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# New Approaches to Feline Diabetes Mellitus: Glucagon-like peptide-1 analogs.

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**Abstract**

**CLINICAL RELEVANCE:** Incretin-based therapies are revolutionizing the field of human diabetes mellitus (DM) by replacing insulin therapy with safer and more convenient long-acting drugs.

**MECHANISM OF ACTION:** Incretin hormones (glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic peptide [GIP]) are secreted from the intestinal tract in response to the presence of food in the intestinal lumen. GLP-1 delays gastric emptying and increases satiety. In the pancreas, GLP-1 augments insulin secretion and suppresses glucagon secretion during hyperglycemia in a glucose-dependent manner. It also protects beta cells from oxidative and toxic injury and promotes expansion of beta cell mass.

**ADVANTAGES:** Clinical data have revealed that GLP-1 analog drugs are as effective as insulin in improving glycemic control while reducing body weight in people suffering from type 2 DM. Furthermore, the incidence of hypoglycemia is low with these drugs because of their glucose-dependent mechanism of action. Another significant advantage of these drugs is their duration of action. While insulin injections are administered at least once daily, long-acting GLP-1 analogs have been developed as once-a-week injections and could potentially be administered even less frequently than that in diabetic cats.

**OUTLINE:** This article reviews the physiology of incretin hormones, and the pharmacology and use of GLP-1 analogs, with emphasis on recent research in cats. Further therapies that are based on incretin hormones, such as DPP-4 inhibitors, are also briefly discussed, as are some other treatment modalities that are currently under investigation.

1. incretin-secreting K cells and L cells in the gut sense the type and amount of digested nutrients and secrete incretins to other organs.
   a. K and L cells
      i. L cells in jejunum, ileum and colon (increases toward colon)
      ii. K cells in duodenum, jejunum, and feline ileum and feline colon (decreases toward colon)
   b. incretin effect: in the pancreas the main effect of incretin hormones is to increase sensitivity to glucose. oral glucose leads to greater insulin secretion than IV glucose
      i. mediated by glucagon like peptide 1 (GLP-1) from L cells and glucose-dependent insulinotropic peptide (GIP) from K cells
      ii. GLP-1 inhibits glucagon secretion, decreases appetite and decreases energy intake
         1. senses lipids, carbs and proteins

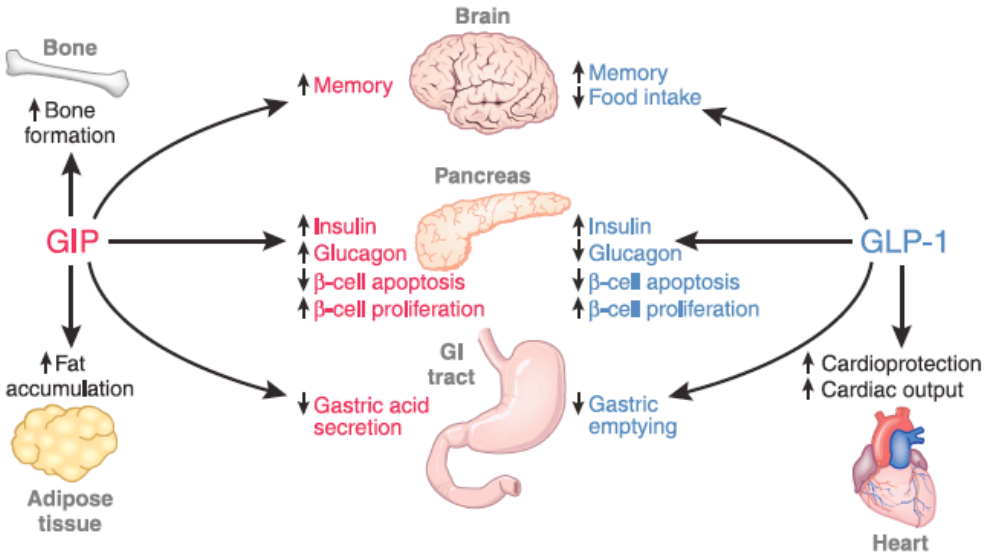


**Figure 2** | Pancreatic and exopancreatic function of glucose-dependent insulinotropic polypepide (GIP) and glucagon-like peptide (GLP)-1. GIP acts directly on the endocrine pancreas, bone, fat, gastrointestinal (GI) tract and brain. GLP-1 acts directly on the endocrine pancreas, gastrointestinal tract, heart and brain.

iii. GIP stimulates glucagon secretion (stimulates pancreatic alpha cells directly) and increases sensitivity of adipose tissue to insulin
1. senses fat and carbs (fat in cats)

c. GLP-1 and GIP are degraded by DPP-4 (dipeptidyl peptidase-4, CD26) and NEP-24.11 (neutral endopeptidase 24.11) in tissue and blood leading to short half life in blood of 1-2 minutes for GLP-1 and 5 minutes for GIP. Once degraded, cleared by kidneys.

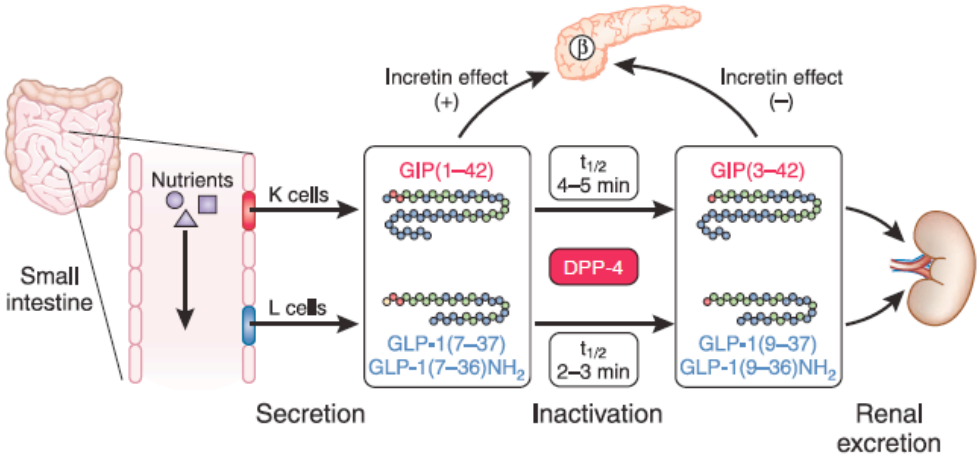


**Figure 3** | Secretion and metabolism of glucose-dependent insulinotropic polypepide (GIP) and glucagon-like peptide (GLP)-1. GIP is secreted from K cells of the upper intestine; GLP-1 is secreted from L cells of the lower intestine. Released GIP and GLP-1 rapidly undergoes proteolytic processing by dipeptidyl peptidase-4 (DPP-4), and is thereby inactivated and excreted from the kidney. The intact incretins, GIP(1–42), GLP-1(7–37), and GLP-1(7–36)amide, have insulinotropic effects on pancreatic β cells, whereas the DPP-4-processed incretins, GIP(3–42), GLP-1(9–37), and GLP-1(9–36)amide, have lost their insulinotropic effects.

2. People with diabetes
a. decreased incretin effect due to glucose intolerance, postprandial hyperglycemia
i. obesity also decreases incretin effect
b. GIP
i. normal to slightly decreased amount BUT decreased effect on pancreas
ii. NOT a good target for treating diabetes:
1. decreased sensitivity of pancreatic Beta cells to GIP in diabetes
2. increased glucagon secretion
3. increased sensitivity of adipose tissue to insulin
4. promotes obesity
c. GLP-1
i. decreased secretion but normal effect
ii. GOOD effects BUT short half life
1. DPP4 inhibitors prolong half life
2. GLP-1 analogs are long acting DPP4 resistant synthetic GLP-1 receptor agonists.


3. GLP-1 analogs
a. Exenatide (Byetta)
i. from the Gila monster (Heloderma suspectum)

ii. 1000 x the affinity for the GLP-1 receptor
iii. NOT a substrate for DPP4 or NEP
iv. Eliminated in kidneys
v. T 1/2 = 3-4 hours in people, 20 minutes in cats
vi. humans: improves 1st phase insulin response, pro-insulin/insulin ratio and ability of beta cells to respond to rapid changes in [BG]
vii. cats: causes weight loss but no effect on remission rates or insulin dose
    1. exenatide + glargine leads to weight loss (vs weight gain with glargine alone)

b. Exenatide ER
i. administered once/week SQ, effective concentration > 60 days
ii. injectable microspheres of exenatide and a biodegradable medical polymer
iii. humans: more effective than once daily insulin glargine for glycemic control. Also decreased risk of hypoglycemia, decreased weight, decreased fasting BG, fewer side effects.
iv. cats:
    1. healthy cats 0.13 mg/kg SIM dose improves glucose tolerance, increases insulin concentration, decreases glucagon concentration, decreased fasting BG (but no clinical signs of hypoglycemia), no side effects, NO decrease in weight
    2. diabetic cats: once weekly 0.2 mg/kg only found trend to increase remission rates and improved glycemic control.
        a. need pancreatic beta cells (pancreatitis, advanced disease with decreased pancreatic cell mass could affect treatment) to be present and a disease that can be reversed by GLP-1 (decreased response to glucose.)
        b. BUT cats can have insulin resistance.

c. Liraglutide (Victoza)
i. probably not as advantageous as exenatide ER
ii. GLP-1 analog: 2 amino acid substitution and a fatty acid acyl group that leads to non-covalent binding to albumin
iii. humans: better once weekly and once daily than BID exenatide BUT with more GI side effects (nausea, vomiting, diarrhea)
    1. fluctuation in drug levels may prevent down regulation
    2. hydrophobic properties may give better BBB penetration
    3. can be used to treat obesity in non diabetic patients
iv. cats: 0.6 mg/cat q24hrs
    1. T1/2 12 hours
    2. dramatic decreased weight, decreased appetite, increased glucose tolerance, increased insulin concentrations and decreased glucagon concentration
    3. no change in fasting glucose

d. Albiglutide and dulaglutide
i. not studied in cats
ii. albiglutide: 2 GLP-1 molecules linked to albumin
iii. dulaglutide: 2 GLP-1 molecules plus modified human IgG4 Fc fragments

iv. slow absorption from injection sites
v. protect GLP-1 component from degradation by DPP-4
vi. decreased renal clearance (prolonged T1/2)
vii. in humans superior to insulin, no weight gain, decreased risk of hypoglycemia. SIM can control glycemia but increased GI side effects.

e. DPP-4 inhibitors (sitagliptin, vildagliptin)
i. PO
ii. no association with hypoglycemia when used alone
iii. increased plasma GLP-1 and GIP concentrations post meal, increased glucose stimulated insulin secretion, decreased glucagon secretion, decreased proinsulin to insulin ratio (improved beta cell function)
iv. no nausea or vomiting BUT nasopharyngitis, UTI, headaches reported
v. increased weight

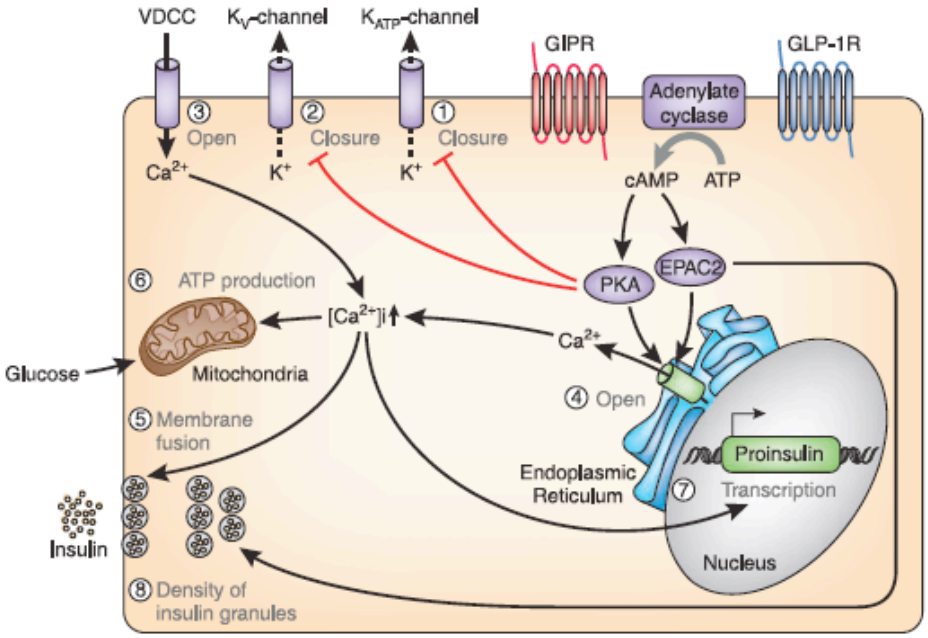


**Figure 5** | Molecular mechanisms underlying the insulinotropic effects of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP)-1. Binding of GIP and GLP-1 to their specific receptors, the GIP receptor (GIPR) and the GLP-1 receptor (GLP-1R) leads to activation of adenylate cyclase and subsequent elevation of intracellular cyclic adenosine monophosphate (cAMP) levels. Increased cAMP then activates protein kinase A (PKA) and exchange protein activated by cAMP2 (EPAC2)/cAMP-guanine nucleotide exchange factor (GEF)II. Activation of PKA promotes closure of $K_{ATP}$ channels and facilitates membrane depolarization. PKA also leads to inhibition of the delayed rectifying $K^+$ (Kv) channel, a negative regulator of insulin secretion in pancreatic β cells, resulting in prolongation of action potentials. Depolarization opens the voltage-gated $Ca^{2+}$ channels (VDCC), allowing an increase of intracellular $Ca^{2+}$ concentrations that mobilizes $Ca^{2+}$ from intracellular stores through PKA- and EPAC2-dependent mechanisms. The increased $Ca^{2+}$ concentrations eventually trigger fusion of insulin-containing granules with the plasma membrane and insulin secretion from the β cells. Increased $Ca^{2+}$ levels also promote transcription of the proinsulin gene, thereby increasing the insulin content of the β cell. Activation of EPAC2 has been shown to increase the density of insulin-containing granules near the plasma membrane to potentiate insulin secretion from the β cell. ATP, adenosine triphosphate.

QUESTIONS:

1. Which type of incretin- secreting cell (K or L) is more prominent in the duodenum?

2. GLP-1 is secreted by _____ cells and GIP is secreted by _____ cells.

3. In the pancreas the main effect of incretin hormones is to.....

4. Which GLP-1 analog has been studied in cats and shown to have trend toward increased remission rates and improved glycemic control at once weekly SQ administrations?

5. Binding of GIP and GLP-1 to thei receptors on the pancreatic beta cell leads to increased intracellular calcium which in turn causes _____ and _____.

QUESTIONS:

1. Which type of incretin- secreting cell (K or L) is more prominent in the duodenum?
   a. K
2. GLP-1 is secreted by _____ cells and GIP is secreted by _____ cells.
   a. GLP-1 L
   b. GIP K
3. In the pancreas the main effect of incretin hormones is to.....
   a. increase the sensitivity to glucose
4. Which GLP-1 analog has been studied in cats and shown to have trend toward increased remission rates and improved glycemic control at once weekly SQ administrations?
   a. Exenetide ER
5. Binding of GIP and GLP-1 to their receptors on the pancreatic beta cell leads to increased intracellular calcium which in turn causes _____ and _____.
   a. fusion of insulin containing granules with the plasma membrane
   b. promote transcription of the pro-insulin gene (increasing insulin content of the beta cell.)