8

Cardiovascular Autonomic Dysfunction in Diabetes as a Complication: Cellular and Molecular Mechanisms

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1. Introduction

Diabetes is a major world health problem, which affects more than 23 million people in the US and an estimated 250 million worldwide. Diabetes mellitus is a metabolic disease characterized by high blood glucose levels resulted from an inability in pancreatic insulin secretion or insulin resistance. Usually diabetes mellitus is mainly divided into type 1 diabetes characterized by loss of the insulin production from beta cells of the pancreatic islets and type 2 diabetes characterized by insulin resistance (defective responsiveness of body tissues to insulin) and relatively reduced insulin secretion. Although type II diabetes is by far the most common affecting 90 to 95% of the US diabetic population, the studies focusing on the type 1 diabetes cannot be ignored because about 1 in every 400 to 600 children and adolescents has type 1 diabetes and about 2 million adolescents aged 12-19 have pre-diabetes in the US.

Diabetes mellitus is chronic progressive disease that usually cannot be cured. Following the natural progression of disease, diabetes without proper treatments can cause many severe complications including diabetic ketoacidosis, cardiovascular disease, chronic renal failure, retinal damage. These complications obviously enhance the risk for diabetic patients. In these complications of the diabetes mellitus, cardiovascular autonomic dysfunction is a serious although poorly understood long term diabetic complication. Indeed, diabetic patients with cardiovascular autonomic dysfunction have consistently been shown to have an enhanced risk of premature death (Rosengard-Barlund *et al.*, 2009). More importantly, the age-adjusted relative risk for cardiovascular disease in type 1 diabetes far exceeds that of type 2 diabetes (Krolewski *et al.*, 1987; Libby *et al.*, 2005). Therefore, exploring the mechanisms responsible to the cardiovascular autonomic dysfunction can provide an important and new pharmacological and genetic target for improving the prognosis and reducing the mortality in diabetic state.

2. Baroreflex dysfunction in type 1 diabetes and the contribution of the baroreflex dysfunction in prognosis and mortality of the type 1 diabetes

Cardiovascular autonomic function is the autonomic neural regulation of cardiovascular function, which presents the balance between sympathetic and parasympathetic innervation

resulting in periodic fluctuation in heart rate and rhythm. Although there are many invasive and non-invasive methods to evaluate the cardiovascular autonomic function in diverse clinical and research settings, cardiovascular autonomic function typically is measured by a short-term evoked cardiovascular reflex, especially arterial baroreflex.

2.1 Baroreflex dysfunction

The arterial baroreflex normally acts to prevent wide oscillations in blood pressure and heart rate, acting on both sympathetic and parasympathetic limbs of the cardiovascular autonomic nervous system. Dysfunction of the arterial baroreflex control on the blood pressure and heart rate has been described in many studies not only in the type I diabetic patients, but also in experimental models of the type I diabetes.

In the diabetic patients, heart rate variability is the most widely used index of the arterial baroreflex function. Some studies in more heterogeneous groups of patients with type 1 diabetes have indicated that: (1) showing lower global heart rate variability; (2) relative increase in the low-frequency component (sympathetic activity) of the heart rate variability; (3) relative reduction in the high-frequency component (parasympathetic activity) of the heart rate variability; and (4) higher ratio of the low frequency to the high-frequency (Lishner *et al.*, 1987; Rosengard-Barlund *et al.*, 2009; Ziegler *et al.*, 2001). Clinical research data have confirmed that arterial baroreflex sensitivity is reduced in type 1 diabetic patients with a wide range of age and diabetic duration (Lefrandt *et al.*, 1999; Weston *et al.*, 1996;Weston *et al.*, 1998; Dalla *et al.*, 2007). More importantly, this attenuated arterial baroreflex function was found in the type 1 diabetic patients without the clinical complications, the alterations of the other autonomic function tests, or the overt autonomic neuropathy (Lefrandt *et al.*, 1999; Rosengard-Barlund *et al.*, 2009). Therefore, it is of note that the reduced arterial baroreflex sensitivity can be an earlier sensitive marker of the cardiovascular autonomic dysfunction in the type 1 diabetic patients.

In order to obtain new insights into human type 1 diabetes, animal models of the type 1 diabetes have been widely used in the biomedical studies focusing on the type 1 diabetes, such as alloxan-induced diabetic rabbits (McDowell *et al.*, 1994b), streptozotocin-induced diabetic rats (Hicks *et al.*, 1998; Maeda *et al.*, 1995; Van *et al.*, 1998; Chen *et al.*, 2008), and calmodulin transgenic OVE26 diabetic mice (Gu *et al.*, 2008). Streptozotocin (STZ)-induced diabetic rat is an animal model of insulin-dependent diabetes usually used to study the cardiovascular alterations including cardiovascular autonomic dysfunction caused by diabetes even if the changes of cardiovascular function in this animal model don't fully match the alterations observed under the clinical type 1 diabetic states (Hicks *et al.*, 1998). In the STZ-induced diabetic rats, the arterial baroreflex dysfunction is presented as early as 5 days after the STZ administration (Maeda *et al.*, 1995). Much evidence has documented that the arterial baroreflex is decreased in all kinds of type 1 diabetic models (Chen *et al.*, 2008; Dall'Ago *et al.*, 1997; De Angelis *et al.*, 2000; Gu *et al.*, 2008; Maliszewska-Scislo *et al.*, 2003; McDowell *et al.*, 1994b; Van *et al.*, 1998).

2.2 Association of cardiovascular autonomic dysfunction with mortality rate

30 years ago, Ewing et al (Ewing *et al.*, 1980) first reported that there was a mortality rate of 53% after 5 years in diabetic patients with abnormal autonomic function, compared with a mortality rate of about 15% over the 5 year period among diabetic patients without abnormal autonomic function. Thereafter the growing evidence has confirmed that

cardiovascular autonomic dysfunction is associated with a high risk of cardiac arrhythmias and with sudden death in the diabetic state. A longitudinal study by O'Brien et al (O'Brien *et al.*, 1991) has investigated 5-year survival in 506 randomly selected patients with insulin-dependent diabetes mellitus. In this study, the cumulative 5-year mortality rate in the diabetic patients with cardiovascular autonomic dysfunction (27%) is about 5-fold more than in the diabetic patients with normal cardiovascular autonomic function (5%). However, there is no difference in duration of diabetes between the deceased diabetic patients with and without cardiovascular autonomic dysfunction (O'Brien *et al.*, 1991). A meta-analysis (Maser *et al.*, 2003) and the epidemiology of diabetes complication study (Orchard *et al.*, 1996) also showed that cardiovascular autonomic dysfunction could contribute to the increased risk of mortality rate in the individuals with diabetes. In the recent EURODIAB prospective complications study, the researchers have found that cardiovascular autonomic dysfunction is an important risk marker for mortality rate, exceeding the effect of the traditional risk factors (such as age, waist-to-hip ratio, pulse pressure, and non-HDL cholesterol) (Soedamah-Muthu *et al.*, 2008).

Since the diabetic patients are more likely to have many known diabetes-associated risk factors besides cardiovascular autonomic dysfunction (Soedamah-Muthu *et al.*, 2008), the question is whether cardiovascular autonomic dysfunction is an independent risk factor to predict the mortality rate of the diabetic patients. Some studies have addressed this question to minimize the potential interference of other risk factors (for example age, sex, height, smoking, diabetes duration, etc) by matching these variables in the diabetic patients with and without cardiovascular autonomic dysfunction (O'Brien *et al.*, 1991; Orchard *et al.*, 1996; Rathmann *et al.*, 1993). In Rathmann's study (Rathmann *et al.*, 1993), diabetic patients with and without cardiovascular autonomic dysfunction were matched for age, sex, and duration of diabetes. The 8-year survival rate estimate in patients with cardiovascular autonomic dysfunction was 77% compared with 97% in those with normal cardiovascular autonomic function in this study (Rathmann *et al.*, 1993). O'Brien et al. have also matched age, sex, and duration of diabetes in the diabetic patients with and without cardiac autonomic dysfunction in their study (O'Brien *et al.*, 1991). They found that the cardiovascular autonomic dysfunction was associated with the mortality rate of the type 1 diabetic patients (O'Brien *et al.*, 1991).

2.3 Potential mechanisms responsible for cardiovascular autonomic dysfunction-increased mortality rate

Although many studies mentioned above have confirmed that the cardiovascular autonomic dysfunction is involved in increasing mortality rate of type 1 diabetic patients, we really don't know whether cardiovascular autonomic dysfunction is directly or indirectly responsible for the increased mortality rate. It is possible that several possible mechanisms are involved in this clinical phenomenon.

First, a few clinical studies have reported that some type 1 diabetic patients in good health the previous day are found dead in the morning in an undisturbed bed with no sign of the symptoms (such as sweating and struggle) and negative autopsy results, which is named as the 'dead in bed' syndrome (Tattersall & Gill, 1991; Weston & Gill, 1999). One recent clinical study has found that ECG abnormalities including QT prolongation, cardiac rhythm disturbance, and subsequent ventricular tachyarrhythmia appear in the ambulant patients with type 1 diabetes (Gill *et al.*, 2009). The ECG abnormalities can serve as

principal underlying causes of the 'dead in bed' syndrome (Gill *et al.*, 2009). Cardiovascular autonomic dysfunction itself can link to the QT prolongation and sudden death (Weston & Gill, 1999). In another study, type 1 diabetic adolescents with impaired cardiovascular autonomic function are associated with the possible development of cardiac arrhythmias and left-ventricular hypertrophy (Karavanaki *et al.*, 2007). In addition, decreased heart rate variability is also a predictive risk factor for ventricular arrhythmia and sudden cardiac death (Kleiger *et al.*, 1987). Loss of cardiac vagal drive combined with loss of baroreceptor reflex sensitivity is thought to mediate the decreased heart rate variability and autonomic instability that exacerbate arrhythmia susceptibility (Binkley *et al.*, 1991). These studies indicate that cardiovascular autonomic dysfunction (decreased heart rate variability and loss of baroreceptor reflex sensitivity) is correlated with the prognosis and mortality in patients with type 1 diabetes via increasing the susceptibility to the lethal arrhythmias.

Second, although cardiovascular autonomic dysfunction is an independent risk factor to predict the mortality rate of the diabetic patients described above, other abnormalities (such as increased stiffness of the vascular walls at the site of the arterial baroreceptors, left ventricular hypertrophy, endothelial dysfunction, renal failure, peripheral neuropathy, etc) usually coexist with cardiovascular autonomic dysfunction in type 1 diabetic patients (Toyry *et al.*, 1997; Lluch *et al.*, 1998; Lefrandt *et al.*, 2010). Therefore, it is possible that the interaction between cardiovascular autonomic dysfunction and other concomitant abnormalities is responsible for the increased mortality rate in type 1 diabetic patients. It has been shown that cardiovascular autonomic function is easily impaired in type 1 diabetic patients with microalbuminuria (renal dysfunction) (Lefrandt *et al.*, 1999; Clarke *et al.*, 1999). O'Brien et al have reported that renal failure-induced mortality rate is higher in type 1 diabetic patients with cardiovascular autonomic dysfunction than in those without cardiovascular autonomic dysfunction (O'Brien *et al.*, 1991). In a 23 year follow-up study, cardiovascular autonomic dysfunction may be involved in a higher mortality rate induced by microalbuminuria in type 1 diabetic patients (Messent *et al.*, 1992). Similarly, renal disease also can partially explicate the cardiovascular autonomic dysfunction-increased mortality rate in patients with diabetes mellitus (Weinrauch *et al.*, 1998; Kim *et al.*, 2009). In addition, using logistic regression analysis, one recent study has addressed the relationship between cardiovascular autonomic dysfunction and other abnormalities in 684 type 1 diabetic patients (Pavy-Le *et al.*, 2010). The research data have shown that retinopathy, peripheral neuropathy, and erectile dysfunction are closely correlated to the severity of the cardiovascular autonomic dysfunction (Pavy-Le *et al.*, 2010). Furthermore, some studies have also found a consistent association between cardiovascular autonomic dysfunction and silent myocardial ischemia, in which the patient's risk coefficient related to the cardiovascular autonomic dysfunction is higher in asymptomatic diabetic patients with silent myocardial ischemia than in those without silent myocardial ischemia (Valensi *et al.*, 2001; Vinik & Ziegler, 2007; Katz *et al.*, 1999).

Finally, several studies reported the involvement of cardiorespiratory arrest in the mortality of the diabetic patients with cardiovascular autonomic dysfunction (Page & Watkins, 1978; Bergner & Goldberger, 2010; Douglas *et al.*, 1981). The research data from Page et al. (Page & Watkins, 1978) have demonstrated that young diabetic patients with severe cardiovascular autonomic dysfunction can appear to have cardiorespiratory arrest due to the impairment of cardiorespiratory function. The cardiorespiratory arrest may be responsible for the mortality of these diabetic patients (Page & Watkins, 1978).

3. Mechanisms responsible for the reduced baroreflex function in type 1 diabetes

The arterial baroreflex is a homeostatic mechanism that alters heart rate and blood pressure in response to changes in arterial wall tension detected by the baroreceptors in the carotid sinus and aortic arch. The arterial baroreflex arc includes an afferent limb, a central neural component and autonomic neuroeffector components. As the primary afferent limb of the baroreceptor reflex, baroreceptor neurons sense blood pressure by increasing their discharge (excitation) when arterial blood pressure rises. This excited signal in baroreceptor neurons reaches to the dorsal medial nucleus tractus solitarii (NTS, the first site of baroreceptor neuron contacting with central nervous system), in which the integrated input signal inhibits the efferent sympathetic outflow to the heart and peripheral vascular, and activates efferent parasympathetic activity to the heart those decrease peripheral vascular resistance, heart rate, and arterial blood pressure. Conversely, the baroreceptor afferent signal decreases when arterial blood pressure falls, which reflexly induces an increase in heart rate and arterial blood pressure.

As mentioned above, blunted arterial baroreflex sensitivity is observed in type 1 diabetic patients and animal models. What are the mechanisms responsible for the attenuated arterial baroreflex sensitivity in type 1 diabetes? Every site within the baroreflex arc may be responsible for the depressed baroreflex sensitivity in type 1 diabetes. Therefore, we will discuss the fact that the reduced baroreflex sensitivity results from functional and/or structural changes in the baroreceptors (including nerve terminals and neuron somata), central neural integration, and autonomic efferent component.

3.1 Role of baroreceptor in the blunted arterial baroreflex in type 1 diabetes

As the primary afferent limb of the arterial baroreceptor reflex, baroreceptor neurons are pseudo-unipolar neurons (T-shaped neurons) consisting of a cell body existing in the nodose or petrosal ganglia and an initial axon segment. This axon segment bifurcates near the soma into a peripheral process innervating aortic arch and carotid sinus for sensing the alteration of the arterial blood pressure and a central process terminating in the NTS for conveying the afferent signals to the central nervous system. The mechanisms responsible for mediating afferent sensitivity of barosensitive neurons to pressure are complex and not thoroughly understood. The process of translating changes in arterial wall tension into impulse traffic to the NTS involves 2 broad functional steps: 1) mechanotransduction which is governed by the properties of mechanosensitive ion channels in the nerve terminal and the mechanical properties of the coupling of the arterial wall to the sensory terminal; and 2) spike initiation which is governed by the excitability of membrane voltage sensitive ion channels that influence the electrical (cable) properties of the axonal process and cell body. All of these factors could be (and likely are) altered in type 1 diabetes, which can directly affect the arterial baroreflex function.

3.1.1 Changes of baroreceptor afferent nerve and terminal in type 1 diabetes

Although some studies have suggested that diabetes-induced postural hypotension results from impairments of afferent baroreceptors and of sympathetic neurons innervating the vascular wall and heart in diabetic patients (Low *et al.*, 1975; Iovino *et al.*, 2011), there is only fragmentary evidence to support this assumption because of the inability of clinical cardiovascular autonomic function tests to separate the role of the afferent, central, and

efferent components of the arterial baroreflex. In general, the function of the baroreceptor afferent nerve and terminal is investigated by recording the single fiber or multifiber activity of the aortic depressor nerve or carotid sinus nerve in a perfused isolated aortic arch/carotid sinus preparation (do Carmo *et al.*, 2007; Doan *et al.*, 2004; Fazan, Jr. *et al.*, 1997; McDowell *et al.*, 1994b; Reynolds *et al.*, 1994; Reynolds *et al.*, 1999; Xiao *et al.*, 2007; Zhang *et al.*, 2004). However, the baroreceptor function in the diabetic state is studied only in the aortic depressor nerve (Fazan, Jr. *et al.*, 1997; Fazan, Jr. *et al.*, 1999; McDowell *et al.*, 1994b; Reynolds *et al.*, 1999) but not in the carotid sinus nerve (Salgado *et al.*, 2001). This may be because there are only baroreceptor afferent fibers and no chemoreceptor afferent fibers in rat aortic depressor nerve unlike the carotid sinus nerve (Fan *et al.*, 1996; Kobayashi *et al.*, 1999; Sapru & Krieger, 1977; Sapru *et al.*, 1981). Based on the results from some studies, there is no evidence to show the changes of the aortic depressor nerve activity in STZ-induced type 1 diabetic rats (Fazan, Jr. *et al.*, 1997; Reynolds *et al.*, 1999; Dall'Ago *et al.*, 2002) and alloxan-induced diabetic rabbits (McDowell *et al.*, 1994b), compared to the sham animals. In addition, Gu *et al* (Gu *et al.*, 2008) have found that the baroreceptor function of the aortic depressor nerve is preserved in the ascending phase of the arterial blood pressure but is blunted in the descending phase of the arterial blood pressure in type 1 diabetic mice. Nevertheless, the results obtained by a new approach, named as cross-spectral analysis, indicate that a significant decrease of the aortic baroreceptor nerve function is observed in anesthetized rats with either short term (10-20 days) or long term (12-18 weeks) STZ-induced diabetes (Fazan, Jr. *et al.*, 1999). This new approach uses the magnitude of the transfer function obtained by analyzing the relationship between beat-by-beat time series of mean arterial blood pressure and aortic depressor nerve activity as the index of the aortic baroreceptor nerve function, whose advantage is to evaluate the aortic baroreceptor nerve function under more physiological conditions (Salgado *et al.*, 2001; Fazan, Jr. *et al.*, 1999; deBoer *et al.*, 1987) compared to the arterial blood pressure/aortic depressor nerve activity curve used in other studies (Dall'Ago *et al.*, 2002; Fazan, Jr. *et al.*, 1997; Gu *et al.*, 2008; McDowell *et al.*, 1994b; Reynolds *et al.*, 1999). In addition, Fazan et al have found that the morphological change in the aortic depressor nerve, an afferent arm of the baroreflex may result in the arterial baroreflex impairment in the STZ-induced diabetic rats (Fazan *et al.*, 2006). Therefore, the functional and structural alterations of the baroreceptor afferent nerve in type 1 diabetes still need to be further clarified in future study.

By light, electron, and confocal microscopies, some researchers have identified the aortic baroreceptor terminals in the adventitia of the aortic arch from dogs, rabbits, cats, rats, and mice (Aumonier, 1972; Cheng *et al.*, 1997; Krauhs, 1979; Li *et al.*, 2010). More importantly, Li et al have demonstrated that diabetes induces morphological atrophy of the aortic baroreceptor terminals in type 1 diabetic mice (Li *et al.*, 2010). However, there is no report on the functional role of the aortic baroreceptor terminals in sham and type 1 diabetic animals because it is difficult to separate aortic baroreceptor terminals to other tissues (such as smooth muscle and endothelium) in the aortic arch. It is possible that using gene and short hairpin RNA (shRNA) transfection can solve this problem in future study.

3.1.2 Role of aortic baroreceptor neurons in the arterial baroreflex in the type 1 diabetes

Many studies have used the responses of blood pressure and heart rate to electrical stimulation of baroreceptor-containing nerve (aortic depressor nerve) for the evaluation of the baroreflex sensitivity in rats (Fan & Andresen, 1998; Salgado *et al.*, 2007; Tang &

Dworkin, 2007). The aortic depressor nerves (the peripheral process of the aortic baroreceptor neuron) are composed of both afferent A-type (myelinated) axons (about 25%) and C-type (unmyelinated) axons (about 75%) (Yamasaki *et al.*, 2004). There are very different dynamic sensory discharge characteristics between A-type and C-type baroreceptor afferents. C-type afferents are activated mainly at very high pressure and have lower firing frequencies, irregular discharge patterns (Thoren *et al.*, 1999), and appear to be the primary regulators of tonic baseline levels of arterial blood pressure besides regulating the baroreflex sensitivity (Seagard *et al.*, 1993). A-type afferents have lower pressure thresholds with very stable, proportional firing patterns (Thoren *et al.*, 1999), which are thought to regulate the baroreflex sensitivity but not baseline levels of arterial blood pressure (Seagard *et al.*, 1993). Electrical Stimulation of the rat aortic depressor nerve has several advantages to examine the baroreflex function. First, the rat aortic depressor nerve contains only baroreceptor afferent fibers and no chemoreceptor afferent fibers to transmit the chemoreceptor information (Fan *et al.*, 1996; Kobayashi *et al.*, 1999; Sapru & Krieger, 1977; Sapru *et al.*, 1981). Second, the baroreflex induced by stimulating rat aortic depressor nerve is measured without the aortic baroreceptor terminals in the reflex arc, which allows us to specifically examine the role of electrical excitability of aortic baroreceptor in the baroreflex function (second process mentioned above). Third, by varying the frequency of stimulus, one can differentially activate A- and C- afferent fibers, and thus evaluate the relative contribution of each to the altered aortic baroreceptor excitability and baroreflex function in STZ-induced diabetes. In our preliminary study, the baroreflex responses of blood pressure and heart rate to the electrical stimulation of the aortic baroreceptor nerve are significantly depressed in STZ-induced diabetic rats (Fig. 1). In addition, our study also found that microinjection of angiotensin II type 1 (AT_1) receptor antagonist (20 μM L158,809) into the nodose ganglia significantly improved the baroreflex sensitivity induced by aortic depressor nerve stimulation in STZ-induced diabetic rats (Fig. 1). Simultaneously, AT_1 receptor antagonist also normalized the depressed cell excitability in the aortic baroreceptor neurons of STZ-induced diabetic rats (Li & Zheng, 2011). The fact is that nodose neurons are found to influence the conduction and frequency of the electrical impulses in the baroreceptor central axons projecting to the central nervous system when electrical signals in the baroreceptor peripheral axons reach the nodose neurons (Ducreux *et al.*, 1993). One review paper has concluded that the excitability of vagal afferent neurons has dramatic consequences for the regulation and modulation of vago-vagal reflex (Browning, 2003). Furthermore, Devor (Devor, 1999) has reported that electrical excitability of the soma in the dorsal root ganglia may be required to insure the reliable afferent electrical impulses transmitted to the spinal cord. These results, taken together, demonstrate that the reduced cell excitability of the aortic baroreceptor neurons contributes to the blunted baroreflex sensitivity in STZ-induced diabetic rats.

However, results from reflex experiments evoked by the electrical stimulation need to be tempered because the electrical stimulation technique does not represent a physiological substrate for baroreceptor activation. Thus, arterial baroreflex evoked by changes in arterial blood pressure should be done to further address the role of the aortic baroreceptor neurons in the arterial baroreflex in the type 1 diabetes. Of course, in this approach (blood pressure-mediated baroreflex sensitivity), possible alterations in the mechanotransduction process at the baro-sensory nerve terminal may also play a role in the suppressed baroreceptor function in response to pressure changes.

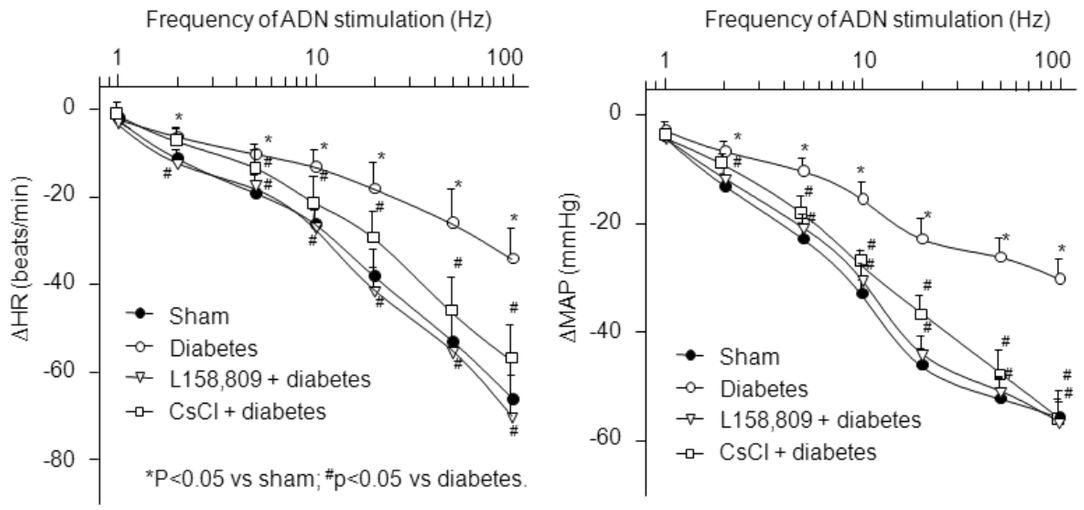

Fig. 1. Reflex ΔMAP and ΔHR in response to different frequencies of ADN stimulation in anesthetized sham and STZ-induced diabetic rats (n=8 in each group). L158,809: AT_1 receptor antagonist; CsCl: HCN channel blocker. MBP, mean blood pressure; HR, heart rate; ADN, aortic depressor nerve.

3.1.3 Contribution of the HCN channel to the cell excitability of aortic baroreceptor neuron in the type 1 diabetes

Until now it is controversial whether either severe degenerative changes or neuronal cell loss in sensory and autonomic nervous tissues are found in STZ-induced diabetic animals (Yagihashi, 1997). Apoptotic cell death was reported in the sensory neurons, satellite cells, and Schwann cells from dorsal root ganglia (DRG) of STZ-induced diabetic rats (Russell *et al.*, 1999; Srinivasan *et al.*, 2000). Kogawa et al. also found that apoptotic cell death of DRG neurons and impaired sensory nerve regeneration were induced by sciatic nerve crush in STZ-induced diabetic rats (Kogawa *et al.*, 2000). On the other hand, the findings from Sango et al (Sango *et al.*, 1991; Sango *et al.*, 1995; Sango *et al.*, 1997) indicated no difference in the dissociated neurons from DRG between sham and STZ-induced diabetic mice. Furthermore, some studies have demonstrated that there are no morphological changes of the peripheral nerves (Sharma & Thomas, 1987) and cell death of the nodose afferent neurons (Sango *et al.*, 2002) in STZ-induced diabetic animals. Our recent study (Tu *et al.*, 2010) also suggests that STZ-induced diabetes does not change the total cell number of the nodose afferent neurons and the ratio of A-/C-type neurons (Fig. 2). These results provide an important piece of information that the parasympathetic reflex dysfunction (Li *et al.*, 2008b; Thomas & Tomlinson, 1993; Ziegler, 1994) in STZ-induced diabetes might be not due to the structural changes in the nodose afferent neurons but most likely due to the functional changes at the cellular and molecular levels.

As everyone knows, many ion channels (such as sodium channels, calcium channels, potassium channels, etc) are responsible for the cell excitation in the excitable cells such as cardiac/skeletal myocytes and neurons including aortic baroreceptor neurons. However, much evidence has indicates that Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels play an important role in the cell excitability of the aortic baroreceptor neurons from sham and STZ-induced diabetic rats.

HCN channels have been found in various types of cells including cardiac and neuronal cells (DiFrancesco, 1985; DiFrancesco, 1993; Pape, 1996). In these spontaneously exciting cells, HCN channels normally associate to the cardiac pacemaker activity and the neuronal oscillatory behavior (Brown *et al.*, 1979; DiFrancesco, 1993; Kaupp & Seifert, 2001; Notomi & Shigemoto, 2004; Pape, 1996; Robinson & Siegelbaum, 2003). However, HCN channels may have a different role in the nodose ganglion neurons (the non-oscillatory and non-automatic exciting cells) because the nodose neurons are inactive except in response to a depolarizing stimulus generated by their peripheral sensory terminals (Doan & Kunze, 1999; Li *et al.*, 2008a). In the nodose neurons, the resting membrane potential is about -50 to -65 mV, in which voltage-dependent sodium, calcium, and potassium channels are almost inactivated (Robinson & Siegelbaum, 2003). The inactivation of these voltage-dependent channels can be recovered to the activation state during the hyperpolarization of the resting membrane potential, which means the number of available voltage-dependent channels for activation is increased if the nodose neurons receive the depolarizing stimulus (Doan & Kunze, 1999). Inhibition of HCN channels has been shown to hyperpolarize the nodose neurons (increasing the resting membrane potential) and to reduce action potential threshold in response to a depolarizing current stimulation, which suggests that HCN channels are involved in the cell excitability of the nodose neurons (Doan *et al.*, 2004; Li *et al.*, 2008a). Results from our recent studies (Li *et al.*, 2008a; Li & Zheng, 2011; Tu *et al.*, 2010) confirm that the HCN current density in A- and C-type aortic baroreceptor neurons from STZ-induced diabetic rats is larger than that from the sham rats (Fig. 3). In addition, the resting membrane potential is depolarized and the current threshold induced the action potentials was elevated in the A-/C-type aortic baroreceptor neurons from STZ-induced diabetic rats, compared with that in sham rats (Li *et al.*, 2008a; Li & Zheng, 2011). Furthermore, HCN channel blockers (CsCl and ZD-7288) lowered the HCN current density, hyperpolarized the resting membrane potential, and raised the cell membrane excitability in A-/C-type aortic baroreceptor neurons from sham and STZ-induced diabetic rats (Li *et al.*, 2008a; Zhang *et al.*, 2010). These results clearly indicate that the HCN channels are involved in the regulation of aortic baroreceptor neuron excitability. The enhancement of HCN currents can contribute to the blunted aortic baroreceptor neuron excitability, and subsequently attenuate the arterial baroreflex sensitivity in STZ-induced diabetic rats. This is true because microinjection of HCN channel blocker (5 mM CsCl) improves the arterial baroreflex sensitivity induced by the electrical stimulation of the aortic depressor nerve (Fig. 1) (Li *et al.*, 2008b).

Four mammalian genes encoding HCN channel isoforms (HCN1, HCN2, HCN3, and HCN4) have been identified (Doan *et al.*, 2004; Ishii *et al.*, 1999; Ludwig *et al.*, 1998; Santoro *et al.*, 1998; Vaccari *et al.*, 1999). In cell lines transfected HCN isoform cDNA, electrophysiological studies have shown that each channel isoform is activated by membrane hyperpolarization with distinct activation kinetics (Ludwig *et al.*, 1999; Moosmang *et al.*, 2001; Qu *et al.*, 2002; Santoro *et al.*, 1998). Activation of the HCN channels is also directly modulated by cAMP, which is dependent on the HCN channel isoform (Stieber *et al.*, 2003; Wainger *et al.*, 2001; Wang *et al.*, 2002). HCN channels are activated with the different activation rates in this order: HCN1>HCN2>HCN3>HCN4 (Accili *et al.*, 2002; Altomare *et al.*, 2001; Moosmang *et al.*, 2001; Stieber *et al.*, 2003; Stieber *et al.*, 2005). HCN1 and HCN3 are only weakly affected by cAMP whereas HCN2 and HCN4 are very sensitive to cAMP (Accili *et al.*, 2002; Stieber *et al.*, 2005; Wahl-Schott & Biel, 2009; Wang *et al.*, 2001). Our studies (Li *et al.*, 2008a; Tu *et al.*, 2010) have found that a fast-activated and cAMP-

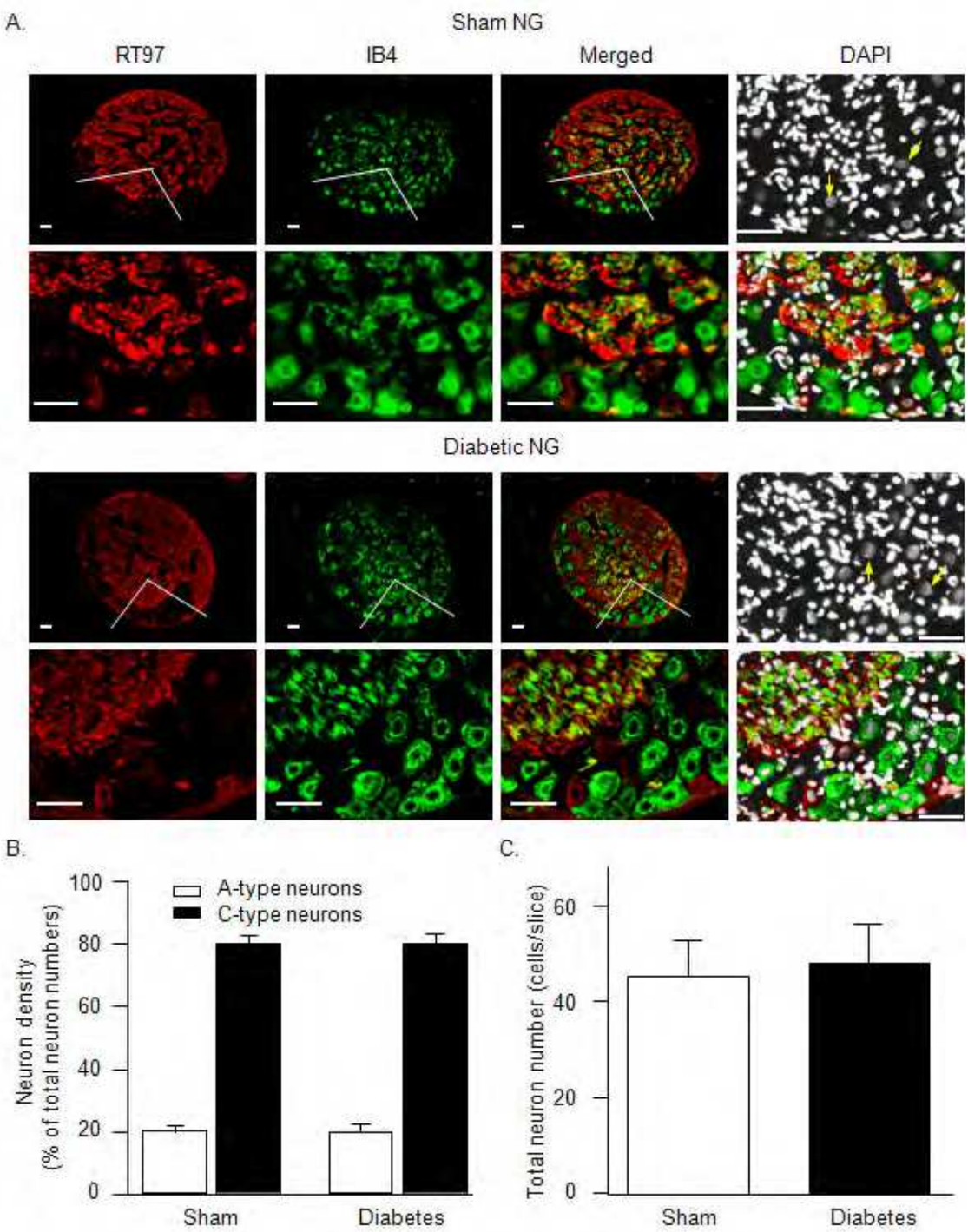

Fig. 2. Ratio of A-type/C-type neurons (A and B) and total neuron number (C) in nodose ganglia from sham and STZ-induced diabetic rats. Calibration bar: 100 μm. RT97, A-type neuron marker; IB4, C-type neuron marker; DAPI, cell nucleus marker. Yellow arrows indicate nodose neurons in DAPI staining (Adapted and reprinted from Tu *et al*., 2010, page 42, with permission from Elsevier)

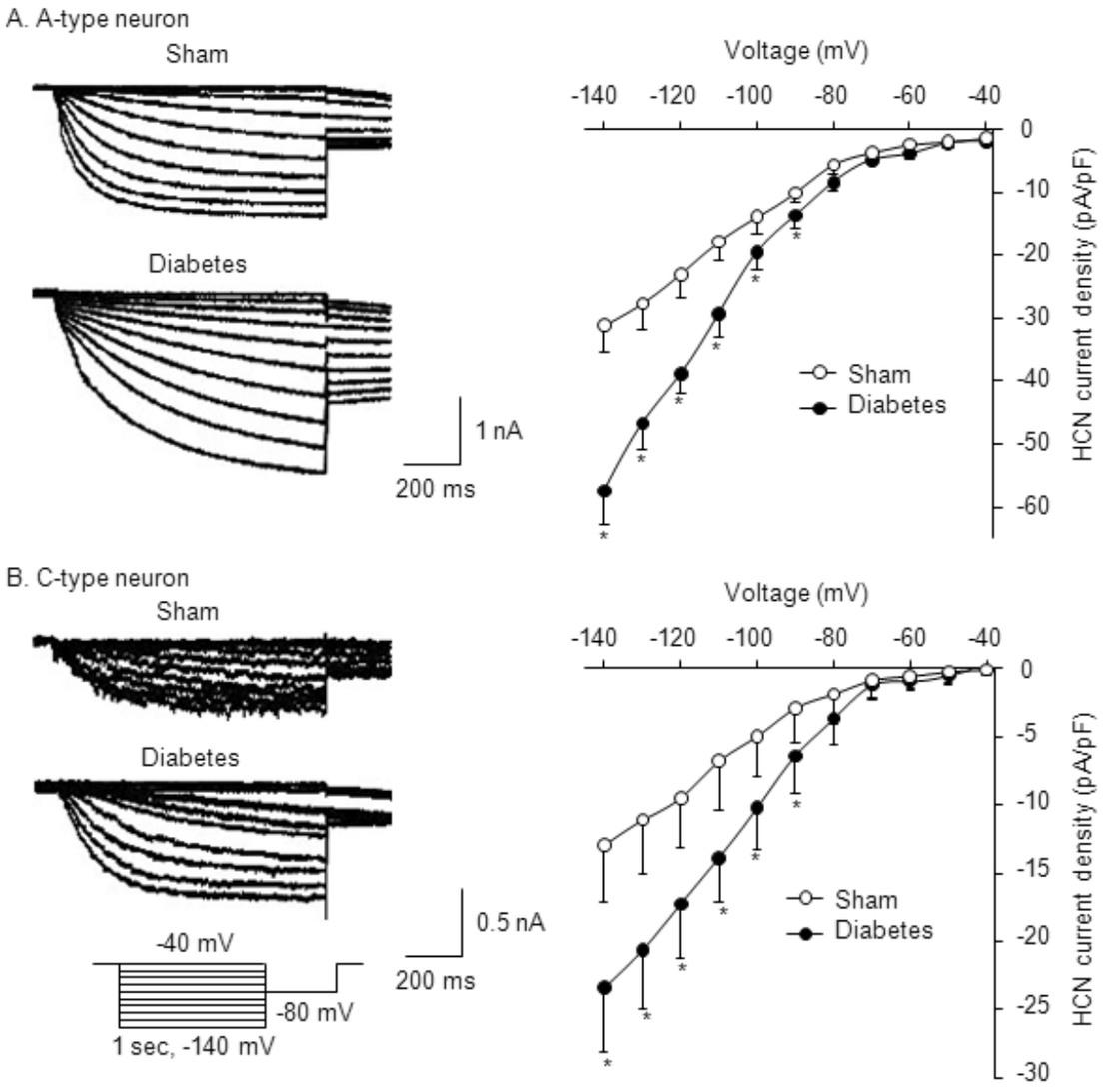

Fig. 3. Original HCN current recording and current density-voltage curves in A- and C-type neurons from sham and STZ-induced diabetic rats. *P<0.05 vs. sham rats (Reprinted from Tu *et al*., 2010, page 48, with permission from Elsevier).

insensitive HCN current is induced in sham A-type aortic baroreceptor neurons whereas a slow-activated and cAMP-sensitive HCN current is induced in sham C-type aortic baroreceptor neurons. From these electrophysiological results, we can imagine that there is a differential distribution of the HCN channel isoforms in the A- and C-type aortic baroreceptor neurons. Data from immunofluorescent double staining also show that HCN1, HCN3, and HCN4 are expressed in sham A-type nodose neurons, whereas HCN2, HCN3, and HCN4 are expressed in sham C-type nodose neurons (Li *et al*., 2008a; Tu *et al*., 2010). Based on these results, it is reasonable to assume that there are marked different activation kinetics and cAMP sensitivity of HCN channels between A-fiber neurons and C-fiber neurons, which might be due to the neuron cell-specific expression of HCN channel isoforms.

Our studies further demonstrate that diabetes enhances the HCN currents and the expression of HCN1, HCN2, and HCH 3 channel proteins in A-type aortic baroreceptor neurons (Li *et al.*, 2008a; Tu *et al.*, 2010). Overexpression of HCN1, HCN2, and HCN3 but not HCN4 channel isoforms can link to the enhanced HCN currents, the slow-activated HCN channel kinetics, and the increased cAMP-sensitivity of HCN channels in diabetic A-type aortic baroreceptor neurons (Li *et al.*, 2008a; Tu *et al.*, 2010). Although diabetes also increases the HCN currents and the expression of HCN2 and HCN3 channel proteins in C-type aortic baroreceptor neurons, diabetes does not change the activation kinetics and the cAMP sensitivity of the HCN channels in C-type aortic baroreceptor neurons due to no expression of HCN1 channel in diabetic C-type aortic baroreceptor neurons (Li *et al.*, 2008a; Tu *et al.*, 2010). From these results, we propose that HCN currents are markedly enhanced via increasing the numbers of HCN channels and sensitivity of HCN channels to cAMP in the aortic baroreceptor neurons. The enhanced HCN currents can contribute to the depressed neuron excitability in diabetic aortic baroreceptor neurons. However, we do realize that these data cannot explain why diabetes induces the different changes of HCN channel protein expression and cannot identify the contribution of the various HCN channel isoforms to the enhanced HCN currents in diabetic A- and C-type aortic baroreceptor neurons.

3.1.4 Regulation of the angiotensin II-superoxide signaling on the HCN channel in the type 1 diabetes

Angiotensin II, an endogenous peptide, has been thought to be a prime candidate in the regulation of the HCN channel function and cell excitability in the diabetic state. It is known that circulating and tissue angiotensin II concentrations are elevated in human and animals with diabetes (Frustaci *et al.*, 2000; Sechi *et al.*, 1994; Shimoni & Liu, 2004). Previous autoradiographic study has identified a high density of angiotensin II receptor binding sites over the nodose neurons (Allen *et al.*, 1988). Widdop, et al. provided evidence for the direct neuronal effects of angiotensin II on the vagal afferent neurons (Widdop *et al.*, 1992). Indeed, our research data not only confirm AT_1 and AT_2 receptors exist in nodose neuronal cells, but also indicate that exogenous angiotensin II enhances the HCN currents and subsequently reduces cell excitability in the aortic baroreceptor neurons from normal rats (Zhang *et al.*, 2010). This is via NADPH oxidase-derived superoxide because a specific HCN channel blocker blunts the inhibitory effect of the exogenous angiotensin II on action potentials (Zhang *et al.*, 2010). More importantly, angiotensin II concentration and protein expression of AT_1 receptors are increased in the nodose neuronal cells from STZ-induced diabetic rats (Li & Zheng, 2011). At the same time, mRNA expression of AT_1 receptors measured by single cell real-time PCR technique is enhanced in the aortic baroreceptor neuron cells from the STZ-induced diabetic rats (Li & Zheng, 2011). In addition, AT_1 receptor antagonist (losartan) significantly normalizes the enhanced HCN currents and the attenuated cell excitability (including depolarization of the resting membrane potential, fall in the input resistance, and decrease in the action potential number) in the aortic baroreceptor neurons induced by diabetes (Li & Zheng, 2011) or exogenous angiotensin II (Zhang *et al.*, 2010). Furthermore, angiotensin II-AT_1 receptor is also involved in the attenuated arterial baroreflex sensitivity in STZ-induced diabetic rats (Fig. 1) (Li *et al.*, 2008b). Based on these results, it is reasonable to assume that elevation of local angiotensin II level can blunt the membrane excitability of the aortic baroreceptor neurons via enhancement of the HCN currents, and consequently attenuate the aortic baroreflex function in the type 1 diabetes.

Above results suggest that elevation of local tissue angiotensin II plays an important role on the enhanced HCN channel activity and the blunted cell excitability in the AB neurons in diabetes. However, it is unclear how angiotensin II and its antagonist within an isolated aortic baroreceptor neuron from diabetic rat interact with AT_1 receptor to affect the HCN channel activity and cell excitability. Classical viewpoint about the effects of angiotensin II binding with AT_1 receptor is that angiotensin II binds with AT_1 receptor at the cell membrane, and following the phosphorylation of the AT_1 receptor, angiotensin II induces intracellular responses via activating intracellular downstream signal transduction. However, Zhuo, et al. (Zhuo *et al.*, 2002) have found that there is substantial intracellular accumulation of angiotensin II in renal cortical endosomes during angiotensin II-dependent hypertension via an AT_1 receptor-mediated process. Recent studies have shown that intracellular administration of angiotensin II increases the peak inward calcium current density and decreases the junctional conductance via intracellular angiotensin II receptors in cardiac myocytes (De Mello, 2003; De Mello & Monterrubio, 2004). Intracellular treatment of losartan (a selective AT_1 receptor antagonist) abolishes the effect of intracellular angiotensin II (Allen *et al.*, 1988; Bacal & Kunze, 1994). Based on these studies, we reason that diabetes-induced elevation of intracellular angiotensin II concentration in the nodose neurons contributes to the enhanced HCN channel activity and the blunted cell excitability in the AB neurons in diabetes. This viewpoint is confirmed by our observation that intracellular administration of losartan (added to the recording pipette solution) decreased the HCN current density and increased the cell excitability in the AB neurons from diabetic rats (Li & Zheng, 2011). Therefore, it is possible there is an intracellular angiotensin II production system in the nodose ganglion tissue. Of course, it would be optimal to measure intracellular angiotensin II concentration in the aortic baroreceptor neurons, but there is no appropriate measurement for it so far due to insufficient cellular material of tiny nodose ganglia. This issue needs to be confirmed by further study.

Growing evidence has shown that the AT_1 and AT_2 receptors are defined on the basis of their opposite pharmacological and biochemical effects (Levy, 2004). Activation of AT_1 receptors mainly results in vasoconstriction, augmentation of cardiac contractility, cell proliferation, vascular and cardiac hypertrophy, oxidative stress, and inhibition of the neuronal potassium currents (Gelband *et al.*, 1999; Levy, 2004; Sumners *et al.*, 1996). On the other hand, stimulation of AT_2 receptors induces vasodilation, anti-growth, anti-hypertrophy, and enhancement of the neuronal potassium currents (Horiuchi *et al.*, 1999; Kang *et al.*, 1995; Martens *et al.*, 1996; Matsubara, 1998; Siragy, 2000). Although AT_2 receptors are expressed in the rat nodose neurons, activation of AT_2 receptors does not affect the activation of HCN channels because AT_2 receptor antagonist (PD123,319) does not alter the effect of angiotensin II on the HCN currents (Zhang *et al.*, 2010). Until now there is no study to explain this result, but it is possible that many factors (such as species, tissue, channel sensitivity, etc) are responsible for this discrepancy.

Now the question is how angiotensin II regulates the activation of HCN channels and what is the downstream of angiotensin II-AT_1 receptor. NADPH oxidase has been considered as a main source of intracellular superoxide in many tissues (Cifuentes *et al.*, 2000; Franco *et al.*, 2003; Gao *et al.*, 2004; Griendling *et al.*, 2000; Li *et al.*, 2007; Schieffer *et al.*, 2000). NADPH oxidase is a multicomponent enzyme composed of three cytosolic subunits ($p40^{phox}$, $p47^{phox}$, and $p67^{phox}$), two membrane-associated subunits ($gp91^{phox}$ and $p22^{phox}$), and the small G-proteins (Rac and Rap1a) (Kim & Iwao, 2000; Lassegue & Clempus, 2003). Angiotensin II significantly activates NADPH oxidase via AT_1 receptors, resulting in the superoxide

production (Touyz & Berry, 2002). In the nodose ganglia from STZ-induced diabetic rats, the protein expression of the NADPH oxidase components (gp91^{phox}, p22^{phox}, p40^{phox}, p47^{phox}, and p67^{phox}) is elevated, compared to sham rats (Li & Zheng, 2011). In addition, NADPH oxidase inhibitor or superoxide scavenger significantly improves the superoxide over-production, the enhanced HCN currents, and the lowered membrane excitability induced by exogenous angiotensin II (Zhang *et al.*, 2010) or diabetes (Li & Zheng, 2011). These results strongly indicate that NADPH-derived superoxide can mediate the effect of endogenous angiotensin II on the HCN channels and membrane excitability in diabetic rat aortic baroreceptor neurons.

3.1.5 Role of other channels in the aortic baroreceptor neuron in the type 1 diabetes

Using patch-clamp technique, all major voltage-gated ion channels including channels subunits are recorded in the nodose neurons, such as sodium channels (tetrodotoxin-sensitive and tetrodotoxin-resistant sodium channels), calcium channels (N-type, L-type, T-/R-type, and other type calcium channels), and potassium channels (4-aminopyridine-sensitive, tetraethylammonium-sensitive, and calcium-activated potassium channels) (Lancaster *et al.*, 2002; Li *et al.*, 2005; Li & Schild, 2006; Schild & Li, 2001). These channels all are involved in the initiation and formation of the action potential and affect the nodose neuron excitability. Angiotensin II is known to modulate the calcium channel kinetics in the nodose neurons (Bacal & Kunze, 1994; Moreira *et al.*, 2005). However, until now we did not obtain any information about the changes of these channels in the aortic baroreceptor neurons in the type 1 diabetes. Therefore, the role of these channels in the diabetic baroreceptor neurons remains to be revealed.

3.2 Involvement of the central neural component in the blunted arterial baroreflex in type 1 diabetes

Central neural integration of the input signals from the baroreceptors usually occurs at the level of nucleus tractus solitarii and rostral ventrolateral medulla (Spyer *et al.*, 1997). Although many studies have shown that diabetes causes a variety of functional and morphological disorders in the central nervous system (including hippocampus, cortex, and cerebellum) (Biessels *et al.*, 1999; Selvarajah & Tesfaye, 2006; Mooradian, 1997a; Mooradian, 1997b; Guven *et al.*, 2009), the role of the central neural component in the blunted arterial baroreflex in type 1 diabetes is less well documented. One recent study from Gu, et al (Gu *et al.*, 2008) suggests that a deficit of the central neural component contributes to the attenuation of arterial baroreflex in OVE26 type 1 diabetic mice. This is because they found that stimulation of the aortic depressor nerve induced a lesser magnitude of bradycardia in OVE26 type 1 diabetic mice as compared to sham mice, but the bradycardic response to vagal efferent stimulation was enhanced (Gu *et al.*, 2008). Immunoreactive study has shown that reduced c-Fos expression (an indicator of early cellular response to many extracellular signals) in the nucleus tractus solitarii links to the attenuated arterial baroreflex sensitivity in STZ-induced diabetic rats (Gouty *et al.*, 2001). In addition, Chen, et al (Chen *et al.*, 2008) have reported that neural firing activity of the nucleus tractus solitarii in STZ-induced diabetes is reduced, which is involved in the impaired arterial baroreflex function in STZ-induced diabetic rats. Furthermore, a chronic intracerebroventricular infusion of leptin (a hormone produced by fat cells and improving glucose utilization, Minokoshi *et al.*, 1999; Wang *et al.*, 1999) totally normalizes the impaired arterial baroreflex sensitivity in STZ-induced diabetic

rats (do Carmo *et al.*, 2008), which indirectly suggests that impairment of the central neural system is associated with the arterial baroreflex dysfunction in type 1 diabetes. These findings allow us to assume the involvement of the impaired central neural integration in the blunted arterial baroreflex in type 1 diabetes even though there is no report focusing on the mechanisms responsible for the impairment of the central neural component of the arterial baroreflex.

3.3 Participation of autonomic neuroeffector component in the blunted arterial baroreflex in type 1 diabetes

The autonomic neuroeffector component of the arterial baroreflex includes intracardiac ganglia, parasympathetic efferents, and sympathetic efferents. Morphological studies have shown that there is a remarkable structural remodeling of the intracardiac ganglia (such as cellular contraction, cytoplasmic condensation, degenerated axons, reduced cell size and number) in STZ-induced diabetic rats (Kamal *et al.*, 1991; Lund *et al.*, 1992), mice (Lin *et al.*, 2010), and diabetic patients (Tsujimura *et al.*, 1986). Biochemical studies also found a decrease in acetylcholine (a neurotransmitter in both the central and parasympathetic nervous system) concentration in alloxan-induced diabetic rats (Kuntscherova & Vlk, 1970) and a reduced choline acetyltransferase activity (an enzyme producing acetylcholine) in the hearts of the STZ-induced diabetic rats (Lund *et al.*, 1992). In addition, the function of the parasympathetic (vagal) efferent is reduced in STZ-induced diabetic rats (Maeda *et al.*, 1995; Yagihashi, 1995). However, functional studies have reported normal, reduced, or enhanced heart rate response to vagal efferent nerve stimulation in diabetic animal models (Dall'Ago *et al.*, 2007; de *et al.*, 2002; Lin *et al.*, 2010; Maeda *et al.*, 1995; McDowell *et al.*, 1994a). This discrepancy might be due to different animal species, experimental diabetic animal models, and time course of development of diabetes. Therefore, further studies are needed to explore whether the altered efferent component of the arterial baroreflex is responsible for the arterial baroreflex dysfunction in type 1 diabetes besides the arterial baroreceptor and central integration.

4. Conclusion

As a homeostatic mechanism, the arterial baroreflex normally alters heart rate and blood pressure in response to changes in arterial wall tension detected by the baroreceptors in the carotid sinus and aortic arch. As illustrated by the above evidence, arterial baroreflex impairment, a characteristic of the autonomic cardiovascular dysfunction is a frequent complication in type 1 diabetic patients and animal models. The arterial baroreflex dysfunction not only is an independent predictor for mortality of the type 1 diabetic patients, but also is associated with a poor prognosis and bad quality of life in the type 1 diabetic patients.

Although the mechanisms responsible for attenuated arterial baroreflex function in the type 1 diabetes are not yet fully understood, any part of the arterial baroreflex arc including an afferent limb, a central neural component, and an autonomic neuroeffector component can contribute to the arterial baroreflex dysfunction in the type 1 diabetic state. Especially at the level of the afferent limb, recent studies have revealed that aortic depressor nerve discharge and excitability of aortic baroreceptor neurons are blunted in the type 1 diabetic animals. HCN channels are significantly suppressed in the aortic baroreceptor neurons and are involved in the blunted baroreceptor neuron excitability in the type 1 diabetes. Angiotensin

II/AT_1 receptor-NADPH oxidase-superoxide signaling regulates this alteration of the HCN channels in the aortic baroreceptor neurons and consequently decreases the arterial baroreflex function. In addition, we also consider that angiotensin II/AT_1 receptor-NADPH oxidase-superoxide signaling affects the changes in the central neural and autonomic neuroeffector components beyond the afferent limb of the arterial baroreflex arc. These studies provide new information on the mechanisms underlying the impaired arterial baroreflex in the type 1 diabetes and unveil important pharmacological and genomic targets for improving the arterial baroreflex function and reducing the mortality in the type 1 diabetes.

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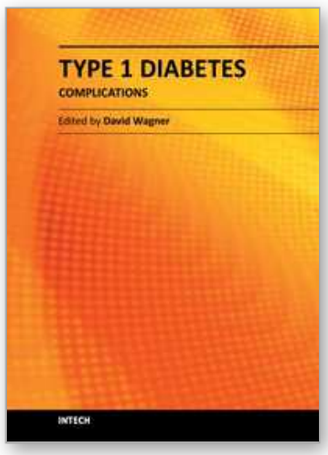

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This book is a compilation of reviews about the complication of Type 1 Diabetes. T1D is a classic autoimmune disease. Genetic factors are clearly determinant but cannot explain the rapid, even overwhelming expanse of this disease. Understanding etiology and pathogenesis of this disease is essential. The complications associated with T1D cover a range of clinical obstacles. A number of experts in the field have covered a range of topics for consideration that are applicable to researcher and clinician alike. This book provides apt descriptions of cutting edge technologies and applications in the ever going search for treatments and cure for diabetes.

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