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Central Sympathetic Overactivity: Maladies and Mechanisms

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Abstract

There is growing evidence to suggest that many disease states are accompanied by chronic elevations in sympathetic nerve activity. The present review will specifically focus on central sympathetic overactivity and highlight three main areas of interest: 1) the pathological consequences of excessive sympathetic nerve activity; 2) the potential role of centrally derived nitric oxide in the genesis of neural dysregulation in disease; and 3) the promise of several novel therapeutic strategies targeting central sympathetic overactivity. The findings from both animal and human studies will be discussed and integrated in an attempt to provide a concise update on current work and ideas in these important areas.

1. Introduction

Since the first suggestion almost 200 years ago that muscle fibres in the blood vessel wall are under neural control, the sympathetic nervous system has become an intense area of research focus (Henle, 1840; Heymans and Folkow, 1982; Stelling, 1867). It is now well established that the tonic rhythmic discharge of the sympathetic nerves contributes importantly to resting vasomotor tone, and through modulation of the arterial baroreflex plays an essential role in blood pressure (BP) homeostasis (Cowley et al., 1973; Ramirez et al., 1985). However, the sympathetic nervous system is not only important for BP control, but is also intimately involved in numerous other physiological processes ranging from metabolism to renal control. Key regulatory sites within the central nervous system that govern sympathetic outflow have been identified and the control of the sympathetic nervous system has been and continues to be an area of intense investigation. Much of the interest in this area stems from the growing evidence that many disease states are accompanied by alterations in central sympathetic regulation and as such, chronically elevated sympathetic nerve activity (SNA). The present review will focus on this central sympathetic overactivity and highlight three main areas of interest: 1) the pathological consequences of excessive SNA; 2) the potential role of centrally derived nitric oxide (NO) in the genesis of neural dysregulation in disease; and 3) the promise of several novel therapeutic strategies targeting central sympathetic overactivity. We have attempted to integrate recent animal and human studies in order to provide a concise update on current work and ideas in each of these areas. Thus, the focus is primarily on more recently published work. Clearly, there is an abundance of research in each of these areas and consequently it would be

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impossible to cover and reference all of the work within each area. To partially rectify this situation, we have cited a number of reviews in an attempt to direct the reader to research that may have been inadvertently omitted.

2. Assessment of SNA

Experimental quantification of the activity of the sympathetic nervous system can be undertaken using several methodologies (Esler et al., 2003; Grassi, 1998; Grassi and Esler, 1999). Direct recordings of SNA (e.g. renal or lumbar) are commonly obtained in animals by the surgical implantation of recording electrodes onto the appropriate sympathetic fibres. In humans, a comparable direct assessment of central sympathetic activity can be made using the microneurography technique to selectively record from postganglionic muscle or skin sympathetic nerves (Vallbo et al., 1979). Alternatively, global sympathetic activity may also be assessed from analysis of plasma or urine catecholamine concentrations. In addition, the work of Murray Esler and associates has pioneered the use of radiotracer techniques in humans for the determination of global or specific organ spillover rates of noradrenaline, the primary neurotransmitter of the sympathetic nervous system (Esler et al., 2003; Grassi, 1998; Grassi and Esler, 1999). Finally, spectral analysis of heart rate or blood pressure variability has also been used to provide an index of sympathetic drive (Pagani et al., 1997) although the validity of these indices has been questioned (Parati et al., 2006). As the focus of this review is on central regulation of SNA, we will predominantly focus on studies employing direct neural recordings of sympathetic outflow, which is suggested to be strongly correlated with renal, cardiac and whole-body noradrenaline spillover (Wallin et al., 1992; Wallin et al., 1996).

3. Central sympathetic control

The central regulation of sympathetic outflow primarily occurs within the cardiovascular areas of the brainstem (i.e. medulla oblongata), which is the site of a complex convergence of descending and ascending neural inputs (Dampney, 1994) (Figure 1). Sympathetic preganglionic neurones located in the intermediolateral cell column (IML) of the spinal cord are known to receive strong excitatory drive from neurones of the rostral ventrolateral medulla (RVLM) located in the medulla oblongata. This excitatory drive from the RVLM may be intrinsically generated, chemically mediated (e.g. glutamate, Angiotensin (Ang) II), or attributable to excitatory inputs from other regions of the central nervous system (e.g. pons, hypothalamus and amygdala) (Dampney, 1994). Furthermore, direct excitatory inputs from other regions of the central nervous system may also directly project to sympathetic preganglionic neurones at the IML (Dampney, 1994). For example, using a retrogradely transported tracer Strack et al., (Strack et al., 1989) identified that sympathetic preganglionic neurones also receive inputs from neurons of the ventromedial medulla, caudal raphe nuclei, A5 noradrenergic cell group of the caudal ventrolateral pons, and the paraventricular hypothalamic nucleus (PVN). In addition, the arterial baroreflex provides a powerful modulation of SNA and is critical for the beat-to-beat, and possibly longer term regulation of BP (Joyner et al., 2008; Thrasher, 2006). Baroreceptor afferents terminate at the nucleus tractus solitarius (NTS) in the medulla oblongata, and the NTS exerts a tonic sympathoinhibitory influence on RVLM neurones by its projections relayed via the caudal ventrolateral medulla (Dampney, 1994). Furthermore, afferent inputs from other peripheral reflexes (e.g. arterial chemoreflex) can impinge on the NTS and alter SNA (Loewy, 1990; Schultz et al., 2007). In addition, the circumventricular organs, which lack a blood brain barrier, represent a pathway by which circulating factors can influence key central regions involved in the regulation of SNA and thus, modulate central sympathetic outflow (Simpson, 1981). Although alterations in each of these areas, and/or the reciprocal interactions amongst them, has the potential to modulate central sympathetic outflow, our understanding of the complex neuroanatomical

interactions governing the central regulation of SNA is incomplete and remains an intense area of research focus.

4. Consequences of central sympathetic overactivity

An overactive sympathetic nervous system has become an identified characteristic of several cardiovascular diseases including, ischemic heart disease (Graham et al., 2004), chronic heart failure (Leimbach et al., 1986), and hypertension (Grassi, 1998). However, elevated SNA is not isolated to diseases of the cardiovascular system and has also been reported in a plethora of other conditions including: kidney disease (Converse et al., 1992), type II diabetes mellitus (Huggett et al., 2003), obesity (Grassi et al., 2007), metabolic syndrome (Grassi et al., 2005), obstructive sleep apnea (Narkiewicz and Somers, 1997), pre-eclampsia (Greenwood et al., 2003), depression (Barton et al., 2007), and ulcerative colitis (Furlan et al., 2006). Importantly, sympathetic overactivity is associated with poor prognosis in patients with chronic heart failure (Barretto et al., 2008; Cohn et al., 1984) and end-stage renal disease (Zoccali et al., 2002) as well as in community dwelling elderly individuals (Reuben et al., 2000). For example, a recent study of heart failure patients showed that increased muscle SNA was a significant independent predictor of one-year cardiac mortality (Barretto et al., 2008) (Figure 2). The scale and potential pathological significance of excessive sympathetic nerve activity becomes clear when one considers the prevalence and mortality rates of conditions with which it is associated. These diseases represent some of the major causes of death in industrialised nations (Lloyd-Jones et al., 2008).

One notable deleterious consequence of an increase in SNA is an increase in arterial BP, which is also a common co-morbidity in a number of pathophysiological conditions, including end stage renal disease and obesity (Grassi et al., 1996; Kotanko, 2006). Indeed, there is compelling evidence that sympathetic activation plays a pathogenic role in triggering the essential hypertensive state (Abboud, 1982; Grassi, 1998; Grassi, 2004a; Grassi, 2004b; Smith et al., 2004), although this concept is not universally accepted (Joyner et al., 2008). Muscle SNA (Grassi, 1998), plasma noradrenaline concentrations (Esler et al., 1977; Goldstein, 1983) and noradrenaline spillover from the heart and kidneys (Esler et al., 1990) have been reported to be elevated in patients with essential hypertension. In addition, muscle SNA is elevated in both white coat hypertensives and borderline hypertensives (Anderson et al., 1989; Smith et al., 2004), supporting the role of the sympathetic nervous system in the pathogenesis of hypertension. Furthermore, the degree of sympathetic overactivity has been found to be related to the magnitude of hypertension in cross-sectional patient studies (Grassi et al., 1998) and in longitudinal studies of spontaneously hypertensive rats (Judy et al., 1979). Thus, it appears that the relationship between central sympathetic overactivity and the hypertensive state is not simply associative, but the increase in SNA likely plays a significant role in both the initiation and the development of the hypertension (Abboud, 1982; Grassi, 1998; Grassi, 2004a; Grassi, 2004b; Smith et al., 2004).

An important deleterious consequence of the hypertensive state is that it can give rise to both structural and functional abnormalities of the vasculature. Indeed, it has been recognised for some time that chronic elevations in BP increase vascular smooth muscle cell hypertrophy and hyperplasia, along with inducing structural and biochemical changes in endothelial cells (Feihl et al., 2008; Folkow, 1982). This can lead to abnormal wall to lumen ratio, increased resistance to flow and accelerate the progression of atherosclerosis (Failla et al., 1999; Folkow, 1982). However, there is now accumulating evidence to suggest that sympathetic overactivity can have a deleterious effect on the vasculature that is independent of an increase in BP. Indeed, chronic sympathetic activation without an increase in BP has been demonstrated to cause morphological changes in vascular smooth muscle cells such as hypertrophy and proliferation (Bevan, 1984), an effect that is attenuated by sympathetic denervation (Bevan, 1975). Such

sympathetically-mediated vascular remodelling can cause increased aortic medial thickening and enhanced blood pressure variability (Dao et al., 2001), which has been implicated in the mediation of end-organ damage (Mancia and Parati, 2003). Along with such changes in vascular structure, sympathetic tone can also profoundly influence vascular function. In this regard, surgical sympathetic denervation and pharmacological blockade have been shown to increase arterial distensibility in both animals as well as healthy and diseased patient populations (Mancia et al., 1998; Mangoni et al., 1997). Conversely, acute increases in sympathetic tone as caused by mental stress, lower body negative pressure or a cold pressor test have been reported to decrease radial artery compliance in healthy subjects (Boutouyrie et al., 1994; Salzer et al., 2008). Furthermore, Grassi et al., (Grassi et al., 1995) have demonstrated that the increase in SNA with heart failure is associated with the reduced radial artery compliance noted in these patients. The clinical significance of sympathetically-mediated increases in arterial stiffness is evident from the results of large epidemiological studies indicating a strong relationship between increased arterial stiffness and increased mortality rates in populations of patients where elevations in SNA are prevalent, such as hypertension (Blacher et al., 1999a), end stage renal disease (Blacher et al., 1999b; London et al., 2001) and type II diabetes (Cruickshank et al., 2002).

Recent evidence suggests that arterial stiffness is not only determined by vascular smooth muscle tone and the passive properties of the structural components of the vessel (i.e. elastin and collagen cross linking), but also by changes in endothelial function (Kinlay et al., 2001). Indeed, removal of the endothelium in rats causes significant changes in the mechanical properties of the carotid artery, indicating the importance of the endothelium to large artery distensibility (Levy et al., 1989). The clinical significance of impairments in endothelial function in the development of atherosclerosis (Neunteufl et al., 1997) and as a predictor of future cardiovascular risk (Fischer et al., 2005; Neunteufl et al., 2000; Perticone et al., 2001; Schachinger et al., 2000) is now well established. However, perhaps less well appreciated is the interaction between endothelial function and the sympathetic nervous system. Acute increases in SNA induced by experimental sympatho-excitatory manoeuvres have been reported to impair endothelial dependent vasodilatation in response to shear stress in groups of healthy subjects (Hijmering et al., 2002; Thijssen et al., 2006) and patients with chronic heart failure (Santos et al., 2005). Although these findings have not been universal (Dyson et al., 2006), these acutely induced impairments in endothelial function support the suggestion that chronic sympathetic activation may contribute to the endothelial dysfunction and the subsequent development of atherosclerosis (Neunteufl et al., 1997). Experimental support of this contention is provided by classic studies of normocholesterolemic *cynomolgus* monkeys, where social stress mediated increases in sympathetic activity have been found to be directly related with impairments in vascular function and an increased risk of coronary artery atherosclerosis (Kaplan and Manuck, 1997; Kaplan et al., 1983). Notably, this atherogenic effect was observed to occur independently of changes in heart rate or BP, but was decreased following administration of β-blockade (Kaplan et al., 1987), suggesting that sympathetic arousal may make a direct contribution to the pathogenesis of atherosclerosis with chronic stress. Further, mechanistic insight into the association between sympathetic activation and atherosclerosis comes from the work of Pettersson et al., (Pettersson et al., 1990) who demonstrated that chloralose anaesthesia-induced increases in SNA caused endothelial cell damage; an effect that was completely abolished by pre-treatment with β-blockade. Collectively, these studies suggest that pathological elevations of SNA play a significant role in the process of vascular remodelling and endothelial dysfunction, and as such may represent one way in which sympathetic overactivity precipitates and accelerates the development of cardiovascular disease.

Sympathetically-induced increases in peripheral vascular resistance and arterial stiffness also have notable influences on cardiac function, via a process of ventricular-arterial coupling

(Frenneaux and Williams, 2007). Increased arterial stiffness leads to increased pulse wave amplification and BP (Kannel, 1976), and the subsequent increase in aortic impedance and afterload necessitate a greater myocardial energy demand for a given stroke volume, thus reducing cardiac reserve (Frenneaux and Williams, 2007). Furthermore, this can increase cardiac wall stress and lead to the development of ventricular stiffness and hypertrophy (Frenneaux and Williams, 2007). However, independent of sympathetically-mediated changes in peripheral vascular function, chronically elevated SNA can have direct effects on myocardial structure and function. Administration of sub-pressor doses of noradrenaline have been reported to have a direct trophic effect on cardiac myocytes and increase left ventricular mass and wall thickness in animals (Sen and Young, 1991; Simpson, 1983). Similarly, it has recently been demonstrated in essential hypertensive patients that left ventricular hypertrophy, as determined using cardiac magnetic resonance imaging, is related to elevations in muscle SNA (Burns et al., 2007). This observation has clinical significance as left ventricular hypertrophy is associated with the progression to diastolic heart failure (Frenneaux and Williams, 2007) and is an independent risk factor for future cardiovascular events and sudden cardiac death (Levy et al., 1990). In fact, experimental increases in SNA raise the incidence of fatal cardiac rhythm disturbances, particularly when combined with decreased parasympathetic nerve activity (Lown and Verrier, 1976). These data suggest that sympathetic overactivity may contribute to the increased risk of sudden cardiac death in several conditions strongly associated with elevated SNA, including heart failure (Packer, 1985) and hypertension (Grassi, 1998).

The pathological consequences of sympathetic activation are not restricted to the cardiovascular system. Indeed, increased SNA can also have profound negative effects on the function of other organs. One such organ is the kidney, where elevated renal SNA increases vascular tone while altering renal sodium and water homeostasis, thus contributing to excessive fluid volume, oedema formation and increases in BP (DiBona, 2002). Notably, renal nerve transection ameliorates excess fluid retention indicative of the direct role of sympathetic overactivity in renovascular hypertension (DiBona, 2002). Moreover, evidence suggests that elevated SNA can impair renal function, independent of increases in BP. Indeed, in spontaneously hypertensive rats the administration of non-hypotensive doses of the central sympatholytic agent moxonidine has been shown to reduce SNA and the development of glomerulosclerosis (Amann et al., 2000). More recently, it has been reported that non-hypotensive doses of moxonidine can also elicit an antialbuminuric effect in type I diabetic patients (Strojek et al., 2001). These observations highlight the potential beneficial effects of reductions in SNA on renal function in humans, independent of any changes in BP.

Pathological sympatho-excitation has also been linked with metabolic diseases. Over two decades ago Landsberg proposed a link between the development of metabolic abnormalities, such as insulin resistance and dyslipidemia, and the activation of the sympathetic nervous system (Landsberg, 1986). According to this hypothesis elevations in circulating insulin levels, resulting from the insulin resistance associated with obesity, cause increases in central SNA which precipitate the development of hypertension (Landsberg, 2001). In support of this contention, subsequent studies in healthy human volunteers demonstrated that infusions of insulin, with glucose concentrations clamped, increased muscle SNA, an effect which appeared to be independent of the vasodilatory effects of insulin (Anderson et al., 1991; Hausberg et al., 1995). Furthermore, muscle SNA has been reported to be elevated in the obese (Grassi et al., 2007) and in some cases in the absence of elevations in BP. However, it has been known for some time that obesity is a strong predictor of future hypertension (Kannel, 1987). More recently it has been proposed that accumulating adiposity also partly mediates age-related increases in SNA (Seals and Bell, 2004). However, the connection between obesity, insulin resistance and elevated SNA is arguably a ‘chicken and egg’ scenario, and it is possible that elevated SNA can itself lead to insulin resistance, particularly in hypertensive individuals (Julius and Valentini, 1998). Indeed, acute increases in sympathetic activation have been shown

to increase plasma insulin concentrations (Jamerson et al., 1993). In addition, it has been proposed that chronic elevations of SNA and subsequent α-adrenergic vasoconstriction may impede postprandial increases in muscle blood flow, thus limiting glucose clearance and causing exaggerated pancreatic insulin release (Julius and Valentini, 1998). In support of this possibility, the administration of vasoactive agents to offset peripheral vasoconstriction in patient populations has been reported to improve insulin sensitivity (Pollare et al., 1989; Pollare et al., 1988). Overall, there is clear evidence to support a linkage between elevated SNA and insulin resistance. This is indeed a rapidly evolving area of research (Grassi et al., 1996; Julius and Valentini, 1998; Tentolouris et al., 2006).

5. Potential mechanisms for sympathetic overactivity

Given the diverse range of pathological conditions associated with sympathetic overactivity and its potential to accelerate the progression of cardiovascular, renal and metabolic pathology, the sympathetic nervous system constitutes an important putative target for arresting the progression of disease (Grassi, 2004a; Grassi, 2004b). To develop effective countermeasures, it is important to identify the signal driving the sympathetic overactivity. However, the mechanisms underlying this sympathetic dysregulation are complex and multifactoral, encompassing alterations in autonomic reflex pathways, central autonomic neuroanatomical sites as well as hormonal factors. Indeed, intense work has focused on the potential role of impairments in sympathetic restraint provided by arterial and cardiopulmonary baroreflexes (Brown, 1980), and of exaggerated sympathetic drive attributable to augmented somatic reflexes (Smith et al., 2006) and central/peripheral chemoreflexes (Schultz et al., 2007). Furthermore, functional alterations in several autonomic nuclei (e.g. RVLM, NTS, and PVN) associated with changes in central concentrations of NO, Ang II, reactive oxygen species (ROS), aldosterone and inflammatory cytokines have also been proposed to contribute to pathological elevations in SNA (Gao et al., 2005b; Guggilam et al., 2008; Patel et al., 2001; Waki et al., 2006; Yu et al., 2008; Zhang et al., 2008; Zimmerman and Davisson, 2004; Zucker, 2006; Zucker et al., 2001). In this regard, accumulating evidence has implicated alterations in central NO in the genesis of central sympathetic overactivity.

Several studies have demonstrated that NO is not only an endothelial-dependent vasodilator but also a key signalling molecule involved in the control of sympathetic outflow from the brainstem (Lepori et al., 1998; Patel et al., 2001; Sander et al., 1997; Sander et al., 1995). All NO synthase (NOS) isoforms are plentiful in brain stem centres involved in the central regulation of SNA and BP (Rodrigo et al., 1994). Indeed, an abundance of animal literature has advanced the hypothesis that centrally-derived NO acts to tonically restrain sympathetic outflow from the brainstem, placing a brake on α-adrenergic vasoconstriction. The administration of NOS inhibitors by intravenous injection (Sakuma et al., 1992), intracisternal injection (el Karib et al., 1993; Togashi et al., 1992), or by direct injection into the RVLM (Zanzinger et al., 1995) or PVN (Zhang and Patel, 1998), has been shown to elicit acute increases in renal SNA and BP, implying a central role of NO on the sympathetic control of BP (Zanzinger, 1999; Zanzinger et al., 1995). A direct influence of NO on central sympathetic neuronal activity has also been derived from studies using rat brainstem slice preparations (Tagawa et al., 1994) and from work demonstrating that gene transfer mediated over expression of NOS at the RVLM decreases urinary noradrenaline in rats (Kishi et al., 2002). Collectively, these studies have demonstrated that alterations in centrally derived NO have functional consequences on central sympathetic outflow.

Initial attempts to extrapolate these findings of NO mediated control of central sympathetic outflow to the conscious state provided somewhat equivocal results (Barres et al., 1992; Hansen et al., 1994; Manning et al., 1994; Sander et al., 1995; Zanchi et al., 1995). Part of the explanation for these contradictory findings was likely related to reductions in endothelial-

derived NO from the peripheral vasculature when NOS inhibitors were infused systemically. In this regard, experimental systemic NOS inhibition rapidly increases BP due to the removal of endothelial-dependent vasodilation and activates an arterial baroreflex-mediated sympatho-inhibitory response which counteracts any potential increase in SNA from a baroreflex-independent (i.e., central) mechanism (Hansen et al., 1994). Nevertheless, studies of conscious rats with and without sympathectomy during systemic NOS inhibition with N^G-nitro-L-arginine (L-NAME) lend clear support for NO control of central SNA in that initial increases in BP were similar in both groups whereas over time BP continued to rise in intact rats but not in the sympathectomized rats (Sander et al., 1997). These results indicate the importance of SNA to the pathogenesis of NO deficient hypertension and have recently been extended to include direct measures of renal SNA (Augustyniak et al., 2006) (Figure 3). During systemic L-NAME, renal SNA exhibited an initial decrease (baroreflex-mediated) but then progressively increased up to 3 hours post infusion, whereas renal SNA remained suppressed throughout when BP was increased to a similar extent with the hypertensive control phenylephrine. Collectively, these data indicate that systemic NOS inhibition and the removal of NO does indeed alter central sympathetic outflow however, arterial baroreflex inhibition and the time for NOS inhibitors to cross the blood brain barrier need to be considered.

In support of these findings from animal investigations, studies in humans have indicated a dose dependence of the sympathetic response to systemic intravenous administration of a NOS inhibitor, with low dose infusion of N^G-monomethyl-L-arginine (L-NMMA) not altering muscle SNA and higher dosages suppressing SNA (Hansen et al., 1994; Lepori et al., 1998; Owlya et al., 1997). The lack of a sympathetic effect at the lower dosage in comparison to the sympatho-inhibition evoked by an equal pressor response elicited by phenylephrine was taken as evidence for a sympatho-excitatory effect of NOS inhibition. Additionally, minimizing the L-NMMA induced increase in BP with the co-infusion of nitroprusside caused SNA to increase. Thus, prevention of the arterial baroreflex-mediated suppression of muscle SNA unmasked a sympatho-excitatory effect of L-NMMA infusion. Further human studies by Sander et al., (Sander et al., 1999) have identified that inhibition of endothelium-dependent vasodilation is the primary mechanism underlying the initiation of the hypertensive response to systemic NOS inhibition but the sympathetic nervous system plays an important role in the full expression and maintenance of the BP raising effect. Recently, our laboratory has provided preliminary evidence that systemic NOS inhibition with L-NAME causes pronounced increases in sympathetic outflow in humans (Young et al., 2008). We made direct recordings of skin SNA during L-NAME infusion and time and hypertensive (phenylephrine) control experiments in healthy subjects. Our rationale for recording skin SNA is that unlike muscle SNA, cutaneous SNA is not under arterial baroreceptor control in normothermic conditions (Wallin et al., 1975) whereas it is responsive to alterations in central sympathetic outflow. We found that skin SNA increased significantly after L-NAME but remained unchanged during time and hypertensive controls. Although it is not possible to determine the precise site at which NO is acting within the central nervous system to alter SNA (e.g. RVLM, PVN, ganglionic synapse), these preliminary findings support a clear role for NO in the tonic restraint of central sympathetic outflow in humans. Given the potential for oestrogen to modulate NOS activity, sex differences may require consideration when examining the regulation of central SNA (Xue et al., 2007).

Considering that administration of an exogenous NOS inhibitor can increase SNA, it is plausible that physiological accumulation of endogenous NOS inhibitors could also raise SNA. L-NMMA and asymmetric dimethylarginine (ADMA) are naturally occurring NOS inhibitors that circulate in the plasma and are excreted in the urine (Vallance et al., 1992). ADMA is normally found in higher concentrations than L-NMMA and has been reported to be elevated in a number of pathophysiological conditions such as hypercholesterolemia, atherosclerosis, hypertension, chronic renal failure, and chronic heart failure (Boger, 2003). Most striking are

the 4 to 12 fold increases in plasma ADMA in patients with end stage renal disease in comparison to healthy subjects with normal renal function (Vallance et al., 1992). Although a strong relationship between plasma concentrations of the sympathetic neurotransmitter noradrenaline and plasma ADMA has been reported among patients with end stage renal disease (Mallamaci et al., 2004), there is currently no direct evidence in humans indicating that excessive ADMA causes a reduction in central NO and increases SNA. However, consistent with this idea are recent findings from Augustyniak et al., demonstrating that systemic intravenous infusion of ADMA increases renal SNA in rats (Augustyniak et al., 2006). Further studies in healthy subjects and patients are needed to examine the potential for elevated ADMA concentrations to influence NO-mediated regulation of central sympathetic outflow.

Aside from changes in NOS activity, peripheral and central NO are also critically dependent upon a balance between ROS and antioxidants. Increased ROS generation will lead to scavenging of NO and thus the removal of central sympathetic inhibition (Lindley et al., 2004; Zimmerman and Davisson, 2004). Coupled with this, increases in ROS have been proposed to directly activate or sensitize sympathetic neurones via alterations in membrane ion channel function (Peterson et al., 2006; Veerasingham and Raizada, 2003; Zimmerman and Davisson, 2004). Conversely, intra-cerebroventricular infusion of the antioxidant tempol (a superoxide dismutase mimetic) has been shown to decrease SNA (Campese et al., 2004). Potential central enzymatic sources of ROS generation include, xanthine oxidase, cyclooxygenase, cytochrome p450, NOS and nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase (Zimmerman and Davisson, 2004). The latter being considered as a particularly important source of central ROS (Peterson et al., 2006), and all the NAD(P)H oxidase subunits have been shown to be expressed in sympathetic neuron cultures (Tammariello et al., 2000) and throughout the fore-, mid-, and hindbrain (Serrano et al., 2003). It was first demonstrated that vascular smooth muscle NAD(P)H oxidase is activated by Ang II and subsequently increases vascular ROS levels (Griendling et al., 2000). However, more recent work has shown that a similar phenomenon occurs within the central nervous system where Ang II up-regulates NAD(P)H oxidase via activation of Ang II type 1 (AT_1) receptors (Zimmerman and Davisson, 2004; Zucker et al., 2001). Importantly, this process has been shown to occur at neuroanatomical areas implicated in central sympathetic regulation such as the RVLM. Indeed, up-regulation of NAD(P)H oxidase in the RVLM has been shown to increase renal SNA (Gao et al., 2005b). Zucker and colleagues have suggested that this pathway becomes very important in heart failure and contributes to the well known reductions in arterial baroreflex sensitivity and increases in central sympathetic drive present in this disease state (Gao et al., 2005b; Zucker, 2006). In this regard, circulating plasma Ang II is elevated in heart failure and it is thought that the circumventricular organs, which lack a blood brain barrier and are rich in AT_1 receptors, are the primary regions where circulating Ang II mediates its central effects by activating NAD(P)H oxidases (Simpson, 1981; Zucker et al., 2001). In addition, an up-regulation of locally produced Ang II and a consequent increase in ROS is also thought to contribute (Zimmerman and Davisson, 2004). Overall, these animal investigations indicate that increases in central sympathetic outflow in heart failure are mediated via Ang II activation of NAD(P)H oxidase and subsequent production of ROS, which may directly activate central SNA pathways along with scavenging NO thereby removing the tonic restraint on sympathetic outflow.

It is important to note that the mechanisms contributing to central sympathetic activation in heart failure, and indeed other disease conditions, are more complex than described above because multiple central neural sites, neurotransmitters and neuromodulators are involved (Weiss et al., 2003). For example, along with the pathophysiological changes in NO signalling reported at the RVLM, NO has been shown to also play a role in other brainstem regions important for the regulation of SNA. Indeed, reductions in neuronal NOS have been reported in the PVN, dorsal pons and hypothalamus in experimental heart failure, which may facilitate

an enhanced descending drive to sympathetic pre-motor neurons and enhancement of SNA (Patel et al., 1996; Zhang et al., 1998; Zucker, 2006). A further important consideration is that the actions of NO may be regionally specific. Indeed, work from Paton and colleagues suggests that an Ang II mediated over expression of NO at the NTS decreases arterial baroreflex sensitivity and contributes to the elevated BP in spontaneously hypertensive rats (Paton et al., 2006; Waki et al., 2006). Thus, despite recent progress in this area, future studies in animals and humans focusing on changes in NO as well as potential alterations in Ang II, ROS, aldosterone and inflammatory cytokines are required to better understand the mechanisms contributing to central sympathetic overactivity in disease. Undoubtedly, this research will have a significant impact on future treatments targeting central sympathetic overactivity in disease.

6. Therapeutic strategies for targeting sympathetic over-activity

6.1 Central sympathetic agents

Protecting the heart from sympathetic overactivity by β-adrenergic blockers has proven to be beneficial for survival in hypertensive and heart failure patients and therefore β-blockers have become a mainstay of therapy in these conditions (Clark and Cleland, 2000). Although, angiotensin converting enzyme (ACE) inhibitors are also standard therapy in heart failure and hypertension, their survival benefits may be mediated through non-sympathetic mechanisms as reductions in SNA with ACE inhibition have been shown to be somewhat modest (Benedict et al., 1995; Grassi, 2004b; Swedberg et al., 1990). Likewise, studies in patients with chronic renal failure and essential hypertension have found that following either long term ACE inhibition (Ligtenberg et al., 1999) or AT_1 receptor blockade (Klein et al., 2003; Krum et al., 2006) muscle SNA remained significantly elevated. These findings are somewhat surprising given the considerable evidence from animal studies detailing the important role of central Ang II and AT_1 receptors in the genesis of elevations in central SNA (Veerasingham and Raizada, 2003; Zucker, 2006) and its amelioration with central administration of ACE inhibitors or AT_1 receptor blockers (DiBona et al., 1995; Murakami et al., 1996; Murakami et al., 1997). The reason for these divergent findings is unclear but may reflect differences in central concentrations of the pharmacological agents achieved between animal and human studies (Krum et al., 2006).

An important consideration in the treatment of hypertension is that some pharmacological regimens that effectively reduce BP may actually exacerbate SNA, presumably due to baroreflex unloading (Fu et al., 2005). Thus, to further reduce the deleterious consequences of increases in sympathetic drive, a more effective therapeutic approach may be to inhibit central sympathetic outflow directly by stimulating α_2 or imidazoline receptors in the central nervous system. However, even though clonidine (α_2 and imidazoline receptor agonist) and moxonidine (selective imidazoline receptor agonist) have both proven to be effective in reducing SNA in chronic heart failure patients, both pharmacological agents have undesirable side effects which limit the potential benefit of these drugs on SNA (Aggarwal et al., 2003; Azevedo et al., 1999; Grassi et al., 2001; Planitz, 1984; Swedberg et al., 2002). In addition, it has been suggested that the excessive blockade of the sympathetic nervous system with moxonidine in heart failure may in fact prove deleterious (i.e. resting SNA may be insufficient to support cardiac output and peripheral resistance) (Floras, 2002). Although further studies titrating the dosage of moxonidine may be beneficial (Aggarwal et al., 2003), other treatment strategies aimed at reducing the sympathetic overactivity are warranted. More recently, the promising beneficial effects of the new imidazoline receptor agonist rilmenidine have come to light (Gerova et al., 2004). Along with acting as a powerful sympatholytic and antihypertensive agent (Head and Burke, 2000), rilmenidine has also been shown to be successful in reducing left ventricular hypertrophy in hypertensives (Koldas et al., 2003), improving arterial distensibility in patients with left ventricular hypertrophy (Trimarco et al., 1995), providing

antiarrhythmic protection in the rabbit (Roegel et al., 1998), and improving glycemic control in patients with metabolic syndrome (De Luca et al., 2000). Given the multifaceted beneficial effects of rilmenidine, coupled with the finding that it is generally well tolerated, it is not surprising that it has been purported to be a "first-line antihypertensive option for all groups of hypertensive patient" (Reid, 2000). However, further work is required to explore the extent to which the beneficial effects of rilmenidine extend to other disease states characterised by elevations in central SNA.

6.2 Statins

Reductions in LDL cholesterol with 3-hydroxy-3-meythl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are strongly associated with reductions in coronary heart disease risk (Holme, 1990). However, abundant evidence suggests that statins also have numerous cholesterol independent or "pleiotropic" effects (McFarlane et al., 2002). Indeed, recent findings from clinical trials indicate that statins improve survival in heart failure patients irrespective of cholesterol lowering (Horwich et al., 2004; Horwich and Middlekauff, 2008). Importantly, several studies in pacing-induced heart failure rabbits have demonstrated that statins normalise excessive sympathetic activation in the heart failure state by restoring central sympathetic inhibition and decreasing central sympathetic outflow (Gao et al., 2005a; Pliquett et al., 2003a; Pliquett et al., 2003b). Specifically, simvastatin down-regulates AT_1 receptors, NAD(P)H oxidase subunit gene expression and superoxide while up-regulating neuronally derived NOS in the RVLM, in heart failure (Gao et al., 2005a; Gao et al., 2008). Such centrally mediated changes in neural regulation are associated with reductions in SNA and improvements in arterial baroreflex sensitivity and left ventricular function (Gao et al., 2005a). Collectively, this extensive series of studies by Zucker et al., provide clear support that independent of cholesterol lowering stains reduce sympathetic overactivity in heart failure. These are exciting data given the limited success of conventional anti-adrenergic strategies in reducing SNA in heart failure. To examine whether these findings in experimental heart failure could be translated to the clinical setting of human heart failure we recently measured muscle SNA before and after 1 month of simvastatin (40 mg/day) in a small group of heart failure patients (Figure 4). Our preliminary human data suggests that short-term statin therapy is indeed capable of reducing resting central sympathetic outflow in heart failure patients (Fisher et al., 2007). Although very promising, these findings require validation in a larger cohort of patients. In addition, an understanding of the underlying mechanisms and the extension of these SNA-reducing effects of statins to other patient populations with known sympathetic hyperactivity await further investigation.

6.3 Exercise training

Exercise training is a widely prescribed non-pharmacological therapeutic strategy for improving the quality of life in several diseases characterized by high SNA (e.g. heart failure, hypertension, type II diabetes and obesity), and conferring numerous other physiological benefits (Pedersen and Saltin, 2006). In particular, exercise training is well known to produce marked reductions in BP in hypertensive patients (Pescatello et al., 2004). Reductions in BP induced by exercise in healthy individuals have been associated with attenuated noradrenaline spillover and plasma concentrations (Jennings et al., 1986; Mueller, 2007) and in some instances physical activity has also been reported to reduce muscle SNA in healthy individuals (Grassi et al., 1994). However, the majority of evidence from both longitudinal and cross-sectional studies suggests that exercise training has minimal effects on resting muscle SNA in healthy humans (Ray and Hume, 1998). In contrast, exercise training has been shown to produce robust reductions in central sympathetic outflow in recent studies of experimental animals (Gao et al., 2007; Liu et al., 2000; Zucker et al., 2004; Zucker et al., 2001) and patients (Fraga et al., 2007; Roveda et al., 2003) with heart failure. In particular, work by Zucker et al., using an experimental model of heart failure in the rabbit, has made significant contributions

to our understanding of the central molecular mechanisms underlying the sympatho-inhibitory effects of exercise in disease (Gao et al., 2007; Liu et al., 2000; Zucker et al., 2004). Recent evidence from this group has demonstrated that exercise training restores the sympatho-inhibitory effects of central NO and enhances arterial baroreflex regulation of renal SNA (Liu et al., 2000). In addition, an exercise induced up-regulation of central antioxidants and down-regulation of NAD(P)H oxidase in the RVLM, with concomitant suppression of central pro-oxidant mechanisms has been reported (Gao et al., 2007). However, it is important to note that other central neural pathways also likely contribute to exercise mediated alterations in central regulation of SNA, and this remains an area of intense research focus (Mueller, 2007). Nevertheless, the emerging evidence from both animal and human studies supports the value of exercise training as a therapeutic strategy for reversal of pathological increases in central sympathetic outflow.

7. Summary

Central sympathetic overactivity has been identified in a plethora of clinical conditions. Aside from a role in the development of hypertension, sympathetic overactivity has been implicated in the initiation and progression of numerous pathophysiological processes independent of increases in BP (e.g. vascular hypertrophy, atherosclerosis, glomerulosclerosis, and insulin resistance). Valuable work to elucidate the mechanisms underlying pathological elevations in central SNA and to develop effective therapeutic strategies is ongoing, which given the increasing prevalence of diseases associated with sympathetic overactivity is clearly a pressing issue.

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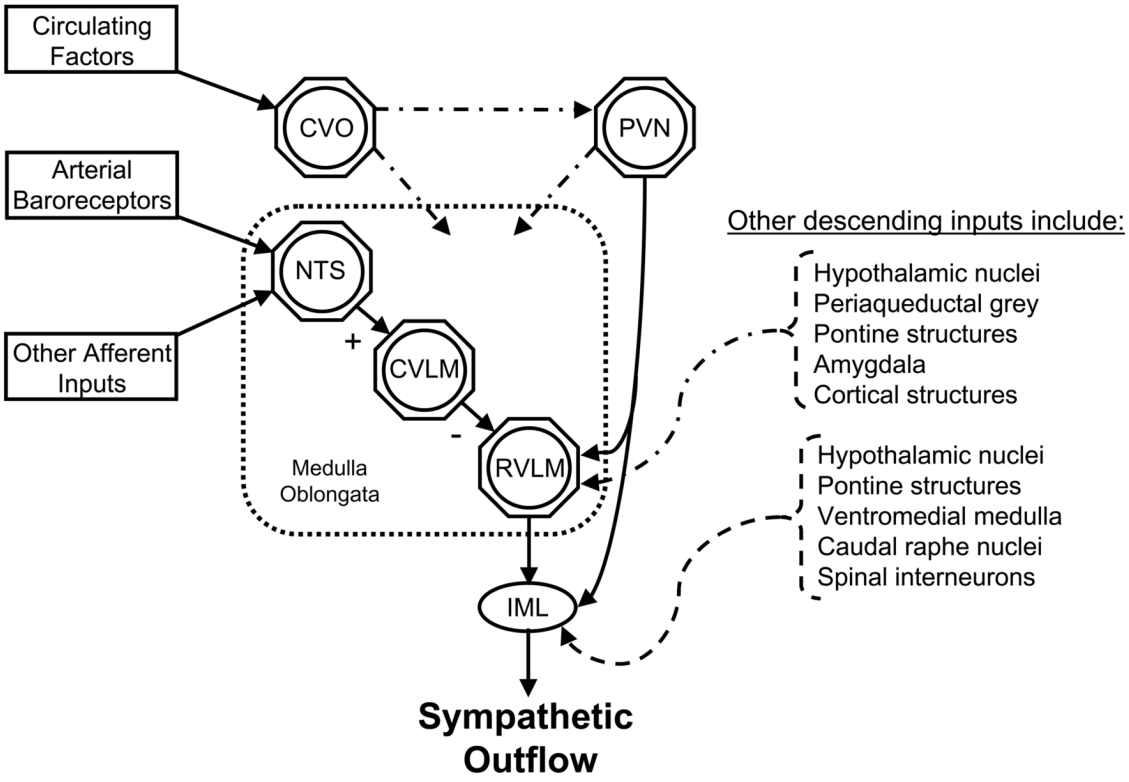

Figure 1.

General schematic identifying potential central neural sites involved in the regulation of sympathetic outflow. See text for details. CVO, circumventricular organs; PVN, paraventricular nucleus; NTS, nucleus tractus solitarus; CVLM, caudal ventrolateral medulla; RVLM, rostral ventrolateral medulla; IML, intermediolateral cell column.

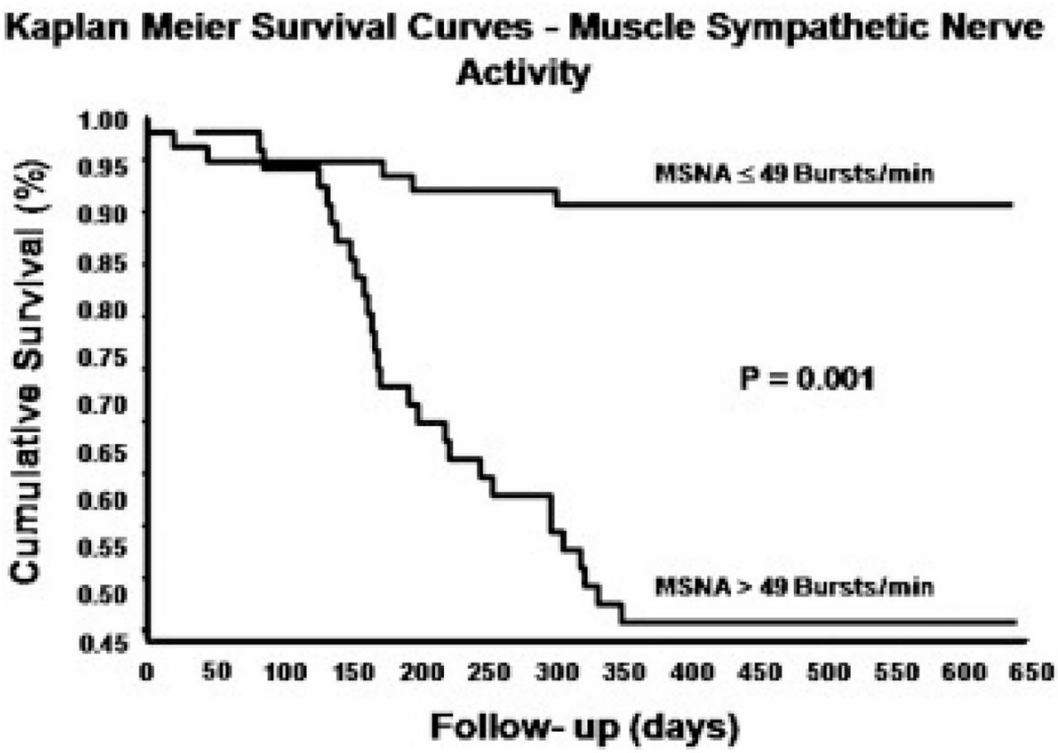

Figure 2.
Kaplan-Meier analysis of the cumulative rates of survival in patients with heart failure stratified in two groups on the basis of resting muscle SNA (MSNA, bursts/min). Rates of survival were significantly poorer in patients with resting muscle SNA values above the median value of 49 bursts/min. From Barretto et al., (2008), with permission.

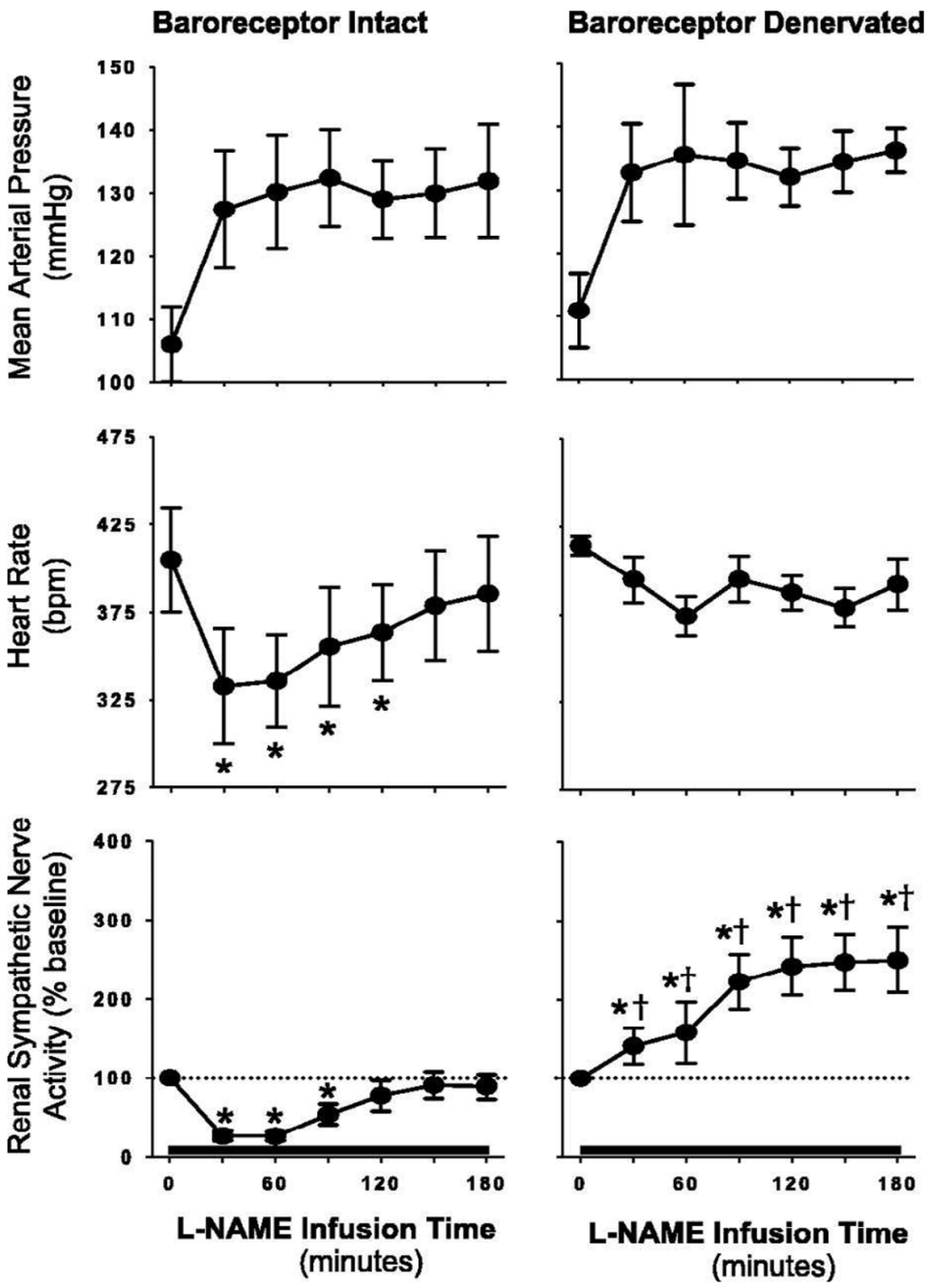

Figure 3.

Summary data showing the mean arterial pressure, heart rate, and renal SNA responses to intravenous infusion of NG-nitro-L-arginine methyl ester (L-NAME) in arterial baroreceptor intact rats (left panel) and baroreceptor denervated rats (right panel). In baroreceptor intact rats, systemic L-NAME evoked an initial baroreflex-mediated reduction in renal SNA that returned to baseline at 120 minutes of infusion. In contrast, a marked and sustained increase in renal SNA was found in baroreceptor-denervated rats. *P<0.05 vs. baseline; † P<0.05 vs. baroreceptor intact. Values are means ± SE. From Augustyniak et al., (2006), with permission.

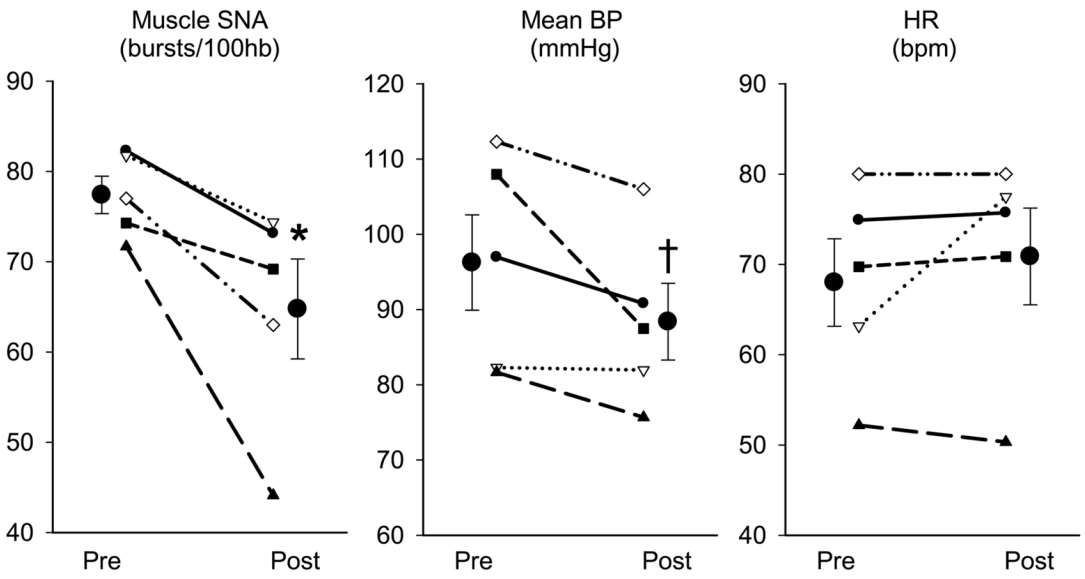

Figure 4.

Individual and mean data showing changes in muscle sympathetic nerve activity (Muscle SNA; bursts/100 heart beats), mean blood pressure (BP) and heart rate (HR) in 5 heart failure patients before and after one month of Simvastatin (40 mg/day). Muscle SNA was significantly reduced following statin therapy, whereas mean BP was slightly decreased and HR was largely unchanged. * represents $P<0.05$ vs. Pre-Simvastatin; † represents $P=0.08$ vs. Pre-Simvastatin. Values are means ± SE.

Table 1

Potential pathological consequences of elevated central sympathetic nerve activity

Vascular effects	*Cardiac effects*
VSM cell hypertrophy and proliferation	Cardiac myocyte hypertrophy
Medial thickening	Left ventricular hypertrophy
Endothelial cell damage	↑ Incidence of arrhythmia
Endothelial dysfunction	Tachycardia
Arterial stiffness	
↑ Blood pressure variability	*Renal effects*
↑ Peripheral vascular resistance	Renal vasoconstriction
Hypertension	Sodium and fluid retention
Atherosclerosis	Glomerulosclerosis
	Microalbumineria
Metabolic effects	RAAS activation
Insulin resistance	
↑ Plasma insulin concentration	
Dyslipidemia	

VSM, vascular smooth muscle; RAAS, Renin-angiotensin-aldosterone system.