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SPONTANEOUSLY ARISING DISEASE

Oxidative Modification, Inflammation and Amyloid in the Normal and Diabetic Cat Pancreas

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Summary

The pathogenesis of β-cell dysfunction leading to pancreatic β-cell failure seen in type 2 diabetes mellitus is incompletely understood. Pancreatic tissues were collected from nine control cats and nine diabetic cats and labelled immunohistochemically to examine expression of interleukin (IL)-1β, insulin, islet amyloid polypeptide (IAPP) and 4-hydroxynonenal (4-HNE). Thioflavin-S was used to stain for amyloid. All control cats showed positive labelling for IL-1β and 4-HNE. Diabetic cats showed varying degrees of inflammation and oxidative modification, owing in large part to the very small amount of islet structure remaining in the typical diabetic cat pancreas. Amyloid deposition was identified in 8/9 diabetic cats and 1/9 control cats. In order to validate these findings, paired biopsy samples taken from an additional group of cats enrolled in a study of obesity and hyperglycaemia (sampling at baseline and after 8–16 weeks of obesity and hyperglycaemia) were labelled for IL-1β and 4-HNE. A similar pattern of labelling was identified in the baseline samples to that seen in control cats. A significant increase in IL-1β and 4-HNE expression was seen after a period of hyperglycaemia and obesity. Taken together, these findings suggest that while present in normal cats, markers of inflammation and oxidative modification increase very early during the development of disease. Future studies focusing on these earlier time points are needed to understand the factors that function in protection of the islet β cell and the development of islet pathology in type 2 diabetes mellitus in the cat.

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Introduction

It is estimated that type 2 diabetes mellitus (T2D) will affect nearly one in three adults in the USA by the year 2050 (Boyle *et al.*, 2010). The domestic cat population has undergone a similarly remarkable increase in morbidity associated with this disease. It was estimated that the incidence of T2D in cats was 0.08% in 1970, but it is now estimated to be as high as 1.2% (Prahl *et al.*, 2007; Rieder *et al.*, 2008).

The pathogenesis of β-cell dysfunction and failure resulting in T2D is incompletely understood. It is clear that development of disease is not the result of any single mechanism. By the time clinical signs of T2D are manifest, the underlying pathological processes have been developing for weeks, months or even years. Diet, genetics, activity, obesity and environment, as well as cellular processes such as accumulation of oxidative damage, inflammation and misfolded proteins, interact, ultimately resulting in a loss of functional β-cell mass and overt hyperglycaemia (O'Brien, 2002; Boni-Schnetzler *et al.*, 2008).

Insulin demand is dictated by peripheral insulin sensitivity, dietary glucose intake and gluconeogenic mechanisms. The early stages of T2D are characterized by relative compensatory hyperinsulinaemia in response to peripheral insulin resistance. At some point, the insulin producing capacity of the β cell is exhausted and a permanent relative or absolute hypoinsulinaemic state develops.

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Apart from insulin, the other major secretory product of pancreatic β cells is islet amyloid polypeptide (IAPP), also known as amylin. In health, IAPP is stored in secretory granules at a 1:50 molar ratio to insulin (Westermark *et al*., 2011). During periods of hyperinsulinaemia there is a concurrent rise of circulating IAPP and it has been reported that the serum ratio of IAPP to insulin changes with disease (Pieber *et al*., 1993; Mulder *et al*., 1995, 1996; Lutz and Rand, 1996; Gasa *et al*., 2001).

In the majority of spontaneously arising T2D in man and cats, IAPP-derived amyloid is deposited within the islets (O'Brien *et al*., 1986; Johnson *et al*., 1989). The presence of islet-associated amyloid deposits is associated with a loss of β-cell mass and loss of insulin secretion by the pancreas (Lutz and Rand, 1997; Höppener *et al*., 2002).

Reactive oxygen species are produced as the result of normal aerobic metabolic processes and there is a constant interplay between oxidative and antioxidant forces in cells. Diabetic people have increased oxidative stress both systemically and locally and it is believed that oxidative stress is involved in the process of β-cell dysfunction and apoptosis (Ihara *et al*., 1999; Bast *et al*., 2002; Robertson *et al*., 2004; Li *et al*., 2009; Acharya and Ghaskadbi, 2010; Modak *et al*., 2011).

Proinflammatory cytokine signalling has also been implicated as a central player in the initial maintenance and ultimate destruction of the pancreatic β cell. It has been proposed that interleukin (IL)-1β signalling is useful in stimulating pro-survival signals through promotion of nuclear factor (NF)-kB signalling. Through autocrine feedback, prolonged IL-1β signalling eventually pushes the cell in a pro-apoptotic direction and may ultimately be partly responsible for loss of β-cell mass (Boni-Schnetzler *et al*., 2008). The importance of IL-1β signalling is supported by a clinical study of an IL-1β receptor antagonist that resulted in improved β-cell survival, insulin production and resolution of hyperglycaemia in human subjects (Larsen *et al*., 2009).

The aim of the present study was to characterize markers of oxidative modification, inflammation and amyloid within the pancreatic islets of normal and diabetic cats. Immunohistochemical and fluorescence labelling techniques were employed to detect markers of inflammation (IL-1β and IL-6), markers of oxidative modification (4-hydroxynonenal [4-HNE]), insulin, IAPP and amyloid. We hypothesized that the islets of diabetic cats would show increased oxidative modification, inflammation and amyloid accumulation compared with the islets of normal cats.

Materials and Methods

Case Selection

Cases of spontaneous diabetes mellitus in cats were identified by reviewing the submission records of the Oklahoma Animal Disease Diagnostic Laboratory, Stillwater, Oklahoma, USA. Cases were included on the basis of a diagnosis of diabetes mellitus (characterized by spontaneous and persistent hyperglycaemia) made by the submitting veterinarian and sufficient paraffin wax-embedded tissue available for study. Cats with severe systemic disease (e.g. fungal infection or sepsis) were excluded. Additionally, microscopical evidence of severe acute or chronic pancreatitis resulted in exclusion of that individual. Nine cases met inclusion criteria for the diabetic group. A summary of signalment, cause of death and, if available, duration of disease is included in Table 1.

A group of apparently healthy research cats ($n = 4$) enrolled in an unrelated study were evaluated before and after induction of obesity and hyperglycaemia and served as an additional control group. Paired, surgical biopsy samples were taken from these individuals at the time of enrollment and again after the cats had been maintained obese and hyperglycaemic for 8−16 weeks. All samples were collected in accordance with IACUC guidelines following approval of the Oklahoma State University Animal Care and Use Committee.

Pancreases were collected from apparently healthy cats ($n = 9$) killed as a part of routine population control by a local animal shelter. Cats were deemed apparently healthy by shelter staff and showed no signs of respiratory, dermatological or neurological disease during the time they were observed at the shelter. Pregnant individuals were excluded. No exclusions were made based on age or gender. Haematoxylin and eosin (HE)-stained sections of pancreatic tissue from each case were reviewed by a board certified pathologist. Any evidence of acute or chronic pancreatitis resulted in exclusion from the normal study group.

The samples used in this study were from various locations within the pancreas. Previous publications have demonstrated that there is a fairly homogenous distribution of islets within the feline pancreas and so no attempts were made to try to localize the origin of the sample (O'Brien *et al*., 1993; Lutz *et al*., 1994).

Histopathology and Immunolabelling

HE-stained sections (4 μm) of pancreas were examined by a board certified pathologist (MAB) for evidence of acute or chronic pancreatitis or other changes.

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