The Beauty and the Beast: Aspects of the Autonomic Nervous System

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Sympathetic nerve activity is altered and is a prognostic factor for many cardiovascular diseases such as hypertension, coronary syndromes, and congestive heart failure. Therefore, the selection of vasoactive drugs for the treatment of these diseases should also take into consideration their effects on the sympathetic nervous system.

There are different methods to assess sympathetic nervous system (SNS) effects on the cardiovascular system in humans. Besides the assessment of endorgan responses such as blood pressure and heart rate, the most widely used measurements are plasma-norepinephrine (NE) assay, NE spillover technique, microneurographic recordings of postganglionic muscle and skin sympathetic nerves, and power spectrum analysis of blood pressure and heart rate variability. The technique of microneurography allows a direct and continuous assessment of SNS activity (3, 13) and represents the only measure to detect small and short-lasting changes within the system. Superficial nerves such as the peroneal nerve are particularly suitable for microneurography since their anatomic location allows the placement of a recording microelectrode. Sympathetic outflow is regulated in the brain stem and the medulla oblongata. Sympathetic nerves travel along the nerve column into ganglia, in which acetylcholine is responsible for transmission of activity from the pre- to the postganglionic adrenergic neurons innervating the heart and many other organs of the body. Depolarization of postganglionic sympathetic nerve fibers leads to increases in intracellular calcium in adrenergic nerve endings where NE is released

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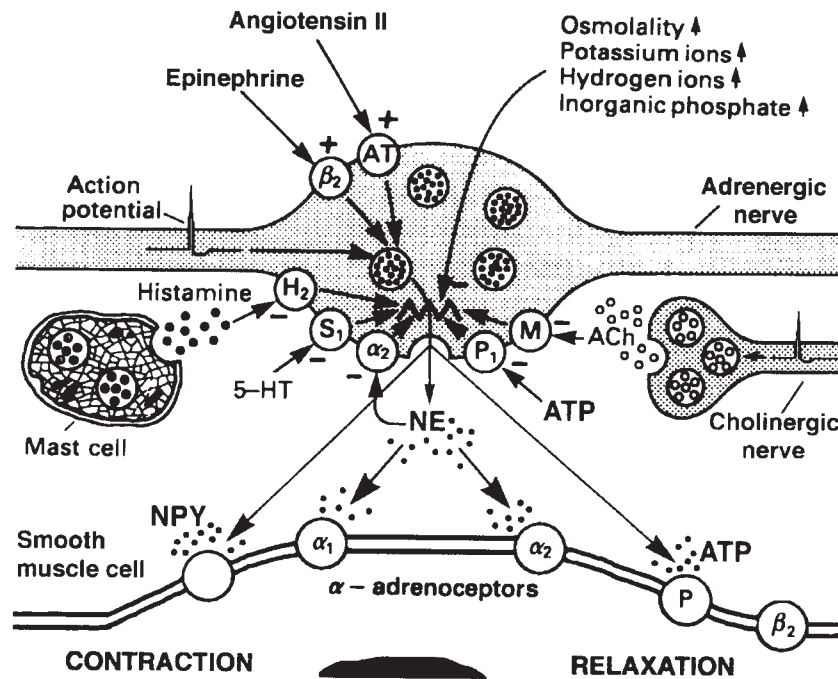
FIGURE 1. Regulation of vascular smooth muscle cell tone by sympathetic nervous system (SNS). Release of neurotransmitters, norepinephrine (NE), neuropeptide Y (NPY), and ATP at sympathetic nerve endings is influenced by several substances acting on presynaptic receptors. Thus acetylcholine (ACh), histamine, serotonin (5-HT), and dopamine can inhibit (–) release of NE. NE itself can inhibit its release by acting on presynaptic α_2-receptors. Vasoactive substances such as epinephrine and angiotensin II can increase (+) release of NE by activating presynaptic receptors. On smooth muscle cells, NE can stimulate α_1-receptors, causing contraction, and α_2-receptors, causing relaxation; ATP acting on P receptors induces relaxation, whereas NPY can induce constriction.

from vesicles located in the nerve terminals. NE is the main neurotransmitter, although neuropeptide Y and ATP may also participate. The amount of NE and other neurotransmitters released is tightly regulated by negative feedback mechanisms involving the neurotransmitter itself (via presynaptic α_2-adrenergic receptors), but also other mediators such as adrenaline, serotonin, histamine, acetylcholine, and many others (Fig. 1) (12).
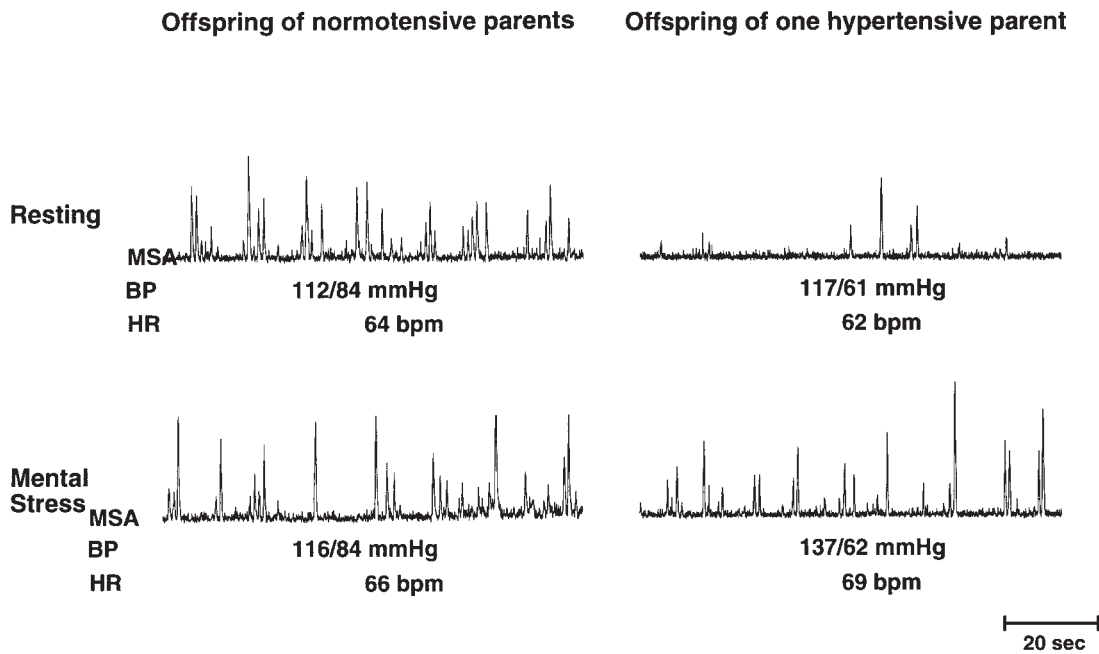
The effects of NE at the postjunctional level, i.e., vascular smooth muscle cells of blood vessels and myocytes of the myocardium, involve β-adrenergic receptors, as well as α_1- and α_2-adrenergic receptors. The former are involved in vasodilatation (β$_2$-adrenergic receptors), inotropy, and chronotropy (β$_1$-adrenergic receptors), and the latter mediate vasoconstriction of the blood vessel wall.

Of particular interest is the fact that SNS activity is very heterogeneous in the body. Indeed, the system is capable of activating certain organs but not others, depending on the pattern of activation and the physiological stimulus involved. Sympathetic fibers in the peroneal nerve innervate blood vessels in muscle tissue or the skin of the leg. Electrical activity within muscle and skin sympathetic nerve fibers can be identified according to its characteristic pattern. The neurogram of muscle sympathetic activity (MSA), which significantly contributes to the regulation of peripheral vascular resistance, reveals spontaneous, intermittent, pulse-synchronous sympathetic bursts that increase during apnea. MSA can be stimulated by different maneuvers such as physical activity, mental stress, hypoxia, and unloading baroreceptors. During a cold pressor test, a massive increase in MSA occurs (3, 13).

SNS and cardiovascular disease

The sympathetic nerve fibers are ubiquitously distributed within the heart, the blood vessels, the kidney, and major peripheral baroreceptor sites, a finding that suggests a direct effect on fluid control, cardiac output, and peripheral vascular resistances. In fact, SNS significantly regulates cardiovascular homeostasis (11), and SNS activity is altered in various forms of cardiovascular disease. Activation of the SNS plays an important role in the pathophysiology and the prognosis of cardiovascular disease such as hypertension, ischemic heart disease, and heart failure.

Hypertension. In hypertension, hyperactivity of the SNS was postulated decades ago. It has been demonstrated that, particularly in the early phases of the hypertensive process, the sympathetic drive is increased. In patients with borderline or mild hypertension, increased cardiac β-adrenergic and vascular α-adrenergic drive has been documented by selective receptor blockade. The evidence from pharmacological studies is in line with the slightly increased plasma levels of NE in young subjects with mild hypertension. These findings were confirmed by experiments that showed an increase of NE spillover in the heart and the kidney of hypertensives in particular. Furthermore, using the technique of microneurography it has been clearly demonstrated that resting MSA is increased in patients with borderline hypertension (1). In addition, an exaggerated blood pressure response to mental stress has been demonstrated in patients with essential hypertension. In normotensive offspring of hypertensive parents, we found that the MSA response to mental stress is more pronounced than in offspring

	Offspring of normotensive parents	Offspring of one hypertensive parent
Resting MSA		
BP	112/84 mmHg	117/61 mmHg
HR	64 bpm	62 bpm
Mental Stress MSA		
BP	116/84 mmHg	137/62 mmHg
HR	66 bpm	69 bpm

20 sec

FIGURE 2. Muscle sympathetic activity (MSA) in peroneal nerve at rest and during mental stress in normotensive offspring of normotensive (*left*) and hypertensive (*right*) parents. Increase of MSA during mental stress is more pronounced in offspring of hypertensive parents. BP, blood pressure; HR, heart rate. Modified from Ref. 9.

of normotensive parents, but resting MSA is comparable (Fig. 2) (9). Thus it is now clear that in offspring of hypertensive parents in which resting blood pressure is still normal, MSA is abnormally stimulated during mental stress (9). It is possible that early on in the disease process the SNS is only activated abnormally during episodes of increased stress and that resting MSA is increased during development of high blood pressure, whereas at later stages of hypertension SNS activity may again become normal, although the values may still be too high for the level of blood pressure of these patients.

Coronary artery disease. In patients with coronary artery disease, the SNS and its activity may be important as triggers for acute coronary syndromes in general and sudden death in particular. Indeed, abnormal SNS activity as assessed by heart rate variability greatly determines prognosis in patients after myocardial infarction (5).

Heart failure. In heart failure, the SNS is markedly activated (4, 6), probably because of an activation of baroreflex mechanisms to compensate for low blood pressure and decreased perfusion of vital organs as a consequence of abnormal left ventricular function. This activation of SNS may initially lead to an increase in cardiac output, but in severe heart failure SNS-mediated increase in peripheral vascular resistance further deteriorates cardiac function and may actually be harmful. In the vasodialator-heart failure trial study, patients with the highest levels of plasma NE had the poorest prognosis (2). This suggests that indeed in heart failure the degree of activation of the SNS may be an important prognostic variable.

Modulation of sympathetic nerve activity by cardiovascular drugs

The efficacy of cardiovascular drugs primarily depends on their action on blood vessel wall and myocardium. However, some of the beneficial effects of the drugs in the circulation, i.e., vasodilatation and stimulation of myocardial contractility, may be overcome at least in part by their effects on neurohumoral regulators.

Various drugs are used to treat patients with cardiovascular disease, e.g. β-blockers, calcium antagonists, ACE-inhibitors, and nitrates. Indeed, certain drugs may be very efficacious antihypertensive or vasodilator agents yet activate the SNS, and others inhibit it (7). Given the important prognostic relevance of SNS activity in patients with cardiovascular disease, understanding the effects of these vasoactive drugs on the SNS may have great clinical relevance.

Calcium channel blockers are potent vasodilators acting directly on vascular smooth muscle cells. These drugs are widely used for the treatment of hypertension and angina pectoris. In secondary prevention after myocardial infarction, calcium antagonists did not have beneficial effects on cardiovascular events and survival, particularly in patients with heart failure. This could be due to either negative inotropic effects or a baroreceptor-mediated activation of the SNS (2).

Dihydropyridines such as nifedipine also have important effects on the SNS in healthy human subjects. Oral administration of short-acting nifedipine leads to a marked increase of MSA and NE plasma levels (Fig. 3). The degree of activation of MSA is comparable to a cold pressor test (which is the most potent stimulus of sympathetic nerve activity). Most interestingly, nifedipine remains a very important stimulus for SNS activity even in the presence of a cold pressor test (14). This finding indicates that with short-acting dihydropyridines, the peripheral and cardiac portions of the SNS are highly activated and remain responsive to these stimulatory maneuvers. Indeed, the potent vasodilator effects under acute conditions together with the negative inotropic effects of the drug may lead to marked activation of the baroreflex
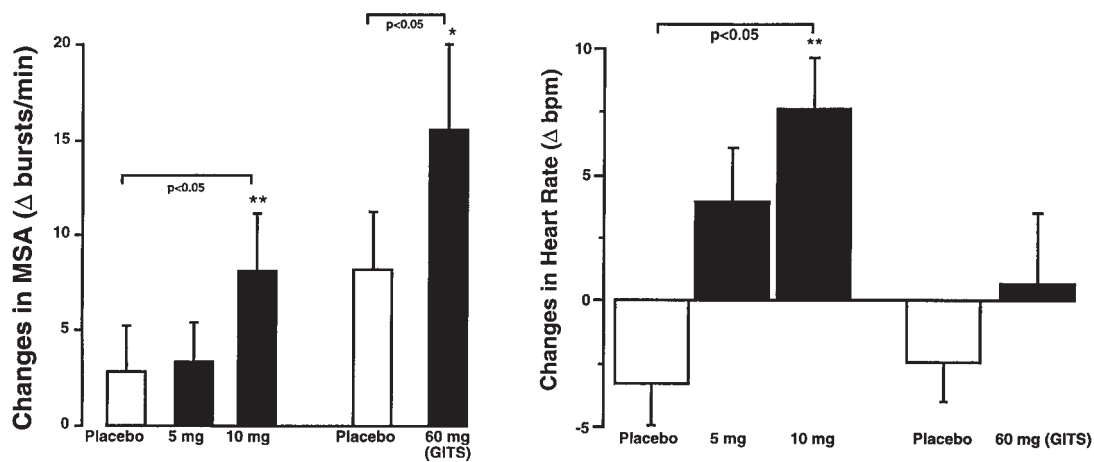
FIGURE 3. MSA expressed as bursts/min (*left*) and heart rate (*right*) before and after oral nifedipine [5 mg, 10 mg, and GI theraputic system (GITS) of 60 mg] or placebo. bpm, Beats per minute. Modified from Ref. 14.

and in turn an increase in heart rate and SNS activity. It is conceivable that such effects are less pronounced with a more slowly acting form of nifedipine. The nifedipine gastrointestinal therapeutic system (GITS), which is a slow-release form of nifedipine, indeed does not significantly change heart rate even under acute conditions, suggesting that the baroreflex is less activated. However, in the peroneal nerve, a marked activation of MSA can still be documented (Fig. 3) (14). This suggests that a slower onset of vasodilatation as it occurs with slow-release nifedipine does not lead to a generalized sympathetic nerve activation and does not significantly increase sympathetic outflow to the heart. Nevertheless, sympathetic outflow to peripheral muscles is still activated under these conditions. Whether such effects also occur during chronic treatment with nifedipine remains to be demonstrated.

Due to its different pharmacological profile, verapamil is associated with a decrease rather than an increase in heart rate even under acute conditions. During chronic therapy in patients with hypertension, verapamil lowers rather than increases plasma NE. Although studies with microneurography have not been performed yet, there is indirect evidence that verapamil affects the SNS differently from dihydropyridines (10).

Angiotensin-converting enzyme (ACE) inhibitors also act as vasodilators, inhibiting the formation of the vasoconstrictor peptide angiotensin II. ACE inhibitors tend to lower heart rate in normotensive subjects, although they do slightly decrease blood pressure. These drugs not only improve symptoms in patients with left ventricular dysfunction and/or congestive heart failure but also reduce acute coronary events and death. Experimentally, angiotensin II stimulates SNS activity by activating specific binding sites in the brainstem and, at presynaptic levels, it increases the release of NE from sympathetic nerve endings (Fig. 1). These mechanisms could explain the increased MSA observed in patients with renovascular hypertension, characterized by a high plasma level of angiotensin II. After administration of captopril in healthy volunteers, MSA remained constant despite a significant decrease in diastolic blood pressure (Fig. 4) (8). These findings are in line with the observation that in rat model of renal

hypertension lisinopril and losartan had no influence on splanchnic sympathetic nerve activity despite a reduction in blood pressure. This effect on SNS activity could explain the favorable effects of ACE inhibitors on the prognosis of patients with heart failure in whom activation of the SNS is an important prognostic factor. Hence, ACE inhibitors and possibly angiotensin II receptor antagonists may be particularly efficacious in blunting or even inhibiting the untoward effects of the SNS in patients with cardiovascular disease.

Similar reduction of blood pressure is achieved with nitrates, but these drugs are associated with marked activation of the SNS. Earlier studies demonstrated that intravenous administration of nitrovasodialators is associated with a marked increase in MSA. In healthy subjects, an acute oral administration of isosorbide dinitrate causes a marked increase in MSA (Fig. 4) and heart rate and has little effect on blood pressure. Indeed, this effect of the nitrates may be partially responsible for the clinically observed tolerance, or rather pseudotolerance, since the baroreflex-mediated
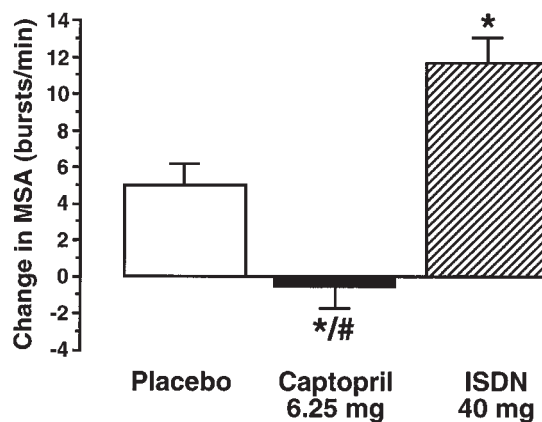
FIGURE 4. Change in resting MSA 90 minutes after oral administration of placebo, 6.25 mg captopril, and 40 mg isosorbide dinitrate (ISDN). A significant increase in MSA was observed in subjects who received placebo. Increase in MSA after ISDN was more pronounced compared with placebo. In subjects treated with captopril, MSA did not change. *$P < 0.05$ vs. placebo; #$P < 0.05$ vs. ISDN. Modified from Ref. 8.

activation of the SNS in part blunts the vasodilator effects of these drugs in the intact organ (8).

Centrally acting drugs, i.e., clonidine and α-methyl-DOPA, have been used for the treatment of hypertension for a long time. It has been postulated that this antihypertensive effect is due to a central inhibitory effect on the SNS. Moxonidine belongs to a new generation of centrally acting drugs that activate I_1-imidazoline receptors in the brain stem. The oral administration of moxonidine in healthy volunteers and hypertensive patients leads to a significant decrease of systolic and diastolic blood pressure, NE, and MSA (15). This demonstrates that the I_1-imidazoline receptor agonist moxonidine reduces blood pressure in untreated hypertensive subjects through the reduction in central sympathetic outflow (15). This effect may be beneficial not only in hypertensives but also in patients with heart failure.

Clinical Implications

In conclusion, it is clear that sympathetic activity is an important prognostic factor in patients with cardiovascular disease and in heart failure in particular. Its true importance, however, has been revealed more recently though new techniques allowing precise assessment of its activity and its control over cardiovascular functions in the intact organism.

Recent data suggest that activation of the SNS during mental stress may precede the increase in resting activity present in early stages of hypertension. These data suggest that responsiveness as well as activity of the SNS may play an important role in the development of hypertension. Hence, the effects of drugs on this important regulatory system should be more thoroughly investigated since this may have important implications for the effects on the prognosis of these patients. In regard to calcium antagonists, it appears that the effects of calcium antagonists on SNS activity depend on pharmacokinetics of these drugs as well as their genuine pharmacological properties. Activation of the SNS is most pronounced with short-acting dihydropyridines and less so with long-acting preparations of these drugs. These properties of certain calcium antagonists deserve further investigation to elucidate their clinical implications. ACE inhibitors, besides their favorable influence on hemodynamics, seem to lower SNS activity, an effect that may contribute to the beneficial effects on the prognosis of patients with impaired left ventricular function. Assessment of the influence of pharmacotherapy on the SNS by sensitive techniques may allow the tailoring of drug treatment for different patient populations in the future.

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