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Cardioprotective Effect of *p*-Tyrosol in the Acute Period of Cardiovascular and Cerebral Ischemia

A. P. KRYSIN, I. V. SOROKINA, E. E. SHULTS

Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russia

E-mail: schultz@nioch.nsc.ru

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Abstract

The review examines the pharmacological effects of 4-(hydroxyethyl)phenol (*p*-tyrosol) and its metabolite 2-hydroxytyrosol in acute ischemic disorders of the cardiovascular system and cerebral stroke. The antithrombotic, antioxidant, anti-inflammatory and antiarrhythmic activity of this compound is discussed in detail, its antimicrobial, anti-cancer and anti-metastases effects are noted. *p*-Tyrosol contributes to the creation of a new vascular system in the affected area (neoangiogesis), which leads not only to the restoration of blood supply in the organ affected by ischemia, but also improves geodynamics in the whole body. Studies in animals have proven the effectiveness of parenteral administration of *p*-tyrosol in the preoperative period of exacerbation of heart ischemia and stroke of the brain. The use of this substance leads in most cases to arresting arrhythmias and thrombosis, has a beneficial effect on the nervous system, which generally helps to reduce the area of damage to the heart and other organs with ischemia, significantly increases the number of surviving animals. The positive effect of plants containing *p*-tyrosol and its derivatives on the human cardiovascular system is considered, along with pharmacokinetics and the routes of the introduction of these phenolic compounds into the organism at different stages of ischemia.

Keywords: *p*-tyrosol, 2-hydroxytyrosol, biological activity, global cardiovascular and cerebral ischemia

INTRODUCTION

The problem of the improvement of atherosclerosis treatment is one of the most urgent tasks of pharmacology and cardiology. Atherosclerosis manifests itself clinically as the ischemic heart disease, acute disturbance of cerebral circulation according to the ischemic type, and the diseases of peripheral arteries. The risk factors of the development of cardiovascular diseases are: misbalance between various lipid fractions and generally increased level of lipids in blood, arterial hypertension, smoking, obesity, sedentary way of life, diabetes, male sex, elderly and old age.

Pathological processes connected with atherosclerosis [1, p. 4–13] disturb both the cardiovascular system and the nervous system.

By present, the pathogenic role of an increase in blood viscosity leading to thrombosis has been confirmed experimentally [2]. The authors of [3] stressed the most important ability of 4-(hydroxyethyl)phenol (*p*-tyrosol) to reduce the development of severe neurological disorders accompanying the disease through the reduction of neurological status during the post-ischemic period. According to the data reported in [4], one of the major targets of the activity of *p*-tyrosol in eliminating these disorders is the nitrergic mediator system of the brain.

The diversity of the biological action of *p*-tyrosol on an organism defines the keen interest of researchers and practical doctors treating ischemias of any origin. This compound is an adaptogen, it is distinguished by polyfunctionality and

prevents various pathological states caused by ischemia. At the background of substantial losses of the mankind in the struggle against myocardial infarction [1], definite optimism arises with the hope that *p*-tyrosol cures not only this pathology but also other accompanying diseases: tumours and diabetes (see below), which corresponds to the principles of adaptogenic activity [5].

DIVERSITY OF THE BIOLOGICAL FUNCTIONS OF *p*-TYROSOL

Effect of p-tyrosol on the decrease in the size of necrosis zones

Insufficient blood supply to tissues under the conditions of myocardial ischemia causes hypoxia, oxidative stress, aseptic inflammation and disturbance of microcirculation in the lesion focus, followed by necrosis of cardiomyocytes and disturbance of the contractive and conductive functions of the heart [1]. It should be stressed that this mechanism of the suppression of healthy heart functions with the formation of a zone of necrosis is close, according to the data reported in [1], to the pathologies of other organs, in particular to acute disturbance of brain circulation according to the ischemic type and the diseases affecting peripheral arteries.

In the search for a polyfunctional non-toxic preparation for the treatment of the acute stage of infarction, the team of pharmacologists from Tomsk paid attention to the properties of water-soluble and low-toxic *p*-tyrosol (aurol), or tyrosol, 4-(hydroxyethyl)phenol [6]. The unique properties of *p*-tyrosol may be due to its ability to multiple participation in oxidation-reduction processes in an organism, with the formation of peroxides and radicals at intermediate stages, transformed then into stable oxidation products with diverse biological activity [7]. One of the best studied metabolites of this compound, efficient in its biological properties, is 2-hydroxytyrosol [8, 9].

For prophylaxis of acute manifestation of diseases caused by ischemia, it is proposed to apply the preparations that improve blood microcirculation and at the same time possess antioxidant action, *p*-tyrosol being an example. It was established that one of the most important properties of *p*-tyrosol is the improvement of blood rheology due to an increase in the flexibility of vascular membranes, as well as the membranes of erythrocytes, which are no more destroyed when in thin capillaries. This allows blood supply and maintenance of vitality for tissues in the ischemic region [10].

Attention should be paid to the fact that among preparations allowed in Russia for the treatment of thyroid gland there is Tirosol (the active agent: thiamazole). This mercaptan should not be confused with *p*-tyrosol (aurol): they differ from each other both in the structures and in the action on the organism [11].

Among other medicines, widely used Pentoxyfillin improves blood rheology and renders plasticity to the membranes of erythrocytes, however, its application in the acute period of myocardial infarction does not promote the elimination of oxidative stress and inflammation. Other known preparations (Tanakan, Askovertin) also exhibit the same activity as Pentoxyfillin but are not recommended for application during the acute period of myocardial infarction [10].

In the opinion of the authors of [12], the main task for the first stage of the treatment of acute ischemic disturbances of myocardium and brain is to limit the zone of necrosis with the help of water-soluble antioxidants. One of them is Histochrom – a derivative of pentahydroxynaphthoquinone extracted from sea-urchins, marine invertebrates. This compound possesses a pronounced ability to suppress thrombosis. It may be expected that the multifunctionality of Histochrom is connected first of all with its high antioxidant activity providing high hypocholesteremic effect of the preparation [13].

A decrease in the size of the infarction-affected zone was observed in the clinical tests of Histochrom in patients as a result of 10 days with the injections of the 1 % solution [14]. Official recommendations were elaborated for the application of this preparation for successful therapy of acute myocardial infarction in combination with thrombolytic preparations (antioxidants) [15]. Registration certificate of Histochrom in the State Registry of Pharmaceuticals: R No. 002363/01–2003.

Complivit, a complex of vitamins and antioxidants, has a positive effect on a decrease in thrombocyte aggregation. Its action was studied in the case of obliterating atherosclerosis of blood vessels of the lower limb in patients with the 4th degree ischemia [16].

In the opinion of the authors of [17], a reliable protectant of vessels from thrombosis is the enzymatic antioxidant complex based on superoxide dismutase and catalase which increases the time of vascular occlusion in the model of accelerated thrombosis from 17 (reference) to 55 min.

Antiinflammatory action of p-tyrosol

Efficient inhibition of the oxidative outburst caused by zymosan was observed as a result of the treatment of cell cultures with *p*-tyrosol [18]. It was established that the concentration of *p*-tyrosol necessary for 50 % inhibition of chemiluminescence that accompanies the oxidative inflammation process is 48 mM. The parameters of the anti-inflammatory activity of *p*-tyrosol and its derivatives were established during the subsequent investigation of their pharmacological properties in rats *in vivo*. The efficient concentration of *p*-tyrosol necessary for the inhibition of oxidative stress developing during the acute disturbance of brain circulation according to the ischemic type was 0.5–1.0 mg/kg of body weight [19].

It was shown [20] that, unlike the majority of pharmaceuticals possessing antiinflammatory action but requiring caution in application because of the side ulcerogenic effect, *p*-tyrosol entering the stomach and intestines of animals is non-toxic; it even exhibited definite antiulcer activity, which was established in experiments [20].

The authors of [21] studied the antiinflammatory properties of *p*-tyrosol, 2-hydroxytyrosol and oleuropeine. The clinical studies were carried out *in vivo* in humans and animals. It was determined that the efficiency of these compounds is high and comparable. They are not less efficient than Ibuprofen, a pharmaceutical preparation known in Russia. We also established the efficiency of these compounds in the treatment of oncological diseases of mammary glands, rectum and prostate due to the inhibition of metastasis of tumour cells.

Investigation of the antioxidant activity of p-tyrosol and 2-hydroxytyrosol

Determination of the antioxidant activity in olefins did not reveal any advantage of tyrosol in comparison with other phenol antioxidants. In particular, the induction period of methyl oleate oxidation for antioxidant concentration $2.5 \cdot 10^{-4}$ mol at a temperature of 333 K is 40 min for *p*-tyrosol, 62 min for 2-hydroxytyrosol and 240 min for 4-methyl-2,6-di-*tert*butylphenol. However, *p*-tyrosol and 2-hydroxytyrosol are water-soluble, unlike for the majority of efficient liposoluble antioxidants, and they exhibit comparable antioxidant activity in water. This determines the significance of *p*-tyrosol and its water-soluble derivatives as efficient antioxidants in biological media [22].

Effect of p-tyrosol on the aggregation capacity

The effect of *p*-tyrosol on the aggregation ability of thrombocytes was studied using the model of blood hyperviscosity *in vitro* [23], which allows one to obtain the values of blood viscosity and aggregation of erythrocytes and thrombocytes. Blood viscosity was measured with a rotation viscosimeter AKR-2, spontaneous aggregation of erythrocytes was detected using the syllectometric method, and the amplitude of thrombocyte aggregation was estimated in standardized plasma with AT-2 instrument. It was shown that the most valuable parameter is spontaneous aggregation of erythrocytes as a syndrome of increased blood viscosity in the case of brain ischemia.

A similar effect was observed in the rats after the intake of pentoxyfillin in the dose of 100 mg/kg and in parallel experiment after the intake of *p*-tyrosol in the dose of 20 mg/kg: the amplitude of ADP-induced aggregation of thrombocytes was in each case lower by 36 % than the reference [24]. So, *p*-tyrosol applied in the low dose (20 mg/kg) exhibits the same high *antiaggregation effect* as the known preparation Pentoxyphillin in the concentration of 100 mg/kg. In Russia, *p*-tyrosol was patented as an anti-ischemic drug [25].

Further studies showed that the introduction of *p*-tyrosol in the acute period of myocardial ischemia reduced the development of the rheological disorders of blood: blood viscosity was reliably lower than that for the reference ground of animals. The concentrations of diene and triene conjugates in blood decreased by 16 and 20 %, respectively, which pointed to a decrease in the oxidative stress in the tissues f myocardium in the early post-perfusion period of ischemia development.

It was established that the intravenous introduction of the 1 % physiological solution of *p*-tyrosol causes an increase in the survival of animals after myocardial ischemia with reperfusion, a decrease in the zone of myocardial ischemia and promotes higher integrity of the tissue of myocardium [26]. The reference was mexidol (the active agent: 2-ethyl-6-methyl-3-oxypyridine succinate), which possessed all the above-indicated positive characteristics of *p*-tyrosol but the number of survived animals under the conditions of acute ischemia with the application of Mexidol (80 %) turned out to be noticeably smaller in comparison with *p*-tyrosol under the same conditions (93 %).

The possibility of the enhancement of cardioprotective action of Mexidol by a factor of 2.5 was demonstrated in the case of combined application with the preparation possessing high antioxidant efficiency, SO-4 stabilizer (di[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propyl]disulphide) manufactured at the NIOCh SB RAS. It was demonstrated that the synergism of the joint action of vitamin E, as an antioxidant, with mexidol is also observed by an order of magnitude lower than with SO-4 [27].

Effect of p-tyrosol on thrombosis

It was established in the studies of the effect of *p*-tyrosol on thrombosis that in the group of six rats after the intake of *p*-tyrosol, for four of them the reaction observed for 90 min in response to the application of iron (II) chloride involved a decrease in blood circulation by 60–70 % of the initial level in the absence of vascular occlusion. A complete stop of blood circulation was observed only in two animals.

In the reference group without the introduction of *p*-tyrosol, a complete stop of blood circulation was observed in all animals; compared with the above result, this points to the pronounced capacity of *p*-tyrosol to inhibit thrombosis [26].

It was established in the studies of pharmacotherapy of ischemia in animals in the acute period of myocardial infarction that *p*-tyrosol after intravenous administration rapidly enters the organs with a high level of perfusion: brain, heart and kidneys, where it is detected in 1 min after the introduction. A comparison of the pharmacokinetic parameters of *p*-tyrosol after its introduction in applications in the doses of 50, 100 and 200 mg/kg allows us to conclude that the pharmacokinetics of the preparation is linear within the indicated dose range [27]. By present, pharmacokinetic studies of not only *p*-tyrosol but also its metabolites were carried out [28].

The half-life of *p*-tyrosol was determined to be about 70 min [28]. It is assumed that the major route decreasing its concentration in the organism is its chemical transformation in liver [29].

The effect of p-tyrosol in the treatment of arrhythmia

The disturbance of cardiac rhythm is detected in 90–95 % cases in the patients suffering from heart ischemia. 12 kinds of arrhythmia are known [1, p. 63–84]. Ischemic regions in the heart prevent the regular passage of electric pulses over the conducting system. The time separation of the contraction pulses creates the prerequisites for the seizures of arrhythmia.

Recommendations concerning the treatment of arrhythmia using the preparations are initially evaluated relying on the results of investigation for animals. Occlusion of the coronary artery in the reference group of animals caused the disturbance of the rhythm of heart ventricles in 84 % of the animals, and subsequent reperfusion – up to 89 %. Preliminary introduction of *p*-tyrosol before occlusion in rats in the form of injections of a 1 % aqueous solution caused an increase in the number of animals without arrhythmia and a decrease in the number of animals with pronounced ventricular extrasystoles and fibrillations. *p-Tyrosol reliably caused a decrease in the average level of arrhythmia severity from 2.5 to 1.1 points,* preventing arrhythmia in the most severe form; it promoted conservation of the hearth rate revealing the chronotropic effect, which manifested itself in 34–39 % animals of the reference group [30].

Under the conditions of acute infarction or stroke, it is most reasonable to use the injection of the aqueous solution of *p*-tyrosol. The intravenous introduction of a 1 % aqueous solution of *p*-tyrosol in the dose of 20 mg/kg into rats with myocardial infarction caused a reliable decrease in mortality [31].

Good results in the reduction of acute forms of heart arrhythmia and its complete elimination by 70 % were achieved in the animals by preliminary intravenous injections of the aqueous solution of *p*-tyrosol before the surgical intervention. In this case, the suppression of heart arrhythmia proceeded first of all due to a decrease in the size of the lesion focus. Without the introduction of *p*-tyrosol, the surgical success of arrhythmia suppression was 30 % [30]. It was shown with the model of early occlusion and reperfusion arrhythmia that *p*-tyrosol and the extract of rosewort (*Rhodiola rosea*) exhibit antiarrhythmic activity causing a decrease in the incidence of ventricular tachycardia and fibrillation and an increase in the fraction of animals without ventricular arrhythmias and in general causing a decrease in their severity [31]. In this work, an integrated attempt is made to investigate the mechanism of the action of *p*-tyrosol on the ischemic area. Optimal directions of extensive research were outlined for the reconstruction of the range of the joint action of *p*-tyrosol and its metabolites on the complex of diseases caused by ischemia.

Neoangiogenesis

A decrease of the lesion focus associated with ischemia, recovery of the healthy connective tissue of the affected hearth is the key problem of the therapeutic practice of cardiology.

The ability of *p*-tyrosol to stimulate the formation and growth of new vessels in the region affected by burn was established [32]. This is an essential observation in the model-based investigation of the mechanism of the action of *p*-tyrosol on the ischemic area of the heart. A simple and evident model is also available for investigation: indolent ischemia caused by diabetes at extremeties. The data on the favourable treatment of diabetes with *p*-tyrosol may be useful [33].

The feature of *p*-tyrosol application to treat oncological diseases should be stressed [34], in the course of treatment, attention is paid not only to the antioxidant status of the organism but to the most complex oxidation-reduction status of the organism in general and organs in particular. The level of *p*-tyrosol efficiency as an oncoprotector was stressed in review [35].

Neuroprotective action of p-tyrosol

It is known that the application of neuroleptics enhances the tolerance of brain to global ischemia. The major factors of their action are the conservation of body temperature and a decrease of the size of the lesion zone. The necessity of the search for compounds having integrated action is indicated [36]. These compounds include *p*-tyrosol, which exhibited high efficiency at the level of reference products MK-80/C and CNQX, the structures of which are not presented in [37].

Detailed investigation of the neuroprotective action of *p*-tyrosol was carried out by the authors of [3, 4]. It was established that this action is so substantial that the preparation was recommended for the treatment of schizophrenia and narcotism [4]. Then the work concerning the neuroprotective action of *p*-tyrosol under the conditions modeling the global ischemia (2 h occlusion and 22 h reperfusion of the cerebral artery) in rats followed [38]. The dose-dependent neuroprotective effect of *p*-tyrosol was revealed; it was 64.9 % with the optimal dose of 30 mg/kg. The authors assume to carry out further investigation of the properties of *p*-tyrosol towards the development of a complex pharmaceutical to treat acute ischemia [39]. The recent data also point to the complex neuroprotective action of *p*-tyrosol [2, 38].

Two zones of *p*-tyrosol action are distinguished:

1) low-dose, tablets for oral intake: 8-20 mg per person, causing burst of energy, lucidity of mind, are necessary in the case of physical and mental load, for example, for accident-free driving at night, and 2) high-dose, injection: 100 mg per person and more, providing calming of human functions, deep sleep, which is necessary for survival during the acute period of infarction or stroke [7].

In the acute period of ischemia, the most reasonable injection method of *p*-tyrosol administration is in the physiological solution containing 0.9 % NaCl (in ampoules 5 or 10 mL in volume). The course of treatment with this solution of *p*-tyrosol for the prevention of fatal threats involves 5–10 injections, according to the data submitted by Professor E. A. Krasnov (Israel).

The action of p-tyrosol in the treatment of stroke

A new important feature of *p*-tyrosol was revealed during the treatment of the global ischemia in animals: the ability to recover the circulatory system in the affected zone, which leads to a decrease in necrosis.

This feature becomes apparent after the introduction of *p*-tyrosol in the dose of 1–2 mg/kg and higher; it was patented in the Russian Federation [40]. The experimental data associated with the patent were thoroughly described in [39]. The proposed method for the diagnostics of the newly formed capillary system and determination of the amount of newly formed capillaries in the existing circulation system required layer-by-layer examination of the brain tissues in three groups of animals: 1) reference, 2) ischemic, and 3) ischemic animals receiving *p*-tyrosol. After 2 weeks of *p*-tyrosol intake, the circulatory system of ischemic animals of the third group recovered due to the formation of the new circulatory system and reached the level of the reference group. In the second group, the brain circulatory system remained unchanged: lower than in the reference group by one third.

TYROSOL-CONTAINING PLANTS

Because of the absence of *p*-tyrosol production in Russia, at present, the most available source of this compound is olive oil (extra virgin olive oil) [41]. This type of oil is characterized by the max-

imal content (up to 0.017 %) of *p*-tyrosol and the sum of its derivatives (~0.03 %). The bitter and specific taste of unrefined olive oil is connected with the presence of phenol compounds represented mainly by *p*-tyrosol and 2-hydroxytyrosol. The recommended dose of olive oil to treat cardiovascular and other diseases is 25–50 mL/day or 15–30 mg of *p*-tyrosol [41].

Investigation of the properties of olive oil was carried out with 11 volunteers who were taking 50 mL of cold-pressed olive oil [42]. Nine products of the oxidative transformation of above-indicated phenols present in initial olive oil were isolated from the urine and identified. In the opinion of the authors, this set of products depicts the diversity of the biological properties of olive oil.

The information on the biological properties of phenols present in olive oil is described in the most detailed manner in [43], citing the works in which the antimicrobial activity of olive oil was established with 14 strains of microorganisms. The studies of its anti-inflammatory and antioxidant activity, which is directly connected with the action of *p*-tyrosol and 2-hydroxytyrosol, are widely represented in that review too.

Another form of the application of *p*-tyrosol for the prevention of the acute forms of cardiovascular diseases and the prophylactics of inflammation, cancer, diabetes, oxidative and nervous stress is rosewort (*Rhodiola rosea)*. In this plant, the content of *p*-tyrosol together with its ester (salidroside) and other biologically active phenols reaches 1 % [6, 10]. The maximal amount of the active agents is detected in the roots of a plant growing in mountainous and polar regions of the Earth [44]. The manufactured form is the liquid extract of rhodiola, 30 mL, registration certificate No. LSR-009852/09 of 04.12.2009. The application of this extract is recommended for the treatment of global ischemia [31]. The maximal activity of the cardioprotective action is observed after 5 days of the application of the extract; the pronounced antiarrhythmic activity is achieved after intake for 8 days. The authors state that the extract is to be applied for a long time (up to 45 days) for therapeutic purposes. This causes a decrease in the area of the infarction zone by a factor of 2. The positive effect of the indicated ethanol extract and individual *p*-tyrosol is considered in that paper.

The amount of *p*-tyrosol and 2-hydroxytyrosol in grape wine [45] is two-three times lower than in olive oil and even more so in rosewort [10]. It should be noted that the removal of ethanol from wine activates *p*-tyrosol present in it.

ACCUMULATION OF *p*-TYROSOL IN THE ORGANISM

Investigations [28] of the possible accumulation of *p*-tyrosol in the organism were carried out with male rats. After the intravenous introduction of *p*-tyrosol in the experimental animal, the content of the substance in blood was determined after a fixed time interval. Even in the case of large doses (200 mg/kg) of *p*-tyrosol, at the moment of 24 h after the introduction, only the traces are detected in the blood of animals. Accumulation of *p*-tyrosol in the organism was not observed also after the introduction of the preparation many times in high doses, which points to the rapid and high degree of its metabolic transformation in the organism.

CONCLUSION

By present, preclinical tests of *p*-tyrosol have been completed. NIOCh SB RAS participated in the tests. The documents for subsequent clinical tests in the clinics of Siberia and Moscow for the treatment of acute ischemia were prepared [46]. At least, there is no doubt that we deal with the unique polyfunctional preparation with high efficiency and rapid effect, which is especially important for the treatment of organisms in the critical state.

The range of the biological action of *p*-tyrosol on the human organism is very broad. In the arising organism, it ensures the reliability of the vascular and nervous systems, as well as the brain performance systems, which forestalls the health of a full-fledged baby and causes a decrease in baby mortality. *p*-Tyrosol enhances the rheological properties of blood: the flexibility of vessels and the shells of red blood cells thus providing blood supply (to a definite extent) to ischemic regions, which means the preservation of life signs in these regions.

p-Tyrosol has a strong anti-inflammatory action at the level of ibuprofen but it does not cause the formation of stomach or rectum ulcer, which distinguishes this drug in comparison with the majority of anti-inflammatory drugs. *p*-Tyrosol heals wounds, ulcers and ischemic tissues rapidly and reliably.

Foreign sources also point to the necessity to include *p*-tyrosol along with 2-hydroxytyrosol

and olive oil into the list of efficient means for the treatment of global ischemia.

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