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Incretin therapy in feline diabetes mellitus – A review of the current state of research

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ABSTRACT

Incretin hormones potentiate the glucose-induced insulin secretion following enteral nutrient intake. The best characterised incretin hormones are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) which are produced in and secreted from the gut in response to nutrient ingestion. The property of incretins to enhance endogenous insulin secretion only at elevated blood glucose levels makes them interesting therapeutics for type 2 diabetes mellitus with a better safety profile than exogenous insulin. While incretin therapeutics (especially GLP-1 agonists, and more recently also GLP-1 / GIP dual agonists and other drugs that influence the incretin metabolism (e.g., dipeptidyl peptidase-4 (DPP-4) inhibitors)) are already widely used treatment options for human type 2 diabetes, these drugs are not yet approved for the therapy of feline diabetes mellitus. This review provides an introduction to incretins and feline diabetes mellitus in general and summarises the current study situation on incretins as therapeutics for feline diabetes mellitus to assess their possible future potential in feline medicine. Studies to date on the use of GLP-1 receptor agonists (GLP-1RA) in healthy cats largely confirm their insulinotropic effect known from other species. In diabetic cats, GLP-1RAs appear to significantly reduce glycaemic variability (GV, an indicator for the quality of glycaemic control), which is important for the management of the disease and prevention of long-term complications. However, for widespread use in feline diabetes mellitus, further studies are required that include larger numbers of diabetic cats, and that consider and test a possible need for dose adjustments to overweight and diabetic cats. Also evaluation of the outcome of GLP-1RA monotherapy will be neceessary.

1. Introduction to Incretins

The term incretin is assigned to humoral or neural factors produced in the gut which potentiate glucose-induced insulin secretion following enteral nutrient uptake. The two acknowledged incretin peptides are represented by glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) (for review: [1]). The definition of the incretin effect describes the potentiated insulin secretion in response to oral glucose uptake compared with intravenous glucose administration leading to similar changes in circulating blood glucose levels. The insulinotropic effect of incretins occurs only at elevated plasma glucose concentrations, but not during hypoglycaemia, which makes them interesting pharmacological targets to treat hyperglycaemia while avoiding hypoglycaemic episodes (for review: [2]).

1.1. GLP-1

GLP-1 is a tissue-specific post-translational product of the pre-proglucagon gene (Gcg) which is expressed in α cells of the endocrine pancreas, in L cells of the intestine, and in neurons of the caudal brainstem and hypothalamus [3,4]. Processing of GLP-1 gives rise to different forms of GLP-1: GLP-1 (1-37) and two shorter forms, GLP-1 (7-36amide) and GLP-1 (7-37) [5]. Relative ratios of these forms vary between species [6]. The peptides with the highest biological efficacy are the two truncated forms which are equally potent in stimulating insulin secretion [7], whereas GLP-1(1-37) has significantly lower insulinotropic properties [8]. GLP-1 secretion after food intake occurs biphasically with an early phase after 10–15 min and a prolonged second phase after 30–60 min [9]. Native GLP-1 undergoes rapid degradation within 1-1.5 min [10,11]. Proteolytic cleavage is accomplished by the enzyme dipeptidyl peptidase-4 (DPP-4) at the penultimate

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alanine residue of GLP-1, producing the biologically inactive forms GLP-1(9-36amide) and GLP-1(9-37) [12,13]. GLP-1 and its metabolites are excreted through the kidneys [14].

The GLP-1 receptor (GLP-1R) is a member of the guanine nucleotide-binding protein (G-protein) coupled receptors of the class B family. The GLP-1R is expressed in various organs. In humans, expression of the receptor mRNA has been detected in the endocrine pancreas, brain, kidneys, stomach, heart and lungs. No detection was provided early studies in important organs for glucose turnover such as liver, skeletal muscle and adipose tissue [15]. However, more recent studies have not only demonstrated that the GLP-1R is present in human adipose tissue, but also that the amount of the GLP-1R gene and its protein expression in visceral adipose tissue may correlate positively with the extent of obesity and insulin resistance [16]. Several studies on GLP-1R expression in pancreatic islets have been performed, yet the results are partially conflicting; part of the conflicting results may be due to the notorious lack of specificity of commercial GLP-1R antibodies for immunohistochemistry (for review: [17]). While it has been uniformly demonstrated that the GLP-1R is expressed on 80-95 % of β cells, it is more controversial within α and δ cells [17]. GLP-1Rs have also been detected in vagal afferents and ganglion nodosum neurons (VAN-GLP1Rs) [18] which convey a neuronal component of the incretin action of GLP-1.

1.1.1. *Effects of GLP-1*

1.1.1.1. Effects on pancreatic beta cells. The insulinotropic effect of GLP-1 consists of stimulating insulin secretion and mobilising further insulin granules via cAMP-dependent mechanisms. Converging pathways of glucose metabolism and GLP-1 receptor signalling allow the insulinotropic effect to manifest itself only at elevated blood glucose levels. GLP-1 also exerts stimulatory effects on β cell proliferation and inhibits cell apoptosis. Effects of GLP-1 on β cell proliferation seem to be dependent on various factors. Whereas short term administration of Exendin-4 (Ex-4; natural GLP-1 agonist from the saliva of the Gila monster, see chapter 4.1) indeed stimulates β cell proliferation, prolonged administration results in sensitisation of peripheral organs to insulin rather than increased β cell proliferation. In addition, treatment dose and nutrition composition also seem to exert an influence on these effects. Acute treatment (three successive days) with high doses of Ex-4 (24 nmol/kg/day) significantly stimulated β cell proliferation, while there was no effect with low doses (300 pmol/kg/day). High dose treatment suppressed bodyweight gain in mice fed standard diet and high fat diet, respectively, with the effect being more robust in mice fed high fat diet [19]. Furthermore, GLP-1-induced β cell proliferation seems to be age-dependent, with Ex-4 stimulating cell growth in juveniles more than in adults [20].

1.1.1.2. Effects on glucagon secretion. GLP-1 suppresses glucagon secretion from α cells of the endocrine pancreas [21]. The inhibitory effect of GLP-1 on glucagon secretion has therapeutic relevance since glucagon suppression fails in type 1 & 2 diabetes, thus contributing to postprandial hyperglycaemia [22,23]. Hyperglucagonemia is an important characteristic in feline diabetes as well [24], making GLP-1 an interesting therapeutic agent in this regard. The inhibitory effect of GLP-1 on glucagon secretion is lost in hypoglycaemia [25], suggesting that the counter-regulatory mechanisms against hypoglycaemia are preserved during treatment with GLP-1, which is an important safety aspect.

1.1.1.3. Effects on gastric motility. GLP-1 decelerates gastric emptying in healthy and type 2 diabetic humans [26,27], and this effect has also been demonstrated in other species like mice [28], rats [29], dogs [30] and pigs [31]. In addition to stimulating insulin secretion and inhibiting glucagon secretion, this effect most likely also contributes to the blood glucose lowering effect of GLP-1 and attenuates postprandial glycaemic excursions. Due to the protracted transfer of food from the stomach to the small intestine, glucose resulting from food digestion is therefore absorbed more slowly [27,32]. The decelerating effect on gastric emptying is subject to rapid tachyphylaxis: especially with the administration of liraglutide, a long-acting GLP-1R agonist, to overweight humans and healthy rats. Here, the inhibitory effect on gastric emptying decreases significantly after 14-16 weeks of treatment, even though the effect is still significant compared to placebos.

1.1.1.4. Effect on food intake and body weight. GLP-1 has been shown to reduce food intake in several species including mice [33], rats [34], chicken [35], pigs [36] and primates [37,38]. Since the effect is maintained even in obesity [39] and type 2 diabetes [40], GLP-1 and its DPP-4 resistant agonists have become pharmaceutically interesting agents for treating these diseases. The reduction in food intake and body weight mediated by GLP-1 and GLP-1RA is believed to be controlled by both peripheral (paracrine mechanisms) and central signalling pathways (for review: [41]).

1.1.1.5. Further effects. GLP-1 exerts additional effects on other organ systems. For example, GLP-1 has been shown to have beneficial effects on myocardial performance when used after cardiac injury or to exert a neuroprotective effect in models of Parkinson's disease (for review: [2,42]). However, these effects will not be discussed in detail in this review.

1.2. *GIP*

Upon its discovery in the 1970s, this peptide was termed gastric inhibitory polypeptide for its ability to inhibit gastric acid secretion in dogs [43]. Later on, it became apparent that this inhibition of gastric acid secretion in humans was more relevant at pharmacological doses, whereas GIP exerts the effect of an incretin hormone at physiological levels [44]. With retention of the acronym GIP, the peptide was therefore renamed to glucose-dependent insulinotropic polypeptide. GIP is synthesised in enteroendocrine K cells, which are mainly located in the duodenum and to a lesser extent in the jejunum [45,46]. While GIP is synthesised predominantly in the proximal gastrointestinal tract and GLP-1 mainly in the distal gastrointestinal tract, it has been shown that there is an overlapping zone in the mid-small intestine where GLP-1 and GIP are co-localised in the same cells (it has not been specified whether these cells represent L cells or K cells) [47,48]. In cats, however, K cells appear to be approximately equally abundant in all segments of the small intestine and can even be found, albeit in smaller numbers, in the caecum and colon [49]. GIP is secreted in response to nutrient uptake, with secretion and increase in plasma GIP mainly reflecting the rate of nutrient delivery from the stomach to the duodenum, therefore is closely related to the rate of gastric emptying [50]. Analogous to GLP-1, native GIP is also degraded by DPP-4 [51], but its half-life ($t_{½}$) seems to be about five times longer than that of endogenous GLP-1. There seems to be a species difference in whether fat or glucose is the more potent stimulator of GIP secretion. In cats, it has been shown that administration of fat or amino acids leads to an increase in plasma GIP, whereby the increase is larger after fat ingestion than after protein ingestion. In contrast, glucose administration via an oesophageal tube does not apparently lead to an increase in plasma GIP [52]. In general, the glucose-induced incretin effect appears to be weaker in cats than in other mammals, possibly reflecting the fact that the cat is by nature a carnivore [53].

Like the GLP-1R, the GIP receptor (GIPR) is also a G-protein coupled receptor [54]. Expression of mRNA of the GIPR has been detected in various organs such as the pancreas, intestine, adipose tissue, heart, pituitary gland, inner layers of the adrenal cortex and several regions of the CNS such as the cerebral cortex, hippocampus and olfactory bulb. Like the GLP-1R, the GIPR could not be detected in the liver [55]. It has

been shown that in the endocrine pancreas the GIPR is expressed on α, β, and δ cells [56].

1.2.1. Effects of GIP

1.2.1.1. Effects in the endocrine pancreas. Similar to GLP-1, GIP also influences insulin gene transcription and protein synthesis, and GIP has a growth factor-like effect on β cells. In contrast to GLP-1, exogenous administration of a supraphysiological amount of GIP to diabetic subjects during a mixed meal resulted in an early postprandial increase in glucagon levels [57]. Hence, GIP was shown to have an insulinotropic effect early postprandially, however, it may also lead to increases in plasma glucagon and late postprandially to an increase in plasma glucose and a decrease in plasma GLP-1. Based on these findings, there have been questions about the usefulness of a GIP agonist for the treatment of diabetes mellitus [57].

1.2.1.2. Paradox concerning the effects of GIPR agonism and antagonism. For a long time, GIP has been neglected as a therapeutic agent for type 2 diabetes, as studies have shown that GIPR agonism in diabetic individuals does not enhance insulin secretion. In addition, GIP stimulates glucagon secretion, potentially leading to further deterioration of hyperglycaemia, and potentially acts as an obesity-promoting hormone. However, this view has dramatically changed. It has been shown that the insulinotropic effect is not completely lost in diabetes. Furthermore, research and clinical studies have provided ample evidence for the use of multireceptor agonists, in particular dual GLP-1 and GIP agonists [58]. Furthermore, the opinion that glucagon exerts solely a glycaemia increasing effect has been reconsidered. Glucagon appears to be an important component of α cell to β cell communication. In the prandial state where blood glucose is elevated, glucagon has been shown to stimulate insulin secretion. It therefore seems possible that glucagon in a prandial condition has a beneficial effect in that its overall effect is a blood glucose-lowering effect on β cells via GLP-1Rs [59,60]. Glucagon has also been shown to increase insulin sensitivity [61]. These results suggest that GIP may play an important role in postprandial glucose homeostasis by enhancing insulin secretion via stimulation of glucagon secretion [62].

The strongest inconsistencies relate to the contribution of GIP agonism or antagonism to weight development. There are studies that hold both agonism and antagonism responsible for weight loss. Chronic agonism is postulated to lead to the same result as antagonism. It has been shown that G-protein coupled receptors respond to repeated or continuous stimulation with desensitisation [63]. This was also demonstrated for the GIPR on adipocytes in culture, where stimulation of the GIPR led to internalisation of the receptor and only slow recycling back to the plasma membrane, which significantly reduced the number of available GIPRs [64]. Therefore, if chronic GIPR agonism eventually leads to a situation like the one present in GIPR knockout mice, this would explain why chronic agonism and antagonism lead to the same result in terms of weight development [65]. In other words, the GLP-1 and GIP receptor dual agonists are successfully used in the treatment of diabetes and obesity, and it is clear that both the GLP-1R and the GIPR are required for this effect. However, it is yet unclear whether agonism or antagonism at the GIPR is responsible for the beneficial effects of these dual agonists; in other words, long-acting GIP agonists may potentially have beneficial metabolic effects by providing a functional blockade of receptor action, rather than its activation.

2. Feline diabetes mellitus

Diabetes mellitus (DM) is characterised by persistent hyperglycaemia as a result of deficient insulin secretion and/or reduced tissue response to insulin. Approximately 80 % of diabetic cats are thought to suffer from a type of DM similar to human type 2 diabetes (T2D) [66]. High body weight, which presumably implies obesity, is a significant risk factor because obesity has been shown to lead to insulin resistance, which represents one of the hallmarks of T2D. It is well established that glucose tolerance and insulin response are altered in obese cats compared to lean cats [67]. Subsequently, obese cats were demonstrated to be insulin resistant and that weight gain leads to a significant reduction in insulin sensitivity [68].

The goals of diabetes therapy are to control clinical signs, to normalise the metabolic situation, e.g., by restoring normoglycaemia, and to avoid long-term consequences of the dysregulated metabolism. The first line medication for cats is currently twice-daily subcutaneous administration of long-acting insulin preparations (e.g., glargine).

The use of incretin analogues, especially GLP-1 receptor agonists (GLP-1RA), in the treatment of T2D in humans is well established [69]. Some GLP-1 analogues have also been studied in feline diabetic patients, but there are still many unknowns about incretin therapy in cats, and these drugs have not yet become standard therapy. GLP-1 stimulates insulin secretion as well as its production, and GLP-1′s effect is abolished when plasma glucose levels decline, therefore it is typically not associated with the risk of a marked hypoglycaemia as it is the case with insulin or sulfonylurea therapy (for review: [70]). Given its short half-life, the pharmacological value of native GLP-1 is highly limited, however, improved GLP-1 analogues have been developed using biochemical modifications leading to, e.g., DPP-4 resistance (for review: [42]).

3. Study results on incretin therapy in cats

3.1. Introduction – GLP-1 based or GLP-1 metabolism-altering therapeutics approved for the treatment of human diabetes

Incretin therapeutics tested in cats include GLP-1RA on the one hand and DPP-4 inhibitors, which delay the degradation of endogenous incretins, on the other hand.

GLP-1RA with resistance to rapid degradation by DPP-4 have been developed. Common side effects of GLP-1RA in humans include gastrointestinal symptoms such as nausea, vomiting and diarrhoea. These side effects seem to be dose-dependent and transient and usually disappear after several days of therapy; for this reason, a typical treatment paradigm in people generally includes a gradual increase of the administered dose over several weeks. Without concomitant insulin therapy, the risk for hypoglycaemic episodes seems to be rather low [71].

Exenatide (Ex; e.g., Byetta®) was the first GLP-1RA on the market; it is a synthetic GLP-1 analogue corresponding to exendin-4, which was originally extracted from the saliva of the Gila monster [72]. GLP-1 and exenatide share only 53 % sequence homology, but Ex is highly potent at the GLP-1R and possesses a 1000 fold higher affinity for the GLP-1R; further, Ex is resistant to rapid degradation by DPP-4 [73]. Exenatide is used as therapy for human diabetes mellitus in a twice-daily regimen via subcutaneous application. It appears to be equally effective as insulin glargine for therapy of T2D, yet leads to fewer undesirable side effects [74].

Exenatide extended-release (ExER; e.g., Bydureon®) is a long-acting formulation of exenatide and allows once-weekly subcutaneous injection in humans for the treatment of T2D [73]. It appears to be more effective for glycaemic control in humans than insulin glargine once daily and exenatide and it has been shown to result in lower fasting glucose in humans, yet still in the euglycaemic range [73,75].

Liraglutide (Lg; e.g., Victoza®) is a synthetic GLP-1 analogue (97 % sequence homology with native GLP-1) with two substituted amino acids and a fatty acid acyl group that allows reversible non-covalent binding to albumin, resulting in a prolonged circulating half-life [76]. In humans, liraglutide subcutaneously once a day is more effective for blood glycaemic control than exenatide twice daily, and leads to less side effects, e.g., nausea and vomiting are less frequent and occur for shorter periods of time [77] .

In human medicine, there are several other GLP-1 analogues for the treatment of T2D, some of which are effective for even longer periods of time [73]. Semaglutide, Dulaglutide and Albiglutide allow once-weekly subcutaneous injections or, in the case of Semaglutide, once-daily oral administration due to their enhanced binding to albumin or the Fc fragment of immunoglobulins in diabetic humans [78–80]. This administration regimen would simplify the management of the feline patient. However, these drugs have until now never been tested in cats and should therefore be considered in future studies. Currently, there is no clear evidence of differences in the mode of action of the different GLP-1 analogues, the main difference being in their pharmacokinetics; in other words, there is no clear recommendation which analogue may work best in cats; clearly, most data available so far are with liraglutide.

DPP-4 inhibitors (DPP4-I) are designed to increase the plasma concentration of both endogenous incretins, thereby enhancing the incretin actions by inhibiting the rapid degradation of native GLP-1 and GIP [71]. In humans, DPP4-I applied orally have been shown to be less effective than GLP-1 analogues for glycaemic control [81,82] and, unlike the latter, which promote weight loss, tend to be weight neutral [83]. However, DPP4-I are less likely to cause gastrointestinal side effects than GLP-1 analogues [84].

3.2. DPP-4 Inhibitors in cats

The administration of DPP4-I in cats has been investigated in four studies [52,85–87], with testing its use only in healthy and lean cats, but not in overweight or diabetic cats. In Furrer et al., the experimental DPP4-I NVP-DPP728 was administered subcutaneously (SC) and intravenously (IV), respectively, while in the other three studies, the DPP4-I sitagliptin was applied perorally.

No serious adverse drug reactions were observed in any of these studies, but no statement can be made from these trials about possible side effects with chronic administration.

A brief summary of the study results can be obtained from Table 1. Validated measurement methods for cats were used in all studies. All studies were crossover studies with placebo control (Furrer et al.) or control without treatment. None of the studies were fully blinded which may have influenced the interpretation.

3.2.1. Effects of DPP4-I on plasma glucose

In the four above-mentioned studies, DPP4-I did not show any impact on plasma glucose, neither on glucose profiles in intravenous glucose tolerance tests (IVGTT) nor following meal response tests (MRT). This was not unexpected because healthy cats may compensate short term influences on GLP-1 signalling. It was only in the study by Mori et al. [87] where sitagliptin tended to reduce the median glucose area under the curve (Glc-AUC) compared to the control group after feeding Hill's urinary care, 5g/kg maltose and 4.2mg/cat sitagliptin po, however, these results did not reach statistical significance ($p < 0.10$).

3.2.2. Effects of DPP4-I on plasma insulin

Effects on plasma insulin showed different results in the studies. In the study by Furrer et al. [85], insulin AUC was significantly higher (dose-dependent 20-25 %) during the first 15 min of the IVGTT compared to placebo treatment, but unaffected in the MRT. The authors suggested as a possible explanation the absence of postprandial hyperglycaemia in the MRT, whereas plasma glucose initially rose sharply in the IVGTT. However, total insulin secretion measured over 3 h was not significantly different between treatment and control.

When glucose was administered via an oesophageal tube [52], plasma insulin after two hours was significantly higher in the group that had received sitagliptin two hours before glucose administration than in the control group. However, insulin AUC was without significant difference over the entire time followed (8 h after sitagliptin or placebo). Feeding a standard dry diet two hours after administration of sitagliptin or placebo did not result in any differences in plasma insulin between the groups at any time point.

In the study by Padrutt et al. [86], sitagliptin led to increased meal-dependent insulin secretion in the MRT. In this study, sitagliptin was compared with exenatide and exenatide extended-release and it was found that the GLP-1RA resulted in a greater increase in insulin secretion than the DPP4-I.

In Mori et al. [87], however, there was a significant reduction in insulin AUC after simultaneous administration of food, 5g/kg maltose and sitagliptin compared to the control group. As a possible reason, the authors cite the application to non-diabetic cats, which can self-regulate their insulin secretion, with the result that sitagliptin could not induce increased insulin secretion. However, if this explanation were correct, similar results should have been observed in the other studies.

3.2.3. Effects of DPP4-I on plasma glucagon

Plasma glucagon was measured in only two out of four studies.

The results of Furrer et al. [85] indicate that plasma glucagon in the IVGTT was reduced by the administration of glucose, i.e. also in the placebo group. This reduction was enhanced by the administration of NVP-DPP728 over the first 15 min of glucose infusion. In the MRT, glucagon output was significantly reduced by the DPP4-I in the first hour after food intake. Over the total course of five hours, no significant

Table 1
Studies on DPP-4 Inhibitors in cats.

Authors	Medication & Dose	Cat population	Treatment duration (acute vs. chronic)	Major outcome	Adverse drug reactions
Furrer et al., 2010	NVP-DPP728 0.5mg/kg IV, 1 mg/kg SC, 2.5mg/kg SC	Healthy n=6 for each dosage	Acute – 3 treatments at 4-week intervals	• Significant ↓ glucagon output • Short-term ↑ insulin secretion after IV administration of glucose, but not after feeding	None
Nishii et al., 2014	Sitagliptin 25mg/cat, 50mg/cat	Healthy n=6 for glucose administration, n=5 for feeding	Acute – maximum 2 treatments at intervals of 1-2 weeks	• Significant ↑ endogenous GLP-1 levels • Short-term ↑ insulin secretion after administration of glucose solution via an oesophageal tube, but not after feeding.	None
Padrutt et al., 2015	Sitagliptin 1-10mg/kg PO	Healthy n=9	acute- 4 administration cycles over 5 consecutive days, with an interval of 2 weeks in between	• ↑ meal-dependent insulin secretion, but less ↑ when compared with GLP-1 analogues • Significant ↓ glucagon output	Occasional mild episodes of diarrhoea, self-limiting, general condition and food & water intake not negatively affected
Mori et al., 2016	Sitagliptin 4.2mg/cat	Healthy n=5	Acute – 2 administrations at 1-3-week intervals	• Significant ↓ insulin AUC after administration of sitagliptin + feed + 5g/kg maltose • Significant ↑ mean postprandial GLP-1 AUC, significant ↓ GIP AUC with sitagliptin	None

difference could be detected between groups, but according to the authors, there was a trend towards reduced glucagon secretion in the treatment group.

In the study by Padrutt et al. [86], a significant reduction of plasma glucagon in the MRT was shown after the administration of sitagliptin for five consecutive days compared to control groups. In a direct comparison with Ex, sitagliptin was shown to reduce glucagon secretion at all dosages tested (1-10mg/kg), whereas Ex only reduced glucagon secretion at the highest dose tested (2μg/kg).

3.2.4. Effects of DPP4-I on endogenous incretins

Endogenous GLP-1 and GIP were measured in only two out of four studies.

In the study by Nishii et al. [52], the GLP-1 AUC was larger with sitagliptin than with placebo. Similarly, in the study by Mori et al. [87], the mean postprandial GLP-1 AUC was significantly increased by sitagliptin. Due to the mechanism of action of DPP-4 inhibitors, these results are in line with expectations.

In contrast, the results for endogenous GIP were mixed. No changes in the concentration of endogenous GIP were observed after glucose administration through an oesophageal tube, neither in the sitagliptin treated nor in the placebo group. After feeding, endogenous GIP increased in both the placebo and treatment group, however without significant difference between the two groups [52]. This result is consistent with the observation that oral glucose does not lead to an increase in endogenous GIP in cats, but this elevation occurs only through the uptake of amino acids and lipids (see 2.2.1). In another study [87], co-administration of food, maltose and sitagliptin led to a significant reduction in GIP compared to the control group. Studies in humans have shown similar results, but with GLP-1 levels being also reduced by sitagliptin. This outcome was attributed to negative feedback on L and K cells, which is thought to be caused by increased circulating GLP-1 and GIP levels due to DPP-4 inhibition. Interestingly, however, only GIP levels were reduced in cats in the aforementioned study.

These two studies in cats indicate that DPP-4 inhibitors in cats may only inhibit the degradation of endogenous GLP-1, but not of GIP. Therefore, the increased insulin and decreased glucagon secretion may only be attributed to the increased GLP-1 levels.

3.2.5. Conclusion on DPP4-I in cats

DPP-4 inhibitors led to an enhancement of insulin secretion after a single administration only for a short term and only with intravenous or enteral administration of glucose solution, but not in response to feeding. Consecutive administration over five days, however, appeared to reliably result in significantly enhanced insulin secretion also after a meal. In addition, DPP-4 inhibitors appear to have a significant glucagonostatic effect, which is a desirable feature given that hyperglucagonemia typically occurs in feline diabetes mellitus.

The studies conducted so far have demonstrated that short-term administration of DPP-4 inhibitors in healthy cats is safe and results in only rare and mild adverse drug reactions. However, the effects of chronic administration of DPP-4 inhibitors in cats still need to be evaluated. A lowering effect on blood glucose has never been demonstrated with DPP-4 inhibitors, however, this parameter represents the most important blood value for clinicians to monitor the success of the therapy. As plasma insulin, glucagon and incretins are hardly ever measured in the clinic, the effects of DPP4-I on these parameters are probably only of particular importance for scientists, but not for clinicians. Due to these circumstances, the benefit of using DPP4-I seems questionable, as the effects on insulin, glucagon and endogenous GLP-1 were not shown to be transferred to blood glucose levels. Whether this is also the case in diabetic cats should be investigated in further studies. The effect and tolerability of DPP4-I over a longer period of time should also be examined. DPP4-I could possibly also be considered as a supportive or supplementary diabetes therapy, but this would also need to be investigated.

Although a direct comparison of DPP4-I and GLP-1RA did not show obvious advantages of DPP4-I [86], the authors of this review recognise a potential use of DPP4-I over GLP-1RA: in cases where the feline patient does not tolerate regular injections or the owner is unable to administer them, as it is necessary with GLP-1RA, the DDP-4 inhibitor may be advantageous as it can be administered perorally. However, this advantage may disappear with the introduction of oral GLP-1RA (like semaglutide) in veterinary medicine.

3.3. GLP-1RA in cats

The administration of GLP-1RA in cats was so far investigated in ten studies. Seven studies were conducted in healthy cats [86,88–93], three of which included overweight but otherwise healthy cats [89–91]. Three studies were conducted in diabetic cats [94–96]; it is important to note that in all these studies, cats received insulin in addition to GLP-1RA or placebo. The study by Krämer et al. [96] retrospectively evaluated additional parameters from the study by Riederer et al. [94] and therefore, in contrast to the other studies, does not represent a prospective clinical trial.

Drugs applied were mainly Exenatide (5 studies) and Exenatide extended-release (4 studies), Liraglutide was tested in only one study. Validated measurement methods for cats were used in all studies. The studies by Gilor et al., Padrutt et al., Hall et al., and Rudinsky et al. were not blinded and used untreated or pre-intervention animals as controls, but no placebo control. The two prospective studies on diabetic cats used placebo controls, with the study by Scuderi et al. being double-blinded and randomised and the study by Riederer et al. being single-blinded (owner does not know, veterinarian knows treatment). All studies, except that of Riederer et al., had fewer than 10 study animals. In addition, varying doses of different GLP-1RAs were used in the individual studies. This heterogenous design of the studies makes comparisons difficult and interpretation of the results needs to be done with caution.

A brief summary of the study results can be obtained from Table 2.

3.3.1. Effects of GLP-1RA on plasma glucose

3.3.1.1. Healthy cats. In most studies in healthy cats in which a hyperglycaemic clamp (HGC) or an IVGTT were performed before and after treatment, no differences in baseline glucose were detected between treatment and control groups [88,89,91]; only in the study by Rudinsky et al. [90], a significantly lowered, but still euglycaemic baseline glucose was found 21 days after a single treatment of healthy cats with ExER. Interestingly, there was no difference in baseline plasma insulin and glucagon measurements between treated and untreated animals in this study, raising the possibility that blood glucose was influenced by factors other than insulin and glucagon. In the same study [90], the amount of glucose infused during the HGC to maintain hyperglycaemia was significantly higher after ExER treatment than in controls, therefore ExER appeared to have a glucose-lowering effect, perhaps by improving insulin sensitivity without a measurable effect on circulating insulin levels. In contrast, no significant difference was found in the HGCs by Gilor et al. [88] and Hall et al. [89]. It is noteworthy that the studies where no difference was found, cats received either Ex or liraglutide; only Rudinsky et al. [90] applied the longer acting ExER. These results in healthy cats would therefore be consistent with findings in diabetic people, according to which ExER, but not Ex, showed a lowering effect on fasting glucose [97]. In another study in healthy cats using ExER [86], however, no influence of a single ExER administration or ExER administration over 5 weeks on Glc-AUC after an MRT was found.

In all studies in healthy cats, almost no clinical hypoglycaemic episodes occurred with GLP-1RA treatment. It was only in one study [91] where an overweight but otherwise healthy cat showed a symptomatic

Table 2
Studies on GLP-1RA in cats.

Authors	Medication & Dose	Cat population	Treatment duration (acute vs. chronic)	Major outcome	Adverse drug reactions
Gilor et al., 2011	Exenatide 5μg/cat SC	Healthy n=9	Acute – one single treatment	• ↑ insulin AUC with Ex during HGC, but no translation into blood glucose-lowering effect	• asymptomatic hypoglycaemia (3.0mmol/L) in 1 cat
Hall et al., 2015	Liraglutide 0.6mg/cat SC	Healthy, 5/8 overweight n=8, 1 withdrawn	Acute – treatment on days 1 and 8-14 SID	• ↑ mean insulin concentration with Lg during HGC, trend towards blood glucose-lowering effect (p=0.087) • ↓ glucagon concentration with Lg during HGC • significant weight loss in all cats	• self-limiting vomiting / diarrhoea in 7/8 cats • complete anorexia in 1 cat, was excluded from the study • weight loss >0.5-2 % of BW per week
Rudinsky et al., 2015	Exenatide ER 0.13mg/kg SC	Healthy, 3/6 overweight n=6	Acute – one single treatment	• ↑ mean insulin concentration with ExER during HGC with translation into blood glucose-lowering effect • ↓ mean glucagon concentration with ExER during HGC	• occasional asymptomatic hypoglycaemia (<2.8mmol/L)
Padrutt et al., 2015	Exenatide 0.2, 0.5, 1, 2 μg/kg SC	Healthy n=3 for each dosage	Acute – 5 days BID	• ↑ insulin secretion with Ex during MRT • ↑ glucagon secretion during MRT with 0.2-1 μg/kg, ↓ with 2 μg/kg	• 66 % of cats with self-limiting vomiting / diarrhoea
	Exenatide ER 40, 100, 200, 400 μg/kg SC	Healthy n=3 for each dosage	Acute – one single treatment	• ↑ insulin secretion with ExER during MRT • ↓ glucagon secretion during MRT	
	Exenatide ER 100, 200 μg/kg SC	Healthy n=3 for each dosage	Chronic – once weekly for 5 weeks	• ↓ insulin secretion with 100 μg/kg over the whole time measured, but ↑ between 0 and 120 min of MRT. ↑ insulin secretion with 200 μg/kg • ↑ glucagon secretion during MRT (with 100 μg/kg > with 200 μg/kg)	None
Hoelmkjaer et al., 2016	Exenatide 0.5μg/kg SC for 4 weeks, then 1μg/kg SC for 8 weeks	overweight (BCS ≥7/9), otherwise healthy n=6	Chronic – BID for 12 weeks	• trend towards ↓ fasting glucagon with Ex (p=0.25) • trend towards ↑ relative weight loss with Ex (p=0.1)	• occasional self-limiting vomiting • 1/6 cats with symptomatic hypoglycaemia (3.5mmol/L)
Riederer et al., 2016	Exenatide ER 200μg/kg SC (+ insulin in all cats)	Diabetic n=30	Chronic – once weekly for 16 weeks	• no TDD of administered insulin dose between groups • ↑ median body weight with placebo, +/- stable with ExER • remission in 6/15 cats with ExER, good metabolic control in 8/9 non-remission cats with ExER, no difference between groups	• self-limiting (exc. 1 cat) GI side effects, no difference in frequency between groups • 1/15 cats with ExER with symptomatic hypoglycaemia (<3.6mmol/L), no difference in frequency between groups
Scuderi et al., 2018	Exenatide 1μg/kg SC (+ insulin in all cats)	diabetic, BCS ≥ 5/9 at beginning of study n=8	Chronic – BID for 6 weeks	• ↑ mean reduction in TDD of administered insulin dose with Ex • ↑ mean weight loss with Ex • remission in 2/8 cats with Ex, remission in 0/8 cats with placebo • trend towards ↓ fasting & 1h postprandial glucagon with Ex (p=0.08 and p=0.15 respectively)	• anorexia in 2/8 cats with Ex, required temporary decrease in Ex dose • symptomatic hypoglycaemia in 1/8 cats, required temporary decrease in Ex dose
Krämer et al., 2020 (retrospective evaluation of Riederer et al., 2016)	Exenatide ER 200μg/kg SC (+ insulin in all cats)	Diabetic n=30	Chronic – once weekly for 16 weeks	• ↓ GV in cats with ExER from week 6 until end of study compared to week 1 • ↓ GV in all remission-cats (Ex and placebo) in week 6 vs. week 1, no difference in all non-remission cats	• self-limiting (exc. 1 cat) GI side effects, no difference in frequency between groups • 1/15 cats with ExER with symptomatic hypoglycaemia (<3.6mmol/L), no difference in frequency between groups
Schneider et al., 2020	Exenatide / [Gln^{28}] Exenatide 10 μg/kg IV	Healthy n=6 for each drug	Acute – one single treatment	• bioavailability of Ex = 52 %, of [Gln^{28}]Ex = 93 % • no difference in insulinotropic effect between medications	None
	Hydrogel-microsphere [Gln^{28}]Ex 19.3 mg/cat SC, 4.8 mg/cat SC	Healthy n=6 for each dosage	One single treatment – acts as depot	• calculation that 0.23mg/kg once per month should achieve required effective dose for antidiabetic effects in rodents and humans • weight loss with low dose until day 21, with high dose until day 28, then return to normal weight	• 5 episodes of vomiting with low dose, 7 episodes of vomiting / diarrhoea in high dose, in each case in the first month
	Exenatide / [Gln^{28}] Exenatide 1 or 5μg/kg SC	Healthy n=6 for each dosage, n=6 for vehicle (Na-Acetat)	Acute – one single treatment	• dose-dependent ↑ insulin AUC with 1 and 5 μg/kg of Ex and [Gln^{28}]Ex, respectively • ↓mean Glc-AUC with 5 μg/kg of Ex and [Gln^{28}]Ex, respectively	None
Klotsman et al., 2021	OKV-119 implant in 2 cadavers	Cadaver n=2		• implant palpable	

(*continued on next page*)

Table 2 (*continued*)

Authors	Medication & Dose	Cat population	Treatment duration (acute vs. chronic)	Major outcome	Adverse drug reactions
				• implant detectable in X-ray, difficult in ultrasound (similar echogenicity to surrounding tissue) • dorsal lumbar and lateral crus are considered the best implantation sites	
	Safety and tolerability: OKV-119 implant, delivers supratherapeutic doses of Ex	Healthy n=4	One single implantation	• Ex plasma concentration >2ng/ml during 28 days in all cats • plasma concentration of Ex correlates with weight loss	• none over 62 days, no licking or scratching at implant site, no inflammation
	Proof-of-concept: OKV-119 with 3 different release rates group 1 fastest rate, group 3 slowest rate	Healthy n=15	One single implantation	• measurable concentrations in all groups for up to 35 days • plasma Ex >2ng/ml in after 7 days groups 1 and 2, 0.76ng/ml in group 3 (2/6 cats below lower limit of detection) • plasma concentration of Ex correlates with weight loss, weight loss in all 3 groups	• none over 42 days, no licking or scratching at implant site, no inflammation

SID = once daily, BID = twice daily

hypoglycaemic episode after three to four weeks of continuous twice-daily exenatide treatment, characterised by fatigue, head bobbing and a plasma glucose of 3.5mmol/L. However, this cat quickly recovered with feeding and no further such episodes occurred. In another study [88], one cat developed hypoglycaemia (3.0 mmol/L) one hour after a single Ex dose but was treated with glucose IV before progressing to clinical symptoms, so in this case it is not possible to assess whether symptoms might have developed. In the other studies in healthy cats no or only asymptomatic episodes of hypoglycaemia were reported [86,89,90].

3.3.1.2. Diabetic cats. In a study with 30 diabetic cats [94,96], of which 15 were treated with ExER for 16 weeks or, in the case of remission, beyond 4 weeks after the end of insulin therapy, a lower mean blood glucose resulted in the ExER group at weeks 6 and 10 after the start of therapy compared to the placebo group. Glycaemic variability (GV), i.e., fluctuations in blood glucose over time as an indicator for the quality of glycaemic control [98,99], was significantly lower in ExER treated cats from week 6 on until the end of the study at 16 weeks compared to week 1. In contrast, there were no significant differences in GV from week 1 to any other time point in the control group [96]. In the study by Scuderi et al. [95], in which diabetic cats were treated with Ex twice daily, no difference in fasting glucose, plasma glucose one hour postprandially or mean plasma glucose over the course of treatment could be detected. However, the latter study included only 8 animals and the study duration was limited to 6 weeks; hence, that study may either have been underpowered, or the negative results may have been due to the use of short-acting Ex.

Symptomatic hypoglycaemic episodes were slightly more common in the studies in diabetic cats (2 out of 30 cats in Riederer et al. and Krämer et al., and 1 of 8 cats in Scuderi et al.) than in healthy cats, however, such episodes occurred equally frequent in cats treated with GLP-1RA and insulin as in cats treated with placebo and insulin [94–96]. This is consistent with a study in diabetic people which found that the frequency of hypoglycaemia episodes was equal in insulin-treated individuals receiving either exenatide or placebo [100].

Taken together across all studies on GLP-1RA, the incidence of clinical hypoglycaemia was very low. A study in diabetic people (T2D) in the years 2016 and 2017 found that 25 % of patients hospitalised for poorly controlled diabetes experienced at least one confirmed or severe hypoglycaemic episode on insulin therapy during hospitalisation, and almost 60 % of patients in the first 6 months after discharge [101]. Therefore, monotherapy or adjunctive therapy with GLP-1RA could provide a significant benefit in this regard.

3.3.2. Effects of GLP-1RA on plasma insulin

3.3.2.1. Healthy cats. In all studies in healthy lean cats, insulin concentrations during HGC and MRT were found to be higher after short-term (maximum of 5 consecutive days) administration of GLP-1RA than in the control groups [86,88–90] which confirms the known GLP-1 biology in other species. Furthermore, three studies [88–90] reported that baseline insulin concentrations before HGC did not differ between treatment and control groups, suggesting that GLP-1RA stimulates insulin secretion only in response to appropriate stimulation, such as, e.g., eating or hyperglycaemia. In the study by Gilor et al. [88], Ex injection was followed by an initial rise in insulin (prior to the start of glucose infusion), however, plasma insulin levels dropped back to baseline, even though serum Ex levels continued to rise. This initial insulin rise was associated with a tendency towards decreasing plasma glucose ($p = 0.06$) but led to hypoglycaemia (3.0 mmol/L) in only one of 9 cats. This cat was treated with glucose IV while still being asymptomatic.

Padrutt et al. [86] investigated the administration of ExER over 5 weeks. At a dose of 100 µg/kg once a week, insulin AUC in a MRT was reduced over the total observation time of 5 h compared to the control group; at a dose of 200 µg/kg once a week, a 15 % increase in insulin AUC was observed. However, at both doses, a significant dose-dependent increase in plasma insulin was observed in the ExER group during the first 2 h of the MRT. As a possible reason, the authors suggested that over the total of 5 h, no significant difference may have been observed between the groups possibly due to a rapid insulin drop after the initial postprandial insulin peak in the ExER group, which may have led to a rapid normalisation of blood glucose levels. Hence, this post-peak drop may have been a part of counter-regulatory mechanism against hypoglycaemia. Similar hypoglycaemic counter-regulatory mechanisms have already been shown in dogs [102] and humans [103] receiving GLP-1RA. In this study in cats [86], no overt hypoglycaemia was detected, possibly due to the mentioned counter-regulation.

In the study by Hoelmkjaer et al. [91], all cats included were overweight (Body Condition Score (BCS) of at least 7/9) but otherwise healthy. No change in plasma insulin levels in the IVGTT occurred after 12 weeks of Ex administration compared to the controls. The authors suggested several possible reasons for this result. A very heterogeneous insulin baseline concentration and a considerable individual variation in

the intensity of the insulin response to Ex were observed. Substantial heterogeneity would perhaps mask the detection of a significant difference and may be due to the fact of not all overweight cats had become insulin resistant [68]. Furthermore, the effect of Ex on insulin secretion may be less pronounced in obese cats. In some obese humans with normal glucose tolerance, the presence of GLP-1 resistance, i.e., the reduced ability of pancreatic β cells to respond to incretins, has been documented [104]. The same condition may occur in obese cats and may explain the results in the aforementioned study.

3.3.2.2. Diabetic cats. The concentration of endogenous insulin was measured in only one study in diabetic cats receiving GLP-1RA [95]. No significant difference in baseline and one hour postprandial insulin concentration was detected. According to the authors, the reason for this result could possibly relate to the fact that the insulin concentration was only determined at a single time point after feeding. Furthermore, the BCS of the study cats was at least 5/9 with a median BCS of 6/9, i.e., mildly overweight. It seems possible that the previously discussed GLP-1 resistance might also have contributed to this finding and indicate that overweight cats may require a higher GLP-1RA dose.

3.3.3. Effects of GLP-1RA on plasma glucagon

3.3.3.1. . Healthy cats. Study results on plasma glucagon under GLP-1RA treatment were rather inconsistent. In two studies [89,90] with HGC being performed, the mean glucagon concentration during the HGC was significantly decreased after a single administration of GLP-1RAs (ExER and Lg, respectively). In a study in overweight cats [91], fasting glucagon was found to be slightly reduced in cats treated with Ex, however, these changes were not significant compared to controls. In another study [86], acute administration of Ex at doses up to 1 μg/kg resulted in increased glucagon AUC in the MRT, while 2 μg/kg reduced glucagon AUC. Acute administration of ExER at doses of 40-400 μg/kg always resulted in a reduction of glucagon AUC. Administration of ExER once a week for 5 weeks resulted in increasing glucagon AUC in the MRT (by 253 % at 100 μg/kg, by 3 % at 200 μg/kg). The authors argue that the increased glucagon secretion during acute administration of Ex may have represented a counter-regulatory mechanism against hypoglycaemia, which is supposed to be maintained even with pharmacological doses of GLP-1 [105]. The reason for the increased glucagon secretion during prolonged administration remained unclear and in the authors' opinion does rather not reflect a counter-regulation, since in addition to the increased glucagon secretion, insulin secretion was simultaneously reduced at the ExER dose of 100 μg/kg [86].

3.3.3.2. Diabetic cats. Plasma glucagon was measured in only one study in diabetic cats receiving GLP-1RA, with no significant difference in fasting or one-hour postprandial glucagon between treatment and control groups [95]. Nevertheless, the p-values between the groups were approaching the significance level ($p = 0.08$ for fasting glucagon, $p = 0.15$ for 1h postprandial), therefore the authors considered to identify a possible potential for lowering endogenous glucagon production by Ex, which would be beneficial in diabetic cats.

3.3.4. Effects of GLP-1RA on body weight

3.3.4.1. Healthy cats. Several studies have shown weight loss in cats treated with GLP-1RA, i.e. 9 % weight loss after 14 days of treatment with once daily Lg on days 1 and 8-14 and dose-dependent 5 to over 10 % weight loss after administration of a long-acting formulation of [Gln^{28}]Ex (see 4.3.8) [89,92,93]. Two studies showed this weight loss to be directly correlated with plasma Ex concentration [92,93]. In one study [91], a trend towards greater relative weight loss was observed in the Ex-treated group (5.1 % with Ex vs. 3.2 % with placebo, $p = 0.1$), but this did not reach the significance level. Only in one study in healthy cats [86], body weight remained stable in all cats, and in none of the studies in healthy cats did GLP-1RA cause significant weight gain.

3.3.4.2. Diabetic cats. In a study in which diabetic cats received Ex or placebo for six weeks in addition to insulin [95], 6/8 cats lost weight (median -0.72kg) under Ex, while 2/8 cats gained minimal weight (median +0.1kg). In contrast, 5/8 cats in the placebo group gained weight (median +0.48kg). The average weight loss was significantly higher in the treatment group than in the control group.

In contrast, in the study by Riederer et al. [94] there was an increase in median body weight with both ExER and placebo, although this increase reached significance only in the placebo group ($p_{ExER} = 0.08$). In the ExER group, 8/15 cats gained weight (median +18.4 %), 6/15 lost weight (median -3.3 %) and 1/15 cats remained stable. Meanwhile, in the placebo group, 13/15 cats gained weight (median + 21.6 %) and only 2/15 lost weight (median -5.9 %). It should be added that the remission rate and the achievement of a good metabolic control (criteria include clinical signs, fructosamine level, plasma glucose, treatment with exogenous insulin) in the treatment group were not associated with changes in body weight. Of the eight cats who gained weight under ExER, three went into remission and additional four cats obtained good metabolic control.

3.3.5. Effects of GLP-1RA on administered insulin dose in diabetic cats

In a study in which diabetic cats were treated with ExER in addition to insulin [94], the median insulin dose administered did not differ between groups, neither when remission periods were included in the calculation nor when excluded. The insulin dose was adjusted during the course of the study based on clinical signs, plasma glucose curves and serum fructosamine levels.

Different results were provided by the study of Scuderi et al. [95] where diabetic cats were treated with short-acting Ex twice daily in addition to insulin. In the treatment group, the total daily dose (TDD) of exogenously administered insulin has been reduced in 4/8 cats over the course of the 6 weeks studied (median of all cats -0.1 U/kg/d), while in the control group, the TDD has been reduced in only 1/8 cats (median of all cats +0.1U/kg/d). In the treatment group, the mean change in the TDD was significantly lower than in the control group.

3.3.6. Effects of GLP-1RA on clinical outcome in diabetic cats

In the study by Riederer et al. [94], 6/15 cats under ExER and 3/15 from the control group went into remission (defined as no clinical signs (polyuria, polydipsia, polyphagia) present, fructosamine levels <350 μmol/L, plasma glucose 4.0-9.0 mmol/L, without administration of exogenous insulin for at least 4 weeks). However, the difference between the groups was not significant ($p=0.43$). Of the remaining cats, 8/9 on ExER and 7/12 on placebo achieved good metabolic control, i.e., no clinical signs present, fructosamine levels 350-450 μmol/L, plasma glucose 4.4-15.0 mmol/L, with administration of exogenous insulin. When all cats were combined, 14/15 achieved remission or good metabolic control under ExER and only 10/15 from the control group, although the difference between the groups was not significant ($p=0.17$). According to the authors, a higher number of study animals may have been needed to reach statistical significance assuming the same percentages for remission and good metabolic control. In general, the remission rate in this study was considered as rather low; the authors saw possible reasons in the duration of the study (here only 4 months), in the exclusion criteria for the study animals (animals with corticosteroid therapy before diagnosis were excluded here, but remission rate may be higher if the animals had previously received corticosteroids [106]). Additionally, Riederer et al. used a tighter definition of remission than other studies (in this case euglycaemia without exogenous insulin for 4 weeks versus 2 weeks in another study [107]), which resulted in 2 cats from the treatment group in this study not achieving the classification of remission, although they would have met the criteria for remission in

the other study.

Krämer et al. [96] retrospectively evaluated parameters from the study by Riederer et al. [94] and related them to glycaemic variability (GV). All cats that went into remission (ExER and control) had a lower GV after 6 weeks of treatment than the cats that did not go into remission. Cats in the treatment group that went into remission had a significantly lower GV at week 6 compared to week 1; in the ExER cats that did not go into remission, the GV took until week 10 to be significantly lower than at week 1. Cats in the treatment group had significantly lower GV from week 6 on until the end of the study at 16 weeks compared to week 1, whereas there were no significant differences in control animals compared to week 1 at any time point. Given the assumption that remission in cats is often due to recovery from glucotoxicity and the fact that high GV seems to represent a risk factor for complications such as e.g., hypoglycaemia, diabetic neuropathy and retinopathy [99,108–110], ExER may be a valuable therapeutic agent.

In the study by Scuderi et al [95], 2/8 cats went into remission under Ex, and no cat went into remission under placebo treatment. However, the authors stated that it was difficult to make a representative statement because the study animals were diagnosed and started treatment at different time points before the beginning of the study. Another study had indicated that the probability of remission decreases if the diabetes has been treated for more than 6 months [111]. The two cats that went into remission in the study by Scuderi et al. had been diagnosed 1 and 2 months before the start of the study, respectively. According to the authors, it seemed possible that the severity of the feline DM and the number of remaining functional β cells were too different between the study cats, therefore these factors may also have influenced the remission rate. In addition, the low power in this study was also a limiting factor in providing a conclusion about the influence of Ex on remission rates.

3.3.7. Adverse drug reactions to GLP-1RA

The most common side effects included gastrointestinal (GI) complaints such as vomiting and diarrhoea. These types of side effects are also common in humans receiving GLP-1RA [112,113]. In some studies on GLP-1RA in cats, these side effects did not occur at all [88,90]; whereas in other studies, they were observed at least temporarily in a large number of cats [86,89], i.e., 66-88 % of the animals. In most studies, these side effects were self-limiting and general well-being was not affected. Furthermore, the frequency of side effects usually seemed to decrease after a few days of consecutive therapy [89]. In one study [89], a cat had to be excluded due to persistent anorexia; thereafter, it started eating again 48 h after discontinuation of Lg. In another study [94], one cat had to be discontinued from ExER due to recurrent vomiting. In the study by Scuderi et al. [95], two cats showed anorexia and weakness, but recovered after a temporary reduction of the Ex dose over 2 days and were able to finish the study at the normal dose without further side effects.

Interestingly, in a study of diabetic cats [94], GI side effects were equally common in the treatment group as in the placebo group, with p-values for differences between the groups for vomiting and diarrhoea of 0.7 and 0.6, respectively. Only the p-value for decreased appetite approached the significance level with p=0.06. Based on these results, it could be concluded that these side effects were not associated with ExER in this case. In another study in which ExER was used [86], GI side effects were only observed with a single acute application, but not with application over 5 weeks. These observations are consistent with the observation in humans where ExER is reported to cause side effects such as nausea less frequently than Ex [114].

Weight loss was not considered as an adverse event per se, however, it should not exceed 0.5-2 % of body weight per week [115]. In one study [89], the mean body weight at baseline was 5.5kg and after 2 weeks of treatment (Lg on days 1 and 8-14), it was 5.07kg. Thus, the weight loss in this study was well above the recommendation for safe weight loss in cats [115] and the authors suggested that it might be appropriate to reduce the dose and/or frequency of administration [89].

The side effect hypoglycaemia has already been discussed under 4.3.1, with incidence of hypoglycaemia being rather low and often asymptomatic. No further adverse reactions have been reported in the studies on GLP-1RA in cats.

3.3.8. New formulations of GLP-1RA

Data from human medicine have shown that poor medication adherence is rather common in diabetics and the desire to reduce the number of injections is relatively frequent [116,117]. No comparable studies exist in cats; however, the issue is thought to be similar or even exacerbated in owners who need to administer injectable antidiabetics to cats [93]. Compared to twice-daily insulin injections, GLP-1RAs such as liraglutide and Exenatide extended-release provide an improvement as they probably only need to be administered once daily or once weekly, respectively.

With the aim of further reducing the number of injections, interesting opportunities have been provided with the development of microsphere-[Gln^{28}]Ex conjugates and the delivery system OKV-119 [92,93].

Schneider et al. [92] have achieved a prolongation of the drug half-life in healthy cats by covalently attaching the medication to a long-lived carrier (here Tetra-PEG (poly ethylene glycol) hydrogel microspheres with pore size 40um) via a linker. The linker is not susceptible to endogenous enzymes [118]. Via β elimination by the linker, the drug is slowly released after injection. The rate of delivery is determined by the properties of a modulator, which is bonded to a carbon atom with an acidic C-H bond and withdraws electrons. The hydrogel-exenatide conjugate achieved a half-life of 7 days when injected into rats [119], however, providing no pharmacokinetic advantage compared to ExER. Upon observation of Ex being deamidated at position Asn^{28} and thereby achieving an *in vitro* and *in vivo* half-life of approximately 2 weeks, a microsphere conjugate with [Gln^{28}]Ex (MS-[Gln^{28}]Ex) was developed [120]. This conjugate was tested in 2 different doses of [Gln^{28}]Ex (low dose 4.8mg/cat, high dose 19.3mg/cat). Using assumptions from a previous study [120], a simulated dose of 0.23 mg/kg [Gln^{28}]Ex injected once monthly in cats should be sufficient to achieve a steady-state at which the minimum concentration needed for an antidiabetic effect in rodents and humans (approximately 70 pmol/L) was maintained [92]. Furthermore, it was demonstrated that the insulinotropic effects of [Gln^{28}]Ex in healthy cats did not differ from Ex. Similar dose-related GI side effects such as vomiting and diarrhoea were observed as with other GLP-1RAs. The high dose reached a plasma drug level of about 500 pM, which is approximately 10 times higher than the level considered therapeutic in rodents and humans (70pM). Therefore, the side effects seemed to be relatively mild and acceptable [92].

Although the authors see this compound as promising, they nevertheless cite concerns about a potential general problem with GLP-1RA. A sufficiently high number of functional β cells is necessary for GLP-1RA to exert the desired effect, however, in cats the disease is usually diagnosed relatively late and not at pre-diabetic stages as in humans. In these later stages of diabetes, too many β cells may already have been destroyed. Therefore, a clinical trial with MS-[Gln^{28}]Ex in diabetic cats should be conducted, in which the cats showing an adequate response to native GLP-1RA in an IVGTT should be pre-selected [92]. However, no such study has been completed to date.

Klotsman et al. [93] have tested another approach in cats. OKV-119, a drug delivery system, i.e. an implant in cats, consists of a titanium reservoir containing the drug and a porous membrane made of titanium oxide with nanotubes [121]. The rate of release of the drug can be adjusted by the number of nanotubes and the diameter of the pores. In a study in cadavers, dorsal lumbar and lateral crus were identified as the most suitable implantation sites and the implant was demonstrated to be easily found in the body via X-ray [93]. In another part of the same study, 4 healthy cats each received an implant under short anaesthesia delivering supratherapeutic doses of Ex. All cats maintained a plasma

drug concentration of >2ng/ml (which corresponds to approximately 470 pmol/L) for 28 days. The implant was well tolerated and did not cause inflammation. All cats lost weight over the first 3 weeks after implantation, and weight loss correlated with the weekly plasma concentration of Ex. In the following part of the same study, 15 cats were divided into 3 groups and received an implant with different drug delivery rates depending on the group. A weight loss correlating with the plasma concentration of Ex was reproduced. Plasma concentrations of the drug were already >2ng/ml on average after 7 days in the two groups with the higher delivery rates, while they were still significantly lower in the group with the slowest rate (0.76 ng/ml, ~ 180pmol/L). In all groups, measurable concentrations could be detected for up to 35 days. The authors suggested that the delivery system may be designed to allow continuous administration of Ex over a period of several months after a single implantation, which could significantly facilitate the treatment regime. However, this system still needs to be evaluated in diabetic cats.

3.3.9. Conclusion on GLP-1RA in cats

GLP-1RA have been shown to lead to a meal-dependent or hyperglycaemia-induced increase in insulin secretion in healthy and lean cats. In overweight cats, however, this effect could not be observed at the same dosage as in lean cats, possibly due to GLP-1 resistance, which also occurs in some overweight humans [104]. The concentration of endogenous insulin was measured in diabetic cats treated with GLP-1RA and exogenous insulin in only one study, which renders a representative statement rather difficult. In this study [95], no insulinotropic effect of GLP-1RA could be demonstrated either. Potential reasons for this are also GLP-1 resistance due to obesity, furthermore it seems possible that the diabetes was too advanced at the time of diagnosis and start of treatment and too many β cells have already been destroyed to respond adequately to the stimulus by GLP-1RA. In light of these observations, it would be reasonable to test whether higher doses produce an insulinotropic effect in overweight and diabetic cats. In addition, with regard to the chanced of remission, it would be interesting to test whether the remission rate is increased by GLP-1RA if only cats with relatively recent onset of DM (e.g., < ½ year) are included.

However, the increased insulin secretion often did not seem to lead to a reduction in fasting glucose, this effect could only be observed with ExER in healthy cats [90]. In diabetic cats, ExER led to lower mean plasma glucose at certain time points, but not over the entire treatment period [96]. It is possible that a higher dose would be necessary to consistently lead to this effect. As already indicated for DPP4-I, it is important for the clinical use of these medications that a blood glucose-lowering effect can be demonstrated. Ultimately, blood glucose will be the parameter that is measured in the clinic and is decisive for the success of the therapy. Nevertheless, the observations on the effects of GLP-1RA on glycaemic variability appear promising.

The relevance of changes in plasma glucagon concentrations due to GLP-1RA is difficult to assess because the study results are rather inconsistent. In healthy cats, lowered glucagon concentrations could be measured in some studies, but also increased concentrations in others. Whether the increased concentrations really serve to counteract hypoglycaemia ultimately remains unclear. In diabetic cats, the glucagon concentration was again only measured in one study. Here [95], a trend towards reduced glucagon secretion after treatment with GLP-1RA was found, which would represent an advantage, as feline diabetics often develop hyperglucagonaemia, which further aggravates hyperglycaemia. Future studies in diabetic cats with more animals and over a longer study period would still have to prove the actual effect of GLP-1RA on plasma glucagon.

In healthy cats, significant weight loss was achieved by administration of GLP-1RA in most studies; only in one study [86] in healthy cats did body weight remain stable. In the studies in diabetic cats, significant weight loss by GLP-1RA was demonstrated in one study [95], and weight remained stable in the other study [94]. In the studies in which weight remained stable, ExER was applied; significant weight loss was observed in both healthy and diabetic cats when Ex, Lg or [Gln^{28}]Ex were administered. Of note, no significant weight gain was observed with any GLP-1RA. This represents an important advantage over the therapy of diabetes with conventional insulin preparations, which are often associated with weight gain [122].

The clinical outcome of diabetic cats by therapy with GLP-1RA in combination with exogenous insulin appears quite satisfactory. In a study of newly diagnosed feline diabetics [94], 93 % of the cats achieved good metabolic control or even remission. In the placebo group, only 67 % of the animals obtained this result. The difference between the groups is in fact not statistically significant, but according to the authors, the number of animals in the study was not high enough to demonstrate a significant difference with these percentages. Larger studies in diabetic cats would therefore be necessary to show whether the advantage of GLP-1RA is really significant in this regard. Furthermore, ExER therapy, in contrast to placebo administration, was shown to result in a significant reduction in GV compared to pre-therapy, which is also important for clinical outcome, as high GV can be associated with complications (see 4.3.6).

In the other study in diabetic cats [95], the clinical outcome was not quite as convincing. Only 25 % of the cats under Ex achieved remission. However, an important point here is that of the total of 8 cats in the study, only 3 had been diagnosed for a maximum of half a year, as it has already been shown that the chances of remission decrease after longer than half a year of therapy [111]. These results, together with the findings that the insulinotropic effect of GLP-1RA appears to be reduced in overweight and diabetic cats, indicate that early diagnosis and therapy are extremely critical for a positive outcome.

The most common side effects of GLP-1RA include mild and usually self-limiting gastrointestinal symptoms, which in most cases disappear after a few days of therapy or otherwise after temporary dose reduction. Interestingly, these side effects are equally common in diabetic cats treated with GLP-1RA and insulin as in diabetic cats receiving insulin and placebo. In this respect, GLP-1RAs do not seem to have any disadvantage compared to insulin alone.

Hypoglycaemia is another side effect of GLP-1RA. However, it often appeared to be asymptomatic or could be treated simply by feeding, at least in healthy cats. Hypoglycaemia occurred with equal frequency in diabetic cats treated with GLP-1RA and insulin as with insulin alone, suggesting that hypoglycaemia in these cases was associated with insulin rather than the GLP-1RA.

One disadvantage of GLP-1RA compared to oral DPP-4 inhibitors is the need to inject them twice a day to once a week, depending on the preparation and the pharmacokinetics of the GLP-1RA. This can be very challenging and burdensome for owners, depending on the cooperativeness of the feline patient. With the development of formulations of GLP-1RA that might allow injection once a month or an implantation every few months, the treatment of feline diabetes may become considerably simplified in the future.

No studies have yet been conducted in diabetic cats using GLP-1RA as monotherapy. The effects of solely these drugs in feline diabetics should also be evaluated in order to make definitive statements about their advantage over conventional insulin.

4. Conclusions and outlook

Feline diabetes mellitus is a complex disease for whose therapy, which nowadays consists of insulin and management changes, no perfect solution exists yet.

The use of GLP-1RA has opened up new possibilities that address some of the problems of insulin therapy, such as weight gain, twice-daily injections and possibly to some extent hypoglycaemia. GLP-1RAs might lead to higher remission rates and better glycaemic control, in part through their pro-proliferative effect on pancreatic β cells. However, until these drugs can become the standard therapy in feline diabetes

mellitus, larger studies in diabetic cats must prove the actual significant effects of the incretin mimetics and ensure their safety over longer periods of time, even at the higher doses that may be necessary.

CRediT authorship contribution statement

Nina Haller: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Thomas A. Lutz:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

Thomas A. Lutz is a consultant for Novo Nordisk, Boehringer Ingelheim, Zealand Pharma, Prolynx, Eracal and Structure Therapeutics. Thomas A. Lutz has ongoing collaborations with Novo Nordisk.

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