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THE RESEARCH OF ANTIHYPOXIC ACTIVITY OF 2-METHYL-3-PHENYLAMINOMETHYLQUINOLIN-4 OF THE PERSPECTIVE ANTIDEPRESSANT WITH NOOTROPIC PROPERTIES

Summary

The results of research determining antihypoxic action of 2-methyl-3-phenylaminomethylquinolin-4 which has also shown the antidepressant properties are revealed in this article. Antihypoxic activity was studied on the models of acute normobaric hypercapnic hypoxia, acute hypobaric hypoxia and acute hemic hypoxia. It has been stated that preventive introduction of investigated substance in dose of 100 mg/kg considerably increases the animal's life span by 13.6% (which became obvious on the example with the normobaric hypercapnic hypoxia). The 3-AMQ indexes of the other two hypoxic models did not differ significantly in comparison with the indexes of a control group.

Key words: 2-methyl-3-phenylaminomethylquinolin-4, antidepressants, antihypoxic activity, experimental hypoxia.

Introduction.

In recent years the prevalence of depression and comorbid psychoneurotic disorders has grown unprecedentedly due to constantly increasing informative pressure and highly intensive psychological component of social conditions of living, which in its turn is considerably increasing stressfulness of the environment that surrounds the modern man. [2] For pharmacological correction of depressions and psychosomatic disorders caused by them drugs from the group of antidepressants [7] are widely used in medical practice, but their use is significantly limited due their

inability to quickly stop a depressive episode, high probability of developing side effects and a wide range of contraindications [9]. Regarding all the above mentioned, the search and study of biologically active compounds which have antidepressant action and would allow increasing the effectiveness and safety of treating depressive disorders is of great importance at present.

The object of this research is 2-methyl-3-phenylaminomethylquinolin-4 (3-AMQ), which was synthesized at the Department of Medical Chemistry at National Pharmaceutical University [4] and studied as a biologically active substance of antidepressant action with evident antiamnesia component. Previously it was shown that this compound when used in doses of 100 mg/kg after the third injection significantly decreases the time of passive stand-by of mice during the experimental test "Behavioral Despair" and has a high protective potential against amnesial effect of Scopolaminum according to CRPA test [12]. On the model with depression caused by the introduction of reserpine, 3-AMQ in the same dose has reduced the severity of hypothermia and blepharoptosis of rats [8]. Studying its influence on the exchange of cerebral monoamines in the brain of mice has revealed significant affecting of this derivative both absolute concentration of cerebral monoamines, particularly serotonin and dopamine, and their ratio [3].

Neuroprotective properties are inherent to many antidepressants [6]. As hypoxia is a typical mechanism of CNS damage, it is advisable to explore the potential impact of antidepressants on brain sensitivity to oxygen deficiency at preclinical stage.

The logical continuation of this work and the aim of this research is to study the antihypoxic properties of 2-methyl-3-phenylaminomethylquinolin-4, since chronic hypoxic damage of brain tissue is often accompanied by neuropsychiatric damage, including depressive disorders. In the pathogenesis of ischemic lesions of the CNS great importance is given to hypersensitivity of nerve tissue to the lack of oxygen and glucose that occurs after ischemia. The correction of these states during complex treatment requires the compulsary use of drugs with antihypoxic action [1]. Thus, the ability of the compound that is used as an antidepressant to increase resistance of

CNS structures to lack of oxygen could improve the clinical symptoms of depressive disorders by stabilization of metabolic processes in the nervous tissue.

MATERIALS AND METHODS

To investigate antihypoxic activity of 3-AMQ the following methods have been chosen: acute normobaric hypoxia with hypercapnia, acute hypobaric and acute hemic hypoxia. Experiments were conducted on random male mice according to the "General ethical principles of animal experiments" (2001).

The design of all three experiments involved applying regimen with preventive intragastric injection of 2-methyl-3-phenylaminomethylquinolin-4 in dose of 100 mg/kg during 3 days in the form of finely dispersed aqueous slurry stabilized by Tween-80. The comparators were administered intragastric in the same regimen as the studied compound, namely piracetam (200 mg/kg) - in an aqueous solution, and melatonin ("Vita-melatonin" OJSC Kyiv Vitamin Plant, 5 mg/kg) - in an aqueous suspension stabilized by Twin-80. Controlled animals were given an appropriate volume of distilled water.

Laboratory animals were divided into 4 groups according to the drug they received:

1. Intact control.
2. 2-methyl-3-phenylaminomethylquinolin-4, 100 mg / kg.
3. Piracetam, 200 mg / kg.
4. Melatonin, 5 mg / kg.

Studying the antihypoxic activity of 3-AMQ on a model with normabaric hypercapnic hypoxia was performed on 49 male mice weighing 26-28 g. To simulate acute hypercapnic hypoxia [10] in 30 minutes after the last injection of the substances the animals were put into transparent air-tight containers of 200 ml volume. With the help of a stopwatch the lifespan of animals from the moment of closing the container to agonal breaths was determined.

Studying the activity of 3-AMQ on a model with hypobaric hypoxia was conducted on 45 male mice weighing 22-30 g. Acute hypobaric hypoxia [10] was caused in 30 minutes after the last injection of substances when raising animals at 50

m/s speed at a height of 11,000 m with a special device (the Komovskiy's device). To stimulate CO2 uptake each of the two transparent containers of this device contains soda lime. As evaluation criteria of activity served an average life span of the animals from the beginning of "raising", which was determined with a stopwatch.

Studying antihypoxic activity of 3-AMQ on a model with acute hemic hypoxia was performed on 49 white male mice weighing 24-28 g. Acute hemic hypoxia [11] was caused in 30 minutes after the last intraperitoneal injection of aqueous solution of sodium nitrite in a dose of 200 mg/kg. The life span of the animals was determined with a stopwatch from the moment of poison introduction.

All results were statistically processed using the Student's t-criterion [11].

RESULTS AND DISCUSSION.

The results of studying antihypoxic activity of 3-AMQ on a model with acute hypercapnic hypoxia prove that preventive input of 2-methyl-3-phenylaminomethylquinolin-4 prolongs the lifespan of the animals by 13.6% at the level of comparator melatonin, but with a higher probability than intact control (see the Table). Piracetam increased the lifespan of experimental animals by 15.2% on avarage in comparison with the control group, but due to high dispersion the difference was not likely to reach the credible level.

On the model with acute Hypobaric hypoxia the 3-AMQ has not affected the lifespan of tested animals, piracetam has shown a slight tendency to increase of this index, but the difference was not likely to reach the credible level is in comparison with intact control. The only substance that has worked on that model was melatonin, which significantly prolongs the life of animals by 8.6% on average.

Table

Antihypoxic activity of 2-methyl-3-phenylaminomethylquinolin-4 (100 mg/kg) in models with acute normabaric hypercapnic, hypobaric and hemic hypoxia.

Group of animals	Hypoxia models		
	Normabaric hypercapnic, n=49	Hypobaric, n=45	Hemic, n=49
	minutes	seconds	minutes
Control	18.43±0.47 (n=22)	276.92±3.93 (n=13)	27.50±2.06 (n=14)
3-AMQ, 100 mg/kg	20.94±0.74$^{\#\#}$ (n=9)	275.43±4.81 (n=14)	29.37±2.43 (n=15)
Piracetam, 200 mg/kg	21.23±1.36 (n=9)	280.33±6.40 (n=9)	28.77±2.06 (n=10)
Melatonin, 5 mg/kg	20.94±1.02$^{\#}$ (n=9)	300.67±3.23$^{*/**}$ (n=9)	26.28±1.56 (n=10)

Note. # − $p<0.05$ та ## − $p<0.01$ according to Student's t-criterion relative to control group; * – $p<0.001$ relative to control group and 3-AMQ; ** – $p<0.05$ relative to piracetam group.

The results of the study on the model with hemic hypoxia have shown a tendency to increase of the evaluation criteria when using 3-AMQ relative to parallel intact control. In general, the absolute indexes of all experimental groups did not differ from those of the control group.

Thus, we can conclude that the preventive use of 2-methyl-3-phenylaminomethylquinolin-4 (in doses of 100 mg/kg) provides a protective effect in conditions of normabaric hypoxia with hypercapnic component, which is probably due to the indirect monoaminergal influence of substances on the development of irreversible processes in the CNS coming along with hypoxia. Absence of any effect of 3-AMQ by hypobaric states proves that the compound in no way affects the development of hypoxic changes in brain tissue due to the lack of oxygen (by decrease of partial pressure in the air that is inhaled), so that does not affect the tissue component of hypoxia. This thesis is also supported by the results of the experiment on the model with hemic hypoxia, i.e. by significant reduction of oxygen in blood.

The results of this research along with the data obtained in previous experiments give the right to suppose that 2-methyl-3-phenylaminomethylquinolin-4 possesses cerebroprotective properties, but this issue requires further research.

CONCLUSIONS

1. Antihypoxic properties of 2-methyl-3-phenylaminomethylquinolin-4 – a perspective antidepressant with nootropic properties - have been studied on the models with hypercapnic, hypobaric and hemic hypoxia.

2. The results of the experiments have shown that preventive administration of 2-methyl-3-phenylaminomethylquinolin-4 in doses of 100 mg/kg prolongs the lifespan of animals by 13.6% on a model with acute normabaric hypercapnic hypoxia and do not significantly affect this index of other models .

3. These results suggest that anti-hypoxic properties of the substance can have a valuable additional pharmacological effect in clinical practice.

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