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The effect of encapsulated glutamine on gut peptide secretion in human volunteers

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ABSTRACT

Context: Weight loss and improved blood glucose control after bariatric surgery have been attributed in part to increased ileal nutrient delivery with enhanced release of glucagon-like peptide 1 (GLP-1). Non-surgical strategies to manage obesity are required. The aim of the current study was to assess whether encapsulated glutamine, targeted to the ileum, could increase GLP-1 secretion, improve glucose tolerance or reduce meal size.
Methods: A single-center, randomised, double blind, placebo-controlled, cross-over study was performed in 24 healthy volunteers and 8 patients with type 2 diabetes. Fasting participants received a single dose of encapsulated ileal-release glutamine (3.6 or 6.0 g) or placebo per visit with blood sampling at baseline and for 4 h thereafter. Glucose tolerance and meal size were studied using a 75 g oral glucose tolerance test and ad libitum meal respectively.
Results: In healthy volunteers, ingestion of 6.0 g glutamine was associated with increased GLP-1 concentrations after 90 min compared with placebo (mean 10.6 pg/ml vs 6.9 pg/ml, $p = 0.004$), increased insulin concentrations after 90 min (mean 70.9 vs 48.5, $p = 0.048$), and increased meal size at 120 min (mean 542 g eaten vs 481 g, $p = 0.008$). Ingestion of 6.0 g glutamine was not associated with significant differences in GLP-1, glucose or insulin concentrations after a glucose tolerance test in healthy or type 2 diabetic participants.
Conclusions: Single oral dosing of encapsulated glutamine did not provoke consistent increases in GLP-1 and insulin secretion and was not associated with beneficial metabolic effects in healthy volunteers or patients with type 2 diabetes.

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1. Introduction

Over several decades, population levels of obesity, defined as individuals having a body mass index of 30 kg/m^2 or more, have increased in many countries worldwide. The World Health Organisation now considers obesity to be one of the greatest public health challenges to be faced in the 21st century [1]. Obesity and related conditions, such as type 2 diabetes mellitus (T2DM), are responsible for rising healthcare costs and a great burden of morbidity and mortality. Both obesity and T2DM can be successfully treated with bariatric surgery, although the precise mechanisms responsible for these beneficial effects remain poorly understood. One possibility is that bariatric surgery improves diabetes and aids weight loss by increasing nutrient delivery to the distal gut, which stimulates release of the satiety-promoting incretin hormone glucagon-like peptide 1 (GLP-1). Although GLP-1 mimetics have been given pharmacologically in the treatment of T2DM and obesity [2], an alternative would be to use agents which enhance endogenous GLP-1 production to harness similar benefits with potentially fewer adverse effects.

GLP-1 is produced in enteroendocrine L-cells in the mucosa of the ileum and colon in response to nutrient exposure. Many different proteins or amino acids have been found to stimulate GLP-1 release by interacting with the calcium-sensing receptor (CaSR)

Abbreviations: AUC, area under the curve; BMI, body mass index; CaSR, calcium sensing receptor; CV, coefficient of variation; DPP-IV, dipeptidyl peptidase-IV; GLP-1, glucagon-like peptide-1; GPCR, G-protein coupled receptor; HV, healthy volunteer; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus; WHO, World Health Organisation.

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[3,4], GPRC6A [5] or PEPT1 [4]. The amino acid glutamine is abundant in the human diet and a particularly effective stimulant of GLP-1 release in vitro because it not only generates an electrical signal in L-cells but also elevates intracellular cAMP levels [6]. Oral ingestion of glutamine in human volunteers was associated with enhanced GLP-1 secretion and improved glucose tolerance, but a dose of at least 15 g was required [7,8], possibly due to the low stability of glutamine in gastric acid [9] and its absorption in the upper GI tract resulting in relatively low levels reaching the ileal L-cells. Encapsulation could circumvent this problem by facilitating targeted release of nutrients into parts of the intestine where the L-cells are most abundant.

The aim of the current study was to assess the effect of encapsulated glutamine on GLP-1 concentrations, glucose tolerance and meal size in healthy human volunteers and in individuals with T2DM.

2. Methods

2.1. Participant recruitment

Healthy male and female volunteers (18–65 years old; body mass index (BMI) 18–35 kg/m^2) were recruited using advertisements in Addenbrooke's Hospital and the University of Cambridge. Patients with T2DM (18–65 years old; BMI of 18–40 kg/m^2) were identified through primary care, outpatient clinics and using advertisements. Participants with anemia or other significant active diseases and those who were pregnant or breastfeeding were excluded. Patients with T2DM who had taken insulin or injectable GLP-1 agonists were excluded from the study. Patients who were taking metformin, sulphonylureas or dipeptidyl peptidase-IV (DPP-IV) inhibitors were asked to withhold these for 12, 24 and 72 h prior to the test respectively.

Participants were provided with written information about the study and gave written informed consent prior to participation. The study was given ethical approval by the Norfolk & Norwich Research Ethics Committee (Reference 12/EE/0389, 25/09/2012; ISRCTN 10757078).

Participants attended the clinical research facility in the morning following an overnight fast. The evening before each visit, participants had a standardized pasta meal (15% protein, 30% fat, 55% carbohydrate) designed to provide 33% of their daily calorie requirement based upon an estimation of their metabolic rate and activity levels [10].

2.2. Capsule production

Capsule development and GMP manufacture was performed by Encap Drug Delivery Ltd. (Livingston, UK). Each capsule contained 600 mg of glutamine or 300 mg microcrystalline cellulose (placebo). The capsules were manufactured with an enteric coating designed to promote capsule release 20 min after exposure to an alkaline environment.

2.3. Study design

The capsules were tested in a series of blinded, controlled studies in human volunteers. The primary endpoint was the effect of the capsules upon circulating concentrations of total GLP-1 in venous blood. The secondary endpoints were safety, the effect of the capsules upon glucose tolerance, meal size and subjective feelings of hunger and fullness.

2.3.1. Fasting study

Initially, a single-blinded, non-randomised, placebo-controlled dose-ranging study in four healthy volunteers was performed to ascertain the optimal dose for further evaluation and provide preliminary safety data. The doses studied included placebo (10 capsules) and 0.6 g, 1.8 g. 3.6 g and 6.0 g glutamine supplemented where necessary with placebo capsules to preserve participant blinding. The remainder of the study used the two most promising doses, 3.6 and 6.0 g Glutamine in comparison to placebo in a double-blind, controlled randomised design.

On each visit, venous blood was taken at baseline and at intervals following capsule ingestion for evaluation of GLP-1 concentrations. Participants recorded adverse events in a symptom diary and completed questionnaires evaluating hunger, fullness and nausea. On one visit, participants had a DXA scan. Ten healthy volunteers were recruited for evaluation of the primary endpoint in the fasting comparison between placebo, 3.6 g Glutamine and 6.0 g Glutamine.

2.3.2. Glucose tolerance and meal size in healthy volunteers and patients with T2DM

For evaluation of the effect on the capsules on glucose tolerance, nine healthy volunteers and eight patients with T2DM were recruited. The study visits were similar to the fasting study except that each participant had a 75 g oral glucose tolerance test (OGTT) at 90 min after capsule ingestion.

2.3.3. Meal size in healthy volunteers

For evaluation of the effect of the capsules on meal size, ten healthy volunteers were recruited to attend the Clinical Research Facility on three occasions for an ad libitum breakfast given 120 min after capsule ingestion. The ad libitum meal consisted of muesli with chopped fruit, nuts and milk in a homogenous mixture designed to provide 15% protein, 30% fat and 55% carbohydrate. A portion of 1.5 kg (2400 kcal) was provided on each occasion and participants were advised to eat until they felt full. The total amount of food eaten was measured using a universal eating monitor.

2.4. Questionnaire design

Hunger, fullness and nausea were assessed using a visual analog scale which has been widely used in the medical literature [11].

2.5. Analytical methodology

For analysis of total GLP-1, samples were taken into EDTA plasma tubes, placed on ice immediately after venesection and centrifuged (3500 × *g* at 4 °C 10 min), aliquotted and frozen using dry ice within 15 min of venesection. Samples were stored at −80 °C prior to batch analysis in duplicate of GLP-1 using the Mesoscale Discovery Total GLP-1 kit, a sandwich immunoassay with electrochemiluminescence detection which measures all endogenous forms of GLP-1. This method has a range of 1.4–1000 pg/ml and coefficients of variation (CVs) of 5–7%.

For biochemistry testing, serum samples were allowed to clot for 10 min then centrifuged, separated and frozen within 30 min of venesection and stored at −80 °C prior to analysis. Glucose, alanine aminotransferase (ALT) and creatinine were measured in a clinically-accredited laboratory at Addenbrooke's hospital using a Siemens' Dimension analyzer with CVs of <2% within the reference range. Thyroid stimulating hormone (TSH) was measured using a Bayer ADVIA Centaur immunoassay system with CVs of <6% within the reference range. HbA1c was measured on fresh whole blood using a Tosoh analyser with CVs of <5% within the reference range.

For measurement of insulin, samples were collected into lithium heparin plasma tubes, placed on ice, centrifuged (3500 × *g* at 4 °C 10 min), aliquotted and frozen using dry ice within 15 min of venesection. Samples were stored at −80 °C prior to batch analysis using the Diasorin Liaison, an immunoassay with chemilumines-

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