was provided in excess 30 min later and subjects were requested to eat until they felt 'comfortably full'. Each individual received an identical study meal on each occasion. Depending on their taste preference this was either: chicken curry (171 kcal, 6 g protein, 19 g carbohydrate, 7.9 g fat per 100 g), mushroom stroganoff (123 kcal, 3.1 g protein, 17.9 g carbohydrate, 4.3 g fat per 100 g) or chicken tagliatelle (129 kcal, 6.9 g protein, 16.7 g carbohydrate, 3.8 g fat per 100 g). The mass of food consumed was measured and used to calculate energy intake. Visual analogue scales (previously described in Batterham *et al*.[20]) were completed by the participants before and after the meal in order to evaluate subjective feelings of appetite, nausea and meal palatability. These scales consisted of a 100 mm line with text expressing the most positive and most negative ratings anchored at each end. In order to assess appetite the volunteers were asked 'How hungry do you feel?', 'How much do you think you could eat?' and 'How full do you feel?' with higher values signifying more positive subjective ratings. Blood samples were taken, at baseline and 30, 60, 90, 120 and 150 min post-injection, from an antecubital fossa cannula into lithium/heparin tubes (LIP Ltd., Cambridge, UK) containing 2000 kallikrein inhibitor units of aprotinin (Trasylol, Bayer). Samples were stored on ice, centrifuged, and the plasma component separated and stored at minus 20°C until radioimmunoassay analysis. Blood pressure and pulse were measured before each blood sample.

Resting energy expenditure was measured by indirect calorimetry (Deltatrac II (Datex-Ohmeda Limited, Hatfield, UK)) on day 4 of each study session. The calorimeter was calibrated immediately before each testing session in accordance with manufacturer's guidelines. Participants attended the research unit having fasted overnight from midnight. They were placed under the hood of the calorimeter and baseline measurements were taken for 30 min. Subjects then had an injection administered into the subcutaneous tissue of their abdomen. A further 30 min of data recording was performed. The indirect calorimetry unit used breath-by-breath expired gases to calculate average VO_2 and VCO_2 per hour while the subject was recumbent and resting. Respiratory quotient (RQ) was calculated and used to derive energy expenditure: Energy expenditure $= 1.32 \times VO_2 \times (1.23 \times \mathrm{RQ} + 3.81)$.

Activity-related energy expenditure was measured using the combined movement and heart rate sensor Actiheart[21] (Cambridge Neurotechnology Ltd., Papworth, UK). This sensor has recently been developed in order to allow measurement of human energy expenditure in a 'free-living' environment and has been validated against whole-body calorimetry using a fixed activity protocol.[22] It consists of a single-piece waterproof monitor attached to two standard ECG electrodes placed on the subjects' chest. For the current study, the sensor was set to measure movement and heart rate every 30 s over the 4-day-period. Participants were instructed to replace the ECG electrodes if necessary and advised that the monitor would not interfere with their daily activities. The monitor was removed on day 4 of the study period; the data was downloaded into a computer, and analysed using Actiheart Software. This software used branched equation modelling to derive 'free-living' daily energy expenditure from movement and heart rate parameters.[23] Each subject had individual calibration of the Actiheart monitor data by input of their measured resting energy expenditure into the model. The subjects also performed a graded exercise test on day 1 of each study session in which they were asked to repeatedly mount a step of height 220 mm, at a speed of 15 steps per minute increasing to 33 steps per minute, over an 8 min period. Using this data, the computer employed linear regression analysis to model the relationship between heart rate and work rate, which was then used to further calibrate the energy expenditure data for each participant.

Participants' fasting weight was recorded on days 1 and 4 of each study session on the same calibrated scale (Marsden, London, UK), accurate to the nearest 100 g. At each recording, an average of three measurements was taken after the subject had voided urine. Participants were requested to record any adverse events which occurred over the study period in a diary.

Hormone analysis

Plasma oxyntomodulin-like activity (OLI) was measured using an established in-house radioimmunoassay.[5] The OLI assay could detect changes of 10 pmol/l (95% confidence limit) with an intra-assay variation of 5.8%. Insulin and ghrelin-like immunoreactivity were measured using in-house radioimmunoassays.[24,25] The insulin assay could detect changes of 6 pmol/l (95% confidence limit) with an intra-assay variation of 5.4%, whereas the ghrelin assay could detect changes of 8 pmol/l (95% confidence limit) with an intra-assay variation of 9.5%. All samples were assayed in duplicate and within one assay to eliminate inter-assay variation. Thyroid stimulating hormone, free T3 and free T4 were measured using an Abbott Architect analyzer. Glucose was measured using an Olympus AU640 clinical chemistry analyzer.

Statistical analysis

Combined data are expressed as mean (±s.e.). The study was a cross-over design and therefore statistical analysis was performed comparing paired data sets with saline administration as a control. Energy intake and energy expenditure data were normally distributed and therefore analysed with paired *t*-tests. Serial measurements of circulating oxyntomodulin levels, pulse and blood pressure over time were compared using two-way analysis of variance (ANOVA). Energy expenditure data from the Actiheart monitor was analysed using Actiheart Software (Version 2.1, Cambridge Neurotechnology Ltd., Papworth, UK). Prism Version 4.0 was used for statistical calculations and $P<0.05$ was considered significant.

Results

Demographics

Fifteen subjects, four males and 11 females were recruited, and all completed the protocol (Table 1). The mean age was 37±2 years (range 23–49 years) and mean body-mass index was 32.3±0.9 kg/m^2 (range 25.1–39.0 kg/m^2). These subjects were not taking prescribed medications.

Energy intake

A subcutaneous injection of oxyntomodulin reduced energy intake during the study meal. When subjects self-administered saline they ingested 792±94 kcal, however, when the same subjects self-administered oxyntomodulin they ingested 663±88 kcal, a reduction of 128±29 kcal ($P=0.0006$). When expressed as a percentage of the intake on the saline day for each individual, this was equivalent to a reduction of 17.3±5.5% ($P=0.0071$, Figure 2). Although energy intake at the study meal was significantly reduced by oxyntomodulin, water intake remained unchanged (saline 0.256±0.038 l versus oxyntomodulin 0.265±0.035 l; $P=0.7468$).

Table 1 Demographic profile of the volunteers, including body mass index (BMI) and mean pre-injection resting metabolic rate (RMR)

Subject	Sex	Age (years)	Weight (kg)	Height (m)	BMI (kg/m^2)	RMR (kcal/day)
1	Male	46	124.9	1.79	39.0	1672
2	Male	28	91.2	1.83	27.2	1498
3	Male	42	105.0	1.76	33.9	1618
4	Female	40	86.4	1.57	35.1	1092
5	Female	23	71.8	1.69	25.1	1140
6	Female	33	88.6	1.75	28.9	1442
7	Male	40	92.9	1.73	31.0	1394
8	Female	45	87.2	1.59	34.5	1175
9	Female	47	80.3	1.55	33.4	941
10	Female	38	90.2	1.63	33.9	1170
11	Female	32	86.8	1.65	31.9	1254
12	Female	25	64.9	1.51	28.5	1032
13	Female	28	108.3	1.78	34.2	1275
14	Female	49	99.8	1.68	35.4	1339
15	Female	43	87.2	1.64	32.4	1255

Immediately before the study meal, there were no differences detected in visual analogue scales assessing subjective appetite. After an injection of saline or oxyntomodulin, the change from baseline for hunger (5±1 versus 2±4 mm, respectively; $P=0.5329$), prospective food intake (3±1 versus 2±6 mm, respectively; $P=0.7304$) and fullness (0±4 mm versus −2±2, respectively; $P=0.7811$) were not significantly different. The subjects' ratings of pre-prandial nausea were not changed by an injection of oxyntomodulin (saline 4±3 mm versus oxyntomodulin 5±2; $P=0.6817$) and the study meal was rated as equally palatable (saline 64±6 mm versus oxyntomodulin 57±6 mm; $P=0.2386$).

Body-weight was reduced over the 4-day study period in which the participants self-administered oxyntomodulin. During the period over which saline was administered, the subjects maintained their body-weight, with a change of 0.0±0.1 kg or 0.1±0.2%. After 4 days of oxyntomodulin injections, the subjects' body-weight decreased by 0.5±0.2 kg ($P=0.0329$) or 0.5±0.2% ($P=0.0232$).

Energy expenditure

Indirect calorimetry demonstrated a mean fasting basal respiratory quotient of 0.92±0.02 and a fasting basal resting energy expenditure of 1293±53 kcal/day before saline administration. As expected, this data was not significantly different from the fasting basal respiratory quotient (0.93±0.02; $P=0.5803$) and resting energy expenditure (1318±64 kcal/day; $P=0.6161$) measured before oxyntomodulin injection. Oxyntomodulin injection did not significantly alter respiratory quotient (saline 0.89±0.02 versus oxyntomodulin 0.88±0.02; $P=0.5534$) or resting energy expenditure (saline 1127±32 kcal/day versus oxyntomodulin 1242±50 kcal/day; $P=0.6987$) over a 30 min post-injection period. Neither was there evidence of an effect of oxyntomodulin on resting energy expenditure when adjusted for individual body-weight measured at the end of each study period (saline 13.6±0.5 kcal/kg/day versus oxyntomodulin 13.7±0.3 kcal/kg/day; $P=0.6555$).

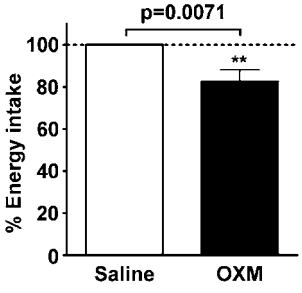

Figure 2 The effect of oxyntomodulin (OXM) on the energy intake of the participants during the study meal. Energy intake was significantly reduced by 17.3±5.5% ($P=0.0071$).

Combined movement and heart rate monitoring measured activity-related energy expenditure. Oxyntomodulin resulted in an increase in daily activity during the 'free-living' period on days 2 and 3. On average participants expended 1172±110 kcal/day during the period of saline administration. However, during the period of oxyntomodulin administration they expended 1301±109 kcal/day, an increase of 143±109 kcal/day. When expressed as a percentage of the activity-related energy expenditure during saline administration for each individual, this represented an increase of 26.2±9.9% ($P=0.0221$; Figure 3a). When adjusted for individual body-weight at the end of each study period, there was a similar increase of 26.8±9.9% ($P=0.0197$). Total energy expenditure was calculated as the sum of resting energy expenditure and activity-related energy expenditure. It is therefore not surprising that oxyntomodulin also increased total energy expenditure (saline 2443±120 versus 2585±111 kcal/day) by a similar amount of 143±109 kcal/day, which represents an increase of 9.4±4.8% for each individual ($P=0.0454$; Figure 3b). When adjusted for individual body-weight at the end of each study period, there was a similar increase of 9.8±4.2% ($P=0.0357$). Physical activity level is a way of expressing the amount of energy each individual is expending relative to their resting energy expenditure, and is calculated by dividing each individual's total energy expenditure by their resting energy expenditure. During saline administration the average physical activity level was 1.65±0.06, increasing to 1.74±0.05 during oxyntomodulin administration, which represents an increase of 9.5±4.6% for each individual ($P=0.0495$; Figure 3c) or 8.1±4.2% ($P=0.0438$) when adjusted for individual body-weight.

In addition to measurement of mean daily energy expenditure, combined movement and heart rate monitoring allows investigation of the intensity of physical activity over time. Intensity can be expressed as the time spent by participants in 'metabolic bands', calculated as multiples of each individuals' resting energy expenditure. During the oxyntomodulin injection period there was a non-significant trend for the subjects to spend greater time in metabolic bands >2.5, compared with controls (52±28% longer, $P=0.0861$).

Hormone assays

Baseline plasma oxyntomodulin levels were 41±7 pmol/l, increasing to 63±16 pmol/l post-prandially. However, when participants self-administered oxyntomodulin, levels increased to 658±85 pmol/l immediately before the study meal (Figure 4).

At 30 min after subcutaneous administration of oxyntomodulin there was a statistically significant increase in pre-prandial insulin levels of +64±15 pmol/l ($P=0.0003$, Table 2). This change in insulin was insufficient to alter plasma glucose levels in this non-diabetic population ($P=0.3175$, Table 2). The potential benefits of this insulin-releasing action have not yet been explored in subjects with abnormal glucose homeostasis.

The injection of oxyntomodulin did not change circulating levels of free T_3 ($P=0.5203$), free T_4 ($P=0.1626$) or thyroid-stimulating hormone ($P=0.4091$) (Table 2). Neither did the injection of oxyntomodulin acutely affect plasma levels of ghrelin, 30 min after injection ($P=0.2863$, Table 2).

Blood pressure and pulse rate

Blood pressure and pulse rate were measured manually in the research unit over a 150 min rest period post-injection. Administration of oxyntomodulin did not result in any significant changes in systolic blood pressure ($P=0.1388$, two-way ANOVA), diastolic blood pressure ($P=0.2282$, two-way ANOVA) or pulse rate ($P=0.0840$, two-way ANOVA) (data not shown). Pulse rate was also measured by the Actiheart monitor every 30 s over the same resting period. The pulse rate was not significantly different following an injection of oxyntomodulin (saline mean 71±1 b.p.m. versus oxyntomodulin mean 72±1 b.p.m.; $P=0.6221$, 2-way ANOVA).

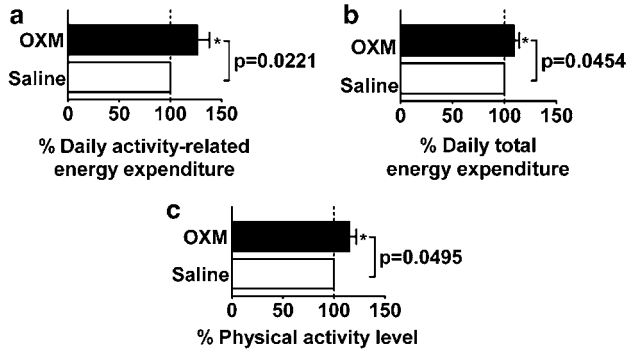

Figure 3 The effect of oxyntomodulin (OXM) on energy expenditure of the participants during the study period. (**a**) Daily activity-related energy expenditure was increased by 26.2±9.9% ($P=0.0221$). (**b**) Daily total energy expenditure was increased by 9.4±4.8% ($P=0.0454$). (**c**) Physical activity level was increased by 9.5±4.6% ($P=0.0495$).

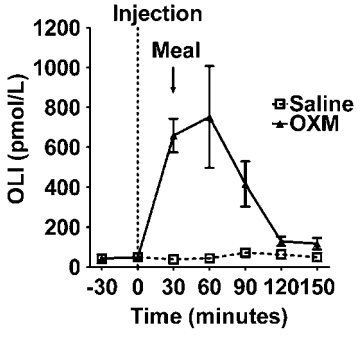

Figure 4 The levels of oxyntomodulin-like activity (OLI) were measured by radioimmunoassay. Baseline levels were 41±7 pmol/l, rising to 63±16 pmol/l post-prandially. After subcutaneous administration of 400 nmol oxyntomodulin (OXM), levels increased to 658±85 pmol/l immediately pre-prandially, and peaked at 752±255 pmol/l 30 min after the meal.

Table 2 The effect of oxyntomodulin on circulating factors 30 min after injection, prior to a meal

Analyte	*Saline*			*Oxyntomodulin*		
	Baseline	*30 min*	*Change*	*Baseline*	*30 min*	*Change*
Insulin (pmol/l)	57±7	54±9	−3±9	57±6	121±18	+64±15***
Glucose (mmol/l)	4.71±0.08	4.64±0.09	−0.07±0.06	4.71±0.06	4.77±0.06	+0.06±0.06
Free T_3 (pmol/l)	4.25±0.14	4.20±0.11	−0.05±0.06	4.19±0.01	4.20±0.11	+0.01±0.05
Free T_4 (pmol/l)	12.10±0.32	11.88±0.40	−0.22±0.28	12.06±0.46	12.36±0.48	+0.30±0.16
TSH (mU)	1.10±0.13	1.10±0.14	0.00±0.03	1.14±0.12	1.04±0.10	−0.09±0.10
Ghrelin (pmol/l)	360±53	392±65	+33±31	399±64	387±63	−12±18

A significant increase in plasma insulin was demonstrated after oxyntomodulin injection (***$P=0.0003$). Thyroid-stimulating hormone is abbreviated to TSH.

Adverse events

Volunteers recorded any adverse events in a diary over the course of the study period. There was no significant increase in the subjects' reporting of nausea during the oxyntomodulin administration period when compared to administration of saline. However, one participant – subject 11 – reported nausea after 71% of oxyntomodulin injections, a level >2 s.d. above the mean. Subject 11 also demonstrated levels of circulating oxyntomodulin significantly higher than the group mean after self-administering oxyntomodulin before the study meal (2-way ANOVA, f = 17.61, $P<0.0001$). This subject's plasma oxyntomodulin levels increased from a baseline value of 50 pmol/l upto 1249 pmol/l immediately pre-prandially, and to 3752 pmol/l 60 min post-injection. During the oxyntomodulin administration period, subject 11 demonstrated a greater than average reduction in energy intake (21.5%, group mean 17.3±5.5%) and greater increase in activity-related energy expenditure (47.7%, group mean 26.2±11.9%), although these changes were within the normal range. There were no other frequently reported adverse events during the trial.

Discussion

Self-administering oxyntomodulin increased energy expenditure back toward normal levels, in addition to reducing energy intake in overweight and obese humans over the study period. Energy expenditure can be partitioned into resting energy expenditure, incorporating both basal metabolic rate and the thermic effect of food, and activity-related energy expenditure.[26] Oxyntomodulin administration did not alter resting energy expenditure, pulse rate or the thyroid axis. However, it did increase daily activity-related energy expenditure by 26.2±9.9%; total energy expenditure by 9.4±4.8% and physical activity level by 9.5±4.6% during the 'free-living' period, despite a reduction in energy intake. The increase in activity of 143±109 kcal/day accounted for the increase seen in total energy expenditure, indicating that it was an increase in physical activity which resulted in increased total energy expenditure. The magnitude of this increase in energy expenditure is significant and comparable to the World Health Organization recommendation of a 200 kcal/day increase in low-intensity physical activity.[27] Although the mechanisms which control energy expenditure are not well-defined, it could be speculated that oxyntomodulin, a signal of positive energy balance, may act to both increase energy expenditure and reduce energy intake, allowing activity during a period of adequate nutrition. The anorectic action of oxyntomodulin is thought to be mediated by the glucagon-like peptide-1 receptor.[28] However, the effect of the endogenous ligand glucagon-like peptide-1 on energy expenditure is unclear. Several studies in rodents and humans have provided contradictory evidence as to whether glucagon-like peptide-1 has a stimulatory or inhibitory effect on energy expenditure.[28–31] To date this is the first study investigating the effect of a gut peptide on 'free-living' energy expenditure in human volunteers.

In accordance with our previous data,[9] oxyntomodulin significantly reduced energy intake at the study meal by 17.3±5.5% without subjective changes in pre-prandial appetite or meal palatability. Reduction in calorie intake after administration of oxyntomodulin suggests an alteration of appetite. However, there was no evidence of a decrease in pre-prandial hunger measured by visual analogue scale, or alteration in the circulating level of the orexigenic hormone ghrelin. This may reflect an alternative mechanism such as an early perception of post-prandial satiety, although this hypothesis requires further investigation. Rodent data has demonstrated that circulating oxyntomodulin activates regions of the brain involved in energy homeostasis within the hypothalamus and brainstem, such as the arcuate nucleus,[8] paraventricular nucleus, area postrema and nucleus of the solitary tract.[28] Within the hypothalamus, the anorectic effect may be mediated by an increase in α-melanocortin-stimulating hormone.[8]

Understanding the effects of oxyntomodulin on energy homeostasis in humans allows an insight into its potential role as a treatment for obesity. Although voluntary dietary restriction is a common intervention for obese patients, it is usually accompanied by a decrease in energy expenditure, at least in the short-term.[13] In evolutionary terms, this can be considered an adaptive trait which occurs in order to conserve energy. However, this contributes to the difficulty experienced by obese individuals who attempt to diet

voluntarily in environments which are not physically demanding. In contrast to this effect of voluntary dietary restriction, the current study demonstrated that administration of oxyntomodulin increased energy expenditure during a period of reduced energy intake. The significant decrease in body-weight over the administration period indicates oxyntomodulin administration resulted in negative energy balance; although it is unclear whether weight loss was secondary to a loss of body-mass or initial fluid shifts during this 4-day study period.[32]

This study suggests that energy expenditure and energy intake may be coupled in humans and demonstrates a possible mechanism of weight-loss during oxyntomodulin administration. Further studies should now be performed in order to investigate whether the effect of oxyntomodulin on energy expenditure is maintained over a period of chronic administration. Although the therapeutic potential of oxyntomodulin requires further investigation, this data supports the role of oxyntomodulin as a potential anti-obesity therapy.

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