Ann. Anim. Sci., Vol. 15, No. 1 (2015) 19–30 *DOI: 10.2478/aoas-2014-0067*

DE GRUYTER
OPEN

DIABETES MELLITUS IN CATS RELEVANT TO HUMAN TYPE 2 DIABETES – CURRENT KNOWLEDGE AND NEW TREATMENT STRATEGIES – A REVIEW*

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Abstract

Diabetes mellitus is one of the most commonly encountered endocrinopathies in domestic cats. Numerous studies have shown that feline diabetes mellitus (FDM) closely resembles human type 2 diabetes mellitus (T2DM), a common pathogenesis including insulin resistance and impaired insulin secretion as well as the same risk factors. This similarity provides ground for better understanding of their pathogenesis as well as more efficient management, novel treatment and prevention options for the disease in both species. Recently, modulation of the incretin system has become a new area of active investigations by several pharmaceutical companies. Concerning the role of incretins in glucose homeostasis, therapies based on activating the incretin axis have proved highly effective in treating T2DM. Glucagon-like peptide 1 (GLP-1) receptors agonists and dipeptidylpeptidase-4 (DPP-4) inhibitors have been recently developed agents for diabetes therapy. Furthermore, studies in healthy cats demonstrated that those drugs stimulate insulin secretion and lower glucagon levels. There is a need of additional clinical evaluation of action of the drugs in cats suffering from FDM. Moreover, studies in cats may contribute to the development of knowledge on the use of new drugs in treatment of human T2DM because cats are an excellent model for the study of diabetes.

Key words: feline diabetes mellitus, human type 2 diabetes mellitus, the incretin effect, DPP-4 inhibitors, GLP-1 receptors agonists

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both and is one of the most commonly encountered endocrinopathies in domestic cats. Currently, there are known four categories of diabetes. Primary diabetes includes type 1 and 2. Type 1 diabetes mellitus, previously called insulin dependent diabetes, appears to be the most common form of diabetes in dogs and is caused by deficiency of insulin,

* Work financed from statutory activity.

resulting from the absence or its insufficient production by the pancreas (Rand et al., 2004). Whereas feline diabetes mellitus (FDM) is analogous to human type 2 diabetes mellitus (T2DB), formerly called non-insulin-dependent, because it shows several similarities such as insulin resistance, impaired β-cell function, decreased β-cell number, islet amyloid deposits and development of complications in several organ systems like retinopathy and peripheral polyneuropathy (Henson and O'Brien, 2006; Reusch et al., 2006; Link et al., 2013). This type of diabetes accounts for 80–95% of FDM (Rand, 1999). The common features between FDM and T2DB are also reflected by environmental risk factors, such as physical inactivity, obesity and relative age of patients (Slingerland et al., 2009; Osto et al., 2013).

In recent years there has been a significant increase in the incidence of diabetes among both humans and cats (Osto et al., 2013). The incidence of diabetes in humans is increasing due to population growth, aging, urbanization, and increasing prevalence of obesity and physical inactivity. The prevalence of diabetes in people was estimated to be 171 million in 2000 and 366 million in 2030, 90% of whom are type 2 diabetes mellitus (Wild et al., 2004; Inzucchi and Sherwin, 2005). Similar to human, the frequency of diagnosis of FDM has increased from approximately 8 to 124 per 10,000 cats between the years 1970–1999 among college veterinary hospital patients in the USA. In Australia the prevalence of FDM was estimated as 74 cases per 10,000 insured cats whereas in the UK it was 44 cases (McCann et al., 2007; Prahl et al., 2007; Lederer et al., 2009). Diabetes mellitus is still not fully understood and is the current topic for clinical trials (Nack and DeClue, 2014).

Etiology

Male gender, obesity, indoor confinement, advancing age, lack of physical activity are the most often occurring predisposing factors of this disease in cats. In addition, Burmese cats are genetically susceptible to developing FDM compared to non-pedigree cats (Lederer et al., 2009; Sallander et al., 2012; Callegari et al., 2013). Some authors also suggest that a missense mutation in the coding sequence of the melanocortin receptor 4 (MC4R), which was identified in the cats' DNA, may predispose them to develop obesity and/or diabetes (Osto et al., 2013). High-carbohydrate diets increase blood glucose and insulin levels and may also lead to feline obesity and diabetes (Rand et al., 2004). Diabetic cats are often older than 6 years, neutered, male gender and usually obese. Characteristic clinical signs include polyuria, polydipsia, polyphagia, muscle wasting and weight loss (Hall et al., 1997). Median survival time of diabetic cats varies significantly and depends on the clinical condition at the time of diagnosis. Older age is considered as a negative prognostic factor for survival time, whereas there was no correlation of body weight, sex and ketonuria with earlier mortality (Kraus et al., 1997; Goossens et al., 1998).

Cats are considered an excellent model for studying T2DM, complementary to previous studies with rodents for both practical and physiological reasons. Moreover, based on the high similarity of spontaneously developed FDM and T2DM opportunity emerges to investigate pathogenesis as well as more efficient management, novel treatment and prevention options for the disease in both species (Henson and O'Brien, 2006; Hoenig, 2012; Osto et al., 2013).

Nowadays domestic cats are the most popular pets in the world and are exposed to similar risk factors for diabetes as people. The aim of this review is point out the current knowledge on the similarities and differences in pathogenesis and new treatment strategies between FDM and T2DM.

Pathogenesis

Pathogenesis of feline diabetes mellitus and human type 2 diabetes has much homology. Both cat and human diabetes results from inadequate insulin secretion combined with resistance to the action of insulin in its target tissues including adipose tissue, skeletal muscle and liver (Rand et al., 2004; Richardson et al., 2013).

Insulin resistance

Insulin resistance is a pathological condition in which the biological response of peripheral tissues to insulin is inadequate (Henson and O'Brien, 2006). The beta cells produce insulin, but cells in the target tissues become resistant to insulin and are unable to use it as effectively, leading to hyperglycemia. Elevated level of glucose in the blood up-regulates the production of insulin, further contributing to hyperinsulinemia (Spellman, 2010; Osto et al., 2013).

It is important to note that mechanism of insulin resistance is common in both species. Factors contributing to insulin resistance include obesity, corticosteroid and progestin treatment and some illnesses: pancreatitis, chronic periodontal disease, sepsis, acromegaly, kidney and liver disease, hyperthyroidism, Cushing's syndrome or vitamin D deficiency (Hall et al., 1997; Rand et al., 2004; Rand, 2013).

Obesity is a common nutritional disorder and the main risk factor leading to insulin resistance and an increase in the incidence of type 2 diabetes (Lutz and Rand, 1995; Crenshaw and Peterson, 1996). Even a small overweight and increase in fat-cell sizes have been associated with a significant increase in the risk of developing diabetes (Colditz et al., 1995). In healthy lean cats, insulin sensitivity is twice higher than in the obese animals. Moreover, each kilogram of weight gain reduces insulin sensitivity and glucose effectiveness in cats by 30%. Obese male cats have a higher concentration of insulin in blood serum and lower innate insulin sensitivity, which predisposes them to a higher incidence of diabetes compared with female cats (Appleton et al., 2001; Hoenig et al., 2006, 2007).

Numerous evidence from several human, rodent and *in vitro* studies has demonstrated functional roles for a number of inflammatory factors in obesity-induced insulin resistance (Osto et al., 2013). Adipose tissue is not only a passive lipid storage depot but it synthesizes and secretes many proteins exerting autocrine, paracrine and endocrine effects, including classical adipokines (leptin – a major regulator of energy balance and adiponectin – an insulin sensitising agent), inflammatory factors (cytokines, chemokines and components of the complement cascade), haemostatic factors (plasminogen activator inhibitor-1 [PAI-1] and tissue factor), and components of the renin–angiotensin system (angiotensinogen and renin) (Trayhurn and Wood, 2004; Richardson et al., 2013). Some studies have demonstrated that plasma concentrations of inflammatory markers, including TNF-α and IL-6, are elevated in obese humans and rodents (Hotamisligil et al., 1995). Obese cats are also char-

acterized by an increase in TNF-α expression in adipose tissue and skeletal muscle (Miller et al., 1998). These cytokines lead to inhibition of insulin action in adipocytes through serine phosphorylation of insulin receptor substrate (IRS) proteins which lowers their activity with the subsequent inhibition of insulin-stimulated glucose transport via GLUT4 (Osto et al., 2013). Furthermore, some authors suggest that in response to obesity upregulation of adipose tissue complement components and complement activation result in enhanced C3a production, which may contribute to insulin resistance and eventually T2DM by promoting inflammatory cell infiltration into adipose tissue (Richardson et al., 2013).

Feline acromegaly, or hypersomatotropism, occurs especially in older male cats and is caused by a pituitary adenoma. Excessive growth hormone secretion leads to the development of diabetes mellitus. The most acromegalic cats are insulin resistant and diagnosis of this endocrine disease may help to control FDM (Niessen, 2010; Greco, 2012). Pancreatitis may also complicate the treatment of diabetic cats through intensification of resistance to the action of insulin in target tissues (Caney, 2013; Rand, 2013). Several recent reports point to a role of vitamin D deficiency in the pathogenesis of insulin resistance and insulin secretion derangements. In addition, vitamin D deficiency coexists with obesity in which insulin resistance is also a common finding (Donath et al., 2005).

Impaired insulin secretion

The mechanism of inadequate insulin secretion by the pancreatic β-cells remains largely unexplored, but may include β-cell failure and reduction in their mass caused by inflammatory mediators, reactive oxygen species, toxic intracellular protein oligomers and toxicity from increased blood glucose concentrations or lipotoxicity (Link et al., 2013; Rand, 2013). Recently, several publications have convincingly confirmed that the major cause of β-cell failure is increased demand on the β-cell to secrete insulin as a result of insulin resistance (Porte, 1991). It leads to β-cell apoptosis and programmed cell death (Rand et al., 2004).

Glucose not only stimulates β-cells to secrete insulin but also controls the regeneration of β-cells. Indeed, short-term hyperglycemia induces proliferation of β-cells (Donath et al., 1999) but long-term exposure to increasing glucose concentration induces B-cell apoptosis leading to significant decrease in β-cell mass (Donath et al., 2005). Chronic hyperglycemia induces β-cells to produce interleukin-1β (IL-1β) followed by changes in β-cell regulation and raises the frequency of apoptosis (Maedler et al., 2001). Interestingly, lipotoxicity is a slightly less certain theory of β-cell apoptosis. Whereas long-term exposure to high level of saturated fatty acids, in particular palmitate, appears highly toxic, monounsaturated fatty acids such as oleate protect against both palmitate- and glucose-induced β-cell apoptosis (Maedler et al., 2003).

Obesity is often accompanied by increased circulating leptin and cytokine levels. Several recent reports point to induced β-cell apoptosis by leptin through increasing release of IL-1β and decreasing release of the IL-1 receptor antagonist in human islets (Maedler et al., 2004). Some other cytokines including TNF-α and IL-6 may also play a role in this process (Donath et al., 2005). In obese cats secretion of adipokines from adipose tissue has also been shown and TNF-α expression in adipose tissue and

skeletal muscle is increased (Osto et al., 2013). Furthermore, in obese humans and in type 2 diabetes elevated plasma concentrations of interleukin-6 (IL-6) were observed. IL-6 stimulate GLP-1 secretion from intestinal L cells and pancreatic alpha cells through increased proglucagon (which is encoded by GCG) and prohormone convertase 1/3 expression, improving insulin secretion and glycemia (Ellingsgaard et al., 2011). There is a need for further research on the role of cytokines, particularly IL-6 in the pathogenesis of diabetes in cats.

Another common feature in the pathogenesis of feline diabetes and T2DM is islet amyloidosis (IA) and significant loss of β-cells in the pancreatic islets (O'Brien, 2002; Henson and O'Brien, 2006). Amyloidosis is a disease in which the extracellular deposition of insoluble fibrous protein occurs impairing the proper functioning of the organ (Palus et al., 2013). Amyloid deposition in pancreatic islets is identified in 90% of humans with type 2 diabetes and in almost all diabetic cats (Johnson et al., 1986). Interestingly, IA occurs only in humans, cats and macaques and has never been shown in rats or mice. Pancreatic amyloid precursor protein is an islet amyloid polypeptide (IAPP), also known as amylin. Amylin is synthesized in pancreatic beta cells, and is co-stored and co-secreted with insulin in both the cat and humans (Lutz and Rand, 1995; O'Brien, 2002). In fact IAPP is a physiological secretory product of β-cell and further studies are needed to elucidate the mechanism of development of IA. However, abnormalities in IAPP synthesis, processing, trafficking, secretion, or degradation by β-cells seems to play an important role in the pathogenesis of IA (Johnson et al., 1989; Henson and O'Brien, 2006). Moreover, increasing level of IA deposition is associated with reduction in β-cell mass. In T2DM IA deposition is correlated with an approximately 60% loss of β-cell mass (Butler et al., 2003). Similarly, 50% loss of β-cell mass has been observed in diabetic cats with IA (O'Brien, 2002).

New therapeutic strategies

In the early stages type 2 diabetes is most commonly managed by drugs that suppress glucose production by the liver (e.g. metformin), increase insulin release from beta-cells (e.g. sulfonylureas), or prevent the digestion of carbohydrates (e.g. alpha-glucosidase inhibitors) (Lee and Jun, 2013). Metformin is an oral antidiabetic drug that improves control of glycemia primarily by inhibiting hepatic gluconeogenesis and glycogenolysis. Nelson et al. studied the usefulness of the metformin for the treatment of diabetes in cats. The treatment was effective in only 20% of cats. In addition, side effects such as intermittent lethargy, inappetence, vomiting and weight loss were observed. Researchers suggest that metformin is useful in treatment of diabetic cats with detectable concentrations of insulin at the time metformin treatment is initiated (Nelson et al., 2004). Sulfonylureas and meglitinides, which lower the blood glucose level by stimulating b-cells to produce more insulin, also met with little success in therapy of diabetic cats. Only in 25% of cats control of glycemia was achieved. However, some authors suggest that this type of drugs may be used to supplement insulin therapy in cats (Nelson et al., 1993; Mori et al., 2009). Recently, modulation of the incretin system has become a new area of active investigations by several pharmaceutical companies.

In the 1960s, the researchers observed that oral glucose administration leads to a much greater degree of insulin secretion than glucose given intravenously (Perley and Kipnis, 1967). This phenomenon is called the incretin effect and is estimated to account for approximately 50–70% of the total insulin secreted following oral glucose administration. Incretins are hormones secreted by the gastrointestinal tract during food intake that enhance glucose-stimulated insulin secretion from the islet β-cell and are responsible for this effect. The first incretin hormone was isolated from crude extract of porcine small intestine and identified in 1971 – glucose dependent insulinotropic polypeptide (GIP). It is secreted by K cells mainly located in duodenum. The second one, called glucagone-like peptide-1 (GLP-1), is synthesized in the L cells in the distal small intestine and in the large intestine. Bioactive GLP-1 exists as two equipotent circulating molecular forms: GLP-1 (7-37) and GLP-1 (7-36) amide. GLP-1 (7-36) is the most common form circulating in human blood plasma (Drucker, 2006). The biological actions of GLP-1 are mainly mediated by the high-affinity GLP-1 receptors (GLP-1R) which are expressed in α and β cells of the pancreas, gastrointestinal tract, kidney, heart, lung, skin, immune cells, hypothalamus, hippocampus and cortex. Stimulation of the GLP-1R leads to cyclic AMP formation and activation of downstream pathways coupled to protein kinase A and cAMP-regulated guanine nucleotide exchange factors. Activation of GLP-1R also results in increasing intracellular calcium, inhibition of voltage-dependent K+ currents and activation of immediate early gene expression through effects on Erk 1/2, protein kinase C, and phosphatidylinositol 3-kinase (PI3K) (Drucker and Nauck, 2006; Winzell and Ahren, 2007).

GLP-1 in two ways stimulates insulin secretion in a glucose-dependent manner with minimal risk of hypoglycemia. The first is based on directly activated insulin secretion by binding to their distinct receptors on islet β-cells. The precise mechanism of stimulation of insulin secretion only at elevated levels of plasma glucose needs further investigation. The second one is associated with activation of a portal glucose sensor, which sends signals via vagal afferents to the central nervous system and then via vagal efferents leads to enhance insulin secretion. GLP-1 not only increases the secretion of insulin, but also inhibits glucagon secretion from α-cells (Drucker, 2006). Both GLP-1 and GIP are eliminated through renal and hepatic clearance and are rapidly degraded by the enzyme dipeptidylpeptidase-4 (DPP-4) in less than 2 minutes after synthesis (Lee and Jun, 2013; Reusch and Padrutt, 2013).

Concerning the role of incretins in glucose homeostasis, therapies based on activating the incretin axis have proved highly effective in treating T2DM (Ezcurra et al., 2013). Glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidylpeptidase-4 (DPP-4) inhibitors have been recently developed agents for diabetes therapy.

GLP-1 receptor agonists

GLP-1 receptor agonists, also known as incretin mimetics, are a group of drugs which have much homology with natural GLP-1. The first incretin medicine used for treatment of T2DM was exenatide. Exenatide is a synthetic form of exendin-4, which is a protein extracted from the saliva of the Gila monster lizard in 1992 and is

resistant to DPP-IV (Lee and Jun, 2013; Reusch and Padrutt, 2013). It is composed of 39 amino acids, demonstrates 53% amino acid identity with human GLP-1 and is a highly potent GLP-1 agonist both *in vitro* and *in vivo*. Exenatide has a half-life of approximately 2.5 hours after subcutaneous injection and needs to be taken twice daily. However, a long-acting version of exendin-4, which is in an encapsulated form, appears to control glucose for weeks after a single injection and was approved in Europe in 2011 (Drucker, 2006).

The second GLP-1 receptor mimetic, which was introduced in 2009, is liraglutide. Liraglutide is the first human GLP-1 analogue with 97% structural homology to native GLP-1. It is more biologically stable thanks to the addition of fatty acid chains leading to increase in its affinity for blood albumin and is used in once-daily subcutaneous injection (Suzuki et al., 2013).

Both GLP-1 receptor agonists regulate glucose levels by stimulating glucose-dependent insulin secretion and suppressing glucagon secretion without increasing the risk of hypoglycemia (Imamura et al., 2013). Furthermore, they exert additional beneficial effects including weight loss, decreased blood pressure, reducing HbA1c concentration, preventing the progression of diabetic nephropathy and improved β-cell function. Studies in rodents have demonstrated that GLP-1R mimetics play an important role in regulation of β-cell mass by enhancing β-cell proliferation and neogenesis and inhibiting β-cell apoptosis. They also inhibit gastric emptying and food intake resulting in weight loss, which was confirmed in clinical studies (Drucker, 2006; Lee and Jun, 2013). In clinical studies liraglutide therapy is more efficient in improving glycemic control and side effects (like nausea or vomiting) occur less frequently than during therapy with exenatide. Moreover, albiglutide (Eperzan and Tanzeum) is a GLP-1 agonist and needs to be injected only once a week instead of daily injections, reducing the discomfort and inconvenience of GLP-1 administration considerably, which seems to be a better option for both cats and their owners (Reusch and Padrutt, 2013).

DPP-4 inhibitors

DPP-4 inhibitors are a family of drugs which have positive effects on incretin degradation and control of blood glucose levels. Sitagliptin is the first drug of this group used in the treatment of T2DM in 2007. The Family of DPP-4 inhibitors include also vildagliptin, saxagliptin and linagliptin and several drugs which are currently being clinically studied (Kirby et al., 2010). DPP-4 inhibitors are given orally once or twice daily depending on particular drug. They prevent the inactivation of both GLP-1 and GIP and lower glucose level in blood. Studies in mice have demonstrated that targeted inactivation of the DPP-4 gene leads to improved glucose tolerance and increased levels of GLP-1, GIP and insulin (Drucker, 2006). DPP-4 inhibitors are effective as monotherapy or given together with other antihyperglycemic medications such as sulfonylureas, metformin, glitazones or insulin. Advantages of DPP-4 inhibitors include an oral route of administration, a mechanism of action based on glucose-stimulated insulin secretion, and a low risk of hypoglycemia. In contrast to GLP-1R agonists, DPP-4 inhibitors do not affect the body weight and appetite (Davidson, 2013).

Incretin therapy in cats

Insulin is currently considered to be the mainstay of treatment in FDM leading to minimize the symptoms and prevent complications (such as peripheral polyneuropathy and diabetic ketoacidosis). Despite the many benefits of insulin therapy it has also many limitations, such as the difficulty in determining the proper dosage, and complications such as abnormal control of blood glucose levels (hyperglycemia and hypoglycemia) and weight gain (Zini et al., 2010). Because the domestic cat spontaneously develops a form of diabetes that closely resembles human T2DM, introducing incretins to the treatment of FDM may lead to a more efficient management of the disease (Reusch and Padrutt, 2013).

Cats are obligate carnivores and their diet consists of fat and proteins and a small amount of carbohydrates. Studies in healthy cats confirmed the presence of the incretin effect in cats. However, cats are devoid of TIR2 sweet-taste receptors and the glucose-induced incretin effect is less important than in other species. The degree of synthesis and release of incretin hormones after stimulation by different nutrients differs between species. In cats GIP is mainly released upon stimulation by lipids and amino acids. Glucose stimulates only GLP-1 secretion but lipids and amino acids lead to stronger stimulation of its secretion (Gilor et al., 2011 b). Other studies in both lean and obese cats also confirm the existence of the incretin effect in cats. Intragastric administration of glucose (2 mg/kg) was followed by an increase in glucose, insulin, and glucagon-like peptide (GLP)-1. However, GLP-1 concentrations were much lower in obese than lean cats (Hoenig et al., 2010).

Gilor et al. studied the effect of the GLP-1 agonist exenatide on insulin secretion by β-cells in healthy cats. Their research demonstrated that exenatide stimulates insulin secretion in a glucose dependent manner in analogy to humans. No side effects were observed even if tenfold higher dose was used than in the human therapeutic regimens. The effect of the drug on the proliferation and survival of β-cell was not tested and requires further study (Gilor et al., 2011 a). Other studies in experimental healthy cats have demonstrated that the dipeptidyl peptidase IV inhibitor NVP-DPP728 reduces plasma glucagon concentration and increases insulin secretion. The authors suggest that the effect is due to inhibition of degradation of the endogenous GLP-1 as in other species. Moreover, the authors believe that both the dipeptidyl peptidase IV inhibitors as well as GLP-1 mimetics receptors may be successfully used in the FDM treatment. However, application of these therapeutics in the treatment of FDM requires the examination of their impact on the incretin system in cats with clinical form of diabetes (Furrer et al., 2010).

Conclusion

Numerous studies have shown that feline diabetes closely resembles human type 2 diabetes mellitus, such as common pathogenesis including insulin resistance and impaired insulin secretion as well as the same risk factors. This similarity is a great opportunity to better understanding of pathogenesis as well as more efficient management, novel treatment and prevention options for the disease in both species.

Incretin-based therapy is one of the latest trends in the effective treatment of diabetic people. Glucagon-like peptide 1 (GLP-1) receptor agonists and dipepti-

dylpeptidase-4 (DPP-4) inhibitors are useful in effective management of diabetes and have many benefits including low risk of hypoglycemia, weight loss, decreased blood pressure, reduction of the HbA1c concentration, prevention of the progression of diabetic nephropathy and improved β-cell function. Studies in healthy cats demonstrated that these drugs stimulate insulin secretion and lower glucagon levels. There is a need for additional clinical evaluation of action of these drugs in cats with FDM. Moreover, studies in cats may contribute to the development of knowledge on the use of new drugs in treatment of human T2DM because cats are an excellent model for the study of diabetes.

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Received: 10 VI 2014
Accepted: 21 VII 2014