Ann Vasc Dis Vol. 7, No. 2; 2014; pp 109–119
Online Month May 16, 2014
doi:10.3400/avd.ra.14-00048
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Review Article

THE RELATIONSHIP BETWEEN VASCULAR FUNCTION AND THE AUTONOMIC NERVOUS SYSTEM

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Endothelial dysfunction and autonomic nervous system dysfunction are both risk factors for atherosclerosis. There is evidence demonstrating that there is a close interrelationship between these two systems. In hypertension, endothelial dysfunction affects the pathologic process through autonomic nervous pathways, and the pathophysiological process of autonomic neuropathy in diabetes mellitus is closely related with vascular function. However, detailed mechanisms of this interrelationship have not been clearly explained. In this review, we summarize fi ndings concerning the interrelationship between vascular function and the autonomic nervous system from both experimental and clinical studies. The clarifi cation of this interrelationship may provide more comprehensive risk stratifi cation and a new effective therapeutic strategy against atherosclerosis.

Keywords: autonomic nervous system, endothelial function, vascular function, endothelial cells

Introduction

The initiation and progression of atherosclerosis depends on profound dynamic changes in vascular biology.1) The endothelium plays a key regulatory role in vascular homeostasis. The understanding of the mechanisms of endothelial dysfunction is of critical importance in designing a therapeutic strategy to inhibit the atherosclerotic process. Risk factors for the progression of atherosclerosis such as diabetes mellitus, hypertension, hyperlipidemia, and smoking, generally impair endothelial function. These factors affect the endothelium from the luminal side of vessels. 2) In addition, endothelial cells (ECs) are also affected from the basal side extracellularly. However, the interaction between the endothelial system andother systems outside of vessels has not been well explained. The autonomic nervous system (ANS) is considered to be one of the potent factors that affects the behavior of endothelial function from outside of vessels. In this review article, we summarize fi ndings concerning the interaction between the endothelium and ANS in the pathologic process of atherosclerosis.

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Received: April 8, 2014; Accepted: April 22, 2014
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Function of Endothelium

The endothelium is a single layer of cells that lines the blood vessel lumen, and organizes the growth and development of underlying connective tissue cells that form the surrounding layers of the blood vessel wall. In addition, ECs interact with various circulating factors in the blood stream and react to these changes to maintain homeostasis. The EC layer acts not only as a passive barrier to keep cells and proteins from escaping freely into the tissue, but also as a source of several vasoactive substances. It plays a central role in the regulation of vascular tone, thrombosis, andinfl ammation through the release of a number of paracrine factors.

Among the regulatory roles, the main role of the endothelium is regulating vascular tone. The primary vasodilator released by the endothelium is nitric oxide (NO).3) NO is generated from L-arginine by the action of endothelial NO synthase (eNOS) in the presence of cofactors such as tetra-hydrobiopterin.4) Other relaxing factors released by the endothelium include endothelium-derived hyperpolarizing factor, prostacyclin, C-type natriuretic factor, 5-hydroxytryptamine serotonin, adenosine triphosphate, substance P, and acetylcholine.5,6) Additionally, ECs can also produce and release vascular constricting factors. Endothelin is a potent vasoconstrictor peptide originally isolated from ECs. The effect of endothelin is powerful and long lasting, in contrast to short-lived prostacyclin and NO.7)

The target of factors that regulate vascular tone is smooth muscle cells adjacent to the endothelium. Other than regulation of vascular tone, the endothelium affects other biological functions via interactions with different cell populations, such as immune cells and blood cells. Infl ammation can be thought of as a vascular response, where ECs become activated, increase leakiness, and enhance leukocyte adhesiveness and procoagulant activity.8) ECs actively participate in both innate and adaptive immune responses. For instance, ECs are one of the fi rst cell types to detect foreign pathogens and endogenous metabolite-related danger signals in the bloodstream, in which ECs function as danger signal sensors.9) In addition, ECs also induce cytokine production by immune cells, in which ECs function as immune regulators either by activating or suppressing immune cell function.10) The expression of adhesion molecules leads to the recruitment of leukocytes in the process of inflammation.11)

There are various methods for measuring endothelial function, but the evaluation of ECs is complicated because one modality evaluating endothelial function can only assess a specifi c and limited aspect among the multi-potencies of the endothelium.12) Endothelium-dependent vasomotion has been the most widely used clinical endpoint for the assessment of endothelial function.

Its assessment involves thepharmacological and/or physiological stimulation of endothelial release of NO and other vasoactive compounds, and often a comparison of vascular response to endothelium-independent dilators such as nitroglycerin. The most popular method evaluating endothelial function, fl ow-mediated dilation, is a measurement of vascular diameter dilation by endothelium- derived NO. A number of new techniques have recently been proposed as potentially applicable screening tools for endothelial testing in humans.13) One example is testing endothelial vasomotor function after reactive hyperemia by pulse amplitude tonometry in the fi ngertips (RH-PAT).14) However, the results of endothelial function tests are somewhat affected by the site and method of measurement. Thus, which methods are selected is a critical issue for analyses concerning the interrelationship between endothelial or vascular function and other systems.

Autonomic Nervous System (ANS) and Vascular Disease

Both the sympathetic and the parasympathetic nervous systems innervate blood vessel walls and regulate contraction and wall tension.15,16) The adrenergic nerve endings of the sympathetic nerve fi bers are found in the muscular layer of vessel walls (Fig. 1). In contrast, cholinergic nerve endings are found both in the muscular and endothelial layers. It has been shown in many arterial vessels that M3 receptors on the vascular endothelium are coupled to the formation of NO, which causes vasodilation. However, acetylcholine causes smooth muscle contraction through smooth muscle M3 receptors and M2 receptors when formation of NO is blocked. Thus, ANS innervation into vessel structures controls vascular tone in an intricate manner. Consequently, ANS imbalance could be a risk factor for cardiovascular disease, and sympathetic nervous activation represents a detrimental and maladaptive phenomenon in vascular function and structural integrity.17) Enhanced sympathetic activity induces sustained increase in blood pressure, by causing peripheral vasoconstriction, reducing venous capacitance, and affecting renal sodium and water excretion.18) Sympathetic activity is enhanced in depression and anxiety disorders and sufferers are reported to be at a higher risk for cardiovascular mortality and sudden death.19) Evidence that psychosomatic factors may contribute to the development of atherosclerosis20) suggests that there may be an underlying mechanism whereby activation of the sympathetic nervous system adversely impacts the process of atherosclerosis.21,22) In addition, Tsuji, et al. demonstrated a link between reduced heart rate variability and risk of cardiac events.22) Similar to these fi ndings, ANS dysfunction may be associated with the development of diabetes in healthy adults, increasing the risk of atherosclerosis progression.23)

Thus, the ANS is thought to interact with atherosclerotic risk factors in various ways, which also affects the process of atherosclerosis.

Correlations between Impairments in the ANS and Endothelial Dysfunction

Endothelial dysfunction and ANS imbalance often co-exist in the development of various cardiovascular disease processes, suggesting that there are complex interactions between these two systems. Recently, several studies suggested a potential association between heart rate variability and endothelial function. We previously reported a correlation between fl ow-mediated dilation and heart rate variability in subjects with ischemic heart disease.24) Interestingly, the relationship was not present in subjects with diabetes and subjects taking beta-blocking agents. The lack of an association between endothelial function and the ANS in subjects taking beta-blocking agents or subjects with diabetes suggests that the hypothesis that the ANS affects the state of endothelial function is possible. Other groups also suggested a relationship between markers of endothelial function and sympathetic activity in healthy subjects. In a study of 314 healthy subjects, endothelial function in the brachial artery was inversely related to plasma norepinephrine level.25) Swierblewska, et al. performed simultaneous measurements of vascular function and sympathetic discharge using sympathetic action potentials to the muscle vascular bed (MSNA) and RH-PAT.26) The authors found that the RH-PAT index was inversely related to MSNA ($r = -0.8$, $p = 0.005$). The relationships between endothelial dysfunction and ANS imbalance imply a close interrelationship between the endothelium and ANS.

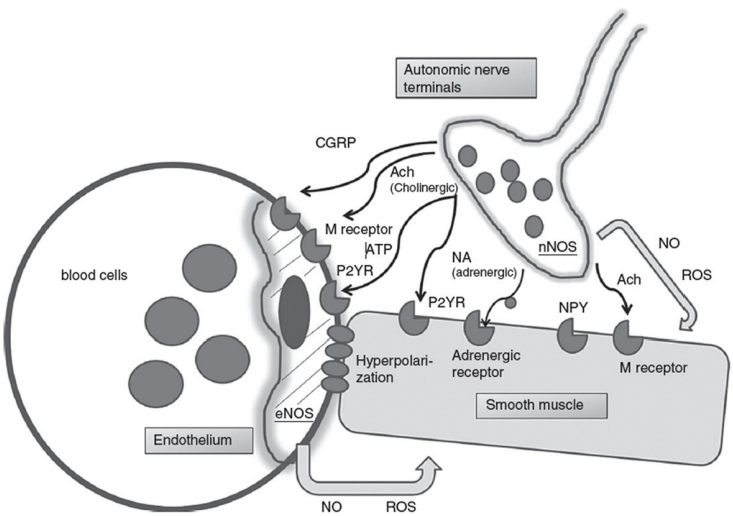

Fig. 1 Schematic illustrate of interrelationship between nerve terminal, smooth muscle cell and endothelial cell. CGRP: calcitonin gene-related peptide; Ach: acetylcholine; ATP: adenosine triphosphate; P2YR: G-protein-coupled P2Y receptors; NA: noradrenalin; NPY: neuropeptide Y; NO: nitric oxide; ROS: reactive oxygen species; nNOS: neuronal nitric oxide synthase; eNOS: endothelial nitric oxide synthase.

In the setting of pathologic conditions such as hypertension, the interrelationship between the ANS and vascular function may contribute to the pathologic process. For instance, Gamboa, et al. investigated the NO-ANS relationship in essential hypertension.27) Endothelial NO is released tonically into the underlying vascular tissues to induce vasodilation. Impairment of this process is thought to be an important component of endothelial dysfunction described in hypertension. However, the impairment of NO availability was insuffi cient to cause dysfunction, and the ANS pathway was considered to be critical for the development of the pathologic process of hypertension.28)

A simple measurement of brachial artery diameter may also have predictive value for cardiovascular risk, and was recently considered to be a marker of vascular function.30) Additionally, it was previously reported to be affected by modulation of the

ANS. Studies using pulsed-Doppler velocimetry revealed that the brachial artery dilates on raising the legs from the supine position, in the absence of changes in blood pressure and heart rate. This dilatation can be explained by a refl ex resulting from stimulation of cardiopulmonary receptors. In this way, the diameter of the brachial artery is controlled mainly by the tone of the ANS.31) In contrast, fl ow-mediated dilation, the purview of endothelial function, is also reported to be heavily affected by brachial artery diameter. Thus, brachial artery diameter represents meaningful information refl ecting ANS and vascular function. Indeed, brachial artery diameter is reported to be useful for risk prediction in atherosclerosis. A larger brachial artery diameter is independently associated with cardiovascular risk factors and increased risk of cardiovascular events.32)

Effect of the ANS on Vascular Function

Several reports have demonstrated an effect originating from the ANS on vascular function. Hijmering, et al. demonstrated that sympathetic stimulation signifi cantly impairs the fl ow-mediated dilation response via an alpha-adrenergic mechanism.33) The inhibitory effect of sympathetic activation is limited to shearmediated NO release; however, the precise mechanism has not been revealed. A similar fi nding was reported by Lemitsu, who demonstrated an inhibitory effect of exercise-induced sympathetic stimulation on NO metabolites in rat heart tissue.34) In contrast, in young healthy volunteers, fl ow-mediated dilation in the femoral artery was not modifi ed by sympathetic activation induced by the cold pressor test, a potent nonbarorefl ex sympathoexcitatory stimulus,35) whereas modifi cation did occur in older healthy subjects.36) Conversely, it has been demonstrated that ANS denervation alters endothelial function in animal studies.37) In humans, ANS modulation by alpha2-adrenoreceptor agonists has also been shown to improve endothelial dysfunction in patients with hypertension.38) These fi ndings suggest a contribution of sympathetic nervous tone on the baseline condition of vascular function. In addition, experimental data suggest that exaggerated sympathetic nervous activity modifi es other aspects of endothelial function, such as increasing the immunoreactivity of ECs, or promoting the uptake of low-density lipoprotein cholesterol by ECs.39,40)

Anatomical View of the Effect of the ANS on the Endothelium

The proximity of the ANS to the endothelium may explain the behavior of their interrelationship. ECs along the major conduit vessels do not receive direct neural innervation from the ANS because of the longdistances involved. However, ECs in the microvasculature do receive ANS input.37) Non-synaptic transmission is characteristic of autonomic neuroeffector junctions, and transmitted substances can reach ECs.41) Additionally, it has been shown that transmitters, such as adenosine triphosphate (ATP) released from varicosities in the perivascular nerve plexus, can act on endothelial receptors and modulate endothelial function in the microvasculature.42) Draid, et al. demonstrated that ATP released from nerve terminals mediates hyperpolarization by acting on P2Y receptors on the endothelium. The adventitia is a site for this autonomic innervations,43) and it can affect the process of endoluminal atherosclerotic progression via several mechanisms.44–46) Consequently, insuffi cient adaptation of the adventitia may increase the risk of end-organ dysfunctions, including infl ammation and thrombosis.

Neurogenic Factor-Mediated Pathway to the Endothelium

Several reports have demonstrated that neurotransmitters from neural cells can affect the behavior of vascular ECs.47) For example, the neurotransmitter dopamine is a potent regulator of important signaling cascades of ECs such as the vascular permeability factor (VPF)/vascular endothelial growth factor (VEGF) pathway. Dopamine inhibits VEGF-induced permeability in human umbilical ECs48) through D2 dopamine receptors. It induces endocytosis of VEGF receptor-2, which is critical for promoting angiogenesis, thereby preventing VPF/VEGF binding, receptor phosphorylation, and subsequent signaling.49)

Neuropeptide Y (NPY), a sympathetic co-transmitter, is the most abundant peptide in the heart and brain. It is another example of a neurotransmitter that affects ECs (Fig. 1). Nerve activation and ischemia cause the release of NPY, resulting in vasoconstriction and smooth muscle cell proliferation. The endothelium contains NPY receptors, the peptide itself, its mRNA, and the NPY-converting enzyme dipeptidyl peptidase IV (both protein and mRNA), which terminates Y1 activity of NPY and cleaves Tyr1-Pro2 from NPY to form an angiogenic Y2 agonist, NPY3–36.50) Thus, the endothelium is not only the site of action of NPY, but also the origin of the autocrine NPY system, which, together with the sympathetic nerves, may be important in angiogenesis during tissue development and repair.51)

Calcitonin gene-related peptide (CGRP) was shown to be a potent vasodilator neurotransmitter, and it was fi rst reported to be produced in the peripheral nerves of rat mesenteric resistance arteries.52) The receptors for CGRP have been shown to be located in the endothelium,53,54) and CGRP is predominantly an endothelium-independent relaxing substance and, in most blood vessels, the cAMP-dependent relaxations are associated with the opening of KATP and, in some instances, BKCa channels.55) CGRPergic vasodilator nerves and sympathetic vasoconstrictor nerves reciprocally regulate the tone of the mesenteric resistance artery.

Some studies attribute a physiologically relevant role for neuronal nitric oxide synthase (nNOS) in the modulation of systemic arterial pressure,56) as nNOS produces NO that affects smooth muscle cell relaxation.16)

Pathological Conditions that Affect or Downregulate ANS Pathways

Pathological conditions that affect or downregulate ANS pathways may provide insight into the interrelationship between the ANS and endothelial function.

Mental stress

Mental stress is a powerful stimulus for central sympathetic excitation.57) In addition, mental stress has been linked with reduced

endothelial function. Thus, there may be a link between the ANS and vascular function in mental stress. Ghiadoni, et al. reported that acute mental stress induced transient endothelial dysfunction, lasting up to 4 h, accompanied by blood pressure, heart rate, and salivary cortisol increases.58) Possibly via a similar mechanism, acute mental stress may contribute to cardiovascular disease progression via ANS effects on the endothelium.59) Anxiety has also been shown to be associated with endothelial dysfunction via autonomic dysregulation, evaluated by spectral analysis of heart rate variability in 41 subjects.60)

Dysautonomia and postural tachycardia syndrome

Dysautonomia is any disease or malfunction of the ANS. Santambrogio, et al. evaluated 31 patients with cerebral dysautonomia to investigate the hemodynamic effects of the disease. The authors showed that blood vessel smooth muscle tone was disturbed, and that post-prandial diastolic and systolic blood pressure fell markedly by the attenuation of sympathetic nerve support.61) However, there are few reports investigating how this lack of sympathetic nervous input affects vascular function. In contrast, postural tachycardia syndrome (POTS) is a heterogeneous disorder characterized by an excessive rise in heart rate, and symptoms consistent with cerebral hypoperfusion in the upright position. The pathological mechanism of POTS is autonomic dysfunction, including vagal withdrawal with intact vasoactive barorefl exes and sympathoexcitation, which may contribute to vasomotor instability and orthostatic intolerance in these patients.62) With regard to vascular function, Liao, et al. demonstrated that abnormally augmented, fl ow-mediated dilation and abnormal function of the vascular endothelium may play important roles in POTS in children.63) A study reporting that NOS3 alleles, which encode the predominant isoform of NOS in the vasculature, represent genetic factors associated with POTS also supports the contribution of the endothelium to the pathology of POTS.64)

Spinal cord injury

Individuals with spinal cord injury (SCI) are also at increased risk for cardiovascular disease (CVD) compared with their able-bodied counterparts,65) and this fi nding suggests an ANS contribution to cardiovascular events. SCI induces vascular deconditioning below the level of injury, and disrupts supraspinal control of the spinal sympathetic circuits that ultimately innervate the adventitial-media layer of blood vessels. Consequently, individuals with SCI exhibit vascular dysfunction below the lesion characterized by a redu ction in conduit artery diameter and blood flow, increased shear rate and leg vascular resistance, and adrenoceptor hyper-responsiveness. Although the mechanisms underlying vascular dysfunction following SCI remain to be elucidated, there is emerging evidence that blood pressure oscillations, such as those occurring in the large majority of individuals with SCI, could potentially exacerbate vascular dysfunction. Further to changes in the peripheral conduit and resistance vasculature, there is alarming evidence for central arterial stiffening in individuals with SCI. Such stiffening is likely to contribute to early onset of CVD, which is currently the number one cause of mortality in patients with SCIs.

Pharmacological or Therapeutic Interventions to Modify ANS Pathways

Beta-blocking agents

The most popular pharmacological agents used to modify the activity of the ANS are beta-adrenergic receptor blockade agents. However, the effect of these agents on vascular function has not been fully clarified. In animal experiments, beta-adrenergic receptor blockade may protect ECs from the negative effect of heightened sympathetic nerve activity.66) In contrast, there are contradictory reports for beta-blocking agent administration in humans. For instance, in subjects with type 2 diabetes and hypertension, atenolol did not improve endothelial function, whereas losartan improved endothelial function and decreased oxidative stress.67) Other studies generally failed to show a benefi cial effect of beta-adrenergic receptor blockade.68,69) In contrast, men treated with atenolol demonstrated a decline in circulating endothelin, suggesting a genderspecific beneficial effect of beta-blocking agents on vascular function.70) Matsuda, et al. also demonstrated that treatment with carvedilol for 4 months improved brachial flow-mediated dilation among patients with ischemic heart disease.71) Thus, the effect of beta-blocking agents on vascular function remains controversial and requires further investigation. In addition, little has been reported about the effect of alpha-adrenergic blocking agents on vascular function.

Renal denervation and vascular function

The renal sympathetic nerves have been identifi ed as a major contributor to the complex pathophysiology of hypertension in both experimental models and in humans.72) Modulation of renal sympathetic-nerve activity through catheter-based radiofrequency ablation has been developed based on experimental and clinical data, and it is considered to be a robust intervention to modulate systemic ANS tone.73) There have been some reports showing that this intervention changes vascular hemodynamics by modifying ANS activity. Katayama, et al. demonstrated that renal denervation in SHR/NDmcr-cp rats signifi cantly ameliorated the impairment of vascular endotheliumdependent relaxation with acetylcholine. It also demonstrated signifi cant attenuation of the increase in vascular superoxide levels in SHRcp rats.74) However, there are few data concerning the effect of renal ablation on vascular function. Therefore, further investigation is warranted.

Effect of Vascular Function on the ANS

Although the ANS may impact on vascular function, the reverse may also be true. However, reports demonstrating a vascular contribution to regulation of the ANS are relatively limited compared with the evidence for an effect of the ANS on vascular function.

Animal experiments showed that removal of the endothelium increased the release of norepinephrine from sympathetic nerve terminals in rabbit carotid artery.75) NO is one important agent that appears to modulate sympathetic nervous system activity during blood pressure control. Although the mechanisms by which NO modulates neuronal activity are unclear, research suggests that NO alters neuronal responses to excitatory amino acids.76) Experiments in animal models, particularly the streptozotocin-induced diabetic rat, have shown that reduced nerve blood flow occurs very early after diabetic induction.77) The perfusion defi cit is suffi cient to cause endoneurial hypoxia, suggesting that endoneurial hypoxia may produce many of the observed morphological and biochemical changes in experimental diabetic neuropathy. 77) Another report showed that NO acts as a sympatho-inhibitory substance within the central nervous system.78)

Plater, et al. demonstrated that endothelial dysfunction may predispose patients with diabetes to impairments in peripheral neural conduction. In recently diagnosed patients with diabetes followed for 3 years, higher von Willebrand factor levels predicted a subgroup of patients with diabetes who subsequently developed defi cits in lower limb nerve conduction velocity.79) However, the direct effect of the endothelium on alterations in neurotransmitter release, reuptake, or receptor sensitivity requires further investigation.80)

Common Regulating Factors between Endothelial Function and the ANS

Evidence from experimental studies indicates that the sympathetic nervous system is critically influenced by the most relevant factors regulating vascular function including NO, reactive oxygen species (ROS), endothelin, and the renin-angiotensin system. For example, oxidative stress simultaneously affects the ANS and vascular function. Increased oxidative stress has been documented in specific nuclei of the brain involved in the regulation of sympathetic control of vasomotor tone in hypertensive rats.81) In addition, oxidation itself induces neuronal cell death, including apoptosis of sympathetic nervous neurons.82) On the other hand, oxidative stress impaired vascular function via endothelial damage.83) Thus, these effects of oxidative stress on both two systems may explain the basal physiological interrelationship between vascular function and the ANS.

The oxidative stress reaction above was enhanced in the presence of NO. The half-life of NO, and its biological activity is critically influenced by the presence of ROS, such as superoxide. This free radical rapidly reacts with NO to form the highly reactive intermediate peroxynitrite. Peroxynitrite, formed from the interaction of superoxide anion with NO, is a principal oxidizing agent of the ANS.84) Because NO and oxidative stress are present in the vascular and nervous environment, peroxynitrite may play a critical role in the interrelationship between vascular function and the ANS, however, few reports have investigated this relationship.

The most potent inducer of oxidative stress, angiotensin II (AngII), also affects both the ANS and endothelial function. The AngII signaling system is present in the brain, and circulating AngII also binds to and activates brain neuronal receptors outside of the blood-brain barrier in circumventricular organs. Moreover, AngII increases the concentration of ROS in ECs, leading to the impairment of endothelial function.83) Inflammation is another candidate that could explain the interactions between endothelial function and the ANS. Vagal nerve stimulation may reduce the inflammatory response, whereas, sympathetic activation may increase the production of inflammatory cells.85) In addition, the presence of inflammation impairs endothelial function.86)

Interaction between Vascular Function and the ANS in Subjects with Diabetes

The pathological process of diabetes impairs both vascular function and the ANS. Both vascular and ANS dysfunction generally co-exist in the setting of diabetes, and generally progress simultaneously. Thus, it is possible that there are interactions between vascular function and the ANS in this setting. The possible interrelationship may also impact on the pathological process of organ damage in diabetes.

In a study of type 2 diabetic subjects, arterial dysfunction with increased pulse wave velocity, carotid intima-media thickness, and reduced systemic arterial compliance were observed. These vascular parameters correlated with autonomic nervous score, suggesting an interrelationship between the ANS and vascular function.87) In addition, in a cohort of young, type 1 diabetic subjects without a history of hypertension and any evidence of macrovascular disease, subjects with a high cardiac autonomic neuropathy score had signifi cantly higher pulse wave velocity compared with subjects with a low score, and a negative correlation between pulse wave velocity and heart rate variation was observed.88) These findings may help to explain the high cardiovascular mortality seen in diabetic subjects with autonomic neuropathy.87) Indeed, impaired cardiac autonomic control is statistically signifi cantly related to the development of ischemic heart disease among individuals with diabetes, independent of markers of the duration/severity of glucose metabolism impairments. 89)

Conversely, hypertension has been implicated as a strong risk factor for diabetic distal polyneuropathy.90) Other imp ortant risk factors for diabetic distal polyneuropathy include smoking, dyslipidemia, microalbuminuria, and body mass index.91) These risk factors are also well-known vascular risk factors, suggesting that the process of diabetic neuropathy may proceed in the presence of vascular risk factors. In addition, angiotensin-converting enzyme inhibitors have shown an improvement of nerve conduction velocity in distal symmetrical polyneuropathy.92) Thus, the pathophysiological process of autonomic neuropathy is closely related with vascular function in subjects with diabetes.

Endothelial, ANS, and Other System Interactions

There are few data reporting on the relationshipbetween the vascular, ANS, and other systems. Mousa, et al. reported that the sympathetic nervous system seems to play an important role in the regulation of infl ammation-induced, vascular endothelial expression of certain adhesion molecules such as ICAM-1. These interactions demonstrated one example of an immune-

endothelial-nerve interaction.93) In contrast, in the setting of obesity, enlarged adipose tissue releases substances (adipokines) that lead to metabolic abnormalities, subclinical infl ammation, endothelial dysfun ction, and sympathetic over-reactivity, 94,95) resulting in obesity-associated hypertension. 96) In particular, the enhanced activation of the sympathetic nervous system is closely associated with organ damage in obesity hypertension.97) Body weight reduction showed an improvement in metabolic measures, indices of infl ammation, endothelial dysfunction, and sympathetic over-reactivity,98) suggesting a complex interaction between these systems. However, evidence concerning the interaction between multiple systems remains scarce, and further explorations are required.

Conclusion

Although there is much evidence linking the ANS and endothelium in healthy and diseased states, this area is still largely unexplored both under physiological and pathological conditions. The clarifi cation of this interrelationship between the ANS and endothelium may provide more comprehensive risk stratification, and a new effective therapeutic strategy against atherosclerosis.

Disclosure Statement

IK received research grant from DAIICHI SANKYO Co., Ltd.

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