Excess Catecholamine Syndrome and Cardiovascular Risk

Heinz Rupp

Molecular Cardiology Laboratory

Department of Internal Medicine and Cardiology

Philipps University of Marburg

Marburg, Germany

Address for correspondence

Heinz Rupp, Ph.D.

Professor of Physiology

Molecular Cardiology Laboratory

Department of Internal Medicine and Cardiology

Karl-von-Frisch-Strasse 1

35033 Marburg

Germany

Tel +49 6421 286 5032

Fax +49 6421 286 8964

E-mail Rupp@mailer.uni-marburg.de

Reduction of arterial high blood pressure is associated with a lower cardiovascular morbidity and mortality. It remains, however, intriguing that the mortality of hypertensives with apparently well controlled blood pressure is higher than in normotensive persons [1]. The question arises, therefore, whether a solely blood pressure oriented therapy is adequate. The need to differentiate antihypertensive drugs is indicated also by the fact that the target high blood pressure is the product of cardiac output and total peripheral resistance. If one could pursue these two factors individually, the time-course of the heterogeneous disorder "essential hypertension" could be analyzed further and a more rational therapeutic approach could be achieved. Antihypertensive drugs have often been rated solely on the outcome of mortality trials with the consequence that the potential of newly developed antihypertensive drugs has been underestimated. Increasing evidence indicates that high blood pressure represents a chronic and slowly progressing disease and should be regarded as a symptom of an underlying complex disorder. It is conceivable that interventions with a lower antihypertensive efficacy can prevent more efficiently end organ lesions. This hypothesis is supported by the observation that antihypertensive therapy has a more pronounced effect on stroke than on coronary heart disease [2]. This "coronary artery disease paradox" is in accordance with the contention that blood pressure lowering may not be sufficient for prevention of certain end organ lesions. The exploration of causes leading to primary hypertension has become particularly relevant since a second class of centrally acting antihypertensive drugs has been developed that lowers sympathetic outflow of the brain without exhibiting the side effects of earlier sympatholytic compounds. Parallel to the development of this class of selective imidazoline-I1 receptor agonists, pathophysiological and psychological studies have led to a further characterization of lifestyle factors that raise sympathetic outflow of the brain. In order to define these pathophysiological states the term "excess catecholamine syndrome" has been used[3,4].

High caloric intake

A caloric intake that is in excess of calories required for physical activity represents the most critical hypertension-promoting lifestyle factor. Since a high proportion of hypertensive persons is overweight, the term overweight hypertension appears more appropriate than "primary hypertension". These considerations are supported by the generally accepted recommendation of weight reduction when high blood pressure has been diagnosed. The blood pressure lowering effect of weight reduction is about 1 mm Hg/kg body weight [5]. We have shown in animal experiments using radio telemetry that an increased caloric intake is associated not only with a higher body weight but also with a parallel rise in heart rate and blood pressure [6,7]. The marked impact of dietary influences is demonstrated also by the recent „Dietary Approaches to Stop Hypertension (DASH) Trial" where a „combination" diet that emphasized fruits, vegetables, and low-fat dairy products provided a significant round-the-clock reduction in blood pressure [8]. It is, therefore, not unexpected that obese persons exhibit a higher risk of death, whereby the obesity-related excess mortality declines, however, with age at all levels of obesity [9]. In view of the many unsuccessful efforts of reducing body weight of overweight persons, the initial rise in body weight should be avoided. It is particularly important to maintain a long-term compliance by providing simple dietary protocols [10]. It is a misconception that disease relevant processes occur only when the body mass index is greater 28. Only approx. 5% of the German population are expected to exhibit a high blood pressure if they had a body mass index of 20. As the constantly increasing proportion of overweight persons over the last fifty years demonstrates, a predisposition for overweight exists while a genetic basis for the observed high incidence of overweight and obesity appears unlikely.

A prerequisite for the manifestation of overweight is a caloric intake that is too high relative to the physical activity. General recommendations regarding the daily caloric intake appear, however, not to be justified, since there is an interindividual variation in food utilization and resting metabolism. If one considers the fact that the incidence of hypertension correlates with the rise in body weight starting with a body mass index of approx. 23, any body weight increase should preferably be prevented and as an adjunctive approach one should rely on pharmacological interventions that counteract changes in the neuroendocrine status of overweight persons. In a set of

experimental and clinical studies it has been shown that overweight persons exhibit a raised activity of the sympathetic nervous system. It was reported by Scherrer et al. [11] that skeletal muscle sympathetic nerve activity correlates closely with body mass index. The increased sympathetic activity is expected to lead initially to hyperkinetic hypertension that is characterized by an increased heart rate and blood pressure. A close relationship between body weight increase and rise in sympathetic activity can be deduced also from the finding that younger hypertensive persons exhibit an increased cardiac output while the peripheral resistance is to a great extent still normal [12,13]. With increasing age, manifestation of high blood pressure occurs that is based on a progressive increase in peripheral resistance and a gradual normalization of cardiac output. Although further studies are needed, it appears that downregulation of ß-adrenergic receptors contributes to the reduced heart rate. Since both an increase in cardiac output and peripheral resistance can lead to high blood pressure, the conventional blood pressure recording does not provide information on this critical time-course of hypertension development. When sympathetic activity is raised over a prolonged period of time, remodeling of resistance vessels occurs leading to a restricted vessel lumen. The hypertrophy of the vascular wall results in an overproportional constriction of the vessel lumen and thereby amplifies the peripheral resistance [14]. This structural remodeling of the resistance vessels also contributes to manifestation of high blood pressure.

High sodium/potassium ratio

An increased caloric intake is frequently associated with a raised salt consumption. The influence of the dietary sodium/potassium ratio for manifestation of high blood pressure remained, however, controversial. It was unresolved whether within a given population an increased sodium intake leads to a statistically provable blood pressure rise [15]. It is expected that the DASH Trial will provide further clarification of this important issue. The preference of food with a low sodium/potassium ratio and a low caloric density is nevertheless to be recommended [16]. It is also suggested to reduce the salt intake from the usual 150-200 mmol/day of western countries to at least 100 mmol/day that does not impair of taste.

There is accumulating evidence that a high sodium intake increases sympathetic outflow of the brain originating from medullary centers [17]. Thus, a too

high calorie and sodium intake accelerate by a common final pathway the manifestation of high blood pressure. In accordance, saccharose intake raised blood pressure in spontaneously hypertensive rats when combined with an increased salt intake [18]. For western industrialized societies it was, therefore, concluded that the relatively high mono/disaccharide consumption in combination with a high salt intake can raise blood pressure [18]. The permissive effect of dietary salt is reflected also in the observation that an increased sodium intake raises blood pressure if a genetic predisposition of e.g. Dahl salt sensitive rats with raised sympathetic outflow is present [19,20].

High alcohol consumption

Alcohol has various adverse central effects and raises sympathetic nervous system activity. As in the case of overweight persons, the enhanced peripheral sympathetic activity can be monitored by measuring nerve action potentials with intraneuronal microelectrodes. Intravenous infusion of alcohol led to a progressive increase of sympathetic nerve discharge, increased plasma catecholamines and raised arterial blood pressure [21]. The study of Scherrer et al. [21] showed that alcohol causes a drastic increase in postganglionic sympathetic outflow. Compared with earlier investigations on oral alcohol intake, any alcohol-induced gastric and insulin-mediated effects could be excluded. The study also showed that alcohol has additional direct peripheral effects that reduce total peripheral resistance and blood pressure during acute administration. The mechanisms underlying the vasodilating effect of alcohol remain unclear. It is also not known why alcohol exhibits a vasodilating effect in the heart but a vasoconstricting action in the vasculature of skeletal muscle [22]. In the intact organism, the acute vasodilating component of alcohol is counteracted by the vasoconstriction arising from sympathetic activation. It should be mentioned that in treated hypertensive persons a moderate consumption of alcohol reduced the cardiovascular risk [23]. If one considers that alcohol has a blood pressure-raising effect this potentially protective action appears overrated [24]. It should also be noted that sudden cardiac death has been associated with a high alcohol consumption particularly during binge drinking [25].

Alcohol was also found to reduce the sensitivity of baroreceptor reflexes. Baro- and pressoreceptors in the aortic arch and carotid sinus adapt to a raised

blood pressure during the development of hypertension. This favors manifestation of hypertension and is accompanied by an increased sympathetic outflow of the brain as well as a reduced activity of the parasympathetic nervous system. The attenuation of baroreceptor reflexes by oral administration of alcohol has been demonstrated in various species [26-28].

The central action of alcohol seems to be limited not only to the Nucleus tractus solitarrii (NTS) but involves also the rostral ventrolateral medulla (RVLM) that has an important integrative role in controlling sympathetic outflow modulated by the baroreceptor reflex [29]. Starting from the NTS, excitatory neurons project to the caudal ventrolateral medulla followed by inhibitory projections to the RVLM. Baroreceptor stimulation leads thereby to inhibition of sympathetic outflow. For the NTS, it was shown that alcohol antagonizes N-methyl-D-aspartate receptors, thus diminishing influences from baroreceptor reflexes [30]. Furthermore, alcohol attenuates baroreflex bradycardia by amplifying the effect of gamma-aminobutyric acid in the medullar dorsal vagus complex [31]. Alcohol is known to increase the secretion of corticotropin-releasing-hormone. The increased cortisol release [32] is expected to raise blood pressure and sympathetic activity [33].

Psychosocial stress

Accumulating evidence points to a crucial influence of psychosocial loads on cardiovascular mortality and morbidity. Of particular interest became the "effort reward imbalance" model [34-38]. The focus of this model is on occupational life where high-cost/low-gain conditions are considered particularly stressful [34]. Variables measuring low reward in terms of low status control (e.g. lack of promotion prospects, job insecurity) in association with high extrinsic (e.g. work pressure) or intrinsic (personal coping pattern, e.g. high need for control) effort independently predicted new cardiovascular events in a prospective study on blue-collar men [34]. Furthermore, these variables partly explained the prevalence of cardiovascular risk factors (hypertension, atherogenic lipids) in two independent studies [34]. For coronary heart disease, an imbalance between personal efforts (competitiveness, work-related overcommitment and hostility) and rewards (poor promotion prospects and a blocked career) was associated with a 2.15-fold higher risk [38].

The studies on the hypertensive effect of psychosocial loads demonstrate that

the pathogenesis of primary hypertension is multifactorial and remains ill-defined. As regards behavior therapy in hypertensive persons suffering from psychological stress, several controlled studies involving stress relief techniques [39,40] did not provide generally accepted recommendations. The question arises also whether other complex pathophysiological effects of psychosocial loads can be influenced or ameliorated by current behavior and relaxation techniques.

It should also be clarified to what extent psychosocial loads re-enforce an unfavourable dietary profile. Contrary to nutrition influences, psychosocial risk factors are difficult to model in animal experiments and molecular events remain, therefore, ill-defined. Among the various experimental stress models [41,42] the so-called "schedule induced stress" appears to be particularly useful [43,44]. Rats were fed 6 - 8 h 35 mg food pellets every 80 seconds. To ensure that food pellets were consumed individually, rats received a calorie-reduced diet. This type of psychological stress led to a rise in systolic blood pressure in salt-loaded rats [45]. Radio telemetric short-term investigations have shown that the blood lowering effect of an omega-3 fatty acid diet was blunted by this schedule-induced stress [44]. Since "schedule induced stress" reduced selectively the function of sarcoplasmic reticulum [46] which is crucial for the intracellular calcium homeostasis of heart muscle, one can infer oxidative damage resulting from released catecholamines. In this respect it should also be mentioned that blood pressure increased after enforced chronic running in SHR [47] arising most probably from the complex coping strategy while spontaneous running lowered the high blood pressure [47].

Excess catecholamines and the metabolic syndrome

The pathophysiology of hypertension is complicated by metabolic disturbances involving a reduced insulin sensitivity of the body. The insulin resistance requires compensatory hyperinsulinemia that is often accompanied by hypertriglyceridemia and an increased sodium and uric acid absorption of the kidney. These symptoms have been referred to as "syndrome X" or "metabolic syndrome". Characteristics of the syndrome X are hypertension, insulin resistance, hyperinsulinemia, hypertriglyceridemia, hyperuricemia and reduced HDL-cholesterol [48]. The PROCAM study has shown [49,50] that parallel to the increase in body mass index those parameters are raised that have been summarized under the term "metabolic

syndrome". For these characteristic changes, the term "prosperity syndrome" has been coined already in the sixties [51].

A prolonged hypercaloric nutrition associated with inadequate physical activity is expected to result in insulin resistance and hyperinsulinemia. An increased sympathetic activity can amplify insulin resistance involving several mechanisms (Fig. 1). The glucose output of the liver is increased while insulin secretion of the pancreatic beta-cells becomes diminished. This mechanism guarantees the supply of glucose for the insulin-independent glucose utilization by the brain under conditions of food shortage. The lipolysis induced increase in plasma fatty acids causes at the same time a further reduction in peripheral glucose utilization ("Randle cycle") [52]. Chronic modifications in the morphology of skeletal muscle contribute to a further reduction in insulin sensitivity. A reduction of the capillary density occurs, i.e. rarefaction that is associated with increased diffusion distances for oxygen and probably also glucose [53] as observed after a chronic ß2-adrenergic stimulation. Furthermore, at the expense of slow-type muscle fibers the proportion of fast-type fibers with a reduced glucose oxidation [54] is increased. Although the ensuing hyperinsulinemia can initially prevent the occurrence of hyperglycemia, this state can frequently not be maintained and leads to established diabetes mellitus type II. For managing hyperglycemia, orally acting antidiabetic drugs are widely used that increase insulin release. Increased insulin levels are, however, associated with the risk that non insulin-resistant organs are exposed to high insulin levels with various consecutive unfavorable processes. Among the consequences are an increased triglyceride and LDL synthesis of the liver and increased absorption of sodium and uric acid by the kidney. Whether the sympathetic nervous system activity is stimulated by chronically increased insulin levels remains controversial [55].

Excess catecholamines and the renin angiotensin aldosterone system
Although the renin angiotensin aldosterone system (RAAS) is crucially involved in maintaining hypertension, a raised sympathetic activity has an important influence on initiating the activation of the RAAS (Fig. 2). Thus, during malignant hypertension as a consequence of kidney injury renin is released that leads to the formation of angiotensin II and aldosterone. Even under these conditions, a ß-blockade reduced renin secretion and lowered blood pressure. The importance of the sympathetic

nervous system is demonstrated also by the finding that renin secretion was strongly reduced after anesthesia-mediated inhibition of sympathetic projections of the spinal cord although perfusion of the kidney was reduced [56]. It has also been pointed out that a healthy kidney releases only minimal amounts of renin [57]. An increased sympathetic outflow of the brain is thus expected to raise the release and to enhance the formation of angiotensin II. Angiotensin II promotes not only noradrenaline release from sympathetic nerve endings but appears to stimulate autonomous centers in the brain which further raise sympathetic outflow. In addition, angiotensin II stimulates the production of aldosterone which causes sodium retention. An increased sodium level increases the reactivity of smooth muscle and enhances also sympathetic nervous system activity. It can thus be concluded that several re-enforcing mechanisms exist which favor the manifestation of hypertension (Fig. 3).

Excess catecholamines and the brain

Most lifestyle factors that represent a cardiovascular risk lead to an increase of sympathetic outflow of the brain. For interfering with an inappropriate sympathetic outflow, various pharmacological targets exist which differ, however, with respect to their side effects. Of recent interest became imidazoline I1-receptors in the RVLM. The neurons of the RVLM interact with the NTS and are responsible also for the phasic excitation of preganglionic neurons in the intermediolateral horn of the spinal cord and have been identified as the "vasomotor center" of the medulla [58]. RVLM neurons are tonically active and unload synchronously to the heart cycle and are also involved in chemoreceptor reflexes [58]. Neurons of the RVLM are crucially involved in the maintenance of normal blood pressure. Since projections occur between neurons of the NTS and higher centers of the brain, the RVLM can also be seen as a center which is involved in the integration of various physiological inputs.

Lowering of excess catecholamines as therapeutic target

Physical exercise lowers sympathetic activity and is associated with an increased parasympathetic tone. Endurance training also leads to an increased capillary density [59] and improves insulin sensitivity [60]. The question arises, therefore, whether certain aspects of physical activity can be mimicked by pharmacological approaches. Interventions would be of interest that reduce an inadequately high sympathetic

outflow of the brain. Although the lowering of sympathetic outflow is a long known therapeutic principle, the use of centrally acting sympatholytic antihypertensives of the "first generation" has been limited due their side effects. Since hypercaloric nutrition, alcohol, high sodium/potassium ratio and psychosocial stress increase the sympathetic outflow of the brain, the question arises whether drugs are available which reduce sympathetic outflow of the brain with side effects comparable to those of widely used antihypertensives. Antisympathotonic drugs of the "first generation", like alpha-methyldopa, guanfacine, guanabenz and clonidine reduced peripheral sympathetic activity and plasma renin activity but were associated with pronounced alpha2-receptor-mediated side effects, such as sedation and "rebound hypertension" after drug withdrawal. The discovery of I1-imidazoline receptors in the RVLM that differ from alpha2-receptors has led to centrally acting drugs of the "2nd generation" [61]. The drug with the highest selectivity for I1-imidazoline receptors is moxonidine [61]. The ratio of 10:1 of I1-imidazoline receptors to alpha-2 receptors in the RVLM underlines the importance of I1-imidazoline receptor-selective antihypertensive drugs. Our own studies in SHR showed that moxonidine does not induce „rebound hypertension" after drug withdrawal [6]. In accordance, clinical data demonstrated a low incidence of sedation and the absence of a significant blood pressure rise after discontinuation of moxonidine [61].

Since the neurons of the RVLM integrate diverse influences from higher centers, it can be expected that also the increase of sympathetic outflow due to hypercaloric nutrition, increased salt intake, alcohol and psychosocial stress can be attenuated at this level. Although not all projections have been identified and I1-imidazoline receptors have not yet been cloned, the pathophysiological evidence supports the use of moxonidine for attenuating a high sympathetic outflow. This intervention is expected to reduce not only high blood pressure but to have additional beneficial effects on various cardiovascular risk factors related to a high sympathetic activity. A recently identified example is the effect of moxonidine on insulin sensitivity. Moxonidine improved the insulin sensitivity in insulin-resistant obese patients with mild hypertension when compared to placebo [62-64]. The insulin response to glucose stimulation was unaffected [62-64]. It remains to be shown whether other unfavorable processes postulated from pathophysiological considerations are also affected by moxonidine.

Excess catecholamines: reflex stimulation of the sympathetic nervous system by antihypertensive drugs

Since effects of the sympathetic nervous system are mediated by various alpha and beta receptor subtypes [65] it appears unlikely that an increased adrenergic activity can be completely counteracted by drugs blocking specific adrenergic receptors. Since catecholamines affect expression of a multitude of genes via phosphorylation of cyclic AMP responsive elements, an unbalanced gene expression is likely contributing to a remodeling of tissues. It appears, therefore, important to prevent the occurrence of excess catecholamines. In contrast to the effect of moxonidine, most beta- and alpha-adrenergic receptor blockers lead to a reflex rise of sympathetic activity and raise plasma catecholamine levels thereby favoring radical-related cell injury.

In summary, it appears that a therapy targeted solely at lowering of high blood pressure does not take into account all pathophysiological consequences associated with hypertension arising from a westernized lifestyle. Based solely on blood pressure lowering, a preference for imidazoline agonists would be difficult to justify since their antihypertensive effect is comparable to that of drugs of the class of diuretics, alpha-receptor blockers, beta-receptor blockers, calcium antagonists and ACE inhibitors [66]. If one considers, however, that a high blood pressure can be only one of several deleterious consequences of an inadequately high catecholamine influence, it can be postulated that an intervention that reduces sympathetic outflow of the brain has various beneficial effects that extend beyond blood pressure control.

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Legends

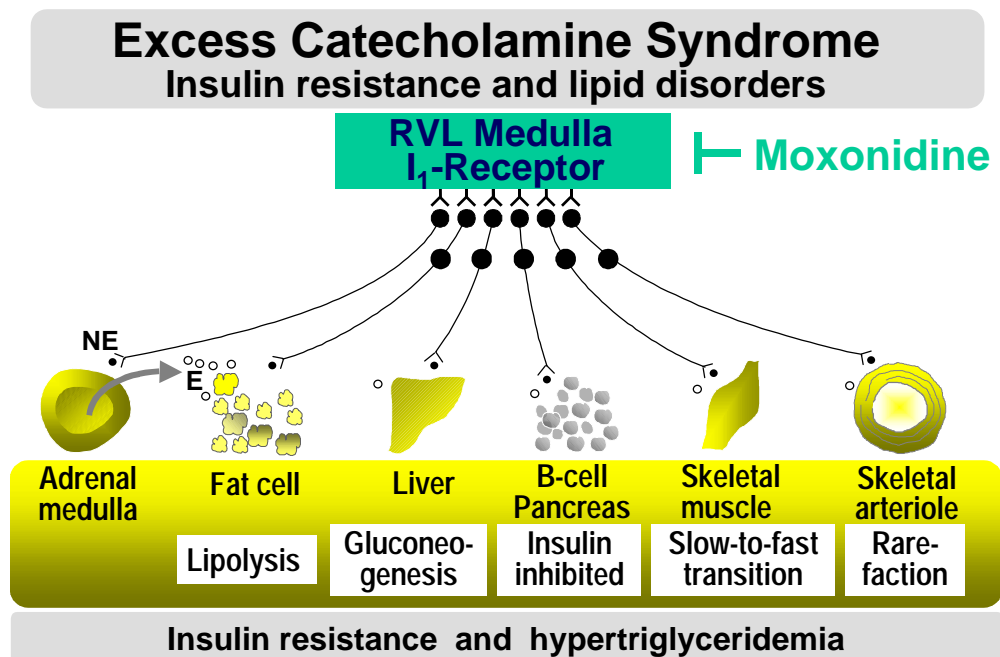Figure 1. Metabolic consequences of excess catecholamines.

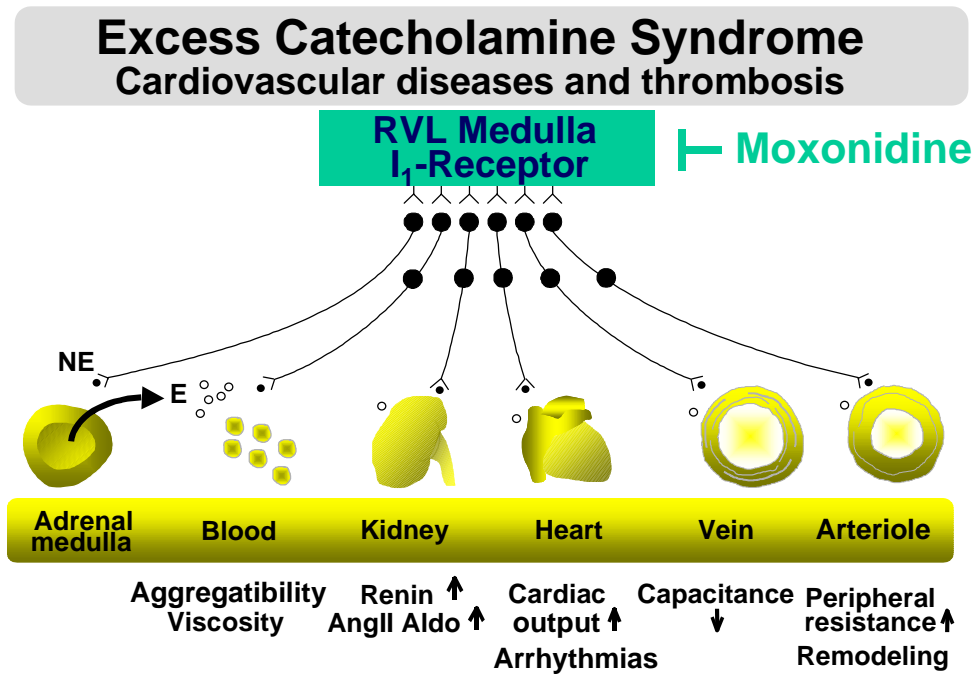Figure 2. Cardiovascular consequences of excess catecholamines.

Figure 3. Re-enforcing mechanisms triggered by an increased sympathetic outflow of the brain.