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Antihypoxic effect of almid-containing metal-complex compounds in the experiment

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ABSTRACT

BACKGROUND: To increase resistance to hypoxia, various methods of hypoxic training, mental effects, and use of pharmacological antihypoxants are employed.

AIM: To test new metal-complex compounds containing the antihypoxant almid in mice under conditions of acute hypoxia to determine their protective properties.

MATERIALS AND METHODS: In the first stage of the study, four new metal-complex compounds of magnesium, calcium, titanium, and vanadium containing the antihypoxant almid were screened in experiments on mice (n = 550) under acute hypoxic conditions with hypercapnia. The antihypoxants almid and amtizole were used as comparison substances. Acute hypoxia was induced by placing the animals in pharmacy glasses with a volume of 0.25 L with closed lapped stoppers. The substances were administered intraperitoneally at doses of 25, 50, and 100 mg/kg previously dissolved in 0.3 mL of NaCl solution. The incubation period was 60 min. The antihypoxic effect was considered confirmed if the lifespan increased by ⩾20%. "Lifespan" refers to the time interval from the moment the mice were placed in a pharmacy glass to the development of the first agonal inhalation, after which the animals were quickly removed to preserve life. The rectal temperature of the animals was measured before the introduction of substances, immediately before being exposed to acute hypoxic conditions with hypercapnia, and after removal. Twenty-four hours after the first stage of the experiment, mice of the control group and mice that proved their ability to resist acute hypoxia with hypercapnia were repeatedly exposed to acute hypoxic conditions with hypercapnia after the use of substances.

RESULTS: A distinct antihypoxic effect exceeding the effectiveness of the comparison substances was obtained only in one substance — πQ2460 with titanium as a metal-complexing agent — and a ligand in the form of fumaric acid. After the administration of πQ2460, a dose-dependent decrease in rectal temperature was observed in mice. The lifespan of animals increased with an increase in the dosage of πQ2460, i.e., by 43.9%, 103.1%, and 152.8% for doses of 25, 50, and 100 mg/kg, respectively. The results of the second stage of the experiment confirmed the stable protective effect of πQ2460 but with an equalization of the effect of the studied doses, which increased the lifespan under acute hypoxic conditions with hypercapnia to an average of 60–70 min (control group, 40.5 min).

CONCLUSION: Among the compounds containing the antihypoxant almid in the complex molecule, πQ2460 (metal, titanium; ligand, fumaric acid) was found to have a stable protective dose-dependent effect on the development of acute hypoxia with hypercapnia in mice exceeding that for almid and the reference antihypoxant amtizole. The antihypoxic effect of πQ2460 persisted 24 h after its administration but leveled off for the studied doses — 25, 50, and 100 mg/kg. Considering the data obtained during the comparison of the indicators of resistance to acute hypoxia in the control group, a hypothesis was proposed regarding the possibility of forming a preconditioning effect in animals from the primary effects of acute hypoxia.

Keywords: mice; acute hypoxia; almid-containing metal-complex compounds; antihypoxants; preconditioning.

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Противогипоксический эффект алмидсодержащих металлокомплексных соединений в эксперименте

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АННОТАЦИЯ

Актуальность. В наши дни для повышения устойчивости к гипоксии практикуют различные способы гипоксической тренировки, психического воздействия, а также применение фармакологических средств — антигипоксантов.

Цель — испытать в опытах на мышах новые, содержащие антигипоксант алмид, металлокомплексные соединения в условиях острой гипоксии для обнаружения защитных свойств.

Материалы и методы. На 1-м этапе исследования в опытах на мышах (n = 550) осуществляли скрининг 4 новых металлокомплексных соединений магния, кальция, титана и ванадия, содержащих антигипоксант алмид, в условиях острой гипоксии с гиперкапнией. В качестве веществ сравнения использовали антигипоксанты алмид и амтизол. Состояние острой гипоксии вызывали, помещая животных в стеклянные аптечные штанглазы с притертой пробкой объемом 0,25 л. Субстанции вводили внутрибрюшинно в дозах 25, 50 и 100 мг/кг, предварительно растворив в 0,3 мл физиологического раствора NaCl. Период инкубации составлял 60 мин. Антигипоксический эффект считали доказанным при увеличении продолжительность жизни на 20 % и более. Под «продолжительностью жизни» подразумевали интервал времени от момента помещения мышей в штанглаз до развития первого агонального вдоха, после чего животных быстро извлекали с целью сохранения жизни. До введения веществ, непосредственно перед помещением в условия острой гипоксии с гиперкапнией и после извлечения у животных измеряли ректальную температуру. Через 24 ч после 1-го этапа эксперимента мышей контрольной группы и мышей, доказавших способность противостоять острой гипоксии с гиперкапнией после применения веществ, повторно подвергали воздействию острой гипоксии с гиперкапнией.

Результаты. Отчетливое антигипоксическое действие, превышающее эффективность веществ сравнения, было выявлено лишь у одного вещества — πQ2460 с титаном в качестве металла-комплексообразователя и лигандом в виде фумаровой кислоты. После введения πQ2460 у мышей наблюдали дозозависимое снижение ректальной температуры. Продолжительность жизни животных возрастала по мере увеличения дозировки вещества πQ2460 — на 43,9; 103,1 и 152,8 % в соответствии с дозами 25, 50 и 100 мг/кг. Результаты 2-го этапа эксперимента подтвердили устойчивый защитный эффект πQ2460, но с выравниванием эффекта для изученных доз, обеспечивавших увеличение продолжительности жизни в условиях острой гипоксии с гиперкапнией в среднем до 60–70 мин (в контроле — 40,5 мин).

Заключение. Среди соединений, содержащих антигипоксант алмид в составе комплексной молекулы, выявлено вещество πQ2460 (металл — титан, лиганд — фумаровая кислота), обладающие устойчивым защитным дозозависимым действием при развитии у мышей острой гипоксии с гиперкапнией, превышающим таковое для алмида и эталонного антигипоксанта амтизола. Антигипоксический эффект вещества πQ2460 сохранялся спустя 24 ч после введения, но выравнивался для изученных доз — 25, 50, 100 мг/кг. С учетом данных, полученных в ходе сравнения показателей резистентности к острой гипоксии в группе контроля, высказана гипотеза о возможности формирования прекондиционирующего эффекта у животных от первичного воздействия острой гипоксии.

Ключевые слова: мыши; острая гипоксия; алмидсодержащие металлокомплексные соединения; антигипоксанты; прекондиционирование.

Как цитировать

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BACKGROUND

Oxygen is crucial for the vital activity of most organisms. The need for oxygen increases with physical exertion, especially in extreme situations, and in conditions of high altitude or confinement. Disruption and dissociation of oxidative phosphorylation processes can lead to acute exogenous hypoxia [1, 2].

Currently, various methods are used to increase resistance to hypoxia, including hypoxia training, mental conditioning, and the use of antihypoxants such as aminothiol derivatives (e.g., gutimin, almid, etomersol, and amtizole), which have been proven to be highly effective. The abovementioned substances significantly enhance the resistance of experimental animals to various forms of acute hypoxia. They induce a considerable increase in life expectancy (acute hypoxia with hypercapnia) and reserve time (acute hypobaric hypoxia). These substances positively affect the stability of oxidative phosphorylation processes in the mitochondrial compartment of cells and mechanisms of redox regulation in the cytosol in cases of excessive free-radical reactions [2–4].

However, toward the end of the 20th century, a group of metal-complex substances, initially determined as physiologically compatible antioxidants, drew the attention of scientists. The newly synthesized compounds exhibited high redox activity in both living and artificial environments. This activity was attributed to the presence of a metal of variable valence in the substance formula, which significantly increased ligand activity [1, 4]. Subsequently, labeled with the cipher πQ, the metal-complex compounds proved to be equally effective in hypoxia models, often competing with antihypoxants of aminothiol origin.

In 2005, E.A. Parfenov synthesized the metal-complex compounds πQ2456, πQ2458, πQ2460, and πQ2461, which included a molecule of aminothiol antihypoxant — almid as one of the ligands. The metal-complexing agents used were magnesium, calcium, titanium, and vanadium, respectively.

The antihypoxant almid (2-allylthiobenzimidazole hydrochloride) is a derivative of bemityl (2-ethylthiobenzimidazole hydrobromide monohydrate) (Fig. 1). Both substances have a moderate psychostimulant effect that enhances physical and mental performance [3]. They activate antioxidant systems, reduce asthenic phenomena of different origins, and have an antihypoxic effect that protects the brain, myocardium, and liver.

This study aimed to examine and compare the protective effects of four newly synthesized metal-complex compounds containing almid with those of amide and the reference antihypoxant amtizole.

MATERIALS AND METHODS

Male CBF1 mice (n = 550) weighing 20–30 g were used to screen four new metal-complex compounds of magnesium, calcium, titanium, and vanadium containing the antihypoxant almid under conditions of acute hypoxia with hypercapnia (AH + Hc). Acute hypoxia was induced in the mice by placing the animals in glass pharmacy calipers of 0.25 L with lapped plugs [5].

Almid-containing substances (πQ2456, πQ2458, πQ2460, and πQ2461) and comparison substances (almid and amtizole) were administered intraperitoneally at doses of 25, 50, and 100 mg/kg. The substances were pre-dissolved in 0.3 ml of physiological sodium chloride solution. The control group received an equal volume of solvent, and the incubation period was 60 minutes. Antihypoxic effect was confirmed by an increased life expectancy of 20% or more in comparison with the control. Lifespan was defined as the period from the moment of placing the mice in the sealed syringe until the first agonal breath, after which the animals were quickly removed to preserve their lives.

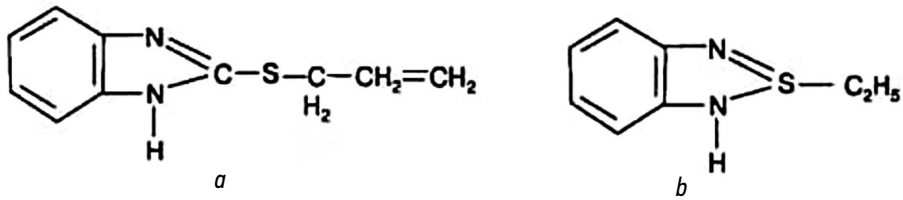
The studied compounds can each be represented by the following formula:

$$[MBL] \times n\mathrm{H_2O},$$

where M is a metal-complexing agent, B is a base (almid), L is a ligand, and n is the number of water molecules. Table 1 presents the characteristics of the studied almid-containing metal-complex compounds.

Rectal temperature was measured three times in animals using an electrothermometer TPEM-1 during the experiment: before administering substances, before being placed in AH + Hc conditions, and after retrieval from the pharmacy calipers.

Two groups of mice were exposed to AH + Hc: the control group and group administered with a metal-complex compound to test its antihypoxic effect. After 24 hours,



a *b*

Fig. 1. Chemical formulas of almid (*a*) and bemitil (*b*)

Рис. 1. Химические формулы алмида (*a*) и бемитила (*b*)

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Table 1. Characteristics of the studied almid-containing metal-complex compounds

Таблица 1. Характеристика исследованных алмидсодержащих металлокомплексных соединений

Cipher of chemical compounds	Base, *B*	Ligand, *L*	Metal-complexing agent, *M*
πQ2456	Almid	Phenylacetic acid	Magnesium
πQ2458	Almid	GHB	Calcium
πQ2460	Almid	Fumaric acid	Titanium
πQ2461	Almid	Dichloroacetic acid	Vanadium (II)

both groups were reexposed to AH + Hc to determine the duration of the antihypoxic effect. In the second stage of the experiment, the mice were kept in sealed conditions until death.

All results were processed statistically. Data comparison was performed by calculating the second-order error and power of *t*-criterion in pharmacological samples using modern information technologies in the public domain. This method was based on automating integration operations of Student's distribution and non-central Student's distribution. The comparison results were statistically significant at $p < 0.05$ [6].

RESULTS AND DISCUSSION

Table 2 summarizes the effects of almid-containing substances and comparison substances on rectal temperature and longevity in AH + Hc mice and shows that the initial core body temperature of the control group animals averaged 36.9°C and remained stable until they were placed in AH + Hc conditions. The animals' life expectancy was 40.53 ± 3.25 min under acute hypoxia conditions, which is typical for this technique [1, 7]. At the end of the experiment, 7 of 10 animals in the control group survived.

Table 2. Effect of almid-containing metal-complex compounds and comparison substances on rectal temperature and lifespan of mice exposed to acute hypoxic conditions with hypercapnia 1 h after administration

Таблица 2. Влияние алмидсодержащих металлокомплексных соединений и веществ сравнения на ректальную температуру и продолжительность жизни мышей, переживавших условия острой гипоксии с гиперкапнией через 1 ч после введения

Groups, *n* = 10 in each	Dose, mg/kg	Rectal temperature before injection (*M* ± *m*), °C	Rectal temperature 1 h after injection (*M* ± *m*), °C	Temperature difference, °C	Lifespan, min (*M* ± *m*)	Number of survivors in a group
Control (1 group)	–	36.9 ± 1.7	36.8 ± 2.0	–0.1	40.53 ± 3.50	7
πQ2456 (3 groups)	25	36.5 ± 2.2	36.5 ± 1.8	0	35.44 ± 2.96	8
	50	37.1 ± 3.6	36.3 ± 12.6	–0.8	47.76 ± 3.61	7
	100	36.2 ± 2.8	35.2 ± 2.5	–1.0	50.20 ± 3.73*	7
πQ2458 (3 groups)	25	37.0 ± 2.4	34.2 ± 2.2*	–2.8	39.48 ± 3.59	5
	50	36.1 ± 3.3	33.5 ± 3.0*	–2.6	34.51 ± 3.74	3
	100	36.6 ± 2.5	31.0 ± 2.4**	–5.6	29.03 ± 2.88*	3
πQ2460 (3 groups)	25	37.2 ± 2.1	34.0 ± 1.9*	–3.2	58.33 ± 4.01*	10
	50	36.4 ± 2.3	32.4 ± 2.6*	–4.0	82.30 ± 4.49**	10
	100	36.7 ± 3.5	29.5 ± 3.7**	–7.2	102.46 ± 5.27**	9
πQ2461 (3 groups)	25	36.4 ± 3.1	35.7 ± 2.8	–0.7	38.77 ± 3.03	9
	50	36.7 ± 3.4	34.9 ± 2.2*	–1.8	40.07 ± 3.21	8
	100	36.7 ± 3.7	33.2 ± 3.1*	–3.5	42.85 ± 3.92	8
Almid (3 groups)	25	37.2 ± 2.7	34.3 ± 2.7	–2.9	39.44 ± 1.63	9
	50	37.2 ± 2.5	32.6 ± 2.4**	–4.6	63.20 ± 3.11*	10
	100	36.5 ± 3.7	31.1 ± 2.3**	–5.4	79.25 ± 3.81**	8
Amtizole (3 groups)	25	37.4 ± 2.2	34.2 ± 2.5*	–3.2	48.99 ± 3.12	10
	50	36.9 ± 2.6	33.6 ± 2.9**	–3.3	57.32 ± 3.40*	10
	100	37.2 ± 2.7	31.3 ± 2.6**	–5.9	87.59 ± 4.79**	8

Note: $p < 0.05$; ** — $p < 0.005$.
Примечание: * — $p < 0,05$; ** — $p < 0,005$.

Other metal-complex agents containing almid were ineffective, such as πQ2456 (magnesium and phenylacetic acid) and πQ2461 (vanadium and dichloroacetic acid), or had negative effects on animal longevity under acute hypoxia, including πQ2458 (calcium and gamma-oxybutyric acid). However, all newly studied compounds induced a statistically significant hypothermic effect, except πQ2456. This raises questions whether a direct correlation exists between a decrease in rectal temperature in animals exposed to a pharmacological agent and the antihypoxic effect of said substance. Nonetheless, studies have reported a correlation between the dynamics of these parameters [2, 4].

The negative impact of πQ2458 on the survival rate of animals under AH + Hc conditions should be noted. Among the 30 mice that received intraperitoneal injections of the substance, only 11 survived. Additionally, all animals that received doses of 50 and 100 mg/kg died within the next 24 hours of observation before the beginning of the second stage of the experiment, making them unusable for the final stage. The results may be attributed to the high toxicity of πQ2458, which is a characteristic of metal-complex compounds [4].

During the study, the comparison substances almid and amtizole were found to be reliable antihypoxants. However, Table 2 shows that their efficacy was weaker than that of πQ2460, which provided superior protection against hypoxia according to all evaluated criteria. Almid increased animal lifespan only at doses of 50 and 100 mg/kg by 55.9% ($p < 0.05$) and 95.5% ($p < 0.005$), respectively. The effect of amtizole was qualitatively similar to the protective effect of almid.

In the second stage of the study, the resistance of surviving mice to AH + Hc was reevaluated 24 hours after administration of the substances (Table 3).

Table 3 reveals that in most animals, rectal temperature gradually returned to normal 24 hours after substance administration. This can be considered an indicator of the termination of the effect of the studied metal-complex compounds [10]. However, even 1 day after the injections, the resistance of mice to AH + Hc remained high (πQ2460, almid, and amtizole). In groups where the effect was doubtful or absent (πQ2456 and πQ2461), a significant increase in resistance was observed in some doses compared to the 1 h control group (exposure of mice to AH + Hc on intact mice, stage 1).

Table 3. Effect of almid-containing metal-complex compounds and comparison substances on rectal temperature and lifespan of mice experiencing acute hypoxia (AH + Hc) with hypercapnia 24 h after administration

Таблица 3. Влияние алмидсодержащих металлокомплексных соединений и веществ сравнения на ректальную температуру и продолжительность жизни мышей, переживавших условия острой гипоксии с гиперкапнией через 24 ч после введения

Groups	Dose received 24 h ago, mg/kg	Number of survivors in the group, *n*	Rectal temperature before AH + Hc (*M* ± *m*), °C	Lifespan, min (*M* ± *m*)
1 h Control (1 group)	–	10	36.9 ± 1.7	40.53 ± 3.50
24 h Control (1 group)	–	7	36.2 ± 4.4	54.57 ± 4.30$^{\#}$
πQ2456 (3 groups)	25	8	35.8 ± 3.7	52.16 ± 3.15
	50	7	35.2 ± 4.9	52.23 ± 5.88$^{\#}$
	100	7	35.1 ± 3.8	54.31 ± 5.13$^{\#*}$
πQ2458 (3 groups)	25	5	–	–
	50	3	–	–
	100	3	–	–
πQ2460 (3 groups)	25	10	35.4 ± 2.8	60.28 ± 3.01$^{\#}$
	50	10	36.1 ± 2.7	67.34 ± 3.82$^{\#*}$
	100	9	34.6 ± 2.5	70.20 ± 4.10$^{\#*}$
πQ2461 (3 groups)	25	9	36.2 ± 3.5	46.52 ± 3.39
	50	8	36.1 ± 3.5	52.98 ± 4.27$^{\#}$
	100	8	35.8 ± 4.3	49.64 ± 4.53
Almid (3 groups)	25	9	36.5 ± 3.6	49.10 ± 3.02
	50	10	37.1 ± 2.2	52.46 ± 3.29$^{\#}$
	100	8	37.0 ± 4.2	57.41 ± 5.14$^{\#}$
Amtizole (3 groups)	25	10	37.2 ± 3.7	50.24 ± 3.03
	50	10	36.3 ± 2.4	53.39 ± 3.63$^{\#}$
	100	8	36.1 ± 4.5	61.88 ± 4.40$^{\#*}$

Note: $^{\#}$ — $p < 0.05$ compared to the 1 h Control group, * — $p < 0.05$ compared to the 24 h Control group.
Примечание: $^{\#}$ — $p < 0,05$ по сравнению с группой «Контроль 1 ч», * — $p < 0,05$ по сравнению с группой «Контроль 24 ч».

The antihypoxic effect of the titanium metal complex πQ2460 was the most significant among all doses tested. The substance showed statistical significance when compared to the 1 h control group for three doses and to the 24 h control group for the 50 and 100 mg/kg doses. The efficacy of almid and amtizole was considerably lower than that of the metal-complex compound (Table 3).

During stage 2 of the experiment, an increased resistance to AH + Hc was detected even in the control group. The lifespan of animals subjected to repeated acute hypoxia (after 24 hours) was 34.6% longer than at the first stage, which was statistically significant ($p < 0.05$).

The results in stage 2 of the experiment confirmed the stable protective effect of πQ2460. After 1 day, the effect of πQ2460 leveled off for all studied doses, with increased lifespan under OH + Gk conditions ranging from 60 to 70 minutes. Based on the data obtained from comparing life expectancy in the control group, a hypothesis regarding the possibility of a preconditioning effect resulting from the primary effect of acute hypoxia on animal organisms was generated. Repeated exposure to acute hypoxic hypoxia has been shown to significantly increase the endurance of animals and humans to hypoxic conditions [1, 11, 12]. Antihypoxants may have a mitigating effect on the formation of the preconditioning effect, as confirmed by the presented experiments, which showed increased resistance of mice to AH + Hc upon administration of low doses of metal complexes and antihypoxants.

The paradoxical effect mentioned was noticeable in relation to πQ2456. An increase in the protective effect of magnesium metal-complex compound was observed 1 day after its intraperitoneal administration, especially in doses of 25 and 50 mg/kg.

CONCLUSIONS

Among the compounds containing the antihypoxant almid as part of the complex molecule, πQ2460 (metal: titanium; ligand: fumaric acid) was found to have a distinct, dose-dependent protective effect in AH + Hc. This effect surpassed the effectiveness of almid and the reference antihypoxant amtizole. Moreover, the antihypoxic effect of πQ2461 persists for 24 hours after intraperitoneal administration, but is equalized for the studied doses of 25, 50, and 100 mg/kg. Additionally, repeated exposure to AH + Hc revealed a preconditioning effect of acute hypoxia, increasing the resistance of mice even with a single exposure to the hypoxic factor after 24 hours. Antihypoxic substances have a mitigating effect on the preconditioning effect of AH + Hc.

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