

Review Article

Central Sympathetic Control of Cardiovascular Function

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Abstract

Cardiovascular function is regulated by a dynamic balance comprised of sympathetic and parasympathetic influences. Sympathetic regulatory centers include the rostra ventrolateral medulla (RVLM) and paraventricular nucleus of hypothalamus (PVN). Pre-sympathetic neurons (PSNs) in these centers project directly to sympathetic preganglionic neurons in the intermediolateral nucleus of the thoracic spinal cord. Altered function of PSNs along with impaired cardiac vagal activity may lead to autonomic imbalance. Enhanced sympathetic activity has been associated with hypertension, heart failure, stroke and cardiac arrhythmias. In this review, we will discuss the central physiological mechanisms of sympathetic cardiovascular regulation and how alteration in these mechanisms may lead to cardiovascular dysfunction reported in individuals with hypertension and sleep apnea.

Keywords

- Autonomic
- Sympathetic
- Preganglionic
- Brain
- Spinal cord
- Cardiovascular

INTRODUCTION

Dual autonomic innervation of the cardiovascular system

The heart is dually innervated by both sympathetic and parasympathetic limbs of autonomic nervous system [1]. Parasympathetic efferent preganglionic axons to the heart are carried in cardiac branches of the vagus nerves and premotor cardiac vagal neurons (CVNs) originate in the nucleus ambiguus (NA) and dorsal motor nucleus of the vagus (DMV) [2-4]. The majority of sympathetic postganglionic axons innervating the heart course in cardiopulmonary nerves originating from the middle cervical, stellate, and upper thoracic ganglia of the paravertebral ganglion chain [2,5]. Increases in sympathetic nerve activity increases heart rate and contractility, whereas parasympathetic activity typically dominates and slows the heart rate [6]. The reciprocal control of cardiac function by sympathetic and parasympathetic limbs of the autonomic nervous system is dynamic and changes dramatically under different physiological and behavioral conditions [7]. For example, at rest there is a tonic level of parasympathetic nerve firing and little, if any, sympathetic activity in both conscious and anesthetized animals including humans [8-11], dogs, cats, and rats. On the contrary, during exercise or decreases in blood pressure there is increased sympathetic and reduced parasympathetic transmission to the heart [12]. However, under some physiological conditions such as during a period of increased atrial filling both sympathetic and parasympathetic inputs to the heart are activated [7]. Regulation of blood pressure occurs via tonically active sympathetic adrenergic vasoconstrictor fibers [13,14]. Increasing sympathetic outflow beyond tonic level causes more vasoconstriction, whereas inhibition of sympathetic tone results in vasodilation [13,14].

Most blood vessels do not have parasympathetic innervations, however, parasympathetic nerves have been shown to innervate salivary glands, gastrointestinal glands, genital erectile tissue and skin where they cause vasodilation [15,16]. Autonomic imbalance, including when vagal inhibitory influences to the heart are deficient and sympathetic activity is enhanced, is associated with an increased risk of arrhythmia and death [17]. The cellular and neurobiological mechanisms responsible for autonomic balance of sympathetic and parasympathetic transmission to the heart may include integration of sensory information, local interactions at the heart as well as sympathetic-parasympathetic interactions in the central nervous system [18,5].

Central sympathetic regulation of cardiovascular function

Activity of the sympathetic branch of the autonomic nervous system predominantly originates from pre-sympathetic neurons (PSNs) that reside in the rostral ventrolateral medulla (RVLM) of the brainstem [19-23]. PSNs project directly to cardio acceleratory and vasomotor sympathetic preganglionic neurons in the intermediolateral nucleus of the upper thoracic spinal cord [24,25]. These neurons project axons to sympathetic postganglionic neurons of intrathoracic ganglia and intrinsic cardiac ganglia [26]. Different types of PSNs have been characterized in the RVLM including those with a regular firing pattern even during pharmacological blockade of synaptic inputs and a different group of PSNs that fire in an irregular mode, and receive significant synaptic activity [27,28]. A substantial proportion of PSNs are contained within the adrenergic C1 group [29]. In addition, both glutamatergic and GABAergic neurons in the RVLM also contribute to pre-sympathetic projections to the spinal cord [30,31]. Electrical or chemical stimulation of the

RVLM produces elevations of arterial pressure, tachycardia, and inhibition of blood flow to many organs due to activation of PSNs [29]. In addition to PSNs in the RVLM, PSNs in the paraventricular nucleus of the hypothalamus (PVN) have been shown to play a crucial role in tonic and reflex neural control of cardiovascular activity. Activation of these neurons contributes to increase in sympathetic nerve discharge, heart rate, blood pressure and breathing [32-35]. Magno cellular PVN cells innervate the posterior pituitary while parvo cellular neurons in the PVN project to the intermediolateral cell column of the thoracic spinal cord [36-38]. Approximately 30% of the spinally-projecting PSNs in the PVN have collateral fibers to pressor region of the RVLM. Therefore, PSNs in the PVN can modulate cardiovascular function via both direct spinal projections and indirect PVN-RVLM-spinal cord pathways [36-38]. The PVN is innervated by glutamatergic, GABAergic, adrenergic, noradrenergic and serotonergic inputs and is known to be a major integrative site for autonomic function [39,36,40].

Central sympathetic dysregulation and cardiovascular diseases

Increased levels of sympathetic activity are implicated in cardiovascular diseases such as hypertension, heart failure and arrhythmias [41-43]. Increased sympathetic activity has also been associated with obstructive sleep apnea (OSA). This disease is characterized by episodes of airway obstruction resulting in intermittent hypoxia and hypercapnia (H/H) [41,44]. OSA participates in initiation and progression of several cardiovascular diseases [45,43]. The compelling evidence supporting the role of OSA in hypertension, and consequent cardiovascular morbidity. The results from recent studies demonstrated a dose-response predictive association between sleep-disordered breathing and the presence of hypertension 4 years later [46,45,43]. This association between OSA and hypertension is independent of other known risk factors, such as baseline hypertension, body mass and habitus, age, gender, and alcohol and cigarette use [43]. For example, recent study assessed the association between sleep-disordered breathing and hypertension in a prospective analysis of data [47]. In addition to assessment of sleep-disordered breathing and blood pressure, many potential confounding factors such as age (average age, 46 ± 8 years), gender, cigarette and alcohol use were assessed [47]. Age and sex minimally confounded the association between sleep-disordered breathing and hypertension [47]. In addition, no evidence was found that cigarette and alcohol use were important confounders [47]. The mechanisms underlying these hypertensive effects of OSA are not fully understood but likely include nocturnal chemo reflex activation by H/H, with consequent sympathetic activation and increased blood pressure [45,48]. The excessive nocturnal sympathetic activity and higher blood pressure may persist during daytime normoxia and in many cases remains resistant to pharmacologic antihypertensive therapy [45]. Clinical findings suggest that 50–56% of patients with OSA have high blood pressure while 30–40% of hypertensive subjects have OSA [49]. In addition, masked hypertension is frequently underestimated in OSA [49]. The prevalence of OSA is considerably higher in patients with resistant hypertension compared with hypertensive patients whose blood pressure is not resistant to

treatment [49,50]. Several mechanisms are involved in causing resistant hypertension in OSA, and the key mechanism includes increased sympathetic activity during repetitive apnea episodes during sleep [45,48]. The increased sympathetic nerve activity is most intense toward the end of the apnea when H/H is most profound [45]. Chronic exposure to this stress may result in the compromised cardiovascular regulation including enhanced sympathetic activity with may cause elevated blood pressure resistant to antihypertensive therapy.

Increased activity of PSNs in the RVLM and/or PVN could be responsible for the excessive sympathetic activity and hypertension associated with OSA. Supporting this hypothesis, increased neuronal activity in the PVN and RVLM has been shown in animals exposed to chronic intermittent hypoxia (CIH), an animal model for OSA [42]. Neuronal activity in the PVN has been postulated to play a substantial role in CIH-induced hypertension and elevated sympathetic nerve activity [51,52]. Recent studies demonstrated CIH increases vasopressin transmission from the PVN to the RVLM [33] and chemical inhibition of neuronal discharge in the PVN reduces lumbar sympathetic nerve activity more in CIH-exposed than in control animals [52]. In addition to increasing sympathetic outflow in CIH-exposed animals, the PVN contributes to diminishing parasympathetic activity to the heart as excitatory neurotransmission from the population of PVN neurons projecting to cardiac vagal neurons in the brain stem is diminished in animals exposed to CIH [53]. Similar to the PVN, spinally-projecting PSNs the RVLM have been postulated to play a role in CIH-induced sympathetic hyperactivity and hypertension. A population of PSNs in the RVLM increases firing activity in response to acute hypoxia and hypercapnia [54]. The findings from another study indicate that the excitatory inputs, probably from expiratory neurons, drive the increased RVLM PSN activities and induce the increased sympathetic activity observed in CIH rats [55]. CIH has been shown to enhance sympatho-excitatory response to ATP microinjections into the ventrolateral medulla, supporting the concept that nucleotides play a role in the dynamic central control of the sympathetic autonomic function. In addition to increasing sympathetic neuronal activity in the brainstem, CIH has been shown to diminish parasympathetic cardiac vagal neuron activity in the nucleus ambiguus [56]. Suggesting that impaired parasympathetic cardiac control may contribute to cardiovascular abnormalities associated with CIH and OSA.

CONCLUSION

Recent work has elucidated the role of hypothalamic and brainstem sympathetic neurons in the mechanisms responsible for changes in central sympathetic activity under control conditions and upon metabolic challenges such as chronic intermittent and acute hypoxia and hypercapnia. Challenges for the future include how to effectively and selectively diminish excessive sympathetic neuronal activity to the heart and blood vessels associated with hypertension and OSA and reduce the risk of developing or maintaining cardiovascular diseases.

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