MEDICAÇÕES PARA TRATAMENTO DA OBESIDADE – já são realidade na medicina veterinária?

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Endocrinologia
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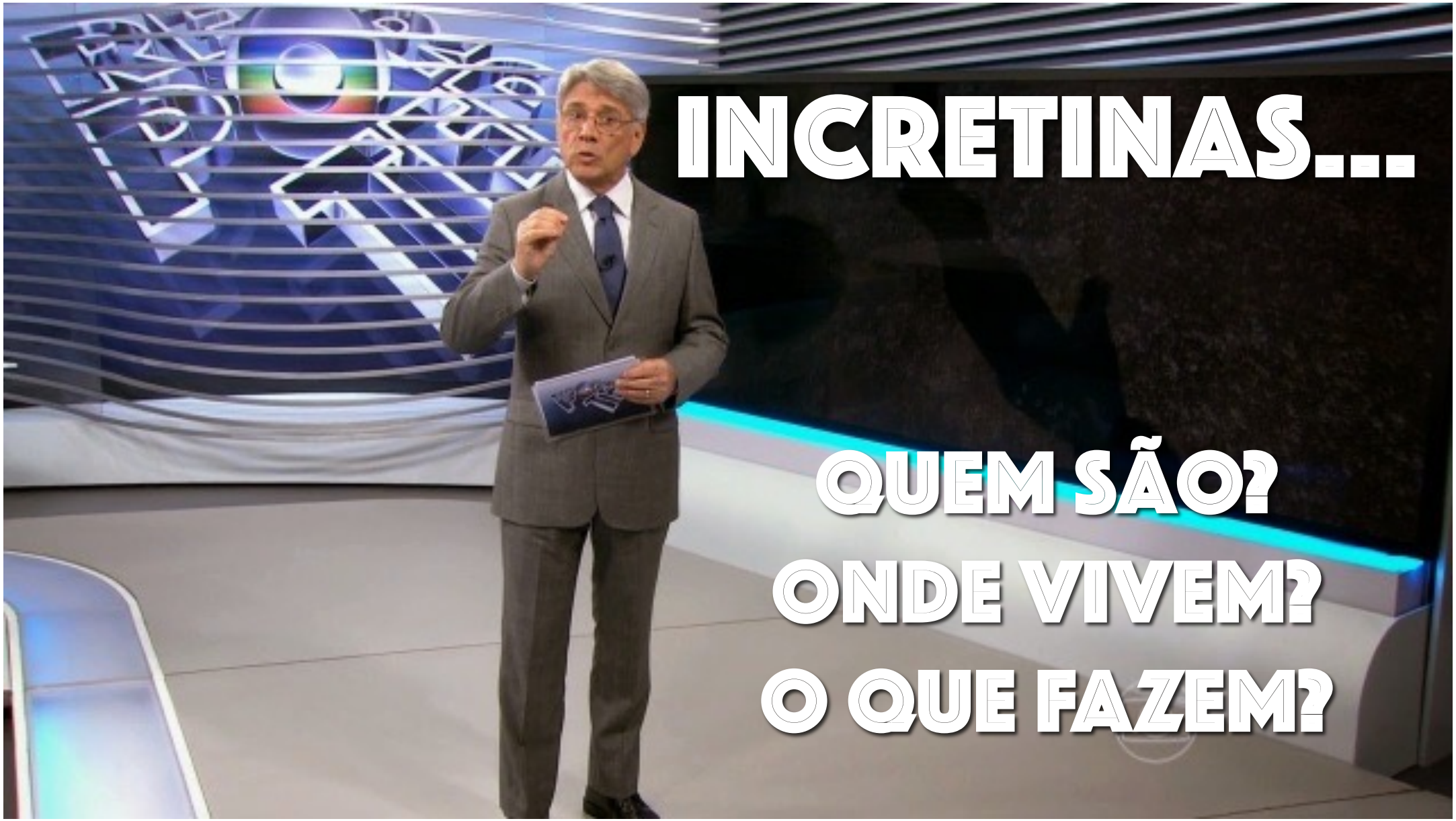
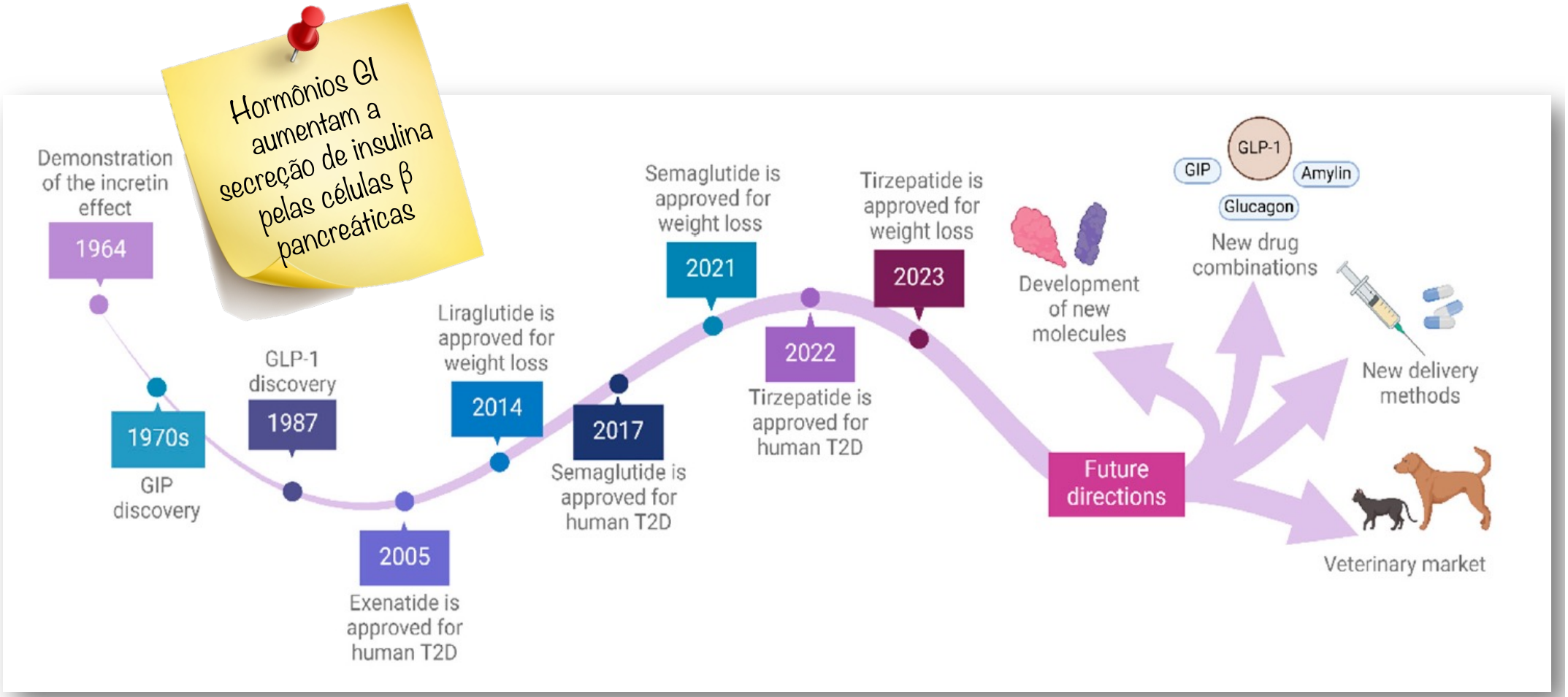

INCRETINAS...
QUEM SÃO?
ONDE VIVEM?
O QUE FAZEM?



Zomer & Cooke. ***Advances in Drug Treatments for Companion Animal Obesity***

Biology 2024, 13, 335. https://doi.org/10.3390/biology13050335


Década de 90
Anos 2000...
BOOM!
CIRURGIAS
BARIÁTRICAS

Reversão do Diabetes Mellitus

Cirurgia	Reversão DM-2
Bypass gastrojejunal	84% (global) → 80,3% (> 2 anos)
Derivação Biliopancreática	98% (global) → 95,1% (> 2 anos)

Reversão do DM-2 Grave após *Bypass*

Usuários de insulina	62%
> 10 anos DM	54%

Reversão do DM-2 após *Bypass* (Brasil)

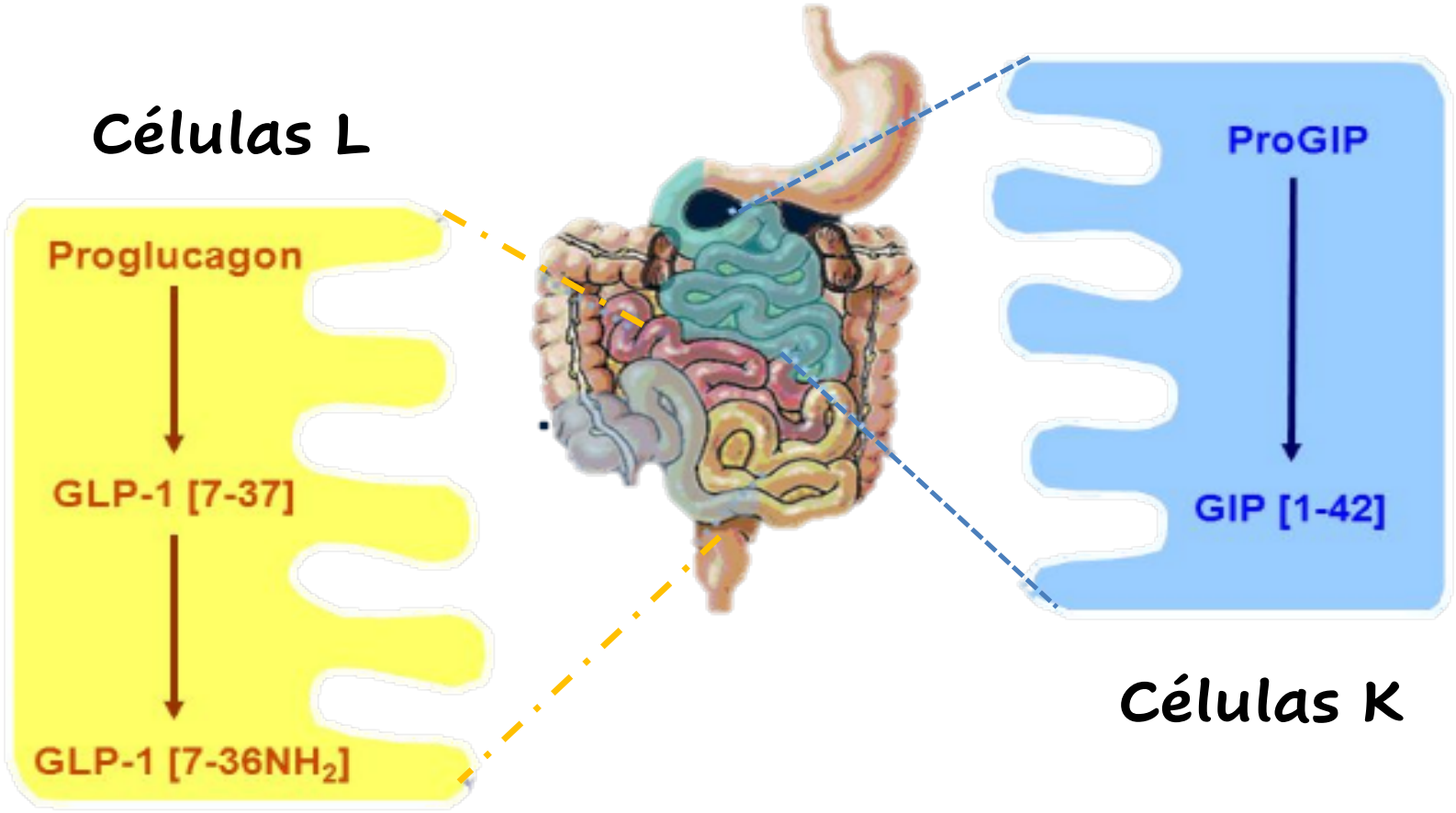
Santo et al.	94,3% (5 anos) / 84,7% (8 anos)
Pajecki et al.	76,5% (> 5 anos)

Schauer (2003)
Buchwald (2004)
Pajecki (2007)
Buchwald (2009)
Santo (2010)

SBC

Como isso é possível se a perda de peso não imediata?

GIP E GLP-1 são sintetizados e secretados a partir do intestino em resposta a ingestão dos alimentos



Cell Tissue Res (1999) 298:287–293
Digital Object Identifier (DOI) 10.1007/s004419900093

REGULAR ARTICLE

Anders B. Damholt · Hans Kofod
Alison M.J. Buchan

Immunocytochemical evidence for a paracrine interaction between GIP and GLP-1-producing cells in canine small intestine

Received: 30 March 1999 / Accepted: 15 July 1999 / Published online: 21 September 1999

Abstract Glucagon-like-peptide 1 (GLP-1) released from the intestine is considered to be an important incretin. We have recently demonstrated that glucose-dependent insulinotropic peptide (GIP) stimulated GLP-1 secretion from canine ileal L cells in culture. To investigate further the interplay between GLP-1- and GIP-secreting cells, we set out to determine the exact location and abundance of both cell types throughout the canine intestine. Canine small intestine was subdivided into 15–20 segments and investigated by immunocytochemistry with computer-assisted imaging. The abundance of GIP-, GLP-1- and somatostatin-immunoreactive cells was determined. GIP-secreting K cells were equally distributed in duodenum and jejunum, with the GLP-1-secreting L cells concentrated in the jejunum (5% duodenum, 73% jejunum and 22% ileum). These results indicated that the middle section of the small intestine containing 69% of the K cells also contained 51% of the L cells. Double immunostaining confirmed this overlap and furthermore over 30% of the L cells in this region were found adjacent to K cells. These results suggest the existence of a paracrine interaction between the K and L cells and indicate the importance of the jejunum in the regulation of insulin release by enteric-derived incretins.

Key words Somatostatin · Enteroinsular axis · Immunocytochemistry · Dog

Introduction

Glucagon-like peptide 1 (GLP-1) secreted from intestinal endocrine cells has been established as a glucose-dependent incretin in a number of species including canines and humans (Orskov et. al. 1996; Holst 1997). Recent data from our laboratory, based on a primary culture of canine epithelium enriched for GLP-1 cells, indicated that glucose itself was incapable of stimulating GLP-1 release. However, glucose-dependent insulinotropic peptide (GIP), another incretin, stimulated GLP-1 release (Damholt et al. 1998). The lack of a direct effect of glucose on GLP-1 secretion has previously been observed in both perfused intestine and isolated cell preparations from rats (Brubaker and Vranic 1987; Roberge and Brubaker 1991). Furthermore, GIP has been demonstrated to stimulate GLP-1 release from rat intestine (Brubaker 1991; Roberge and Brubaker 1993). These data suggest that GIP released from the upper intestine in response to increased luminal glucose levels (Pederson et al. 1975) in turn stimulates GLP-1 release. If this is the case then GIP must interact with GLP-1-containing cells in the intestine.

GLP-1 is a cleavage product of proglucagon and is produced in the intestinal L cells (Holst 1997). Quantitative immunocytochemical studies have demonstrated that the majority of L cells are located in the ileum and colon, with a small number of cells in the distal jejunum (Eissele et al. 1992; Kauth and Metz 1987). In contrast to GLP-1, GIP-immunoreactive (K) cells are concentrated in duodenum and proximal jejunum (Buchan et al. 1982; Varndell et al. 1985).

There are two mechanisms by which GIP can interact with GLP-1 cells: either by the classical endocrine route with GIP released into the circulation from the duodenum and upper jejunum to affect the GLP-1 cells in the ileum or by a paracrine (local) action. In the case of the interaction between GIP and GLP-1 cells the former has been considered to be the more likely due to the non-overlapping distribution of the two cell types. In addition to an interaction between GIP and GLP-1 cells, the release of both peptides is regulated by somatostatin (SS). In this case the interaction is considered to be of the paracrine type as SS-containing D cells are distributed throughout the small intestine (Larsson et al. 1979; Baldissera et al. 1985).

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Domestic Animal Endocrinology 45 (2013) 49–54

Contents lists available at SciVerse ScienceDirect

Domestic Animal Endocrinology

journal homepage: www.domesticanimalendo.com

Short Communication

Distribution of K and L cells in the feline intestinal tract

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ARTICLE INFO

Article history:
Received 21 February 2013
Received in revised form 23 April 2013
Accepted 26 April 2013

Keywords:
Diabetes mellitus
Incretin
Obesity
GLP-1
GLP-2
GIP

ABSTRACT

Glucose-dependent insulinotropic peptide (GIP), glucagon-like peptide (GLP)-1 and GLP-2 are hormones secreted from specialized K cells (GIP) and L cells (GLP-1, GLP-2) in the intestinal mucosa. These hormones play major roles in health and disease by modulating insulin secretion, satiety, and multiple intestinal functions. The aim of this study was to describe the distribution of K cells and L cells in the intestines of healthy cats. Samples of duodenum, mid-jejunum, ileum, cecum, and colon were collected from 5 cats that were euthanized for reasons unrelated to this study and had no gross or histologic evidence of gastrointestinal disease. Samples stained with rabbit-anti-porcine GIP, mouse-anti-(all mammals) GLP-1, or rabbit-anti-(all mammals) GLP-2 antibodies were used to determine the number of cells in 15 randomly selected 400× microscopic fields. In contrast to other mammals (eg, dogs) in which K cells are not present in the ileum and aborally, GIP-expressing cells are abundant throughout the intestines in cats (>6/high-power field in the ileum). Cells expressing GLP-1 or GLP-2 were most abundant in the ileum (>9/high-power field) as in other mammals, but, although GLP-1–expressing cells were abundant throughout the intestines, GLP-2–expressing cells were rarely found in the duodenum. In conclusion, the distribution of GIP-secreting K cells in cats is different from the distribution of K cells that is described in other mammals. The difference in distribution of GLP-2– and GLP-1–expressing cells suggests that more than 1 distinct population of L cells is present in cats.

1. Introduction

The physiology of the enteroendocrine K cells and L cells has been studied in rodents, dogs, pigs, and humans but not in cats. These enteroendocrine cells are dispersed along the epithelium of the intestinal tract where they sense the type and quantity of digested nutrients. They play a crucial role in glucose metabolism by secreting the incretin hormones glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide (GLP)-1 that increase the sensitivity of the pancreas to the stimulatory effect of glucose on insulin secretion [1,2]. Incretin hormones also participate in regulation of pancreatic beta-cell differentiation, proliferation, and survival; affect glucagon secretion; slow the rate of gastric emptying and increase satiety [3]. The hormone glucagon-like peptide-2 (GLP-2) is also secreted from L cells and leads to increased small bowel weight by stimulating enterocyte proliferation and decreasing their apoptosis [4]. It also stimulates glucose absorption in enterocytes, increases blood flow to the intestines, and enhances barrier function in intestinal epithelium, making it a potential

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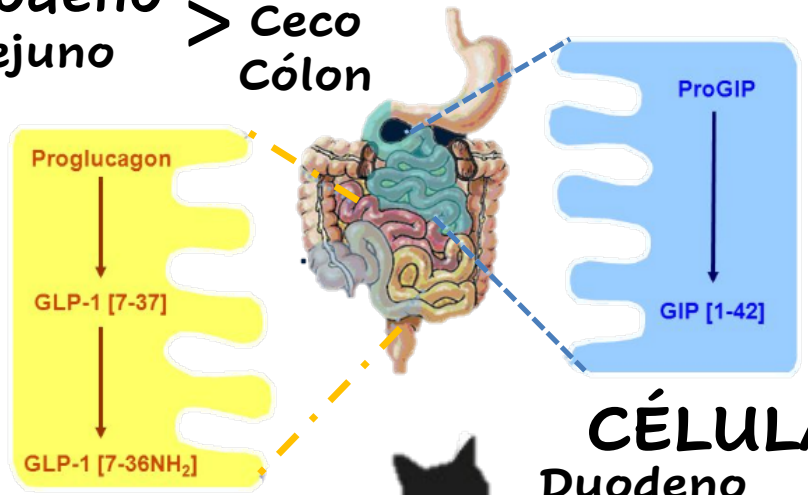
http://dx.doi.org/10.1016/j.domaniend.2013.04.004

CÉLULAS L

Duodeno
Jejuno
> Íleo
Ceco
Cólon



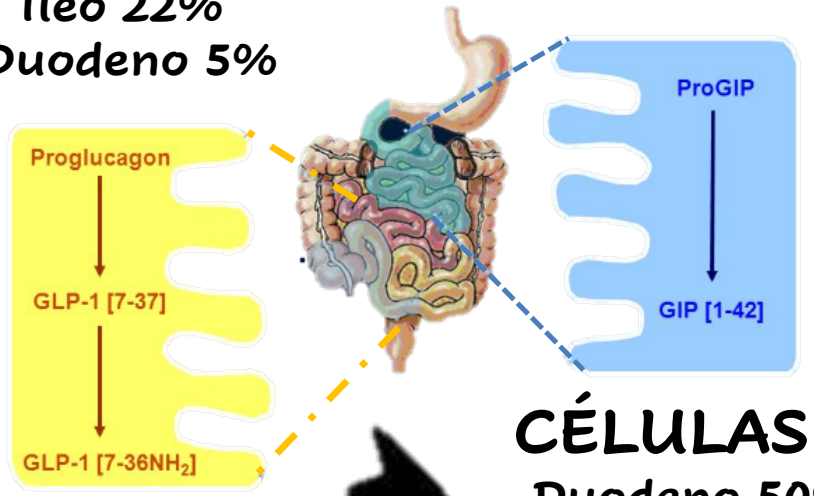
(Gilor et al. 2013)

CÉLULAS K

Duodeno
Jejuno
Íleo
> Ceco
Cólon

CÉLULAS L

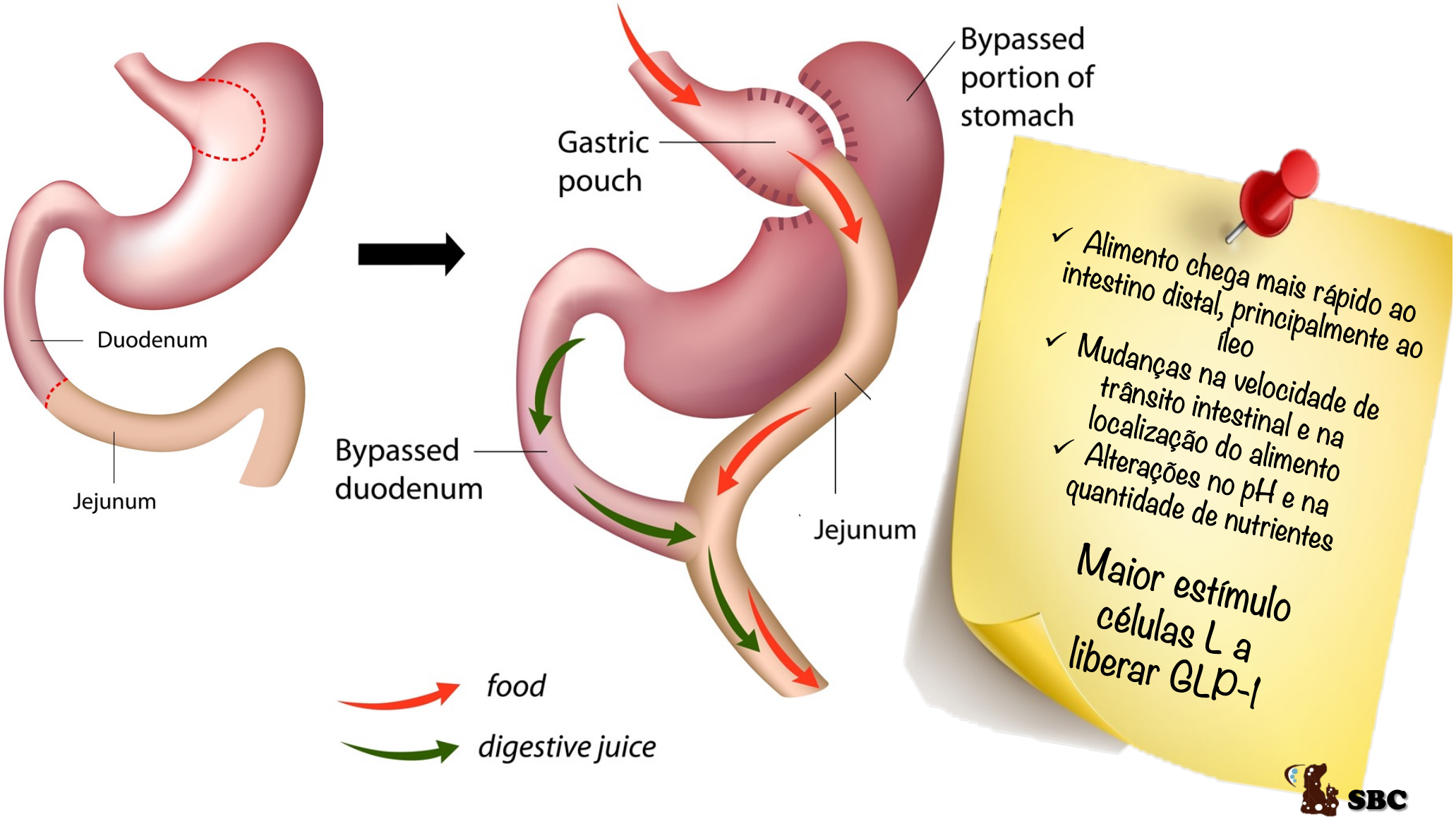
Jejuno 73%
Íleo 22%
Duodeno 5%



CÉLULAS K

Duodeno 50%
Jejuno 50%

(Damholt et al. 1999)

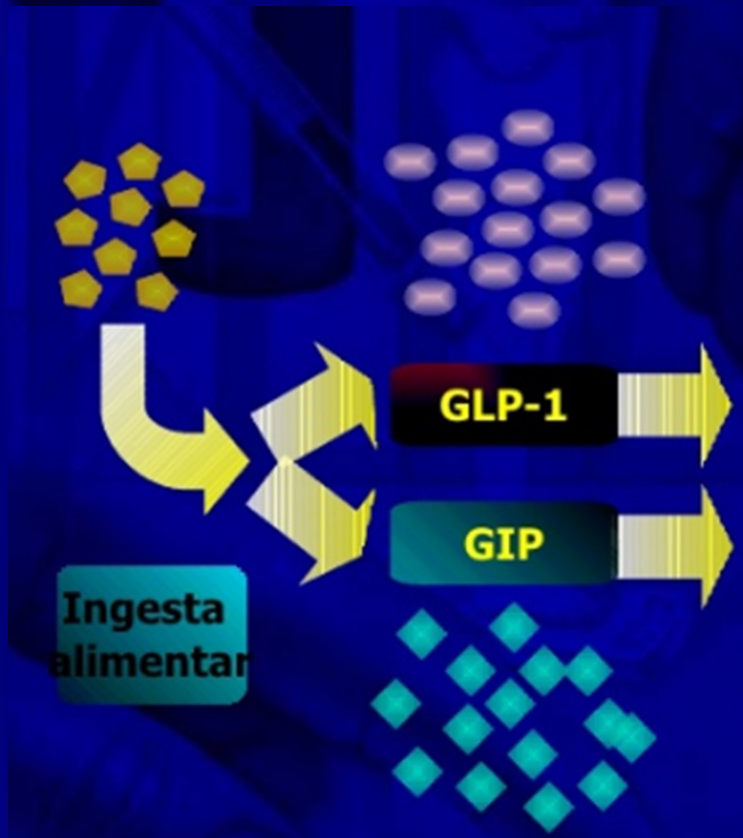

Duodenum
Jejunum
Bypassed
duodenum
Gastric
pouch
Bypassed
portion of
stomach
Jejunum
food
digestive juice
✓ Alimento chega mais rápido ao intestino distal, principalmente ao íleo
✓ Mudanças na velocidade de trânsito intestinal e na localização do alimento
✓ Alterações no pH e na quantidade de nutrientes
Maior estímulo células L a liberar GLP-1
SBC

GIP

Peptídeo insulinotrópico semelhante a glicose

GLP-1

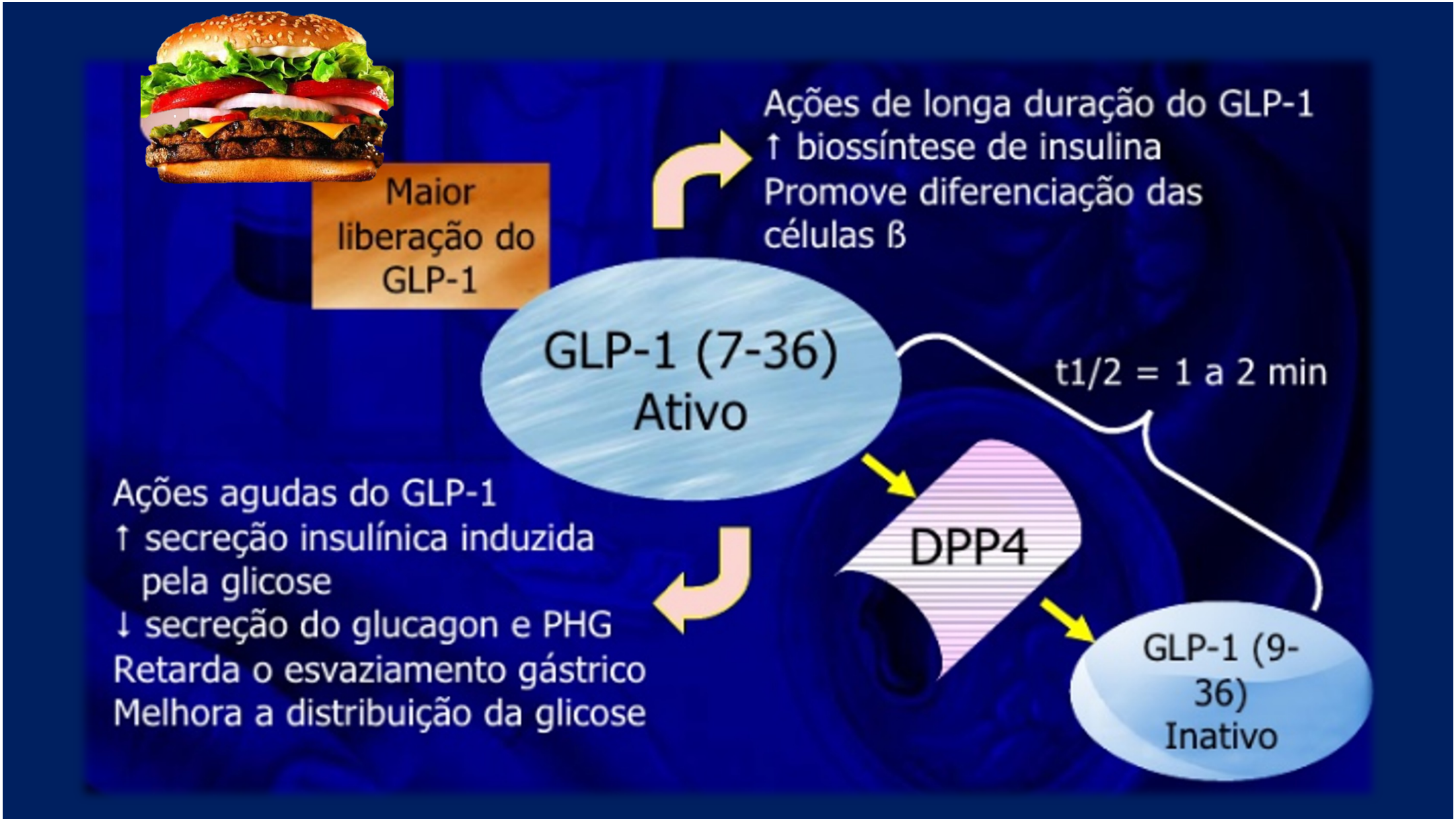
Peptídeo semelhante ao glucagon



Controle metabólico

Regula:

- Influxo de glicose
- Resistência insulínica
- Secreção do glucagon
- Função aguda das células ß
  - Secreção insulínica
- Função crônica das células ß
  - Proliferação
  - Efeito anti-apoptótico


Maior liberação do GLP-1
Ações de longa duração do GLP-1
↑ biossíntese de insulina
Promove diferenciação das células ß
GLP-1 (7-36) Ativo
t1/2 = 1 a 2 min
DPP4
GLP-1 (9-36) Inativo
Ações agudas do GLP-1
↑ secreção insulínica induzida pela glicose
↓ secreção do glucagon e PHG
Retarda o esvaziamento gástrico
Melhora a distribuição da glicose


SBC

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Domestic Animal Endocrinology 38 (2010) 95–102
DOMESTIC ANIMAL ENDOCRINOLOGY
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Oral glucose leads to a differential response in glucose, insulin, and GLP-1 in lean versus obese cats

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Received 20 May 2009; received in revised form 6 August 2009; accepted 9 August 2009

Abstract

The response to oral glucose was examined in 10 obese and 9 lean age-matched, neutered cats. In all cats, oral administration of 2 g/kg glucose was followed by a prompt increase in glucose, insulin, and glucagon-like peptide (GLP)-1. There were significant differences between lean and obese cats in the areas under the curve for glucose, insulin, and GLP-1. However, the responses were variable, and a clear distinction between individual lean and obese cats was not possible. Therefore, this test cannot be recommended as a routine test to examine insulin resistance in individual cats as it is used in people. A further disadvantage for routine use is also the fact that this test requires gastric tubing for the correct administration of the glucose and associated tranquilization to minimize stress and that it was associated with development of diarrhea in 25% of the cats. GLP-1 concentrations were much lower in obese than lean cats. The low GLP-1 concentrations in obese cats might indicate a contribution of GLP-1 to the lower insulin sensitivity of obese cats, but this hypothesis needs to be further investigated.

Keywords: Glucose tolerance; Obesity; Incretin; Insulin sensitivity; Insulin resistance

1. Introduction

The oral glucose tolerance test (OGTT) is a frequently used test in human medicine [1–4], but it is rarely applied in pets. In asymptomatic people, a diagnosis of impaired glucose tolerance or diabetes is usually made based on fasting glucose concentrations and the response to a 75-g glucose load (2-h test), which is increased to 100 g in pregnant women (3-h test) [5]. In children, 1.75 g/kg is administered [6,7]. Based on large studies, strict criteria have been established for the interpretation of the results to separate healthy people from people at risk of developing diabetes or who already have diabetes. Fasting glucose should be below 99 mg/dL. Fasting concentrations between 100 mg/dL and 125 mg/dL are borderline ("impaired fasting glucose"), and fasting concentrations repeatedly above 126 mg/dL are diagnostic of diabetes. The 2-h glucose should be below 140 mg/dL. Concentrations between 140 md/dL and 200 mg/dL indicate "impaired glucose tolerance." Glucose above 200 mg/dL at 2 h confirms a diagnosis of diabetes [8]. To our knowledge, OGTTs have been described in dogs, but not in cats. In dogs, different dosages ranging from 1.0 g/kg to 4 g/kg have been used [9–12], leading to a peak glucose

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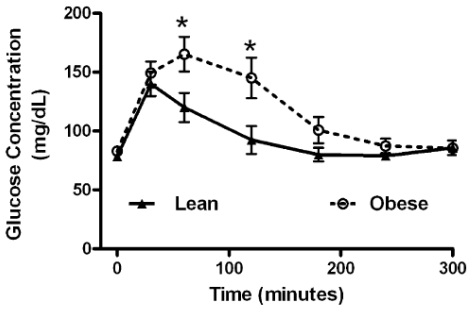
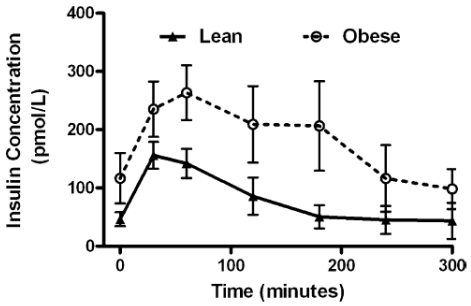
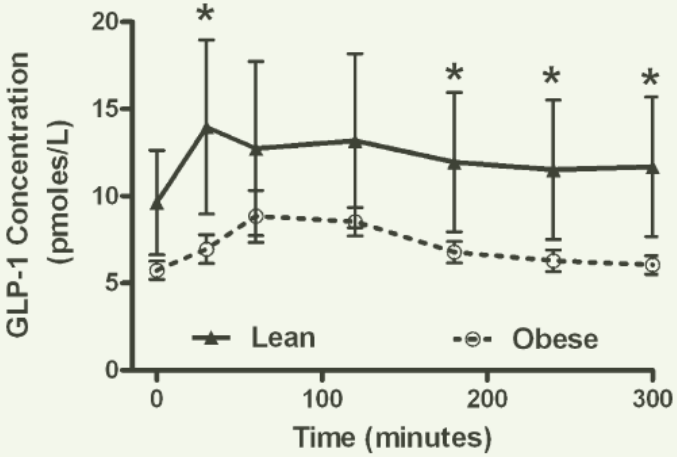
doi:10.1016/j.domaniend.2009.08.004







Gatos obesos ↓ GLP-1 em resposta glicose oral

Domestic Animal Endocrinology 51 (2015) 114–121

Contents lists available at ScienceDirect

Domestic Animal Endocrinology

journal homepage: www.domesticanimalendo.com

Pharmacokinetics and pharmacodynamics of the glucagon-like peptide-1 analog liraglutide in healthy cats

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ARTICLE INFO

Article history:
Received 23 July 2014
Received in revised form 1 December 2014
Accepted 2 December 2014

Keywords:
Feline
Diabetes
Insulin
Glucagon
Incretin

ABSTRACT

Glucagon-like peptide-1 (GLP-1) is an intestinal hormone that induces glucose-dependent stimulation of insulin secretion while suppressing glucagon secretion. Glucagon-like peptide-1 also increases beta cell mass and satiation while decelerating gastric emptying. Liraglutide is a fatty-acid derivative of GLP-1 with a protracted pharmacokinetic profile that is used in people for treatment of type II diabetes mellitus and obesity. The aim of this study was to determine the pharmacokinetics and pharmacodynamics of liraglutide in healthy cats. Hyperglycemic clamps were performed on days 0 (HGC) and 14 (LgHGC) in 7 healthy cats. Liraglutide was administered subcutaneously (0.6 mg/cat) once daily on days 8 through 14. Compared with the HGC (mean ± standard deviation; 455.5 ± 115.8 ng/L), insulin concentrations during LgHGC were increased (760.8 ± 350.7 ng/L; $P = 0.0022$), glucagon concentrations decreased (66 ± 0.4 pmol/L during HGC vs 0.5 ± 0.4 pmol/L during LgHGC; $P = 0.0089$), there was a trend toward an increased total glucose infused (median [range] 1.61 [1.11–2.32] g/kg and 2.25 (1.64–3.10) g/kg, respectively; $P = 0.087$). Appetite reduction and decreased body weight (9% ± 3%; $P = 0.006$) were observed in all cats. Liraglutide has similar effects and pharmacokinetics profile in cats to those reported in people. With a half-life of approximately 12 h, once daily dosing might be feasible. However, significant effects on appetite and weight loss may necessitate dosage or dosing frequency reductions. Further investigation of liraglutide in diabetic cats and overweight cats is warranted.

LIRAGLUTIDA (Victoza®)

1. Introduction

Feline diabetes mellitus (FDM) clinically resembles type 2 diabetes mellitus in people, as both FDM and type II diabetes mellitus (T2DM) are characterized by insulin resistance, relative insulin deficiency, decreased beta cell mass, and islet-amyloid depositions [1,2].

Despite technological advances in insulin formulations and monitoring, insulin therapy across species is still commonly associated with inadequate glycemic control leading to short- and long-term complications such as hypoglycemia, weight gain, and vascular diseases. Incretin-based therapy for T2DM was first introduced in 2005 and has quickly become a widely used adjunctive therapy. The incretin effect is the greater release of insulin occurring after oral glucose administration compared with intravenous administration of the same glucose dose. Two peptide hormones contribute to the incretin effect and are called incretin hormones: glucagon-like peptide-1 and glucose-dependent insulinotropic peptide (GIP). They are secreted from specialized enteroendocrine cells in response to the presence of nutrients in the lumen of the gut (but not in

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0739-7240/$ – see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.domaniend.2014.12.001

AUMENTO DE INSULINA
DIMINUÇÃO DO GLUCAGON
PERDA DE PESO
9% ± 3% (14 dias)
4,9% ± 4,15% kg (28 dias)

Dose 15x superior a de humanos!

REDUÇÃO DO APETITE
VÔMITO/NÁUSEA/ANOREXIA

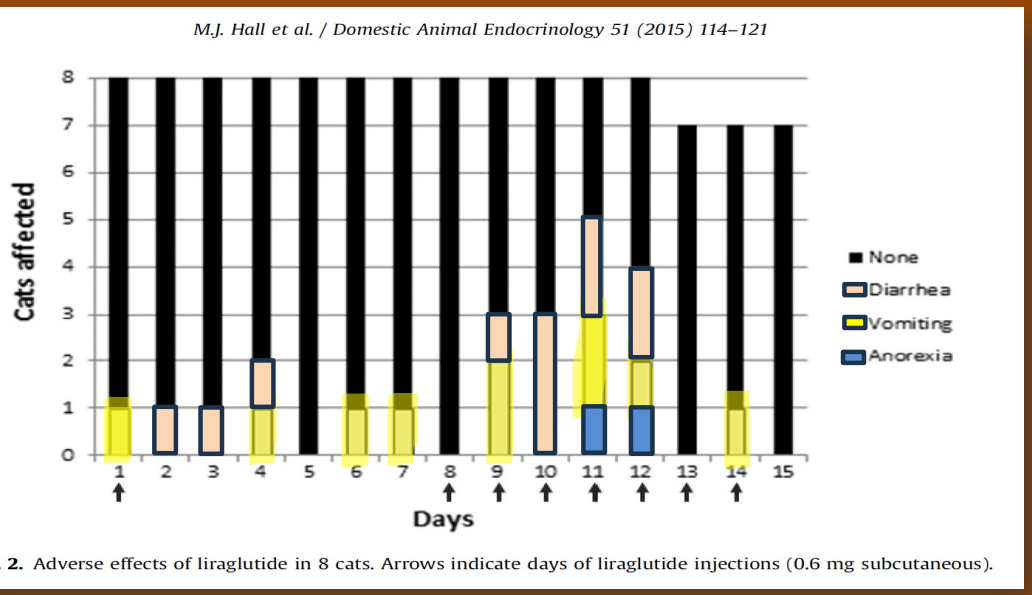
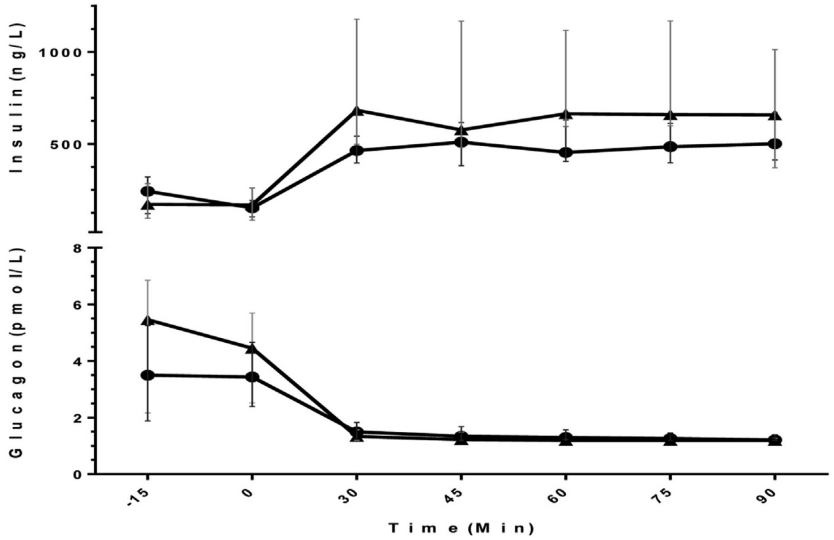


Fig. 2. Adverse effects of liraglutide in 8 cats. Arrows indicate days of liraglutide injections (0.6 mg subcutaneous).



● During hyperglycemic clamp
▲ After exenatide injection

Melhora da tolerância à glicose 3 semanas após uma única injeção!

NENHUM EFEITO ADVERSO!

Domestic Animal Endocrinology 51 (2015) 78–85

Contents lists available at ScienceDirect

Domestic Animal Endocrinology

journal homepage: www.domesticanimalendo.com

Pharmacology of the glucagon-like peptide-1 analog exenatide extended-release in healthy cats

A.J. Rudinsky [a], C.A. Adin [a], S. Borin-Crivellenti [b], P. Rajala-Schultz [c], M.J. Hall [a], C. Gilor [a,*]

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ARTICLE INFO

Article history:
Received 26 August 2014
Received in revised form 8 December 2014
Accepted 11 December 2014

Keywords:
Feline
Exenatide
Incretin
Diabetes
Insulin
Glucagon

ABSTRACT

Exenatide extended-release (ER) is a microencapsulated formulation of the glucagon-like peptide 1-receptor agonist exenatide. It has a protracted pharmacokinetic profile that allows a once-weekly injection with comparable efficacy to insulin with an improved safety profile in type II diabetic people. Here, we studied the pharmacology of exenatide ER in 6 healthy cats. A single subcutaneous injection of exenatide ER (0.13 mg/kg) was administered on day 0. Exenatide concentrations were measured for 12 wk. A hyperglycemic clamp (target = 225 mg/dL) was performed on days −7 (clamp I) and 21 (clamp II) with measurements of insulin and glucagon concentrations. Glucose tolerance was defined as the amount of glucose required to maintain hyperglycemia during the clamp. Continuous glucose monitoring was performed on weeks 0, 2, and 6 after injection. Plasma concentrations of exenatide peaked at 1 h and [illegible] after injection. Comparing clamp I with clamp II, fasting blood glucose decreased [mean ± standard deviation = −11 ± 8 mg/dL, P = 0.02), glucose tolerance improved [median [range] +33% [4%–138%], P = 0.04), insulin concentrations increased [+30% [−[illegible] 274.1%], P = 0.02), and glucagon concentrations decreased [−4.7% [−[illegible]0%–12.1%], P = 0.005). Compared with baseline values on continuous glucose monitoring, glucose concentrations decreased and the frequency of readings <3[illegible] increased at 2 and 6 wk after injection of exenatide ER. This did not progress to clinical hypoglycemia. No other side effects were observed throughout the study. Exenatide ER was safe and effective at improving glucose tolerance 3 wk after a single injection. Further evaluation is needed to determine its safety, efficacy, and duration of action in diabetic cats.

EXENATIDA LONGA-AÇÃO (Bydureon®)

1. Introduction

Diabetes mellitus (DM) remains one of the most common and clinically important diseases in feline medicine. Recent data show that the prevalence of both DM and obesity is increasing in recent years within the domestic feline population [illegible] diabetes therapies have been used to manage feline DM clinically including exogenous insulin administered subcutaneously, dietary modification, weight control, and management of insulin-resistant diseases. However, the vast majority of animals rely on daily insulin therapy to manage the disease, which is associated with various side effects, some of which can be life threatening [1].

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are incretin

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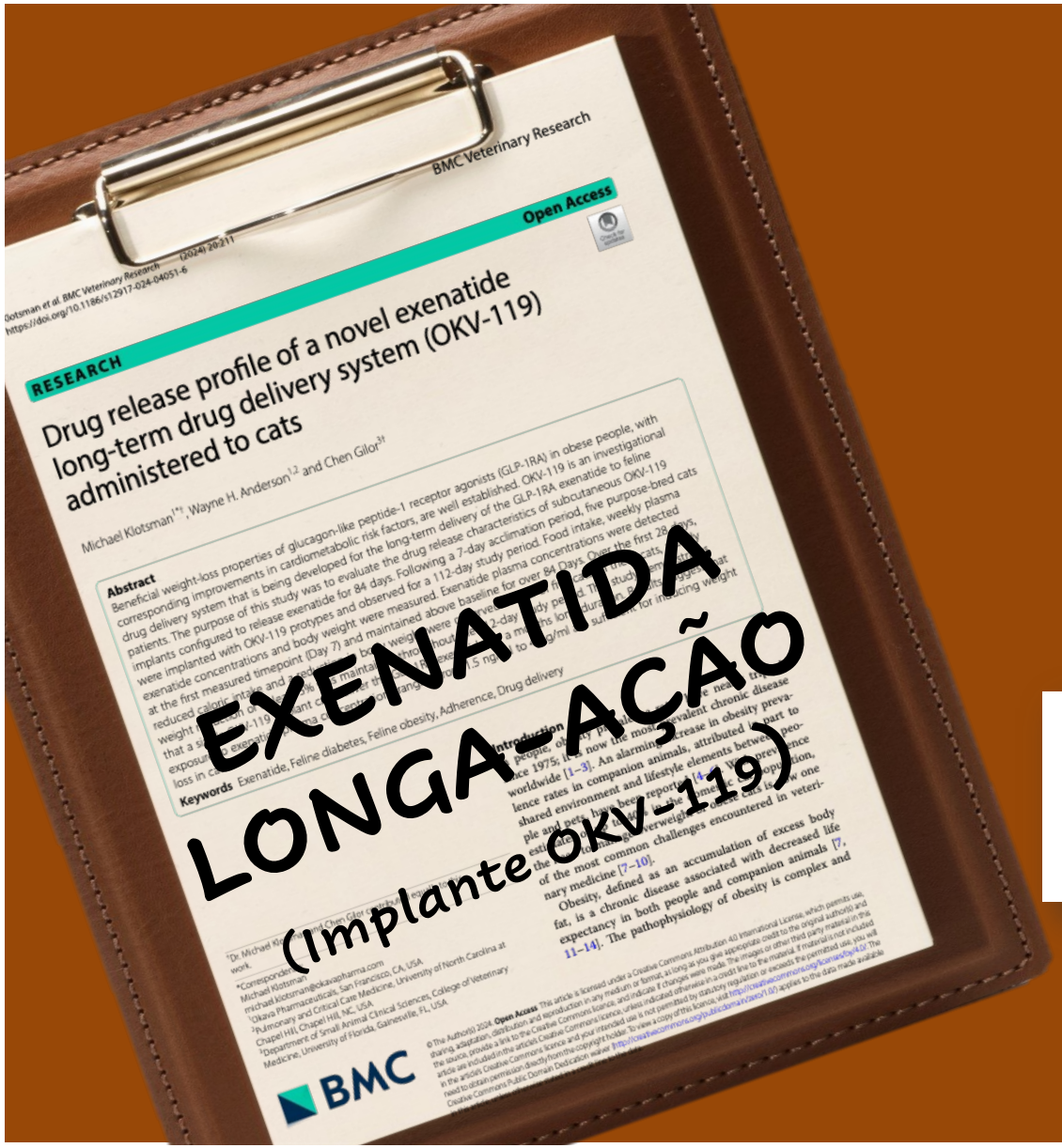
http://dx.doi.org/10.1016/j.domaniend.2014.12.003



EXENATIDA LONGA-AÇÃO

(Implante OKV-119)

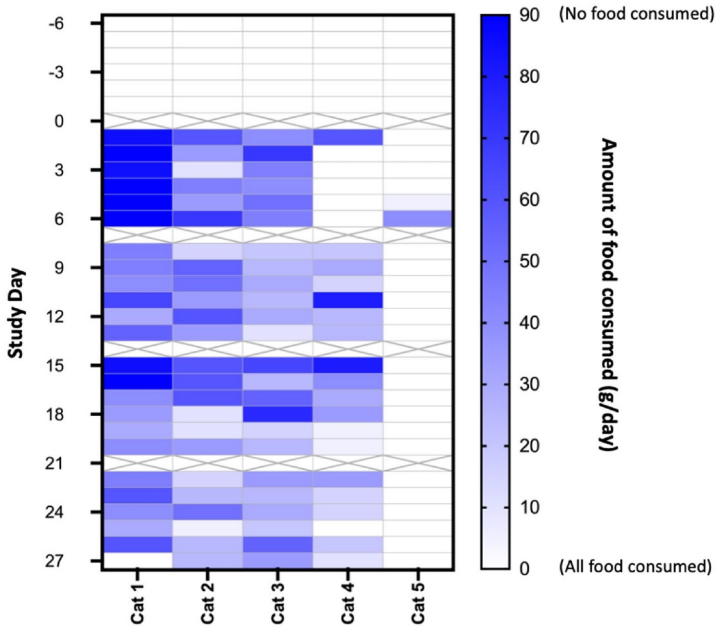


Table 1 Baseline characteristics of five purpose-bred cats prior to the insertion of the OKV-119 systems

Cat Number	Body Weight (Kg)			Percent Change in Weight	
	Day −7	Day 0	Day 112	Day −7 to Day 0	Day 0 to Day 112
1	5.13	5.14	4.51	0%	-12%
2	5.47	5.41	4.89	-1	-10%
3	5.58	5.61	5.01	1%	-11%
4	5.97	5.89	5.50	-1	-7%
5	7.65	7.38	7.82	-4%	6%

Única aplicação = 28 dias de perda de peso/ manutenção por 112 dias!

...Parece que não há muito interesse na espécie...

- DM tipo 1 (não há β céls remanescentes)
- Modelo experimental
- Efeito na perda de peso pouco avaliada...

PLOS ONE

RESEARCH ARTICLE

Exenatide Treatment Alone Improves β-Cell Function in a Canine Model of Pre-Diabetes

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OPEN ACCESS

Citation: Ionut V, Woolcott OO, Mkrtchyan HJ, Stefanovski D, Kabir M, Iyer MS, et al. (2016) Exenatide Treatment Alone Improves β-Cell Function in a Canine Model of Pre-Diabetes. PLoS ONE 11(7): e0158703. doi:10.1371/journal.pone.0158703

Editor: Marta Letizia Hribal, University of Catanzaro Magna Graecia, ITALY

Received: January 8, 2016

Accepted: May 18, 2016

Published: July 11, 2016

Data Availability Statement: All data necessary to replicate the study described are in the paper.

Funding: This work was supported by National Institutes of Health (DK29867 and DK27619 to RNB) (https://report.nih.gov/award/index.cfm). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: I receive funding from Amylin Pharmaceuticals. The drug used in this study was provided by Amylin Pharmaceuticals. This does not alter the authors' adherence to PLOS ONE

Abstract

Background

Exenatide's effects on glucose metabolism have been studied extensively in diabetes but not in pre-diabetes.

Objective

We examined the chronic effects of exenatide alone on glucose metabolism in pre-diabetic canines.

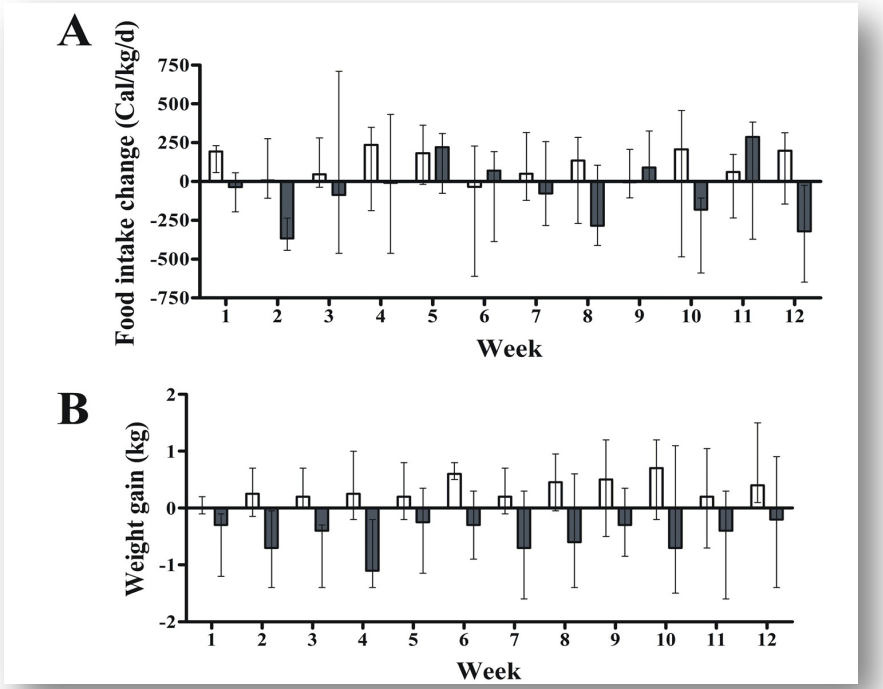
Design and Methods

After 10 weeks of high-fat diet (HFD), adult dogs received one injection of streptozotocin (STZ, 18.5 mg/kg). After induction of pre-diabetes, while maintained on HFD, animals were randomized to receive either exenatide (n = 7) or placebo (n = 7) for 12 weeks. β-Cell function was calculated from the intravenous glucose tolerance test (IVGTT, expressed as the acute insulin response, AIR_G), the oral glucose tolerance test (OGTT, insulinogenic index) and the graded-hyperglycemic clamp (clamp insulinogenic index). Whole-body insulin sensitivity was assessed by the IVGTT. At the end of the study, pancreatic islets were isolated to assess β-cell function.

Results

OGTT: STZ caused an increase in glycemia at 120 min by 22.0% (interquartile range, IQR, 18.31 [...] (P = 0.011). IVGTT: This protocol also showed a reduction in glucose tolerance by 36.8% (IQR, 36.9%) (P = 0.002). AIR_G decreased by 54.0% (IQR, 40.7%) (P = 0.010), leading to mild fasting hyperglycemia (P = 0.039). Exenatide, compared with placebo, decreased body weight (P<0.001) without altering food intake, fasting glycemia, insulinemia, glycated hemoglobin A1c, or glucose tolerance. Exenatide, compared with placebo, increased both OGTT- (P = 0.040) and clamp-based insulinogenic indexes (P = 0.016),

EXENATIDA



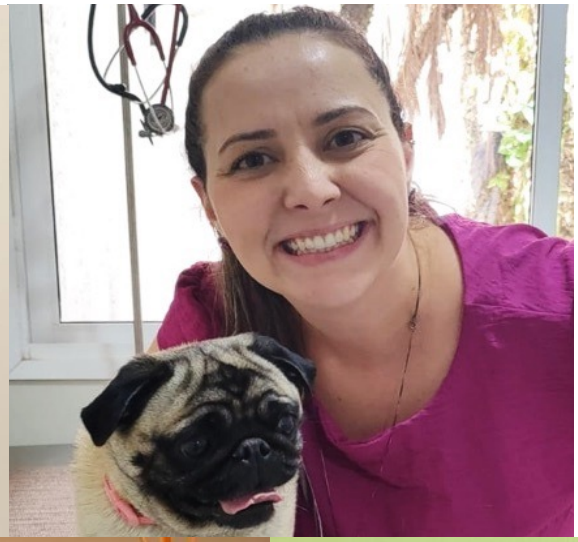
Placebo
Exenatide

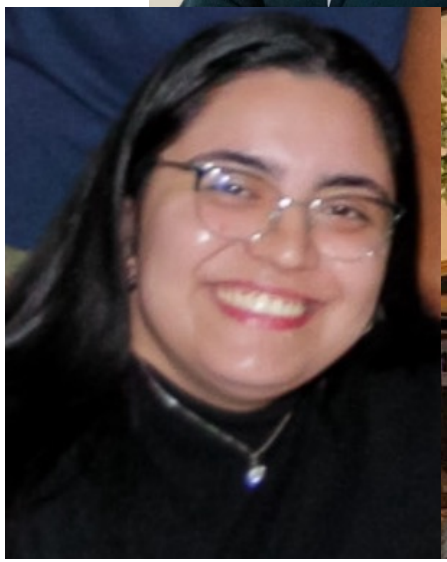
Redução do peso, sem redução na ingestão de alimento

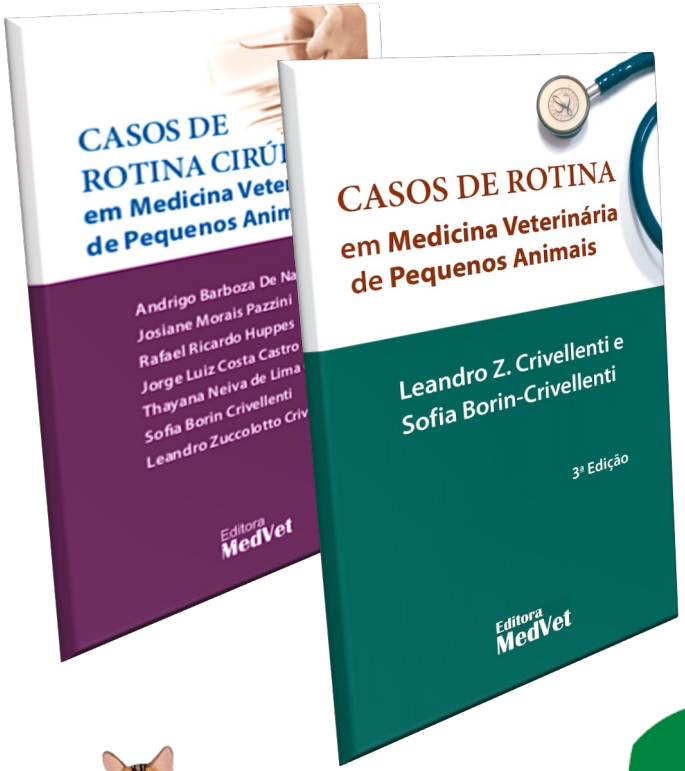
Melhora na função β cél (in vitro), mas não na tolerância a glicose ou sensibilidade à insulina

Minha Equipe 2025!

Endocrinologia
HV-UFU







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OBRIGADA!

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