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Liraglutide suppression of caloric intake competes with the intake-promoting effects of a palatable cafeteria diet, but does not impact food or macronutrient selection.

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ABSTRACT

Liraglutide, a Glucagon-Like Peptide-1 (GLP-1) receptor agonist, is used as a treatment for Type 2 diabetes mellitus and obesity because it improves glycemia and decreases food intake. Here, we tested whether chronic activation of the GLP-1 receptor system with liraglutide would induce decreases in intake accompanied by changes in proportional food or macronutrient intake similar to those seen following RYGB in rats when a variety of palatable food options are available. A "cafeteria diet" was used that included: laboratory rodent chow, refried beans (low-fat/low-sugar), low-fat yogurt (low-fat/high-sugar), peanut butter (high-fat/low-sugar) and sugar-fat whip (high-fat/high-sugar). Liraglutide (1 mg/kg daily, sc, $n = 6$) induced significant reductions in body weight and total caloric intake compared to saline–injected control rats ($n = 6$). Although access to a cafeteria diet induced increases in caloric intake in both groups relative to chow alone, liraglutide still effectively decreased intake compared with saline-injected rats suggesting that chronic GLP-1 activation competes with the energy density and palatability of available food options in modulating ingestive behavior. Even with the substantial effects on overall intake, liraglutide did not change food choice or relative macronutrient intake when compared to pre-treatment baseline. When drug treatment was discontinued, the liraglutide group increased caloric intake and rapidly gained body weight to match that of the saline group. These results demonstrate that, while liraglutide effectively decreases caloric intake and body weight in rats, it does not cause adjustments in relative macronutrient consumption. Our data also show that drug-induced decreases in intake and body weight are not maintained following termination of treatment.

1. Introduction

Obesity is a prominent health concern worldwide which increases the risk of Type 2 diabetes mellitus (T2DM), cardiovascular disease, and some cancers, among other health problems, and increases mortality while decreasing overall quality of life [see 1]. One treatment strategy drawing significant research attention is the activation of the Glucagon-Like Peptide-1 (GLP-1) receptor system. GLP-1 is an incretin hormone released by enteroendocrine cells that inhibits gastric acid secretion [2,3], enhances glucose-mediated insulin release from the pancreas [4], and increases satiation, all of which help to decrease food intake and promote normal glycemia [5–7]. GLP-1 is also expressed in taste buds [8] and in distinct clusters of neurons in the central nervous system, namely the nucleus of the solitary tract [9,10], and the olfactory bulb [11]. Interventions that prolong the positive effects of GLP-1 receptor activation have been adopted as treatment options because, when released endogenously into the periphery, the hormone itself only has a half-life of about 2 min due to protease degradation [see reviews 5,12,13].

Liraglutide (Saxenda), a synthetic GLP-1 receptor agonist used as a T2DM treatment, helps regulate blood glucose by activating GLP-1 receptors, which, in turn, improves glycemic control through its incretin effects [see reviews 7,13,14]. Due to liraglutide's affinity for albumin, which protects it from rapid enzymatic degradation, the biological half-life of the drug is extended to about 13 h [13,14]. Because of its effectiveness at promoting weight loss [e.g. 13,15,16], liraglutide has recently been approved in the United States as a bariatric intervention [16,17].

In the rodent model, liraglutide has also been shown to be effective at promoting weight loss and decreasing food intake [e.g. 18–21]. Some

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studies have even shown that liraglutide can affect food selection; when treated with the drug and given food options, rats will decrease their intake of foods high in sugar and/or fat relative to laboratory chow [20,21]. Similar effects have been reported following peripheral administration of exenatide, another GLP-1R agonist, which appears to have selective effects on "sweet" taste given that its administration in rats maintained on an obesogenic diet causes decreases in preference for sucrose solutions in long-term two-bottle intake tests (vs. water) but has no effect on preferences observed to compounds representing other basic taste qualities [22]. Here we took advantage of a more complex cafeteria diet paradigm in which four food items that varied in their fat and sugar content were offered to rats, in addition to laboratory chow, to investigate whether rats would systematically and progressively modify their relative macronutrient consumption when treated with liraglutide at a dose that is known to cause significant reductions in total caloric intake. This same cafeteria diet paradigm was recently used to demonstrate that Roux-en-Y gastric bypass (RYGB) not only decreases the number of calories consumed, but also causes progressive increases in the relative proportion of calories taken from complex carbohydrates, but not sugar, and progressive decreases in the relative proportion of calories taken from fat [23].

In humans, RYGB is one of the most perennially effective interventions for the treatment of obesity and its comorbidities [24]. The surgery causes weight loss of approximately 25% and significantly reduces caloric intake [e.g. 25,26]. This exceptional weight loss is accompanied by decreases in overall caloric intake and robust increases in postprandial levels of some endogenous gut hormones including GLP-1 and Peptide Tyrosine Tyrosine (PYY), among others [e.g. 25,27,28]. Increases in these gut peptides are thought to be at the root of the effectiveness of RYGB in the treatment of T2DM via their influence on insulin release [29,30]. There is also a prevailing view that after RYGB, some patients experience changes in food preference, choosing to eat fruits and vegetables compared with more calorically dense foods [25,31]. Yet, RYGB-induced changes in relative macronutrient intake reported in the literature are generally small or transient [31] and the majority of these food intake data are from dietary recall or self-report paradigms which are vulnerable to inaccuracies [see 32–34].

In rodents, food intake and choice can be directly, objectively, and quantitatively assessed and the outcomes cannot be influenced by dietary counseling. Therefore, in the study reported here, we sought to identify whether liraglutide-induced decreases in intake would be accompanied by modulations in relative macronutrient intake when calorically dense and highly palatable food options were available, as is seen after RYGB in a rat model. We also sought to determine whether some degree of drug-induced suppression of total caloric intake and/or potential changes in food selection would be maintained following the termination of treatment.

2. Materials and Method

2.1. Subjects

For these experiments, 12 (n = 6/group) male Sprague Dawley adult rats were used over 6 experimental phases. At the beginning of the experiment, animals weighed between 360 and 397 g. Animals were housed individually in cages with chipped wood bedding and a stainless steel Rattle Round (Otto Environmental) toy. In the presence of cafeteria diet, no extra enrichment was offered (i.e. no Rattle Rounds in the cage); however, in phases of the experiment when the animals only had access to chow, the Rattle Rounds were present in the cage. Removing the Rattle Round toys prevented the animals from placing the toy in the jars of food and thus limited spillage and allowed for more accurate intake recordings. Animals were housed in a vivarium on an automated 12:12 light:dark cycle that was controlled for temperature and humidity. Throughout each phase of the study, the rats had 24-h access to standard lab chow (Purina 5001), presented in suspended stainless steel hoppers, and deionized (DI) water. All procedures done in this experiment were approved by the Animal Care and Use Committee at Florida State University.

Table 1
The comprehensive breakdown of the food items in the cafeteria diet by macronutrient composition. This diet was presented to both groups before, during, and after drug exposure.

Diet	Caloric Density[a]	Fat (g/kg; %kcal)	Carbohydrate[b] (g/kg; %kcal)	Sugar (g/kg; %kcal)	Protein (g/kg; % kcal)	Fiber (g/kg)
Chow	3.36	- 13.5	- 58.0	- 6.2	- 28.0	5.1
Refried Beans (Low Sugar/ Low Fat)	0.92	20.8; 20.4	133.2; 57.9	0; 0	49.9; 21.7	5
Vanilla Yogurt (High Sugar/ Low Fat)	0.93	6.7; 6.4	186.4; 80.2	133.2; 57.3	31.1; 13.4	0
Peanut Butter (Low Sugar/ High Fat)	6.40	500.4; 70.6	250.3; 15.7	93.8; 5.9	218.9; 13.7	6.3
Sugar - Fat Whip[c] (High Sugar/ High Fat)	5.80	369.2; 57.3	423.4; 29.2	399.2; 27.5	195.8; 13.5	0

[a] Caloric Density calculated using an approximate 9 kcal/g for fat, 4 kcal/g for carbohydrate and protein, and 0 kcal/g of fiber.
[b] Carbohydrate measure includes sugar.
[c] Sugar Fat Whip was made by combining 208 g each of corn oil (Winn Dixie) and vegetable shortening (Winn Dixie), 300 g whey protein (Jarrows Formulas), and 480 g of powdered sugar (Winn Dixie).

2.2. Diet

In addition to chow, rats were given selective access to a "cafeteria diet". The diet options chosen represented one of four basic macronutrient categories: Low-Fat/Low-Sugar (Old EL Paso® Traditional Refried Beans), Low-Fat/High-Sugar (Yoplait® Low-Fat Vanilla Yogurt), High-Fat/Low-Sugar (JIF® Creamy Peanut butter), or High-Fat/High-Sugar (Sugar-Fat Whip [SFW]; prepared in our laboratory, see Table 1 for recipe). The macronutrient and caloric composition of these foods are presented in Table 1. For all phases of this project involving the cafeteria diet, the food options were presented to the animals in pre-weighed 4-oz. glass jars. The jars were tethered to a cage corner via stainless steel wire. At the same time each day, 24-h intake was recorded and food jars were replaced with new jars, filled with the respective fresh food, and jar positions were rotated counterclockwise to a new cage corner. We also recorded overnight intake of chow and water and recorded daily body weight.

2.3. Drug Acclimation

The animals were acclimated to a 1.0 mg/kg dose (s.c.) of liraglutide (Novo Nordisk; Saxenda; diluted in 0.9% sterile saline) by starting at 0.1 mg/kg and incrementing the daily dose (always in 1.0 ml/kg BW) by 0.1 mg/kg over 13 days. This was done to adapt the animals to