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Exogenous glucagon-like peptide-1 reduces body weight and cholecystokinin-8 enhances this reduction in diet-induced obese male rats

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ABSTRACT

The sites of action regulating meal size (MS) and intermeal interval (IMI) length by glucagon like peptide-1 (7–36) (GLP-1 (7–36)) and cholecystokinin-8 (CCK-8) reside in the areas supplied by the two major branches of the abdominal aorta, celiac and cranial mesenteric arteries. We hypothesized that infusing GLP-1 near those sites reduces body weight (BW) and adding CCK-8 to this infusion enhances the reduction. Here, we measured BW in diet-induced obese (DIO) male rats maintained and tested on normal rat chow and infused with saline, GLP-1 (0.5 nmol/kg) and GLP-1 + CCK-8 (0.5 nmol/kg each) in the aorta once daily for 21 days. We found that GLP-1 and GLP-1 + CCK-8 decrease BW relative to saline vehicle and GLP-1 + CCK-8 reduced it more than GLP-1 alone. Reduction of BW by GLP-1 alone was accompanied by decreased 24-h food intake, first MS, duration of first meal and number of meals, and an increase in latency to first meal. Reduction of BW by the combination of the peptides was accompanied by decrease 24-h food intake, first MS, duration of first meal and number of meals, and increase in the IMI length, satiety ratio and latency to first meal. In conclusion, GLP-1 reduces BW and CCK-8 enhances this reduction if the peptides are given near their sites of action.

1. Introduction

Glucagon-like peptide-1 (GLP-1) [1] is a peptide secreted by a variety of enteroendocrine cells in the gastrointestinal tract [2] and evokes responses such as stimulation of insulin secretion [3,4] and reduction of food intake [5,6]. However, rapid degradation by the enzyme dipeptidyl peptidase IV (DPP-IV) [7] prevents the natural bioactive form of GLP-1 or GLP-1 (7–36) [8] from producing long-lasting actions e.g. reduction of body weight (BW) despite its ability to reduce meal size (MS). As a result, synthetic analogues of GLP-1 receptor e.g. exenatide have been developed to study this peptide and investigate its therapeutic potentials.

We have used an intra-arterial infusion technique to localize the gastrointestinal sites of action that regulate MS and intermeal interval (IMI, time between first and second meal) length by a variety of gut peptides e.g. GLP-1, gastrin releasing peptide (GRP) and cholecystokinin (CCK) [9–16]. Using this technique we found that the areas supplied by the two major branches of the aorta, celiac artery (CA, supplies stomach and upper duodenum) and cranial mesenteric artery (CMA, supplies small and part of the large intestine) contain sites of action regulating MS (normal rat chow) and IMI length by GLP-1 (7–36) [9].

In the current study, we tested the hypothesis that delivering GLP-1 (7–36) near its gastrointestinal sites of action reduces BW. This hypothesis is based on the prediction that delivering the peptide at those sites may minimize its degradation by DPP-IV and leads to prolongation of activity. As a result, GLP-1 may reduce BW in addition to reducing food intake.

Furthermore, recently Trevaskis et al. have shown that combining AC3174, a GLP-1 receptor agonist and exenatide analogue, with a stabilized acetylated version of CCK-8 reduce BW but failed to do so when the peptides were given individually [17]. Therefore, we also hypothesized that delivering CCK-8 with GLP-1 (7–36) near their gastrointestinal sites of action may produce more reduction of BW than by GLP-1 alone. Cholecystokinin [18] is a peptide hormone secreted by the I cells of the small intestine and evokes responses such as reduction of food intake [19] through gastrointestinal sites, similar to GLP-1, supplied by the CA and the CMA [11,12,15]. In addition, when given near these sites CCK-8 also reduced BW [10].

The two parts of our hypothesis have been tested in a suitable animal model to study human obesity, the diet-induced obese (DIO) rat model [20,21]. Here, we have used the same doses of GLP-1 and CCK-8,

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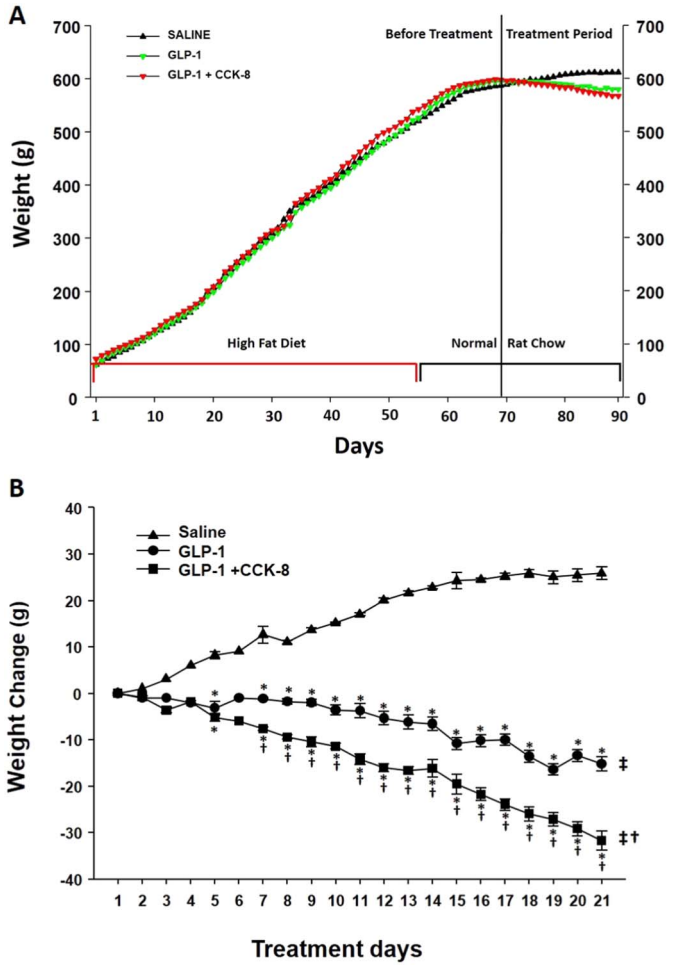

Fig. 1. Effect of glucagon-like peptide-1 and combination of cholecystokinin-8 and glucagon-like peptide-1 on body weight. Three groups of free feeding diet-induced obese rats (n = 5 rats/group) received a daily injection of glucagon like peptide-1 (GLP-1, 0.5 nmol/kg), GLP-1 + cholecystokinin-8 (CCK-8) (0.5 nmol/kg each) or saline vehicle for twenty one days in the aorta prior to the onset of the dark cycle and body weight (BW) was recoded daily. (A) Depicts the weights of the rats upon arrival until the end of the experiment. (B) Depicts the effect of the peptides on body weight of the rats. GLP-1 and GLP-1 + CCK-8 reduced overall BW relative to saline ($p < 0.001$, ‡), on days 5, 7–21 GLP-1 and GLP-1 + CCK-8 reduced BW relative to saline ($p < 0.05$, *) and on days 7–21 combined GLP-1 + CCK-8 reduced it more than GLP-1 alone ($p < 0.05$, †).

0.5 nmol/kg each, which produced significant reduction of MS and prolongation of the IMI in our previous studies [9,10,13].

Consistent with the two parts of our hypothesis, the current study demonstrated that GLP-1 (7–36) reduces BW in male DIO rats and CCK-8 enhances this reduction if the peptides are given near their sites of action.

2. Materials and methods

2.1. Animals

The Tuskegee University Animal Care and Use Committee approved the animal protocol for this experiment. Following their arrival at the age of 28 days (50–80 g each) rats were fed purified high fat (HF) diet for (D12266B, Research Diets, protein 16.8%kcal, carbohydrates 51.4% kcal and fat 31.8%kcal) 8 weeks until there was a difference in body weight (Fig. 1A) [20,21]. After the 8 week period animals were maintained on regular rat chow (Teklad 2018 global, 18% protein rodent diet, Envigo) for the remainder of the experiment. Experimental grouping was achieved by random assignment and there was no difference in the groups in the pre-treatment data.

Three groups of adult DIO male Sprague Dawley rats (n = 5 rats per group, Charles Rivers, Kingston Facility, NY) with mean starting weight of 594.6 ± 16.2 (group 1), 598.6 ± 17.2 (group 2) and 585.6 ± 18.9 (group 3) were individually housed in the BioDAQ E2 system (Research Diets, New Brunswick, NJ) in a controlled environment (12 h dark/12 h light cycle – lights off at 1800 h, 21.5 °C) with water and pelleted rodent chow (Teklad, Madison, WI) available ad libitum.

2.2. Vascular catheterization

Each animal had one catheter implanted in the aorta as described previously [9–16]. Catheters were inserted in the aorta caudally to cranially (anally to orally) and the tip of each catheter was fixed before the origin of the CMA.

Catheters (Micro-Renathane R-ITC-SP 9.5, Braintree Scientific, Braintree MA) were 24 cm long, the intravascular portion was 0.25 mm OD × 0.12 mm ID and the size of the remaining part was 0.84 mm OD × 0.36 mm ID. Catheterizations were performed using a surgical microscope (Carl Zeiss Opmi 160 12.5 ×/18B, 1 × 250, Monument, CO). General anesthesia, indicated by the absence of a pedal withdrawal reflex, was achieved with intramuscular injection of 1 ml/kg body weight of a mixture of 5.0 ml of Ketaset [100 mg/kg], 2.5 ml of Rompun® [xylazine 20 mg/kg], Bayer, Shawnee Mission, KS, 1.0 ml of acepromazine maleate® [10 mg/kg], Bayer, Shawnee Mission, KS and 1.5 ml of saline. The abdominal wall was clipped and cleaned with three alternating betadine solution and alcohol swabs. A ventral midline celiotomy was performed.

The aorta was exposed and two temporary ligations, 1 cm a part, were placed passing the origin of the CMA in the aborad direction to prevent bleeding. The aorta was punctured with a sterile 30 gauge needle between the two ligatures and the catheter was threaded into the artery without blocking the entrance of the CMA. The catheter was fixed in place using cyanoacrylate glue, the temporary ligations were removed and the catheter was threaded out of the abdominal cavity subcutaneously, exteriorized between the scapulae and secured with sutures and cyanoacrylate glue.

The muscles of the abdominal wall were closed using a polydioxanone II (4-0) absorbable suture in a simple continuous pattern, and the skin was closed using surgical staples. Postoperative care included Metacam® (Meloxicam® [1.1 mg/kg] Boehringer Ingelheim, St. Joseph, MO) subcutaneously for pain control, and Baytril® (Enrofloxacin® [0.05 ml], Bayer, Shawnee Mission, KS) intramuscularly as an anti-bacterial medication, each given daily for 5 d. Rats were allowed two weeks of recovery time. The criteria for complete recovery following surgery included the absence of clinical signs (e.g., signs of pain, porphyria secretion, cold extremities and lethargy) and the return of food intake to pre-operative levels. Catheters were flushed twice daily (0900 h and 1645 h) with 0.3 ml heparinized saline.

2.3. Meal patterns

The BioDAQ E2 Food and Water Intake system detects brief episodes of food intake while minimizing food spillage and hoarding and generates a computerized data stream including times of the initiation of intake activity, the period of the activity, and the weight consumed. The criterion for a meal (normal rat chow) was consumption of ≥ 0.2 g, and the criterion for IMI was no feeding activity for ≥ 15 min [9,11–13,15,16].

2.4. Establishing baseline food intake

Following recovery, rats were habituated to the laboratory environment and experimental design daily for two weeks. At 0900 h the rats were weighed and at 0900 and 1645 h they received a 0.3 ml infusion of heparinized saline in their catheters. At 1700 h, lights were

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