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Research Article

Does succinate enhance the antihypoxic effects of 2-ethylthiobenzimidazole?

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Abstract

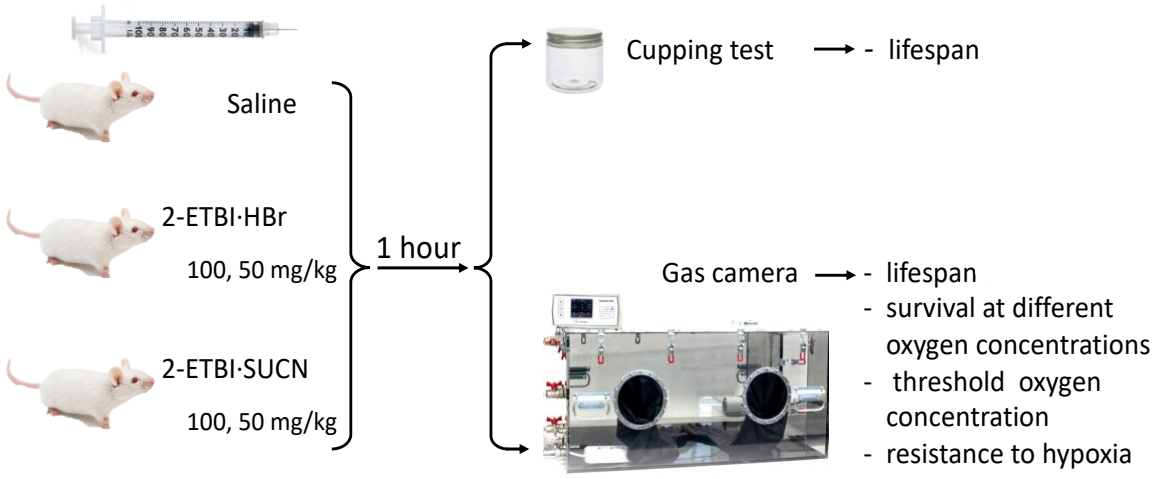
Introduction: 2-Ethylthiobenzimidazole hydrobromide (2-ETBI·HBr) has shown itself as a drug of the restoring therapy after injuries, infections, intoxications, surgeries, and also as actoprotective drug used to increase physical activity in the extreme conditions. 2-Ethylthiobenzimidazole succinate (2-ETBI•SUCN) was synthesized, which is expected to have similar properties. **The aim of this study** was to compare the antihypoxic effects of two 2-ethylthiobenzimidol compounds (2-ETBI•HBr and 2-ETBI•SUCN) in two models of normobaric hypoxia in mice – acute hypoxic hypoxia with hypercapnia and acute hypoxic hypoxia without hypercapnia in gas exchange camera.

Materials and Methods: The experiments were performed on 86 white outbred male mice weighing 20-22 g. Several groups of 8-12 mice were formed. Two of them were served as controls, and the rest received one of the compounds (2-ETBI•HBr or 2-ETBI•SUCN) 50 or 100 mg/kg once intraperitoneally 1 hour before hypoxic exposure. The doses were chosen on the base of the described maximum of antihypoxic effect of 2-ethylthiobenzimidazole. We also took into account acute toxicity (LD_{50}), which was 450±35 mg/kg for 2-ETBI•HBr and 520±30 mg/kg for 2-ETBI•SUCN. Acute normobaric hypoxic hypoxia with hypercapnia was reproduced by placing mice in individual glass chambers with a volume of 0.25 L. The lifespan of the animals was recorded in minutes. Acute normobaric hypoxic hypoxia without hypercapnia was created using a hermetic gas chamber for laboratory studies with automatic monitoring, control and maintenance of the hypoxic gas composition. Normobaric hypoxia in the chamber was modeled by reducing the oxygen concentration in the gas mixture from 21% to 2% by displacing it with nitrogen. Lifespan, survival at different oxygen concentrations, threshold oxygen concentration, and resistance to hypoxia were estimated.

Results: In the model of acute hypoxia with hypercapnia ("cupping test") both 2-ETBI•HBr and 2-ETBI•SUCN showed a moderate antihypoxic effect. It turned out that the dose of 50 mg/kg of both compounds was more effective. Under normobaric hypoxic hypoxia in the gas exchange chamber 2-ETBI·HBr increased the lifespan by 58%, 2-ETBI•SUCN – by 46%, but statistical differences between these values were not noted. Both compounds increased the lifespan of mice at critical oxygen concentrations (6→2%) more than 2 times. At the same time, the tolerance to low oxygen concentrations increased from its concentration of 4.56% in the control to 2.97% after administration of 2-ETBI•HBr and to 3.23% after 2-ETBI•SUCN administration. Finally, both antihypoxants also increased the overall score of resistance to hypoxia in points more than 2 times.

Conclusion: 2-Ethylthiobenzimidazole, regardless of the anionic part of the molecule, exhibits a pronounced antihypoxic effect in tow models of normobaric hypoxic hypoxia in mice. Its value for 2-ETBI•HBr and 2-ETBI•SUCN was similar in the model of normobaric hypoxia in a gas chamber. The minimum oxygen concentration at which mice survived was about 3%. In "cupping hypoxia" with hypercapnia, both antihypoxants showed greater effectiveness at a dose of 50 mg/kg than 100 mg/kg. Thus, succinate does not make a significant contribution to the antihypoxic activity of the 2-ethylthiobenzimidazole.

Graphical Abstract



2-ETBI·HBr and 2-ETBI·SUCN have similar antihypoxic activity

Keywords

gas chamber, hydrobromide, hypoxia with hypercapnia, mice, normobaric hypoxia

Introduction

Oxygen deficiency is one of the important causes of many diseases, as well as a result of special extreme conditions of human vital activity (Shakhmardanova and Galenko-Yaroshevsky 2017). Therefore, it is important to study various approaches to increase the hypoxic resistance. The use of antihypoxants is one of the ways to achieve this goal.

Antihypoxants as compounds protecting against acute oxygen deficiency have been actively promoted since the 1970s, when the first substance of this type was obtained at S.M. Kirov Military Medical Academy (Russia). These compounds were gutimin, amtizol, bemitil, etomerzol (Shabanov 2023). They showed different antihypoxic activity in experimental models on rodents (mice, rats). Later, other types of activity of these substances were also identified, in particular, the ability to increase exercise effectiveness, especially in difficult environmental conditions (exposure to high and low temperatures, injuries, infections, intoxications, etc.). This shifted the focus of research to their actoprotective properties, although they all showed antihypoxic action. The clinical future of these drugs was not at all brilliant: many of them passed clinical trials, but were not widely applied in practice with one exeption – 2-ethylthiobenzimidazole hydrobromide (2-ETBI·HBr), which has been produced (since 2009) under the names bemitil, bemactor, metaprot. It has proven itself as the mean of restoring therapy after injuries, infections, intoxications, surgeries, as a nootropic agent, and as an actoprotective drug used to increase physical activity in extreme conditions (Kim et al. 2024). By analogy with 2-ETBI·HBr, 2-ethylthiobenzimidazole succinate (2-ETBI·SUCN) was synthesized, which presumably should have similar pharmacological properties. In addition, the presence of a succinate anion in the structure of 2-ETBI·SUCN can potentially enhance its effect due to the activation of SUCNR1 receptors, which play a signaling role in metabolic reactions of energy metabolism (Detraux and Renard 2022). Moreover, a number of studies have shown that the introduction of succinate anion into the structure of the chemical molecule (Zarubina et al. 2012) or even the addition of succinic acid or its salts to a combined pharmacological agent (Buznik and Shabanov 2022; Shabanov et al. 2024) can enhance its pharmacological activity.

The aim of this study was to compare the antihypoxic effects of two 2-ethylthiobenzimidol derivatives hydrobromide and succinate in different models of normobaric hypoxia in mice.

Materials and Methods

Animals

The experiments were performed on 86 white outbred male mice weighing 20-22 g obtained from the Rappolovo nursery (Leningrad Region, Russia). The animals were kept under standard vivarium conditions at room temperature of 20-22°, relative humidity of 60-70% and a 12-hour day/night cycle with free access to water and food. After two-week quarantine, the animals were randomized into several groups of 8-12 mice each. Two groups were served as control, and the rest received one of the compounds – 2-ETBI•HBr or 2-ETBI•SUCN – at a dose of 50 or 100 mg/kg once intraperitoneally (i.p.) 1 hour before hypoxic exposure.

The studied compounds were dissolved in physiological solution with the addition of Tween-80. The doses of the compounds were selected on the base of the earlier described maximal antihypoxic effects of 2-ethylthiobenzimidazole, taking into account their acute toxicity (LD_{50}), which was 450±35 mg/kg for 2-ETBI•HBr and 520±30 mg/kg for 2-ETBI•SUCN. Control animals received an equal volume of solvent.

Models

Acute normobaric hypoxic hypoxia with hypercapnia ("cupping hypoxia") was reproduced by placing the mice in individual glass chambers (cups) with a volume of 0.25 L. The cups were hermetically sealed with a lid, turned over and placed in water at the height of the lid to prevent air absorption. The lifespan of the animals was recorded in minutes (Shabanov et al. 2024).

Acute normobaric gas hypoxic hypoxia was created in mice using an airproof gas chamber for laboratory studies completed with a unit for automatic monitoring, control and maintenance of the hypoxic environment composition manufactured by Research Institute GEROPRO (St. Petersburg, Russia) (Fig. 1). The size of the hypoxic chamber was 137x63x43 cm. It was equipped with devices for measuring blood pressure and heart rate, as well as a manipulation unit that allows the introduction of pharmacological compounds to the animals inside the chamber during the experiment with a reduced oxygen concentration. The chamber simulates normobaric hypoxic hypoxia by reducing the oxygen concentration in the gas mixture from 21% to 2% by displacing it with nitrogen. The experiment includes two stages: automatic reduction of oxygen from 21% to 6%, and then a stepwise reduction of oxygen concentration from 6% to 2% with a step of 1% at each subsequent platform and keeping animals at each platform for 5 minutes.

Figure 1. View of the gas exchange chamber for rodents.

The hypoxic chamber was large enough to accommodate mice from the control and experimental groups at the same time, so the experimental conditions were identical for them. The antihypoxic activity of the drugs was estimated using several parameters (Karkishchenko et al. 2017; Kashirin et al. 2021): 1 – total lifespan in s (time from placing the animal in the chamber until its death); 2 – lifespan at critical oxygen concentrations in s (time from the start of the animal's stay on the 6% oxygen platform until the animal's death); 3 – survival at different oxygen concentrations (6 → 2%) in s; 4 – threshold oxygen concentration (TOC) in %, at which the animal died by formula: TOC = A-(B/300), where: A is the oxygen concentration of the platform where the animal's agonal breathing was recorded; B is the animal's lifespan on the platform in s; 300 is the duration of the animal's stay on the platform in s; 5 – resistance to

hypoxia according to the TOC criterion, which was calculated in points based on the animal's survival time at oxygen concentrations decreasing from 6% to 2%. In this case, 1 point was assigned to each time interval of stay on the platform lasting 100 s. The calculation algorithm was the following: 1 point was assigned for survival on the platform with 6% oxygen for 100 s, 2 points – for 200 s, and 3 points – for 300 sec. On the platform with 5% oxygen, survival for 100, 200 or 300 sec gave 4, 5 or 6 points, respectively, at 4% oxygen concentration – 7, 8 and 9 points, respectively, at 3% – 10, 11 and 12 points, respectively, and finally, at 2% oxygen concentration – 13, 14 and 15 points, respectively. However, in our experiments, the minimal oxygen concentration at which mice survived was 3%.

Statistical analysis

Statistical data processing was performed using the GraphPad Prism 6 software package. Comparison of experimental groups was performed using one-way ANOVA with post-hoc Duncan. Student's t-test was used to compare two groups. Differences were considered statistically significant at $p < 0.05$. Data are presented as the arithmetic mean and standard error of the mean (M±SEM).

Results

In the model of acute hypoxia with hypercapnia ("cupping test"), both studied compounds (2-ETBI•HBr and 2-ETBI•SUCN) showed a moderate antihypoxic effect. The dose of 50 mg/kg was more effective. Thus, 2-ETBI•HBr 50 mg/kg increased the life time of mice by 16%, while at a dose of 100 mg/kg it was ineffective in this test. 2-ETBI•SUCN 50 mg/kg increased the lifespan of mice by 21%, while at a dose of 100 mg/kg it increased it only by 13%, although both effects were significant (Table 1). No significant differences were found between the effectiveness of 2-ETBI•HBr and 2-ETBI•SUCN.

Table 1. Effect of 2-ETBI•HBr and 2-ETBI•SUCN on the lifespan of mice in the "cupping test" (hypoxia with hypercapnia), M± SEM

Group	Lifespan, s	% to control	*p*, *t*-test
Control (hypoxia)	21.1±0.8	0	-
Hypoxia + 2-ETBI•HBr 50 mg/kg	24.5±1.1	+16	0.0232
Hypoxia + 2-ETBI•HBr 100 mg/kg	22.1±0.8	+5	0.3945
Hypoxia + 2-ETBI•SUCN 50 mg/kg	25.5±1.8	+21	0.0309
Hypoxia + 2-ETBI•SUCN 100 mg/kg	23.9±0.7	+13	0.0182

Note: 2-ETBI•HBr – 2-ethylthiobenzimidazole bromide, 2-ETBI•SUCN –- 2-ethylthiobenzimidazole succinate.

After obtaining preliminary data in the "cupping hypoxia", the antihypoxic effect of the compounds was studied on mice in the gas exchange chamber (Table 2).

Table 2. Antihypoxic effects of 2-ETBI•HBr and 2-ETBI•SUCN (100 mg/kg) in acute normobaric hypoxia in a gas exchange chamber, M±SEM

Index	Control (hypoxia)	2-ETBI•HBr	% to control	2-ETBI•SUCN	% to control
Total lifespan of mice, s	1142±65	1807±131**	158±12	1671±102*	146±9
Lifespan at critical oxygen concentrations (6→2%), s	492±65	1157±131**	235±27	1021±102*	208±21
Threshold oxygen concentration, %	4.56±0.16	2.97±0.30**	65±7	3.23±0.26**	71±6
Hypoxia resistance, points	4.0±0.5	9.5±0.8***	238±20	8.8±0.7**	220±18

Note: 2-ETBI•HBr – 2-ethylthiobenzimidazole bromide, 2-ETBI•SUCN –- 2-ethylthiobenzimidazole succinate; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ in relation to the control group.

Thus, the lifespan of mice after i.p. administration of 2-ETBI•HBr in a gas exchange chamber increased by 58±12%, and after 2-ETBI•SUCN – by 46±9%; statistical differences between these values were not noted. The lifespan at critical oxygen concentrations (6→2%) after

administration of the compounds increased more than 2-fold; no differences in the effect of either compounds were observed. (Fig. 2).

At the same time, the tolerance to low oxygen concentrations increased. In the control group, the threshold concentration of oxygen at which mice survived was 4.56±0.16%. After the introduction of 2-ETBI•HBr, it decreased to 2.97±0.30%, and after the introduction of 2-ETBI•SUCN – to 3.23±0.26% (Fig. 3); there were no significant differences between the effects of either compounds.

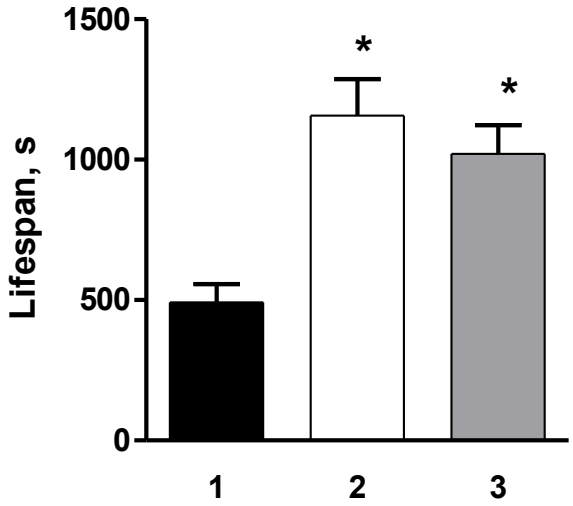


Figure 2. Effect of compounds on the lifespan of mice at critical oxygen concentrations (6→2%). ***Note:*** the ordinate axis shows the lifespan of mice in seconds, the abscissa axis shows animal groups: 1 – control (hypoxia); 2 – hypoxia + 2-ETBI•HBr 100 mg/kg; 3 – hypoxia + 2-ETBI•SUCN 100 mg/kg. *p<0.05 compared to the control.

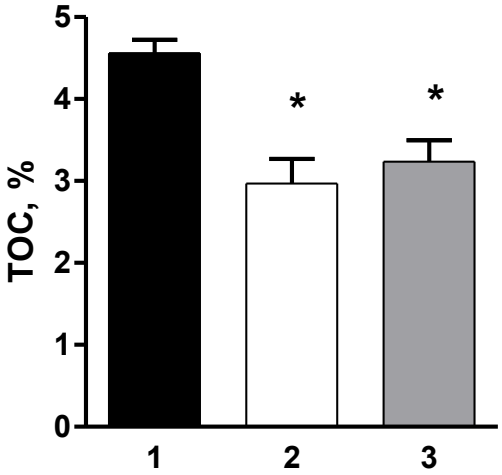


Figure 3. Effect of the compounds on threshold oxygen concentration (TOC). ***Note:*** TOC causes mice death under conditions of acute normobaric hypoxia in a gas exchange chamber. Ordinate axis – threshold oxygen concentration in %, abscissa axis – animal groups: 1 – control (hypoxia); 2 – hypoxia + 2-ETBI•HBr 100 mg/kg; 3 – hypoxia + 2-ETBI•SUCN 100 mg/kg. *p<0.05 compared to control.

Dynamics of the mice survival on the platforms with different oxygen concentrations is a good illustration of the antihypoxic action of the studied substances. In Fig. 4, we can see that the survival curves after the administration of 2-ETBI•HBr and 2-ETBI•SUCN shift to the right, towards lower levels of oxygen concentrations, but no differences in the action of either antihypoxants were detected.

Finally, the overall score of the animals' resistance to hypoxia after the administration of antihypoxants also changed significantly (Fig. 5): in the control it was 4.0±0.5, then after the administration of 2-ETBI•HBr, it increased to 9.5±0.8 ($p<0.001$), and after the administration of 2-ETBI•SUCN, it was 8.8±0.7 points ($p<0.01$); that is, the total score in both cases was more than 2 times higher than the control values.

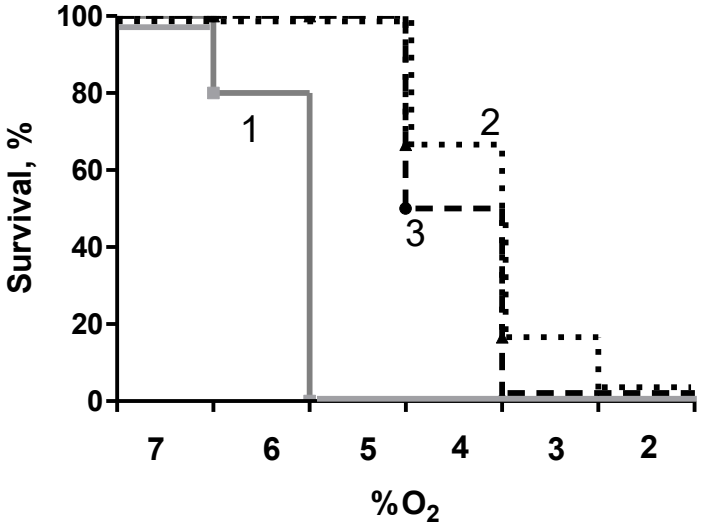


Figure 4. Effect of the compounds on survival of mice on platforms with different oxygen concentration. ***Note:*** The data were obtained under conditions of acute normobaric hypoxic hypoxia in gas exchange chamber. The ordinate axis shows survival of mice in %, the abscissa axis shows concentration of oxygen. 1 – control (hypoxia); 2 – hypoxia + 2-ETBI•HBr 100 mg/kg; 3 – hypoxia + 2-ETBI•SUCN 100 mg/kg.

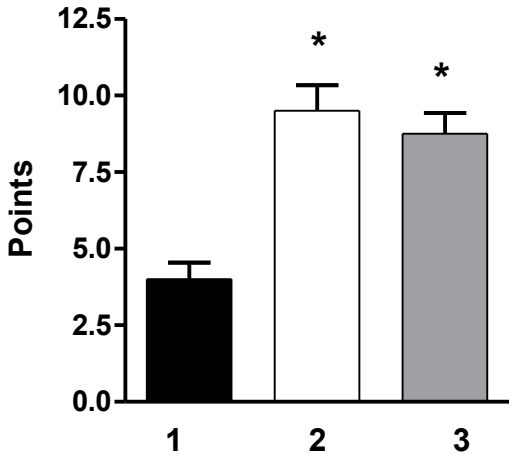


Figure 5. Effect of the compounds on hypoxia resistance according to the threshold oxygen concentration criterion, expressed in points. ***Note:*** The ordinate axis – hypoxia resistance in points, the abscissa axis – groups of mice: 1 – control (hypoxia); 2 – hypoxia + 2-ETBI•HBr 100 mg/kg; 3 – hypoxia + 2-ETBI•SUCN 100 mg/kg. *p<0.05 compared to control.

Thus, the assessment of the antihypoxic activity of 2-ETBI•HBr and 2-ETBI•SUCN (50 and 100 mg/kg) in two models of normobaric hypoxia – ”cupping hypoxia” (hypoxia with hypercapnia) and in a gas exchange chamber showed the presence of this activity both by the criterion of lifespan and by other indexs. At the same time, the values of the antihypoxic activity of both compounds were close to each other.

Discussion

The discussion of the results obtained should begin with a comparison of the doses of the studied compounds. In our experiments, we used doses 50 and 100 mg/kg, which are approximately 1/10 and 1/5 of the LD_{50}. These doses may seem to be too high, but in most studies with hypoxia, the scientists used exactly this order of doses (Sadykov 2009; Tsebulova et al. 2012; Sosin et al. 2013; Kozhurin et al. 2024). In ”cup hypoxia” (hypoxia with hypercapnia), both compounds

showed higher activity at the dose 50 mg/kg than 100 mg/kg, which indicates that the antihypoxic activity is relatively specific just at this dose. Increasing the dose to 100 mg/kg preserves the antihypoxic activity of the compounds, but is not accompanied by its enhancement in comparison with the dose of 50 mg/kg. In acute normobaric hypoxic hypoxia in a gas chamber, both compounds at the dose 100 mg/kg retained a sufficiently high antihypoxic activity according to all obtained data. However, no reliable differences in the effects of 2-ETBI•HBr and 2-ETBI•SUCN were identified.

It is quite difficult to compare our results regarding the antihypoxic activity of the studied compounds with the data of other scientists, since we did not find the description of the 2-ETBI•SUCN pharmacology in the scientific literature. Furthermore, the increase in the mice lifespan under the influence of 2-ETBI•HBr varies significantly (from 0% to +70%) in different studies and depends on the dose of the compound, the route of administration, the design of the study and the laboratory where the study was conducted. In this regard, the characteristics of the chemical substance itself are important, since in a number of studies (Sadykov 2009; Tsebulova et al. 2012) antihypoxic effect of 2-ETBI•HBr was not shown at all, and it is not clear what substance was used. Thus, the scientists from S.M. Kirov Military Medical Academy, St. Petersburg (Russia) (Kozhurin et al. 2024), and Smolensk State Medical University (Russia), who used a substance from St. Petersburg (Sosin et al. 2013), noted the most significant increase in the lifespan of animals – up to +70% after single administration of 2-ETBI•HBr at dose of 50 mg/kg in acute hypoxia with hypercapnia. Similar results were described by colleagues from Belarusian State Medical University (Minsk): lifespan +46% after the administration of 100 mg/kg of 2-ETBI•HBr and +95% with the dose 200 mg/kg (Rashkevich and Volchek 2024). In contrast, in a paper from Bashkir State Medical University (Ufa, Russia), 50 mg/kg of 2-ETBI•HBr had practically no antihypoxic effect (+5%) (Sadykov 2009). One more example is the study from the Institute of Biomedical Problems of the Russian Academy of Sciences (Moscow, Russia), where a single administration of 2-ETBI•HBr at a dose of 50 mg/kg did not cause any antihypoxic effect, but at a dose of 100 mg/kg – increased animal lifespan by 22% (Tsublova et al. 2012). Finally, researchers from the North-West State Medical University named after I.I. Mechnikov (Russia) noted a weak antihypoxic effect (+16%) after a 10-day administration of 2-ETBI•HBr 50 mg/kg orally (Dekkanova et al. 2015). From these data, we can conclude that different laboratories worked with substances with different activity. It is also possible that such different results may be due to various experimental conditions: time of year, age and strain of animals, volume of the hermetic chamber, time of administration, purity of the substance used, and other external factors.

The second aspect of the discussion should concern the mechanism of action of 2-ethylthiobenzimidazole salts. It has now been proven that the antihypoxic effect of ETBI•HBr is associated with the optimization of energy metabolism. It was shown that under hypoxic conditions chronic administration of 2-ETBI•HBr prevents a decrease in the level of macroergs in the brain, liver, myocardium, kidneys, and lungs (Buznik 2022; Shabanov 2023). This triggers the mechanism of gluconeogenesis, an alternative pathway for the formation of glucose from not fully oxidized decay products, which is important during oxygen starvation (Vorobyova et al. 2024). It allows maintaining reduced, but sufficient energy potential, which is required for functioning of the most important organs. This explanation stems from the bioenergetic concept of hypoxia (Vorobyova et al. 2024). Another additional question arises: how significant is succinate in this process and to what extent the antihypoxic effect depends on its presence in the molecule. We have already mentioned that succinate is able to activate succinate receptors (SUCNR1), which play a signaling role in triggering metabolic processes within cells, including those related to energy metabolism (Detraux and Renard 2022). However, in our experiments, no evidence was obtained that 2-ETBI•SUCN is more effective as antyhipoxant than 2-ETBI•HBr. Their effects were similar in direction and magnitude. It is possible that in our case, with a single administration of 2-ETBI•SUCN 1 hour before hypoxic exposure, the mechanism of its action is not associated with the activation of SUCNR1 receptors. And even if it does occur, it makes an insignificant contribution to the antihypoxic potential of 2-ETBI•SUCN.

Conclusion

1. 2-Ethylthiobenzimidazole at doses of 50 and 100 mg/kg, regardless of the anionic part of the molecule, exhibits a pronounced antihypoxic effect during normobaric hypoxia in mice.

2. The level of the antihypoxic effects of 2-ETBI•HBr and 2-ETBI•SUCN in the normobaric hypoxia model in a gas chamber was similar.

3. In hypoxic hypoxia with hypercapnia, 2-ETBI•HBr and 2-ETBI•SUCN showed greater efficacy at a dose of 50 mg/kg than at 100 mg/kg.

4. The antihypoxic effect of 2-ETBI•HBr and 2-ETBI•SUCN is associated with the 2-ethylthiobenzimidazole molecule itself, but not with the anionic part of the molecules.

Additional Information

Conflict of interest

The authors declare the absence of a conflict of interests.

Funding

The study was carried out within the framework of the state task of the Ministry of Science and Higher Education of the Russian Federation FGWG-2025-0020 ”Search for Molecular Targets for Pharmacological Action in Addictive and Neuroendocrine Disorders with the Aim of Creating New Pharmacologically Active Substances Acting on CNS Receptors”.

Ethics statement

All experiments were performed in accordance with the Helsinki Declaration on the Humane Treatment of Animals (2000 edition), the Geneva Convention “International Guiding Principals for Biomedical Involving Animals” (Geneva, 1990) and with the approval of the local ethics committee of the Institute of Experimental Medicine protocol No. 2/23 dated 15.06.2023.

Data availability

Data corroborating the results of this study may be acquired by the corresponding author upon reasonable request.

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