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Lipase inhibition attenuates the acute inhibitory effects of oral fat on food intake in healthy subjects

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The lipase inhibitor, orlistat, is used in the treatment of obesity and reduces fat absorption by about 30%. However, the mean weight loss induced by orlistat is less than expected for the degree of fat malabsorption. It was hypothesised that lipase inhibition with orlistat attenuates the suppressive effects of oral fat on subsequent energy intake in normal-weight subjects. Fourteen healthy, lean subjects (nine males, five females; aged 25 ± 1.3 years) were studied twice, in a double-blind fashion. The subjects received a high-fat yoghurt ‘preload’ (males 400 g (2562 kJ); females 300 g (1923 kJ)), containing orlistat (120 mg) on one study day (and no orlistat on the other ‘control’ day), 30 min before ad libitum access to food and drinks; energy intake was assessed during the following 8 h. Blood samples were taken at regular intervals for the measurement of plasma cholecystokinin (CCK). Each subject performed a 3 d faecal fat collection following each study. Energy intake during the day was greater following orlistat (10 220 (SEM 928) kJ) vs. control (9405 (SEM 824) kJ) (P = 0.02). On both days plasma CCK increased (P < 0.05) after the preload. Plasma CCK 20 min following ingestion of the preload was less after orlistat (4.1 (SEM 0.9) pmol/l) vs. control (5.3 (SEM 0.9) pmol/l (P = 0.028); however there was no difference in the area under the curve 0–510 min between the two study days. Fat excretion was greater following orlistat (1017 (SEM 168) kJ) vs. control (484 (SEM 90) kJ) (P = 0.004). In conclusion, in healthy, lean subjects the acute inhibitory effect of fat on subsequent energy intake is attenuated by orlistat and the increase in energy intake approximates the energy lost due to fat malabsorption.

The lipase inhibitor tetrahydrolipstatin, or orlistat, is used widely in the treatment of obesity and, when given in a dose of 120 mg three times daily, decreases fat absorption by approximately 30% (Zhi et al. 1994). Although the malabsorptive potency of orlistat is maintained with chronic use, the mean weight loss achieved is less than would be predicted by the degree of fat malabsorption (Hill et al. 1999; Kline, 1999), suggesting that some patients taking orlistat may increase their energy intake. There is also substantial variation in the extent of weight loss between individuals with some subjects gaining weight (Hill et al. 1999).

In healthy lean and obese subjects both oral and duodenal administration of fat suppresses hunger and decreases subsequent energy intake (Read et al. 1994; Chapman et al. 1999). These effects are known to be dependent on the hydrolysis of triacylglycerols to non-esterified fatty acids by lipase (Feinle et al. 2003) and may be mediated by cholecystokinin (CCK) (Matzinger et al. 2000; Beglinger et al. 2001) and other gut peptides including glucagon-like peptide-1 (Feinle et al. 2003). It has been demonstrated in healthy lean men that acute lipase inhibition with 120 mg orlistat attenuates the inhibitory effects of a duodenal fat infusion on appetite, as assessed at a buffet meal, as well as the CCK response (Feinle et al. 2003). The acute effects of orlistat on appetite following an oral fat load have not been evaluated, and this would help to clarify if subsequent energy intake is increased. The present study was designed to address the hypothesis that lipase inhibition by orlistat attenuates the suppressive effect of oral fat on subsequent energy intake in healthy subjects.

Subjects and methods

Subjects

Fourteen healthy subjects (nine male, five female) were recruited by advertisements in local newspapers. The subjects had a mean age of 25 ± 1.3 years and were all of...
normal body weight for height (BMI 24±0·6 kg/m²). All subjects completed a number of questionnaires to assess eating habits. Questionnaires completed were the restraint section of the three-factor eating questionnaire which measures dietary restraint (Stunkard & Messick, 1985) (possible score 0–18), the Eating Attitudes Test which detects aberrant attitudes towards food and eating (Garner et al. 1982) (possible score 0–140), and the Zung self-rating questionnaire which detects depression (Zung et al. 1965) (possible score 20–80). Exclusion criteria included evidence of dietary restraint (score >12 on the three-factor eating questionnaire, restraint section), an eating disorder (score ≥30 on the Eating Attitudes Test) or depression (score ≥40 on the Zung self-rating depression scale). In addition, subjects on medication that could affect appetite, body weight or gastrointestinal function or who had a history of gastrointestinal disease or surgery, had an alcohol consumption of >20 g/d or who were smokers, were also excluded. The study protocol, which conformed to the standards set by the Declaration of Helsinki, was approved by the Ethics Committee of the Royal Adelaide Hospital, and each subject gave written informed consent before inclusion. To minimise the possibility of experimental bias subjects were informed that the main purpose of the study was to assess the effect of fat on hormone secretion. The subjects received an honorarium for participation in the study.

**Study design**

Paired studies, separated by 7–9 d, were performed in a randomised, double-blind fashion. Each subject attended the laboratory after an overnight fast and at 09.00 hours a high-fat (70 % energy from fat) yoghurt ‘preload’ (males 400 g (2562 kJ); females 300 g (1923 kJ)), which included 120 mg orlistat (Xenical®; Hoffmann-La Roche, Basle, Switzerland) on one study day. The yoghurt was prepared on-site on the morning of the study. The subjects were given 5 min to consume the preload; 30 min following the end of ingestion a ‘buffet-style’ selection of cold food and drinks, containing palatable items in excess of what the subject would normally eat, was placed in the test room. The subjects had free access to the buffet meal and energy intake was quantified hourly for 8 h (Beckoff et al. 2001). The subjects were blinded to the time of day, and external cues that might affect appetite, for example radio, were minimised. Venous blood samples for the measurement of plasma CCK were taken at baseline and every 10 min for 30 min following ingestion of the preload and then every 30 min between 0 and 510 min. Following each study day, the subjects were asked to maintain a diary to document the timing of all bowel motions and any side effects, and to perform a 3 d faecal fat collection. The completeness of the faecal fat collection was assessed using the diary.

Total energy intake was then calculated using commercially available software (Foodworks version 2.10; Xyris Software (Australia) Pty Ltd, Highgate Hill, QLD, Australia) (MacIntosh et al. 2001a). Serum CCK was determined by a radioimmunoassay as previously described (MacIntosh et al. 2001b). Faecal fat was expressed as g stearic acid and the difference in fat excreted in the faeces following orlistat compared with control was expressed in kJ. Total (calculated) energy intake (kJ) was derived for each study day as energy intake from the preload (allowing for faecal fat excretion) in addition to energy intake for the remainder of the day (8 h). Energy intake and plasma CCK levels at 20 min (when maximum plasma levels were expected following a fat preload (Feinle et al. 2003)) were analysed using Student’s paired t test. Plasma CCK from 0 to 30 min was analysed using repeated measures ANOVA, and the areas under the curve from 0 to 510 min were compared. Data are shown as mean values and standard errors of the mean and a P value <0·05 was considered statistically significant.

**Results**

The study protocol was well tolerated. Of the fourteen subjects, twelve completed faecal fat collections on both days, and plasma samples from one subject were unsuitable for analysis for one study day.

Energy intake for the remainder of the day was greater following orlistat (10276 (SEM 933) kJ) v. control (9449 (SEM 827) kJ) (P=0·02; Fig. 1); there was no difference in the proportion of each macronutrient consumed (data not shown). In all cases fat excretion was greater after orlistat (1017 (SEM 168) kJ) v. control (484 (SEM 90) kJ) (P=0·004). There was no difference in total (calculated) energy intake after orlistat (11282 (SEM 1045) kJ) v. control (10868 (SEM 857) kJ). Plasma CCK increased after both preloads (P=0·0001). Plasma CCK at 20 min was less after orlistat (4·1 (SEM 0·9) pmol/l) v. control (5·3 (SEM 0·9) pmol/l) (P=0·028), but there was no difference in the area under the curve from 0 to 510 min after orlistat (3856 (SEM 527) min × pmol/l) v. control (3801 (SEM 389) min × pmol/l).

Mild side effects were reported by eight subjects, all following orlistat and occurring within 24 h of the completion of the study; these ranged from abdominal discomfort (two subjects) and flatulence (four subjects) to loose, oily bowel motions (five subjects). Only one subject reported side effects (loose bowel motion) 6 h following the ingestion of orlistat.

*Fig. 1. Energy intake at the buffet meal (0–480 min) following ingestion of a high-fat yoghurt preload with no orlistat (□, control) or 120 mg orlistat (●). Data are mean values, with the standard errors of the mean represented by vertical bars. * Mean value was significantly different from that of the control group (P<0·02).*
**Discussion**

The results of the present study demonstrate in healthy subjects of normal body weight that: (i) the acute inhibitory effect of fat on subsequent energy intake and early stimulation of plasma CCK are attenuated by orlistat; (ii) the magnitude of this increase in energy intake approximates the additional energy lost as a result of fat malabsorption.

The suppression of hunger and energy intake (as well as slowing of gastric emptying) induced by fat is dependent on small-intestinal feedback inhibition; the latter is mediated by fatty acids with a chain length of more than twelve C atoms, and not triacylglycerols (Meyer et al. 1998; Matzinger et al. 2000). Previous information relating to the effect of orlistat on energy intake is limited; in most published studies energy intake has not been formally assessed (Hill et al. 1999), or the methodology used has been suboptimal, by relying on self-reporting diet diaries (Franson & Rossner, 2000). In a previous study (Feinle et al. 2003) acute lipase inhibition with orlistat (120 mg) during an intraduodenal fat infusion was associated with a significant increase in energy intake assessed at a buffet meal following the infusion; faecal fat excretion was not measured. A standardised 3 d faecal fat collection was, however, performed in the present study, and although this probably reflects food intake after, as well as during, the study period, significant differences in faecal fat were observed. The present study provides information about the acute effects of orlistat on energy intake in a more realistic setting and using a high-fat preload. The usual therapeutic dose of orlistat is 120 mg three times daily with meals (Hill et al. 1999); hence, it is possible that effects on energy intake may be even greater than those demonstrated. Energy compensation in response to the enteral infusion of fat has been demonstrated previously (Shide et al. 1995) and in both the present study and previously (Feinle et al. 2003) it has been demonstrated that subjects compensate accurately for energy lost through lipase inhibition by increasing their energy intake accordingly.

There is evidence that CCK may play a role in mediating the suppressive effects of fat on subsequent energy intake (Matzinger et al. 2000). CCK concentrations were initially slightly lower following orlistat, but there was no difference in the overall plasma CCK response. While it is inappropriate to attribute differences in food intake over 8 h to the observed suppression of CCK at 20 min, it should be recognised that mean energy intake was greater after orlistat, but there was no difference in the overall plasma CCK response. Hence, it is probable that there was relative suppression which would have favoured an increased CCK response. The observations are not surprising, although they may have substantial implications for the use of orlistat in the treatment of obesity. The present study has focused on the effects of a single dose (120 mg) of orlistat in subjects of normal body weight on energy intake. The results may appear in conflict with data demonstrating a small, but significant, weight loss in obese subjects taking orlistat on a chronic basis. However, it should be recognised that healthy, normal-weight volunteers were studied who were allowed ad libitum access to food; this contrasts to chronic studies of the use of orlistat in obese patients and involving energy restriction. In view of the present observations studies are now indicated to evaluate the ‘chronic’ effects of orlistat on appetite, particularly in obese subjects, that may potentially contribute to the variable response to the drug.

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