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 (e.g., 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.

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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, e.g. 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 pathophysiological 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-adrenergic 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.
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 $\alpha_1$-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 hyperactivity 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 postysmomatic $\beta_1$-receptors 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 linked to the initiation and progression of atherosclerosis lesions in the carotid arteries. Furthermore, the incidence of CHD was significantly higher in healthy middle-aged men with a higher insulin resistance score [13].

SNS Overactivity and Hypertension: Therapeutic Implications

Distinct regions in the central nervous system, especially the brainstem, control SNS activity. Stressful stimuli are transmitted from the sensory cortex to the amygdala and other regions of the limbic system [14]. The next step is the activation of lower brain centres, eg the hypothalamic regions and the rostral ventrolateral medulla (RVLM). The RVLM is be-

![Figure 3](image_url) Figure 3. From hypertension to heart failure. SNS overactivity leads to an increase in growth factors responsible for left ventricular hypertrophy, media hypertrophy (coronary microvessels) and fibrosis. The result may be heart failure.

![Figure 4](image_url) Figure 4. Metabolic changes due to elevated sympathetic tone. SNS overactivity leads to increased glucose production, decreased glucose utilization, increase in triglycerides and VLDL, decrease in HDL and insulin resistance (metabolic syndrome).
lieved to be the final common pathway for a number of descending influences of the SNS activity in response to stress, haemorrhage, hypotension (reflex pathway with vagal afferents), exercise, pain, hypercapnoea and hypoxia [14]. Centrally acting antihypertensives like clonidine and moxonidine decrease SNS activity by activation of I1-receptors in the RVLM (Fig. 5). Stimulation of α2-receptors leads to sedation, which occurs after application of clonidine, which is a non-selective agonist of α2- and I1-receptors. Moxonidine is about 200-fold more selective for the I1- as compared to the α2-receptor. Activation of I1-receptors and not α2-receptors is responsible for the decrease in blood pressure as shown by the strong correlation between the affinity at I1-binding sites (Ki at I1) and the oral antihypertensive dose which is not the case for Ki at α2 in ventrolateral medulla (VLM) (Fig. 6). Stimulation of the I1-receptor in the RVLM leads to a decrease in circulating catecholamines and angiotensin II. The release of norepinephrine from presynaptic stores of the sympathetic nerves as well as the release of epinephrine from chromaffine cells in the adrenal medulla are decreased. This results in vasodilation, a moderate decrease in heart rate, regression of left ventricular hypertrophy and microcirculatory disturbances, nephroprotection in diabetic nephropathy, decrease in insulin resistance and favourable effects on the metabolic syndrome.

Centrally acting antihypertensives like moxonidine might be particularly useful in situations with increased SNS activity, e.g. high heart rate at rest or during exercise, high plasma catecholamines, type A personality, anxiety and depression, salt-sensitivity, sleep apnoea and obesity (metabolic syndrome).

Besides the centrally acting antisympathetic drugs, the α1- and the β-adrenoceptor blocking drugs may be used in SNS overactivity. A disadvantage of most β1-selective β-blockers is their lack of vasodilating properties and the disadvantage of α1-blockers is their lack of influence on β-receptors, which is important for cardioprotection.

References

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