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Chronic stress in the development of essential hypertension, role of rilmenidine in the treatment of stress induced hypertension

Gábor Simonyi

Metabolic Center, Szent Imre University Teaching Hospital, Budapest, Hungary

Email address:
bmbel3@gmail.com

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Abstract: Hypertension is an independent risk factor of cardiovascular diseases. Several factors contribute to its development, including chronic stress, which may induce hypertension by increasing sympathetic activity. The signs of increasing sympathetic activity can be primarily detected in the initial phase of hypertension, which is characterized by the increase in cardiac output. In addition to the hemodynamic consequences (increase in cardiac output, tachycardia, coronary vasoconstriction, proarrhythmia), the increase in sympathetic activity has many harmful effects. Numerous metabolic (insulin resistance, dyslipidemia), structural and trophic effects (endothelial dysfunction, vascular hypertrophy, myocardial hypertrophy), as well as thrombotic and humoral processes (procoagulation, enhancement of thrombocyte aggregation, sodium retention, activation of the renin-angiotensin-aldosterone axis) may develop and consequently damage body functions at many targets. Several different antihypertensive drug classes are available for reducing increased sympathetic activity, including peripheral alpha and beta blockers and compounds with central effects. First generation antihypertensive drugs with central mechanisms of action (e.g. clonidine, guanfacine, alpha-methyldopa) is currently rarely administered and only for a few indications as they have a significant adverse events profile. Among second generation compounds with central effects, rilmenidine stimulates imidazoline-1 receptors and thus beneficially influences mild or moderate hypertension that involves enhanced sympathetic nervous system activity.

Keywords: Sympathetic Nervous System, Stress, Hypertension, Rilmenidine

1. Introduction

Hypertension is one of the most common diseases in the World. It is well known that high blood pressure is one of the main risk factors of cardiovascular diseases and the latter have an indisputable contribution to morbidity and mortality. The role of hypertension in increasing the risk of mortality and also in causing disability is significant[1].

As known, hypertension is a polygenic and complex disease with an increasing incidence worldwide. According to the surveys, hypertension affects approximately 25% of the adult population worldwide[2].

According to the results of epidemiological studies, the incidence of hypertension is higher in Europe than that of North America[3]. As of the forecasts, considering the current trends, the incidence of hypertension might increase to 30% within the adult population in the next 20 years, which means approximately 1.5 billion patients suffering from hypertension.

2. Hypertension and the Sympathetic Nervous System

The very complex pathogenesis of hypertension includes endothelial dysfunction, enhanced renin-angiotensin-aldosterone system (RAAS) activity and the increased functioning of the sympathetic nervous system (SNS) as major factors among others[4].

SNS participates in almost all physiological processes and is thus responsible for responses to physiological stress as well. As a result of different factors, sympathetic nervous system may regulate blood pressure in the short and long term as well. SNS activity has an impact on the organs participating in the regulation of blood pressure

such as the kidneys, the heart, the adrenal glands and the vascular system[5] (Figure 1.).

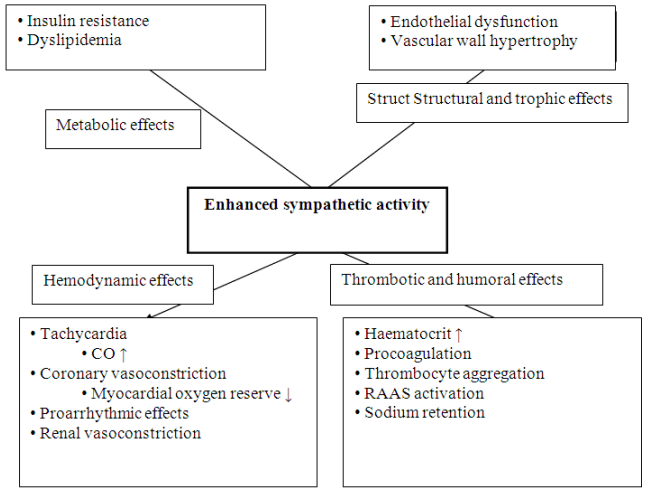

Figure 1. *Metabolic, structural, hemodynamic, humoral and thrombotic effects of increased sympathetic activity.*

Less known, but important is the positive correlation between SNS activity and the body mass index (BMI). SNS hyperactivity increases heart rate and peripheral vascular resistance and as a result blood pressure. According to Landsberg, enhanced sympathetic activity induced by obesity is a compensation mechanism, by which increasing metabolism at rest could decrease body mass. On the other hand, hypertension is the price of the above metabolic effect, which is induced by the enhanced activity of the sympathetic nervous system[6].

3. Sympathetic Nervous System and Blood Pressure

Stress reaction was essential for survival throughout phylogeny, as it aided self-defense against dangerous situations and environmental effects. Its effect is well-known, as it enables survival in critical situations (fight or flight response, Cannon emergency reaction). Stress induces hormonal and neural processes among which sympathetic nervous system effects are dominating. Acute stress such as fear or anxiety usually results in a transitory, rapid and significant increase in blood pressure and heart rate.

The causal relation between essential hypertension and enhanced sympathetic nervous system activity is well-known, and develops through several mechanisms. The rostral ventrolateral nucleus in the medulla oblongata (RVLM) is the main center of blood pressure regulation, known also as the vasomotor center. The functioning of the sympathetic nervous system is mainly influenced by emotions and stress. Many other structures (nucleus ambiguus, hypothalamic regions) also contribute to sympathetic activity. It is well-known that sympathetic activity has a typical circadian rhythm.

The enhancement of the vagal effect and reduction of sympathetic activity is typical during sleep, while sympathetic nervous system activity increases gradually after waking up, characterized by increasing heart rate, blood pressure and body temperature. The increased incidence of vascular events (myocardial infarct, sudden death) may be explained by this enhanced sympathetic activity in the mornings. Seasonal variations of sympathetic activity are also characteristic (Figure 2.).

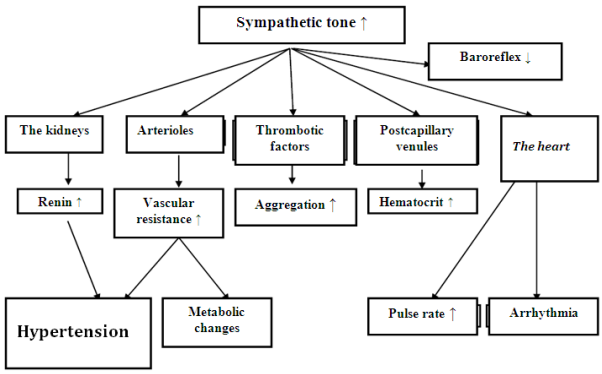

Figure 2. *Consequences of increased sympathetic tone.*

4. Modulating Sympathetic Activity

Sympathetic activity of the central nervous system may be influenced by many chemical agents acting on several receptors. One of these is the alpha-2 receptor with a preganglionic location. Its stimulation decreases sympathetic tone and thus blood pressure. On the other hand, stimulation of enhance sympathetic tone. Therefore, contrary to alpha-2 receptors, blocking agents acting on beta-2 receptors and angiotensin II receptors are needed for blood pressure reduction.

During the last decades, central antihypertensive drugs such as clonidine, guanfacine and alpha-methyldopa have been widely used. As a result of their adverse events, their prescription gradually decreased and they are currently not recommended as first line treatment.

Concerning regulation of blood pressure, imidazoline-1 receptor is probably the most important. Stimulation of

imidazoline receptors in the central nervous system (in particular in the rostral ventrolateral medulla oblongata) results in peripheral vasodilatation[7] (Figure 3.).

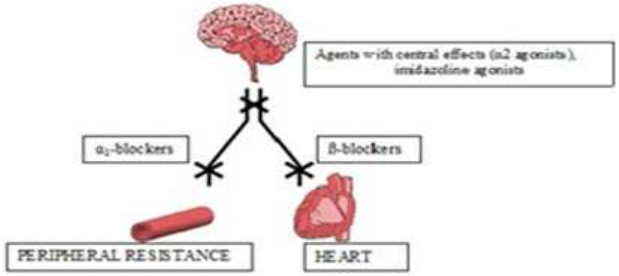

Figure 3. *Central and peripheral inhibition of sympathetic tone*

Drugs that bind to this receptor (rilmenidine, moxonidine and partly clonidine) reduce peripheral resistance by stimulating it (agonists effect) and without significantly changing cardiac output.

4.1. Acute Stress and Panic Disorders

Patients with hypertension often experience palpitation, headache or vertigo, symptoms that may also indicate psychic tension. Panic attacks occur frequently in the population and in hypertensive patients in particular. Panic attacks are characterized by the sudden increase of blood pressure and heart rate.

4.2. Chronic Stress and Hypertension

The role of chronic stress in the development of hypertension is less clear, which is in part due to the fact that chronic stress is quite hard to define. Experiencing stress is highly subjective and while a factor may causes stress to someone, it might not influence an other person.

We know that long-lasting enhancement of sympathetic nervous system activity involves many cardiovascular consequences, including hypertension, heart failure, myocardial ischemia, malignant arrhythmias, etc.[8].

Enhanced SNS activity is also responsible for the development of cardiovascular remodeling, including left ventricular hypertrophy and hypertrophy of the smooth muscles in blood vessels[9, 10], and may also induce life-threatening ventricular tachycardias[11]. The imbalance of the autonomic nervous system characterized by enhanced sympathetic activity and reduced vagal tone is an independent and major risk factor of cardiovascular events, including sudden death[12].

4.3. Centrally Acting Blood Pressure Lowering Agents

Influencing the predominance of sympathetic nervous system by medications potentially protects against the above harmful consequences. SNS activity may also be modulated by acting on the central nervous system, an effect which was typical of the first generation antihypertensive drugs of central acting mechanism, such as clonidine, which proved to be an effective sympatholytic agent[13]. Clonidine blocks sympathoexcitatory neurons in the ventrolateral medulla oblongata by acting on the alpha-2 adrenergic receptors. It is to be noted that the administration of drugs belonging to this class often involves adverse central nervous system events such as sedation or dry mouth as a result of which their clinical use was reduced.

Rilmenidine is second generation central drug the administration of which is safe at a daily dose of 1 to 2 mg and free from the above adverse events. In addition to its antihypertensive effects it has also an antiarrhythmic and anti-ischemic effect in arrhythmias of central origin[13]. These effects were proved in animal models: rilmenidine reduced severe ventricular tachyarrhythmias of central origin by decreasing the level of sympathetic activity by acting on the central imidazoline receptors[14, 15, 16, 17].

Enhanced sympathetic activity that usually develops as a result of mental and psychic stress increases mortality in myocardial infarcts and the risk of arrhythmias in patients suffering from ischemic heart diseases[18].

As a consequence of the above, decreasing sympathetic activity may have a beneficial effect also on the above conditions[19]. A study compared atenolol with rilmenidine to evaluate their effects on mental and psychic stress in hypertensive patients. The results showed that their antihypertensive efficacy was similar at rest, under mental stress and physical load[19].

Castro et al. found that mental stress induced elevations of blood pressure and heart rate may be prevented by one single administration of half of the smallest antihypertensive dose of rilmenidine (0.5 mg)[20].

5. Environmental Impacts and Stress

There is evidence that blood pressure increases in those having deteriorated and poor living conditions and of those moving to a less developed area. Personality (such as a malicious person or someone who is constantly in a hurry) is also a major factor influencing the responses given to environmental impacts. Surveys showed that blood pressure increased all over the United States by 2 mmHg after the terrorist attacks on September 11th, 2001 and it remained elevated until the end of September[21].

6. Employment Load

Employment load is the form of chronic stress that has been subject to the most studies among all. In men with great employment load, increased blood pressure was recorded not only in the place of work but also at home and during sleep showing that chronic stress sets daily blood pressure profile higher, which can be justified by 24-hour blood pressure monitoring. In women, these effects were less significant[22].

7. Determination of Sympathetic and Parasympathetic Predominance of the Patients

In everyday practice, it is a major question to determine whether the sympathetic tone of the patient is increased or not. First of all, phaeochromocytoma and hyperthyreosis must be excluded. The first phase of hypertension is usually characterized by enhanced sympathetic nervous system activity, which causes hyperkinetic circulation and increased cardiac output.

Opavsky et al.[23] elaborated a test that is easy to fulfill in everyday practice to determine whether the patient suffers from sympathicotonia or not (Table 1.). The questionnaire was constructed on the basis of the typical signs and

symptoms of the pathological autonomic nervous system effects (sympathicotonia or vagotonia). The summary of the answers shows the category which the patient mainly belongs to. The result is of course not absolute but may be very helpful in the everyday evaluation of the patient's status of the autonomic nervous system, contributing to the selection of the right medication[4].

Table 1. *Questionnaire for assessing autonomic functions.*

The hands of the patient are usually:	**[A] cold**	**[B] warm**
The mouth of the patient:	[A] is often dry	[B] usually produces lots of saliva
The blood pressure of the patient is	[A] higher	[B] lower
The skin of the patient is rather	[A] dry	[B] sweaty
The patient	[A] loses weight easily	[B] puts on weight easily
Collapses take place	[A] never or rarely	[B] repeatedly
The patient has a predisposition to	[A] constipation	[B] diarrhea
When nervous, the hands of the patient	[A] shake	[B] do not shake
The patient experiences palpitation:	[A] often	[B] never
The patient is rather	[A] pale	[B] flushed
The patient experiences	[A] tension	[B] calmness
After being anxious, the patient experiences	[A] lack of appetite	[B] greater appetite
The patient	[A] has difficulties to fall asleep	[B] falls asleep easily
The patient's eyes	[A] produce tears very rarely	[B] produce tears often
The patient deals with high temperature	[A] badly	[B] easily
The patient deals with low temperature	[A] easily	[B] badly

The questionnaire concerns the easily identifiable characteristics that help to distinguish the predominance of sympathetic nervous system activity from predominance of parasympathetic activity on physiological and/or pharmacological grounds. Predominance if the Answers: A answers– predominance of the sympathetic nervous system (……. answers) B answers– predominance of the parasympathetic nervous system (……. answers) Answers marked by "A" show the predominance of sympathetic effects, while answers marked by "B" show the predominance of parasympathetic effects.

8. Medication Alternatives in the Treatment if Hypertension with Sympathicotonia

The second generation drug of central mechanism of action, rilmenidine (an I1 receptor agonist) efficiently reduces sympathetic nervous system activity in a dose-dependent manner by acting on imidazoline-1 receptors in the brainstem, on the periphery and in the kidneys. Therefore, it reduces both systolic and diastolic blood pressure for a 24-hour period (Figure 4.).

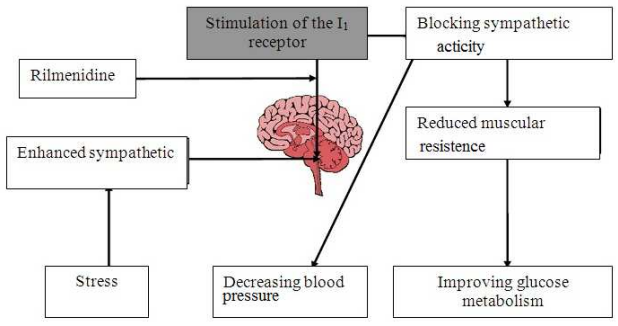

Figure 4. *Effect of rilmenidine on enhanced sympathetic activity induced by stress.*

Rilmenidine maintains its antihypertensive effect by decreasing total peripheral resistance while cardiac output remains unchanged. It does not cause any changes in cardiac muscle contractility, neither does it induce orthostatic hypotension in the elderly or have any impacts on the load-dependent change of heart rate.

In an earlier prospective study were involved 47 obese patients suffering from mild or moderate hypertension. The following parameters were investigated: ambulatory blood pressure monitoring parameters, heart rate, serum cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and serum glucose levels. Then patients were treated with 1 mg rilmenidine once daily. The doses of rilmenidine from 1 mg/day to 2 mg /day was elevated when the blood pressure did not fall below 140/90 mmHg. After 3 months were found the following: heart rate reached significant reduction at month 3, but in clinical terms it was only a modest decrease. The study has found that the circadian rhythm of blood pressure almost entirely normalized in non-dipper patients at month 3. The metabolic parameters (lipids, uric acid, and serum glucose) improved but changes were not statistically significant in this short period[24].

9. Conclusion

Chronic stress can contribute to the development of hypertension by enhancing sympathetic nervous system activity and thus causing pathological effects. Symptoms of increased sympathetic activity can primarily be observed during the initial stage of hypertension. Several drug classes with either central or peripheral mechanisms of action have been developed to reduce such increased sympathetic tone. Due to their adverse effects, first generation agents with central nervous system targets have

been neglected in everyday practice. Rilmenidine, a second generation imidazoline-1 receptor agonist can be effectively used without marked side effects in mild or modest hypertension in cases when signs of enhanced sympathetic activity can be observed.

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