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The effect of diet, adiposity, and weight loss on the secretion of incretin hormones in cats

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ABSTRACT

Degree of adiposity and dietary macronutrient composition affect incretin hormone secretion in humans and mice, but little is known about their effect in cats. In this study, 7 overweight cats were fed a maintenance diet (MD) for at least 2 wk followed by a reduced calorie diet (RCD), which was lower in fat and higher in carbohydrates and fiber. Cats were fed ad libitum initially, and then, food was restricted to achieve 1%–2% loss of body weight weekly (11 wk). When lean, cats were fed MD for 2 wk. A standardized meal test (SMT) using a third diet was performed after at least 7 d on each diet, before and after weight loss (four SMT's total). Glucose, insulin, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic peptide (GIP) concentrations were measured immediately before and over 6 h after feeding the SMT. Area under the curve (AUC) was compared for GLP-1, GIP, and insulin concentrations using 2-way analysis of variance. Leaner cats had increased GIP_{AUC} compared to obese cats ($P = 0.025$). There was a trend toward increased GIP_{AUC} on RCD compared to the MD ($P = 0.085$). There was a moderate negative correlation between body fat percentage and $GLP\text{-}1_{AUC}$ ($r = -0.45$; $P = 0.05$). There was no effect of diet on $GLP\text{-}1_{AUC}$. In conclusion, degree of adiposity and dietary macronutrient content could be important in determining GIP responses not only acutely but also on a long-term basis. Further investigation of GIP responses in cats should take both diet and degree of adiposity into account.

1. Introduction

Enteroendocrine cells (EECs) are found throughout the intestinal tract and act as sensors of luminal nutrient content, integrating information regarding composition of the diet and quantities of nutrients [1,2]. Secretion of the hormones glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2), glucose-dependent insulinotropic peptide (GIP), and Peptide YY (PYY) from EEC is stimulated by the presence of nutrients in the lumen of the gut, with different nutrients having variable potency in stimulating secretion of these hormones. Nutrient sensing is achieved through the use of nutrient-specific mechanisms that include a variety of fatty acid- and carbohydrate-specific G protein–coupled receptors as well as other mechanisms [1,2]. The hormones GLP-1 and GIP have profound systemic effects including potentiation of insulin secretion [3], inhibition [4] and stimulation [5] of glucagon secretion (GLP-1 and GIP, respectively), slowing gastric emptying time [4] (GLP-1), increasing satiety [6,7] (GLP-1), and increasing insulin sensitivity in adipose tissue (GIP) [8].

Degree of adiposity and dietary macronutrient composition affect the secretion of incretin hormones but little is known about their effect in cats. In 1 study,

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glucose-stimulated GLP-1 secretion was lower in overweight cats compared to lean cats, but the effect of weight loss was not examined [9]. Obese people have decreased GLP-1 secretion compared to lean individuals [10,11]. In insulin resistant people, GIP [12] and GLP-1 [12,13] secretion is decreased, and at least for GLP-1, the overall magnitude of that decrease is related to the degree of insulin resistance [12]. Moreover, obese people with decreased GLP-1 secretion have improvements in GLP-1 secretion following weight loss [11].

The acute GIP and GLP-1 secretory response to various macronutrients has been described in domestic cats. In other mammals (humans, rodents, pigs, and dogs), glucose has a strong effect on the stimulation of GIP and GLP-1 secretion. However, in cats, glucose does not stimulate GIP secretion [14,15]. Fat is a strong stimulant of GIP and GLP-1 secretion in cats, similar to other mammals (although variability exists in the response to different types of fatty acids).

Although the acute effects of diet on EEC secretion have been well-characterized, little is known about the chronic effects of diet on the proliferation of EEC and on their hormone secretion capacity. Stimuli of hormone secretion usually cause a cellular response that, in addition to immediate secretory response, also increases the capacity of the cell to respond to future stimuli of the same type and magnitude (eg, chronic hypersecretion of ACTH will result in adrenal cortical hyperplasia). This type of response seems to be universal to all endocrine systems, but this has not been previously demonstrated for EECs in cats. Chronic consumption of a high-fat diet by obese hyperglycemic mice led to significant hyperplasia of GIP-secreting K cells, whereas no change in K cell density was seen with a high-carbohydrate diet [16]. In people, studies examining the effect of macronutrient content on GIP and GLP-1 secretion have yielded mixed results [17–20].

A long-term evaluation of the effects of weight loss and diet on EEC hormones has not been performed to this date in cats. The purpose of this study was to determine the impact of weight loss and long-term dietary manipulation on selected EEC hormone secretion in healthy cats. Because the acute secretory response differs for different macronutrients, we hypothesized that continuous exposure to different macronutrients will result in different secretory responses to a standard stimulus of EEC. In particular, because glucose has no effect on acute GIP secretion in cats, but fat is a strong stimulus, we hypothesized that GIP secretion in response to a standard stimulus would be increased after exposure to a high-fat diet (that is low in carbohydrates) compared with exposure to a low-fat diet (that is high in carbohydrates). Our second hypothesis was that changes in body condition would also cause a different response to a standardized nutrient stimulus, independent of dietary effect. Gaining a better understanding of the factors that regulate EEC cell proliferation will reveal new potential targets for treatment of gastrointestinal and endocrine disease.

2. Materials and methods

2.1. Animals

The study protocol was approved by The Ohio State University Institutional Animal Care and Use Committee. Seven purpose-bred cats were used in this study, including 5 castrated males and 2 spayed females. Seven cats were selected for this study based on a power calculation for detecting a 30% difference between independent means when the standard deviation (SD) $\leq$10% of the means (for an alpha error of 5% and 80% power). At the start of the study, all cats were 4 yr of age. Body condition score (BCS), as assessed on a 9-point scale, was 9 in 1 cat, 8 in 3 cats, and 7 in 3 cats [21]. Body weights (BWs) and body fat percentages (BF%) are presented in Table 1.

Cats were group-housed in Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC)-accredited facilities. All cats were acclimatized and socialized for more than a year before the start of experiments with environmental enrichment provided. Routine laboratory tests, including complete blood count, serum chemistry, and urinalysis were performed at the beginning of the experiment, and all cats were considered healthy except for being overweight.

2.2. Study design

2.2.1. Treatment sequence

Each cat was treated with 2 diets over 4 consecutive phases of dietary treatments in the following order: (1) maintenance diet (Purina Friskies Classic Paté Mariner's Catch Canned, Nestlé Purina PetCare, St. Louis, MO) fed ad libitum for at least 2 wk from day 0–14 (ObMD), (2) reduced calorie diet (Purina Veterinary Diets OM Overweight Management Feline Formula Canned, Nestlé Purina

Table 1
Mean ± SD, median (range) body weight (BW), body fat percentage (BF%), body condition score (BCS), and body fat mass (BFM) before and after the period of controlled weight loss.

Parameter	Central tendency and distribution	Before weight loss	After weight loss	Change
BW (kg)	Mean ± SD	5.9 ± 0.9	4.6 ± 0.7	−1.3 ± 0.3
	Median (range)	5.6 (5.1–7.4)[a]	4.3 (4.0–5.9)[b]	−1.2 (0.9–1.9)
BF%	Mean ± SD	41.3 ± 7.3	20.2 ± 10.0	−21.1 ± 5.3
	Median (range)	40.6 (31.4–52.4)[a]	16.9 (12.5–40.3)[b]	−21 (19–28.8)
BCS (1–9)	Mean ± SD	7.7 ± 0.8	5.3 ± 0.8	−2.4 0 ± 0.5
	Median (range)	8 (7–9)[a]	5 (5–7)[b]	2 (2–3)
BFM (kg = BW × BF%)	Mean ± SD	2.5 ± 0.8	1.0 ± 0.7	−1.5 ± 0.4
	Median (range)	2.3 (1.6–3.9)[a]	0.7 (0.5–2.4)[b]	1.4 (1.1–2.1)

Median values within a row with unlike superscript letters (a,b) were significantly different ($P = 0.02$).