Physiology & Behavior 135 (2014) 34–43

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Effects of varying the inter-meal interval on relationships between antral area, gut hormones and energy intake following a nutrient drink in healthy lean humans

Tanya J. Little [a,b,*,1], Natalie D. Luscombe-Marsh [a,b,2], Diana Gentilcore [a,c], Emma J. Brook [c], Christine Feinle-Bisset [a,b]

[a] University of Adelaide Discipline of Medicine, Adelaide, South Australia 5000, Australia
[b] NHMRC Centre of Research Excellence in Translating Nutritional Science to Good Health, University of Adelaide, Adelaide, South Australia 5000, Australia
[c] University of South Australia, School of Health Sciences, Adelaide, South Australia 5001, Australia

HIGHLIGHTS

- Energy intake suppression was correlated inversely with gastric content, and directly with stimulation of gut hormones.
- As the inter-meal interval increased suppression of energy intake diminished.
- Reduced suppression of energy intake was strongly related to a reduction in antral content.

ARTICLE INFO

Article history:
Received 11 March 2014
Received in revised form 2 May 2014
Accepted 28 May 2014
Available online 5 June 2014

Keywords:
Appetite
Antral volume
Gut peptides
Peptide YY
Cholecystokinin
Ghrelin
Meal-timing

ABSTRACT

The aim of this study was to determine: (i) the effects of varying the inter-meal interval on subsequent energy intake, and (ii) temporal relationships between postprandial changes in antral area and gastrointestinal hormone concentrations with energy intake. 16 healthy lean participants (10 M, 6 F) were studied on 4 occasions in randomized fashion. Participants consumed 500 ml of water 180 min ("control"), or 500 ml of a mixed-nutrient drink (750 kcal) 30 ("EI-30"), 90 ("EI-90") or 180 ("EI-180") min, prior to a cold, buffet-style meal, from which energy intake was quantified. Antral area was measured using 2D-ultrasound, perceptions of hunger and fullness were scored using visual analogue scales, and blood samples collected at regular intervals for analysis of plasma cholecystokinin (CCK), peptide YY (PYY) and ghrelin concentrations. All nutrient drinks increased antral area, stimulated CCK and PYY, and suppressed ghrelin and energy intake (EI-30: -367 ± 69, EI-90: -291 ± 69, EI-180: -219 ± 72 kcal, $P < 0.05$, for all), compared with control. Energy intake was related directly to the length of the inter-meal interval ($R = 0.33$, $P < 0.01$), such that as the inter-meal interval increased, energy intake increased. There was a strong relationship between antral area ($R = -0.76$, $P < 0.001$), and weaker relationships between CCK ($R = -0.36$, $P < 0.01$) and PYY ($R = -0.34$, $P < 0.01$), with the inter-meal interval. In conclusion, energy intake increased as the inter-meal interval increased. This was associated with temporal changes in gastric content (antral area) and plasma gut hormone concentrations.

1. Introduction

Studies examining the acute control of energy intake in humans classically use a paradigm in which the effects of a nutrient "preload" on subsequent energy intake are evaluated. In such studies, the length of the inter-meal interval (i.e. the interval between ingestion of the preload and the subsequent meal) has been suggested to be an important determinant of energy intake from that meal [1,2]. Thus, while a recent meta-analysis of studies using the preload paradigm indicated that energy compensation (i.e. the ability to reduce subsequent energy intake to compensate for the calories ingested in the preload) was greatest when the inter-meal interval was in the range of 30–120 min [3], these results also demonstrate substantial variability in effects. Nevertheless, the effects of a preload to suppress energy intake appear to diminish over time. For example, energy intake at a subsequent meal was much less when the meal was

* Corresponding author at: University of Adelaide Discipline of Medicine, Adelaide, South Australia 5000, Australia. Tel.: +61 2 9036 3061.
E-mail address: tanya.little@sydney.edu.au (T.J. Little).
[1] Present address: Boden Institute of Obesity, Nutrition, Exercise and Eating Disorders, University of Sydney, Sydney, New South Wales 2006, Australia.
[2] Present address: CSIRO Animal, Food and Health Sciences, Adelaide, South Australia 2001, Australia.

http://dx.doi.org/10.1016/j.physbeh.2014.05.040
0031-9384/

ingested 30 min, when compared with 90 or 180 min, after a high-fat or high-carbohydrate yoghurt preload [1]. Understanding the mechanisms that underlie the effects of the inter-meal interval on energy compensation will be critical for optimizing the timing in preload studies for the evaluation of the satiating capacity of novel foods, as well as for the development of novel dietary-behavioral interventions.

It is well established that both gastric distension and intestinal factors, including contractile events and gut hormones, contribute to the control of acute energy intake. For example, we have recently identified the stimulation of pyloric pressures (which serve to slow gastric emptying and, thus, prolong gastric distension) and gut hormone release (particularly cholecystokinin (CCK)) as independent gastrointestinal (GI) determinants of energy intake in response to nutrients in the small intestine [4]. Since emptying of a meal from the stomach occurs over time, leading to a gradual reduction in gastric content and increased exposure of the small intestine to nutrients, with associated stimulation of gut hormones, such changes may explain the temporal differences in the effects of a preload on energy intake suppression. Thus, it is surprising that, despite the knowledge of these distinct temporal changes in postprandial gastrointestinal (GI) motor and hormonal functions, there is a lack of knowledge about the relationships between the stimulation of these GI factors relative to the duration of the inter-meal interval and the resulting energy intake compensation.

Upon ingestion, a meal is accommodated in the stomach and empties gradually over a number of hours as a result of the GI feedback mechanisms activated by the presence of nutrients in the small intestine [5]. The resulting distension of the stomach, particularly of the antrum, as measured by 2D ultrasound, is associated directly with the perception of fullness [6] and inversely with energy intake at a subsequent meal [7]. As nutrients, even in small amounts, enter the small intestine, their interaction with small intestinal receptors, and the prompt release of CCK from I-cells located predominantly in the duodenum, as well as the interaction with gastric distension, results in "meal-like" sensations of fullness [8] and suppression of food intake [9]. Thus, early after meal ingestion, the combination of gastric distension and proximal small intestinal signals is a likely candidate to mediate the suppression of subsequent food intake.

As gastric emptying continues, the influence of gastric distension diminishes, while more distal regions of the small intestine are increasingly exposed to nutrients. Thus, while the release of CCK is rapid, with peak levels occurring within ~10–30 min following ingestion of an oral preload [10,11], the concentrations of peptide YY (PYY) and glucagon-like peptide-1 (GLP-1), which are produced by L-cells (considered in humans to be located with greatest density in the distal small intestine and colon, respectively [12]), generally increase more slowly and progressively over time, and in a load-dependent fashion [13–15] reaching a plateau from ~90–180 min after meal ingestion [13–15]. In contrast, ghrelin concentrations are elevated during fasting and their suppression occurs ~60 min after meal ingestion [16]. Given the sequential changes in the profiles of these GI factors, it is, therefore, conceivable that the timing between the ingestion of a preload and a subsequent meal influences energy intake at that meal. It may, thus, be postulated that gastric volume, and/or signaling arising from the proximal small intestine early after meal ingestion may lead to greater energy intake suppression 30 min after a preload, compared with later time points.

Therefore, the aim of this study was to directly examine temporal relationships between postprandial changes in distal gastric volume and the release of GI hormones after a nutrient drink (preload) with appetite perceptions and subsequent energy intake. Energy intake was assessed 30, 90 and 180 min after the preload to allow evaluation of the role of gastric, as well as proximal and distal small intestinal feedback signals, respectively.

2. Participants and methods

2.1. Ethics statement

The study protocol was approved by the Royal Adelaide Hospital Research Ethics Committee and conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All participants provided informed, written consent prior to their enrollment in the study. The trial was registered on the Australian and New Zealand Clinical Trial Registry (Trial Number: ACTRN12610000568011).

2.2. Participants

16 healthy, lean participants (10 male, 6 female) with a mean age of 26 ± 2 (range 21–40) years and normal body weight for their height (mean body mass index (BMI): 22.3 ± 0.5 kg/m^2, waist circumference: 76.6 ± 1.7 cm) were studied. Based on estimates of effect size and variance from previous studies [7], power calculations determined that 16 participants were required to detect a difference of 150 kcal in energy intake between visits in a 4-way design ($\alpha = 0.01$, and $\beta = 0.2$). All participants were unrestrained eaters (scoring <12 (mean score: 5 ± 1) on the eating restraint section of the Three Factor Eating Questionnaire [17]), had no GI diseases or symptoms, were non-diabetic (mean fasting glucose: 5.3 ± 0.1 mmol/l), had normal iron, hemoglobin and ferritin concentrations, and were not taking medication known to affect GI function or appetite. Consumption of a vegetarian diet, >20 g of alcohol/day, or smoking, also represented exclusion criteria. Female participants were not pregnant, as determined by a pregnancy test conducted prior to enrollment, and were included in the study only if they were using an appropriate hormonal contraceptive to exclude differences in gastric emptying and energy intake across the phases of the menstrual cycle [18].

2.3. Study design

Participants were each studied on four occasions, separated by 7–14 days, in a single-blind, randomized, fashion to evaluate the effects of a mixed-nutrient drink ingested 30 ("EI-30"), 90 ("EI-90"), or 180 ("EI-180") min prior, or a control drink 180 min prior, to a subsequent meal, on energy intake at that meal, and the relationships with antral area and GI hormone release.

2.4. Protocol

All participants were asked to maintain their normal eating habits between study days and to refrain from vigorous exercise and alcohol intake for 24 h before each study. To further standardize conditions, participants were provided with a ready-to-eat meal (beef lasagna, 2472 kJ, McCain Foods (Aust) Pty. Ltd.) for dinner the night before each study visit, to be consumed at 1900 h with only water allowed as a drink. After this time participants were required to fast from all food and fluid (except water).

The outline of the study design is presented in Fig. 1. On each study day, participants arrived fasted at the Discipline of Medicine at 0900 h. On arrival, participants were seated comfortably in a chair (upright and in a relaxed position, so that the angle between the upper and lower part of the body was ~120°). An intravenous cannula was placed in an antecubital vein for blood sampling, and a baseline blood sample (10 ml, t = −185 min), for the analysis of blood glucose, plasma CCK, PYY and ghrelin concentrations, was collected. Participants also completed a visual analogue scale questionnaire (VAS), assessing appetite perceptions and GI symptoms, and a 2D ultrasound scan was performed to assess fasting antral area, and to confirm that the stomach was empty. On the EI-30 and EI-90 days, an additional baseline ultrasound measurement, blood sample and VAS was collected 5 min prior to ingestion