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tion, and oral hypoglycemics. This issue is dedicated to the relief of animal and human suffering through the pursuit of diabetes research.

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PATHOGENESIS OF FELINE DIABETES MELLITUS

Thomas A. Lutz, DMV, and Jacqueline S. Rand, BVSc, DVSc

TERMINOLOGY

Diabetes mellitus may occur as a primary disease process or secondary to destruction of beta cells or insulin resistance caused by another disease. Primary diabetes in humans was subdivided initially based on the clinical characteristics of the disease, such as age of onset, insulin dependence, and susceptibility to ketosis. In most human diabetics, the clinical features correspond well to the underlying pathology. Hence, insulin-dependent diabetes is generally used to describe type 1 diabetes, which is caused by immune-mediated destruction of beta cells.[9] Non–insulin-dependent diabetes is used to describe type 2 diabetes, associated with islet amyloid deposition.[53] Direct translation of this terminology to feline diabetes has lead to confusion and inaccurate classification. Although there is strong evidence that type 1 and type 2 diabetes both occur in cats, type 2 seems to be more frequent, and in contrast to humans, most cats are insulin dependent. In this article, the terms *type 1* and *type 2* diabetes are used to imply a specific underlying pathology, and insulin-dependence or non-dependence is used only as a description of the clinical characteristics of the disease. Therefore, insulin-dependent diabetes may occur as a result of either type 1 or type 2 diabetes or secondary diabetes. Impaired glucose tolerance replaces the terms *latent*

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and *subclinical* diabetes,[90] and refers to cats with increased glucose concentration or glucose half-life after a glucose tolerance test, and fasting normoglycemia or mild hyperglycemia.[61, 95] In cats and humans, impaired glucose tolerance is associated with type 2 diabetes, obesity, and stress reactions to disease (Link KRJ, Rand JS, unpublished data, 1994).[22, 91, 95]

SECONDARY DIABETES MELLITUS

Secondary diabetes is also referred to as type 3 diabetes and is the result of another primary disease producing destruction of beta cells or insulin resistance.[90] In cats, secondary diabetes is less frequent than primary DM and occurs with hyperadrenocorticism, hyperthyroidism, excessive growth hormone secretion, or long-term administration of progesterone.[26, 31, 95, 104, 105] Whether insulin therapy is required in cats with secondary diabetes depends on the severity and duration of insulin resistance, or the extent of beta cell destruction. Prolonged overstimulation of beta cells in response to excessive concentrations of insulin antagonistic hormones leads to beta cell degeneration, loss of insulin secretory capacity, and eventual dependence on insulin therapy.[25, 114]

PRIMARY DIABETES MELLITUS: TYPE 1

Spontaneous or primary diabetes is subdivided into type 1 and type 2 diabetes.[90] Type 1 diabetes results from an autoimmune destruction of pancreatic beta cells by T cells and antibodies.[9] Oxygen free radicals and nitrous oxide released from T cells and macrophages induce mitochondrial damage; DNA breakage leads to beta cell death.[108] The end result is almost total loss of beta cells and insulin secretion.[9, 28] In humans, there is a confirmed association of type 1 diabetes mellitus with certain human lymphocyte antigen (HLA) haplotypes.[135] In genetically susceptible patients, uncontrolled immune destruction of beta cells is triggered by environmental factors such as viruses, toxins, and early exposure of infants to foreign antigen in food.[35, 63, 115] Classic type 1 diabetes has not been well documented in cats, although lymphocytic insulitis has been reported and associated with clinical signs of diabetes; and juvenile-onset insulin-dependent diabetes has been reported in a kitten with anti-islet cell antibodies.[88, 136] In contrast to cats, type 1 diabetes seems to be a more frequent cause of diabetes mellitus in dogs (see article by Hoenig, this issue).[1, 40, 41]

PRIMARY DIABETES MELLITUS: TYPE 2

Comparison of Feline and Human Type 2 Diabetes

Histologic, clinical, and laboratory data indicate that the most frequent form of diabetes in cats is analogous to human type 2 diabetes.[53, 92, 93, 95] Except for the fact that insulin dependence and ketosis are more frequent, feline diabetes has many of the same characteristics of the human disease. In both cats and humans, beta cell function is impaired and insulin secretion in response to a glucose load is abnormal.[65, 95, 107] In both species, the characteristic histologic finding is amyloid deposition in pancreatic islets.[53] Most cats (72%) are 7 years or older when clinical signs develop, which corresponds to the peak incidence in older humans.[90, 103] In North America, male cats have a 1.5 times greater risk of developing diabetes than female cats.[103] In humans with type 2 diabetes, there is a trend to male excess in North American whites with a higher socio-economic status, but there is no consistent worldwide gender bias.[60] Obesity has been documented to be a significant risk factor in the development of feline and human diabetes, although many cats are not overweight at the time of diagnosis.[103, 107] Oral hypoglycemic drugs provide satisfactory glycemic control in some cats and in most humans, although up to 25% of humans and the majority of cats eventually require insulin.[32, 61, 85, 86, 90, 93] Thus feline diabetes has many of the same characteristics as human type 2 diabetes.

Genetic Predisposition

In humans, a genetic predisposition is important for the development of type 2 diabetes.[43, 116] This is demonstrated by the development of concordant diabetes in 80% to 90% of homozygous twins.[3] The genes involved have not been elucidated yet, but specific HLA haplotypes predispose to impaired glucose tolerance and type 2 diabetes.[125] Although no breed predilection has been reported in North America,[30, 103] Burmese cats are over-represented in Australia (Rand JS, Bobbermien LM, unpublished data, 1994).

METABOLIC HALLMARKS OF TYPE 2 DIABETES

A major advance in the understanding of type 2 diabetes was the finding of Yalow and Berson that adult-onset human diabetics had fasting insulin concentrations similar to non-diabetics, but reduced initial insulin secretion after a glucose load.[137] It is now recognized that the two hallmarks of type 2 diabetes are decreased insulin secretion and insulin resistance.[51, 75, 80, 95]

Impaired Insulin Secretion

Several characteristic abnormalities of insulin secretion have been observed in diabetic cats and humans with type 2 diabetes mellitus. In both cats and humans, the first phase insulin secretion (acute insulin response) is markedly reduced or absent, and the second phase is de-

layed and often exaggerated.[95] Figure 1 shows a typical insulin secretory pattern for cats with impaired glucose tolerance. Peak insulin concentration is delayed, and the insulin response 20 minutes after glucose injection is reduced by approximately 80% compared with normal cats. This is at the threshold for development of fasting hyperglycemia and onset of clinical signs of polyuria and polydipsia. These occur once the total maximal capacity to release insulin is reduced by 80% to 90%.[17, 51, 107] The severity of metabolic abnormalities observed, particularly impaired glucose clearance and increased lipolysis, best correlate with the degree of impairment of the first phase of insulin release.[21] During the early stages of feline diabetes, these abnormalities in insulin secretion usually are not associated with histologic changes in the beta cells.[51]

In humans, the normal pulsatile pattern of insulin secretion is also disturbed, with both a reduction in the amount of insulin delivered per pulse and a disruption of the normal temporal pulse pattern.[65] Both seem to be important for maximum effectiveness of secreted insulin.[21, 65]

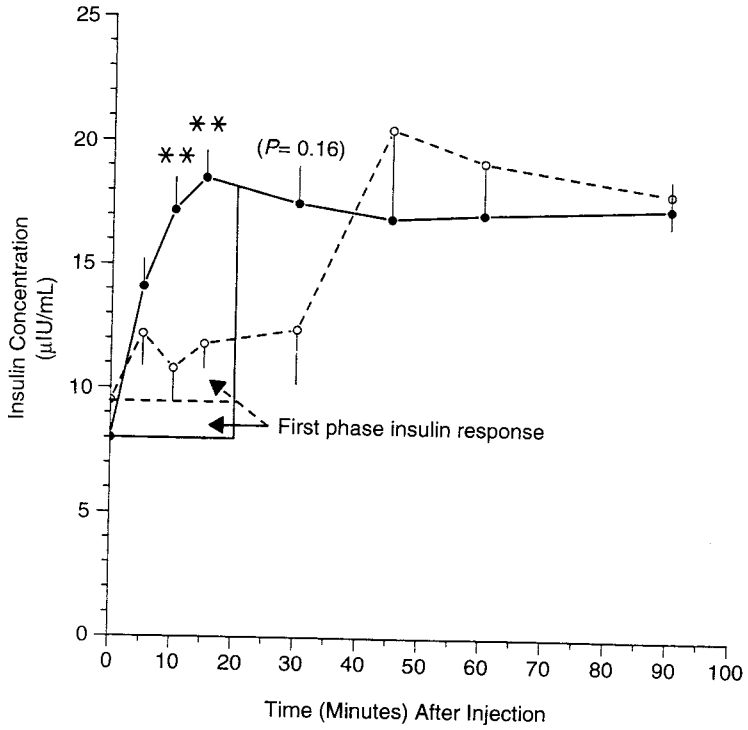


Figure 1. Plasma insulin concentration during a glucose tolerance test (injection of 1 g glucose/kg body weight at t = 0 minute) in normal cats (glucose $T_{1/2} \leq 80$ minutes; n = 14) and cats with impaired glucose tolerance (glucose $T_{1/2} > 80$ minutes; n = 3) cats. First phase insulin response (integrated area under the insulin curve in first 20 minutes after glucose injection) is indicated. ** Significant difference between glucose tolerant and intolerant cats ($P < 0.01$). ● = normal cats (n = 14); ○ = impaired glucose tolerance (n = 3).

To the authors' knowledge, pulsitility of insulin secretion has not been investigated in normal or diabetic cats.

Most studies into the mechanism of impaired insulin secretion in type 2 diabetes have been in laboratory animals, and there are no data available from cats. For glucose-stimulated insulin secretion to occur, extracellular glucose binds to glucose receptors on pancreatic beta cells, which function both as glucose sensors and glucose transporters. Subsequent intracellular glucose metabolism creates signals leading to insulin secretion.[39, 44] The main defect in beta cell function in type 2 diabetes is an impaired glucose sensoring, or glucorecognition.[5, 65, 107] Because of this defect, the ability of extracellular glucose to stimulate insulin release is decreased markedly. It is thought that impaired glucose sensoring occurs because of reduced synthesis of the glucose transporter located in the beta cell membrane, resulting in decreased intracellular glucose concentration to trigger insulin release.[5, 65, 107]

Glucagon-Like Peptide-1 and Impaired Insulin Secretion

Glucagon-like peptide-1 is the most important gastrointestinal hormone associated with postprandial insulin release.[39] It is synthesized in intestinal endocrine L cells and secreted after ingestion of food.[45] Glucagon-like peptide-1 acts synergistically with glucose to initiate insulin secretion.[45] In isolated beta cell preparations, glucagon-like peptide-1 restores glucose sensitivity to glucose-resistant beta cells.[45] Glucagon-like peptide-1 also decreases glucagon secretion from pancreatic alpha cells.[39] The effect of glucagon-like peptide-1 to stimulate insulin secretion is entirely glucose dependent. In humans, it is attenuated as glucose decreases to less than 90 mg/dL (5 mmol/L) and is abolished at glucose levels of $\leq$ 50 mg/dL (2.8 mmol/L).[89] In type 2 diabetes, augmentation of insulin secretion by glucagon-like peptide-1 is reduced despite increased glucagon-like peptide-1 secretion.[39] This is attributed to a desensitization effect, because the glucagon-like peptide-1 receptor is desensitized rapidly by increased glucagon-like peptide-1.[29, 39]

Glucose Toxicity and Impaired Insulin Secretion

Once chronically elevated glucose concentrations are established, glucose toxicity further impairs insulin secretion and self-perpetuates the diabetic state (Link KRJ, Rand JS, unpublished data, 1994).[61, 92] Glucose toxicity has also been incriminated in contributing to the insulin resistance observed in type 2 diabetes.[139] Glucose toxicity describes the phenomenon of inhibition of insulin secretion by persistent marked hyperglycemia. Long-term hyperglycemia causes downregulation of the glucose transporters on beta cell membranes, resulting in reduced insulin secretion.[139] In cats, marked suppression of insulin secretion may occur within days when persistent marked hyperglycemia of approximately 540 mg/dL (30 mmol/L) is present (Link KRJ, Rand JS, unpublished data, 1994). Evidence of glucose toxicity in suppressing insulin

secretion has been reported in transiently diabetic cats. After a period of normoglycemia induced with oral hypoglycemic therapy, beta cell function and insulin secretion was improved even after cessation of therapy.[92, 93]

Insulin Resistance in Type 2 Diabetes

The second hallmark of human type 2 diabetes is insulin resistance, and this has been documented in cats with impaired glucose tolerance.[95, 107] In an insulin-resistant state, higher insulin concentrations are required to achieve a given amount of glucose uptake and utilization.[107] Skeletal muscle is the most important site for insulin resistance, but other tissues including the liver are also involved.[5, 10, 17, 110] In skeletal muscle, insulin resistance leads to reduced glycogen synthesis.[110] In the liver, the ability of insulin to suppress hepatic gluconeogenesis and glucose output.[10, 17] Insulin binding to its receptors is less affected, and the main defect associated with insulin resistance is at the postreceptor level, which involves the sequence of events occurring after insulin binds with its receptor.[5, 101] Although the primary defect at the postreceptor level is not fully understood, the major effect is decreased insulin stimulated activation of the two key enzymes for glycogen synthesis and glycogenolysis, and glycogen synthase and pyruvate dehydrogenase, respectively.[5, 10, 17, 101] Hypersecretion of the pancreatic hormone amylin has been incriminated in playing a role in these postreceptor defects.[20, 146] The basal hyperinsulinemia and exaggerated insulin response to glucose that is often present early in the course of human type 2 diabetes is thought to be a compensatory response to insulin resistance.[107] Insulin resistance and exaggerated second phase insulin secretion have also been reported in cats with impaired glucose intolerance.[95]

In humans, insulin resistance is determined genetically, but is worsened by environmental factors such as obesity or stress.[107] A genetic predisposition to insulin resistance has not been demonstrated yet in cats, but obesity and intercurrent disease have been reported to cause insulin resistance.[91, 94] Physiologic stress such as illness increases catecholamine and corticosteroid levels, which antagonize the effects of insulin.[5, 17, 107]

OBESITY AND DIABETES

Obesity is probably the best known risk factor for the development of human type 2 diabetes mellitus,[90, 102, 107] and many cats are obese when clinical signs of diabetes first develop.[61, 81, 91, 92] Even in nondiabetic cats and humans, obesity produces insulin resistance and impaired glucose tolerance.[5, 91, 107] The mechanism of obesity-induced insulin resistance has been partly clarified. There is evidence from animal experiments that obesity causes internalization of insulin receptors in many tissues including muscle and fat.[17, 120] Obesity also reduces insulin receptor affinity, and produces postreceptor defects leading to impaired intracellular nonoxidative and oxidative glucose metabolism.[5, 17, 33, 91]

Basal hyperinsulinemia and an exaggerated insulin response to glucose can partly compensate for the deleterious effect of obesity-induced insulin resistance in nondiabetic cats and humans with normal beta cell function. Although impaired glucose tolerance can be demonstrated, fasting glucose concentration remains in the normal range.[65, 91, 107] In contrast, the beta cells of diabetics are less able to compensate for obesity-induced insulin resistance by increasing insulin secretion.[65] Obesity alone, however, does not cause the beta cell dysfunction associated with type 2 diabetes.[65]

AMYLIN AND AMYLOID IN THE PATHOGENESIS OF FELINE DIABETES

The characteristic histologic finding in feline and human type 2 diabetes is the deposition of amyloid in pancreatic islets.[53, 56] These deposits are found in up to 90% of human type 2 diabetic patients and in most diabetic cats.[51, 95] In cats and humans, amyloid deposition begins well before the onset of clinical signs of diabetes mellitus.[53, 76] Cats are very susceptible to pancreatic amyloid deposition. In a study of randomly selected cats, 96% had some histological evidence of amyloid deposition (Fig. 2). In most cats, it comprised less than 20% of total islet volume (Fig. 3), but nearly 10% of cats had more than 50% of the islet

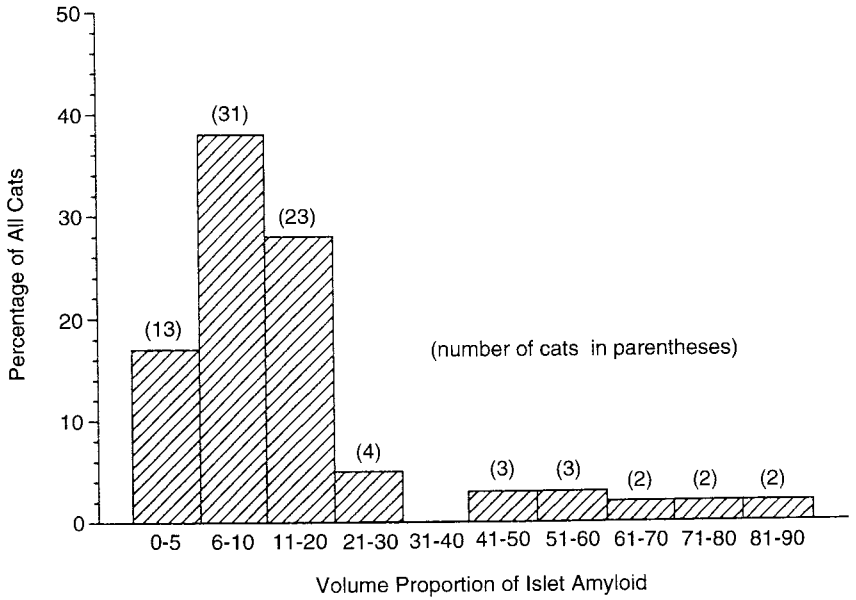


Figure 2. Frequency distribution for the amount of pancreatic amyloid deposition (expressed as the volume proportion of islet amyloid in percent) in a random population of 83 Australian cats. Most cats have ≤ 20% islet amyloid.

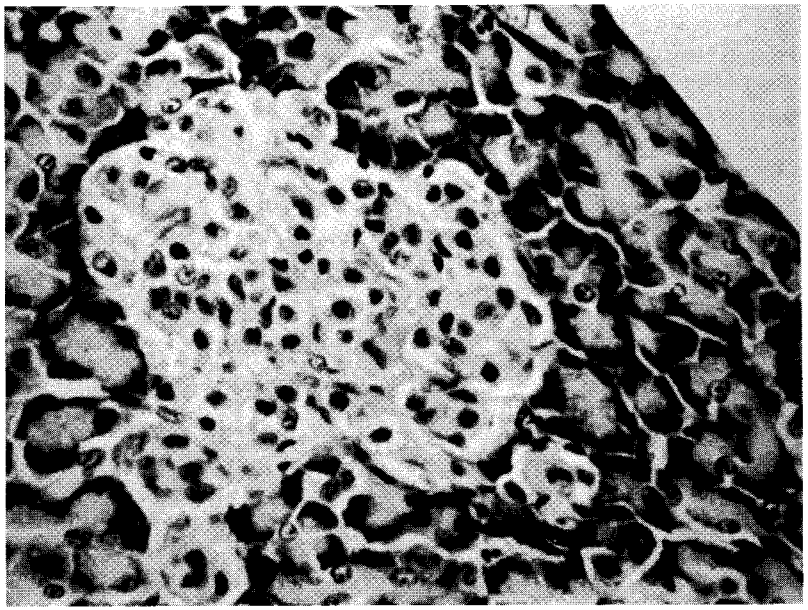


Figure 3. Normal feline pancreatic islet with pancreatic amyloid comprising less than 4% of islet volume. (Congo Red and hematoxylin, × 400.) (*From* Lutz TA, Ainscow J, Rand JS: Frequency of pancreatic amyloid deposition in cats from southeastern Queensland Aust Vet J 71:254, 1994; with permission.)

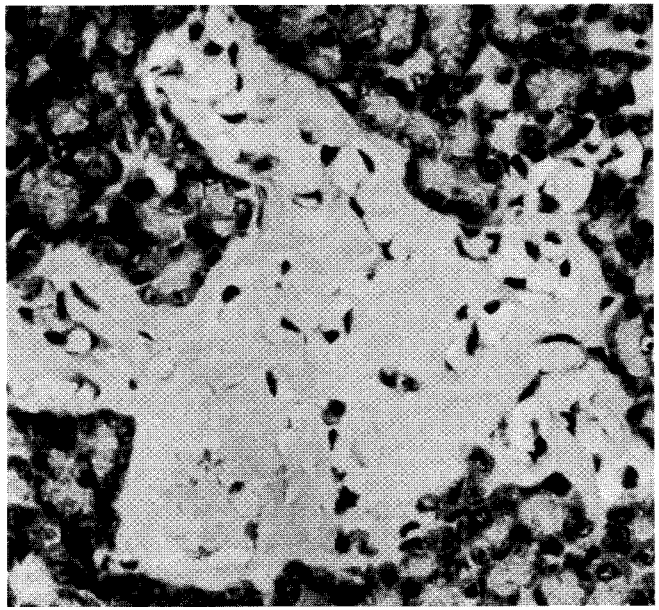


Figure 4. Abnormal feline pancreatic islet with loss of islet cells and pancreatic amyloid comprising greater than 50% of islet volume. (Congo Red and hematoxylin, × 400.) (*From* Lutz TA, Ainscow J, Rand JS: Frequency of pancreatic amyloid deposition in cats from southeastern Queensland Aust Vet J 71:254, 1994; with permission.)

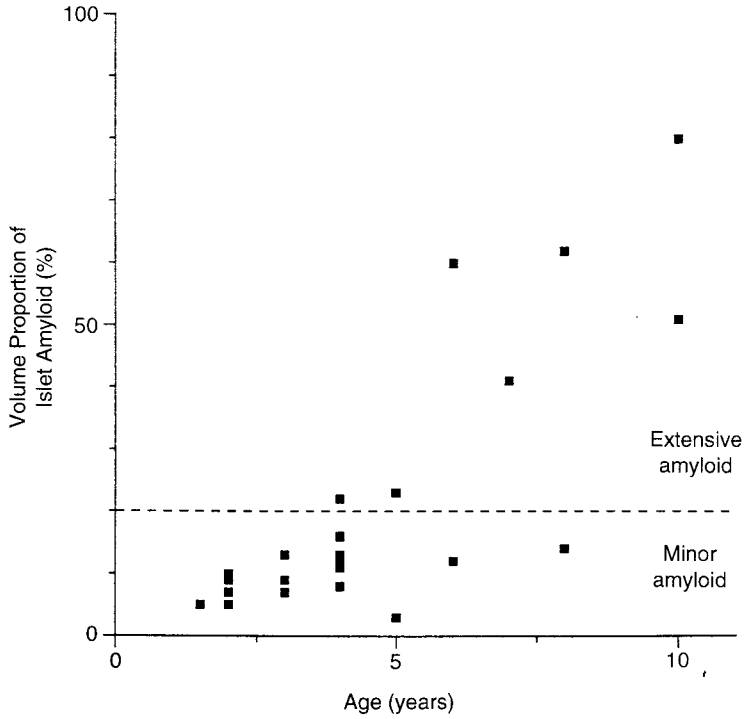
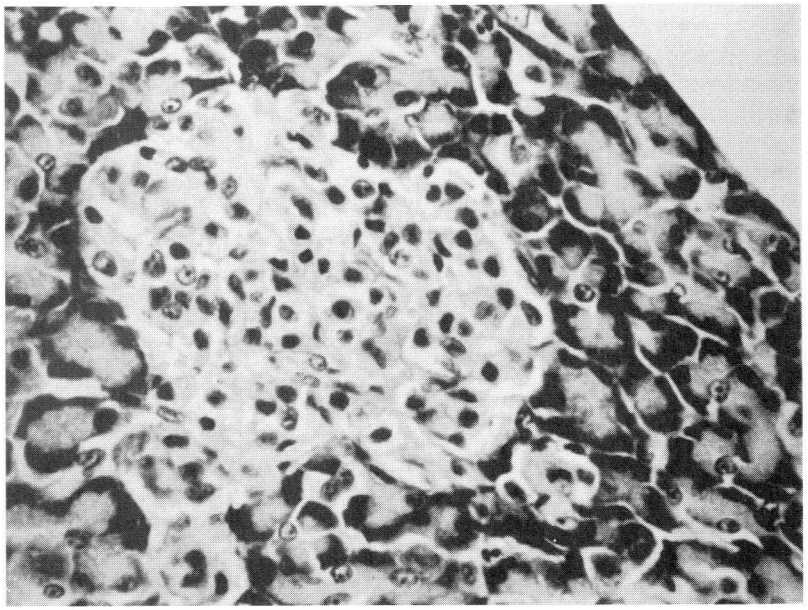


Figure 5. Relationship between the age of the cat and amount of pancreatic amyloid deposition (expressed as the volume proportion of islet amyloid in percent; n = 22).

volume replaced by amyloid (Fig. 4). Amyloid deposition increases with age, and in cats seven years of age or older, it frequently comprised more than 50% of the islet volume (Fig. 5).[51, 53, 76, 77, 96]

Although small amounts of pancreatic amyloid do not result in fasting hyperglycemia,[76, 138] a direct correlation has been found between the amount of amyloid and the degree of glucose intolerance (Fig. 6).[76, 96] Islet amyloid deposition is thought to contribute to beta cell dysfunction and degeneration, both directly and indirectly. Islet amyloid surrounds beta cells, isolating them from adjacent pancreatic tissue and blood capillaries, and is believed to act as a barrier to the diffusion of nutritive substances and glucose. The resultant effect would decrease the ability of beta cells to detect blood glucose and hormone concentrations, which would lead to impaired beta cell function.[53, 96] Intracellular amyloid formation and contact of amyloid fibrils with cell membranes has also been shown to impair beta cell function and to cause cell death.[68, 100] Initially, islet cell degeneration involves mainly beta cells, but later there is almost total loss of all islet cells and replacement by amyloid.[55, 77, 107] It seems, however, that islet amyloid deposition in type 2 diabetes mellitus is a secondary event that occurs only after primary beta cell dysfunction.[52, 95, 96]



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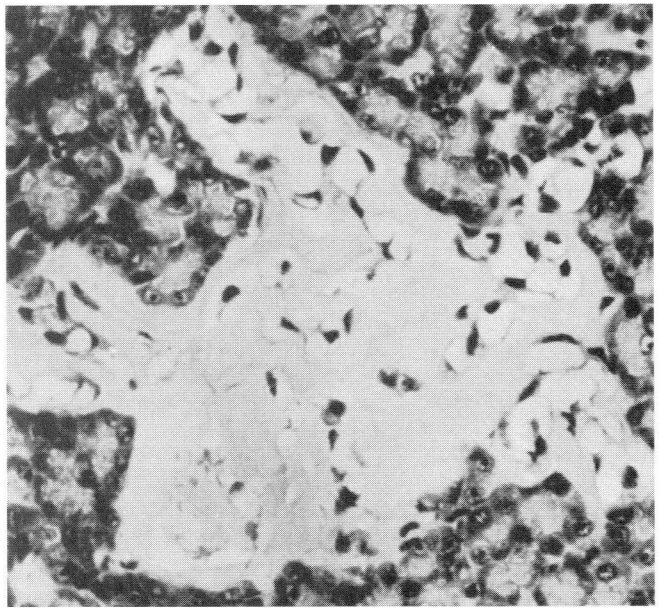

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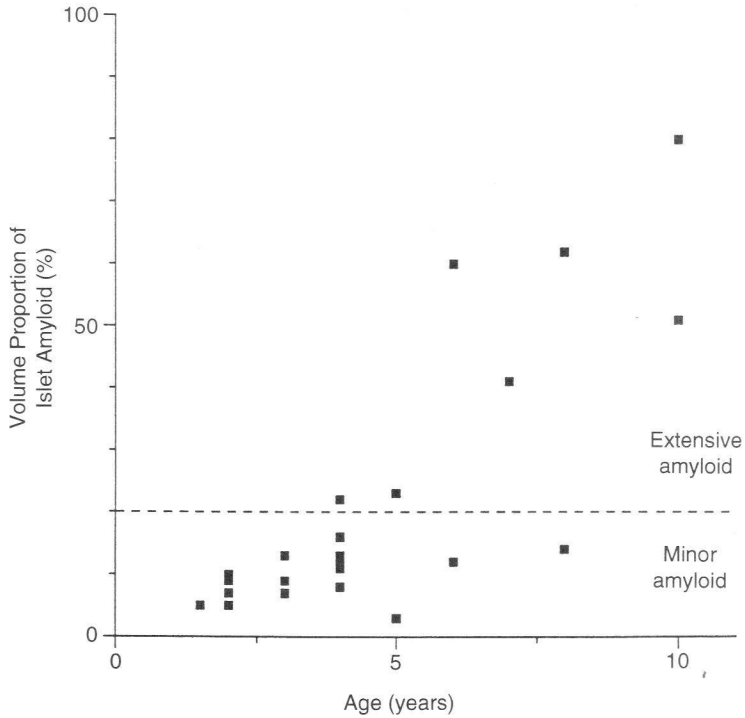

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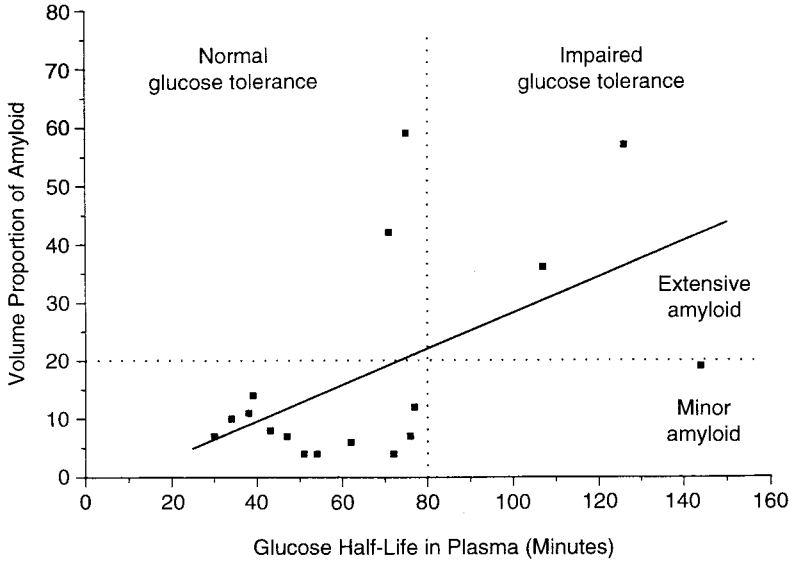

Figure 6. Relationship between the amount of pancreatic amyloid deposition (expressed as the volume proportion of islet amyloid in percent) and the glucose half-life in plasma (inversely related to glucose tolerance) in 17 cats.

Recent data suggest that islet amyloid initially forms intracellularly in beta cells and accumulates extracellularly after exocytosis or cell death.[100] In cats, amyloid deposition first occurs in the islet periphery and extends to the center of the islet with increasing deposition.[77] This corresponds to the distribution of pancreatic beta cells, which are mainly located in the islet periphery.[77, 96]

The major constituent of cat and human islet amyloid is the pancreatic hormone islet amyloid polypeptide (IAPP), also called amylin.[18, 53, 56, 131, 132] The main production site for amylin is pancreatic beta cells in which it is stored with insulin in the secretory granules. In response to an adequate stimulus, such as elevation of the plasma glucose concentration or food intake, amylin is cosecreted with insulin.[13, 47, 58, 71, 82]

Although amylin is secreted from beta cells of all species investigated to date, only a few species (human, primates, cats) develop amyloid deposits in association with diabetes mellitus.[7, 46, 96] For islet amyloid deposition to occur, two prerequisites have to be fulfilled. Both a specific amino acid sequence of amylin and an increased local amylin concentration are required. The propensity of amylin to form amyloid fibrils is determined by the amino acid sequence between positions 20 and 29 of the amylin molecule, and particularly at positions 25 and 26.[7, 56, 99] This section of the molecule has the greatest interspecies variability, whereas the terminal regions of the molecule are well conserved among species and seem to be important for biological activity.[20] Cats and humans have the same amyloidogenic sequence in this critical molecular section, and both develop islet amyloid deposition in association with diabetes.[7, 134] Rats and mice have a different amino acid sequence in the amyloidogenic region of amylin, and do not develop pancreatic amyloid associated with diabetes or in experimental models of amylin hypersecretion.[7, 46, 96] The dependency on a certain amyloidogenic molecular structure for pancreatic amyloid deposition recently was demonstrated in a study using transgenic mice.[46] Amyloid deposition occurred only in mice in which the human amylin gene was transferred into their genome, but not in mice in which the rat amylin gene was transferred.

The second prerequisite believed to be important for amyloid deposition is overproduction of amylin. This is demonstrated in dogs in which amylin overproduction seems to be the major determinant for amyloid deposition. Dogs have the same amino acid sequence in the amyloidogenic portion of the amylin molecule as cats, but they only develop pancreatic amyloid in association with insulinomas, and not with diabetes.[57] As amylin is cosecreted with insulin, and massive insulin overproduction is well documented in canine insulinomas, amylin overproduction in insulinomas is also highly probable. In contrast, most diabetic dogs usually have very low insulin secretion and, presumably, amylin secretion, as a result of beta cell destruction by generalized pancreatitis or immune mechanisms similar to human type 1 diabetes.[1, 31, 112] The local amylin concentration therefore, is presumed to be so low that amylin does not precipitate as fibrils. In human type 1 diabetics, amylin concentration has been reported to be almost undetectable, and amyloid deposition is not a feature of the disease.[107, 126]

One current theory is that initial overproduction of amylin leads to islet amyloid deposition, progressive beta cell degeneration, loss of insulin secretory capacity, and eventually overt diabetes mellitus.[19, 53, 111, 133] Evidence for this theory of disease progression is supported by the finding of increased intracellular amylin concentration, suggesting increased amylin production, in cats with impaired glucose tolerance compared with normal cats and cats with overt diabetes.[52] In contrast, cats with overt diabetes mellitus had significantly greater islet amyloid deposition and beta cell degeneration and decreased insulin secretion during a glucose tolerance test than cats with impaired glucose tolerance.[88, 95] Whether overproduction of amylin results from a primary beta cell dysfunction, or whether it is secondary to overstimulation of beta cells as a compensatory mechanism for peripheral insulin resistance, currently is not known.

Metabolic Actions of Amylin

Amylin is thought to be associated with the pathogenesis of type 2 diabetes not only as a result of amyloid deposition and subsequent beta cell degeneration, but also directly through its metabolic actions.[56, 99, 111] The role of amylin, however, is still not clear, and it remains the object of conflicting and contradictory debate. This is partly because the metabolic actions of amylin in earlier studies were observed at pharmacologic

rather than physiologic concentrations.[12, 59, 97] Recent studies, however, have documented the effects of amylin on glucose metabolism at physiologic concentrations.

The metabolic effects of amylin have been studied more extensively in rats, but there is evidence that the effects are similar in cats.[54] In cats, dogs, and rats, amylin inhibits insulin secretion and produces insulin resistance—the two metabolic hallmarks of type 2 diabetes mellitus.[19, 54, 121, 142] Amylin reduces both basal- and glucose- or arginine-stimulated insulin secretion at physiologic concentrations in rats.[24, 118, 119] The finding that amylin receptor antagonists increase insulin secretion is additional evidence for the inhibitory effect of amylin on insulin secretion.[6, 37, 118, 130, 143]

Amylin receptor antagonists also have been shown to reduce insulin resistance.[23, 128, 143] Based on studies in rats, amylin produces peripheral insulin resistance because it decreases insulin-stimulated glucose uptake by skeletal muscle. This is mediated by an effect on nonoxidative glucose metabolism (glucose storage in the form of glycogen), whereas glucose transport into the muscle cell seems to be influenced secondarily.[18, 19] In vitro experiments using muscle preparations demonstrated that amylin-reduced glycogen synthesis and increased glycogen breakdown by a direct effect on the key enzymes. Amylin inhibited glycogen synthase and stimulated glycogen phosphorylase by mediating their phosphorylation.[23, 64, 66, 140, 141] Increased glycogen breakdown leads to enhanced release of lactate from skeletal muscle cells. Subsequent lactate uptake by hepatocytes stimulates gluconeogenesis and release of glucose into the circulation.[144, 145, 146] Both amylin and glucagon produce hyperglycemia, but by different mechanisms and have additive effects.[144] Glucagon directly stimulates hepatic gluconeogenesis, whereas amylin indirectly stimulates hepatic gluconeogenesis via increased lactate availability.[144] Amylin's effect on glycogen metabolism is summarized in Figure 7.

Because amylin inhibits insulin secretion and stimulates muscle glycolysis, it has been suggested that amylin plays an important role in the control of insulin secretion and in the modulation of glucose metabolism.[111, 118, 146] Although the action of amylin is controversial, its conservation in a wide range of species supports its metabolic importance.[11, 34, 46, 87, 99] Whether abnormalities of amylin secretion represent the primary metabolic defect in type 2 diabetes, or a secondary response to hyperglycemia, is unknown. Recent studies of transgenic mice that hypersecrete human amylin have shown that the mice did not develop hyperglycemia or hyperinsulinemia, despite a marked increase in plasma amylin.[34, 46] This suggests that hypersecretion of amylin is not the primary event in type 2 diabetes.

Amylin Concentrations in Diabetes

There have been conflicting results from studies of amylin concentrations in type 2 diabetic humans and rodent models. One explanation

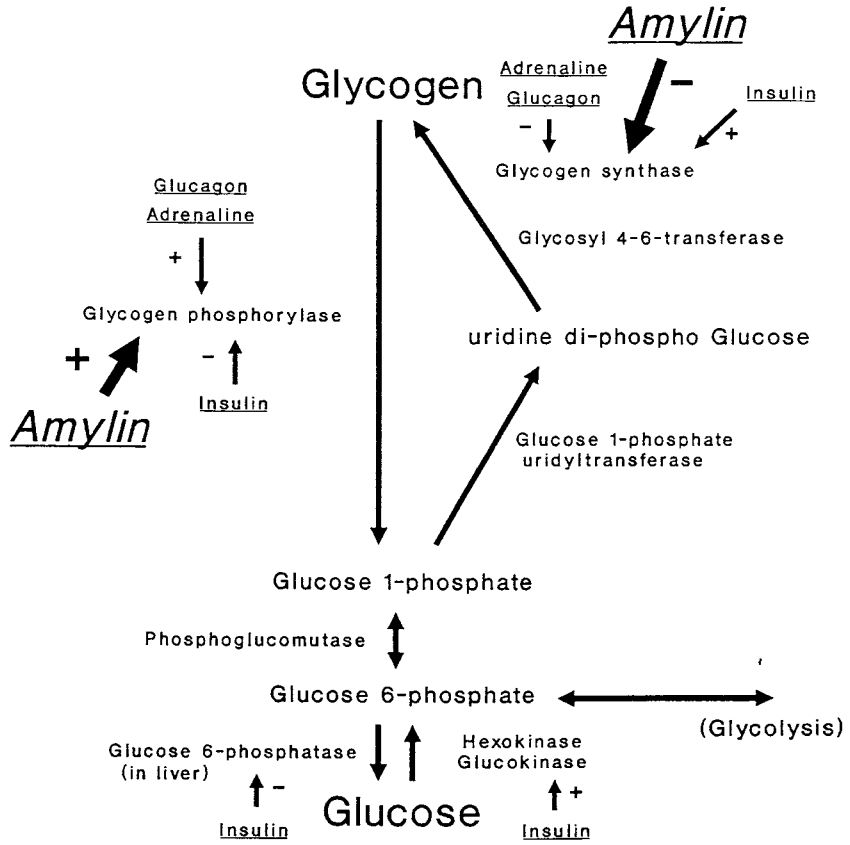

Figure 7. Summary of effects of amylin on glycogen metabolism. Stimulation = +; inhibition = −.

for this controversy is that the studies were performed during different stages in the development of diabetes.[27, 52] Recent evidence supports the theory that amylin concentrations are elevated in insulin-resistant individuals with impaired glucose tolerance and in the early stages of type 2 diabetes.[8, 48, 49, 52, 69, 122] In contrast, subnormal amylin concentrations occur later in the disease as a result of beta cell degeneration.[27, 70]

Recently, amylin concentrations in unextracted plasma were measured in normal cats, cats with impaired glucose tolerance, and in overtly diabetic cats (Lutz TA, unpublished data, 1993).[75] Mean basal amylin concentration in normal cats was 100 ± 4 pmol/L (Table 1). This is similar to values reported for normal rats, but higher than values reported in humans and dogs.[50, 62, 124] Injection of glucose resulted in a parallel increase in plasma amylin and insulin concentrations (Figs. 1 and 8).[75] This cosecretion of amylin and insulin at a constant amylin:insulin ratio has also been reported in nondiabetic humans and laboratory animals.[70]

Table 1. MEAN (± SEM) BASAL PLASMA INSULIN AND AMYLIN IN NORMAL AND DIABETIC CATS

	References Values for Normal Cats (n = 14)	Diabetic Cats (n = 22)
Glucose (mmol/L)	3.3 – 6.9	19.9 ± 0.9
Fructosamine (μmol/L)	326 ± 11	546 ± 18
Plasma insulin (μIU/mL)	8.2 ± 1.0	5.6 ± 0.8
Plasma amylin (pmol/L)	97 ± 4	180 ± 12 (n = 8)

SEM = standard error of mean.

In cats with fasting normoglycemia but impaired glucose tolerance, fasting plasma amylin concentration was similar to normal cats (Fig. 8). After glucose injection, however, cats with impaired glucose tolerance had a delayed increase in plasma amylin concentration, which paralleled the delayed increase in plasma insulin (see Figs. 1 and 8). These findings are similar to some reports from laboratory animals and humans with

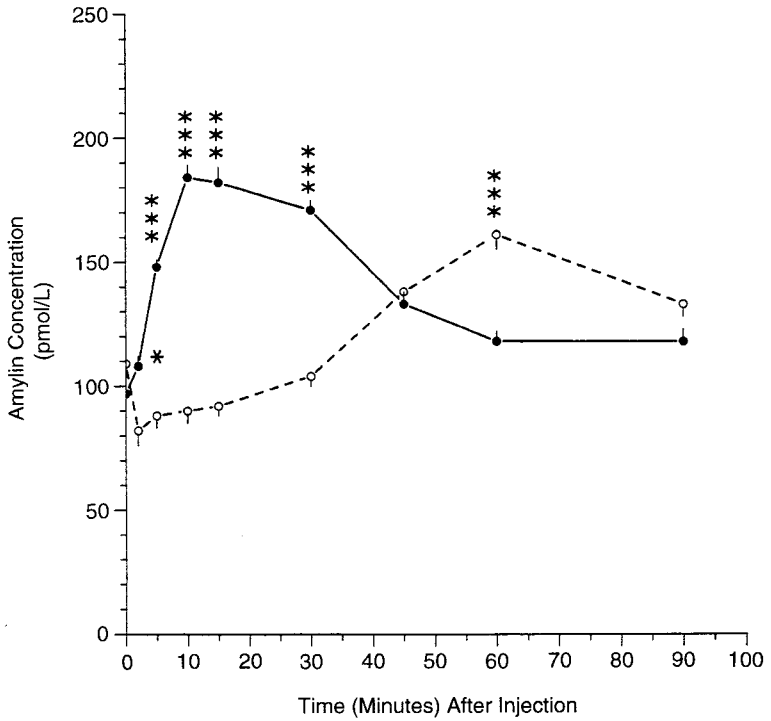

Figure 8. Plasma amylin concentration during a glucose tolerance test (injection of 1 g glucose/kg body weight at t = 0 minutes) in normal cats (glucose $T_{1/2} \leq 80$ minutes; n = 14) and cats with impaired glucose tolerance (glucose $T_{1/2} > 80$ minutes; n = 3) cats. *** Significant difference between glucose tolerant and intolerant cats ($P < 0.001$). ● = normal cats (n = 14); ○ = impaired glucose intolerance (n = 3).

impaired glucose tolerance,[20, 27, 95, 98, 111] but other studies have found increased fasting amylin concentrations associated with impaired glucose tolerance and insulin resistance.[122] In diabetic cats, fasting plasma amylin concentration was elevated markedly, despite a lower than normal insulin concentration. Relative hyperamylinemia, at least in early stages of type 2 diabetes, has been reported in other species.[48, 49, 106, 111, 122] Hyperamylinemia occurs once fasting hyperglycemia is present.[98, 106] This may explain why cats with impaired glucose tolerance but fasting normoglycemia had normal fasting amylin concentrations, and why diabetic cats were hyperamylinemic.

These findings of hyperamylinemia and hypoinsulinemia support the hypothesis that excessive amylin concentrations are involved in the pathogenesis of feline diabetes by reducing pancreatic insulin secretion and by inducing peripheral insulin resistance.[54] Long-term excessive amylin secretion may then lead to increased deposition of amylin as pancreatic islet amyloid and further impair B-cell function.[52, 53]

Amylin and Obesity

Amylin causes peripheral insulin resistance by impairing glucose utilization in skeletal muscle. Adipose tissue, however, has been shown to be insensitive to the action of amylin.[18, 19, 67, 72] Hence, increased concentrations of amylin have been theorized to promote fat synthesis and the development of obesity, by shifting glucose deposition from glycogen in muscle, to fat in adipose tissue.[67] According to this theory, hypersecretion of amylin is the primary event, and the resultant insulin resistance in muscle leads to secondary obesity. Therefore, obesity would be the consequence of type 2 diabetes mellitus, rather than a contributing factor inducing insulin resistance.[19]

Most reports investigating the relationship between amylin and obesity are from studies in laboratory animals. Elevated levels of plasma amylin have been observed in genetically obese experimental animals,[124] but there is still controversy concerning the sequence of events. Does amylin hypersecretion lead to obesity? Or does obesity-induced insulin resistance lead to secondary amylin hypersecretion? Because insulin resistance caused by obesity results in compensatory hyperinsulinemia, concurrent hypersecretion of amylin would be expected to follow secondarily, because it is cosecreted with insulin. Excessive amylin secretion may then contribute to the metabolic derangements of type 2 diabetes mellitus.[69, 124] Because transgenic mice secreting excessive amounts of amylin did not become obese, it suggests that obesity is a cause rather than a consequence of hyperamylinemia.[46] To date, there have been no published studies in diabetic cats that have investigated the relationship between amylin secretion and obesity.

Further Metabolic Effects of Amylin

Amylin has other metabolic effects, mostly investigated in laboratory animals, that do not seem to be linked directly to the development

of diabetes.[20] Amylin has been shown to have a strong anorectic effect when administered peripherally or into the central nervous system. The anorectic effect seems to be specific, because it primarily acts on food intake and not via an influence on water intake, gastric emptying, or the induction of a food aversion.[2, 14, 83] This effect is independent of the effect of amylin on glucose metabolism,[2, 14, 15, 16, 74, 78, 83, 84] and seems to be mediated via the hypothalamus, because hypothalamic amylin receptors have been demonstrated.[4, 78, 79]

Amylin shares some structural homology with calcitonin,[147] and it has been shown to induce hypocalcemia,[129, 145, 147] probably via interaction with calcitonin receptors.[117] Calcitonin–gene-related peptide is another hormone structurally related to amylin. It is a strong vasodilator agent, an effect that is shared by amylin.[38, 145] Amylin has also been implicated, however, in the hypertension often associated with diabetes, via an influence on the renin-angiotensin-aldosterone system.[36, 113]

IMPAIRED GLUCOSE TOLERANCE AND TRANSIENT DIABETES

Cats with impaired glucose tolerance have a normal or slightly increased fasting blood glucose and an increased glucose concentration or glucose half-life after a glucose tolerance test.[61, 95] These cats do not have clinical signs of diabetes. Humans with impaired glucose tolerance progress to overt diabetes at a rate of 1% to 5% per year, although decompensation is not inevitable.[42] Those with highest risk of progressing to overt diabetes have the lowest insulin response during a glucose tolerance test.[65] Impaired glucose tolerance is relatively common in cats (Lutz TA, Rand JS, unpublished data, 1993), but the rate of progression to overt diabetes is unknown.

In some diabetic cats, treatment with insulin or oral hypoglycemic drugs can be discontinued after several weeks to months. These cats are transient diabetics and comprise approximately 15% of diabetic cats.[92] Although the literature is scarce, some transiently diabetic cats still have impaired glucose tolerance once fasting glucose is normal.[61, 92, 109] The mechanism for transient diabetes is unknown. Intercurrent disease and obesity, however, cause insulin resistance and decrease beta cell function (Link KRJ, Rand JS, unpublished data, 1994).[22, 91, 95] If superimposed on pre-existing impaired glucose tolerance, these additional factors could cause decompensation to fasting hyperglycemia and clinical signs of diabetes. The subsequent effect of glucose toxicity on beta cells would further impair beta cell function. Because transiently diabetic cats spontaneously revert to fasting normoglycemia after receiving hypoglycemic agents or insulin therapy, it suggests that glucose toxicity is involved in the pathogenesis.[61, 93] However, another self-limiting cause of impaired beta cell function or insulin resistance cannot be discounted; with recovery to fasting normoglycemia being dependent on time rather than hypoglycemic therapy. In humans with type 2 diabetes, transient worsening of glucose tolerance can occur secondary to stress or illness, and necessitate short-term insulin therapy.[90] Conversely, some human diabetics on oral hypoglycemic drugs can discontinue therapy, usually because of better dietary compliance.[86]

PERSPECTIVES IN THE TREATMENT OF FELINE DIABETES

Although 75% of human type 2 diabetics can be managed with oral hypoglycemics,[85, 86] these drugs are only successful in 30% to 50% of cats.[61, 92, 93] Sulfonylureas are the most common class of oral hypoglycemic drugs. They act by increasing insulin secretion from beta cells and the sensitivity of peripheral tissues to insulin; therefore, they are only useful if some functional beta cells are present. Because amyloid deposition in cats seems to be more profound than in humans and many diabetic cats have few remaining islet cells, insulin therapy is more frequently required. Additionally, diabetes in cats is often undiagnosed longer than in humans, and the resultant toxic effect of prolonged severe hyperglycemia on beta cell function may explain why a high proportion of diabetic cats need at least temporary insulin replacement therapy. Reduction of blood glucose to less than 360 mg/dL (20 mmol/L) is important for beta cell recovery from glucose toxicity (Link KRJ, Rand JS, unpublished data, 1994).

New perspectives for the treatment of feline diabetes have emerged as a result of the discovery of the metabolic effects of amylin and glucagon-like peptide-1. As excess amylin may contribute to the metabolic derangements of diabetes, amylin receptor antagonists are being developed to treat human type 2 diabetics, and could be useful in diabetic cats.[36] Amylin antagonists increase basal and glucose-stimulated insulin secretion, and there is evidence that they improve insulin sensitivity and glucose tolerance. Preliminary studies with amylin antagonists in rats have yielded promising results, but clinical studies are required to prove the effectiveness of these agents in the treatment of feline and human diabetes.[36] In contrast, in insulin-dependent patients with negligible endogenous insulin and amylin secretion, amylin replacement therapy may prove beneficial. It is hoped that treatment with amylin analogs will reduce the severity of hypoglycemic episodes associated with insulin therapy and result in more normal glucose metabolism.[111]

Glucagon-like peptide-1 stimulates both insulin production and secretion, in contrast to sulfonylureas that mainly stimulate insulin secretion.[39] Because the action of glucagon-like peptide-1 is abolished when glucose levels decrease to below normal, it would not be associated with the risk of significant hypoglycemia as are insulin or sulfonylureas, and thus, it would provide unique advantages in the treatment of non–insulin-dependent diabetes.[39, 123] Glucagon-like peptide-1 also has the potential to increase insulin secretion in beta cells affected by glucose toxicity[45] and to normalize the increased glucagon concentration often

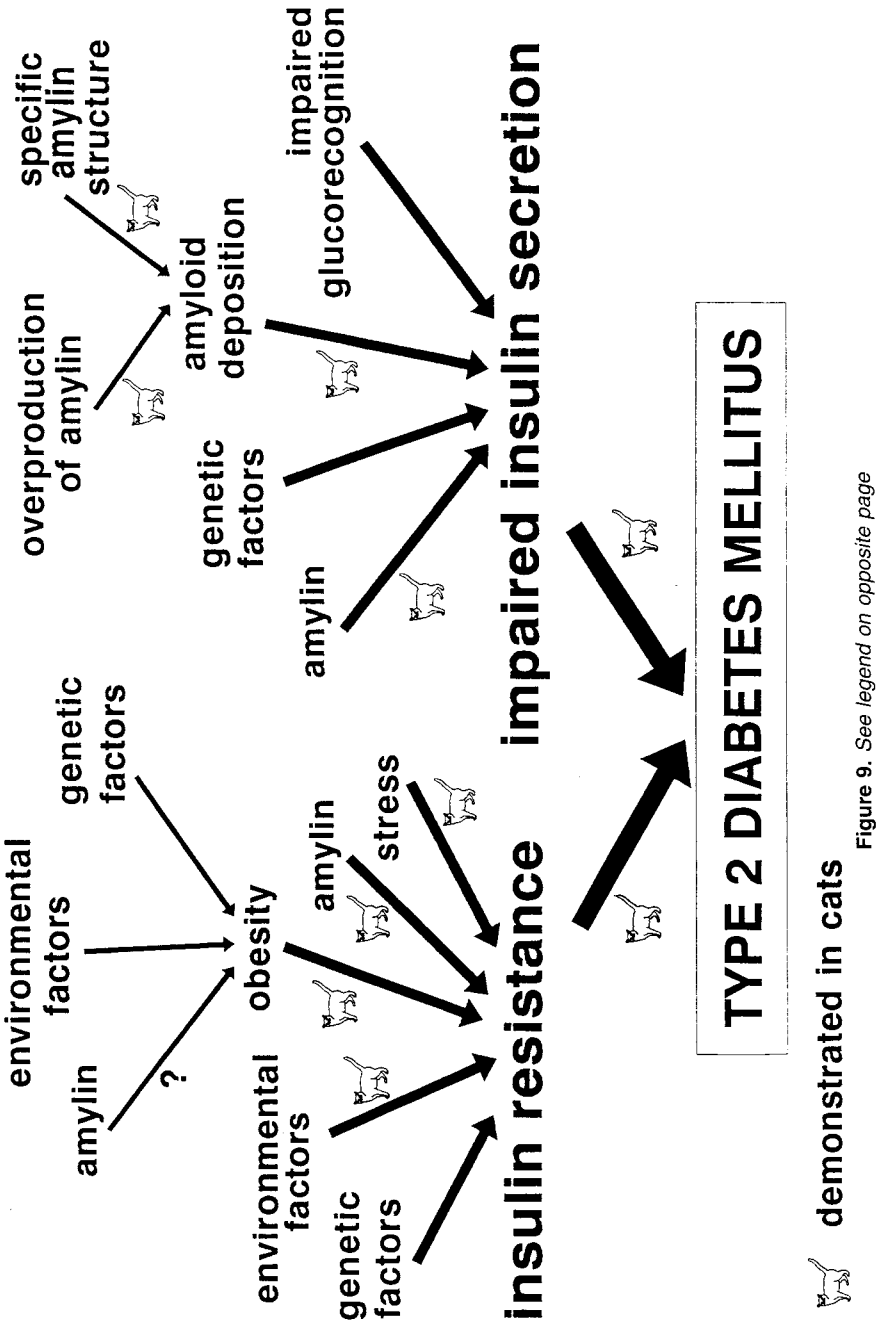

Figure 9. *See legend on opposite page*

found in diabetic cats.[95] However, increased glucagon-like peptide-1 secretion and receptor desensitization has been reported in diabetics; therefore, the usefulness of glucagon-like peptide-1 in the treatment of type 2 diabetes is at present theoretical, although early results are promising.[127] Although glucagon-like peptide-1, amylin, and amylin antagonists require parenteral administration, orally effective analogs currently are being developed.[36, 39, 123]

SUMMARY

Cats are one of the few species that develop a form of diabetes mellitus that is clinically and histologically analogous to human type 2 diabetes mellitus. Figure 9 summarizes the etiologic factors thought to be involved in the development of feline and human type 2 diabetes.

The main metabolic characteristics of type 2 diabetes mellitus are impaired insulin secretion and resistance to the action of insulin in its target tissues. Impaired beta cell function occurs before histologic changes become evident. The characteristic histologic finding in cats with type 2 diabetes is deposition of amyloid in pancreatic islets. Amyloid deposition occurs before the onset of clinical signs, but does not seem to be the primary defect. Pancreatic amyloid is derived from the recently discovered pancreatic hormone amylin. Amylin is synthesized in pancreatic beta cells, and is co-stored and co-secreted with insulin. Amylin has been postulated to be involved in the pathogenesis of feline diabetes mellitus both through its metabolic effects, which include inhibition of insulin secretion and induction of insulin resistance, and via progressive amyloid deposition and beta cell degeneration. Increased amylin concentration has been documented intracellularly in cats with impaired glucose tolerance and in the plasma of diabetic cats, and supports the hypothesis that amylin is involved in the pathogenesis of type 2 diabetes. Obesity is a common finding in diabetic felines and is a contributing factor to the insulin resistance present in type 2 diabetes.

Clinical signs of diabetes develop once total insulin secretion decreases to 20% to 25% of normal levels. Many diabetic cats have been treated successfully with oral hypoglycemics, but 50% to 70% of diabetic cats are insulin dependent. Based on histologic evidence, this is the result of extensive amyloid deposition and subsequent beta cell degeneration, rather than autoimmune destruction of pancreatic beta cells associated with type 1 diabetes.

Alternative ways of treating type 2 diabetes currently are being investigated. Amylin antagonists recently have been proposed as a novel treatment to reverse the deleterious effects of excessive amylin concen-

Figure 9. Summary of etiological factors involved in the pathogenesis of type 2 diabetes mellitus. Factors documented to be involved in feline diabetes are indicated by a cat symbol. (*From* Lutz TA, Rand JS: A review of new developments in Type 2 diabetes in human beings and cats. Br Vet J 149:527, 1993; with permission.)

trations. The gastrointestinal hormone glucagon-like peptide-1 may also prove useful in treating diabetic cats, because of its stimulatory effect on insulin secretion and synthesis, and the absence of significant hypoglycemic effect.

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PATHOPHYSIOLOGY OF CANINE DIABETES

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PATHOGENESIS OF DIABETES MELLITUS

The term *diabetes mellitus* (DM) encompasses etiologically unrelated diseases and includes many different causes for disturbed glucose tolerance. Characteristic for all types of diabetes is the impairment of insulin release from the pancreatic beta cells. Because of major problems with nomenclature, a classification system was developed in 1979[43] and revised in 1985[58] in which diabetes was divided into four groups: (1) insulin-dependent diabetes mellitus (IDDM); (2) non–insulin-dependent diabetes mellitus (NIDDM); (3) gestational diabetes; and (4) diabetes associated with certain syndromes or conditions (secondary diabetes). In dogs, diabetes usually is divided broadly into IDDM and NIDDM. Because the pathogenesis and clinical picture in some stages of the disease are quite different, they are discussed separately. Only a few studies have examined the mechanisms involved in the pathogenesis of diabetes in dogs. Much of the information presented in this article, therefore, is based on studies in humans and other in vivo or in vitro models of diabetes with the hope that it will stimulate investigations into the pathogenesis of canine DM.

GENERAL PRINCIPLES

Insulin is produced in the beta cells of the islets of Langerhans in the endocrine pancreas. The islets also contain glucagon-secreting alpha

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