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Review

Diabetes and cardiovascular autonomic dysfunction: Application of animal models

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ABSTRACT

When diabetes is associated with cardiovascular autonomic dysfunction, there is a poor prognosis and increased morbidity and mortality. Information on the mechanisms of diabetes-associated autonomic dysfunction has been provided by advanced studies using physiological, pharmacological, anatomical and molecular methods in experimental animal models of insulin deficiency and resistance. This has been augmented by new approaches which combine diabetes induction with genetically modified animal models. The aim of this review is to outline and discuss the animal models used for the study of insulin deficiency and insulin resistance with a focus on autonomic neural interactions. The goal is to better understand the clinical relevance of cardiovascular autonomic dysfunction associated with diabetes.

Contents

1. Introduction

Diabetes mellitus has reached epidemic levels in the United States (US) and worldwide. The prevalence estimate by the Center for Disease Control (CDC) in 2008 is 8% of the US population or 24 million people. It is of particular concern that the disease incidence is expected to increase worldwide by more than 100% between 2000 and 2030 (Wild et al., 2004). Clinical issues related to the disease are focused not only on glucose metabolism, but also on cardiovascular pathologies which are the likely cause of morbidity and mortality. It is well established that diabetics are likely to develop cardiovascular diseases such as hypertension, atherosclerosis, stroke and congestive heart failure (Resnick and Howard, 2002). Furthermore, it is known

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that cardiovascular autonomic neuropathy is common in diabetics and contributes to the overall clinical pathology (Jermendy, 2003; Ewing et al., 1980).

In the 1920s, Walter Cannon, the patriarch of physiological sciences, divided the autonomic nervous system into the sympathetic and parasympathetic divisions. He proposed that the two systems antagonize each other in order to maintain "homeostasis", a word that he coined (Cannon, 1939). The concept of altered autonomic function as a pathophysiological condition dates from the 1920s with a report from Bradbury and Eggleston that suggested a neurogenic cause for postural hypotension (Bradbury and Eggleston, 1925). In more general terms, dysautonomia refers to a condition in which altered autonomic function adversely affects health. These conditions range from transient episodes in otherwise healthy individuals to progressive neurodegenerative diseases (Goldstein et al., 2002).

Clinical studies have demonstrated that chronic diabetic complications occur late after disease onset, reflecting structural abnormalities in nerves, kidney, retina and blood vessels with the appearance strongly correlated with the duration of the diabetes and the level of glycemic control (The Diabetes Control and Complications Trial Research Group, 1993; UKPDS Group, 1998; Resnick and Howard, 2002). Autonomic neuropathy is a frequent complication of diabetes which is associated with high morbidity and mortality (Ewing et al., 1980; Kempler et al., 2002). The reported prevalence of diabetic autonomic neuropathy varies widely depending on the population studied and the methods of assessment. There are estimates that a large proportion of diabetics (up to 50%) show evidence of autonomic neuropathy (Kempler et al., 2002; Maser et al., 2003). Diabetic autonomic neuropathy typically occurs as a system-wide disorder affecting all parts of the autonomic nervous system (Vinik et al., 2003). The neuropathology is usually manifest first in the longer autonomic nerves such as the vagus which accounts for almost 75% of parasympathetic activity (Ziegler, 1999). It is for this reason that even early onset effects of diabetic autonomic neuropathy are seen system wide. Vagal impairment seen in early diabetes leads to a relative predominance of sympathetic activity in sympatho-vagal balance. The increased mortality in diabetics is likely related to disorders in cardiovascular control, including impairment of autonomic reflexes leading to orthostatic hypotension, exercise intolerance, non-symptomatic myocardial infarction and sudden death from cardiac arrhythmias (Page and Watkins, 1978; Hilsted et al., 1982). Meta analysis on the relationship between cardiovascular autonomic neuropathy and risk of mortality in diabetics showed an increase in diabetics with autonomic dysfunction (Maser et al., 2003). The average mortality rate for ten studies over variable time spans was 29% in diabetics with autonomic dysfunction.

It should be emphasized that blood pressure and heart rate are not direct correlates of autonomic neural function. For evaluation of diabetic/autonomic interactions, it is necessary to examine the influence of the disease on heart rate and blood pressure variability, response to autonomic pharmacological blockade, functional changes in baro- and chemo reflexes and neuroanatomical changes. Autoregressive spectral analysis is a non-invasive, statistical means for studying autonomic function in both humans and animals (Malliani et al., 1991; Joaquim et al., 2004; Farah et al., 2004). Heart rate variability (HRV) and blood pressure variability (BPV), estimated in time or frequency (spectral analysis) domain, are used to detect early abnormalities in autonomic modulation of the cardiovascular system (Pagani et al., 1988; Spallone and Menzinger, 1997). Changes often occur before or without alterations in blood pressure and heart rate. For example, in human diabetics spectral analysis revealed a significant decrease in HRV, which was easily apparent before changes in other cardiovascular parameters (Pagani et al., 1988). There is also an association between reduced HRV and increased risk for sudden death in patients with chronic heart failure (La Rovere et al., 2003) or diabetes (Kataoka et al., 2004). The importance of BPV in clinical pathologies was established with reports that increased BPV was associated with end-organ damage (Parati et al., 1987; Zanchetti and Mancia, 1987).

In type 1 diabetes, there is evidence for early impairment of parasympathetic function, as evaluated by spectral analysis (Weston et al., 1998; Poulsen et al., 1997) or other cardiovascular function tests (Weinrauch et al., 1998). Type 1 diabetics also show high levels of plasma epinephrine and increased cardiac flow velocity, both signs of sympathetic activation (Ferraro et al., 1990). In type 2 diabetes, glucose intolerance is the first step followed by insulin resistance and a resultant hyperinsulinemia (van Haeften et al., 2002). It is thought that insulin and glucose activate the sympathetic nervous system with a consequent hyperdynamic state (increased heart rate and cardiac output), increased peripheral resistance, sodium retention and eventual development of hypertension (Facchini et al., 1996; Lembo et al., 1992; Anderson et al., 1991). The consensus is that diabetic autonomic neuropathy is associated with parasympathetic withdrawal, sympathetic dominance and high blood pressure.

Composite clinical results suggest that autonomic dysfunction is a common characteristic of both type 1 and type 2 diabetes. This neural disorder is of prime importance in the development of a variety of cardiovascular pathologies from atherosclerosis to myocardial infarction. This is emphasized in a recent publication by the American Diabetes Association for healthcare professionals that highlights the significance of diabetic neuropathy in disease evaluation and therapy (Boulton et al., 2005). The objective of this review is to outline and discuss the animal models used for the study of insulin deficiency and insulin resistance with a focus on autonomic neural interactions. The ultimate goal is to understand the clinical relevance of cardiovascular autonomic dysfunction associated with diabetes.

2. Insulin deficient models

2.1. Streptozotocin induced diabetes

Experimental diabetes induced by streptozotocin (STZ) has been used extensively to study the relationship between diabetes and autonomic cardiovascular dysfunction. STZ destroys pancreatic ß cells, resulting in a diabetic syndrome in animals, similar to that seen in human type 1 diabetes, characterized by hyperglycemia, hypoinsulinemia, glucosuria and loss in body weight (Junod et al., 1969; Tomlinson et al., 1992). With regard to cardiovascular parameters, STZ diabetic rats showed either no change or a reduction in blood pressure (Maeda et al., 1995a,b; De Angelis et al., 2000; Dall'Ago et al., 1997; Chang and Lund, 1986; Tomlinson et al., 1990; Harthmann et al., 2007; Souza et al., 2007). In mice, STZ diabetes was associated with a mild hypertension which was corrected by treatment with angiotensin converting enzyme (ACE) inhibitors (Katoh et al., 2000; Wichi et al., 2007). With regard to heart rate, a resting bradycardia was observed in STZ diabetic rats, while in mice there were no changes (Maeda et al., 1995a; De Angelis et al., 2000, 2002; Senges et al., 1980; Chang and Lund, 1986; Tomlinson et al., 1990; Harthmann et al., 2007; Souza et al., 2007; Wichi et al., 2007; Gurley et al., 2006).

The arterial baroreflex system is a key mechanism for rapid adjustments in blood pressure. Indeed, the minimization of blood pressure variability by baroreflexes is important in maintenance of physiological homeostasis. Reduced baroreflex activity is an independent risk factor for sudden death after myocardial infarction (La Rovere et al., 1998). Diabetic patients with normal cardiovascular reflexes have a lower incidence of mortality than diabetics with abnormal reflex function (Ewing et al., 1980). Since arterial baroreflexes influence both sympathetic and parasympathetic outflow, disorders in autonomic neuronal systems (efferent or afferent) could have important consequences for cardiovascular health. The mechanisms of reflex dysfunction in diabetes have been widely investigated using animal models of insulin deficiency. In STZ diabetic rats, there was a reduction in cardiac vagal tone in the face of unaltered sympathetic tone. (Maeda et al., 1995a; De Angelis et al., 2000; Souza et al., 2007). This was consistent with previous results which showed