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Research Article

Pentoxifylline treatment enhances antihypertensive activity of captopril through hemorheological improvement in spontaneously hypertensive rats during development of arterial hypertension

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Abstract

The rheological properties of blood play a significant role in the onset and progression of arterial hypertension. The aim of our work was to evaluate the effect of the angiotensin-converting enzyme inhibitor captopril (20 mg/kg/d), pentoxifylline (PTX; 100 mg/kg/d), and the combination of captopril + PTX (20 + 100 mg/kg/d) on the hemodynamic and hemorheological parameters in spontaneously hypertensive rats (SHRs) during the development of arterial hypertension. In the group of animals that received captopril, the mean arterial pressure (MAP) was significantly lower by 30% due to a decrease in cardiac output of 23% and in total peripheral resistance (TPR) of 26% compared with the control group, whereas blood viscosity did not change significantly. PTX-treated SHRs had significantly lower MAP and TPR (by 19% and 31%, respectively) and blood viscosity (by 4%–6%) and a higher erythrocyte deformability index (by 1.5%–2%) than the control group. In the group of animals that received captopril + PTX, MAP and TPR were significantly lower, by 41% and 46%, than those in the control group, and by 16% and 27% than those in the captopril group. The combination of the angiotensin-converting enzyme inhibitor captopril and the hemorheological agent PTX, affecting various systems that are involved in blood pressure regulation, exhibits synergism and prevents an increase in arterial blood pressure during the development of arterial hypertension in SHRs (ie, from 5 to 11 weeks of life). J Am Soc Hypertens 2017;■(■):1–10.

Keywords: Blood pressure; blood viscosity; RBC aggregability; RBC deformability.

Introduction

To achieve target blood pressure during the treatment of arterial hypertension (HT), most patients require the administration of at least two medications.[1] The efficiency of using combinations of two drugs, for example, an angiotensin-converting enzyme (ACE) inhibitor and a thiazide diuretic, a calcium antagonist and an angiotensin receptor blocker, or a thiazine diuretic and an angiotensin receptor blocker, has been proved. Typically, these are combinations of drugs acting on various systems that are involved in the regulation of blood pressure and therefore exhibit synergism in reducing arterial pressure.[2]

The effect of modern antihypertensive drugs is focused primarily on reducing the work of the heart and lowering the peripheral vessel tone. However, blood viscosity (BV) is an important component of the total peripheral resistance (TPR) in addition to the peripheral vessel tone.[3] In cases of

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Conflict of interest: None.

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essential HT, an increase in BV can significantly contribute to the increase in TPR and hemodynamic disorder,[4,5] and a pathogenetic link between blood pressure and hemorheological disorders could be conjectured.[6] On the basis of these data, there is an opportunity to lower TPR and arterial pressure with the help of hemorheological agents that reduce BV. However, the classification of antihypertensive drugs contains no group of medications that reduce BV.[2]

Pentoxifylline (PTX) is a methylxanthine derivative that has been used as a hemorheological agent for several decades.[7,8] Because of the abundance of information on this substance, evidence of its clinical efficacy is clearly stronger than that of other drugs with hemorheological action.[9] In our previous study, it was shown that PTX can attenuate hyperviscosity syndrome by improving the microrheology parameters (erythrocyte aggregation and deformability) in spontaneously hypertensive rats (SHRs) with stable HT.[10] However, PTX had no effect on hemodynamic parameters, viz., blood pressure, cardiac output (CO), and TPR. Apparently, one of the explanations for this insufficient effect may be the severity of HT in SHRs that already have a relatively persistent form of the disease at the age of 20 weeks.[11] It is a well-established fact that magnitude of the hypotensive effect of the antihypertensive drug strongly depends on the phase of HT. For example, an early start of antihypertensive therapy with ACE inhibitors is more effective and leads to the delay and development of mild HT after drug cessation.[12] This can partly be explained by the pronounced vascular and cardiac remodeling, which develops in SHRs rapidly.[13] For this reason, the present study was aimed to investigate the long-term effect of PTX during the development of HT and to evaluate the effectiveness of the combination of the ACE inhibitor captopril and the hemorheological agent PTX in SHRs.

Materials and Methods

Chemicals

Sodium thiopental (Sintez, Russia), captopril (Bristol-Myers Squibb, Australia), and PTX (Trental; Sanofi India Ltd) were used in this study.

Experimental Animals

This study was approved by the Institutional Animal Care and Use Committee at the Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk National Research Medical Center, Russian Academy of Sciences in Tomsk, Russia (protocol no. 72052014). SHRs were obtained from the Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry at the Russian Academy of Sciences (Pushchino, Russia). The rats were housed in groups of five animals per cage (57 × 36 × 20 cm) under standard laboratory conditions (ambient temperature of 22 ± 2°C, relative humidity of 60%, light–dark period of 12/12 h/d) in cages with sawdust bedding, and they were provided with standard rodent feed (PK-120-1; Laboratorsnab Ltd, Russia) and *ad libitum* water access in the Department of Experimental Biomodels at the Goldberg Research Institute of Pharmacology and Regenerative Medicine. The animal care provided here complied with the rules of the Guide for the Care and Use of Laboratory Animals.[14]

Study Design

SHRs (n = 40) that had reached the age of 5 weeks were randomized into four equal groups: the control group, a captopril (20 mg/kg) group, a PTX (100 mg/kg) group, and a captopril + PTX (20 + 100 mg/kg) group. The drugs were administered intragastrically daily in 1% starch mucilage for 6 weeks. The control group received only the vehicle (1% starch mucilage) according to the same schedule. The last drug administration was given 3 hours before measuring the study parameters. The systolic arterial pressure (SAP) was measured in conscious animals. The rats were then anesthetized with sodium thiopental, and the cardiac performance parameters were measured. Then, a Teflon catheter was implanted in the right common carotid artery for registration of the mean arterial pressure (MAP) and blood sampling. Finally, the animals were euthanized in a CO_2 chamber and left ventricular index (ratio left ventricular weight/body weight [LV/BW]) was measured.

Selection of the Captopril and PTX Doses and Duration of the Treatment Course

The choice of the captopril dosage (20 mg/kg/d) and 6-week duration of treatment were based on previous investigations.[15,16] The choice of the PTX dosage (100 mg/kg/d) and 6-week duration of treatment was based on the ability of PTX to exert an antihypertensive effect on the arterial HT models at that dose and duration[17] and on the results of our own study in which PTX was used as a positive control in studying novel substances with hemorheological activity.[18] In clinical settings, sustained therapeutic benefits were achieved when PTX was used as a hemorheological agent for 4–8 weeks and longer in patients with intermittent claudication.[19] Positive changes in the hemorheological profile in patients were observed after 4 weeks of PTX therapy,[20,21] and in SHRs, after 6 weeks of PTX therapy.[22]

Measuring Hemodynamic and Cardiac Parameters

The hemodynamic and cardiac parameters were registered by an MP150 high-speed data acquisition system with matching amplifiers (Biopac Systems, Inc). The SAP was registered in awake rats using an NIBP200A system for noninvasive blood pressure measurement. The stroke volume