Available online at www.sciencedirect.com
ScienceDirect
Domestic Animal Endocrinology 41 (2011) 42–49
DOMESTIC ANIMAL ENDOCRINOLOGY
www.domesticanimalendo.com

The GLP-1 mimetic exenatide potentiates insulin secretion in healthy cats

C. Gilor[a,1], T.K. Graves[a,*], S. Gilor[b,2], T.K. Ridge[a], M. Rick[a]

[a] *Department of Veterinary Clinical Medicine, College of Veterinary Medicine, University of Illinois at Urbana-Champaign, Urbana, IL 61802, USA*

[b] *Department of Pathobiology, College of Veterinary Medicine, University of Illinois at Urbana-Champaign, Urbana, IL 61802, USA*

Received 6 November 2010; received in revised form 2 March 2011; accepted 4 March 2011

Abstract

The glucagon-like peptide-1 mimetic exenatide has a glucose-dependent insulinotropic effect, and it is effective in controlling blood glucose (BG) with minimal side effects in people with type 2 diabetes. Exenatide also delays gastric emptying, increases satiety, and improves β-cell function. We studied the effect of exenatide on insulin secretion during euglycemia and hyperglycemia in cats. Nine young, healthy, neutered, purpose-bred cats were used in a randomized, cross-over design. BG concentrations during an oral glucose tolerance test were determined in these cats previously. Two isoglycemic glucose clamps (mimicking the BG concentration during the oral glucose tolerance test) were performed in each cat on separate days, one without prior treatment (IGC) and the second with exenatide (1 μg/kg) injected subcutaneously 2 h before (ExIGC). BG, insulin, and exenatide concentrations were measured, and glucose infusion rates were recorded and compared in paired tests between the two experiments. After exenatide injection, insulin serum concentrations increased significantly (2.4-fold; range 1.0- to 9.2-fold; $P = 0.004$) within 15 min. This was followed by a mild decrease in BG concentration and a return of insulin concentration to baseline despite a continuous increase in serum exenatide concentrations. Insulin area under the curve (AUC) during ExIGC was significantly higher than insulin AUC during IGC (AUC ratio, 2.0 $\pm$ 0.4; $P = 0.03$). Total glucose infused was not significantly different between IGC and ExIGC. Exenatide was detectable in plasma at 15 min after injection. The mean exenatide concentration peaked at 45 min and then returned to baseline by 75 min. Exenatide was still detectable in the serum of three of five cats 8 h after injection. No adverse reactions to exenatide were observed. In conclusion, exenatide affects insulin secretion in cats in a glucose-dependent manner, similar to its effect in other species. Although this effect was not accompanied by a greater ability to dispose of an intravenous glucose infusion, other potentially beneficial effects of exenatide on pancreatic β cells, mainly increasing their proliferation and survival, should be investigated in cats.

Keywords: Feline; Diabetes mellitus; Incretin; Glucagon

[1] C. Gilor is currently affiliated with the Internal Medicine Service at IDEXX Laboratories LTD., Wetherby, LS22 7DN, United Kingdom.

[2] S. Gilor is currently affiliated with the Clinical Pathology Department at IDEXX Laboratories LTD., Wetherby, LS22 7DN, United Kingdom.

* Corresponding author. Department of Veterinary Clinical Medicine, 1008 W Hazelwood Dr, Urbana, IL 61802, USA. Tel.: +1 217-333-8900; Fax: +1 217-244-9554.

E-mail address: tgraves@illinois.edu (T.K. Graves).

0739-7240/11/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.domaniend.2011.03.001

1. Introduction

Diabetes mellitus (DM) is common in cats. Although diet change and oral medications may help initially, most diabetic cats depend on insulin therapy to survive [1]. Insulin therapy does not halt the progression of the disease, and it has potential side effects. Weight gain may indicate good response to therapy initially but can eventually become a problem. Hypoglycemia is a common complication of insulin therapy and can be life threatening [1].

Glucagon-like polypeptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are incretin hormones. They are secreted from the gastrointestinal tract into the circulation in response to ingestion of nutrients and enhance glucose-stimulated insulin secretion. These hormones are responsible for the incretin effect in which oral glucose administration is associated with a much greater increase in plasma insulin concentrations than with the same amount of glucose given intravenously [2,3]. In diabetics, the secretion of GIP is normal or slightly reduced, but its insulinotropic effect on the pancreas is markedly impaired. In contrast, GLP-1 retains its insulinotropic effects in type 2 diabetes (at least at supraphysiologic concentrations), but secretion of GLP-1 is decreased [3-6]. The effects of incretins extend well beyond potentiating insulin secretion. GLP-1 decreases glucagon secretion, increases satiety, and slows gastric emptying. It also increases proliferation of pancreatic β cells and decreases their apoptosis [7]. Because of these beneficial effects, incretin-based drugs have been recently developed and successfully used as adjunctive treatments in human patients with DM.

The peptide exendin-4 is a 39-amino acid peptide that shares 53% homology with GLP-1. It was first isolated from the poisonous venom of the Gila monster (*Heloderma suspectum*) [7]. Exendin-4 is a potent GLP-1 receptor-agonist, but, unlike GLP-1, it is not a substrate for dipeptidyl peptidase 4 (DPP-4) and neutral endopeptidase. DPP-4 and neutral endopeptidase are ubiquitous in tissues and in plasma of humans and rodents [8]. They are responsible for the fast degradation and short half-life of GLP-1 (a few minutes). Exenatide is a synthetic exendin-4. Resistant to degradation, exenatide is eliminated by the kidneys and has a half-life of 3 to 4 h in humans. Its biologic effect lasts about 8 h after subcutaneous injection, and it can be detected in the plasma for $\leq$15 h [9]. Exenatide has minimal side effects in humans. It is sometimes associated with nausea and less frequently with vomiting. Infrequently, and especially when combined with other hypoglycemic drugs, it may cause hypoglycemia [10]. Exenatide has been shown to be as effective as insulin glargine in the treatment of human type 2 DM but with fewer side effects such as weight gain and hypoglycemia [11-13]. In a 2-year follow-up of human patients receiving exenatide, patients achieved sustained and significant reductions in glycosylated hemoglobin, accompanied by significant weight loss. Most importantly, treatment with exenatide improved β-cell function [14]. Exenatide has also been used recently to improve the survival and function of transplanted pancreatic islets in type 1 DM [15]. These effects of exenatide on the function and survival of pancreatic β cells open the door for halting the progression of diabetes as opposed to merely managing it.

Despite the crucial role incretins play in the pathogenesis and treatment of type 2 diabetes in humans, and despite the similarities between diabetes in humans and in cats [16], little is known about incretins in cats. Recently, it was shown that GLP-1 concentrations increase in cats after intragastric administration of glucose [17]. In another study, a DPP-4 inhibitor led to a decrease in glucagon concentration and, to a lesser degree, to an increase in insulin concentrations after glucose challenge [18]. To the best of our knowledge, studies of incretin mimetics, such as exenatide, have not been reported in cats.

We hypothesized that in cats exenatide can potentiate insulin secretion without causing hypoglycemia. We also hypothesized that exenatide can be detected in plasma of cats for $\leq$8 h after subcutaneous injection.

2. Materials and methods

2.1. Animals

All animal use was approved by the University of Illinois Institutional Animal Care and Use Committee. Nine young, healthy, purpose-bred cats were used in this study. There were four spayed females and five neutered males with a median age 56 mo (range, 38 to 58 mo) and a mean body weight 4.8 $\pm$ 0.7 kg. Body condition score was 4/9 in four cats, 5/9 in four cats, and 6/9 in one cat. None of the cats were obese. 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 the experiments, and extensive environmental enrichment was provided. Cats were fed a commercial cat food (Purina DM; Nestlé Purina Pet Care Company, St Louis, MO, USA) and monitored daily by physical

examinations. Body weight was measured weekly and was stable for the period of the experiment as well as the acclimatization period. Routine laboratory tests (including complete blood counts, serum chemistry, serum total thyroxine, coagulation profile, and urinalysis) were performed at the time the cats were acquired and just before the first part of the experiment in each cat. Packed cell volume, plasma total solids, and complete blood counts were repeated before the second part of the experiment, and a complete blood count and a serum chemistry profile were repeated 2 wk after exenatide injection in each cat.

2.2. Study design

A repeated-measures study design was used. An intravenous glucose infusion administered at a variable rate was used to mimic hyperglycemia as recorded during an oral glucose tolerance test previously [19]. For each cat, blood glucose (BG) concentrations were measured every 5 min, and the rate of infusion was adjusted to match the BG that was recorded for the specific cats in a previous experiment. This isoglycemic glucose clamp was performed twice: On the first day with no other treatment (IGC) and 2 wk later, 2 h after an injection of exenatide (ExIGC; Byetta 5 μg injectable pen; Amylin Pharmaceuticals, Inc. San Diego, CA, USA). In the ExIGC, a 2-hour interval between the exenatide injection and the IGC was used to study the effect of exenatide during euglycemia. For glucose intravenous infusion, a 50% dextrose solution (50% Dextrose USP; Hospira Inc, Lake Forest, IL, USA) was diluted with saline to a 20% solution. Infusion rate was set on a syringe pump. Cats were maintained in a fasting state for 17 h before each experiment (4:00 PM the afternoon before). Between 8:00 and 9:00 AM two blood samples for measurement of BG concentrations were obtained. On one occasion in which hyperglycemia was detected, the experiment was postponed until the next day. In the IGC, glucose infusion started at 9:00 AM. During the IGC, BG concentration was measured at time zero and then every 5 min until euglycemia was restored. Blood samples for insulin were collected at 0, 15, 30, 45, 60, 75, 90, 120, 150, and 180 min.

2.3. Isoglycemic glucose clamp after injection of exenatide

The ExIGC was performed 2 wk after the IGC. At 9:00 AM (time zero of exenatide injection, −120 min from initiation of dextrose infusion) exenatide was injected with the use of a 31g hypodermic needle that was attached to the prefilled injection pen, as directed by the manufacturer. The pen delivers a fixed dose of 5 μg (mean dose, 1.04 ± 0.18 μg/kg). The injection was given subcutaneously, in a previously shaved area in the mid abdomen. Two hours after the exenatide injection (zero minute of the IGC), an intravenous dextrose infusion was started, and an IGC was performed with BG target concentrations of the previous IGC. Blood samples for measurements of insulin and exendin-4 concentrations were obtained at time zero (exenatide injection), 15, 30, 45, 60, 75, 90, 120 (initiation of IGC), 135, 150, 165, 180, 195, 210, 240, 270, and 300 min. Samples were further obtained for exendin-4 measurements at 6, 8, 12, and 24 h after injection. In one cat, the dextrose infusion was started at 60 min after injection because of hypoglycemia. In this cat, for statistical analysis, time 60 was considered time zero of the glucose infusion. In all cats, further monitoring for detection of potential exenatide-related side effects included daily thorough physical examinations and observation of the injection site, as well as close observation of general attitude, level of activity, food intake, urination, and defecation, throughout the 2 wk after injection. At the end of the 2 wk, a complete blood count and a serum chemistry profile were obtained.

2.4. Blood collection and storage

Blood was collected through indwelling jugular catheters (BD Angiocath AutoGuard; Becton Dickinson Infusion Therapy Systems, Inc, Sand, UT, USA). 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.

2.5. Catheter placement and maintenance

On the morning before each part of the experiment, cats were sedated with intramuscular injections of dexmedetomidine (0.009 mg/kg), butorphanol (0.22 mg/kg), and atropine (0.022 mg/kg) to facilitate catheter placement. Jugular catheters were placed before the oral glucose tolerance test. These catheters were 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 IGC and ExIGC and were removed at the end of the dextrose infusion. These catheters were used exclusively for glucose infusion. An area 1 sq inch in diameter on the mid abdomen was shaved before the ExIGC to facilitate accuracy of subcutaneous injection and to allow

monitoring of the injection site. The sedation was reversed with atipamezole (0.009 mg/kg), and the cats were monitored until full recovery.

2.6. Glucose and hormone measurements

Blood glucose concentrations were measured with a hand-held point-of-care glucose meter (OneTouch Ultra; LifeScan Inc, Milpitas CA, USA) that was validated for use in cats [20]. Insulin concentrations were measured with a feline ELISA (Feline Insulin ELISA; Mercodia AB, Uppsala, Sweden). Validation information for this assay is available (http://www.mercodia.se/uploads/modules/Mercodia/posters/Feline%20Insulin%20ELISA%20poster%20ACVIM%202009.pdf). Exendin-4 was measured with a specific EIA kit (Exendin-4 EIA; Bachem Americas Inc, Torrance, CA, USA). This assay has a range of 0 to 25 ng/mL and a sensitivity of 0.01 ng/mL. It has 100% cross reactivity with active exendin-4 (3–39) and its antagonist exendin (9–39) and 0% cross reactivity with GLP-1, GLP-2, and glucagon. The manufacturer of the assay reports an intra-assay CV of 5% and an inter-assay CV of 14%. Because this assay was not designed for use in cats, we used pooled feline serum to replace the assay diluent in preparation of the standard curve so that potential matrix interference would be similar in the standard curve and in samples. We found the intra-assay CV to be 12% and the inter-assay CV to be 25%.

2.7. Statistical analysis

Statistical analysis was performed with computer software (GraphPad Prism; GraphPad Software Inc, CA, USA). The Shapiro-Wilk test was used to assess deviance from normal distribution of data. Grubbs' test was used to detect outliers. Data are reported as mean ± SE if normally distributed or as median (range). Comparisons between treatment groups were analyzed with paired *t* tests. Comparisons between time points were analyzed with one-way repeated-measures ANOVA. Fold increase or fold difference was calculated as the deviation of a ratio from 1.0 with the use of a one-sample *t* test. The correlation between sets of abnormally distributed data was tested with Spearman rank correlation coefficient ρ.

The area under the curve (AUC) was calculated with the trapezoidal method for the BG and insulin concentrations. The AUC was used to represent total insulin secretion.

All statistical tests were performed as two-tailed tests. A P value < 0.05 was considered significant for all tests except the Grubbs' outlier test in which $P < 0.01$ was considered significant.

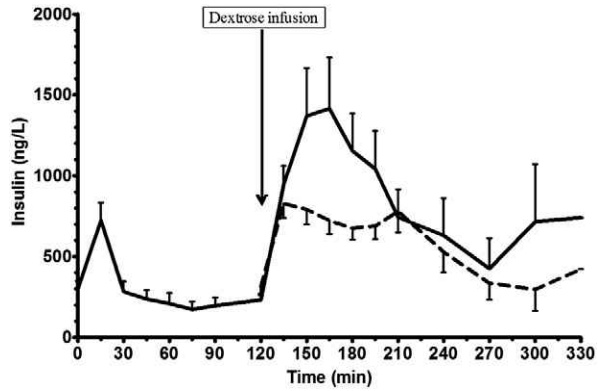

Fig. 1. Serum insulin concentrations (ng/L) after exenatide injection (solid line) and during an isoglycemic clamp (broken line). Exenatide was injected at zero minute. Intravenous dextrose infusion was started at 120 min. Error bars represent the SEM.

3. Results

Results of the oral glucose tolerance test and the incretin effect are reported elsewhere [19].

In all cats, the injection of exenatide was not associated with any side effects and no local or systemic adverse reactions were observed. Complete blood counts and serum chemistry profiles performed 2 wk after the exenatide injection showed no significant abnormalities in any of the cats.

Baseline BG concentrations did not differ significantly between the IGC and ExIGC (83.0 ± 2.9 mg/dL vs 82.3 ± 3.3 mg/dL, respectively; $P = 0.78$). Baseline insulin concentrations also did not differ significantly between the IGC and ExIGC (313 ± 42 ng/L vs 301 ± 47 ng/L. respectively; $P = 0.84$). Fifteen minutes after exenatide injection, insulin concentrations peaked at 724 ± 110 ng/L (an increase of 2.4-fold; range, 1.0- to 9.2-fold; $P = 0.004$; Fig. 1). Insulin then returned to baseline at 30 min and decreased below baseline at 75 min (173 ± 48 ng/L; $P = 0.008$). This was associated with a trend toward a decrease in BG concentration below baseline at 45 min (−6.9 ± 3.2 mg/dL; $P = 0.06$; Fig. 2). Hypoglycemia was observed in only one cat (54 mg/dL; 1 h after exenatide injection). In this cat, the glucose infusion was started at the time hypoglycemia was observed (instead of waiting the full 2 h) to avoid further decrease in BG concentration.

At 120 min (initiation of intravenous dextrose infusion), insulin and BG concentrations were not significantly different between the IGC and ExIGC ($P = 0.25$

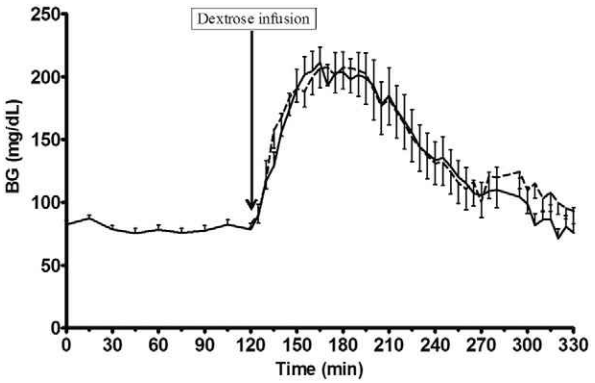

Fig. 2. Blood glucose concentrations (BG) after exenatide injection (solid line) and during an isoglycemic clamp (broken line). Exenatide was injected at zero minute. Intravenous dextrose infusion was started at 120 min. Error bars represent the SEM.

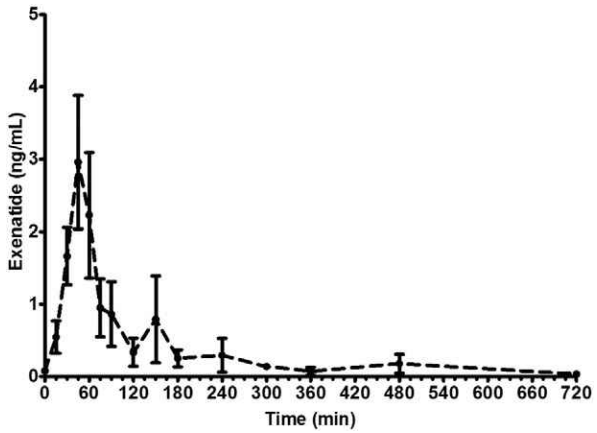

Fig. 4. Serum exenatide concentrations (ng/mL) after a subcutaneous injection at zero minute. Error bars represent the SEM.

and $P = 0.4$, respectively). Blood glucose concentrations during intravenous dextrose infusion did not differ significantly between the IGC and ExIGC (mean AUC difference, 0.02% ± 4%; $P = 0.95$; Fig. 2). Total glucose infused also did not differ significantly between the IGC and ExIGC (0.49 ± 0.06 g/kg and 0.56 ± 0.09 g/kg, respectively; $P = 0.35$; Fig. 3). In only six of the nine cats, more glucose was infused during the ExIGC. In the cat that had a BG concentration of 54 mg/dL, the amount of glucose infused during the ExIGC was almost double the amount infused during the IGC. Insulin AUC during intravenous dextrose infusion was significantly higher with exenatide injection than with no treatment (AUC ratio, 2.0 ± 0.4; $P = 0.03$; Fig. 1). No correlation was observed between the degree of stimulation at 15 min (calculated as the ratio of insulin concentration at 15 vs zero min) and the overall effect (represented by the ratio of AUC of insulin concentration during glucose infusion in the ExIGC and IGC).

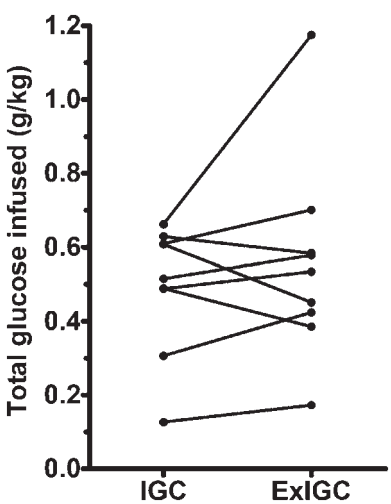

Fig. 3. Total glucose infused during an isoglycemic glucose clamp without prior treatment (IGC) and an isoglycemic glucose clamp following an exenatide injection (ExIGC) in individual cats in paired experiments.

Exenatide was measured in six cats. One cat was excluded from analysis. In this cat, serum concentrations of exenatide were consistently high and were calculated as outliers for all but two time points. Importantly, preinjection concentrations were also high, which suggested a matrix interference effect of this cat's serum. The results for the five other cats are presented in Figure 4. The mean exenatide concentration increased at the first measurement (15 min after injection) and reached a peak at 45 min after injection ($P = 0.016$). By 90 min, the mean concentration was no longer significantly different from baseline. The mean exenatide concentration from 120 to 240 min (during the IGC) was 0.4 ± 0.14 ng/mL. Exenatide was still detectable in the serum at 8 h after injection in three of five cats. The exenatide concentration at 15 min tended to have positive correlation with the fold increase of insulin concentrations from 0 to 15 min (Spearman's $\rho = 0.9$, $P = 0.083$).

4. Discussion

In this study we demonstrated that exenatide stimulates insulin secretion in a glucose-dependent manner in cats. A subcutaneous injection of exenatide caused a marked increase in serum insulin concentration within 15 min, followed by a small decrease in BG concen-

trations and a return of insulin to baseline concentrations. The return of insulin to baseline concentrations occurred despite a continuous increase in exenatide concentrations in the serum. When exenatide concentrations peaked 45 min after injection, the BG concentration was already below baseline, and no further stimulation of insulin secretion occurred. When the BG concentration was elevated with the use of a glucose infusion, the potentiating effect of exenatide was seen again. Serum insulin concentrations during the glucose infusion were significantly higher than serum insulin concentrations that were measured during an IGC.

The marked effect on insulin secretion at euglycemia was not unexpected. In isolated rat pancreas, GLP-1 and exenatide caused similar increases in insulin secretion at an ambient BG concentration of 54 mg/dL [21]. In healthy fasted humans, a subcutaneous injection of GLP-1 caused a 5-fold increase in plasma insulin concentrations within 10 min, followed by a decrease in the BG concentration [22]. Hypoglycemia developed in 3 of 10 subjects in that study with one of those subjects becoming symptomatically hypoglycemic. Severe hypoglycemia is a rare side effect of exenatide in diabetic people and is always associated with concurrent treatment with sulfonylurea drugs [10]. A single hypoglycemic event occurred in our study, but glucose infusion was begun before clinical signs could have developed and its severity could not be assessed. Nausea, decreased appetite, and less frequently vomiting are observed in a subset of people with daily use of exenatide. No side effects were seen in our study despite giving approximately 10 times the dose recommended in humans. Subtle side effects of exenatide that might have been detected on more frequent blood tests cannot be ruled out.

In clinical use, subcutaneous exenatide injections show glucoregulatory and weight-loss effects with sustained plasma concentrations in the range of 0.2 to 0.4 ng/mL [23]. In our study, during the glucose infusion the mean exenatide concentration in the five cats was 0.4 ng/mL. This was associated with a mild but significant effect on insulin secretion compared with an IGC with no prior treatment. Despite the difference in insulin concentrations, the total amount of glucose that needed to be infused to maintain an IGC was not significantly different between the IGCs. The mundane reason for that could be a lack of sufficient statistical power; however, a physiologic explanation should be considered. In general, if exenatide caused an increase in insulin concentrations with no net effect on blood glucose, it should have either increased hepatic glucose output or decreased glucose disposal. Neither of these potential effects has been described with GLP-1. Multiple studies, both in vitro and in vivo, have shown that exenatide in general has the same physiologic effects as GLP-1[24]. Recently, however, a study in rats showed an unexpected consequence of acute exenatide administration [25]. Exenatide, whether administered into the circulation or into the central nervous system, caused stimulation of the sympathetic nervous system, leading to hyperglycemia. This effect was independent of the glucose-dependent insulinotropic effect of exenatide, and it waned with more chronic administration (after 6 d). A similar effect of exenatide in cats might cause an increase in hepatic glucose output and explain our results. Importantly, it would also justify examining the effect of chronic exenatide administration in healthy and diabetic cats.

Increased hepatic glucose output might also be mediated through a direct effect of exenatide on the pancreas to increase glucagon secretion. In general, GLP-1 inhibits glucagon secretion in a glucose-dependent manner, thus reducing hepatic glucose output especially in hyperglycemia. It is widely accepted that the effect of GLP-1 to inhibit glucagon secretion is mostly indirect, mediated by the insulinotropic effect of GLP-1. Insulin, in turn, suppresses glucagon secretion. A direct effect of GLP-1 on α cells is questionable because GLP-1 receptors cannot be shown in α cells of rodents and humans [26]. In addition, when GLP-1 receptors were artificially expressed in α cells, the effect was stimulation of glucagon secretion [27]. Perhaps in cats, exenatide stimulates glucagon secretion (either by GLP-1 receptor or by a different mechanism), similar to the effect GIP has in α cells [24]. If that is the case, the direct stimulatory effect of GLP-1 might lead to increased hepatic glucose output if it is not overcome by an insulinotropic effect. Our results suggest that in healthy cats in the fasted state, exenatide has a smaller insulinotropic effect compared with other species. This might contribute to an overall lack of a glucose-lowering effect. The hypothesis that exenatide stimulates glucagon secretion is not supported, however, by the results of a recent study that showed in cats a reduction in glucagon secretion after injection of DPP-4 inhibitor [18].

Exenatide was detectable in plasma as early as 15 min after injection (the earliest time point sampled), showing its rapid absorption after a subcutaneous injection. The mean plasma exenatide concentration peaked 45 min after -injection and then sharply decreased, but exenatide was still detectable in the serum

8 h after injection in three of five cats. These results are consistent with a prolonged half-life in vivo and a resistance to degradation by DPP-4 as is seen in other species [9]. This is in sharp contrast to GLP-1, which is rapidly degraded after a subcutaneous injection with a half-life of 1 to 2 min [7]. In this study we did not examine the biologic effect of exenatide throughout the duration of its presence in the serum; therefore, its duration of action could not be determined. Future studies should examine the duration of action of exenatide in cats, as well as its effect on lowering the BG concentration in diabetic cats. We have shown that exenatide has an insulinotropic effect in cats. Even if this effect is not translated into a glucose-lowering effect, as might be suggested from our results with the IGC, other biologic effects of exenatide might be useful in the treatment of diabetes in cats and should be explored.

In conclusion, exenatide has a glucose-dependent insulinotropic effect in healthy cats. A single injection at a dose of 1.0 μg/kg was associated with hypoglycemia in one of nine cats, but no other side effects were observed. Our study justifies the use of exenatide in a clinical trial in diabetic cats as well as further studies of novel long-acting GLP-1 analogs.

Acknowledgments

This study was conducted at the College of Veterinary Medicine, University of Illinois at Urbana-Champaign. This study was supported by the Winn Feline Foundation. Dr. C. Gilor is the receiver of the Brasley Fellowship Award for the years 2008 to 2010. Cat food was supplied by Nestlé Purina PetCare Company. A part of this study was presented as an abstract at ECVIM, Toulouse, France, 2010.

References

[1] Nelson RW. Diabetes Mellitus. In: Ettinger SJ, Feldman EC, eds. Textbook of Veterinary Internal Medicine - Diseases of the Dog and Cat. 6 ed. Philadelphia, PA: WB Saunders Co.; 2005: 1563–1591.

[2] McIntyre N, Holdsworth CD, Turner DS. Intestinal factors in the control of insulin secretion. J Clin Endocrinol Metab. 1965; 25:1317–1324.

[3] Holst JJ, Vilsbøll T, Deacon CF. The incretin system and its role in type 2 diabetes mellitus. Mol Cell Endocrinol. 2009;297: 127–136.

[4] Nauck MA, Heimesaat MM, Orskov C, Holst JJ, Ebert R, Creutzfeldt W. Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. J Clin Invest. 1993;91:301–307.

[5] Toft-Nielsen MB, Damholt MB, Madsbad S, et al. Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. J Clin Endocrinol Metab. 2001;86:3717–3723.

[6] Toft-Nielsen MB, Madsbad S, Holst JJ. Determinants of the effectiveness of glucagon-like peptide-1 in type 2 diabetes. J Clin Endocrinol Metab. 2001;86:3853–3860.

[7] Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology. 2007;132:2131–2157.

[8] Deacon CF. What do we know about the secretion and degradation of incretin hormones? Regul Pept. 2005;128: 117–124.

[9] Kolterman OG, Kim DD, Shen L, et al. Pharmacokinetics, pharmacodynamics, and safety of exenatide in patients with type 2 diabetes mellitus. Am J Health Syst Pharm. 2005;62: 173–181.

[10] Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. JAMA. 2007;298:194–206.

[11] Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG; GWAA Study Group. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med. 2005;143:559–569.

[12] Barnett AH, Burger J, Johns D, et al. Tolerability and efficacy of exenatide and titrated insulin glargine in adult patients with type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: a multinational, randomized, open-label, two-period, crossover noninferiority trial. Clin Ther. 2007;29:2333–2348.

[13] Glass LC, Qu Y, Lenox S, et al. Effects of exenatide versus insulin analogues on weight change in subjects with type 2 diabetes: a pooled post-hoc analysis. Curr Med Res Opin. 2008; 24:639–644.

[14] Buse JB, Klonoff DC, Nielsen LL, et al. Metabolic effects of two years of exenatide treatment on diabetes, obesity, and hepatic biomarkers in patients with type 2 diabetes: an interim analysis of data from the open-label, uncontrolled extension of three double-blind, placebo-controlled trials. Clin Ther. 2007; 29:139–153.

[15] Ghofaili KA, Fung M, Ao Z, et al. Effect of exenatide on beta cell function after islet transplantation in type 1 diabetes. Transplantation. 2007;83:24–28.

[16] Rand JS, Fleeman LM, Farrow HA, Appleton DJ, Lederer R. Canine and feline diabetes mellitus: nature or nurture? J Nutr. 2004;134:2072S–2080S.

[17] Hoenig M, Jordan ET, Ferguson DC, de Vries F. Oral glucose leads to a differential response in glucose, insulin, and GLP-1 in lean versus obese cats. Domest Anim Endocrinol. 2010;38:95–102.

[18] Furrer D, Kaufmann K, Tschuor F, Reusch CE, Lutz TA. The dipeptidyl peptidase IV inhibitor NVP-DPP728 reduces plasma glucagon concentration in cats. Vet J. 2010;183:355–357.

[19] Gilor C, Graves TK, Gilor S, Ridge TK, Weng H, Dossin O. The incretin effect in cats: comparison between oral glucose, lipids and amino acids. Domest Anim Endocrinol, in press.

[20] Gilor C, Ridge TK, Attermeier KJ, Graves TK. Pharmacodynamics of insulin detemir and insulin glargine assessed using an isoglycemic clamp method in healthy cats. J Vet Intern Med. 2010;24:870–874.

[21] Parkes DG, Pittner R, Jodka C, Smith P, Young A. Insulinotropic actions of exendin-4 and glucagon-like peptide-1 in vivo and in vitro. Metabolism. 2001;50:583–589.

[22] Edwards CM, Todd JF, Ghatei MA, Bloom SR. Subcutaneous glucagon-like peptide-1 (7-36) amide is insulinotropic and can cause hypoglycaemia in fasted healthy subjects. Clin Sci (Lond). 1998;95:719–724.

[23] Gedulin BR, Smith PA, Jodka CM, et al. Pharmacokinetics and pharmacodynamics of exenatide following alternate routes of administration. Int J Pharm. 2008;356:231–238.

[24] Kim W, Egan JM. The role of incretins in glucose homeostasis and diabetes treatment. Pharmacol Rev. 2008;60:470–512.

[25] Perez-Tilve D, González-Matías LC, Aulinger BA, et al. Exendin-4 increases blood glucose levels acutely in rats by activation of the sympathetic nervous system. Am J Physiol Endocrinol Metab. 2010;298(5):E1088–E1096.

[26] Tornehave D, Kristensen P, Rømer J, Knudsen LB, Heller RS. Expression of the GLP-1 receptor in mouse, rat, and human pancreas. J Histochem Cytochem. 2008;56:841–851.

[27] Dillon JS, Lu M, Bowen S, Homan LL. The recombinant rat glucagon-like peptide-1 receptor, expressed in an alpha cell line, is coupled to adenylyl cyclase activation and intracellular calcium release. Exp Clin Endocrinol Diabetes. 2005; 113:182–189.