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Targeting the Sympathetic Nervous System to Improve Vascular Function in Diabetes

Alvejar o Sistema Nervoso Simpático para Melhorar a Função Vascular na Diabetes

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Abstract

Diabetes is a high prevalent disease, whose numbers are expected to rise in the coming years. Individuals with diabetes face elevated risks of both microvascular and macrovascular complications, which are significant factors contributing to morbidity and mortality. The overactivation of the sympathetic nervous system (SNS) which plays a pivotal role in the genesis and maintenance of insulin resistance and glucose intolerance has been described to be linked with the vascular complications of diabetes. Herein, we review in a concise manner the link between diabetes, vascular function and the sympathetic nervous system and focus on the several factors including nitric oxide, reactive oxygen species, endothelin, the renin-angiotensin system, and peripheral chemoreceptors contributing to this intricate relation. Moreover, emphasis will be placed on the different methods of evaluating vascular function and sympathetic activity in humans. In light of the growing evidence indicating that overactivation of the SNS contributes to vascular dysfunction in diabetes, we may suggest that the evaluation of SNS activity and its targeting might be important to prevent and reverse vascular dysfunction in diabetes.

Keywords: diabetes; vascular function; sympathetic nervous system; nitric oxide; endothelin; reactive oxygen species; renin-angiotensin system; carotid body

Resumo

A diabetes é uma doença com elevada prevalência, cujos números se espera que aumentem nos próximos anos. Os indivíduos com diabetes enfrentam elevados riscos de complicações microvasculares e macrovasculares, sendo estes, fatores significativos que contribuem para a morbidade e mortalidade. A sobre-ativação do sistema nervoso simpático desempenha um papel fundamental na génese e manutenção da resistência à insulina e intolerância à glucose e tem sido descrita como estando relacionada com as complicações vasculares da diabetes. Aqui, revemos de forma concisa a ligação entre a diabetes, a função vascular e o sistema nervoso simpático, focando-nos nos diversos fatores que contribuem para esta, nomeadamente o óxido nítrico, as espécies reativas de oxigénio, a endotelina-1, o sistema renina-angiotensina e os quimiorreceptores periféricos. Além disso, destacamos também os diferentes métodos de avaliação da função vascular e atividade simpática em humanos. À luz das crescentes evidências que indicam que a sobre-ativação do SNS contribui para a disfunção vascular na diabetes, podemos sugerir que a avaliação da atividade do SNS e a sua modulação poderão ser importantes para prevenir e reverter a disfunção vascular na diabetes.

Palavras-chave: diabetes, vascular function, sympathetic nervous system, nitric oxide, endothelin, reactive oxygen species, renin-angiotensin system, carotid body

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> INTRODUCTION

The prevalence of diabetes among adults has been steadily rising worldwide, [1] with the number of people affected exceeding half a billion by 2040. [2] Individuals with diabetes are at higher risk of both microvascular and macrovascular complications, which are major contributors to illness and death. [3]

The overactivation of the sympathetic nervous system

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(SNS) that plays a pivotal role in the genesis and maintenance of insulin resistance and glucose intolerance, two pathological features of diabetes, [4] has been described to be linked with the vascular complications of diabetes. [5] Sympathetic activity and vascular function are closely linked and are influenced by various factors including nitric oxide (NO), reactive oxygen species (ROS), endothelin, the renin-angiotensin system and peripheral chemoreceptors [6] (Figure 1). Furthermore, there is evidence indicating a reciprocal relationship between endothelial function and SNS activity. [6] Therefore, targeting the SNS in diabetes might be important to prevent and reverse vascular dysfunction in diabetes.

> DIABETES AND VASCULAR FUNCTION

Diabetes *mellitus* exerts a profound impact on vascular function, contributing to the development of both microangiopathy and macroangiopathy, two interrelated complications that significantly increase morbidity and mortality among affected individuals. [7] Microangiopathy refers to damage to small blood vessels throughout the body, particularly in organs such as the eyes, kidneys, and nerves. One of the hallmark manifestations of microangiopathy in diabetes is diabetic retinopathy, a leading cause of blindness worldwide. Chronic hyperglycemia and associated metabolic abnormalities lead to endothelial dysfunction, oxidative stress, and inflammation, resulting in microvascular damage and impaired blood flow regulation. In the kidneys, diabetic nephropathy manifests as progressive kidney dysfunction and is a major cause of end-stage renal disease. Neuropathy, characterized by nerve damage, can lead to sensory deficits, pain, and impaired wound healing, further complicating the management of diabetes. [7]
Macroangiopathy, on the other hand, involves the large blood vessels and is primarily associated with accelerated atherosclerosis, leading to coronary artery disease, stroke, and peripheral vascular disease. Individuals with diabetes are at significantly higher risk of cardiovascular events compared to the general population, with diabetes serving as an independent risk factor for the development of atherosclerosis and its complications. Hyperglycemia promotes the formation of advanced glycation end-products (AGEs), which contribute to endothelial dysfunction, inflammation, and the formation of atherosclerotic plaques. Moreover, diabetes is often accompanied by dyslipidemia, hypertension, and obesity, further exacerbating the risk of macrovascular complications. [8] The mechanisms underlying both microangiopathy and ma-

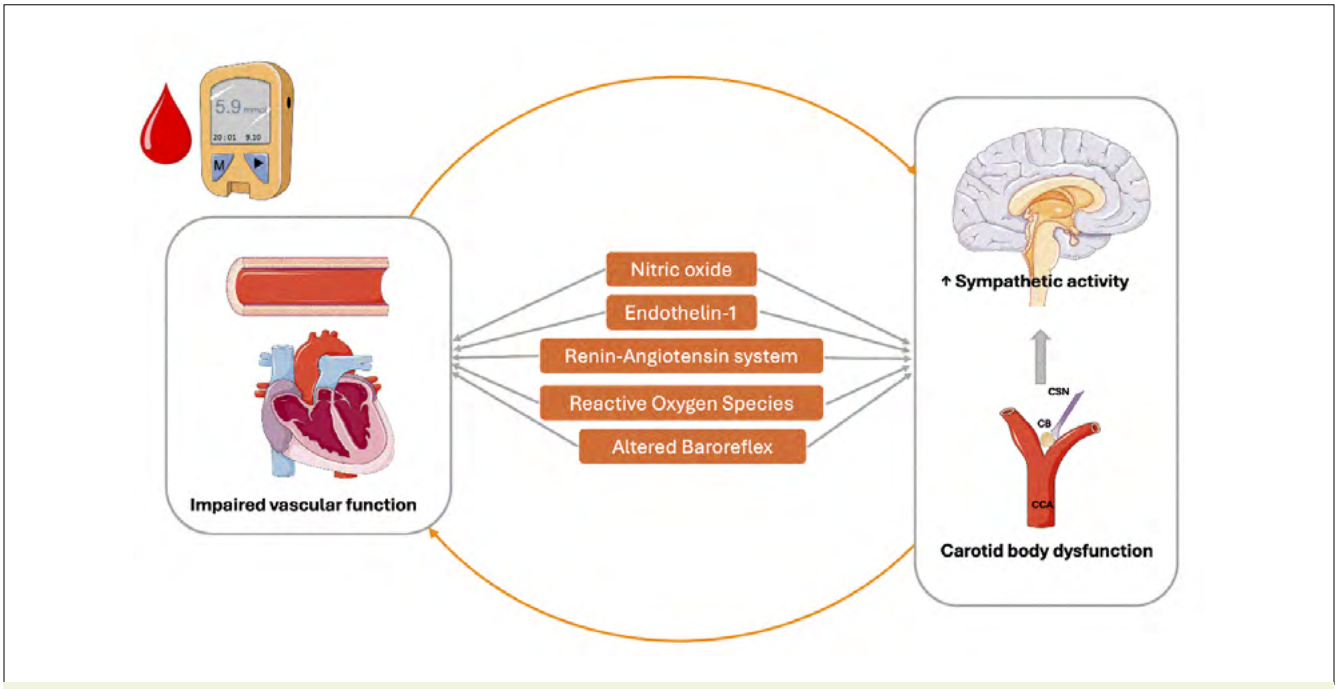

Figure 1 - Schematic representation of the interrelationships between the sympathetic nervous system (SNS) and vascular function in diabetes. Alterations in several factors, like nitric oxide, endothelin-1, reactive oxygen species, renin-angiotensin system and altered baroreflex contribute to carotid body (CB) dysfunction and to sympathetic overactivity as well as to vascular dysfunction. Furthermore, CB dysfunction itself contributes to sympathetic overactivity and therefore could be a target to improve vascular function in diabetes.

croangiopathy in diabetes are complex and multifactorial, involving interactions between metabolic, inflammatory, and hemostatic pathways. Endothelial dysfunction, characterized by impaired vasodilation and increased vascular permeability, plays a central role in the pathogenesis of vascular complications. Additionally, chronic low-grade inflammation, oxidative stress, and dysregulated angiogenesis contribute to the progression of vascular damage in diabetes.

> SYMPATHETIC NERVOUS SYSTEM AND DIABETES

The SNS, a branch of the autonomic nervous system, exerts profound influence over glucose metabolism, making it a crucial player in the pathogenesis of diabetes. In individuals with type 2 diabetes (T2D), the overactivation of the SNS contributes significantly to the development and progression of insulin resistance and glucose intolerance. [4,9] The SNS innervates key metabolic tissues such as the liver, adipose tissue, and skeletal muscle and its activation results in the targeted release of norepinephrine (NE) from nerve terminals as well as hormonal release of epinephrine (Epi) from the adrenal medulla and their action throughout the body. The SNS modulates processes as glycogenolysis and gluconeogenesis in the liver, [10] lipolysis and thermogenesis in the adipose tissue [9] and protein and glucose metabolism, ionic transport across the membrane, and contractility in the skeletal muscle. [9,10] Moreover, in the pancreas, the SNS inhibits insulin secretion. [9] Therefore, the overactivation of the SNS, manifested as increased neuronal sympathetic activity and release of catecholamines [11,12] lead for instance to increase hepatic glucose output through glycogenolysis and gluconeogenesis, [9] decreased lipolysis due to catecholamine resistance in the white adipose tissue, [9,13] decreased thermogenesis in the brown adipose tissue [14] and decreased glucose uptake by the muscle [9,10] culminating into elevated blood glucose levels, contributing to hyperglycemia in diabetes. Moreover, the SNS contributes to the dysregulation of vascular function in diabetes (Figure 1). It has been implicated in the development of endothelial dysfunction, [6] impaired vasodilation, [6] and increased vascular tone, [6] all of which are associated with diabetic vascular complications.

Furthermore, emerging evidence suggests a bidirectional relationship between sympathetic activity and insulin resistance, where insulin resistance may also potentiate sympathetic activation, creating a vicious cycle that exacerbates metabolic dysfunction in diabetes. [4,15]

> SNS AND VASCULAR FUNCTION: COMMON REGULATING PATHWAYS AND THERAPEUTIC TARGETS - RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system (RAS) is important to regulate blood volume, electrolyte balance and systemic vascular resistance. Angiotensin-II is able to act centrally or in the periphery to potentiate the SNS activity. At central level, intracerebral injection of angiotensin-II triggers a blood pressure increase associated with systemic vasoconstriction. [16] At peripheral level, intravenous angiotensin-II administration decrease muscle sympathetic nervous activity (MSNA). [17] Moreover, also in the periphery angiotensin-II stimulate the release of catecholamines from adrenal medulla. [18] Angiotensin-II also facilitates sympathetic neurotransmission within sympathetic ganglia. [19,20] By acting on presynaptic receptors, angiotensin-II promotes the release of norepinephrine by sympathetic nerve terminals [21] and increases α-mediated vasoconstriction in arterioles. [22] In diabetes there is also an overactivation of the RAS leading to an increased production of angiotensin II, angiotensin type 1 activation and aldosterone release [23] promoting increased oxidative stress, fibrosis, cardiac remodeling and increased SNS activity (Figure 1).

Reactive Oxygen Species

Reactive oxygen species (ROS) in the vascular system play a physiological role in the control of endothelial function and vascular tone. However, ROS also play a pathophysiological role in inflammation, hypertrophy, proliferation, apoptosis, migration, fibrosis, angiogenesis and rarefaction, which are important in endothelial function and vascular remodeling that are associated with chronic diseases, as hypertension. [24] ROS, such as superoxides, contribute to oxidative stress, which can stimulate central and peripheral sympathetic outflow in several pathological conditions. [25] In hypertensive rats, oxidative stress is augmented in rostral ventrolateral medulla and contributes to the increase in blood pressure, probably due to an increase in the SNS. [26] Moreover, excessive ROS generation and oxidative stress in obesity and diabetes represent common denominators associated with altered insulin secretion [27] and adverse insulin-sensitive tissue remodeling. [28] Targeting the oxidative status, antioxidant administration, such as vitamin C, lowered blood pressure and muscle sympathetic nerve activity in hypertensive patients but not in normotensive subjects. [29] However, for diabetic patients the clinical trials using antioxidants are limited.

Vitamin E failed to provide any benefit in improving cardiovascular outcomes in diabetes, but α-lipoic acid has proven to be effective. [30] More clinical information is needed to confirm if lowering the oxidative status decrease sympathetic activity and improves vascular function in diabetes.

Endothelin-1

Endothelin-1 (ET-1) is a potent vasoconstrictor produced by endothelial cells that can act on ETA and ETB receptors. Through ETA receptors, ET-1 can stimulate central and peripheral SNS. [28,32] In hypertensive and normotensive animals, ET-1 intracerebral administration promoted an increase in blood pressure and in SNS drive via ETA receptors. [33,34] In the peripheral nervous system, ET-1 can act in cervical superior and nodose ganglia, [35] and in the carotid body. [36] Intracarotid administration of ET-1 induced a decrease in baroreceptor discharge, while increase the chemoreceptor discharge, showing that ET-1 contributes to the regulation of baroreflex and chemoreflex. [37] Additionally, ET-1 is also produced and released by post-ganglionic sympathetic neurons, [38] which may contribute to regulate vascular tone and to promote catecholamine release from adrenal glands. [39] Moreover, the effect of ET-1 on blood pressure may be also due to its interaction with aldosterone, angiotensin II, renin and vasopressin. [40]

Nitric Oxide

The SNS and nitric oxide (NO) interplay a delicate balance in cardiovascular regulation. The SNS exerts control over vascular tone by releasing neurotransmitters like norepinephrine, which can constrict blood vessels, leading to increased vascular resistance. Conversely, NO, a potent vasodilator synthesized by endothelial cells, counteracts vasoconstriction by relaxing smooth muscle cells in blood vessel walls. Among several examples of how this dynamic interplay modulates vascular tone, blood pressure, and tissue perfusion is the recent data indicating that renal sympathetic overactivity can reduce the expression of neuronal nitric oxide synthase in the paraventricular nucleus and that reduced NO levels in the paraventricular nucleus increase sympathetic outflow, creating a vicious cycle that can contribute to resistant hypertension. [41] Hence, dysregulation of the SNS tone/ NO production balance, such as heightened sympathetic activity or reduced NO bioavailability, contributes to cardiovascular pathologies.

Baro and Chemoreflex

The term baroreflex typically refers to the physiological responses triggered by fluctuations in baroreceptor activity, particularly the reflex adjustments in blood pressure and heart rate due to alterations in autonomic outflow to the cardiovascular system. [42] Conversely, the chemoreflex refers to the physiological responses elicited by the carotid body (CB) chemoreceptors and usually to the reflexive changes in ventilation in response to hypoxia and hypercapnia. [43] However, the baro and chemoreflexes are potent modulators of the sympathetic nervous system, with the baroreceptors influencing sympathetic activity directed toward renal, mesenteric, splanchnic, and muscle vascular beds [42] and the CBs controlling the kidney, the muscle, the heart, the brown adipose tissue among others (Figure 1). [44] Impairment of baroreflex response is one of the earliest indicators of cardiovascular autonomic imbalance and is widely acknowledged that individuals with diabetes typically exhibit reduced baroreflex sensitivity, [45] although the precise pathophysiological mechanisms remain unclear. Therefore, we can postulate that altered baroreflex sensitivity leading to altered sympathetic activity innervating the vascular beds may contribute to vascular dysfunction in diabetes. Moreover, the CB is implicated in the pathophysiology of several cardiovascular diseases, such as chronic heart failure, [46,47] several forms of hypertension [48,49,50] and in diabetes [51,52] playing a fundamental role in the genesis and maintenance of these diseases. In diabetes, the decrease of CB activity through the cut of the carotid sinus nerve (CSN) was able to normalize sympathetic activity and prevent and revert insulin resistance, glucose intolerance and hypertension. [51,52] Moreover, CSN denervation in animals fed with hypercaloric diets, mimicking T2D improved endothelial function. [53]

> EVALUATING VASCULAR FUNCTION AND SYMPATHETIC ACTIVITY IN HUMANS - MUSCLE SYMPATHETIC NERVE ACTIVITY

One of the major factors influencing endothelial function and vascular tone, outside of the vessels, is the Autonomic Nervous System (ANS) imbalance, once both sympathetic and parasympathetic systems innervate blood vessel walls, thus regulating the contraction and tension of the vessels. This ANS dysregulation, mostly due to the overactivation of sympathetic outflow, is a risk factor for cardiovascular diseases, in particular compromising vascular function affected by sustained high blood pressure and peripheral vasoconstriction. [54] The

SNS is the effector of neurogenic control of vascular tone, inducing mainly vasoconstriction of small resistance arteries, still there is also evidence of its role in long--term blood pressure control. The way to directly access this efferent neural information is the recording of post--ganglionic sympathetic discharge to several body regions by means of microneurography. When the sympathetic discharge is registered in the path vasomotor regulation, it is called muscle sympathetic nerve activity (MSNA). [55]

Although the invasive nature of the technique (typically by inserting a tungsten electrode at peroneal or radial nerves) it is reproducible over the years, and mostly important, the sympathetic activation obtained by the technique is highly correlated to the sympathetic traffic towards other parts of the human body such heart and kidney. Moreover, the obtained signal has high level of time-resolution, allowing for instantaneous recordings and reactions to specific stimulus. [56] MSNA is a mandatory technique to obtain direct measures of sympathetic efferent activation to study mechanisms of autonomic reflexes and the relation between peripheral neural activities suck vascular function. [6]

Arterial Stiffness

Arterial Stiffness (AS) has shown independent prediction of cardiovascular events in several studies, in particular by predicting cardiovascular and total mortality in patients with diabetes and glucose intolerance. [57] AS can be obtained using a multitude of methodologies (including ultrasound and MRI imaging), still, Pulse-Wave velocity (PWV) with their variants (brachial–ankle PWV, carotid–femoral PWV) are examples of some ways to assess AS to be applied in complement to BP at the clinical exam. [58]

Endothelial Function

The endothelium is a single layer of cells lining blood vessels that has important roles in regulating vascular tone, inflammation, and thrombosis. Several methods are employed to evaluate endothelial function, with one of the most common flow-mediated vasodilation (FMD) in brachial artery using ultrasound. [59] FMD measures the ability of arteries to dilate in response to increased blood flow, reflecting endothelial nitric oxide bioavailability. Endothelial function can also be assessed through biochemical markers such as circulating levels of endothelial-derived molecules like nitric oxide metabolites or the vasoconstrictor endothelin-1. [60] Additionally, newer techniques like peripheral arterial tonometry (PAT) offer non-invasive means to evaluate endothelial function by measuring digital pulse amplitude and have been used in clinical studies. [61]

> CONCLUSION AND FUTURE PERSPECTIVES

We can conclude that overactivation of the SNS and vascular dysfunction in diabetes are closely linked and influenced by various factors including NO, ROS, endothelin-1, RAS, and peripheral chemoreceptors, among others. Considering the growing evidence indicating that overactivation of the SNS contributes to vascular dysfunction in diabetes, we may suggest that the evaluation of SNS activity and its targeting might be important to prevent and reverse vascular dysfunction in diabetes. One approach to address the sympathetic overactivation responsible for vascular dysfunction could involve modulating the various factors contributing to this complex relationship, such as employing antioxidants to reduce reactive oxygen species (ROS) levels or utilizing modulators of the renin-angiotensin system (RAS) like angiotensin receptor antagonists or angiotensin-converting enzyme (ACE) inhibitors. However, it's worth noting that these strategies are not innovative and have been previously tested. A novel way to decrease sympathetic activity to improve vascular function can be the targeting of the CB. The CB is known to control sympathetic activity and the ablation of its activity in T2D was shown to normalize sympathetic activity, blood pressure and endothelial function. [51-53] Therefore, the evaluation and modulation of its activity might be a good approach to decrease sympathetic overactivation to improve vascular function in diabetes. <

Conflicts of interests/*Conflitos de interesses*:
The authors declare that they have no conflicts of interests./*Os autores declaram a inexistência de conflitos de interesses.*

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