

First discovered effect of L-norvaline on tissue saturation and the activity of respiratory chain enzymes in ischemic and reperfusion injury of the small intestine

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Abstract

Introduction: Prevention and treatment of ischemic and reperfusion injury plays an important role in correcting the pathological manifestations of acute mesenteric thrombosis. The development of effective therapy and the study of the mechanisms of pharmacological agents' action are an important problem faced by researchers.

Materials and Methods: All studies were performed on 12 female Wistar rats weighing 250±25 g. Isolated mesenteric ischemia and reperfusion were reproduced by ligation and subsequent removal of ligatures from three segmental arteries in the ileum. The saturation and activity of respiratory enzymes were studied by hyperspectral imaging and biofluorescence.

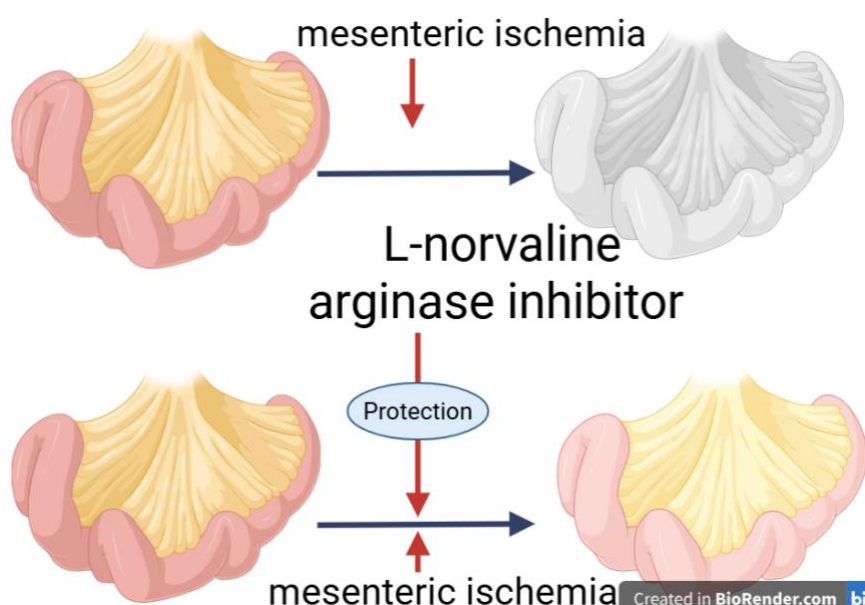
Results and Discussion: For the first time, we investigated the effect of L-norvaline at a dose of 15 mg/kg on tissue saturation and the activity of respiratory chain enzymes in ischemic and reperfusion injury of the small intestine. The study revealed an increase in the level of tissue saturation and NADH activity against the background of L-norvaline administration during ischemia, in the absence of a significant effect on saturation during reperfusion during the restoration of NADH activity.

Conclusion: The arginase inhibitor L-norvaline has a protective effect in ischemic and reperfusion injuries of the small intestine.



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Graphical Abstract



Keywords

ischemic and reperfusion injuries of the small intestine, [L-norvaline](#)

Introduction

Ischemic and reperfusion injury play an important role in the pathogenesis of acute abdominal pathology, becoming particularly important in acute mesenteric thrombosis. The study of pharmacological agents capable of influencing the volume and depth of damaged tissues is the most important task of pharmacotherapy (Miyake et al. 2020). Previously, the involvement of the nitric oxide system in such a pathology as endothelial dysfunction was established, and a positive effect on this system was shown (Korokin et al. 2015). Arginase blocker [L-norvaline](#) is one of the promising drugs for the correction of ischemic and reperfusion disorders.

We have studied the effect of [L-norvaline](#) at a dose of 15 mg/kg on tissue saturation and the activity of respiratory chain enzymes in ischemic and reperfusion injury of the small intestine.

Material and Methods

Experimental animals

All studies were performed on 12 female white Wistar rats weighing 250 ± 25 g. The experimental studies were approved by the Bioethical Commission of Kursk State Medical University (minutes №4 of 15.12.2022).

Pharmaceutical substances

During investigation, the effect of the arginase inhibitor [L-norvaline](#) was studied. [L-norvaline](#) was administered intraperitoneally at a dose of 15 mg/kg 60 minutes before the recurrence of an episode of 30-minute ischemia (Bezhina et al. 2020).

Study design

Acute mesenteric ischemia and reperfusion were reproduced by applying ligatures to three segmental arteries for a period of 30 minutes, followed by removal and resumption of blood flow also lasting 30 minutes. Tissue oxygen saturation was measured using a hyperspectral imaging software and hardware complex with the study of NADH biofluorescence activity using a blue-spectrum laser in the 350-560 nm wavelength range (Adamenkov et al. 2024).

Statistical data processing

All the data obtained were processed by the method of variation statistics. Descriptive statistics were applied to all the data: the data were checked for the normality of the distribution. The type of distribution was determined by the Shapiro-Wilk criterion. In the case of a normal distribution, the mean (M) and the standard error of the mean (m) were calculated.

Results

During the study, it was found that the basic tissue saturation of intact small intestine tissue was at the level of $67.4 \pm 5.3\%$. A 30-minute segmental ischemia of the small intestine leads to a decrease in tissue perfusion to a level of $56.6 \pm 4.2\%$. Tissue saturation, after restoration of blood flow in the mesenteric vessels for a period of 30 minutes of reperfusion, increases to the level of $68.5 \pm 4.8\%$.

Intraperitoneal administration of L-norvaline at a dose of 15 mg/kg resulted in a decrease in tissue perfusion to a level of $64.5 \pm 5.4\%$ during a 30-minute ischemia, which is 13.3% higher than in the case of ischemia in the intact group. At the same time, L-norvaline had no statistically significant effect on tissue saturation during the 30-minute reperfusion episode, which was at the level of $67.2 \pm 4.6\%$.

In order to study the effect of L-norvaline on the severity, nature, and mechanisms of ischemic and reperfusion injury, we studied the activity of respiratory chain enzymes, namely NADH, by biofluorescence in the wavelength range from 350 to 560 nm.

During the study, it was found that NADH activity in the intact group was at the level of 45.72 ± 3.12 units.

An episode of 30-minute ischemia resulted in a decrease in the fluorescence level to 31.84 ± 2.25 units.

Reperfusion for 30 minutes resulted in a slight increase in NADH activity to the level of 34.76 ± 3.12 units.

Intraperitoneal administration of L-norvaline at a dose of 15 mg/kg caused a decrease in NADH activity of 38.63 ± 4.3 units, for a period of 30 minutes from the moment of ischemia modeling, which is 1.18 times higher than in the group without correction. With 30-minute reperfusion during administration, it led to an increase in NADH to 42.10 ± 3.78 units.

Conclusion

Thus, based on the data obtained during a combined study of tissue saturation measured by hyperspectral analysis and biofluorescence with determination of NADH activity, it can be concluded that ischemia leads to a decrease in tissue saturation and activity of respiratory coenzymes. Restoration of blood flow in the segmental arteries with subsequent reperfusion leads to an increase in tissue saturation, while not leading to a significant change in the activity of respiratory chain coenzymes by 30 minutes of reperfusion. Such a reaction may be one of the manifestations and a possible mechanism for the pathological effects of reperfusion injury, when, despite the resumption of blood flow, the damaging effects are aggravated. Administration of L-norvaline at a dose of 15 mg/kg 30 minutes before the simulation of mesenteric ischemia leads to both an increase in tissue saturation and an increase in the level of biofluorescence. It is interesting that L-norvaline does not significantly affect tissue saturation during reperfusion, while increasing the activity level of respiratory chain coenzymes. The effect of L-norvaline on respiratory chain enzymes may explain its positive action on necrotic tissue volume in the segmental mesenteric thrombosis model (Alekhin et al. 2023).

Additional Information

Conflict of interest

The authors declare the absence of a conflict of interests.

Funding

The authors have no funding to report.

Ethics statement

The experimental studies were approved by the Bioethical Commission of Kursk State Medical University (minutes №4 of 15.12.2022).

Data availability

All of the data that support the findings of this study are available in the main text.

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