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Research Article

First discovered positive effect of L-norvaline on the volume of small intestine tissues necrosis in a model of segmental mesenteric thrombosis in rats

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Abstract

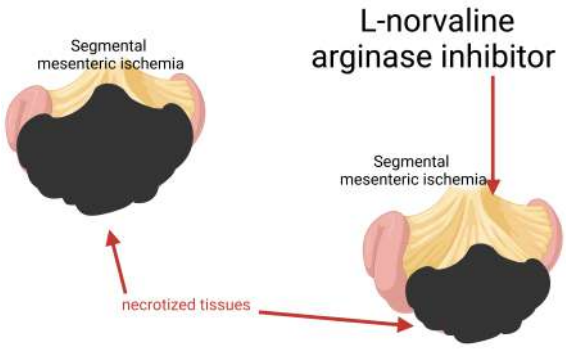
Introduction: Mesenteric thrombosis is a severe pathology with necrotization of intestinal tissues and death of the patient. The development of effective pharmacotherapy is an important task facing researchers.

Materials and Methods: All studies were performed on 42 female white rats of the Wistar line, weighing 250±25 g. Segmental mesenteric thrombosis was reproduced by ligation of three segmental arteries in the area of the ileum. The volume of necrosis was determined by the triphenyl tetrazolium method.

Results and Discussion: We have studied for the first time the effect of the arginase inhibitor L-norvaline on the volume of small intestine necrotized tissues in a model of acute segmental mesenteric thrombosis in rats. The study revealed a decrease in the volume of necrotic tissues from 32.39±0.47% to 23.84±0.39%, and the administration of glibenclamide did not cause complete cancellation of the L-norvaline action and led to a decrease in the volume of necrosis to 29.69±0.42%.

Conclusion: Arginase inhibitor L-norvaline has protective effect in intestinal ischemia.

Graphical abstract:



Keywords

mesenteric thrombosis, L-norvaline, volume of necrotised tissues

Introduction

Occlusive lesions of the small intestine occur with thrombosis and embolism of the mesenteric arteries, accounting for 45-56% of the total number of cases of abdominal ischemia, in 5-15% of cases complicated by the phenomena of venous thrombosis, aggravating the course of an already formidable pathology. The leading causes of acute abdominal occlusive lesions are arterial thrombosis and thromboembolism, accompanied by thrombotic occlusion of the abdominal aorta visceral branches, which subsequently causes severe necrotic intestinal lesions and death of the patient (Coelho et al. 2016; Cheruiyot et al. 2021). The development of effective pharmacotherapy is an important task facing researchers (Miyake et al. 2020). Previously, the participation 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). We have studied for the first time the positive effect of L-norvaline arginase inhibitor on the volume of small intestine necrotic tissues in the model of segmental mesenteric thrombosis.

Materials and Methods

Experimental animals

All studies were performed on 42 female white rats of the Wistar line, 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 the research work, the protective effect of the drug arginase inhibitor L-norvaline was studied. L-norvaline was administered at a dose of 15 mg/kg intraperitoneally 60 minutes before the recurrence of an episode of deep ischemia.

The pharmacological analyzer glibenclamide was administered at a standard dosage of 5 mg/kg, sufficient to cancel ischemic preconditioning and block ATP-dependent potassium channels.

Study design

Segmental mesenteric thrombosis was reproduced by ligation of three segmental arteries in the area of the ileum. The study of the volume of necrosis was performed a day after the simulation, excising a section of the intestine in the pool of occluded arteries with a length of 5 cm.

Direct and remote ischemic preconditioning was performed according to the invented method (Bezhina et al. 2020).

The volume of necrosis was determined by the triphenyl tetrazolium method.

Statistical data processing

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 and Discussion

When modeling acute segmental mesenteric ischemia, the effectiveness of reducing mesenteric blood flow at the level of the microcirculatory bed was controlled by laser Doppler flowmetry. As soon as 30 minutes from the moment of reproduction, the separation of damaged and undamaged segments of the small intestine is clearly visible (Bezhina et al. 2020).

During the study, it was found that the volume of necrotic tissues of the small intestine by the first days of modeling acute segmental mesenteric ischemia was 32.39±0.47% of the total volume of tissues in the area of blood flow restriction.

The effect of direct ischemic preconditioning for 30 minutes before modeling acute segmental mesenteric ischemia leads to a decrease in the volume of necrotic tissues by 29.43%, which corresponds to a lesion volume of 22.85±0.36% ($p \leq 0.05$). The introduction of a pharmacological analyzer glibenclamide leads to the abortion of the protective effect of direct ischemic preconditioning and, as a consequence, to an increase in the necrosis zone to the level of 32.13±0.41% ($p \leq 0.05$), which is comparable to the model of acute segmental mesenteric ischemia.

The use of remote ischemic preconditioning 30 minutes before the modeling of acute segmental mesenteric ischemia has a protective effect on the volume of necrotic tissue, which is manifested by a decrease in this indicator to the level of 25.34±0.29% ($p \leq 0.05$), which is 21.76% less than in the control group. The effect of distant ischemic preconditioning is realized through K^+ dependent ATPases, which is confirmed by the cancellation of the protective effect of DIPC with the introduction of glibenclamide, so, the volume of lesion in this group of studied animals was 32.18±0.34% ($p \leq 0.05$).

The use of L-norvaline arginase blocker at a dose of 15 mg/kg intraperitoneally 60 minutes before the modeling of acute segmental mesenteric ischemia leads to a marked decrease in the lesion volume to the level of 23.84±0.39% ($p \leq 0.05$), which is 26.38% less than in the control group.

The protective effect of L-norvaline is not fully realized through K^+ dependent ATPases, which is with the introduction of a pharmacological analyzer glibenclamide. Thus, the volume of necrotic lesion was 29.69±0.42% ($p \leq 0.05$).

Conclusion

The obtained data clearly indicate that the arginase inhibitor L-norvaline has protective properties with respect to the damaging effect of ischemia/reperfusion, while the degree of the protective effect exceeds that of distant ischemic preconditioning, but does not achieve the effectiveness of direct ischemic preconditioning. This is true both for modulating the effect of ischemia/reperfusion on the structural components of the small intestine, and for changing its effect on the functional state of both muscle elements and epithelial lining, which is confirmed by the data of the study of epithelial damage and stimulated contractile activity of an isolated segment of the ileum.

However, the most interesting thing is that the protective effect of the action of L-norvaline is partially canceled by the action of the K^+ potassium channel blocker glibenclamide at a dose of 5 mg/kg, which indicates the partial realization of the protective action by the mechanisms of the first window of preconditioning, and partly by the mechanisms of the second window of ischemic preconditioning.

Conflict of Interest

The authors declare no conflict of interests.

References

- Bezhina EN, Alekhin SA, Artyushkova EB, Orlova AY, Sernov LN, Denisuk TA, Peresypkina AA (2020) Effect of L-norvaline on the small intestinal wall blood perfusion in a model acute segmental mesenteric thrombosis. Archivos Venezolanos de Farmacologia y Terapeutica 39(5): 556–560. https://doi.org/10.5281/zenodo.4266263
- Cheruiyot I, Kipkorir V, Ngure B, Misiani M, Munguti J, Ogeng'o J (2021) Arterial thrombosis in coronavirus disease 2019 patients: A rapid systematic review. Annals of Vascular Surgery 70: 273–281. https://doi.org/10.1016/j.avsg.2020.08.087 [PubMed] [PMC]
- Coelho A, Logo M, Gouveia R, Campos J, Augusto R, Canedo A (2016) Acute mesenteric ischemia: epidemiology, risk ractors and determinants of mortality. Revista Portuguesa de Cirurgia Cardio-Torácica e Vascular 23(3-4): 137–143. [PubMed]
- Korokin MV, Pokrovskii MV, Gudyrev OS, Korokina LV, Pokrovskaia TG, Lazarev AI, Philippenko NG, Gureev VV (2015) Pharmacological correction of endothelial dysfunction in rats using e-NOS cofactors. Research Journal of Pharmaceutical, Biological and Chemical Sciences 6(5): 1548–1552.
- Miyake H, Koike Y, Seo S, Lee C, Li B, Ganji N, Pierro A (2020) The effect of pre- and post-remote ischemic conditioning reduces the injury associated with intestinal ischemia/reperfusion. Pediatric Surgery International 36(12): 1437–1442. https://doi.org/10.1007/s00383-020-04762-5 [PubMed]

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