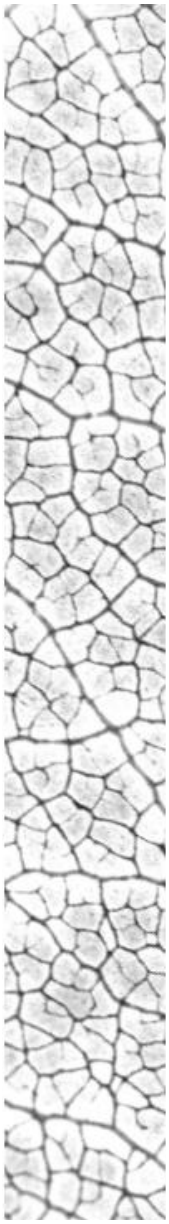

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The effect of a selective arginase 2 inhibitor imidamethazoline class on the development of monocrotoline-induced pulmonary hypertension

Sergey A. Demchenko [1*], Ivan S. Koklin [1], Anna V. Zagrebelnaya [1], Ludmila M. Danilenko [1], Andrey S. Nagich [1]

[1] Belgorod State University, 85, Pobedy St., Belgorod, 308015, RUSSIA
*Corresponding author: demchenkoserg@mail.ru

Abstract

Introduction: The study of innovative drugs at the molecular, tissue, organ, systemic and organismic levels with an assessment of their safety are part of preclinical studies. In this case, studies aimed at specific pharmacological targets are especially important. The search for a selective arginase 2 inhibitor is necessary in terms of the treatment of pulmonary hypertension. One of the most common models of LH is the monocrotalin model of pulmonary hypertension.
Research tasks: To evaluate the protective effects of a selective arginase 2 inhibitor, including the right ventricular contractility parameters on a monocrotalin model of pulmonary hypertension in rats.
Material and Methods: A study was conducted of 5 groups of animals of 10 rats. After using a selective arginase 2 inhibitor, blood pressure, heart rate, Fulton's index, BT index, and condition of the right ventricle were evaluated.
Results and Discussion: It was found that L207-0525 at doses of 1 and 3 mg/kg and tadalafil 10 mg/kg prevents the development of pulmonary hypertension. This is expressed in preventing an increase in systolic pressure in the right ventricle, Fulton, RV/BW and WT indices. L207-0525 showed a dose of 3 mg/kg for the activity shown.
Conclusion: The results indicate a dose-dependent protective activity of the selective arginase 2 inhibitor L207-0525 in relation to the development of monocrotaline pulmonary hypertension.

Keywords: arginase 2 inhibitor, tadalafil, the monocrotalin model, pulmonary hypertension

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INTRODUCTION

Pulmonary and cardiovascular diseases have achieved global emphasis and represent one of the main global health problems (Khadieva, Pokrovskaya, Belousova, 2019). The spread and increase in the impact on society of risk factors for these conditions is increasing every year and may soon reach the scale of the epidemic. The leading role in the course of pathological processes is assigned to endothelial dysfunction, which is expressed in a decrease in the bioavailability of nitric oxide (Khadieva, Pokrovskaya, Belousova, 2019- Levkova, et al. 2019- Soldatov, et al. 2018 - Sarycheva, et al. 2019).

Currently, studies are underway on the effect of endothelial dysfunction in the development of a number of vascular disorders, accompanied by an increase in blood pressure, including pulmonary hypertension (Koklin, Danilenko, 2019 - Korokin, et al. 2011- Skachilova, et al. 2016- Korokin, et al. 2009). In terms of correction of endothelial dysfunction, the action of these substances is aimed at restoring the required amount of NO. There is evidence that L-arginine replacement therapy in patients with lower limb atherosclerosis, coronary heart disease, and pulmonary hypertension significantly improves endothelial status (Korokina, et al. 2018, Korokin, et al. 2011).

In the speaking of the bioavailability of NO, one cannot fail to note the role of the essential amino acid arginine, which is a substrate of such competitive enzymes as for NO synthase and arginase (Gumanova, et al. 2007- Chernomortseva, et al. 2009 Zuckerbraun, George Gladwin 2011. Durante, Johnson, Johnson, 2007- Pokrovskii, et al. 2012). It is these metabolic enzymes that maintain the balance of the axis of NO synthase-arginine-arginase and provide a stable level of nitric oxide. Two fundamental mechanisms for reducing the amount of NO are described: a decrease in its synthesis catalyzed by NO synthase and an increase in

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the inactivation of reactive oxygen species (ROS) (Voronkov, Pozdnyakov, 2018).

Arginase, an enzyme in the urea synthesis cycle that is more than 1000 times more active than NO synthase. It is presented as two isoforms: arginase 1 – the liver form and arginase 2 – the extrahepatic form (localized more often in the kidneys, prostate, small intestine, and vascular endothelium) (Félétou, Köhler, Vanhoutte, 2010). Enhanced expression of arginase, which competes for substrate (arginine) with NO synthase, reduces the bioavailability of nitric oxide (Kaminskii, et al. 2011, Khong, et al. 2012).

At the Scientific Research Institute of Pharmacology of Living Systems, Belgorod State University, together with the KhimRar TVC, as a result of highly effective molecular screening, compounds with high selectivity for arginase II inhibition were selected. One of the most promising compounds is L207-0525.

One of the most common models of LH is the monocrotalin model of pulmonary hypertension. Monocrotaline (MKT) is a macrocyclic pyrrolisidine alkaloid extracted from Crotalaria spectabilis. Lots of pyrrolisidine alkaloids, products of tropical plants of several genera, are toxic to mammals (Berkowitz, et al. 2003).

Monocrotaline, used in large doses (more than 100 mg/kg, subcutaneously), like many other toxins, causes necrosis of liver cells. However, in low doses (40-60 mg / kg, subcutaneously), this substance selectively acts on the endothelium of the pulmonary vessels. An increase in the total dose of monocrotaline leads to violations of the vessels of the kidneys and small intestine. Now it is generally accepted that the MKT itself does not have a pneumotoxic effect, but its derivative, which is formed in the liver, perhaps this is a dehydrogenated product - monocrotaline-pyrrole. When administered to animals, MKT-pyrrole has a stronger toxic effect on the vessels of the lungs than MKT, its effective dose is 12-15 times less than that of its predecessor. The metabolite reaches the pulmonary vessels, accumulating in red blood cells. First of all, the metabolite MKT acts on the endothelial cells of the pulmonary vessels, causing their inflammation, followed by remodeling of the vascular wall.

Arginase inhibitors are one of the most studied and promising groups of drugs for correcting endothelial dysfunction. (Durante, Johnson, Robert 2007- Joe, et al. 2012, Korokin, et al. 2014.) To date, possible ways of pharmacological correction of endothelial dysfunction, but also voiced drugs have been identified, as well as the mechanisms of their effect on hemovascular homeostasis require further comprehensive study. In this regard, the assessment of the quantitative characteristics of experimental models of pulmonary hypertension formation is of great importance.

MATERIALS AND METHODS

The study was conducted on 5 groups of animals. In each group, 10 animals were used. Monocrotalin 60 mg/kg (MKT) was administered to the 1st animals. 2nd group of intact – animals are in the vivarium for 4 weeks. In this group, age control was carried out. In the 3rd and 4th groups of animals against the background of the introduction of MKT, L207-0525 at 1 and 3 mg / kg is used, and in the 5th group - tadalafil 10 mg / kg.

Four weeks later, the animals were introduced into a physiological experiment and the necessary manipulations and measurements were performed. Catheterization of the femoral vein was performed and a sensor was inserted into the right ventricle of the heart for measurement. Systemic blood pressure (SBP), heart rate (HR) and right ventricular pressure (PSD) were measured. The measurements were carried out continuously using the Biopac hardware-software complex and the AcqKnowledge computer program.

After a physiological experiment, the level of development of hypertrophy of the right ventricle of the heart was evaluated. This was done by weighing the right ventricle of the heart of animals. Histological preparations of pulmonary vessels were also made.

The following parameters were used to assess the degree of development of pulmonary hypertension:

1. systolic pressure in the right ventricle (mm Hg);
2. Fulton's index – right ventricular weight/weight of left ventricle plus interventricular septum (%);
3. RV/BW index (mg / g);
4. thickness index of the wall of the pulmonary artery (%).

The study was conducted on Wistar rats in accordance with all ethical and legislative standards.

RESULTS AND DISCUSSION

Modeling of monocrotaline pulmonary hypertension showed that animals after 4 weeks reduced body weight gain compared with the control group.

A direct measurement of pressure in the right ventricle made it possible to show that with the development of monocrotaline pulmonary hypertension, systolic pressure in the right ventricle increased to 41.3 ± 2.3. Moreover, in animals of the control group, this value was 23.0 ± 1.2 mm Hg. ($p < 0.05$). Simultaneously with the pressure in the right ventricle, the Fulton index increased from 23.5 ± 1.2 to 32.1 ± 1.3%.

The RV / BW index also increased from 0.6 ± 0.02 to 0.8 ± 0.02 mg /kg. And the average wall thickness of the pulmonary artery increased from 0.18 ± 0.01 to 0.23 ± 0.01%, respectively. All assessed indicators when modeling monocrotoline-induced pulmonary hypertension were significantly higher than in the control group.

The data obtained on changes characteristic of pulmonary hypertension in the right stomach of the heart

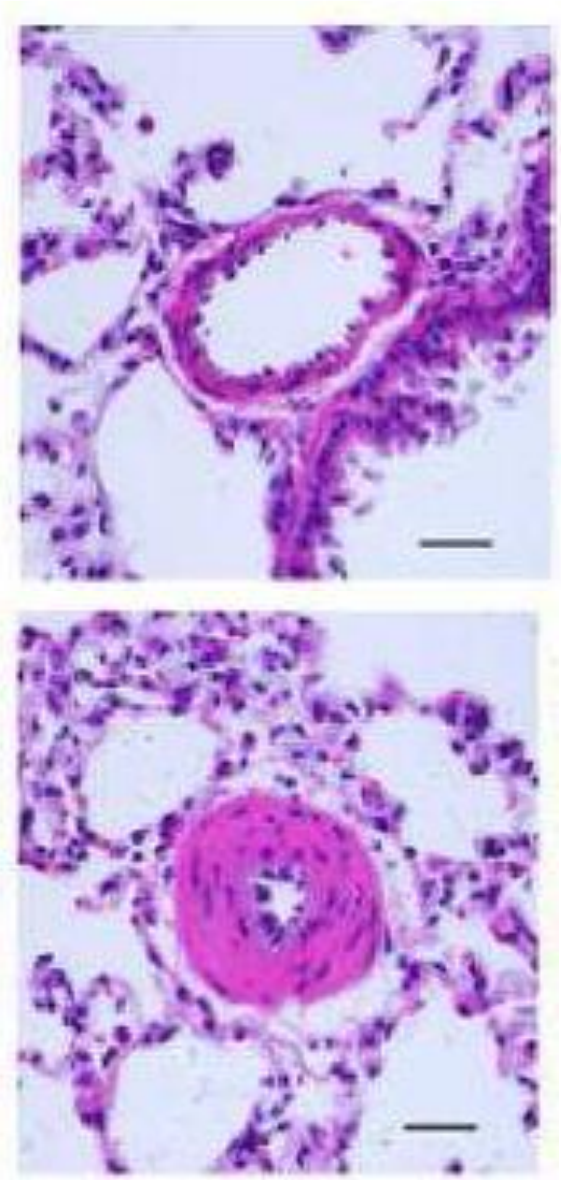

Fig. 1. Hyperplasia of the smooth muscle wall of the pulmonary artery. In the picture on the left - control; on the right - against the background of monocrotaline pulmonary hypertension

and the wall of the pulmonary artery. In animals that were injected with monocrotaline, an increase in systolic pressure in the right stomach was noted, because of this, hyperplasia of the wall of the pulmonary artery formed over time [17, 18]. Changes in the Fluton index, RV / BW index are also explained by this pathophysiological process. The changes obtained in the MKT group compared with control animals showed that this model of pulmonary hypertension is applicable in research practice.

The histological picture of hyperplasia of the muscle layer of the pulmonary vessels is shown in **Fig. 1**.

Table 1. The effect of the selective arginase 2 inhibitor imidamethazoline class L207-0525 and tadalafil on the development of monocrotaline-induced pulmonary hypertension (M ± m; n = 10)

№	Experimental series	RVSP	Fulton's index	RV/BW index	WT index
1.	Intact animals	23.0±1.2	23.5±1.2	0.6±0.02	0.18±0.01
2.	МКТ 60 мг/кг (МКТ)	41.3±2.3*	32.1±1.3*	0.8±0.02*	0.23±0.01*
3.	МКТ + L207-0525 1 mg / kg	36.4±1.9*	29.1±1.2*	0.7±0.02*	0.22±0.01*
4.	МКТ + L207-0525 3 mg / kg	27.1±1.8#	24.5±1.1#	0.6±0.02#	0.19±0.01#
5.	МКТ + Tadalafil 10 mg / kg	32.5±2.1#	2.,4±1.5#	0.7±0.02#	0.20±0.01#

Note: RVSP - systolic pressure in the right ventricle (mm Hg); Fulton's index - weight ratio of the mass of the right ventricle / left ventricle and septum (%); - RV / BW index (mg / g); WT index - pulmonary artery wall thickness (%). * p <0.005 compared with the control; # p <0.005 compared to MKT

The effect of a selective inhibitor of arginase 2 and tadalafil on the development of pulmonary hypertension is presented in **Table 1**.

During the experiment, it was found that the use of a selective inhibitor of arginase 2 L207-0525 at doses of 1 and 3 mg/kg and tadalafil 10 mg/kg prevented the development of pulmonary hypertension. This proves the prevention of an increase in systolic pressure in the right ventricle, as well as the stabilization of the Fulton, RV/BW and WT indices.

A decrease in systolic pressure in the right ventricle causes a decrease in the load on the right atrium and normalization of pressure in the pulmonary circulation [18]. The pulmonary artery wall thickness index (WT) shows the state of the vascular wall better than others. As a result of the use of MKT in a dosage of 3 mg/kg, its value turned out to be as close as possible to that of intact animals.

As is known, an increase in arginase 2 gene expression and/or an increase in the activity of this enzyme leads to the development of endothelial dysfunction and the formation of damage to the vascular wall (Shin, Berkowitz, Ryoo, 2012. El-Bassossy, et al., 2013. Spillmann, et al. 2014.

Fraga-Silva, et al.. 2014. El-Bassossy, El-Fawal, Fahmy, 2012. Jung, et al. 2014.)

The basis of the pathway of exposure to arginase 2 is realized through a competitive effect on NO synthase and a decrease in NO production (Holowatz, et al., 2011. Vanhoutte, et al. 2009. Zhang, et al., 2004

The data obtained indicate that a decrease in the activity of arginase 2 after the use of the selective inhibitor L207-0525 has a protective effect on the vascular wall of the pulmonary artery and myocardium of the right ventricle. This drug imidomethazolines class has a preventive effect against pulmonary hypertension.

Compared with tadalofil, the drug L207-0525 at a dose of 3 mg/kg showed greater activity. Thus, the dose-dependent effect of the angiotensin 2 inhibitor was shown: the effectiveness of the drug at a dose of 3 mg/kg exceeds 1 mg/kg.

The data obtained in the experiment indicate a clear protective dose-dependent effect of the selective arginase 2 imidometosaline class inhibitor in relation to the development of pulmonary hypertension.

CONCLUSION

The results of the study allow us to conclude that, after monocrotaline-induced pulmonary hypertension on the 28th day of the rat's life, hypertrophy of the pulmonary vascular wall forms, an increase in systolic pressure in the right stomach and the regular dynamics of the Fulton and RV/BW indices. The use of selective arginase 2 inhibitor imidamethazoline class L207-0525 in the case of the development of monocrotaline pulmonary hypertension showed a positive trend. Dose-dependent efficacy has also been proven.

MAIN FINDINGS

1. It was found that L207-0525 at doses of 1 and 3 mg/kg and tadalafil 10 mg/kg prevents the development of pulmonary hypertension. This is confirmed by stopping the increase in systolic pressure in the right ventricle and the Fulton, RV/BW and WT indices.
2. The highest activity was shown by L207-0525 at a dose of 3 mg/kg, which indicates its dose-dependent protective activity in relation to the development of monocrotaline pulmonary hypertension.

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