The Role of the Sympathetic Nervous System in Cardiovascular Disease

Borchard U

Homepage:

www.kup.at/jcbc

**Online Data Base Search
for Authors and Keywords**

The Role of the Sympathetic Nervous System in Cardiovascular Disease

U. Borchard

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. I_1-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 I_1-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, I_1-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 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-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
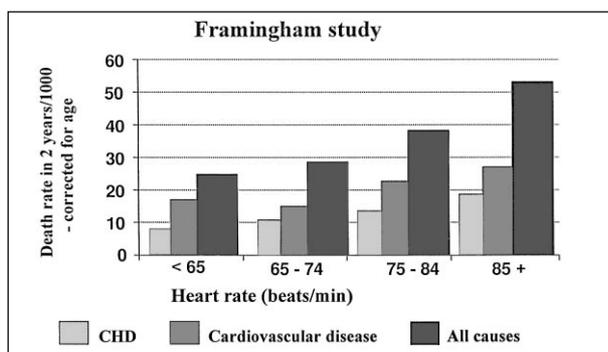
Figure 1. Increase in heart rate is correlated to mortality due to coronary heart disease (CHD), cardiovascular disease or all causes (modified according to [2])
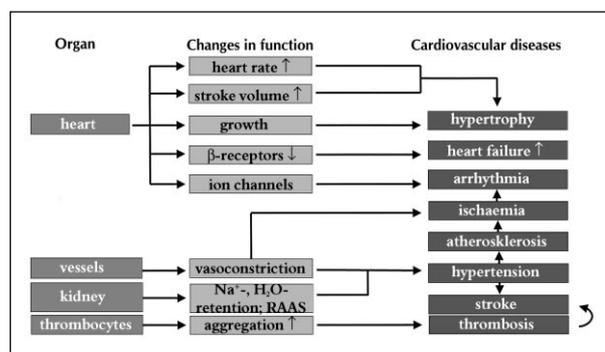
Figure 2. Sustained SNS overactivity induces functional and structural changes of different organs leading to cardiovascular diseases.

From the Institute of Pharmacology and Clinical Pharmacology, University of Düsseldorf, Germany
Correspondence to: Prof. Dr. Dr. med. Ulrich Borchard, MD, PhD, Institute of Pharmacology and Clinical Pharmacology, University of Düsseldorf, Moorenstraße 5, D-40225 Düsseldorf; e-mail: heide.lohse@uni-duesseldorf.de

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 I_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 β_1-receptors are down-regulated. As a consequence, β-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 β-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 hyperreactivity 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 postsynaptic β_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 α_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 even in the absence of increases in blood pressure and total cholesterol [10]. In accordance with these findings is the observation that centrally acting sympatholytic agents or α_1- or β-adrenoceptor antagonists are able to reverse atherosclerosis induced by SNS-activation [10]. The atherogenic effects of catecholamines may be explained by their increase in blood pressure as well as by their action on glucose and lipid metabolism (see below).

SNS Overactivity and Metabolic Diseases

SNS overactivity plays a key role in the development of the metabolic syndrome, which is characterised by the combination of high blood pressure and impairment of glucose and lipid metabolism (Fig. 4). Catecholamines stimulate glycogenolysis and gluconeogenesis in the liver and inhibit insulin release from pancreatic β-cells and glucose uptake into skeletal muscle. This leads to impaired glucose tolerance and to insulin resistance. In isolated adipocytes β-adrenergic stimulation induces a rapid down-regulation of insulin receptors together with a decrease in insulin-mediated glucose transport [11]. Insulin resistance leads to a breakdown of stored triglycerides in the adipose tissue and an increase in plasma free fatty acids. As a consequence, hepatic synthesis of triglycerides from free fatty acids and conversion of triglycerides to VLDL-cholesterol is enhanced. Catecholamines may further increase lipolysis in adipocytes which results in an elevated release of free fatty acids into the blood stream. Free fatty acids decrease glucose-stimulated insulin release from the pancreas, which further enhances glucose intolerance. Furthermore, catecholamines may inhibit lipoprotein lipase and thus increase VLDL, which is linked to a decrease in HDL.

About 10 % of non-diabetic people and about 80 % of patients with type 2 diabetes exhibit impaired glucose tolerance. The clinical significance of impaired glucose tolerance has been shown by several epidemiological studies. In the Bruneck Study [12] impaired glucose tolerance as well as type 2 diabetes were independent predictors of the development of atherosclerotic 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-
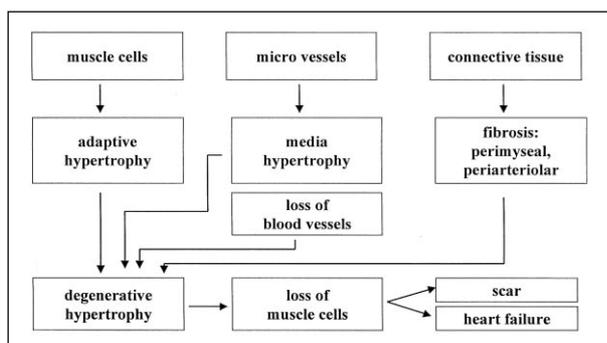
Figure 3. From hypertension to heart failure: SNS overactivity leads to an increase in growth factors responsible for left ventricular hypertrophy, media hypertrophy (coronary microvessels) and fibrosis. The result may be heart failure.
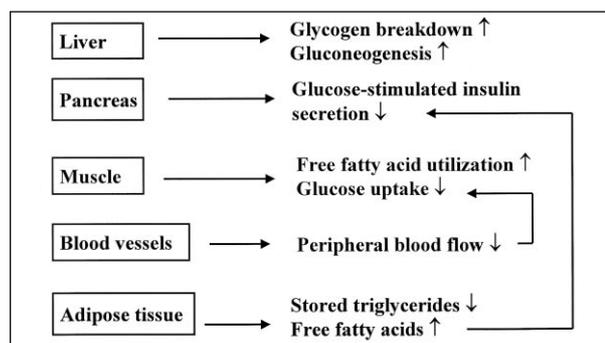
Figure 4. Metabolic changes due to elevated sympathetic tone: SNS overactivity leads to increased glucose production, decreased glucose utilization, increase in triglycerides and VLDL, decrease in HDL and insulin resistance (metabolic syndrome).

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 I_1-receptors in the RVLM (Fig. 5). Stimulation of α_2-receptors leads to sedation, which occurs after application of clonidine, which is a non-selective agonist of α_2- and I_1-receptors. Moxonidine is about 200-fold more selective for the I_1- as compared to the α_2-receptor. Activation of I_1-receptors and not α_2-receptors is responsible for the decrease in blood pressure as shown by the strong correlation between the affinity at I_1-binding sites (K_i at I_1) and the oral antihypertensive dose which is not the case for K_i at α_2 in ventrolateral medulla (VLM) (Fig. 6). Stimulation of the I_1-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 chromaffin 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, eg 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 antisympathotonic drugs, the α_1- and the β-adrenoceptor blocking drugs may be used in SNS overactivity. A disadvantage of most β_1-selective β-blockers is their lack of vasodilating properties and the disadvantage of α_1-blockers is their lack of influence on β-receptors, which is important for cardioprotection.

Figure 5. Moxonidine selectively stimulates I_1-receptors in the rostral ventrolateral medulla (RVLM). The sympathetic outflow from the RVLM to the periphery is decreased.

Figure 6. There is a strong correlation between the affinity of different I_1-agonists at the I_1-receptor in the ventrolateral medulla (VLM) and the oral dose needed to lower blood pressure in hypertensive patients. There is no such correlation for K_i at α_2-receptors (modified according to [15])

References

1. Goldberg RJ, Larson M, Levy D. Factors associated with survival to 75 years of age in middle-aged men and women. Arch Intern Med 1996; 156: 505–10.
2. Kannel WB. Office assessment of coronary candidates and risk factor insights from the Framingham study. J Hypertension 1991; 9 (Suppl): 13–9.
3. Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. Circulation 1995; 91: 1326–31.
4. Ng AV, Callister R, Johnson DG, Seals DR. Age and gender influence muscle sympathetic nerve activity at rest in healthy humans. Hypertension 1993; 21: 498–503.
5. Motz W, Vogt M, Scheler S, Strauer BE. Hypertensive coronary microcirculation – effects of the imidazoline-receptor-agonist moxonidine. Cardiovasc Risk Factors 1995; 5: 28–32.
6. Cohn JN. Plasma norepinephrine and mortality. Clin Cardiol 1995; 18 (Suppl 1): 109–12.
7. Messerli FH. Essential hypertension in the elderly. Triangel 1985; 24: 25–47.
8. Philipp Th. Sympathisches Nervensystem bei essentieller Hypertonie: Aktivität und Reaktivität. In: Rosenthal J (ed). Arterielle Hypertonie. Springer-Verlag, Berlin-Heidelberg-New York-Tokyo, 1986; 50–7.
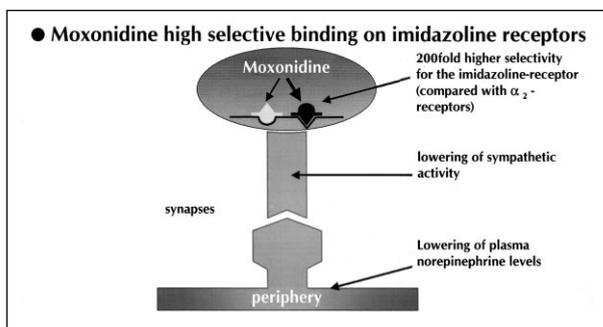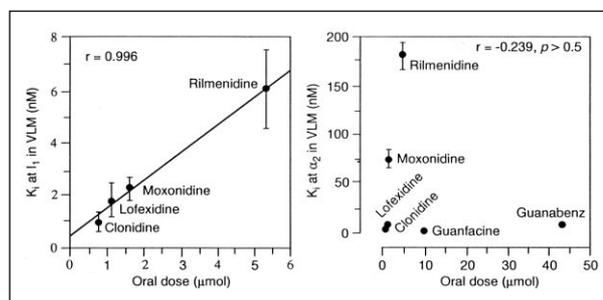9. Kaplan JR, Pettersson K, Manuk SB, Olsson G. Role of sympathoadrenal medullary activation in the initiation and progression of atherosclerosis. Circulation 1991; 84 (Suppl 6): V123–V132.
10. Pauletto P, Scannapieco G, Pessina AC. Sympathetic drive and vascular damage in hypertension and atherosclerosis. Hypertension 1991; 17 (Suppl III): III75–III81.
11. Lonnroth P, Smith U. β-Adrenergic dependent downregulation of insulin binding in rat adipocytes. Biochem Biophys Res Commun 1983; 112: 972–9.
12. Bonora E, Kiechl S, Oberhollenzer F, Egger G, Bonadonna RC, Muggeo M, Willeit J. Impaired glucose tolerance, Type II diabetes mellitus and carotid atherosclerosis: prospective results from the Bruneck Study. Diabetologia 2000; 43: 156–64.
13. Pyörälä M, Miettinen H, Halonen P, Laakso M, Pyörälä K. Insulin resistance syndrome predicts the risk of coronary heart disease and stroke in healthy middle-aged men. Arterioscler Thromb Vasc Biol 2000; 20: 538–44.
14. Ernsberger P, Koletsky RJ, Friedman JE. Contribution of sympathetic nervous system overactivity to cardiovascular and metabolic disease. Rev Contemp Pharmacother 1998; 9: 411–28.
15. Hamilton CA. Chemistry, mechanism of action and experimental pharmacology of moxonidine. In: von Zwieten PA, Hamilton CA, Julius S, Prichard BNC. The I_1-Imidazoline Receptor Agonist Moxonidine: A New Antihypertensive. Royal Society of Medicine Press Limited, London-New York, 1996; 7–30.

Mitteilungen aus der Redaktion

Besuchen Sie unsere
zeitschriftenübergreifende Datenbank

☑ **Bilddatenbank**   ☑ **Artikeldatenbank**   ☑ **Fallberichte**

e-Journal-Abo

Beziehen Sie die elektronischen Ausgaben dieser Zeitschrift hier.

Die Lieferung umfasst 4–5 Ausgaben pro Jahr zzgl. allfälliger Sonderhefte.

Unsere e-Journale stehen als PDF-Datei zur Verfügung und sind auf den meisten der marktüblichen e-Book-Readern, Tablets sowie auf iPad funktionsfähig.

☑ **Bestellung e-Journal-Abo**

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 α-adrenergic receptors by norepinephrine has been implicated to play a role in the progression of various cardiovascular diseases (40). Normal stimulation of α-adrenoceptors has a positive chronotropic effect; however, pro-longed stimulation has been implicated in myocyte hypertrophy, myo-cardial 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.