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Minireview

Diabetes from humans to cats

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ABSTRACT

Diabetes mellitus is a common endocrinopathy in humans and in cats. The general prevalence of diabetes mellitus, and in particular of type 2 diabetes, has risen dramatically in recent years. This increase has often been linked to the rise in the obesity pandemic because obesity and the ensuing metabolic consequences constitute major risk factors for human type 2 and for feline diabetes. Feline diabetes shares many features of human type 2 diabetes in respect to its pathophysiology, underlying risk factors and treatment strategies. This review will briefly summarize major characteristics in the human and the feline disease and where available, point out the current knowledge on similarities and differences.

1. Human type 2 diabetes mellitus

Human type 2 diabetes (T2DM) is a metabolic disorder which arises from the relative inability of the endocrine pancreas to meet increasing metabolic demands and to compensate for insulin resistance. Insulin resistance is a state of reduced responsiveness of insulin-target tissues to normal circulating levels of insulin. The degree to which glucose tolerance deteriorates in insulin-resistant individuals varies as a function of both the magnitude of insulin resistance and the capacity of the pancreas to adequately compensate for this defect. If insulin secretion fails to fully compensate, a condition of hyperglycemia despite hyperinsulinemia occurs. Hence, the worsening of insulin resistance together with abnormalities in compensatory insulin secretion and finally a failure of beta-cell function may eventually lead to the development of T2DM [64].

1.1. Epidemiology

1.1.1. Genetics

T2DM is a multifactorial disease influenced by heterogeneous factors including diet, physical activity, age and genes. Genetic predisposition is a key contributing factor in T2DM; the expression of a number of gene variants, including some genes encoding for transcription factors, enzymes involved in glucose metabolism proteins and molecules of the insulin signaling pathways, has been associated with islet cell dysfunction. However, none of the known genetic factors alone seems to be responsible for the vast majority of T2DM patients, despite the high overall heritability of T2DM [11].

1.1.2. Glucotoxicity and lipotoxicity

Among the several acquired factors that impair β-cell function, the role of glucose toxicity and lipotoxicity is of particular importance. The mechanism of β-cell loss is attributed to an increase in β-cell apoptosis that is not compensated by adequate regeneration. Chronic exposure to hyperglycemia has been shown to cause β-cell hypertrophy and eventually apoptosis; prolonged exposure of human and rodent β-cells to high glucose levels leads to increased production and release of interleukin-1β (IL-1β) followed by β-cell specific up-regulation of the rate of apoptosis [42,44].

Although fluctuations in free fatty acids (FFAs) levels are critical for normal insulin release, a prolonged increase in FFAs concentrations (lipotoxicity) is associated with impairments in insulin biosynthesis and glucose-stimulated insulin secretion. High levels

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of saturated FFAs, in particular palmitate, induce apoptosis independently from glucose in cultured human and rat islets [40,43].

1.1.3. Amyloid deposition

Concurrent with the effects of hyperglycemia and hyperinsulinemia, abnormalities in amylin secretion, and in particular abnormalities in the processing of amylin and its local deposition as amyloid in the islets, may contribute to the progressive loss of β-cells in T2DM. In humans, monkeys and cats, but not in mice or rats (which do not spontaneously develop a T2DM like syndrome), amylin has an amyloidogenic-promoting region, which resides within amino acids 20–29 of the 37 amino acid peptide hormone, and which predisposes amylin to aggregate and form pancreatic islet amyloid in the species named above. Islet amyloidogenesis involves the stepwise aggregation of monomers of amylin into oligomers, fibrils and, ultimately, mature amyloid deposits that can be observed under light microscopy. However, rather than these large amyloid deposits, the small amylin oligomers, which are formed in the early stages of fibril aggregation, might be the toxic principle responsible for amylin-mediated β-cell cytotoxicity and death. In fact, the toxicity of amylin oligomers seems to derive from the disruption and leakage of β-cell membranes due to the formation of ion channels/pore into the membrane [32,50]. Further, the subsequent growth of amylin fibrils in the extracellular space impairs nutrients and oxygen uptake into the β-cell which in turn contributes to endoplasmic reticulum (ER) stress, and ultimately apoptosis [33].

1.2. Inflammation and diabetes

More recently, it has been proposed that inflammation might be the possible common mechanism embracing the effects of glucotoxicity, lipotoxicity and increased amyloid deposition on β-cell dysfunction in T2DM. This is suggested by the pathologically elevated levels of islet-derived cytokines, e.g. IL-1β, and the subsequent chemokines-mediated recruitment of macrophages observed in diabetic patients [13,46].

The first evidence of a possible involvement of inflammation in diabetes can be traced back to more than a century ago [15,69], however, it was only in 1993 that the pioneering work by Hotamisligil and colleagues [28] causally linked inflammation to the pathogenesis of obesity, insulin resistance and T2DM. The revolutionary idea that adipose tissue-derived pro-inflammatory cytokines (e.g. tumor necrosis factor-α [TNF-α]) are overproduced by fat tissue of obese individuals and that these cytokines are able to induce insulin resistance in obese subjects, stimulated extensive research regarding the role of inflammation in the pathogenesis of insulin resistance, obesity and T2DM.

1.2.1. Inflammation and insulin resistance

Originally considered to be a passive lipid storage site, adipose tissue is now known to produce and secrete many signaling proteins that modulate many metabolic processes. These secretory products, known as ‘‘adipokines’’ or ‘‘adipocytokines, either directly or indirectly control triglyceride (TG) accumulation and differentiation of pre-adipocytes and initiate inflammatory responses in adipose tissue.

1.2.1.1. Adipokines. Primary adipokines (such as leptin and adiponectin) are produced primarily or exclusively by adipocytes.

The plasma leptin concentration correlates with body fat mass and increases and decreases in response to weight gain or weight loss, respectively, but leptin increases also more acutely in response to food intake [21]. Leptin stimulates β-oxidation of FA and inhibits lipogenesis in peripheral tissues; hence leptin functions to decrease TG content in these tissues and to decrease FA levels in the circulation.

In obesity, the physiological responses to leptin are diminished in the hypothalamus and possibly elsewhere, and leptin-target cells become resistant to its actions. The resistance to leptin's effects in the hypothalamus and the concurrent lowering of the body's energy metabolism may lead to further weight gain in obese subjects. Resistance to leptin action is often associated with severe insulin resistance as the result of increased ectopic fat accumulation and lipotoxic effects in insulin-sensitive tissues.

Furthermore, chronically elevated concentrations of leptin may provoke inflammatory reactions and apoptosis in β-cells. Glucose and leptin-induced β-cell apoptosis are both related to the activation of the c-jun-NH2-terminal kinase (JNK) pathway in human islets and in insulinoma cells [41].

Adiponectin is produced exclusively by mature adipocytes and circulates in plasma in multimeric form, with the high molecular weight form being the most biologically active. Its secretion is stimulated by insulin and by dietary constituents such as amino acids [8]. Adiponectin levels inversely correlate with fat mass, hepatic lipid content, dyslipidemia and insulin resistance. Adiponectin increases insulin sensitivity and influences glucose metabolism by increasing glycolysis and FA oxidation. Plasma levels of adiponectin are lower in subjects with obesity, T2DM, cardiovascular disease, hypertension, and metabolic syndrome compared to healthy patients [68].

1.2.2.2. Adipocytokines. Among the numerous chemoattractant cytokines secreted by hypertrophied adipocytes in obesity, monocyte chemotactic protein-1 (MCP-1) has the role to attract circulating monocytes to migrate into adipose tissue. These recruited monocytes mature into classically activated macrophages; by secreting TNFα and other cytokines such as IL-1β, they continue to attract more macrophages.

TNF-α and IL-6 plasma levels are elevated in obese humans and animals, and their production in visceral fat seems to be higher than in subcutaneous adipose tissue; this in principle is consistent with the more deleterious effect of visceral compared to subcutaneous fat accumulation. Both cytokines inhibit insulin action in adipocytes in part through serine phosphorylation of insulin receptor substrate (IRS) proteins which lowers their activity with the subsequent inhibition of insulin-stimulated glucose transport via GLUT4. In addition, the activation of inflammatory pathways contributes to induce and propagate ER stress with detrimental consequences on insulin sensitivity and systemic metabolism [10].

1.2.2.3. Inflammatory lipid mediators. During prolonged caloric overload, the inappropriate accumulation of lipids in tissues other than fat, such as liver, skeletal muscle, heart and pancreatic β-cells, which rarely occurs under physiological conditions, overwhelms the capacity of the cells to oxidize fat and negatively affects the normal metabolic response and the functional integrity of the ER. By binding to Toll-like receptor-4 (TLR4) on adipose cells and macrophages, FFAs can directly drive the activation of the inflammatory signaling cascade via JNK and NF-κβ-Iκβ kinase (IKKβ), which is directly linked to serine phosphorylation of IRS-1 and IRS-2 and to the impairment of insulin sensitivity and glucose transport [62]. Therefore, the ‘‘sensing’’ of saturated FFAs by TLR4 causes a classical activation of inflammatory pathways and contributes to the development of insulin resistance, suggesting a coupling between inflammation and insulin resistance, in the setting of obesity.

1.2.2. Inflammation and pancreatic β-cell function

During infections and immunologic responses as well as during the metabolic syndrome, chronic metabolic stress may be respon-