New Incretin Hormonal Therapies in Humans Relevant to Diabetic Cats

Claudia E. Reusch, DVM, Dr Med Vet*, Isabelle Padrutt, DVM

KEYWORDS

• Cat • Feline • Diabetes mellitus • GLP-1 receptor agonist • DPP-4 inhibitor
• Exenatide • Sitagliptin

KEY POINTS

- In humans, glucagon-like peptide 1 (GLP-1) agonists and dipeptidylpeptidase-4 (DPP-4) inhibitors are novel therapeutic options for type 2 diabetes.
- Both classes enhance glucose-dependent insulin secretion, and reduce postprandial hyperglycemia and glucagon secretion.
- GLP-1 agonists additionally decelerate gastric emptying, induce satiety and weight loss, and may have beneficial effects on blood pressure.
- In cats, GLP-1 agonists and DPP-4 inhibitors have so far only been investigated in healthy individuals, resulting in a substantial increase in insulin secretion.
- Although results of clinical studies are not yet available and costs may currently be prohibitive, it is likely that incretin-based therapy opens up an important new area in feline diabetes.

Glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidylpeptidase-4 (DPP-4) inhibitors are relatively recently developed agents for the treatment of diabetes in humans. Because of the underlying mechanism, these agents are called incretin-based therapeutics.

In general terms, incretins are hormones released from the gastrointestinal tract during food intake, which potentiate insulin secretion from the β cells of the pancreas. As early as 1906 Moore and colleagues[1] demonstrated that the oral application of an extract of porcine duodenal mucous membrane was able to reduce glucosuria in patients with diabetes mellitus, in some of whom glucosuria even disappeared.[1] Thereafter, numerous investigators tried to unravel details on the gastrointestinal factors responsible for this phenomenon. The term "incretin" (derived from the Latin word *increscere*, to increase) was used for the first time by La Barre and Still[2] in

Vetsuisse Faculty, Department of Small Animals, Clinic for Small Animal Internal Medicine, Winterthurerstrasse 260, CH-8057 Zurich, Switzerland
* Corresponding author.
E-mail address: creusch@vetclinics.uzh.ch

Vet Clin Small Anim 43 (2013) 417–433
http://dx.doi.org/10.1016/j.cvsm.2012.11.003 **vetsmall.theclinics.com**
0195-5616/13/$ – see front matter

1930, although at that time they were not able to prove that incretins definitively exist. Progress on the incretin concept was made after radioimmunoassays for the measurement of insulin became available in 1960.[3] In the following years at least 3 research groups showed that glucose given orally induces a greater insulin response than glucose given intravenously, even if the blood-glucose concentrations were higher after intravenous injection.[4–6] The first incretin, called gastric inhibitory polypeptide (GIP), was isolated and sequenced in 1971,[7] followed by the characterization of the second incretin, GLP-1, in 1985.[8] It took approximately another 20 years until incretin-based therapeutics became available for clinical use. In 2005 the first GLP-1 receptor agonist (exenatide [Byetta]; Amylin Pharmaceuticals, San Diego, CA) and in 2007 the first DDP-4 inhibitor (sitagliptin [Januvia]; MSD, Whitehouse Station, NJ) were introduced as new classes of antidiabetic agents.

BIOSYNTHESIS, SECRETION, AND METABOLISM OF GLP-1 AND GIP

GLP-1 and GIP are encoded by different genes in mammalian genomes. The proglucagon gene encodes GLP-1, as well as the nonincretin peptide hormones glucagon and GLP-2. Gene distribution includes L cells in the intestinal tract with the highest density in the ileum and colon, α cells of the endocrine pancreas, and some neurons of the hypothalamus and the brain stem.[9–12] Proglucagon processing differs in the different tissues, which is largely due to the differential expression of prohormone convertase (PC) enzymes. Whereas α cells express PC2 and generate glucagon, L cells and brain express PC1/3 and produce GLP-1 and GLP-2 (**Fig. 1**).[13] Plasma levels of GLP-1 are low in the fasted state and increase within minutes after food intake, triggered by local luminal nutrient-sensing pathways and, possibly, additional endocrine and neural factors.[13,14] Various forms of GLP-1 exist. To date, GLP-1(7–37) and GLP-1(7–36) NH_2 are known to be the biologically active forms, in humans the latter being most abundant.[15] GLP-1 acts through binding to a G-protein–coupled receptor (GLP-1-1R), which is expressed in α cells and β cells of the pancreas, kidney, lung, heart, gastrointestinal tract, and various regions of the nervous system.[16] The half-life of biologically active GLP-1 is very short (less than 2 minutes). It is degraded by the enzyme

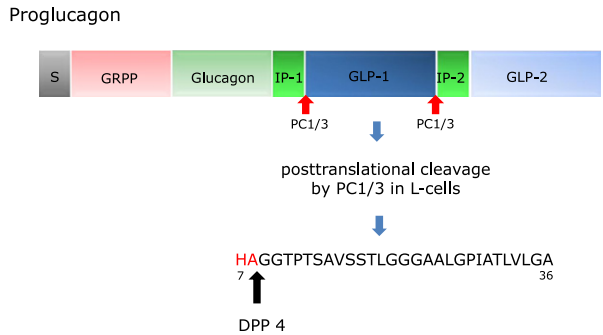

Fig. 1. Proglucagon and posttranslational cleavage of GLP-1 by prohormone convertase (PC) 1/3. GLP-1(7–36) is a major form of biologically active GLP-1 in humans. GRPP, glicentin-related pancreatic polypeptide; IP-1, IP-2, intervening peptides 1 and 2; S, signal peptide. (*Data from* Baggio LL, Drucker DJ. Islet amyloid polypeptide/GLP1/exendin. In: DeFronzo RA, Ferrannini E, Keen H, et al, editors. International textbook of diabetes mellitus. Chichester (UK): John Wiley & Sons Ltd; 2004. p. 191–223; and Kim W, Egan JM. The role of incretins in glucose homeostasis and diabetes treatment. Pharmacol Rev 2008;60:470–512.)