The incretin effect in cats: comparison between oral glucose, lipids, and amino acids

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Abstract

Incretin hormones are secreted from the intestines in response to specific nutrients. They potentiate insulin secretion and have other beneficial effects in glucose homeostasis. We aimed to study the incretin effect in cats and to compare the effect of oral glucose, lipids, or amino acids on serum concentrations of insulin, total glucose-dependent insulinotropic peptide (GIP) and total glucagon-like peptide 1 (GLP-1). Ten healthy cats were used in a repeated measures design. Glucose, lipid, or amino acids were administered through nasoesophageal tubes on separate days. Blood glucose (BG) concentrations were matched between experiments by measuring BG every 5 min and infusing glucose intravenously at a changing rate. Intravenous glucose infusion with no prior treatment served as control. The incretin effect was estimated as the difference in insulin area under the curve (AUC) after oral compared with intravenous glucose. Temporal changes and total amount of hormone secretions were compared between treatment groups with the use of mixed models. Total glucose infused (TGI) at a mean dose of 0.49 g/kg resulted in slightly higher BG compared with 1 g/kg oral glucose ($P = 0.038$), but insulin concentrations were not significantly different ($P = 0.367$). BG and the TGI were not significantly different after the 3 oral challenges. Total GIP AUC was larger after lipids compared with amino acids ($P = 0.0012$) but GIP concentrations did not increase after oral glucose. Insulin and GIP concentrations were positively correlated after lipid ($P < 0.001$) and amino acids ($P < 0.001$) stimulations, respectively, but not after oral glucose stimulation. Total GLP-1 AUC was similar after all three oral stimulations. Insulin and GLP-1 concentrations were positively correlated after glucose ($P = 0.001$), amino acids ($P < 0.001$), or lipids ($P = 0.001$) stimulations. Our data indirectly support an insulinotropic effect of GIP and GLP-1. Potentiation of insulin secretion after oral glucose is minimal in cats and is mediated by GLP-1 but not GIP.

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1. Introduction

Stimulation of insulin secretion by glucose ingestion is partly due to direct action of glucose on the pancreatic $\beta$ cells. In addition, the entero-insular axis enhances the total amount of insulin released. The incretin effect is the difference between insulin secretion after glucose ingestion and that after an isoglycemic intravenous glucose infusion [1]. In human beings, the incretin effect accounts for about 80% of insulin secreted after glucose ingestion, and it is mediated by the two incretin hormones: glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1) [1]. Incretin hormones potentiate insulin secretion, resulting in increased insulin secretion at any given concentration of blood glucose (BG). Incretins also participate in regulation of pancreatic $\beta$-cell differentiation, proliferation, and survival; incretins affect glucagon secretion, slow the rate of gastric emptying, and increase satiety. Thus, incretins play a major role in glucose homeostasis [2].

Because the domestic cat spontaneously develops a form of diabetes that closely resembles human type 2 diabetes, it is a compelling animal model [3]. Cats, human beings, and macaques are the only species that spontaneously develop islet amyloid deposits. Other similarities include onset at middle age or older, a genetic predisposition, association with obesity as a major risk factor, and impaired $\beta$-cell function with residual but declining insulin secretion. In contrast to other models of type 2 diabetes, cats are obligate carnivores. As such, their natural diet is based mostly on fat and protein and contains less carbohydrate. Sugar sensing in taste buds is unnecessary to the cat, and cats lack the T1R2 sweet-taste receptor [4]. Sugar sensing, however, is an important function of enteroendocrine cells that secrete incretin hormones. In rodents and human beings, glucose is sensed in enteroendocrine cells by T1R2 sweet-taste receptors but also by mechanisms similar to its sensing in pancreatic $\beta$ cells (involving its entry through SGLT1/GLUT-2, its metabolism through glucokinase and then closure of $K_{ATP}$ channels) [2,5–7]. Because cats lack the T1R2 sweet-taste receptor and because they are obligate carnivores, it is likely that their enteroendocrine response to glucose and other nutrients is different from other species.

$K$ and $L$ cells are enteroendocrine cells dispersed along the epithelium of the intestinal tract. Their physiological role is to sense the type and quantity of digested nutrients in the gut. They then secrete GIP and GLP-1 (respectively) as preparatory signals to other remote organs (eg, brain, pancreas). Glucose sensing was described above. Lipids are digested to free fatty acids that then act as ligands on specific G protein–coupled taste receptors. The mechanism of amino acid stimulation is less clear [2,8]. $K$ and $L$ cells are polar cells. Nutrient sensing is exclusive to their luminal side, whereas hormone secretion takes place in the basolateral side. The degree of GIP and GLP-1 stimulation by different nutrients is species dependent. Fat is more potent than carbohydrates in stimulating GIP secretion in human beings but the opposite is true in pigs. Amino acids are weak stimulators of GIP secretion in human beings but strong stimulators of it in dogs and rats [2,8]. GLP-1 secretion is stimulated by ingested lipid, carbohydrate, and protein as well as by GIP [2,9,10]. Different distributions of GLP-1–secreting cells along the intestinal tract in different species determine, in part, the importance of different stimuli of GLP-1 secretion [2,11].

GIP and GLP-1 are ligands to the G protein–coupled receptors GIPR and GLP-1R, respectively. Both receptors are present on pancreatic $\beta$ cells. The effects of GIP and GLP-1 on the $\beta$ cell are similar and additive. Through activation of adenylyl cyclase and production of adenosine cyclic phosphate, GIP, and GLP-1 stimulate the cellular components of insulin secretion and enhance the glucose-sensing apparatus by increasing the expression of its components. They also have a synergistic effect with glucose to promote insulin gene transcription, mRNA stability, and biosynthesis [2].

On the basis of the view of the domestic cat as an obligatory carnivore, we hypothesized that the glucose-induced incretin effect in cats would be less than is observed other species. We also explored the effects of glucose, lipid, and amino acids on secretion of incretin hormones in the cat.

2. Materials and methods

2.1. Animals

All animal use was approved by the University of Illinois Institutional Animal Care and Use Committee. Ten young, healthy, purpose-bred cats were used in this study (4 spayed females and 6 neutered males; median age: 48 mo; age range: 36 to 58 mo; mean $\pm$ SD of body weight: 4.8 $\pm$ 0.7 kg, body condition score was 4/9 in four cats, 5/9 in five cats, and 6/9 in one cat). Cats were group housed in facilities accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. All cats were acclimatized and socialized for at least 4 wk before the start of experiments, and extensive environmental enrich-
ment was provided. Cats were fed commercial cat food (Purina DM; Nestlé Purina PetCare Company, St Louis, MO, USA) and monitored daily by physical examinations. Body weight was measured weekly. Routine laboratory tests [including complete blood counts, serum chemistry panels, total tetraiodothyronine, coagulation panels, and urinalysis] were performed at first arrival and just before the first part of the experiment in each cat. Packed cell volume, total solids, and complete blood counts were repeated before each part of the experiment in each cat.

2.2. Study design

A repeated measures design was used. The experiment was divided to four parts: oral glucose tolerance test (OGTT), isoglycemic clamp (IGC), oral lipid challenge with an isoglycemic clamp (LIGC), and oral amino acids challenge with an isoglycemic clamp (AAIGC). First, an OGTT was performed and BG concentrations were measured every 5 min until euglycemia was restored. In the second part, IGC was performed 2 to 3 d after the OGTT. During the IGC, BG was measured every 5 min, and glucose was infused intravenously at a changing rate. The rate of infusion was adjusted to match or exceed the BG concentration that was recorded during the OGTT at the next time point by no more than 10%. The third and fourth parts of the experiment were done 4 wk later: LIGC and AAIGC were performed 3 d apart, in random order. In these clamps the target BG was 0% to 10% less than the BG concentration recorded during the IGC. Another IGC was performed 2 wk after the OGTT. This IGC was preceded by an injection of the GLP-1 mimetic exanatide with the goal of studying the effect of exanatide on insulin secretion during hyperglycemia. The results of this part of the study are reported elsewhere (C. Gilor et al, unpublished data, 2010).

On the day of each experiment, BG concentration was measured twice between 8:00 AM and 9:00 AM. If hyperglycemia was detected, the experiment was postponed until the next day. At 9:00 AM a sample was obtained for hormone measurement and then a solution of glucose (2 mL/kg, Dextrose 50% USP; Hospira Inc., Lake Forest, IL, USA), lipids (1.7 mL/kg, Liposyn II 20%; Hospira Inc.) or amino acids (8.5 mL/kg, Aminosyn II 10%; Hospira Inc.) was administered through a nasoesophageal tube. The three solutions were calorically equivalent (3.4 Kcal/kg), and the volumes were matched by flushing the tubes with water to reach a total volume of 9 mL/kg. All 3 solutions (water flush included) were administered over 4 min. Time zero was defined as the end of glucose and amino acid administration in the OGTT and AAIGC, respectively, and the beginning of glucose infusion in all three IGCs. In the LIGC, the end of lipid administration was defined as −15 min; BG concentration was still measured every 5 min, and time zero was still defined as the beginning of the IGC. This 15-min delay was meant to adjust for a possible delay in the effect of lipids (as a result of slower gastric emptying and the need to be digested to free fatty acids before causing incretin secretion). For glucose intravenous infusion, a 50% glucose solution was diluted with saline to a 20% solution. Infusion rate was set on a syringe pump.

Serum samples for insulin, GIP, and GLP-1 measurement were collected during the OGTT, LIGC, and AAIGC at baseline (immediately before nutrient administration or at time zero in the IGC) and then at 15, 30, 45, 60, 75, 90, and 120 min and then every 30 min thereafter until euglycemia was restored. In the IGC, insulin was measured similarly, but GIP and GLP-1 were measured only at baseline and at 30 min and only in five cats. Blood was collected through indwelling jugular catheters. The samples were collected into chilled glass tubes and then immediately centrifuged (at 4°C and 4,000 rpm) and separated. Serum was stored at −20°C until analysis.

2.3. Catheters and nasoesophageal tube placement

On the morning before each part of the experiment, cats were sedated with intramuscular injections of dexmedetomidine (0.009 mg/kg) and butorphanol (0.22 mg/kg) to facilitate catheter placement. Atropine was given (0.022 mg/kg intramuscularly) to prevent bradycardia. Jugular catheters (BD Angiocath AutoGuard; Becton Dickinson Infusion Therapy Systems, Inc., Sand, UT USA) were placed before each OGTT. Patency of these catheters was maintained by flushing heparinized saline daily until the end of the study. Cephalic catheters (V-Cath, 3.0F; NeoMedical, Inc, Fremont, CA USA) were placed before each IGC and were removed at the end of the IGC. These were used exclusively for glucose infusion. The sedation was reversed with atipemazole (0.009 mg/kg), and the cats were monitored until full recovery. Food was given as usual at 3:00 PM, 1 h later the cats were lightly sedated with acepromazine (0.04 mg/kg) and butorphanol (0.22 mg/kg), and a 3.5F red rubber nasoesophageal feeding tube was placed. The tube was premeasured and marked to reach the ninth rib. Cats were conscious during the procedure, and proper placing was verified by observing an intact swallowing reflex and by checking the
tube for negative pressure after placement. Elizabethan collars were used to prevent the cats from removing the nasoesophageal tubes. Food and water were then withheld until after the experiment the next day. Nasoesophageal tubes were placed before OGTT, AAIGC, and LIGC but not before IGC.

2.4. Glucose and hormone measurements

Blood glucose concentrations were measured with a handheld point-of-care glucose meter (OneTouch Ultra; LifeScan Inc., Milpitas, CA, USA) that was validated for use in cats [12]. Insulin concentrations were measured with a feline ELISA (Feline Insulin ELISA, Mercodia AB, Uppsala, Sweden). Total GIP concentrations and total GLP-1 concentrations were measured with human ELISA kits that were validated for use in cats [Human GIP (total) ELISA, Millipore Inc., St Charles, MO, USA; GLP-1 (7-36 and 9-36) ELISA; ALPCO Diagnostics, Salem, NH, USA]. The total GIP ELISA had an intra-assay CV of 4.9% ± 3.3% and interassay CV of 6.2% ± 2.1%. Linear regression results for expected vs observed results in serial dilutions were \( R^2 = 0.99 \) (\( P < 0.0001 \)), slope = 0.98 ± 0.02, and a Y intercept = 3.67 ± 2.25. The total GLP-1 ELISA had an intra-assay CV of 7.3% ± 5.6%. Interassay variation was not examined. Linear regression results for expected vs observed results in serial dilutions were \( R^2 = 0.85 \) (\( P < 0.0001 \)), slope = 0.60 ± 0.06, and a Y intercept = 0.58 ± 0.38.

2.5. Statistical analysis

Statistical analysis was performed with the use of computer software (GraphPad Prism; GraphPad Software Inc., San Diego, CA, USA; SAS Software; SAS Institute Inc., Cary, NC, USA).

OGTT and IGC were performed in 10 cats. LIGC and AAIGC were performed in only 8 of the 10 cats because of sampling catheter failure. The area under the curve (AUC) was calculated with the use of the trapezoidal method and was used to represent total hormone secretion. The Shapiro-Wilk test was used to assess deviance from normal distribution of data. Mean ± SE are presented for normally distributed data. Skewed data were normalized with the use of natural log transformations, and the results are presented as geometric mean and confidence interval. Data that were not normally distributed are presented as median and range. When normally distributed, paired \( t \) tests were used for comparisons of AUC or TGI between the IGC and OGTT. Repeated-measures ANOVAs were used for comparisons of AUC or TGI between the IGC, OGTT, LIGC, and AAIGC. The Wilcoxon signed-rank test and the Friedman test were used for data that were not normally distributed.

Baseline concentrations of GIP and GLP-1 are presented as median and range. Changes in total GIP concentrations and total GLP-1 concentrations over time were calculated after standardizing the absolute concentration to the time zero concentrations (time x/[(time 0)], and the results are presented as fold change. Temporal changes in insulin, total GIP, and total GLP-1 concentrations during OGTT, LIGC, and AAIGC were analyzed with the mixed model with compound symmetry covariance structure (SAS Software, SAS Institute Inc.). Treatments (ie, OGTT, LIGC, and AAIGC), time points, and their interaction were included in the mixed model.

All statistical tests were performed as two-tailed tests, and a \( P \) value ≤0.05 was considered significant.

3. Results

3.1. Baseline BG

Baseline BGs in the IGC were lower than in the other experiment days, but the differences were not significant (IGC: 81.8 ± 2.8 mg/dL vs 87.5 ± 2.3 mg/dL in the OGTT, 87.5 ± 3.4 mg/dL in the LIGC, and 84.8 ± 1.4 mg/dL in the AAIGC).

3.2. Glucose-induced incretin effect

The AUC of BG concentrations in the IGC was slightly higher than the AUC in the OGTT (1.07-fold ± 0.03-fold; \( P = 0.038 \); Fig. 1). Compared with the 1 g/kg glucose that was given orally for the OGTT, the total glucose infused during the IGC was significantly lower at 0.49 ± 0.06 g/kg (\( P < 0.001 \); Fig. 2). Total insulin secretion was not significantly different (1.31-fold ± 1.38-fold higher during the OGTT; \( P = 0.367 \); Fig. 3).
Median baseline GIP concentration was 11.4 pg/mL (range, 3.5 to 61.1 pg/mL). GIP concentration did not increase significantly during the OGTT. Median baseline GLP-1 concentration was 8.9 pmol/L (range, 4.5 to 26.5 pmol/L). GLP-1 concentrations increased 30 min after oral glucose administration (1.3-fold; range, 1.2- to 1.6-fold], peaked at 75 min (1.5-fold; range, 1.2- to 1.9-fold), and returned to baseline at 120 min (Fig. 4). As expected, GIP and GLP-1 concentrations did not change significantly between time zero and 30 min of the IGC (data not shown).

3.3. Lipid and amino acid stimulation

The AUC of BG concentrations in the LIGC was 0.91-fold ± 0.04-fold lower than the AUC in the IGC and the difference was not significant \( (P = 0.151; \text{Fig. 5})\). The AUC of BG concentrations in the AAIGC was 0.90-fold ± 0.03-fold lower than the AUC in the IGC \( (P = 0.002; \text{Fig. 6})\). The AUC of BG concentrations in the LIGC and AAIGC were not different from the AUC in the OGTT \( (P = 0.870\) and \( P = 0.887\), respectively) or from one to the other \( (P = 0.778\). The total glucose infused during the LIGC or AAIGC was not significantly different from 1 g/kg (LIGC: 0.91 ± 0.14 g/kg, \( P = 0.535\); AAIGC: 0.88 ± 0.09 g/kg, \( P = 0.258\; \text{Fig. 2})\). Insulin concentration increased within 15 min of lipid administration (at time zero of the isoglycemic clamp, whereas BG was still unchanged). Insulin AUC during AAIGC was 2.23- ± 0.3-fold greater than the insulin AUC during the LIGC \( (P = 0.002)\). Insulin AUC during LIGC was 2.24- ± 1.26-fold greater than the insulin AUC during the OGTT \( (P = 0.005; \text{Fig. 7})\).

On the basis of the mixed model, GIP concentrations varied significantly between time points in each treatment \( (P < 0.0001)\) and between treatments across time points \( (P < 0.0001)\) with a significant interaction between time and treatment (ie, the pattern of secretion varied significantly between treatments, \( P < 0.0001\)). Total GIP concentrations peaked 15 min after lipids (20.4-fold increase; range, 12.3- to 33.8-fold increase) and amino acids (fold increase 8.0-fold increase; range, 3.7- to 17.2-fold increase; \( \text{Fig. 8})). GIP concentrations returned to baseline at 195 min (180 min of the glucose clamp) after lipids and 150 min after amino acids (Fig. 8). Total GIP secretion (as measured by the area under
the time-concentration curve) in response to lipids was 3.2-fold (range, 1.9- to 4.7-fold) greater than to amino acids \((P = 0.0012)\). The mixed model indicated that the GIP secretion patterns were not different after amino acids and lipid stimulations \((P = 0.051)\). Insulin concentrations were positively correlated with GIP concentrations across time points after the lipid \((P < 0.001)\) and amino acid \((P < 0.001)\) stimulations, representing similar secretion pattern.

GLP-1 concentrations during LIGC and AAIGC were measured in only six cats because of insufficient sample volume. On the basis of the mixed model, GLP-1 concentrations varied significantly between time points in each treatment \((P = 0.0044)\) and between treatments across time points \((P = 0.003)\). The interaction between time and treatment approached significance \((P = 0.065)\). GLP-1 peaked 15 min after lipid administration \((1.8\text{-fold increase}; \text{range, } 1.3\text{- to } 2.5\text{-fold increase}; \text{Fig. 4})\) and returned to baseline at 60 min. GLP-1 concentration peaked 30 min after amino acid administration \((1.9\text{-fold increase}; \text{range, } 1.4\text{- to } 2.6\text{-fold increase})\) and returned to baseline at 75 min. Although the observed difference in secretion patterns among three treatments were not significant \((P = 0.064)\), the overall effects on GLP-1 were different across the three treatments \((P = 0.004)\) and across time \((P = 0.003)\). Total GLP-1 secretion after amino acid stimulation was greater than its secretion after lipids \((1.2\text{-fold increase}; \text{range, } 1.0\text{- to } 1.3\text{-fold increase}; P = 0.015)\) or glucose \((1.2\text{-fold increase}; \text{range, } 1.1\text{- to } 1.3\text{-fold increase}; P = 0.003)\). No significant difference was observed between total GLP-1 secretion after glucose or lipids \((P = 0.865)\).

Insulin concentrations were positively correlated with GLP-1 concentrations across time points after glucose \((P = 0.001)\), amino acid \((P < 0.001)\), or lipid \((P = 0.001)\) stimulations, representing similar secretion pattern.

4. Discussion

Consistent with the fact that the cat is an obligate carnivore, we found that the glucose-induced incretin effect in cats is minimal compared with other species [1]. Although we found no significant difference between insulin AUC during the OGTT and IGC, our findings overall suggest that potentiation of insulin secretion did occur because the BG concentration during the IGC was higher and the total glucose infused was lower compared with the OGTT. Incretin hormones increase the sensitivity of the pancreas to the effect of glucose and allow greater glucose absorption without development of hyperglycemia. In their absence, the higher BG concentration during the IGC should have been accompanied by higher insulin AUC compared with the OGTT. Also in their absence, a dose of 1 g/kg glucose should have resulted in higher BG concentrations compared with the 0.49 g/kg dose given during the IGC. It is also plausible that the presence of an incretin
effect with lack of a more pronounced difference in insulin secretion (as seen in other species [1]) is related to a more dominant role of incretin hormones on glucagon inhibition. This is supported by the results of a recent study in which the effect of a DPP-4 inhibitor in cats on lowering BG were mostly mediated by a decrease in glucagon and less so by an increase in insulin [13].

One limitation of our study was that glucose and other nutrients were administered by a nasoesophageal tube. The tube was placed the day before each experiment, and by the time the experiment begun there was no apparent discomfort to the cats (except for occasional sneezing). In addition, our cats were well acclimated to the conditions of the laboratory and had participated in previous studies. Although we did not perceive the cats to be stressed, it cannot be completely ruled out that some degree of stress was affecting them. In that case, a sympathetic response could inhibit insulin secretion, increase glucagon secretion, and interfere with the incretin effect. The small difference in baseline BG between the OGTT and the IGC might be evidence of stress in these cats. Perhaps if stress had been completely avoided, a greater incretin effect would have been seen. A stress-free voluntary consumption of a glucose solution is not a viable option in cats, however, and we consider the method of glucose administration we chose to be the most practical.

If there is a glucose-induced incretin effect in cats, it might be mediated by GLP-1, but it is clearly not mediated by GIP. GIP, however, may be responsible for an incretin effect stimulated by lipids and amino acids. Our data indirectly support an insulinotropic effect of GIP and GLP-1. Insulin concentrations were positively correlated with GLP-1 throughout the duration of the isoglycemic clamps after all three treatments. Insulin concentrations were also positively correlated with GIP throughout the duration of the isoglycemic clamps after amino acids and lipids. Interestingly, insulin concentrations increased despite euglycemia 15 min after lipid administration. This was accompanied by a significant and marked increase in GIP and GLP-1 concentrations. In human beings, oral triglycerides trigger incretin release, but this results in insulin secretion only during hyperglycemia [14]. We did not measure triglycerides and fatty acid concentrations in the blood, and it is possible that the increase in insulin concentration in the 15 min after lipid administration was a result of direct stimulation of pancreatic $\beta$ cells by triglycerides or fatty acids.

In dogs, secretion of GLP-1 is not directly stimulated by oral glucose. Rather, K cells are stimulated by glucose to secrete GIP, which in turn stimulates L cells to secrete GLP-1, probably in a paracrine way [11]. Although dogs are the closest model to cats (at least among animal models in which the incretin effect has been reported), it seems that, in stimulation of L cells by glucose, cats are more similar to other species. Stimulation of GLP-1 secretion was observed in our study with no appreciable increase in serum GIP concentrations. Although this does not rule out a paracrine effect of GIP on L cells, it makes it unlikely.

In this study, caloric and volume equivalent stimulations with oral glucose, lipids, or amino acids were followed by similar responses in GLP-1 secretion, with a slightly greater secretion of GLP-1 after amino acids. In contrast, glucose did not stimulate GIP secretion, amino acids were associated with a strong stimulation of GIP secretion, and lipids were associated with an even stronger stimulation. For the magnitude of stimulation by the three nutrients, it is important to note that the three solutions we administered were not equal in molar concentrations. K and L cells are stimulated by fatty acids via specific G protein-coupled receptors. The mechanism of stimulation by amino acids and glucose are more controversial, but it is either mediated by G protein-coupled receptors, by sodium-coupled transporters, or by both. Regardless, stimulation of K and L cells by nutrients is proportional to the molar content of the nutrients. Notably, degradation of triglycerides to fatty acids is critical to stimulation of GLP-1 secretion [15] so that the final molar content affecting stimulation is up to 3 times the original molar content. In our study the molar content of amino acids and glucose were 5.6 and 3.8 times higher than the molar content of fatty acids (assuming all lipids were digested to fatty acids). We can therefore hypothesize that, on a molar basis, lipids are more potent stimulators of GLP-1 secretion in cats compared with amino acids and glucose, even though on a caloric basis they resulted in similar responses. Moreover, degree of stimulation of K and L cells varies between saturated and unsaturated fatty acids and between different amino acids [16,17]. The lipid solution we used was composed mainly of unsaturated fatty acids. As obligate carnivores, the cat’s natural diet contains mostly saturated fat, and it is plausible that their L and K cells respond to saturated fat more than to unsaturated fat. Further studies of the differential effect of specific fatty acids and amino acids should elucidate the potential of manipulating the composition of the diet to affect incretin secretion in cats. This might have implications to the treatment of diabetes and obesity.

In human beings basal GIP concentrations in peripheral venous blood are typically 9 to 11 pM and they increase 5- to 10-fold postprandially. Basal GLP-1 con-
centrations in peripheral venous blood in human beings are typically 5 to 10 pM and increase 2- to 3-fold after a meal [2]. In cats, we found baseline GIP concentrations that are about one-fifth of the basal concentration in human beings, but there was much higher increase in response to lipids. Basal GLP-1 concentrations are similar in cats and human beings, with similar postprandial fold increases. The differences in basal GIP between human beings and cats could be explained by a low cross activity of the anti-GIP antibody used in our assay. In contrast to GLP-1, the homology of GIP among mammals is not 100%. We used an assay with a rabbit-anti-human antibody because feline GIP or feline-specific GIP assays are not commercially available. If low cross reactivity was the issue, then concentrations after stimulation of GIP were also underestimated. This would strengthen the finding that GIP is not stimulated by glucose in cats and that lipid- or amino acid–stimulated concentrations are much higher than in human beings. In human beings, GIP is crucial in maintaining glucose tolerance in the postprandial phase. Lack of GIP response to glucose and an overall weak incretin effect could render the cat relatively glucose intolerant and might lead to inappropriate glycemic control in cats fed a diet high in carbohydrates. Although a recent study showed no correlation between dietary carbohydrate content and development of diabetes in cats [18], other studies showed that diets low in carbohydrates are beneficial in the treatment of diabetic cats [19,20].

In conclusion, we found that the glucose-dependent insulinovertropic effect of incretins in cats is minimal compared with other species. We also explored the differential effects of glucose, lipids, and amino acids on secretion of incretin hormones. In contrast to other species, glucose did not stimulate GIP secretion. Oral lipids and amino acids were followed by a fast and pronounced increase in serum GIP concentrations, with much greater fold increase than reported in other species. GLP-1 responses were similar to previous reports from other species.

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