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EDITORIAL OPEN ACCESS

Impact of long-term diabetes mellitus on the heart innervation

Magdalena Chottova Dvorakova

Heart is innervated by sympathetic (adrenergic) and parasympathetic (cholinergic) nervous system, which plays an important role in the regulation of cardiac functions. The mammalian heart receives efferent sympathetic and parasympathetic nerve supply with norepinephrine (NE) and acetylcholine (ACh) as principal neurotransmitters. The intrinsic cardiac neurons that were previously regarded as simple relay stations of the parasympathetic innervation represent a heterogeneous population of afferent, efferent, interconnecting local circuit neurons and small intensely fluorescent (SIF) cells that integrate sensory information from the heart and vessels and efferent inputs generated in the medulla oblongata and the spinal cord. Afferent inputs are transmitted through sensory fibers. Intracardiac nervous system employs a number of neurochemicals, including neuropeptides such as vasoactive intestinal polypeptide (VIP), neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP) or substance P (SP) in addition to ACh and NE [1].

Diabetes mellitus is a disease with high incidence and high socio-economic relevance. The prevalence of diabetes mellitus is an alarming global health issue. The heart is among those organs whose functional and structural impairment during progression of this disease are limiting for life quality and survival. Diabetic cardiomyopathy involves both the contractile cardiomyocytes and the sensory and autonomic innervation of the heart [2].

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Cardiovascular autonomic neuropathy (CAN) is one of the most common complications of diabetes and accompanies later stages of diabetes mellitus where it contributes significantly to the morbidity and mortality of diabetic patients. It is associated with the damage of nerve fibers innervating the heart. It can results in both parasympathetic and sympathetic dysfunction, which leads to increasing of resting heart rate and loss of the heart rate variability. Impairment of sensory fibers is associated with painless myocardial ischemia. Incidence of CAN is 16.8% for type 1 diabetes and 22.1% for type 2 diabetes [3]. Autonomic dysfunction was found to be an independent risk factor with a poor prognosis [4].

Cardiac nerves contain a broad spectrum of neurotransmitters and neuromodulators including fast-acting, short-lived small molecules such as acetylcholine, noradrenalin and nitric oxide, and long-acting neuromodulators of the peptide class. Diabetic conditions lead to changes in concentrations of ACh and NE in the heart that may be different in early and later stages of the disease [5, 6]. An imbalance between sympathetic and parasympathetic influences to the heart in diabetes could be a basis of impaired heart rate variability. Signaling systems of several neuropeptides released by these nerve fibers are also affected in diabetic patients. Nerve fibers innervating the heart are damaged due to pathophysiological processes associated with diabetes, such us hyperglycemia, increased oxidative stress and/or proinflammatory processes. Cardiac nerve ending are altered containing degenerated mitochondria and membrane fragments [7]. Additionally, intracardiac ganglia are also morphologically deranged with swollen mitochondria, accumulation of neurofilaments and neurotubules [8].

ALTERATION IN SYMPATHETIC INNERVATION

Sympathetic denervation is an important feature of CAN in diabetes. It has been demonstrated in the atria as well as in the ventricles. Left ventricular denervation

is characterized by maximal deficits occurring distally but relative sparing of the proximal myocardium [5]. Several authors have demonstrated cardiac sympathetic dysfunction in diabetic patients [9]. Duration of diabetes seems to be a crucial factor for activity of cardiac sympathetic innervation. In short-term diabetic, NE content and β-adrenergic receptor (β-AR) density are significantly increased, which lead to enhancement of cardiac sympathetic activity with toxic effects on the heart [10]. Over-expression of β1-adrenergic receptors causes marked myocyte hypertrophy, interstitial fibrosis, and reduced contractile function. In STZ rats, short-term diabetes was associated with decrease in β1-AR and an increase in β2-AR density [11]. In animals with short-term diabetes, the number of both α and β-AR was reduced, while cardiac NE was maintained at a high level partly due to an increased uptake of released NE by adrenergic nerve terminals [12–14]. Long-term diabetes was associated with decreased NE concentrations in the heart of patients as well as STZ-rats [15, 16]. Additionally, β1-AR and β2-AR were downregulated, while β3-AR were upregulated in the heart [17]. Stimulation of β3-AR in the heart led to decrease of cardiac contractile force [18], hence its upregulation could contribute to the impaired cardiac function in patients with diabetes. Functional impairment in cardiac sympathetic nerve fibers could also be associated with depletion of myocardial catecholamine stores in long-term diabetic patients [19]. Several studies have confirmed that early deficits of cardiovascular sympathetic innervation are reversible by improved metabolic control [17, 20].

ALTERATION IN PARASYMPATHETIC INNERVATION

Effect of diabetes on the parasympathetic heart innervation has not been studied as deeply as on the sympathetic one. Nonetheless it has been postulated that the impairment is similar in parasympathetic and sympathetic control [21]. ACh release is affected in diabetic heart. Presynaptic M2-receptor function is upregulated, leading to reduced ACh release. Additionally, atrial muscarinic receptors are downregulated in STZ treated animals [22]. This impaired local parasympathetic activity may be an important risk factor for sudden cardiac death.

ALTERATION IN PEPTIDERGIC INNERVATION

Among the numerous neuropeptides found in cardiac innervation, the most abundant is NPY, a 36-amino acid peptide produced by cleavage from a large precursor, preproNPY [23]. In the heart, postganglionic sympathetic axons are the most prominent source of NPY, the majority originating from cell bodies located in the cervicothoracic sympathetic chain ganglia. Additionally, NPY is expressed by the parasympathetic neurons of the intrinsic cardiac ganglia and in some non-neuronal cells such as endothelial cells [23]. Diabetes mellitus is associated with impairment of NPY signaling system in the heart. Expression of NPY gene and NPY protein level has been found to be decreased in patients as well as in animal models, while partial recovery of diabetes was associated with increased levels of NPY in the atria [24–27]. Results of experiments studying expression of specific NPY receptors in diabetic heart are not consistent. NPYR1 was found to be upregulated in STZ-rats but unchanged in diabetic patients [24, 26]. Also NPYR2 and NPYR5 were affected in the heart of diabetic patients [24, 25]. The reason for such diversity in results could lie in differences in diabetes stage, and probably also in presence of other cardiovascular pathologies. Altered regulation of the NPY system in diabetic heart may be, at least in part, responsible for decreased angiogenesis, increased apoptosis, and increased vascular smooth muscle proliferation that finally lead to coronary artery disease and heart failure in this patient population [25].

The VIP is found in the extrinsic and intrinsic autonomic innervation of the heart [28]. It can act directly on cardiomyocytes and relaxes coronary vascular smooth muscle, thereby improving cardiac perfusion [29]. In addition, it promotes survival of peripheral neurons in culture and inhibits neuronal cell death after injury, thereby serving as neuroprotective factor [30]. The actions of VIP are mediated through G protein-coupled receptors that also recognize pituitary adenylate cyclase-activating peptide and are denoted VPAC1 and VPAC2 receptors [31]. In the course of diabetes, gene expression as well as VIP peptide levels were down regulated in each of four heart chambers, while expression of VPAC1 and VPAC2 were differently affected in each heart compartment. Cardiac neuropathy of VIP-containing neurons manifests progressively during the first four months of diabetes, and is accompanied by initial down-regulation of VPAC2 at smooth muscle cells of coronary arterioles. After initial changes, both VPAC1 and VPAC2 expression return to levels of control despite ongoing loss of VIP [32].

CGRP, a 37-amino acid peptide, is the major neuropeptide released from sensory nerve terminals in the heart [33], which increases heart rate, contractile force [34] and coronary artery perfusion [35]. It acts through calcitonin-receptor-like receptor and exerts cardioprotective functions of ischemic preconditioning, which is abolished in diabetes [36]. The amount of CGRP is slightly elevated in the heart of STZ treated rats [37], while signaling system for CGRP remains unaffected with exception of RAMP3 upregulation [38]. Impairment of this signaling system has been also demonstrated also during ischemic preconditioning experiment carried out in STZ rats [39].

SP, an 11-amino acid peptide functions as a neurotransmitter and vasodilator and is released from the autonomic sensory nerve fibers. In the course of diabetes, both expression of SP and its receptor NK1R are significantly decreased in the atrial muscle [24]. Changes in SP signaling system in diabetes can lead to impairment of cardiac response to ischemia.

All these data suggest that signaling systems of classical mediators as well as neuropeptides in the diabetic heart are impaired, and that duration of diabetes plays important role. Additionally, several pathological changes in these signaling systems could be prevented or even eliminated by appropriate treatment of blood glucose level.

Keywords: Calcitonin gene-related peptide (CGRP), Neuropeptide Y (NPY), Parasympathetic innervation, Peptidergic innervation, Vasoactive intestinal polypeptide (VIP)

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Author Contributions

Magdalena Chottova Dvorakova – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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