The Role of Functional Lipids in Appetite Regulation and Weight Management

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Summary

The satiating properties of fat emulsions are poorly understood. An innovative vegetable oil-in-water emulsion was studied extensively in human interventions trials, in terms of its short-term effect on energy intake, longer term appetite suppressant action and its effects on weight control parameters. The objective of this paper is to review current evidence of a vegetable emulsion in weight management. Dose-response studies with 2, 4 and 6 grams of vegetable fat (Fabuless™) (at the expense of milk fat) demonstrated sustained, but disproportional, reductions in energy intake which coincided with an appetite suppressive effect. Discrepancy however exists in the data of short-term studies with several studies also showing smaller and neutral effects. Given the variability in outcome of short-term studies on satiety and food intake, long-term studies were conducted to evaluate and confirm whether in the long-term consistent changes in body weight and or body composition would be found with this fat emulsion. Overweight women followed a weight loss regime and subsequently returned to free living conditions resulting in statistically significant weight regain. However, the vegetable fat emulsion (Fabuless™) prevented the women from regaining significant weight and also reduced waist circumference. In addition, hunger feelings were reduced, as compared to the placebo (p<0.05). To conclude, short and long-term placebo-controlled clinical studies in which dairy fat is replaced by the functional vegetable fat emulsion show effects on appetite regulation, reduction of energy intake at the next meal, and body weight maintenance after a weight loss regime.

KEY WORDS: lipid emulsion, satiety, food intake, body weight, human intervention studies

Introduction

Rising prevalence of obesity in Asia and the Pacific region

The rise in the prevalence and incidence of overweight and obesity (body mass index ≥25 kg m⁻²) is emerging rapidly in both developed and developing countries in the Asian Pacific region. The most recent national representative estimates for the prevalence of overweight and obesity in 14 countries of the region indicate that overweight and obesity is endemic in much of the region, with prevalence ranging from less than 5% in India to 60% in Australia. In Japan, data from the National Nutrition Survey (1990-94) indicate that less than 3% of the population is classified as obese (BMI 30 kg m⁻²) and approximately 24.3% of men and 20.2% of women are classified as overweight (BMI 25-29.9 kg m⁻²). The numbers of overweight adults have increased 2 to 4 times over the last 30 years, especially in rural areas. In Japanese schoolchildren (6-14 years of age) the prevalence of obesity ranges between 5 to 11%.

This has led to an increase in overweight-related morbidity which imposes a heavy burden on health care systems and lowers quality of life for a significant percentage of the population. Obesity and overweight are associated with several chronic conditions, such as type 2 diabetes; hypertension and cardiovascular disease. The prevalence of overweight and obesity and its associated conditions is likely to increase further. Across various countries in the Asia and Pacific region population attributable fractions, related to overweight and obesity, ranged from 0.8% to 9.2% for coronary heart disease mortality, 0.2% to 2.9% for haemorrhagic stroke mortality and 0.9% to 10.2% for ischaemic stroke mortality. Health risks associated with obesity apparently occur at a relatively low body mass index in Asian populations.

Development of overweight and obesity and the complexity of appetite regulation

Overweight and obesity develop from a persistent imbalance between energy intake and expenditure. If intake exceeds energy loss over a longer period of time, excess energy will be stored in fat mass. The imbalance can be caused by multiple factors of which most well-known are a moderately higher energy intake and lower physical activity, but also genetic make-up, ageing, stress and other factors appear to play a role. Progress is being booked in identifying the genes that predispose a person to be more vulnerable to become obese. However, these genes are evidently not causally related to the sharp rise in overweight people seen over the last decade. Lifestyle changes are likely to be mostly responsible, such as sedentary life together with slightly higher energy intakes and possibly energy dense diets.
Multiple physiological pathways interact to initiate and terminate food intake and regulate the level of body adiposity and the overall energy balance. A diversity of hormones is released in the gastrointestinal tract in response to and also in the absence of food and those signals are subsequently integrated by peripheral nerves and in specific parts of the brain (hypothalamus; the so-called “brain-to-gut axis”. Delicate regulation of energy homeostasis is critical to obtain a stable body weight over lifetime. Contrary to what might be expected, actually very small changes in calorie intake or expenditure appear to be responsible for the epidemic developments in overweight worldwide.

In case energy stores in the body are low, the hypothalamus initiates a cascade of orexigenic signals to induce the feeling of hunger and stimulate food intake. High levels of the hormone ghrelin are found in the blood during a period of fasting, and these rapidly drop in the postprandial period. In contrast, high blood levels of anorexigenic peptides suppress appetite and lead to termination of the intake of foods. The peptides cholecokinin (CCK), PP-fold peptide (PYY) or glucagon-like peptide 1 (GLP-1), are released in the intestinal tract in response to food. In addition, the presence of nutrients in the blood (e.g. glucose, amino acids and free-fatty acids), modulates hormone secretion, e.g. insulin which levels are high in case of a positive energy balance.

The extent to which food or food ingredients can influence food intake and control appetite is dependent on the effect food has on ‘satiation’ (feeling full during meals) and/or ‘satiety’ (not feeling hungry between meals). Satiation determines when to stop eating and is affected by meal size. Satiety is initiated at the end of a meal and determines the time period between two subsequent meals and the amount of foods eaten during the next meal. The periodic occurrence of such events can be expressed as the “satiety cascade”.

In normal physiological conditions, unabsorbed nutrients (e.g. fatty acids) can reach the distal part of the small intestine and more particularly the ileum, to induce activation of the so-called “ileal brake mechanism”. The ileal brake mechanism is a feed-back mechanism which slows down gastrointestinal transit time, initiates the release of satiety hormones (e.g. GLP-1) and subsequently induces feelings of satiety. GLP-1 is a peptide secreted by the L-cells in the distal small intestine and colon, predominantly in response to carbohydrate and fat and a powerful anorexigenic hormone. GLP-1 itself can inhibit gastrointestinal motility, relaxes the proximal stomach, stimulates phasic and tonic motility of the pylorus and inhibits gastric acid and exocrine pancreas secretion. The ileal brake mechanism has been suggested as a sensible target for appetite control by food ingredients by which sustainable effects on the body’s caloric management systems, and consequently on body weight and fat mass, may be achieved.

**Functional lipids**

Extensive research is currently ongoing about the role of functional lipids in activating the ileal brake mechanism to enhance the feeling of satiety after a meal, thereby reducing (or postponing) food intake at subsequent meals and to decrease the total food intake over the day. Fat infusions (as triacylglycerol emulsions) into the small intestine of normal weight and obese men have been shown to suppress short-term hunger ratings and food intake. There is little doubt that emulsified fats can increase satiety when infused directly into the small intestine; however whether the oral intake can induce similar effects was, until recent years, not clear.

Fats with different physico-chemical characteristics may have varying effects on feelings of satiety. Structural differences such as chain length, degree of saturation, degree of emulsification and emulsion stability may influence satiety efficiency. For instance, reduction of hunger and food intake increases with increasing fatty acid chain length. Feltrin et al. showed that a reduction in energy intake and in hunger was stronger after isocaloric infusion of lauric acid (12:0) than of decanoic acid (10:0). French et al. measured food intake and satiety after various intraduodenally infused fat emulsions. Emulsions enriched with linoleic acid (18:2) reduced food intake more than did oleic (18:1) or stearic (18:0) acids without affecting satiety. In addition, Maljaars et al. demonstrated that, when infused into the ileum, triacylglycerols with unsaturated fatty acids increase satiety, whereas triacylglycerols with saturated fatty acids do not.

Depending on those characteristics, functional fat emulsions can be developed aiming to regulate appetite. One such innovation was the development of an oil-in-water emulsion composed of 42% of vegetable oil and water (Fabuless™). The oil droplets are made from natural palm oil (39.5% w/w) and coated with galactolipids from natural oat oil (2.5% w/w). The effects of this emulsion appear to be due to its different physico-chemical characteristics compared to control milk fat emulsions, somehow acting on feed back mechanisms. The composing fatty acids are 49% saturated fatty acids (C16:0 and C18:0 ratio 90:10), 40% mono-unsaturated fatty acids (C18:1) and 11% polyunsaturated fatty acids (C18:2). Milk fat, on the other hand, contains approximately 65% saturated (4:0, 6:0, 8:0, 10:0, 12:0, 14:0, 16:0, 18:0), 30% mono-unsaturated (16:1 and 18:1) and, 5% polyunsaturated fatty acids (18:2 and 18:3) (only the major fatty acids are mentioned, making-up 90% of the milk fat).

**Short-Term Human Studies on Satiety and Food Intake**

The first evidence on the effect of the functional vegetable fat emulsion on satiety and energy intake was obtained in two randomised double-blind and placebo-controlled (cross-over) studies of Burns et al. In the first study, healthy volunteers ingesting yoghurt (200 g) containing either the vegetable fat emulsion (test period) (5 g Fabuless™ fat emulsion + 1 g milk fat) or placebo (6 g of normal milk fat) at lunch time significantly reduced their (ad libitum) energy intake 4 hours later at the dinner meal by 14.1% (6.4 MJ for the test vs. 7.6 MJ for the placebo period, p=0.05). Similar data were obtained in the second study having a similar design showing energy intakes during the dinner meal of respectively 6.9 MJ for the test period and 7.9 MJ for the placebo period (p=0.001) resulting in a reduction of about 12.5 %. In addition, in both studies, energy intakes remained significantly lower during the remainder of the evenings following the consumption of the test yoghurts (p=0.022 vs. placebo period in study 1 and p=0.005 vs. placebo in study 2). Mean ratings for hunger (p=0.002), desire to eat (p=0.006) and pre-occupation with thoughts of food (p=0.001) were also significantly lower after the test yoghurt throughout the day when compared to the placebo period (Figure 1). However, these differences could not be observed in the second study. No consistent effects of the vegetable fat emulsion on appetite ratings were also observed in the study of Logan et al. in healthy subjects. In this randomized,
Subjective feelings of hunger (a), desire to eat (b) and pre-occupation with thoughts of food (c) over time 4 hours after intake of the functional fat emulsion (Fabuless™) or placebo. Values are presented as mean of rating for each 5 h period and analyzed by ANOVA (analysis of variance). a) $p=0.002$, b) $p=0.006$ c) $p<0.001$. 

**Figure 1a**

**Figure 1b**

**Figure 1c**

**Fig. I.** Subjective feelings of hunger (a), desire to eat (b) and pre-occupation with thoughts of food (c) over time 4 hours after intake of the functional fat emulsion (Fabuless™) or placebo. Values are presented as mean of rating for each 5 h period and analyzed by ANOVA (analysis of variance). a) $p=0.002$, b) $p=0.006$ c) $p<0.001$. 

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**Functional Lipids for Weight Management**
double-blind and placebo-controlled (cross-over) study no effects were found of the vegetable fat emulsion (5 g of Fabuless™ fat) on mean energy intake at lunch 4 hours post-consumption or self-reported food intakes for the remainder of the day when compared to the placebo period. Considerable individual variation, however, existed in food intakes with 46%, 59% and 57% of the subjects reducing their energy intakes at lunch on days 1, 8 and 22 after consumption of the vegetable fat emulsion. Such inconsistencies demonstrate the numerous confounding factors influencing eating behavior and the difficulties in running intervention studies with primary objective the effects on satiety and energy intake. Indeed, in addition to human appetite, other factors may exert powerful effects on food intake and eating behavior. These factors may over-ride normal appetite sensations in certain individuals.

To investigate further the short-term effects of the vegetable fat emulsion on satiety and energy intake in healthy, overweight and obese subjects, Burns et al. randomized volunteers in a double-blind and placebo-controlled (cross-over) manner to receive either yoghurt containing the vegetable fat emulsion (5 g of Fabuless™ fat emulsion + 1 g of milk fat) or placebo (6 g of milk fat) for breakfast. Energy intakes were significantly reduced at 4 hours post-consumption of the test yoghurts in the healthy (3.79 MJ, p < 0.001) 24-hours following intake. The minimum dose tested (2 g of vegetable (Fabuless™ fat) gives a significant and substantial lowering of energy intakes. Although two-fold or three-fold increases in the vegetable fat (Fabuless™ fat) gives a significant and substantial lowering of energy intake lasts as long as 36 hours following consumption of the test yoghurt. In addition, subjects had significantly reduced hunger desire to eat, preoccupation with thoughts of food and perceived fullness throughout the day with ingestion of the test yoghurt when compared to the placebo period (p < 0.05). Reduced hunger and desire to eat in the morning (p < 0.05), increased fullness for 3 hours (p < 0.05) and, increased inter-meal interval (3.7 ± 1.2 hours in the test and 2.9 ± 1.0 hours in the placebo group, p < 0.05) when compared to the placebo was also observed in healthy subjects ingesting the functional fat emulsion (Fabuless™) in a randomized, double-blind and placebo-controlled manner in the study of Stijns et al. Furthermore, the test yoghurt reduced desire to eat (1 and 3 hours after yoghurt ingestion, p < 0.05) and prospective food consumption (1 hour after yoghurt consumption, p < 0.05) in both healthy and overweight volunteers when compared to placebo. No effects on energy intake were seen.

The presence of a dose-response effect of the vegetable fat emulsion was subsequently investigated in a single-blind and placebo-controlled (cross-over) study in healthy subjects giving portions of 200 g of yoghurt containing 15 g of fat of which 0, 2, 4 and 6 g of vegetable (Fabuless™) fat. Relative to the placebo yoghurt, mean energy intakes were progressively reduced with increasing doses of the functional fat by respectively 21, 25 and 30% after the 2, 4 and 6 gram doses (p < 0.001 vs. placebo) (Figure 2). In addition, mean energy intakes for the remainder of each study day and over the following 24-hours were significantly lower for all dose levels when compared to the control (p < 0.001). No significant differences, however, in hunger, desire to eat or perceived fullness between the test and control yoghurts were seen.

These data indicate that yoghurt containing the vegetable fat emulsion significantly reduces ad libitum energy intakes relative to milk fat in healthy, overweight and obese individuals after 4, 8, 12 and 24 hours following intake. The minimum dose tested (2g Fabuless™ fat) gives a significant and substantial lowering of energy intakes. Although two-fold or three-fold increases in the dose do enhance the response these were not proportional to

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**Fig. 2** Energy intakes at 4 hours post-consumption of different doses of the functional fat emulsion (Fabuless™). Values are presented as means ± s.e.m. a) p<0.05 compared to the 0 g dose; b) p<0.05 compared to the 2 g dose.
the increase in dose level. However, great individual variation in
the response to the vegetable emulsion exists which is consistent
with the multitude of factors that influence food intake and eating
behavior and consequently the difficulties in measuring human
appetite and food intake.

**Long-Term Human Studies on Satiety and Food
Intake**

Diepvens et al. 25) conducted a study to investigate the
long-term effects of the vegetable fat emulsion, and to improve
understanding of the possible mechanism underlying the observed
short-term reduction in energy intake. In a randomized,
placebo-controlled and double-blind (parallel) study fifty, adult,
overweight females were given either the vegetable fat emulsion
(test: 3 g milk fat and 2 g vegetable fat provided by 5 g FabulessTM
emulsion) or placebo (5 g of milk fat) twice daily during an 18
weeks weight maintenance phase which followed a 6 weeks very
low caloric weight management program. During the weight
maintenance phase, subjects resumed their habitual eating patterns.
Subjects lost substantial weight during the very low caloric diet
phase, respectively 7.76 ± 1.5 kg and 7.65 ±1.4 kg in the test and
placebo groups. During the weight maintenance phase, however,
subjects in the placebo group significantly increased body weight
(+2.95 ± 3.1 kg) after 18 weeks of intervention \(p<0.001\), whereas
they did not gain significant weight in the test group (+1.13 ± 3.4
kg). Differences in weight regain between both groups were
significant \(p=0.05\) (Figure 3). Body mass index and waist
circumference also significantly increased in the placebo group
\(p<0.05\), but not in the test group (Figure 4). At the end of the
study period, subjects in the test group were significantly less
hungry (4 hours after intake) as compared to placebo \(p<0.05\). The
levels of glucagon-like peptide 1 (GLP-1) at 180 min after

**Mode of Action**

Although the ileal brake has been hypothesized as the
mechanism of action by which the vegetable fat emulsion can
affect appetite and food intake, it is until recently that this mode of
action has been proven in healthy men in a double-blind and
placebo-controlled intervention study. A statistically significant
delay in the appearance of sulfapyridine in the serum was obtained
after intake of the vegetable fat emulsion (FabulessTM) when
compared to milk fat (added to yoghurt) \(p<0.05\). The delay
corresponded to a 45-min longer orocecal transit time. Sulfapyridine is formed in the colon and, subsequently absorbed in
the blood upon colonic metabolization of the marker salazopyrine
which has been orally ingested before intake of either of the
yoghurts 26).

This study demonstrates that the vegetable fat emulsion
(FabulessTM) can affect the ileal brake mechanism by slowing
down the gastrointestinal transit time, which might explain the
weight control and appetite suppression observed in previous studies.

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![Change in body weight over time](image-url)

**Fig. 3.** Changes in body weight over time.

VLCD: Very Low Caloric Diet. WMD: Weight maintenance Diet. Values are presented as means ±
S.D.: a \(p<0.05\) over time difference compared to baseline (ANOVA repeated measures), values are
significant for both the test (FabulessTM) and placebo groups. b \(p<0.05\) over time difference
compared to VLCD (ANOVA repeated measures), value is significant only for the placebo group.
\(p=0.05\) treatment over time difference, test (FabulessTM) vs. placebo group after WMD (ANOVA
repeated measures).
Fig. 4. Changes in waist circumference over time.

VLCD: Very Low Caloric Diet. WMD: Weight maintenance Diet. Values are presented as means ± s.d. a: p<0.05 over time difference compared to baseline (ANOVA repeated measures), values are significant for both the test (Fabuless™) and placebo groups. b: p<0.05 over time difference compared to VLCD (ANOVA repeated measures), value is significant only for the placebo group. c: p=0.05 treatment over time difference, test (Fabuless™) vs. placebo group after WMD (ANOVA repeated measures).

Safety

High-fat diets, in excess of energy needs, have been associated with adverse effects in humans. The highest proposed intake level of Fabuless™ emulsion is 5 g/person, three times per day. This corresponds to about 6.3 g Fabuless™ oil, i.e. about 6 g palm oil and 0.3 g oat oil. This intended oil intake level is within the total daily oil intake and the estimated Acceptable Macronutrient Distribution Range for total fat.

Palm oil and oats are part of the daily human diet and therefore, have a history of safe use. Since oil is a macro-ingredient, it is difficult to apply classical toxicology tests in animals. Increasing palm oil contents, i.e. >10 to 30% of the diet have shown to induce general toxicity (dose-dependent) which is likely to be attributed to the diets caloric character. The 10% oil-enriched diets, however, showed no adverse effects and are considered as the no-observed-effect level (NOEL) which corresponds to 8.3 g palm oil/kg of body weight/day.

In vitro standard genotoxicity studies showed that the galactolipid-containing oat oil fractions (of Fabuless™) do neither induce mutations in the standard Ames test (bacterial reverse mutation assay) or chromosome aberrations in the cultured human lymphocytes (chromosome aberration test) (non published data).

Sub-acute (28-day) in vivo toxicity studies with the oat oil fraction in rats and dogs resulted in a NOEL of 5000 mg oat oil/kg body weight/day (corresponding to the highest dose tested) (non published data). This corresponds to a margin of safety (MOS) of at least 1000 compared to the intended human dose of 5 mg oat oil/kg body weight (= 0.3 g oat oil/60 kg person).

Double-blind and placebo-controlled intervention studies using doses ranging from 2 to 6 g of Fabuless™ fat per day with daily exposure of 3 weeks up to 4 months showed good tolerance and no adverse effects.

Conclusion

To date vegetable fat emulsions have been extensively studied for their effects on appetite regulation and subsequently body weight maintenance. From the above evidence, vegetable fat emulsions (Fabuless™) have been demonstrated to affect the release of satiety hormones, to induce satiety, reduce energy intake at the next meal and subsequently affect long-term body weight maintenance. Recently, the effect of vegetable fat emulsions on slowing down gastrointestinal transit time has been demonstrated which is indicative for their mode of action on triggering the ileal brake mechanism.
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