NEW DERIVATIVES OF 2-OXOINDOLIN-3-GLYOXYLIC ACID-AMID AND ETHER, AND THEIR COMPARATIVE ANTIHYPOXIC ACTIVITY

Results of comparative antihypoxic activity of amid and ether – new derivatives of 2-oxoindolin-3-glyoxylic acid among various types of hypoxia are suggested in the article. It is indicated that they give evidence of antihypoxic property among all basic types of hypoxia. When acute hystotoxical and acute hemic hypoxias existed their effectiveness was higher than effectiveness of medicine of comparison of mexidol. Antihypoxic activity of ether, amid and mexidol was almost identical on experimental models of acute normobaric hypoxia and acute hypobaric hypoxia. It is suggested that mechanism of antihypoxic activity of new derivatives of 2-oxoindolin-3-glyoxylic acid is stipulated by means of stabilization of cellular membranes, optimisation of cellular respiration and reduction of sensitivity of tissues and oxygen deficiency.

Key words: 2-oxoindolin-3-glyoxylic acid; different types of hypoxias; mechanism of antihypoxic action

INTRODUCTION

The pharmacological medicines have been applied in therapeutic practice since ancient times, which improve the utilization of a circulating oxygen, reduce a need of it for organs and tissues, and in such a way they enable the reducion of an hypoxia and the increase of a steadfastness of an organism to an oxygen deficiency. The frequency of the hypoxic conditions, a polymorphism of their appearance affects the necessity of a search for the methods and the means of struggle with an oxygen deficiency. At least, the contents of the antihypoxic means remain slight. We learned 10 ethers and 10 amids – new derivatives of 2-oxoindolin-3-glyoxylic acid for the period of screening reaserches, among which one amid and one ether were selected for further preclinic research, which gave evidence of the most antihypoxic activity.

Aim of research. To carry out a research in the comparative aspect of antihypoxic action of ether and amid – new derivatives of 2-oxoindolin-3-glyoxylic acid in diferent experimental models of oxygenous hunger.

MATERIALS AND METHODS

The experiments were carried out on the nonlineal white mice of the different weight 18-22 grams in the cases of different types of hypoxias [2]. The acute hypobaric hypoxia was created by means of lifting of the animals at the height of 11,000 metres with speed of 50 metres per second by means of the device Komovsky; the hypoxic hypoxia was created by means of arranging the animals in hermochamber 200 milliliters; the acute hemic hypoxia was obtained by means of injection of nitrite sodium 200 mg/kg within a skin; hystotoxical hypoxia – by means of injection of sodium nytroprusid 25 mg/kg within stomach [1]. The mexodil as antyhipoxant of new generation was selected as medicine of comparison [3]. The control and experiments carried out and registered simultaniuos the duration of life per minutes. The mexidol 100 mg/kg and experimental substances (ether – 13.9 mg/kg, amid – 18.6 mg/kg) were injected within a stomach before half an hour of the beginning of an experiment. All obtained results were processed by means of methods of nonparametric statistics by means of the application of the assessment of Student [4]. In all cases differences were thought to be obvious under p < 0.05.

RESULTS AND DISCUSSION

According to the researches, ether and amid – derivatives of 2-oxoindolin-3-glyoxylic acid practically gave evidence of the identical antihypoxic property in all experimental models (Table). However their effectiveness was higher than mexidol in the cases of the acute hystotoxic (327.9 % and 290.2 %) and the acute hemic hypoxia (197.0 % and 165.9 % correspondenly). The antihypoxic activity of ether, amid and mexidol was almost identical in the experimental models of the acute normobaric hypoxia and acute hypobaric hypoxia. One should remark, in the case of hemic hypoxia we watched relatively low antihypoxic activity of ether, amid and mexidol (26.2 ± 2.2 min, 26.6 ± 2.1 min and 22.4 ± 1.9 min correspondenly) as compared with different types of hypoxias. We obtained data of mexidol they coincide with results of other scientists [2].

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**COMPARATIVE ASSESSMENT OF ANTIHYPOXIC PROPERTIES OF NEW DERIVATIVES OF 2-OXOINDOLIN-3-GLYOXYLIC ACID AND MEXIDOL IN DIFFERENT MODELS OF HYPOXIA, M ± m, n = 10**

| Types of hypoxia               | Acute hemic hypoxia | Normobaric hypercapnic hypoxia | Acute hypobaric hypoxia | Acute hystotoxic hypoxia |
|-------------------------------|---------------------|--------------------------------|-------------------------|--------------------------|
| Medicine                      | minutes %           | minutes %                      | minutes %               | minutes %                |
| Amid                          | 26.6 ± 2.1*         | 197.0                          | 29.4 ± 2.0*             | 244.6                    | 12.7 ± 2.9*              | 204.1                    | 20.9 ± 2.2*              | 327.8                    |
| Ether                         | 26.2 ± 2.2*         | 196.8                          | 29.0 ± 2.6*             | 242.8                    | 12.8 ± 2.9*              | 203.8                    | 20.6 ± 2.3*              | 327.4                    |
| Mexidon                       | 22.4 ± 1.9*         | 165.9                          | 29.3 ± 2.5*             | 242.1                    | 12.7 ± 2.6*              | 200.9                    | 18.6 ± 2.1*              | 290.2                    |
| Control                       | 13.5 ± 0.7          | –                              | 12.1 ± 0.72             | –                        | 6.32 ± 0.9               | –                        | 6.41 ± 0.35              | –                        |

Footnote. 1. Duration of life of controled animals accepted by 100 %, 2. * – p < 0.05 concerning control.

One can arrange the models in such an order by means of antihypoxic activity of ether and amid: acute hystotoxic hypoxia > normobaric hypercapnical hypoxia > acute hypobaric hypoxia > acute hemic hypoxia.

The mexidol as antihypoxant of new generation, we chose it as a medicine of comparison, in some way studied in the experimental models of the acute oxygenous hunger as well as in clinics of the Russian Federation in the cases of the different illnesses. For all it every single type of hypoxia has its "launch" mechanism of the development, one can carry one's point of view quite clearly concerning the possible mechanisms of antihypoxic action of new substance separately in every single case.

According to the references it is noted that hystotoxic hypoxia appears in the case of failures in the system of utilization of oxygen when enough supply of its to the tissues happens. Under these circumstances the ferment of the biological oxygenation inhibit that enables the disconnection of the oxygenation and phosphorylation to the energetic hunger of tissues. [5] The mechanisms of antihypoxic activity of mexidol are studied and bring about an effect on the stabilization of the biological membranes and energetic exchange of tissues, an activization of the energe – synthetic functions of mitohondrias, an increase of an effectiveness of the reactions of a chain of respiration by means of sycsinate [6]. Considering that new derivatives of 2-oxoindolin-3-glyoxylic acid and a mexidol gave evidence of rather high activity on a current model of oxygenous hunger, one can suggest, that new substances have such mechanisms of realization of antihypoxic effect as well as a medicine of comparison.

One of the main pathogenetic chains of an acute normobaric and acute hypobaric hypoxia is hypoxemia and hypoxemia or hypocapnia [6]. We think that a discovery of enough activity of research substances can have to do with a reduction of the sensitivity of tissues to oxygen deficiency.

Addition of methgemoglobin in the case of gemic hypoxia causes the reduction of oxygenous volume of blood because of inability of methgemoglobin to transport oxygen [5]. However one of a mechanism of antihypoxic action of mexidol is impact on the level of gemooglobin of blood by means of a stabilization of the biological membranes of erithrositons [6], one can suggest, that effectiveness of new derivatives of 2-oxoindolin-3-glyoxylic acid which exceeded an effectiveness of medicine of comparison in the experiment has to do with the identical mechanism which optimizes the cellular respiration.

**CONCLUSIONS**

1. Ether and amid – new derivatives of 2-oxoindolin-3-glyoxylic acid – gave evidence of antihypoxic activity in all experimental models of hypoxia.
2. In the cases of an acute hystotoxic and acute gemic hypoxia an effectiveness of the research substances was higher than an effectiveness of the research substances of medicine of comparison – mexidol. An antihypoxic activity of ether, amid and mexidol are almost identical in the experimental models of an acute normobaric hypoxia and acute hypobaric hypoxia.
3. When the reduction of an antihypoxic effect of ether and amid – derivatives of 2-oxoindolin-3-glyoxylic acid happens – one can arrange types of hypoxias in such an order: acute hystotoxic hypoxia > normobaric hypercapnic hypoxia > acute hypobaric hypoxia > acute gemic hypoxia.

**Prospects of further researches.** Prospective is further preclinical study of new derivatives of 2-oxoindolin-3-glyoxylic acid and precision of mechanisms of their antihypoxic action.

**REFERENCES**

1. Kuznetsov N. A. Methodical recomendations concerning application of medicine MEXIDOL in complex treatment the sick for acute pancreas / [N. A. Kuznetsov, G.V. Rodman, L.A. Laberkto et al.]. – M.: Ros. State Med. University, 2003. – 26 p.
2. Lukjanova L. D. Methodical recomendations concerning selection of antihypoxants / L. D. Lukjanova. – M., 1990. – 18 p.
3. Lukjanova L. D. Problems of pharmacological correction of hypoxia and search for antihypoxants // Cellular mechanisms of realization of pharmacological effect / L. D. Lukjanova. – M.: Medicine, 1990. – P. 184-216.
4. Lukjanova L. D. Particularities of antihypoxic action of mexidol connected with its specific impact on energetic exchange / L. D. Lukjanova, V. E. Romanov // Chem.-pharm. magazine. – 1990. – № 8. – P. 9-11.
5. Sernov L. N. Antihypoxants. Means, affecting the transportation of oxygen to tissues / L. N. Sernov, V. V. Gachura // Elements of experimental pharmacol. – M., 2000. – P. 117-119.

6. Sernov L. N. Statistic methods of assessments of authentity of results of pharmacological researches / L. N. Sernov, V. V. Gachura // Elements of experimental pharmacol. – M., 2000. – P. 308-323.

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НОВІ ПОХІДНІ 2-ОКСОНДОЛІН-3-ГЛІОКСИЛОВОЇ КИСЛОТИ – АМІД І ЕФІР ТА ЇХ ПОРІВНЯННА
АНТИГІПОКСИЧНА АКТИВНІСТЬ

Представлені результати порівнянної антигіпоксичної активності ефіру та аміду – нових похідних 2-оксоніндолін-3-гліоксилової кислоти при різних видах гіпоксії. Показано, що вони проявляють антигіпоксичні властивості при всіх основних видах гіпоксії. При гострій гістотоксичній і гострій гемічній гіпоксії їх ефективність була високою за ефективність препарату порівняння мексидолу. На експериментальних моделях гострої нормобаричної гіпоксії та гострої гіпобаричної гіпоксії антигіпоксична активність ефіру, аміду та мексидолу була майже однаковою. Припускається, що механізм антигіпоксичної активності нових похідних 2-оксоніндолін-3-гліоксилової кислоти зумовлений стабілізацією клітинних мембран, оптимізацією клітинного дихання і зменшенням чутливості тканин до недостачі кисню.

Ключові слова: 2-оксоніндолін-3-гліоксилова кислота; різні види гіпоксії; механізм антигіпоксичної дії

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НОВЫЕ ПРОИЗВОДНЫЕ 2-ОКСОИНДОЛИН-3-ГЛЮКСИЛОВОЙ КИСЛОТЫ – АМИД И ЭФИР
И ИХ СРАВНИТЕЛЬНАЯ АНТИГИПОКСИЧЕСКАЯ АКТИВНОСТЬ

Представлены результаты сравнительной активности эфира и амид – новых производных 2-оксонидолин-3-глюксиловой кислоты при разных видах гипоксии. Показано, что они проявляют антигипоксичные свойства при всех основных видах гипоксии. Однако при острой гистотоксической и острой гемической гипоксии их эффективность была выше, чем у препарата сравнения мексидола. На экспериментальных моделях острой нормобарической гипоксии и острой гипобарической гипоксии противогипоксическая активность эфира, амид и мексидола была почти одинаковой. Предполагается, что механизм антигипоксической активности эфира и амид обусловлен стабилизацией клеточных мембран, оптимизацией клеточного дыхания и уменьшением чувствительности тканей к недостатку кислорода.

Ключевые слова: 2-оксонидолин-3-глюксиловая кислота; гипоксия; механизм антигипоксического действия

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