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
FOCUS ON SYMPATHETIC TONE

SNS Overactivity and Cardiovascular Disease

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 (e.g., heart, blood vessels, kidneys) as well as disturbances of glucose and lipid metabolism are the consequence of SNS overactivity. 

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, homocysteine 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 α1-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 β1-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 Ca2+-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 as it leads to a high cardiac output [7]. Another important mechanism for the development 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 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 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 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 de-
secending 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 seda-
Figure 5. Moxonidine selectively stimulates I1-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 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 α2-receptors (modified according to [15]).

References


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

Haftungsausschluss

Bitte beachten Sie auch diese Seiten:
- Impressum
- Disclaimers & Copyright
- Datenschutzerklärung