The Role of the Sympathetic Nervous System in Cardiovascular Disease

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Many epidemiological studies have shown that increased activity of the sympathetic nervous system (SNS) leads to an increase in cardiovascular morbidity and mortality. Functional and morphological alterations of different organs (eg, heart, blood vessels, kidneys) as well as disturbances of glucose and lipid metabolism are the consequence of SNS overactivity. I1-receptors in the rostral ventrolateral medulla are believed to be involved in the final common pathway for a number of descending influences of the SNS activity. Selective stimulation of these I1-receptors by moxonidine decreases the SNS activity in the periphery. This results in cardiovascular protection and reversal of metabolic disorders due to SNS overactivity. J Clin Basic Cardiol 2001; 4: 175–177.

Key words: SNS overactivity, I1-receptors, organ damage, hypertension, moxonidine

The sympathetic nervous system (SNS) plays an important role in the fight-or-flight response in mammals, which is essential for survival in critical situations. However, sustained increase in sympathetic tone may lead to deleterious alterations in the cardiovascular system and/or may be responsible for severe metabolic disturbances.

Epidemiology

Many epidemiological data have shown that increased heart rate as indicator of sympathetic overactivity is a cardiovascular risk factor and a predictor of cardiovascular as well as all-cause mortality [1, 2]. Goldberg et al. [1] investigated 1720 participants all 50 years old and healthy at the beginning of the study (no diabetes, no carcinoma, no cardiovascular disease) with respect to the question of which factors are responsible for a long duration of life. After a follow-up of 25 years the study showed that a longer life was achieved if the heart rate was low, the parents became old, cigarette smoking was less or blood pressure was low. When the study was started a long time ago, other cardiovascular risk factors were not yet looked at, eg cholesterol, fibrinogen, homocystein etc. Data of the Framingham study [2] have also demonstrated that increased heart rate is a significant risk factor of cardiovascular and all cause mortality (Fig. 1). There is accumulating evidence that increased heart rate is correlated with the incidence of left ventricular hypertrophy, with the incidence of hypertension, and is an independent risk factor in patients after myocardial infarction, a risk factor of cardiac failure and an independent cardiovascular risk factor. The pathophysiolog-ical significance of sympathetic overactivity is underlined by the observation that the use of high doses of nifedipine capsule (80 mg) in coronary artery disease may significantly increase mortality as compared to placebo [3]. As a consequence calcium channel blockers of the dihydropyridine type should only be used if they guarantee a slow onset of action without reflex activation of the sympathetic tone. On the other hand, it has been shown that β-adrenoceptor blocking drugs and centrally acting antihypertensives like moxonidine are particularly useful for the treatment of cardiovascular disease.

Interestingly, the activity of the SNS is higher in women and increases with age [4] as measured by muscle sympathetic nerve activity or circulating plasma catecholamines. Therefore, sympatholytic drugs may be very effective even in the elderly.

SNS Activation and Cardiovascular Diseases

Sustained elevation of the sympathetic tone may lead to diseases of the cardiovascular system, which are summarised in Figure 2. Increases in heart rate, stroke volume, peripheral resistance and plasma catecholamines favour the development of hypertension and left ventricular hypertrophy. Some hypertensive patients show ST-segment depression during physical exercise without signs of coronary artery stenosis.

Figure 1. Increase in heart rate is correlated to mortality due to coronary heart disease (CHD), cardiovascular disease or all causes (modified according to [2]).

Figure 2. Sustained SNS overactivity induces functional and structural changes of different organs leading to cardiovascular diseases.
during coronary angiography. These patients have signs of disturbance of the coronary microcirculation consisting of media hypertrophy, loss of blood vessels and an increase in connective tissue (Fig. 3). Growth factors like catecholamines and angiotensin II play an important role in the development of these alterations which may lead to degenerative hypertrophy and finally to heart failure. Decrease in sympathetic tone by the centrally acting $\alpha_2$-agonist moxonidine is able to reverse the described morphological changes to a high extent [5].

In patients with severe heart failure the sympathetic tone is elevated and high norepinephrine levels are predictors of mortality [6]. In these patients especially the $\beta_1$-receptors are down-regulated. As a consequence, $\beta$-adrenoceptor blocking drugs are meanwhile first line drugs to treat severe heart failure.

The SNS has a strong influence on cardiac ion channels, especially the $Ca^{2+}$-channels that are essential for excitation in cells of the SA- and AV-node and for the regulation of contraction in the working myocardium. Sympathetic overactivity has been shown to decrease threshold of excitation and fibrillation, an observation which is extremely important for patients with heart failure or after myocardial infarction, so that $\beta$-adrenoceptor blocking drugs are drugs of first choice in these patients. They are also recommended for those patients in whom tachyarrhythmias are observed during activation of the SNS (eg physical or mental stress).

Increase in sympathetic tone has been discussed as playing a pathophysiological role especially in the early stages of hypertension as it leads to a high cardiac output [7]. Another important mechanism for the development of high blood pressure seems to be the hypertrophy of the blood vessels to catecholamines [8]. One might speculate that those patients with essential hypertension benefit mostly from sympatholytic drugs who show signs of increased sympathetic tone.

There is an important interaction between the SNS and the renin-angiotensin-aldosterone system (RAAS). Activation of the SNS leads to stimulation of postmyocyte $\beta_1$-receptors in renin producing cells in the kidneys. As a consequence the RAAS is activated and angiotensin II and aldosterone are increased. This mechanism participates in the increase in blood pressure and left ventricular hypertrophy during SNS-activation.

It has been shown that platelets possess $\alpha_1$-receptors the stimulation of which leads to platelet aggregation and facilitation of thrombosis. Furthermore, increased SNS-activity has been linked to the initiation and progression of atherosclerosis [9]. Experimental studies in monkeys and rabbits suggest that epinephrine and norepinephrine induce atherosclerosis of thrombosis. Furthermore, increased SNS-activity has been shown by several epidemiological studies. In the Bruneck Study [12] impaired glucose tolerance as well as type 2 diabetes exhibit impaired glucose tolerance. The clinical significance of impaired glucose tolerance has been shown to decrease threshold of excitation and fibrillation, an observation which is extremely important for patients with heart failure or after myocardial infarction, so that $\beta$-adrenoceptor blocking drugs are drugs of first choice in these patients. They are also recommended for those patients in whom tachyarrhythmias are observed during activation of the SNS (eg physical or mental stress).

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scenting influences of the SNS activity in response to stress,
haemorrhage, hypotension (reflex pathway with vagal affer-
ets), exercise, pain, hypercapnoea and hypoxia [14].
Centrally acting antihypertensives like clonidine and mox-

![Image](310x613 to 524x723)

**FOCUS ON SYMPATHETIC TONE**

SNS Overactivity and Cardiovascular Disease

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Moxonidine selectively stimulates I1-receptors in the rostral ventrolateral medulla (RVL M). The sympathetic outflow from the RVL M to the periphery is decreased.

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Figure 5. Moxonidine selectively stimulates I1-receptors in the rostral ventrolateral medulla (RVM). The sympathetic outflow from the RVM to the periphery is decreased.

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Figure 6. There is a strong correlation between the affinity of different I1-agonists at the I1-receptor in the ventrolateral medulla (VLM) and the oral dose needed to lower blood pressure in hypertensive patients. There is no such correlation for Ki at I2-receptors (modified according to [15]).

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References


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sympathetic nerve terminal may play a critical role in elevating the levels of catecholamines in circulation due to prolonged stress. An excessive amount of catecholamines has both direct and indirect consequences that may have deleterious impact on normal heart function (32,39). First, stimulation of $\alpha$-adrenergic receptors by norepinephrine has been implicated to play a role in the progression of various cardiovascular diseases (40). Normal stimulation of $\alpha$-adrenoceptors has a positive chronotropic effect; however, pro-longed stimulation has been implicated in myocyte hypertrophy, myocardial This review examines how the sympathetic nervous system plays a major role in the regulation of cardiovascular function over multiple time scales. This is achieved through differential regulation of sympathetic outflow to a variety of organs. This differential control is a product of the topographical organization of the central nervous system and a myriad of afferent inputs. A key feature of many cardiovascular diseases is increased SNA. However, rather than there being a generalized increase in SNA, it is organ specific, in particular to the heart and kidneys. These increases in regional SNA are associated with increased mortality. Understanding the regulation of organ-specific SNA is likely to offer new targets for drug therapy.