Effect of *n*-Tyrosol on Blood Viscosity and Platelet Aggregation

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Experiments on rats showed that *n*-tyrosol limited the increase in blood viscosity during thermal exposure at a shear rate of 5-300 sec^{-1} and inhibited ADP-induced platelet aggregation. The effects of *n*-tyrosol are comparable to that of pentoxyphylline.

Key Words: *n-tyrosol; blood viscosity; platelet aggregation*

Changes in blood rheology united under a common notion of increased blood viscosity syndrome are an important component in the chain of disorders developing in cardiovascular pathology [3,10-12, 14]. In some cases (coronary heart disease, cerebrovascular diseases), therapy aimed at blood viscosity reduction is needed [5,9]. Previous studies validate the search for effective correctors of blood rheology disturbances among bioactive compounds (extracts of ecdysteroid- and flavonoid-containing plants with adaptogenic activity [7]. However, these substances and their complexes are characterized by low water solubility, which prompts the search for prospective hemorheological drugs among water-soluble bioactive compounds, which can become the basis for the development of injection dosage form. Here we studied *n*-tyrosol-4-(2-hydroxyethyl) phenol. *n*-Tyrosol is an aglycone of salidroside, active principle of Rhodiola rosea, a well-known adaptogen [8].

We evaluated the effects of *n*-tyrosol on blood viscosity and platelet aggregation.

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MATERIALS AND METHODS

Experiments were carried out on 33 male Wistar rats (250-300 g). The blood was collected from the common carotid artery under ether narcosis and stabilized with 3.8% sodium citrate (1:9 citrate/blood ratio). The drug effects on blood viscosity were evaluated using the *in vitro* blood hyperviscosity model, reproduced by blood incubation at 44°C. The type and intensity of shifts in individual hemorheological values in this model are comparable to changes developing in some pathological states, which suggests the use of this model for evaluation of hemorheological characteristics of drugs [13].

Blood viscosity was measured on an AKP-2 rotation viscosimeter at shear rates of 5-300 sec^{-1} before and after 60-min incubation of the samples. Platelet-rich and platelet-poor plasma (PRP and PPP, respectively) were prepared and platelet count was evaluated [1]. Platelet count in PRP was standardized by diluting PRP with PPP to a concentration of 400±30 thousand platelets/mm^3 plasma. Platelet aggregation in standardized plasma was induced by ADP in a final concentration of 4×10^{-6} M. The amplitude of platelet aggregation was evaluated in standardized plasma on an AT-02 device, aggregograms were recorded on a Recorder 2210 device.

Pentoxyphylline (PP) was selected as the reference drug. This drug is characterized by antithrombocytic and hemorheological effects: it reduces platelet aggregation, increases erythrocyte deformability, reduces blood viscosity, and improves microcirculation, due to which PP is used in many spheres of medicine for the correction of peripheral circulation disorders [2,4]. The vasodilating effect characteristic of PP can lead to the coronary stealing syndrome, and therefore PP is contraindicated for patients with acute myocardial infarction, unstable angina, and severe heart failure [4]. However, these myocardial diseases are associated with severe disorders in blood rheology, presenting as increased blood viscosity, increased aggregation of blood cells, which requires drug correction of these parameters.

A 5-day course of intragastric treatment with PP and *n*-tyrosol in a dose of 100 mg/kg was used in studies of their effects on blood viscosity. Single intragastric doses of the drugs were used in studies of antithrombocytic activity: 400 mg/kg (PP), 100 mg/kg (*n*-tyrosol). The doses and protocol of drug treatment (single dose or a course) were selected in preliminary experiments.

RESULTS

In controls, the incubation of blood for 60 min at 44°C led to increase of blood viscosity by 24-53% at shear rate values of 5-300 sec^{-1} (Table 1). In rats treated with PP, blood viscosity before incubation was lower than in the controls at shear rates of 50 and 100 sec^{-1} by 10 and 5%, respectively. In this group incubation of blood increased its viscosity by 15-39% for the entire range of shear rates, blood viscosity values being 10-15% lower in comparison with the control. Hence, PP in a dose of 100 mg/kg limited the increase in blood viscosity in an *in vitro* model of blood hyperviscosity.

In rats treated with *n*-tyrosol, blood viscosity before incubation was below the control value (by 5-8% for shear rates of 10-300 sec^{-1}). Incubation at 44°C increased blood viscosity by 16-26%, but this increase was less pronounced than in the control (by 14-23%, Table 1). The intensity of hemorheological effect of *n*-tyrosol was comparable to that of PP.

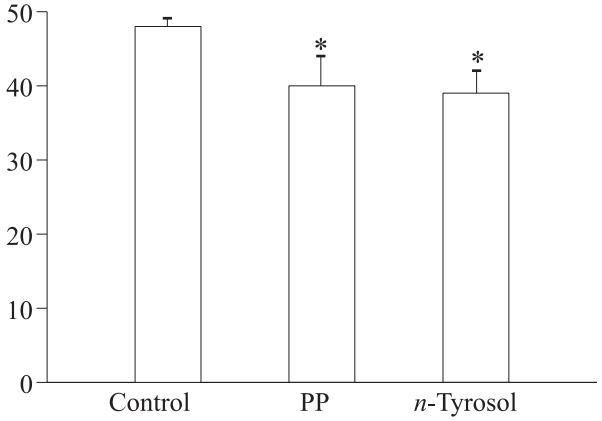

Fig. 1. Effects of PP (400 mg/kg) and *n*-tyrosol (100 mg/kg) on the amplitude of ADP-induced platelet aggregation in rats. *$p<0.05$ compared to the control.

The amplitude of ADP-induced platelet aggregation in standardized plasma of control animals was 48±1%. In rats treated with PP (400 mg/kg) and *n*-tyrosol (100 mg/kg) the amplitude of ADP-induced platelet aggregation was 40±4 and 39±3%, respectively, *i.e.* this parameter was below the control by 17-19% ($p<0.05$; Fig. 1). Hence, *n*-tyrosol administered intragastrically in a single dose of 100 mg/kg exhibited a pronounced antiaggregation effect comparable to the effect of PP in a dose of 400 mg/kg.

The study showed that *n*-tyrosol exhibits pronounced antiaggregant and hemorheological activities. These results and the data on antioxidant effects of *n*-tyrosol [8], essential for its use in myocardial infarction accompanied by oxidative stress [6], prompt the development of a new drug with hemorheological and antithrombocytic activities on the basis of *n*-tyrosol.

TABLE 1. Effects of PP and *n*-Tyrosol on Rat Blood Viscosity (mPa×sec) before and after Incubation at 44°C (*M*±*m*)

Shear rate, sec^{-1}	Control (*n*=5)		PP, 100 mg/kg (*n*=5)		*n*-Tyrosol, 100 mg/kg (*n*=5)	
	before incubation	after incubation	before incubation	after incubation	before incubation	after incubation
5	7.6±0.4	11.7±0.8	7.4±0.4	10.3±0.6	7.2±0.3	9.1±0.4*
10	6.8±0.2	9.7±0.5	6.7±0.3	8.3±0.3*	6.3±0.2*	7.9±0.3*
50	5.0±0.1	6.7±0.3	4.5±0.1*	6.0±0.2*	4.6±0.1*	5.7±0.2*
100	4.4±0.1	5.9±0.2	4.2±0.1*	5.2±0.1*	4.2±0.1*	5.1±0.1*
300	4.1±0.1	5.1±0.2	4.0±0.1	4.6±0.1*	3.8±0.1*	4.4±0.1*

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