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Acute oral administration of lauric acid reduces energy intake in healthy males

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SUMMARY

Background and aims: We have established that acute intraduodenal infusion of the fatty acid, lauric acid ("C12"), markedly reduces energy intake in healthy subjects in the absence of adverse effects. The aim of this study was to investigate the hypothesis that increasing doses of orally ingested C12 would result in a dose-related suppression of appetite and subsequent energy intake at breakfast and lunch.
Methods: 14 healthy men were studied on four separate occasions in double-blind, randomised fashion. Following ingestion of C12 (2 g (77 kJ), 4 g (153 kJ), or 6 g (230 kJ)) or control, energy intake at breakfast (30 min after C12 ingestion), perceptions of appetite, nausea and bloating (for 180 min following breakfast), and energy intake at lunch (180 min after breakfast), were measured.
Results: C12 ingestion did not induce nausea or bloating. While there was no effect of C12 on energy intake at breakfast, energy intake at lunch was reduced significantly after ingestion of both C12(2 g) (by 13.7%, $P < 0.05$) and C12(6 g) (by 18.1%, $P < 0.01$) compared with control, and tended to be less (by 8.7%, $P = 0.1$) following C12(4 g) (kJ; control: 4232 ± 151, C12(2 g): 3667 ± 283, C12(4 g): 3874 ± 315, C12(6 g): 3474 ± 237). Total energy intake (breakfast + lunch + C12 dose) was less following ingestion of C12(6 g) compared with control (by 7.8%, $P < 0.05$) (kJ; control: 8256 ± 297, C12(2 g): 7905 ± 269, C12(4 g): 8443 ± 421, C12(6 g): 7611 ± 384).
Conclusion: Acute administration of oral C12 reduces energy intake in lean humans.
Clinical trial registration: This study was performed in 2006/2007, i.e. prior to the requirement of clinical trial registration and, therefore, was not registered at the time.

1. Introduction

While numerous pharmacological treatments for obesity have been developed, most of these therapies result in only modest weight loss of 5–10%, that is often not maintained in the longer-term, and several drugs have a high prevalence of adverse effects, with both rimonabant and sibutramine recently withdrawn from the market.[1,2] Moreover, these drugs do not take advantage of the pivotal role of the gastrointestinal (GI) tract in the regulation of energy intake in response to nutrients,[3] or body weight following Roux-en-Y gastric bypass surgery.[4] The only currently available drug that claims to facilitate weight loss by a GI mechanism is orlistat (Xenical®), which inhibits GI lipases and, thus, impairs fat digestion and absorption. However, this is associated with unpleasant adverse effects, and we have established that orlistat has acute effects on GI function, which favour an increase, rather than a decrease, in energy intake and also compromise glycaemic control.[5,6]

The presence of nutrients, especially fat, in the small intestine stimulates the release of gut hormones, including cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1) and peptide YY (PYY),[7–9] and suppression of ghrelin.[9] These mediate, at least in part, the effects of fat on the reduction of hunger and subsequent energy intake,[10,11] and the modulation of GI motility,[12] leading to slowed gastric emptying,[13] and improved glycaemic control.[6,14,15] The effects of fat on appetite and GI function are mediated by their

Abbreviations: C12, lauric acid; GI, gastrointestinal.

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digestive products, free fatty acids,[5,6] and the effects of fatty acids are chain length-dependent, i.e. fatty acids with a chain length of ≥12 C atoms are more potent than those with a chain length of <12 C atoms,[8,16–18] and lauric acid (C12) appears to also be more potent than oleic acid (C18:1).[19]

Our previous studies have demonstrated that intraduodenal C12, at the small load of 0.4 kcal/min, decreases energy intake without inducing nausea, associated with changes in upper GI function, particularly the stimulation of pyloric motility and CCK secretion.[19,20] Since both the stimulation of pyloric pressures and plasma CCK are independent predictors of subsequent energy intake,[3] they are likely to mediate, at least in part, the suppression of energy intake by C12. It is currently not known, whether the effects of intraduodenal C12 are evident when C12 is ingested orally, because the rate of gastric emptying of fatty acids is very slow.[17,21] Furthermore, gastric emptying may be independent of the dose of C12 administered, particularly if the volume (e.g. in capsule form) is very small. A previous study[18] has, however, demonstrated that intragastric administration of C12 suppresses antral contractions, relaxes the proximal stomach, and stimulates CCK secretion in healthy subjects. Accordingly, it is likely that orally administered C12 would produce comparable changes in GI function, associated with a reduction in energy intake.

The aims of this study were, therefore, to investigate the hypothesis that oral C12 would suppress energy intake both at breakfast (30 min after C12 ingestion) and lunch (180 min after breakfast) in healthy subjects.

2. Materials and methods

The study protocol consisted of a pilot study and the main study, both of which were approved by the Royal Adelaide Hospital Research Ethics Committee, and each subject provided written, informed consent prior to their inclusion. The procedures followed in the studies were in accordance with the Declaration of Helsinki. Recruitment for the study commenced in February 2006, and data collection was completed in May 2007.

2.1. Pilot study: effects of oral ingestion of C12 on GI symptoms

As the effects of oral C12 had not been evaluated previously, it was not known whether it would be tolerated without inducing adverse effects, such as nausea. Accordingly, prior to investigating the effects of oral C12 on appetite and energy intake, a pilot study was conducted to determine the effect of increasing doses of oral C12 on GI symptoms.

2.1.1. Subjects

5 healthy, males, with a mean age of 25 ± 4 (range 19–45) years and of normal body weight for their height (BMI 22.5 ± 0.6 kg/m^2) were studied (Supplemental Fig. 1). All subjects were unrestrained eaters (mean score on the eating restraint part (Factor 1) of the Three Factor Eating questionnaire[16]: 4.6 ± 1.4 (range: 0–8)), had no known GI disease or symptoms, and were not taking any medication. No subject smoked or habitually consumed >20 g alcohol per day.

2.1.2. Study design

Each subject was studied on five occasions, separated by 3–10 days, to evaluate in single-blind fashion, the effects of increasing doses of oral C12 at 1 g ("C12(1 g)"), 2 g ("C12(2 g)"), 3 g ("C12(3 g)") and 4 g ("C12(4 g)"), providing ~38 kJ, 76.5 kJ, 115 kJ and 153 kJ, respectively, or control, on perceptions of nausea and bloating. The doses of C12 were based on our previous studies, in which C12 was administered intraduodenally at infusion rates that equalled total loads of ~1–5 g,[16,19,20] and a study delivering C12 into the stomach at loads of ~2–5 g.[18]

2.1.3. Preparation of C12 capsules

Hydroxypropylmethylcellulose (HPMC) capsules (size 00, Capsuline Inc, Pompano Beach, FL, USA) were filled with 0.5 g C12 (Sigma–Aldrich, Milwaukee, WI, USA) each. Thus, in order to provide doses of 1, 2, 3 or 4 g C12, subjects received 2, 4, 6 or 8 capsules. Control capsules were filled with 0.5 g ascorbic acid (Chem-Supply, Gillman, SA, Australia). Each subject received 8 capsules on each day, i.e. the required number of C12 capsules to provide the dose of C12, supplemented with between 0 and 8 placebo capsules. The control day was randomised (i.e. on any of the 5 visits), however, as this was, to our knowledge, the first study of the effects or orally ingested C12, the dose of C12 was increased with each visit (starting with 1 g of C12), although the subjects were unaware of this.

2.1.4. Protocol

Subjects were instructed to maintain their normal diet between study days and refrain from vigorous exercise and alcohol intake for 24 h before each study day. Subjects attended the Discipline of Medicine at 0830 h following an overnight fast from solids and liquids from 2200 h the previous night.

Upon arrival subjects were seated in a chair and completed a visual analogue scale questionnaire (VAS) for the assessment of nausea and bloating, as well as appetite-related sensations (t = 0 min).[22] Each VAS consisted of a 100-mm horizontal line, where 0 represented 'sensation is not felt at all' and 100 'sensation is felt the greatest'. Subjects were asked to place a vertical stroke on the line to indicate what they were feeling at that particular point in time. Subjects then ingested the capsules with 250 ml of water. Subsequently, VAS were administered every 15 min between t = 15–90 min, and every 30 min between t = 90–180 min. At t = 180 min subjects were offered a light sandwich lunch, after which they were allowed to leave the laboratory. Subjects were asked to report any adverse effects in the subsequent 24 h.

2.2. Main study: effects of oral ingestion of C12 on appetite and energy intake

2.2.1. Subjects

14 healthy males were included in the study (Supplemental Fig. 2); the number of subjects was based on power calculations derived from a previous study[23]; it was calculated that with 14 subjects a 15% decrease in energy intake could be detected at α = 0.05, with a power of 80%. Subjects had a mean age of 24 ± 1 (range 19–41) years, were of normal body weight for their height (BMI 23.2 ± 0.4 kg/m^2), were unrestrained eaters (scores: 3.7 ± 0.8 (range: 0–9)), had no known GI disease or symptoms, and were not taking medication. No subject smoked or habitually consumed >20 g alcohol per day. Once subjects were enrolled into the study, they were allocated a random sequence of all 4 treatments, generated using the #RAN function in Microsoft Excel, by a research officer. Both the subject, and investigator assessing outcomes (KLF), were blinded to the random allocation sequence.

2.2.2. Study design

Each subject was studied on four occasions, separated by 3–10 days, in double-blind, randomised fashion, to evaluate the effects of oral C12 at (i) 2 g ("C12(2 g)"), (ii) 4 g ("C12(4 g)") or (iii) 6 g ("C12(6 g)"), providing ~76.5 kJ, 153 kJ or 230 kJ, respectively, or (iv) control, on appetite perceptions, nausea and bloating (from 45 min before, until 180 min after, breakfast), energy intake at breakfast (30 min after C12 ingestion) and energy intake at lunch (180 min after breakfast) (Fig. 1). As no adverse effects occurred in