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Interaction of the Sympathetic Nervous System with Other Pressor Systems in Antihypertensive Therapy

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Regulation of blood pressure homeostasis and cardiac function is importantly regulated by the sympathetic nervous system (SNS) and other pressor systems including the renin-angiotensin system (RAS) and the vascular endothelium. Increases in SNS activity increase mortality in patients with hypertension, coronary artery disease and congestive heart failure. This review summarizes some of the interactions between the main pressor systems, ie, the SNS, the RAS and the vascular endothelium including the endothelin-system.

Different classes of cardiovascular drugs interfere differently with the SNS and the other pressor systems. Beta-blockers, ACE-inhibitors and diuretics have no major effect on central SNS activity. Pure vasodilators including nitrates, alpha-blockers and DHP-calcium channel blockers increase SNS activity. In contrast, central sympatholytic drugs including moxonidine reduce SNS activity. The effects of angiotensin-II receptor antagonist on SNS activity in humans are not clear, experimental data are discussed in this review.

There are important interactions between the pressor systems under experimental conditions. Endothelin-A-receptor-antagonists inhibit angiotensin II and noradrenaline induced vasoconstriction. On the other hand, with L-NMMA and yohimbine, α_2-adrenoceptor-mediated endothelial vasodilation can be unmasked.

Ongoing and future studies have to assess the impact of combination therapy with different antihypertensive classes on SNS activity and on the other pressor systems and establish the ideal combination regarding hard end points, efficacy and side effects. It can be assumed, that in cardiovascular diseases with already enhanced SNS activity drugs, which do not increase SNS activity or even lower it, are preferable. Whether this reflects in lower mortality has to be investigated in intervention trials. *J Clin Basic Cardiol 2001; 4: 185–192.*

Key words: muscle sympathetic nerve activity, endothelin system, renin-angiotensin system, microcirculation, endothelin antagonists, nitric oxide, endothelium

The sympathetic nervous system (SNS) is an important regulator of cardiovascular function. Its activity is determined by psychological, neuronal and humoral factors [1–3]. Activation of neurohumoral systems as well as impairment of local regulatory mechanisms plays a significant role in the pathogenesis and prognosis of cardiovascular diseases.

SNS activity increases with age independently of disease state [4]. Furthermore, in congestive heart failure, SNS activity is markedly elevated and strongly correlates with mortality [5]. Elevated sympathetic activity not only plays a role in the induction of ischaemia due to reflex-tachycardia and coronary vasoconstriction [6], but also correlates with hypertension, insulin-resistance and the coronary risk [7].

Although its role in advanced hypertension is controversial, the SNS seems to contribute to the development of hypertension in early stages of the disease [8–10]. Essential hypertension is thought to be associated with an enhanced sympathetic activity triggered at the level of the central nervous system in a complex manner [4, 9, 11]. Therefore, in theory, it is likely, that interference with neuronal centers and pathways involved in the regulation of sympathetic activation at the level of the central nervous system may reduce blood pressure and cardiovascular risk. Thus, antihypertensive pharmacotherapy and its influence on the SNS is of great importance and will be discussed in this paper.

Anatomy and Physiology of the SNS

The efferent fibers arise from neuronal structures of the medulla oblongata called vasomotor-center (Fig. 1). The effector organs are innervated with two neurons, which are switched in ganglia. From the cytosomes of the preganglionic neurons in thoracic and lumbar medulla myelinated axons lead to the postganglionic neurons in the truncus sympathicus and the prevertebral ganglia. Acetylcholine is the neurotransmitter from the pre- to the postsynaptic neuron and binds nicotinic to receptors. Adrenergic receptors with the transmitter noradrenaline mediate the transduction to the effector organ (Fig. 1).

The catecholamines epinephrine, noradrenaline and dopamine are released from the adrenal medulla, which is phylogenetically a ganglion. In peripheral vessels sympathetic activation leads to vasoconstriction mediated by α_1-adrenoceptors on smooth muscle cells, whereas effects on the heart are mediated by β-adrenoceptors ($\beta_1 > \beta_2$). Alpha$_2$-adreno-

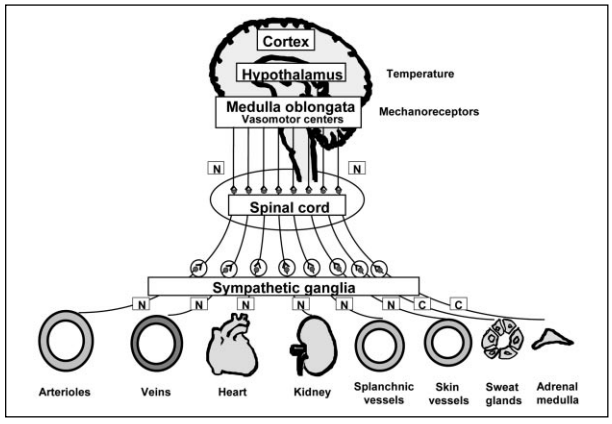

Figure 1. Scheme of the sympathetic nervous system (SNS). N = nicotinergic; C = cholinergic; reproduced with permission from [2].

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ceptors may be secondary in the sympathetic regulation of the cardiovascular system, however, experimental and first clinical data suggest, that α_2-adrenoceptors on the vascular endothelium modulate adrenergic vasoconstriction [12, 13].

The SNS interacts with the renin-angiotensin-system (RAS) and the vascular endothelium (Fig. 2). Angiotensin II influences the release and reuptake of noradrenaline through presynaptic receptors [14] and stimulates the sympathetic nervous system through a central mechanism [15, 16]. Furthermore, stimulation of β_1-adrenoceptors of the juxtaglomerular apparatus leads to activation of the RAS via elevation of renin [17]; this mechanism increases blood pressure as well as sodium and water-retention.

Besides purines, histamin, dopamine and prostaglandines, noradrenaline itself inhibits noradrenaline-release through presynaptic receptors, whereas epinephrine and angiotensin II stimulate noradrenaline-release presynaptically.

How can SNS Activity be Assessed?

We can assess SNS activity using different more direct or indirect methods (Fig. 3). We have to distinguish between direct release and effector organ responses. The latter are blood pressure, blood flow and heart rate; they are well known indirect measures of SNS activity. As effector organs in part react slowly to variations of the sympathetic activity and they depend on local-chemical, mechanical and hormonal influences, too, the interpretation of these parameters is complex. In clinical practice measuring plasma noradrenaline assesses sympathetic activity. Plasma noradrenaline, however, is only an indirect measure of sympathetic nerve activity as only the overflow of the adrenergic neurotransmitter from the synaptic cleft is measured. Furthermore, plasma noradrenaline does not only reflect the activity of adrenergic neurons, but also that of the adrenal medulla (Fig. 3). Finally, most methodologies to measure plasma catecholamines are prone to considerable variation [18], so that the more specific measurement of noradrenaline-spillover from the heart and other methods like blood pressure and heart rate variability have been introduced [19, 20].

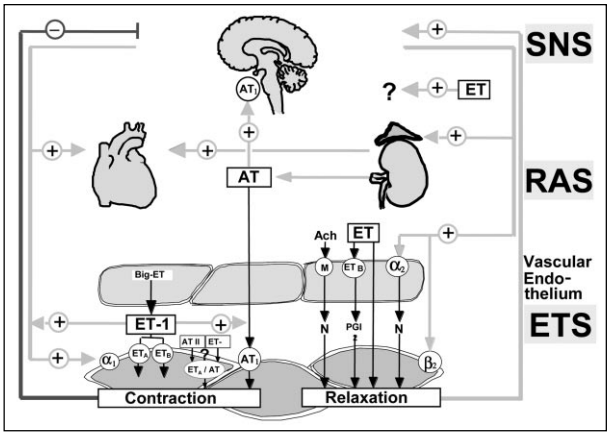

Figure 2. Main mechanisms and interactions between the sympathetic nervous system (SNS), the renin-angiotensin-system (RAS) and the endothelin system (ETS) in regulating blood pressure homeostasis. AT_1 = angiotensin-receptor type 1; AT II = angiotensin II; Ach = acetylcholine; ET = endothelin; ET_A/ET_B = endothelin-receptor type A/B; M = muscarinic receptor; $\alpha_1/\alpha_2/\beta_2$ = alpha$_1$/alpha$_2$/beta$_2$-adrenoceptor; NO = nitric oxide; PGI_2 = prostaglandine I_2; reproduced with permission from [2].

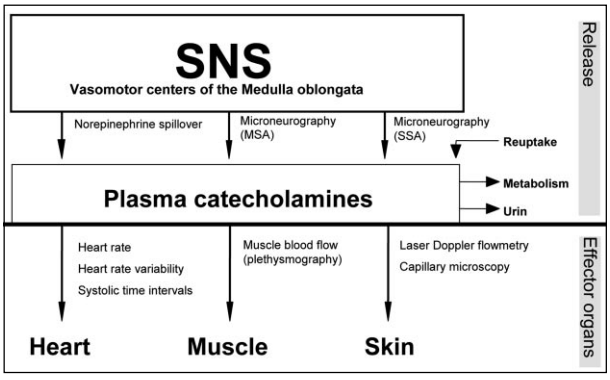

Figure 3. Methods to asses sympathetic activity. SNS = sympathetic nervous system; MSA = muscle sympathetic activity; SSA = skin sympathetic activity; reproduced with permission from [2].

Microneurography allows assessment of skin sympathetic nerve activity (SSA) or muscle sympathetic nerve activity (MSA) directly in a peripheral nerve [21, 22] (Fig. 3). The signals can be obtained on-line and hence also small and short lasting changes during stimulatory maneuvers as well as their time course can be recorded [21–25]. This methodology directly assesses electrical outflow of the sympathetic nervous system from the medulla oblongata. The latter property of microneurography allows to characterize changes in sympathetic nerve activity during application of cardiovascular drugs and to analyze the importance of pharmacokinetic properties of a given preparation under these conditions [26] (see below).

Furthermore the measurement of systolic time intervals, the impedance cardiography, the laser Doppler flowmetry and the measurement of muscle blood flow can be applied to assess the influence of the sympathetic nerve activity on effector organs [18, 27–30] (Fig. 3).

How do Cardiovascular Drugs Affect SNS Activity?

Central sympatholytic agents

Central sympathicolytics are one of the oldest antihypertensive drugs. Indeed, the "classical" central sympathicolytics, ie, clonidine, guanfacine, guanabenz and alpha-methyl-DOPA are well known centrally acting antihypertensive agents and act on central α_2-adrenoreceptors. This leads to sympathoinhibition and hence reduction in blood pressure, predominantly as a result of vasodilation and a consequent decrease in peripheral vascular resistance. Although these drugs are effective antihypertensives, they are no longer used as first-line drugs in the treatment of hypertension because of their unpleasant side effects like dizziness, dry mouth and sedation. In case of clonidine there was also concern about rebound hypertension [31]. These side effects are to a major extent mediated by α_2-adrenoceptors [32].

A new generation of centrally acting antihypertensive drugs with less adverse effects (ie, moxonidine and rilmenidine) has been introduced into clinical treatment. It has been shown that they mainly act on central imidazoline$_1$-receptors and less so on central α_2-adrenoceptors [32–34]. In contrast, other centrally acting antihypertensives, ie, alpha-methyl-DOPA, guanfacine or guanabenz, mainly act on central α_2-receptors [35]. In animals, moxonidine led to a decreased sympathetic tone to resistance vessels, the heart and the kidney [32, 36]. We showed in a double-blind, placebo-controlled study with direct measurement of sympathetic outflow in humans using microneurography under *in vivo* conditions for the first time, that the imidazoline$_1$-receptor agonist moxonidine reduces systolic and diastolic blood pres-

sure in both healthy volunteers and untreated hypertensive subjects through a reduction in central sympathetic outflow [37]. Moxonidine decreased muscle sympathetic nerve activity (Fig. 4) and plasma noradrenaline levels in both healthy volunteers and hypertensives, whereas epinephrine and renin levels did not change [37]. Heart rate decreased after moxonidine in healthy subjects; in hypertensives, heart rate decreased only during the night hours [37] (Fig. 5).

The potential of moxonidine to control blood pressure is similar to other antihypertensive agents such as α- and β-blockers, calcium antagonists or ACE-inhibitors, although we have to await the clinical trials assessing the responder rates of moxonidine in comparison with other antihypertensives; side effects such as dizziness and dry mouth were less pronounced than with the older centrally acting antihypertensives, eg clonidine [38, 39].

Rilmenidine is another imidazoline$_1$-receptor agonist with a high affinity for the imidazoline receptors [40]. Patient trials confirmed effective blood pressure lowering and fewer side effects than with clonidine [41–43]. Rilmenidine in comparison with the β-adrenoceptor antagonist atenolol was similarly well tolerated and both drugs caused similar decreases in systolic and diastolic blood pressure. However, in contrast to atenolol, rilmenidine did not influence autonomic function such as heart rate during exercise and the Valsalva maneuver [44]. Studies directly assessing effects of rilmenidine on SNS activity in humans are lacking.

Diuretics

Diuretics inhibit the salt- and water-reabsorption in the tubulus and thus they lead to a reduction of preload and afterload. The diuretic-induced loss of salt and water activates several hormonal systems such as vasopressin, the renin-angiotensin-aldosterone system and the sympathetic nervous system which tend to compensate for the changes in sodium and water balance [45, 46].

The long-term haemodynamic adaptation to diuretic treatment may be related to altered cardiovascular reflexes. Changes in sympathetic nerve activity and reduced vascular sensitivity to noradrenaline may contribute to the adaptation. In clinical practice, the combination of a β-blocker and a diuretic is well established because the complimentary mechanisms of antihypertensive effects with increased sympathetic outflow and renin-angiotensin axis activation induced by the diuretic can be blunted by β_1-adrenergic blockade. Whether the combination with a central sympathicolytic drug has similar additive effects is not extensively studied; however, in combination therapy, the diuretic hydrochlorothiazide with moxonidine had the lowest responder rates, whereas the combination with a calcium channel blocker (amlodipine) resulted in much higher responder rates; possibly, the central sympathicolytic moxonidine prevents the reflex SNS activation induced by amlodipine which otherwise would attenuate the vasodilator capacity of the calcium antagonist [47].

Nitrates

Nitrates are peripheral vasodilators, which cause endothelium-independent relaxation of vascular smooth muscle. Reflex tachycardia is a known unwanted reaction to the application of several vasodilators. In a double-blind placebo-controlled study isosorbide-dinitrate markedly increased both heart rate and muscle sympathetic nerve activity (MSA) as assessed by microneurography [26], confirming earlier studies of intravenous administration of other vasodilatators [48–50]. This effect can be explained by an arterial baroreceptor-mediated mechanism, a decrease in pulse-pressure and an activation of low pressure receptors caused by a possible decrease in central venous pressure [26].

ACE-inhibitors (ACEI)

By blocking the converting enzyme, ACEI inhibit the synthesis of angiotensin II, a strong vasoconstrictor, which enhances the release of noradrenaline through stimulation of peripheral presynaptic receptors [51]. Furthermore, angiotensin II stimulates central SNS activity [52]. ACEI also seem to prevent the breakdown of bradykinin inducing further vasodilation via stimulation of nitric oxide and prostacyclin release. Bradykinin leads to release of nitric oxide and prostacyclin from the endothelium, which may contribute to the haemodynamic reactions to ACE-inhibition. On the other hand bradykinin may also be responsible for the adverse reactions such as cough and angioneurotic oedema [53–57].

In contrast to pure vasodilators (ie, nitrates or calcium antagonists), which activate the SNS, ACEI induce no reflex tachycardia or increases in plasma noradrenaline [58]. In a double-blind placebo-controlled study the ACEI captopril after acute administration in healthy volunteers reduced muscle sympathetic nerve activity (MSA) despite lowering blood pressure without influencing the responsiveness to mental or physical stress, whereas nitrates strongly activated MSA [5, 26]. This indicates, that reduction of circulating angiotensin II, which stimulates SNS activity, lowers sympathetic tone [52]. This might be one possible explanation for the beneficial effects of ACEI on survival in patients with left ventricular dysfunction, in which activation of sympathetic nervous system is strongly associated with morbidity and mortality [59]. These positive effects of the ACEI on morbidity and mortality of patients with heart failure and im-

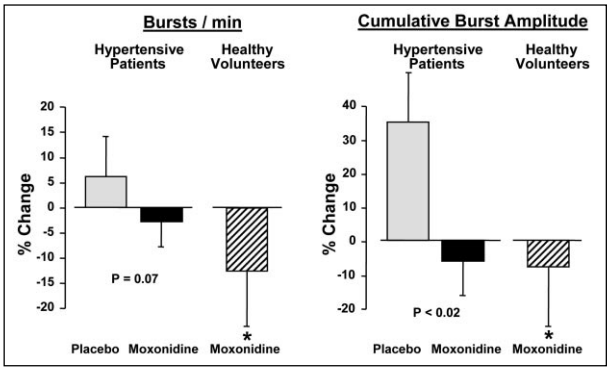

Figure 4. Effect of the central sympathicolytic moxonidine on central SNS activity (muscle sympathetic nerve activity) as assessed by microneurography. Modified from reference [127]

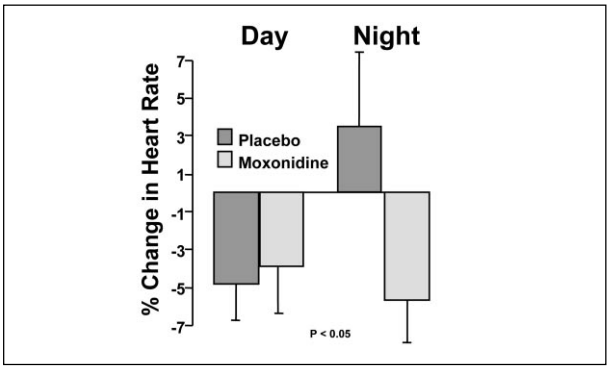

Figure 5. Effect of the central sympathicolytic moxonidine on heart rate (Details see text). Modified from reference [127]

paired left ventricular function and patients after myocardial infarction have been documented in numerous clinical studies [59–63].

However, with chronic administration a number of mechanisms exist which may partially co-interact the beneficial effects of ACE inhibition after acute dosing. Especially angiotensin II may be synthesized by alternate non-ACE-dependent pathways (so called chymases), which may in part oppose the acute depressing effects on SNS activity [64–66]. On the other hand it has been shown, that chronic ACE inhibition did not change biosynthesis, storage or release of catecholamines [67]. From the fact that bradykinin stimulated noradrenaline release dose-dependently, almost during converting enzyme inhibition, it has been concluded that bradykinin may compensate for the lack of effect of converting enzyme inhibitors on catecholamine release [67]. At least, in heart failure, chronic ACE inhibitor treatment is accompanied by a marked reduction in central sympathetic outflow, that may depend on a persistent restoration of baroreflex restraint on the sympathetic neural drive [68]. Furthermore vagal activity seems not to be influenced, as acute and chronic ACE inhibition did not blunt important cardiovascular reflexes [69].

AT_1-receptor antagonists

The blockade of the angiotensin II receptor is the most direct way to inhibit the renin-angiotensin system (RAS). In contrast to the ACEI, which do not affect noradrenaline release because of the activation of compensatory mechanisms and inhibition of noradrenaline-reuptake and noradrenaline-metabolism, AT_1-receptor antagonists *in vitro* suppress the angiotensin-induced noradrenaline release and thus its proliferative effects [70, 71].

The effects of AT_1-receptor antagonists have not yet been studied extensively in humans *in vivo*. The Evaluation of Losartan in the Elderly (ELITE)-study showed that the effects of the AT_1-antagonist losartan on mortality of patients with symptomatic heart failure older than 65 were more pronounced than with the ACEI captopril [72]. There was no significant difference between plasma levels of noradrenaline in the losartan compared with the captopril group. Candesartan has shown similar effects on exercise capacity, ventricular function and neurohormones than the ACE-inhibitor enalapril in heart failure patients [73].

Experimental data suggest, that AT_1-receptor antagonists lead to a more complete suppression of catecholamines than ACEI [74]. The newer non-peptide AT_1-receptor antagonist eprosartan has been shown to inhibit the pressor response induced by spinal cord stimulation in pithed rats, whereas equivalent doses of other nonpeptide AT_1-receptor antagonists, such as losartan, valsartan and irbesartan, had no effect on sympathetic outflow; this has been interpreted as a more effective inhibition of prejunctional angiotensin II-receptors [75].

Whether these effects on SNS activity play a role *in vivo* in humans, is not known. However, first clinical data from a double-blind, placebo-controlled study suggest, that at least losartan does not reduce basal nor exercise-induced sympathetic activity when compared to placebo or enalapril [76]. Other trials investigating hard clinical endpoints such as mortality and morbidity, e.g. in heart failure patients, are ongoing (CHARM) [77].

Furthermore, combination of ACE-inhibitors and AT-receptor antagonists seems to improve therapeutic effects and end-organ damage compared to monotherapy, but large-scale clinical trials are lacking [73, 78].

Beta-blockers

Beta-adrenoceptor antagonists inhibit ß$_1$-adrenoceptor-mediated positive inotropism and chronotropism of catecholamines on the heart and the β_2-adrenoceptor-mediated relaxation of the vascular smooth muscle [38, 79–81]. Furthermore, blockade of β-adrenoceptors antagonizes the metabolic effects of catecholamines like lipolysis or glycogenolysis [80].

In the therapy of cardiovascular diseases selective blockade of β_1-adrenoceptors protects the heart from enhanced sympathetic tone reducing heart rate and inotropism and thus cardiac oxygen consumption.

β-adrenoceptor-antagonists are established in the therapy of hypertension and ischaemic heart disease as they positively influence mortality, ischaemic episodes, risk for myocardial (re)-infarction and sudden death [82–85].

In the last few years, β-adrenoceptor antagonists have been introduced in the therapy of congestive heart failure [86–88]. The positive effects of β-blockade in congestive heart failure have been shown for bisoprolol [89], metoprolol [90] and carvedilol [91] and seem to result from a better efficiency of the SNS under β-blockade. They improve haemodynamics and symptoms and have recently been shown to reduce mortality [92]. Thus, β-adrenoceptor antagonists inhibit the downregulation of β-adrenoceptors and increase the sensitivity to β-adrenoceptor agonists [93]. Yet, the benefits of β-blockers are seen in patients already receiving ACE inhibitors, suggesting that combined blockade of two neurohormonal systems (renin-angiotensin system and sympathetic nervous system) can produce additive effects. The effect of β-blockade on central sympathetic nerve activity is controversial and not extensively studied [94, 95]. Some studies show decreases in SNS activity, whereas others did not find central effects. Effects may, at least in part, depend on whether the drug is lipophile or not. Although acute treatment with a β-blocker may enhance central SNS activity, no study found SNS activation after chronic β-blocker therapy [94, 95].

Calcium antagonists (CA)

CA lead to peripheral vasodilation and inhibit the effects of vasoconstrictor hormones at the level of vascular smooth muscle by reducing the calcium inflow through blockade of slow voltage-dependent L-type calcium channels. The lowered intracellular calcium concentration inhibits electromechanical coupling and hence leads to vasodilation and lowering of blood pressure. Three groups of CA exist, dihydropyridine-type (eg, nifedipine), phenylalkylamine-type (eg, verapamil) and benzothiazepine-type (eg, diltiazem) which bind to different sites of the α_1-subunit of the calcium channel. While dihydropyridine calcium antagonists are mainly peripheral vasodilators, verapamil-type calcium antagonists have also direct effects on the SA-node and possibly reduce SNS activity [96, 97].

CA are effective antihypertensive drugs and exert antiischaemic effects [98]. Furthermore, they exhibit vascular protective properties; they improve endothelial function in atherosclerosis and hypertension, both experimentally [99] and in human hypertension [100]. They inhibit proliferation of human coronary artery smooth muscle cells [101] and slightly reduce the development of new atherosclerotic lesions [102].

In spite of these vascular protective effects, clinical trials with CA yielded disappointing results in patients with coronary artery disease and impaired left ventricular function and diabetes [103–110].

Activation of the SNS may not only depend on the class of CA used, but also on its pharmacokinetics. Indeed, CA of the dihydropyridine-type (ie, nifedipine, felodipine, amlodipine)

lead to sympathetic activation with reflex-tachycardia [37, 111]. In contrast, verapamil leads to a reduction of heart rate and sympathetic activity as assessed by plasma noradrenaline [112]. After acute administration in healthy volunteers, nifedipine markedly increased muscle sympathetic nerve activity as assessed by microneurography; interestingly, this occurred not only with short acting, but also with very slow release formulation of nifedipine, ie, the GITS formulation. In contrast, HR increased only with short acting, but not with slow release nifedipine [37]. Therefore, nifedipine differently activates cardiac and peripheral sympathetic tone depending on pharmacokinetics. Thus, heart rate not necessarily predicts SNS activity, so that a lack in heart rate increase is no proof for missing SNS activation [37].

Amlodipine, a newer slow-acting dihydropyridine-type CA seems to stimulate SNS to a lesser degree than other dihydropyridines. Nevertheless heart rate and plasma noradrenaline increased significantly in hypertensives after acute application, but there was no long-term effect on heart rate [111]. Furthermore, in renal hypertension, amlodipine activates central SNS activity during chronic therapy, whereas an ACE-inhibitor reduces SNS activity [113].

Other vasodilators including peripheral alpha$_1$-blockers

The pure vasodilators minoxidil (potassium channel opener) and hydralazin are effective antihypertensives, which lower preload and afterload. However, they stimulate SNS activity and with long-term treatment compensatory activation of the sympathetic and the renin-angiotensin-systems predominate [114].

Selective α_1-adrenoceptor-antagonists like prazosin also lower pre- and afterload through inhibition of peripheral sympathetic vasoconstriction, but do not influence the sympathetic activity to the heart which is predominantly β-adrenoceptor-mediated [115]. This might explain why the Veterans Administration Cooperative Study with prazosin could not show a better prognosis of patients with heart failure [116]. Interestingly, the α_1-adrenoceptor-antagonist doxazosin induces significant sympathetic overactivation both at rest and under physical exercise, when compared to placebo [76, 79].

A recent study showed, that in hypertensive patients with renal artery stenosis the nonspecific vasodilator dihydralazine in comparison to the ACE-inhibitor enalapril lead to a similar fall in blood pressure but, in contrast to enalapril, dihydralazin increased plasma angiotensin II, muscle sympathetic nerve activity, heart rate, and total body noradrenaline spillover [117].

Interactions of the SNS with the Vascular Endothelium

The vascular endothelium with the underlying vascular smooth muscle cells plays an important role in the regulation of vascular tone. Functional changes in the secretion of endothelium-derived mediators may be involved in the pathogenesis and progression of cardiovascular diseases, eg hypertension and atherosclerosis. Experimental data suggest various interactions between SNS and the vascular endothelium (Fig. 2). Endothelin-1, which is released from endothelial cells, is the strongest vasoconstrictor, plasma levels of endothelin-1 are elevated in several cardiovascular diseases [118]. Thus, endothelin leads to peripheral vasoconstriction, an elevation of blood pressure and plasma catecholamine levels in rats, intrathecally injection of endothelin stimulates sympathetic activity [119]. Furthermore it is at least a comitogen of the proliferation of vascular smooth muscle cells [118]. Different ET-receptors have been cloned [118]. Whereas the major effect of vasoconstriction is mediated through ET_A-receptors on smooth muscle cells, ET_B-receptors on the vascular endothelium may release vasodilating substances like NO and prostacyclin [120, 121]. In human skin microcirculation the ET_A-selective antagonist BQ-123 inhibits vasoconstriction to angiotensin II and noradrenaline *in vivo* in healthy subjects, indicating the potential synergistic effect of a combination of endothelin receptor antagonists with the established therapeutic regime inhibiting the sympathetic nervous system and the renin-angiotensin system [122]. In clinical hypertension the antihypertensive effects of the endothelin antagonist bosentan were comparable with the ACE-inhibitor enalapril and there may be beneficial effects in CHF, but further clinical trials have to confirm these results [123–125].

Endothelin receptors on endothelial cells are linked to voltage-operated calcium channels via G-proteins [126]. This may explain why calcium antagonists reduce endothelin-induced vasoconstriction in the human forearm circulation, ie, intraarterial application of verapamil or nifedipine prevents contractions to intraarterial infused endothelin [30]. On the other hand, drugs, which stimulate SNS activity (eg nitrates, nifedipine) increased endothelin plasma levels *in vivo* in humans, whereas ACE-inhibitors and moxonidine decreased SNS activity and did not increase plasma endothelin [26, 127].

Table 1. Summary of the effects of cardiovascular drugs on SNS activity in human cardiovascular disease. Note the table gives only an overview on the effects; individual responses vary depending on age, disease and differences within the drug classes. For details and references, see text. HR: heart rate; Catechol: catecholamines; MSA: muscle sympathetic nerve activity as assessed by microneurography. n.a.: no data/insufficient data available.

Drug	HR (acute)	HR (chronic)	Catechol. (acute)	Catechol. (chronic)	MSA (acute)	MSA (chronic)
Central sympathicolytics	⇓	⇓ / ⇔*	⇓	⇓	⇓	n.a.
ACE-inhibitors	⇔	⇔	⇓	⇓	⇓	⇓
Angiotensin receptor antagonists	⇔	⇔	⇔*	⇔*	n.a.	n.a.
Beta-blockers	⇓	⇓	⇑	⇓	⇑	⇓
Diuretics	⇑	⇔	⇑	n.a.	n.a.	n.a.
Nitrates	⇑	⇔*	⇑	n.a.	⇑	n.a.
Peripheral alpha-blockers	⇔	⇔	⇑	n.a.	n.a.	n.a.
Dyhidropyridine-type calcium-antagonists (slow release formulation)	⇑ / ⇔*	⇑ / ⇔*	⇑	⇑ / ⇔*	⇑*	⇑ / ⇔#
Verapamil-type calcium-antagonists (slow release formulation)	⇔	⇓	⇔	⇓	n.a.	⇔#
Endothelin-antagonists	⇔	⇔#	⇔#	⇔#	n.a.	n.a.

* Differences within the drug classes exist and/or study results are controversial. # Only few data available by now. ⇓ = reduction; ⇑ = increase; ⇔ = unchanged

Chronic therapy with calcium antagonists in experimental and human hypertension improved endothelium-dependent relaxation to acetylcholine [128]. ACE-inhibitors stimulate endothelium-dependent relaxation indirectly through prevention of bradykinin breakdown, which leads to formation of NO and prostacyclin. In experimental approaches in the resistance circulation of spontaneously hypertensive rats, chronic blockade of the renin-angiotensin system with a nonpeptidic angiotensin II-receptor antagonist CGP 48369, the ACE-inhibitor benazepril HCl, or the calcium antagonist nifedipine reduced blood pressure and improved endothelial dysfunction [99]. Clinical studies showed that the ACE-inhibitor quinapril could reverse endothelial dysfunction and reduce the frequency of coronary ischaemia [129–131]. Administration of the ACEI lisinopril to patients with essential hypertension has been shown to selectively increase vasodilatation in response to infusion of bradykinin [132].

Intrinsic differences exist between different ACEI, ie, quinaprilat and enalaprilat, which determine the ability to improve endothelium-mediated vasodilation, ie, their different affinity to tissue ACE, because quinaprilat could improve flow-dependent dilation in patients with chronic congestive heart failure as the result of increased availability of nitric oxide, whereas enalaprilat could not [133].

Experimental and first clinical trials in the human skin microcirculation suggest, that adrenoceptor agonists can stimulate endothelial α-adrenoceptors leading to the release of nitric oxide (NO) and other vasodilating substances [134, 135]. Indeed, α_1-adrenoceptor-mediated constriction of vascular smooth muscle cells could be potentiated by NO-inhibition both *in vitro* and *in vivo* in humans [134, 135]. This mechanism may be of pathophysiological importance in atherosclerosis and hypertension where endothelial function is impaired.

Conclusion

There are important effects of cardiovascular drugs on the sympathetic nervous system in humans, which are summarized in Table 1. It must be emphasized, that in several aspects the study results vary depending on the subtype of a drug and the underlying disease under investigation. Table 1, therefore, offers only a coarse overview of the potential effects of the drugs on SNS activity. Most studies, especially the chronic studies, have only assessed SNS activity indirectly, ie, measuring plasma catecholamines or heart rate variability. Data using microneurography, which directly records central sympathetic nerve traffic, are only incomplete. Nevertheless, the trends observed in the trials in most cases are consistent.

The complex effects of antihypertensive drugs on the pressor systems (SNS, RAS and ETS) seem to be relevant for clinical use, especially for the therapy of patients with cardiovascular diseases. A potential mediator of untoward effects of cardiovascular drugs is an activation of the SNS. Indeed, the fact that an increased SNS activity, ie, high heart rates and high plasma noradrenaline levels, is associated with an increased mortality in patients with cardiovascular disease and especially with congestive heart failure [5, 136, 137] suggests, that an activation of the SNS is detrimental at least in these patients, but possibly also in other patient groups, e.g. hypertensives [138]. Overactivation of the SNS may also be detrimental in patients with diabetes and coronary artery disease including acute coronary syndromes [139].

The more recently discovered interactions between the pressor systems will importantly impact the guidelines of therapy; the upcoming trials assessing combination therapy in hypertension will help to find out whether these interactions can be prevented with drugs that have synergistic effects and less or no reflex activation of other pressor systems. Importantly, the upcoming endothelin antagonists may broaden the cardiovascular therapeutic arsenal by a drug, which is not only a potent vasodilator, but also inhibits the effects of the SNS and the RAS at various levels.

Whether the beneficial effects of some antihypertensive drugs on the SNS translate into a reduction of hard endpoints, i.e. cardiovascular and total mortality, has yet to be demonstrated in clinical trials.

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