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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.

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, 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 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.
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 glucoseogenesis 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 bloodstream. 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 de-
sceding 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 moxo-
nidine decrease SNS activity by activation of I1-receptors in
the RVLM (Fig. 5). Stimulation of α2-receptors leads to seda-
tion, 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 de-
crease 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, re-
gression of left ventricular hypertrophy and microcirculatory
disturbances, nephroprotection in diabetic nephropathy, de-
ccrease 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,
such as high heart rate at rest or during exercise, high plasma
catecholamines, type A personality, anxiety and depression,
salt-sensitivity, sleep apnoea and obesity (metabolic syn-
drome).

Besides the centrally acting antisympathetic drugs, the
α1- and the β-adrenoreceptor 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.

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