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Signalling networks in focus

Sympathetic nervous system in age-related cardiovascular dysfunction: Pathophysiology and therapeutic perspective

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ABSTRACT

Cardiovascular diseases such as heart failure and metabolic syndrome have high prevalence in the elderly population and are leading causes of death, disability, hospitalization, driving high healthcare costs worldwide. To reduce this social and economic burden there is urgency to find effective therapeutic targets. Several studies have linked the dysfunction of the Sympathetic Nervous System and β-adrenergic receptor signaling with the pathogenesis of age-related cardiovascular diseases. Therapeutic treatments that restore their functions have been shown to be effective in subjects with cardiovascular comorbidities. In fact, lifestyle interventions (such as exercise training and diet) as well as pharmacologic treatments (e.g. β-blockers or moxonidine) and mini-invasive interventions (renal sympathetic denervation) have beneficial effects on age-related cardiovascular diseases. In the current "Medicine in focus" article we will discuss the pathogenic role of the Sympathetic Nervous System in age-related cardiovascular diseases as well as current and new therapeutic approaches.

1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of death, disability, hospitalization and responsible for rising healthcare costs worldwide. CVDs have dramatically high prevalence in the elderly population and include conditions that affect the structures/function of the heart and blood vessels such as heart failure (HF), hypertension, diabetes and peripheral arterial disease (PAD). Based on improved survival and age-expectancy, it is predicted that 40% of the US population will have some form of CVD by 2030 (Heidenreich et al., 2011). Hence, to reduce this social and economic burden there is urgency to find new effective therapeutic targets. The risk of developing CVD is mainly determined by the presence of traditional cardiovascular (CV) risk factors such as hypertension, diabetes, dyslipidemia, metabolic syndrome (MS), sedentary lifestyle, smoking and aging. Small improvements in risk factors earlier in life can have a huge impact (Heidenreich et al., 2011). However, when preventive medicine and measures such as lifestyle changes are not rigorously followed CVDs are the result, especially in the aged. Therefore, it is crucial to use efficient therapeutic treatments to fight multiple comorbidities in the same time.

Accordingly, the Sympathetic Nervous System (SNS) is an interesting therapeutic target as it is activated and dysfunctional in presence of CVDs as well as during aging (Fig. 1). The Autonomic Nervous System plays a central role on CV system regulation during both basal physiological states as well as during disease and is divided into two branches: the SNS and the parasympathetic nervous system. The SNS is composed by postganglionic nerves originating from the paravertebral and prevertebral ganglia, and by the sympathetic endings that are responsible for innervation of several organs including heart and vessels (Fig. 2) (Lymperopoulos et al., 2013). Importantly, the adrenal medulla (AM) is the inner portion of adrenal gland and contains chromaffin cells that act as modified post-ganglionic nerves (Fig. 2).

SNS activity is regulated by several mechanisms including the aortic arch/carotid sinus (SNS inhibition) and cardiopulmonary (SNS inhibition) baroreceptor reflexes, peripheral chemoreceptors (SNS activation) and noradrenergic neurons in subcortical areas (Lymperopoulos et al., 2013). SNS is crucial for the so-called "fight or flight response" and is activated in stress conditions such as hypovolemia, hypoglycemia, hypoxia, as well as CV disease. The action of the SNS is carried out through the release of catecholamines (CATs): norepinephrine (NEpi, released by sympathetic nerve terminals and in a lesser amount by adrenal medulla) and epinephrine (Epi, released into the blood stream by the AM). The norepinephrine transporter (NET) is crucial for NEpi reuptake at the synaptic terminals/chromaffin cells and its function can

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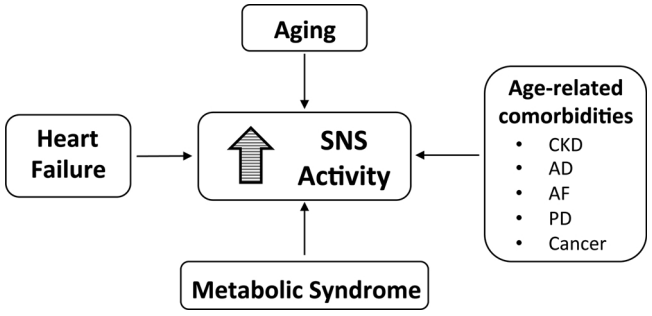

Fig. 1. Sympathetic nervous system overactivity.
Sympathetic overdrive is typical of several age-related cardiovascular (heart failure, metabolic syndrome, AF) and non-cardiovascular diseases (CKD, AD, PD, Cancer) as well as aging per se. Acronyms: SNS, Sympathetic Nervous System, CKD, chronic kidney disease; AD, Alzheimer's disease; AF, atrial fibrillation; PD, Parkinson's disease.

be evaluated with a scintigraphy with radiolabeled metaiodobenzylguanidine (MIBG), a guanethidine analog of NEpi (Fig. 2) (Rengo et al., 2016). CATs bind adrenergic receptors (ARs) that are members of the G protein-coupled receptor (GPCR) family. β-AR stimulation induces contractility in the cardiomyocytes and relaxation in the vasculature stimulating the smooth muscle cells (with β_1-AR being dominant) (Fig. 2) (de Lucia et al., 2018a; Schutzer et al., 2011). In chromaffin cells and sympathetic nerve endings, CA exocytosis is promoted by β_2-ARs, while α_2-ARs provide negative feedback (Lymperopoulos et al., 2013). In the cardiomyocytes, β_1-ARs are prominent and after CAT simulation, triggers the stimulatory G_s protein with cAMP adenylylcyclase-mediated production followed by the activation of protein kinase A (PKA). Then, PKA phosphorylates several proteins including L-type Calcium channels and phospholamban, ultimately increasing cardiac contractility (de Lucia et al., 2018a). Of note, β_2-AR and β_3-AR can also couple to inhibitory G_i protein (de Lucia et al., 2018a).

β-AR function is regulated by homeostatic mechanisms including GPCR kinase (GRK)-mediated receptor phosphorylation, β-arrestin recruitment and eventually the receptor internalization, down-regulation and recycling (de Lucia et al., 2018a). Interestingly, one GRK, GRK2, found in the heart where it desensitizes β-ARs is also important in the SNS as it can mediate α2-AR down-regulation in adrenal medulla (Fig. 2) (Lymperopoulos et al., 2013).

Several tools have been utilized to assess SNS activity/derangement including measurements of plasma CATs, cardiac or renal NEpi spillover, Ewing' s battery tests, cold pressor test, heart rate variability (HRV), radiolabeled analogs of NEpi (e.g. MIBG imaging), and muscle and renal sympathetic nerve activity (MSNA, RSNA) (Lymperopoulos et al., 2013; Rengo et al., 2016). However, there is no gold standard tool for SNS assessment so far. In the current "Medicine in focus" article we will discuss the pathogenic role of SNS in age-related CVDs as well its potential as therapeutic target.

2. Pathogenesis

2.1. Aging

Aging is associated to impaired CV function together with SNS deregulation including cardiac and vascular β-AR signaling. With age plasma NEpi levels increase (due to increased spillover rate together with reduced clearance) and both MSNA (regardless of gender) and NEpi turnover in suprabulbar subcortical are augmented (de Lucia et al., 2018a; Esler et al., 2002). At cardiac level, increased NEpi spillover from sympathetic nerve endings and decreased NEpi metabolic clearance, has been found while Epi secretion from the adrenal medulla has been shown to be unchanged or reduced in older compared with young healthy subjects (Esler et al., 1995). Cardiac sympathetic innervation (evaluated with MIBG imaging) as well as the density/activity of the neuronal NEpi transporter are reduced with age (Leineweber et al., 2002; Rengo et al., 2016). Suprabulbar subcortical NEpi turnover is higher in elderly subjects and is correlated to cardiac NEpi spillover; data on arterial baroreflexes during aging are not consistent, instead (Esler et al., 2002).

Chronic CAT stimulation results in decreased β-AR density as well as impaired exercise tolerance and LV inotropic reserve in aged subjects (de Lucia et al., 2018a). Differently from HF, cardiac GRK expression and activity are unchanged with age and the cellular mechanism involved in the age-related β-AR desensitization is still unclear (de Lucia et al., 2018a). In addition, chronic CAT stimulation induces not only cardiac inflammation but also cardiac expression of p53, a pivotal regulator of cellular senescence in the endothelial cells (Katsuumi et al., 2018). Age-related vascular dysfunction has been associated to CV events (e.g. myocardial ischemia or PAD) as well as augmented risk of frailty/disability (Nappi et al., 2018). Of note, several studies have demonstrated that β-AR-induced vasorelaxation declines with age in with a GRK2-mediated mechanism (β-AR desensitization rather than downregulation) (Schutzer et al., 2011). Protein kinase A and the receptor coupling to $G\alpha_i$ proteins are not involved in the age-related vascular β_2-AR desensitization, instead (Schutzer et al., 2006).

2.2. Heart failure

Cardiac dysfunction and HF result from several etiologies (ischemic injury, hypertension, valve disease, etc.) and are very common in the elderly population, drastically affecting survival rate (de Lucia et al., 2018a). SNS overactivity is a peculiarity of HF and is characterized by increased circulating CATs (secreted from the AM) as well as augmented NEpi spillover from cardiac sympathetic nerve endings (de Lucia et al., 2018a; Lymperopoulos et al., 2013). SNS activation is a compensatory response to counteract reduced contractility however, in the long-term, decisively contributes to cardiac dysfunction. Chronic CA stimulation triggers cardiac GRK2 upregulation impairing β-AR density/signaling, cardiac contractility as well as left ventricular (LV) remodeling and angiogenesis (de Lucia et al., 2018a). Interestingly, GRK2 overexpression is also involved in adrenal α2-AR-mediated CAT-secretion during HF. The crucial contributing role of GRK2 in chronic HF has been widely demonstrated in both animal models and humans (de Lucia et al., 2018a). Lymphocyte GRK2 protein levels (surrogate of GRK2 cardiac levels) and HRV have been proposed as a useful marker for SNS derangement and HF progression in failing patients (de Lucia et al., 2018a). In addition, HF patients show decreased NET and impaired sympathetic innervation within the heart (Lymperopoulos et al., 2013; Rengo et al., 2016). SNS tools such as cardiac MIBG parameters, CAT levels, HRV and MSNA carry independent prognostic information for stratifying the risk of mortality, arrhythmias as well as HF progression in patients with HF (Barretto et al., 2009; Patel et al., 2017; Rengo et al., 2016). Elderly HF patients, show a further reduction in MIBG uptake suggesting additional sympathetic dysfunction in the heart compared to adult HF patients (Rengo et al., 2016).

2.3. Metabolic syndrome

MS, characterized by central obesity, dyslipidemia, elevated fasting glucose and hypertension, is common in older people and predisposes the affected to develop other CVDs (Sumner et al., 2012). Components of MS diverged between young and old adults with the latter showing higher glucose intolerance and blood pressure (BP) (Sumner et al., 2012). Interestingly, several constituents of MS have been associated to SNS hyperactivity (both in patients and animal models) that has a crucial pathophysiological role and contribute to the tremendous CV complications (Lambert et al., 2010). Numerous prospective studies have shown SNS overactivity as well as polymorphisms in the β2- and β3-AR to predict the development of MS features (Lambert et al., 2010;

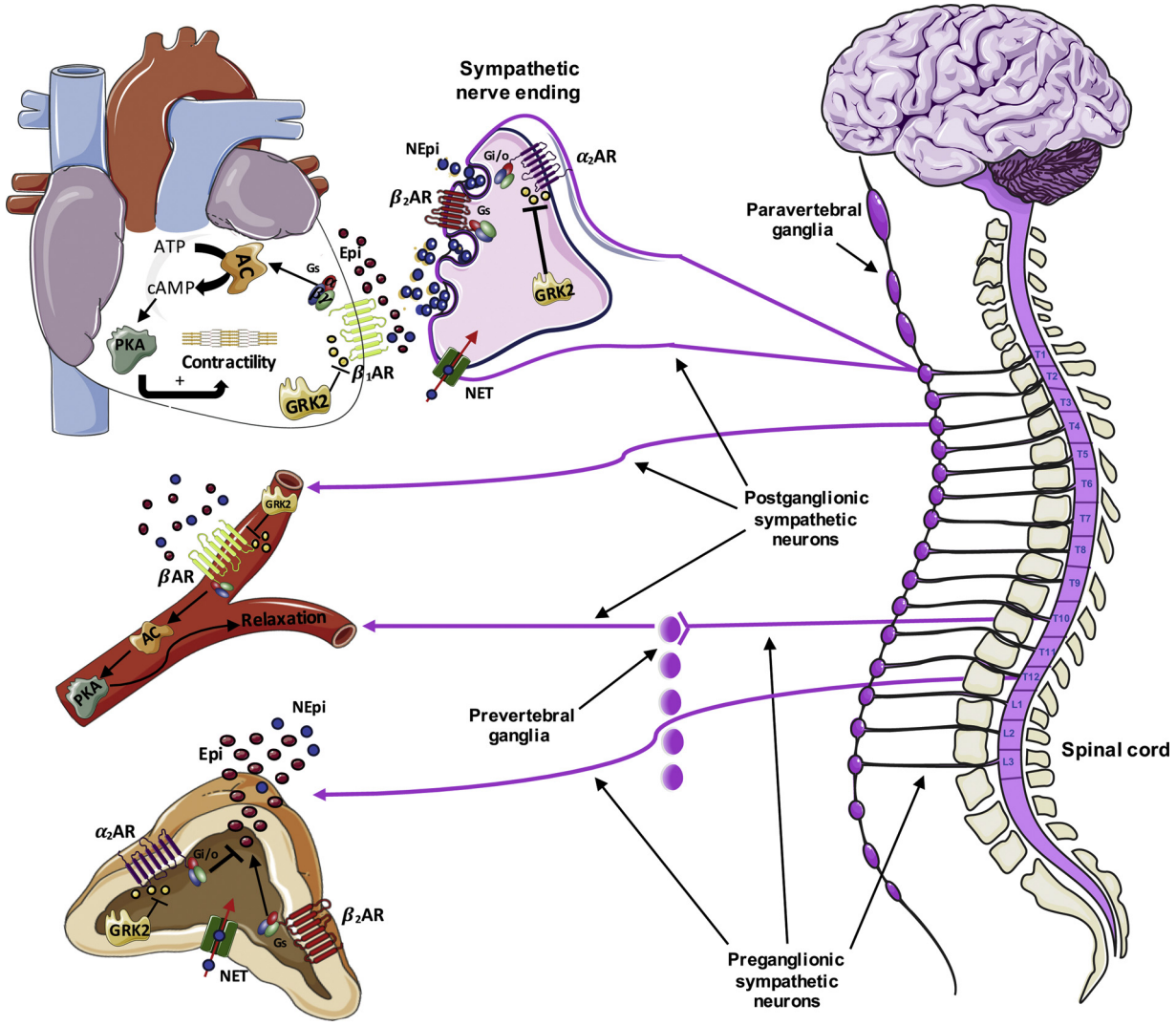

Fig. 2. The Sympathetic Nervous System.

The Sympathetic Nervous System (SNS) includes 2 groups of neurons: the *pre-ganglionic neurons* originate in the lateral horns of the 12 thoracic and the first 2 or 3 lumbar segments of the spinal cord and the *post-ganglionic neurons* originate in *sympathetic ganglia (paravertebral or prevertebral)*. The preganglionic axons terminate either in paravertebral/prevertebral ganglia or in the chromaffin cells of the adrenal gland. The main neurotransmitter of postganglionic axons is norepinephrine (NEpi) (blue dots) while chromaffin cells release approximately 80% epinephrine (EPI) (red dots) and 20% NEpi in physiological conditions. NEpi and Epi bind the adrenergic receptor (AR) subtypes, (α-ARs and β-ARs). Catecholamines (CATs) binding to β-ARs (with β_1-ARs being predominant in cardiomyocytes) activate the $G\alpha_s$ protein (stimulatory G protein) stimulating the adenylyl cyclase (AC) which converts the adenosine triphosphate (ATP) to the second messenger cyclic AMP (cAMP), ultimately activating the protein kinase A (PKA). PKA phosphorylates a variety of substrates (including phospholamban, L-type calcium channels and contractile proteins in the cardiomyocytes) leading to cardiomyocyte contractility or blood vessel relaxation. GRK2 (G protein-coupled receptor kinase 2) phosphorylation of the β-AR induces receptor desensitization, downregulation and recycling and, represents a cellular homeostatic mechanism. Of note, β_2-AR and β_3-AR can be also coupled to inhibitory G_i protein. In pathological conditions when SNS is overactive, GRK2 overexpression leads to β-AR dysregulation. In the chromaffin cells of adrenal medulla as well as the sympathetic nerve endings, the release of CATs is mainly regulated by the inhibitory α_2-AR (acting via the G_i protein o other G_o proteins) and the facilitatory β_2-AR (via the G_s protein). Adrenal GRK2 phosphorylates and regulates the α_2ARs in physiological conditions. During SNS hyperactive state such as heart failure (HF), adrenal GRK2 upregulation induces α_2-AR dysregulation and increased CA secretion. The norepinephrine transporter (NET) is a transporter that is crucial for the clearance/reuptake of extracellular NEpi in both the synaptic cleft and the chromaffin cells. NET activity is impaired during HF as well as aging contributing to β-AR desensitization. Acronyms: NEpi, Norepinephrine; Epi, Epinephrine; AR, Adrenergic Receptor; GRK2, G protein-coupled Receptor Kinase 2; G_s, stimulatory G protein; G_i, inhibitory G protein; G_o, other G protein; ATP, Adenosine Tri-Phosphate; AC, Adenylyl Cyclase; cAMP, cyclic Adenosine Mono-Phosphate; PKA, Protein Kinase A; NET, norepinephrine transporter. Adapted from Circ Res. 2013 Aug 30;113(6):739-53.

Masuo et al., 2005). In fact, obese as well hypertensive subjects show elevated plasma and urinary CAT levels, increased RSNA and MSNA and, SNS measures predict dietary weight loss in obese MS patients (Lambert et al., 2010; Straznicky et al., 2012).

Several factors have been implicated in the sympathetic activation that occurs in obesity such as hyperinsulinemia, hyperleptinemia, non-esterified fatty acids, pro-inflammatory cytokines and obstructive sleep apnea while during hypertension the main drivers are arterial baroreceptor/baroreflex and cardiopulmonary receptor dysfunction and renin–angiotensin–aldosterone system activation (Lambert et al., 2010). Interestingly, the presence of hypertension further increases sympathetic activation in obese patients (Huggett et al., 2004). MS is associated with early cardiac autonomic dysfunction and diabetes has been shown to reduce cardiac β_1-AR and sympathetic innervation in HF patients (Olivieri et al., 2014; Paolillo et al., 2013). Moreover, insulin-resistance has been shown in HF patients and GRK2 appears to be a crucial hub in cross-regulation of insulin receptor signaling and β-AR signaling as it can negative-regulate both pathways (de Lucia et al.,

2018a). Interestingly, chronic β-AR stimulation plays a crucial role in the pathogenesis of insulin resistance in numerous tissues including the heart (Heather et al., 2009; Mangmool et al., 2017, 2016; Morisco et al., 2005). Long-term stimulation of β-ARs impairs insulin signaling (insulin-induced glucose uptake, insulin-induced auto-phosphorylation of the insulin receptor and Glucose transporter type 4 -GLUT4- expression) via Akt- and cAMP/PKA-dependent pathways in cardiomyocytes (Mangmool et al., 2016; Morisco et al., 2005). β_2-AR has been shown as the main subtype involved and β_2-AR stimulation inhibit insulin-induced translocation of GLUT4 to the plasma membrane in cardiomyocytes (Mangmool et al., 2016). Importantly, β-blocker treatment rescue isoproterenol-induced cardiac insulin resistance strongly suggesting the use of these drugs in diabetic patients with heart failure (Giles, 2002; Mangmool et al., 2016).

3. Therapy

Numerous studies have linked the dysfunction of the SNS and β-AR signaling with the pathogenesis of both age-related CVDs as well as aging. Hence, therapeutic treatments that restore their functions are effective in subjects with CV comorbidities. Exercise training and β-blockers have beneficial effects on both cardiac and vascular function in patients with CVDs (de Lucia et al., 2018a). Both these treatments can modulate SNS overactivity and restore β-AR signaling (mediated primarily through GRK2 lowering) in the heart and arteries (as shown in animal models of HF as well cardiac/vascular aging) (Leosco et al., 2003). In addition, adrenal GRK2 down-regulation, leading to restored α_2-AR density and decreased CAT-secretion, has been shown as a crucial mechanism for both the treatments, too (de Lucia et al., 2018a; Lymperopoulos et al., 2013). Therefore, cardiac and adrenal GRK2 inhibition (via gene therapy with a peptide inhibitor known as the βARKct or with emerging pharmacological approaches) has been proposed as an effective treatment to counteract SNS overactivity during HF (de Lucia et al., 2018a). Importantly, β-blocker use in the elderly patients should be started at a low dose and then up-titrated slowly. In addition, it has been demonstrated that β-blockers are associated with reduced risks of death and rehospitalization in elderly patients with HF and reduced systolic function (Hernandez et al., 2009).

Lifestyle interventions (e.g. dietary treatments and physical activity) are commonly recommended in patients with MS to reduce BP as well a lose weight and, are associated to sympathetic inhibition (reduced MSNA and whole-body NEpi spillover) (Straznicky et al., 2010). Exercise training decreases SNS overdrive normalizing levels of sympathetic activity markers such HRV or plasma CAT levels in patients with cardiac dysfunction (Besnier et al., 2017; Leosco et al., 2013). Importantly, physical activity positively affects prognosis in healthy aged patients as well as elderly subjects with CVDs, improving cardiac and vascular performance (Nobre et al., 2016; Sarmento et al., 2017; Seals et al., 1994; Wisløff et al., 2007). Exercise training has additive effects to pharmacological and resynchronization therapy in patients with HF (Nobre et al., 2016; Wisløff et al., 2007). Recently, our group has demonstrated that a dietary restriction is also effective in an animal model of ischemic HF through SNS modulation (restored cardiac β-AR density and sympathetic innervation) (de Lucia et al., 2018b).

In addition, pharmacological inhibition of central sympathetic activity (e.g. the imidazoline I_1 agonist Moxonidine) is effective in MS patients in reducing blood pressure and body weight as well metabolic parameters such as insulin-sensitivity and dyslipidemia (Chazova and Schlaich, 2013). Renal sympathetic denervation (RSD) has emerged as an invasive but safe approach to reduce sympathetic activation (reduced renal and whole-body SNA as well as MSNA) (Hering et al., 2013). This treatment is currently recommended in patients with resistant hypertension and has shown beneficial effects on glucose metabolism, insulin sensitivity and waist circumference in MS subjects (Tsioufis et al., 2017). Variable results have been published on the effects of RSD in HF patients due to small sample sizes. However, recent results from a meta-analysis of human studies and a large-animal HF model, suggest RDN to improve LV function in HF setting increasing the interest in the ongoing human studies evaluating the safety and efficacy of RSD in HF (Fukuta et al., 2017; Liao et al., 2017).

The SNS plays a crucial role in regulating several body's responses. Dysautonomia is a common feature in age-associated CVDs and during ageing. Chronic stimulation of the SNS is particularly detrimental in case of multiple-comorbidities and negatively influences clinical phenotype and outcomes. Sympatho-inhibition (through lifestyle changes, pharmacological/minimally-invasive approaches and in a near future gene therapy) is an effective therapeutic strategy to counteract functional decline in elderly patient with CV comorbidities.

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