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Exploring Novel Pharmacological Approaches to Acute Hypoxic Preconditioning

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ABSTRACT

BACKGROUND: Metal compounds, particularly transition metal salt with various structural complexities, often demonstrate the pro-hypoxic effect. This effect can be used for acute exogenous hypoxic preconditioning.
AIM: The work aimed to assess the potential of specific metal complexes as pharmacological agents for acute exogenous hypoxic preconditioning in an experimental setting.
MATERIALS AND METHODS: The experiments were conducted on 140 male CBF1 mice weighing 20–25 g. Acute exogenous hypoxia was simulated using two methods: by placing animals in an enclosed space to induce acute hypoxia and hypercapnia, and by simulating the high-altitude environment to induce acute hypobaric hypoxia. The mice's tolerance to hypoxia and hypercapnia was evaluated by measuring survival time, whereas survival time at the lethal altitude was used to assess the tolerance to hypobaric hypoxia. The metal complexes πQ1983, πQ2116, and πQ2721—which have been shown to have antihypoxic effects—were administered to mice daily by single intraperitoneal injection at 10, 25, and 40 mg/kg for 7 days prior to the experiments. At 10:00 a.m. on day 8, the animals were exposed to modelled acute exogenous hypoxia to assess the preconditioning effect. The effect of the compounds on thermogenic processes was evaluated by measuring rectal temperature.
RESULTS: Of the 3 compounds examined, only πQ2721 showed the preconditioning effect in the acute hypoxia and hypercapnia model. After 7 days of administration at 25 and 40 mg/kg, animal survival time increased by 56.5 % and 82.6 %, respectively. Each compound demonstrated a beneficial effect on the mice's tolerance to acute hypoxia in the acute hypobaric hypoxia model.
CONCLUSION: In two models of acute, exogenous hypoxia, all three metal complexes—πQ1983, πQ2116, and πQ2721—that were investigated in mouse experiments showed the preconditioning effect, which was most significant in acute hypobaric hypoxia conditions. In contrast to πQ1983 and πQ2116, πQ2721 exhibited the significant dose-dependent preconditioning effect in models of acute hypoxia and hypercapnia and acute hypobaric hypoxia that considerably enhances the animal tolerance to oxygen deficiency. The preconditioning effect of metal complexes is most effectively achieved in conjunction with the induction of hypothermia, which can serve as a valuable marker in the targeted search for novel pharmacological agents for preconditioning.

Keywords: acute exogenous hypoxia; pharmacological preconditioning; metal complexes; mice.

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Поиск новых путей для фармакологического прекондиционирования к острой гипоксии

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АННОТАЦИЯ

Актуальность. Прогипоксическое действие нередко демонстрируют металлосодержащие вещества — соли переходных металлов различной степени сложности. Данный эффект может быть использован для прекондиционирования к острой экзогенной гипоксии.

Цель — оценить возможность применения некоторых металлокомплексных соединений в качестве агентов фармакологического прекондиционирования к острой экзогенной гипоксии в эксперименте.

Материалы и методы. Опыты выполнены на 140 мышах-самцах линии CBF1 массой 20–25 г. Моделирование острой экзогенной гипоксии осуществляли 2 способами — путем помещения животных в замкнутое пространство (острая гипоксия с гиперкапнией) и путем имитации подъема на высоту (острая гипобарическая гипоксия). Толерантность мышей к острой гипоксии с гиперкапнией оценивали по показателю «продолжительность жизни», а к острой гипобарической гипоксии — по показателю «резервное время». Предварительно на протяжении 7 сут осуществляли ежедневное разовое внутрибрюшинное введение металлокомплексных веществ πQ1983, πQ2116 и πQ2721 в дозах 10, 25 и 40 мг/кг, ранее зарекомендовавших себя в качестве антигипоксических средств. На 8-е сутки в 10:00 мышей помещали в условия острой экзогенной гипоксии в соответствии с моделью для оценки результата прекондиционирования. Влияние веществ на процессы теплообразования изучали путем измерения ректальной температуры.

Результаты. В условиях острой гипоксии с гиперкапнией из 3 изученных веществ прекондиционирующий эффект продемонстрировало лишь вещество πQ2721. После 7-суточного его введения в дозах 25 и 40 мг/кг зафиксирован прирост продолжительности жизни животных на 56,5 и 82,6% соответственно. На модели острой гипобарической гипоксии положительное влияние на толерантность мышей к острой гипоксии продемонстрировали все вещества.

Заключение. Во всех 3 комплексных соединениях металлов: πQ1983, πQ2116, πQ2721, — изученных на 2 моделях острой экзогенной гипоксии в опытах на мышах, выявлен прекондиционирующий эффект, который наиболее отчетливо проявляет себя в условиях ОГ + Гб. В отличие от веществ πQ1983 и πQ2116, вещество πQ2721 на моделях острой гипоксии с гиперкапнией и острой гипобарической гипоксии обеспечивает отчетливое дозозависимое прекондиционирующее действие, в значительной степени повышая толерантность животных к дефициту кислорода. Прекондиционирующий эффект металлокомплексных соединений наиболее эффективно осуществляется при развитии сопутствующей гипотермии, что может быть использовано в качестве индикатора в целенаправленном поиске новых агентов для фармакологического прекондиционирования.

Ключевые слова: острая экзогенная гипоксия; фармакологическое прекондиционирование; комплексные соединения металлов; мыши.

Как цитировать

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BACKGROUND

Acute hypoxic preconditioning is a method of periodic exposure of the body, tissues, or organs to hypoxia- or ischemia-inducing factors, followed by restoration of circulation and oxygenation to develop tolerance to severe prolonged hypoxia (ischemia).

The terms "preconditioning" and "tolerance" were first introduced by Janoff in 1964 [1]. In the late 20th century, Marry et al. [2] demonstrated on myocardial tissue that multiple brief episodes of ischemia can protect living tissues from subsequent prolonged ischemic damage, a phenomenon termed "ischemic preconditioning". Shortly thereafter, evidence emerged regarding hypoxic/ischemic tolerance in the brain [1, 2]. Current research has elucidated the mechanisms of cerebral ischemic preconditioning using *in vivo* and *in vitro* models [3, 5–8].

Since some pharmacological agents exert a hypoxia-like effect as part of their primary or adverse effects (acting as hypoxia mimetics), attempts have been made to achieve preconditioning through the administration of various chemical agents. It has been established that pro-hypoxic effects are often exhibited by metal compounds — transition metal salts with various structural complexities, including zinc, nickel, cobalt, iron, chromium, and others [9, 10].

This led to the concept of using zinc- and nickel-containing metal compounds as pharmacological preconditioning agents.

The aim of this study was to assess the potential of specific metal complexes as pharmacological agents for acute exogenous hypoxic preconditioning in an experimental setting.

METHODS

The experiments were conducted on 140 male CBF1 mice weighing 20–25 g. Acute exogenous hypoxia was simulated using two methods: by placing animals in an enclosed space to induce acute hypoxia and hypercapnia (AH+Hc), and by simulating the high-altitude environment to induce acute hypobaric hypoxia (AH+Hb). In both cases, the mice were placed in 0.25 L glass containers (pharmaceutical glass stoppered jars [shtanglas]). For AH+Hc modeling, after sealing the containers, mice's tolerance to hypoxia and hypercapnia was evaluated by measuring survival time [11]. AH+Hb was modeled using an original method [12] involving gradual pressure reduction in the container controlled by a pressure sensor, simulating ascent to 10,000 m ("lethal altitude") at 50 m/s. Mice's tolerance to acute hypobaric hypoxia was evaluated by measuring survival time at the lethal altitude. Animal death in both models was determined at the onset of the second agonal gasp.

For 7 days prior to the induction of acute exogenous hypoxia, the mice received daily single intraperitoneal injections of metal complexes πQ1983, πQ2116, and πQ2721, previously shown to have antihypoxic effects [13, 14]. Their presumed mechanism of action involves suppression of energy metabolism, indirectly supported by their ability to induce significant hypothermic effects within 20–30 minutes post-administration (Table 1).

According to the selected models of acute exogenous hypoxia, the studied compounds, and their dosages, the mice were divided into 20 groups of 7 animals each. Thus, for each hypoxia modeling method, 1 control group (CG) and 9 experimental groups (EGs) were formed.

Mice in the EGs received intraperitoneal injections of the compounds at 10:00 daily at doses of 10, 25, and 40 mg/kg, previously dissolved in 0.3 mL of sodium chloride solution. Mice in the CG received sham injections of 0.9% NaCl (physiological saline) in the same volume and according to the same schedule. At 10:00 on day 8, the animals were exposed to modelled acute exogenous hypoxia to assess the preconditioning effect.

The effect of the metal complexes on thermogenic processes in mice was evaluated by measuring rectal temperature. Measurements were taken twice daily: immediately before compound administration (first measurement) and 60 minutes post-injection (second measurement) using a TM-902C electric thermometer (S-Line, China).

Statistical analysis was performed using methods of variational statistics [15] with Microsoft Excel 2024 and Statistica 10 software packages. Quantitative assessment of parameter typicalness was determined by median. Variation was evaluated using lower and upper quartiles, as well as interquartile range. Due to the small sample size, normality testing was not feasible. Differences between compared values were considered statistically significant at $p < 0.05$.

Table 1. General characteristics of the investigated metal complexes

Code	Metall	Ligand L^1	Ligand L^2	Base
πQ1983	Zn(II)	3-Hydroxy-2-ethyl-5-methylpyridine	No	Dibenzyl diselenide
πQ2116	Ni(II)	4-Hydroxycoumarin	No	Water
πQ2721	Zn(II)	Diselenodipropionic acid	Acetic acid	No

RESULTS

In the CG, rectal temperature fluctuations before and after sham injections were statistically indistinguishable, whereas in the EGs, rectal temperature in animals decreased to varying degrees after each administration of metal complexes, particularly at doses of 25 and 40 mg/kg, but generally returned to baseline on the following day (Figs. 1 and 2).

Analysis of temperature curves over 8 days revealed that the hypothermic effect of the zinc-containing compound πQ1983 was largely dose-independent and significantly diminished by the end of the observation period. Comparing these findings with first measurement results from days 1–4, this may indicate the development of tolerance to this metal complex (Fig. 1). Second measurements showed that the maximum reduction in rectal temperature with πQ1983 was after its administration at doses of 10 mg/kg (day 6) and 25 mg/kg (day 4), decreasing from 37 °C to 34.8 °C, i. e. by ~2.2 °C.

Tolerance to the preconditioning agent was also observed following the administration of πQ2116 and πQ2721 at a dose of 10 mg/kg (Fig. 2). In these experiments, the maximum hypothermic effect reached only 1.6 °C ($p > 0.05$) for πQ2116 and 2.1 °C ($p < 0.05$) for πQ2721, comparable to the effect after the administration of πQ1983 at the same dose. However, at doses of 25 and 40 mg/kg, these two metal complexes induced significant hypothermia. At 25 mg/kg, πQ2116 reduced rectal temperature in mice from 36.8 °C to 34.3 °C (day 6), whereas at 40 mg/kg, it decreased from 37.0 °C to 30.7 °C (day 4), i. e. by 6.6 °C ($p < 0.001$). Given the trend line of the first measurements, no tolerance developed to πQ2721 administered at 40 mg/kg, which can be considered a positive indicator of the potential for preconditioning tolerance to acute hypoxia in mice.

As shown in Table 2, by day 7 of observation, the hypothermic effect according to the first measurements was most pronounced after the administration of the zinc-containing compound πQ2721 at 40 mg/kg (–3.7 °C, $p < 0.005$), enhancing its prospects among other compounds and suggesting this metal complex potential preconditioning effect against acute hypoxia. Even at 25 mg/kg, this compound demonstrated a statistically significant rectal temperature reduction of 1.5 °C ($p < 0.05$).

Based on the findings, it appeared logical to make another assumption regarding the preconditioning effect of the nickel-containing compound πQ2116, which reduced the rectal temperature of the mice by 2.5 °C ($p < 0.05$) on day 7 of the experiment at a dose of 25 mg/kg. However, at the maximum of the studied doses (40 mg/kg), this metal complex did not produce a statistically significant change in rectal temperature.

The second stage of the study examined mice tolerance to acute exogenous hypoxia after 7-day pharmacological preconditioning (Figs. 3, 4).

As shown in Fig. 3, under AH+Hc conditions, of the three compounds examined, only πQ2721 (excluding the 10 mg/kg dose) demonstrated a statistically significant preconditioning effect. After 7 days of administration at 25 and 40 mg/kg, animal survival time increased by 56.5% and 82.6%, respectively ($p < 0.005$).

The effects of metal complexes πQ1983, πQ2116, and πQ2721 on mice tolerance to acute hypobaric hypoxia (AH+Hb) are shown in Fig. 4. It can be concluded that all compounds statistically significantly extended the survival time of the animals at an altitude of 10,000 m (lethal altitude). Even at 10 mg/kg doses, their protective effect exceeded control group indicators by at least twofold. The most substantial changes were observed with πQ2721, which increased mice tolerance to AH+Hb by 3.5- and 4.6-fold at doses of 25 and 40 mg/kg, respectively ($p < 0.001$), and by 2.4-fold at 10 mg/kg.

πQ2721 ranked second by the level of antihypoxic activity in these experiments. Unfortunately, unlike πQ2721, the metal complexes πQ2116 and πQ1983 exerted their protective effects in a dose-independent manner, which is unlikely to be considered their advantages.

DISCUSSION

According to modern scientific concepts, ischemic/hypoxic tolerance in living tissue induced by ischemic preconditioning involves two sequential phases: an early phase (development of tolerance) and a late phase (establishment of tolerance) [3, 7, 8, 16]. The first phase is characterized by rapid cellular changes (minutes to hours), including activation of protein kinases, proteases, conformational changes in ion channel structures, membrane and cytosolic receptors, redox-sensitive molecules, and possibly changes in gene expression to a lesser extent. The second phase (after 24 hours) involves later mechanisms of tolerance formation, manifested through genome activation followed by vigorous synthesis of proteins essential for cell survival under conditions of progressing acute ischemia and hypoxia.

In the described experiments, pharmacological preconditioning agents were chemical compounds capable of rapidly (15–30 minutes) reducing body temperature in healthy animals (mice, rats, cats) via various administration routes. This effect can only be achieved through active suppression (inhibition) of energy production in the body, primarily in skeletal muscle cells [17]. It is well-known that the sole method for rapid reduction of cellular energy charge involves using mitochondrial bioenergetic function inhibitors, accompanied by decreased ATP production. Essentially, this implements an effect described as pro-hypoxic [18, 19]. The pro-hypoxic effects of chemical compounds most commonly involve mechanisms that induce hemic or histotoxic hypoxia, collectively termed “chemical hypoxia” in the literature [10].

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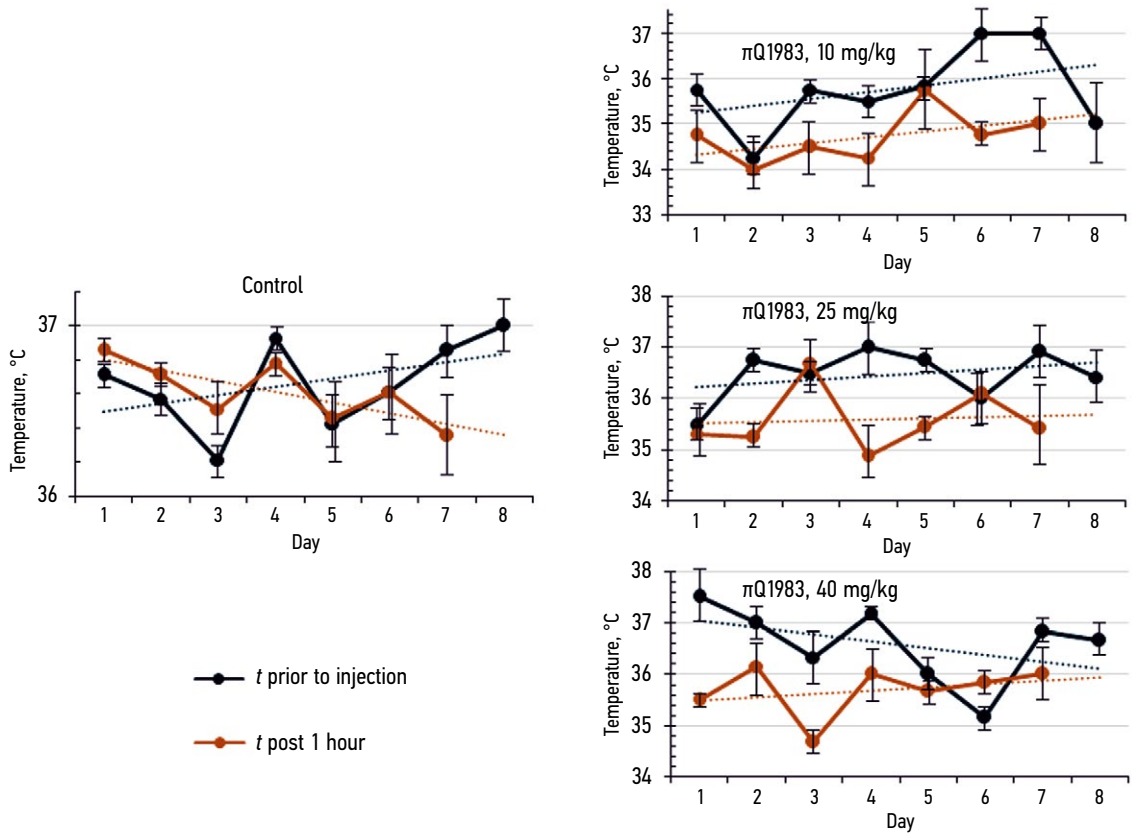

Fig. 1. Rectal temperature patterns in combined control groups (*n* = 14) and during preconditioning with πQ1983.

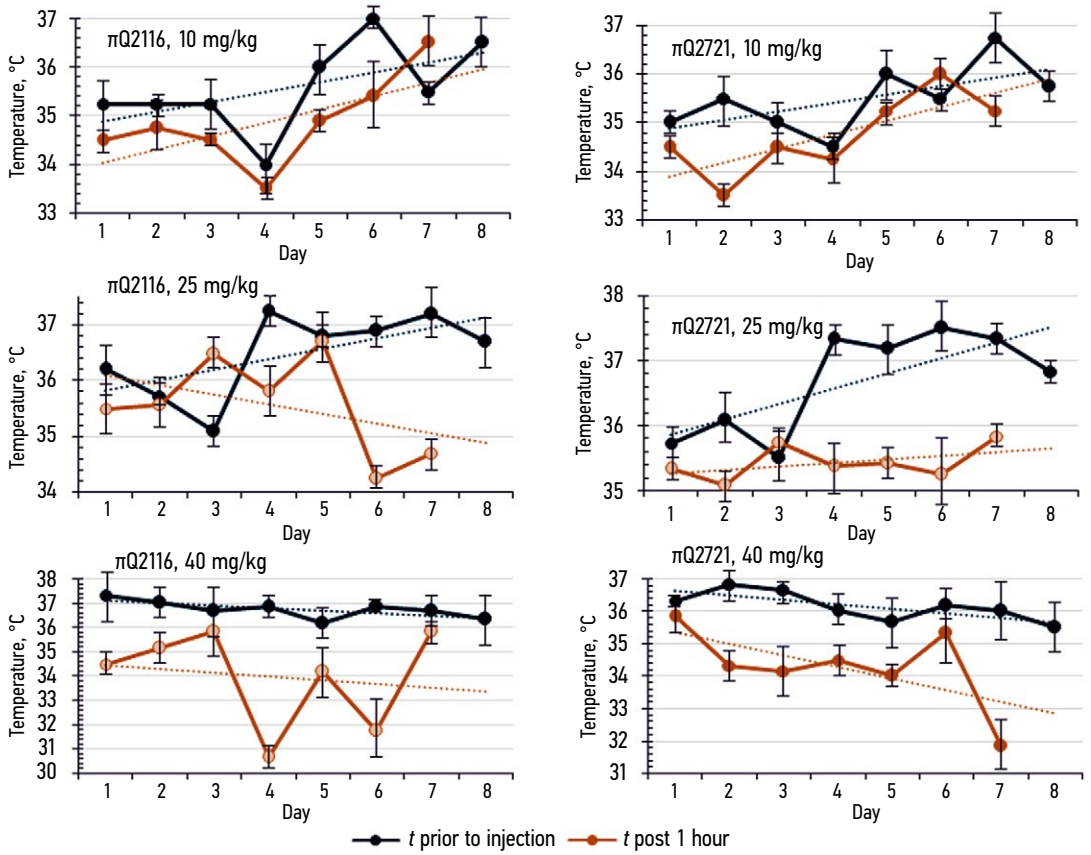

Fig. 2. Rectal temperature patterns during preconditioning with πQ2116 and πQ2721.

Table 2. Rectal temperature variations in mice on days 7 and 8 after preconditioning with metal complexes

Code of the compound	Dose, mg/kg	Temeperature on day 7, first measurement, °C	Temeperature on day 7, second measurement, °C	Temeperature on day 8, °C
Control group (*n* = 14)	–	36.86 (36.83; 37.83)	36.36 (36.5; 37.5)	37.0 (36.0; 37.5)
	10 (*n* = 14)	37.0 (36.5; 37.0)	35.0 (34.5; 35.5)	36.5 (36.0; 36.75)
πQ1983	25 (*n* = 14)	36.92 (36.5; 38.0)	35.42 (34.0; 36.5)	36.42 (35.5; 37.5)
	40 (*n* = 14)	36.83 (36.5; 37.0)	36.0 (35.5; 36.5)	36.67 (36.5; 37.5)
	10 (*n* = 14)	35.5 (35.0; 36.0)	36.5 (36.0; 37.0)	36.5 (36.25; 37.25)
πQ2116	25 (*n* = 14)	37.2 (34.0; 35.0)	34.7 (34.03; 36.92)	36.7 (35.5; 38.0)
	40 (*n* = 14)	36.67 (36.0; 37.0)	35.83 (35.0; 36.5)	36.33 (35.5; 38.0)
	10 (*n* = 14)	36.75 (36.5; 37.0)	35.25 (35.0; 35.5)	35.75 (35.5; 36.0)
πQ2721	25 (*n* = 14)	37.33 (36.0; 38.0)	35.83 (35.0; 37.0)	36.83 (35.0; 38.0)
	40 (*n* = 14)	36.0 (35.5; 36.5)	31.83 (26.5; 35.0)	35.5 (34.5; 36.5)

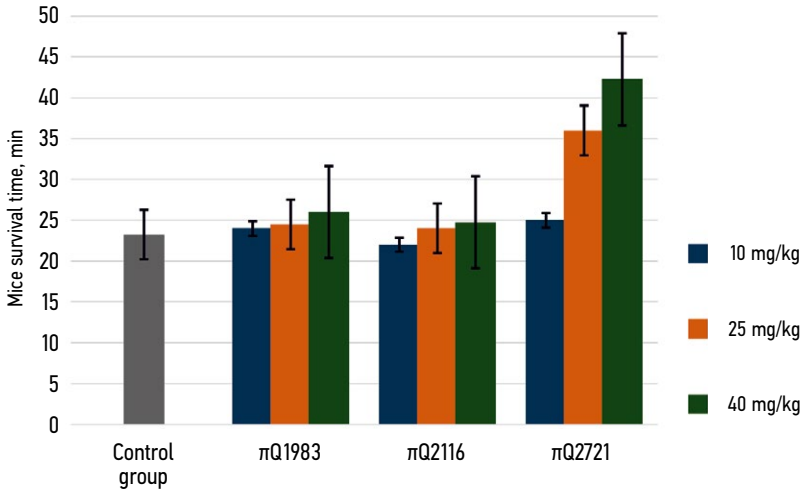

Fig. 3. Tolerance of mice to acute hypoxia and hypercapnia after 7-day preconditioning with metal complexes.

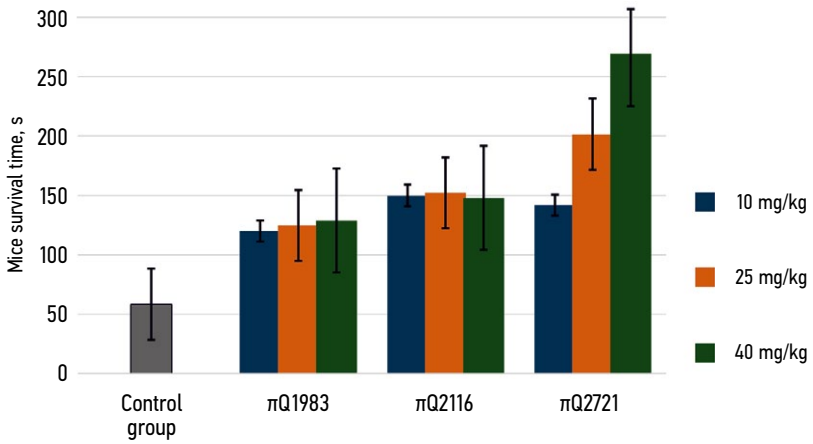

Fig. 4. Tolerance of mice to acute hypobaric hypoxia after 7-day preconditioning with metal complexes.

Although there is no direct evidence of pro-hypoxic effects for the compounds πQ1983, πQ2116, and πQ2721, our experimental data on metal complexes as antihypoxants, combined with literature reports indicating that transition metal ions inhibit mitochondrial function [20], prompted an investigation into their preconditioning effects in models of acute exogenous hypoxia. Further justification for these experiments came from our earlier studies where the zinc-containing metal complex πQ1104 was shown via polarography to reversibly inhibit oxidative phosphorylation in mitochondria of neurons in the somatosensory cortex of cats [21].

Despite the experimentally confirmed antihypoxic effects of the tested metal complexes, only πQ2721 demonstrated a preconditioning effect on the AH+Hc model after 7 days of administration. This effect was observed starting at a dose of 25 mg/kg. The effect became more pronounced at a dose of 40 mg/kg.

At the same time, on the AH+Hb model, the preconditioning effect was observed for all studied compounds, arranged in the order corresponding to the magnitude of this effect: πQ2721, πQ2116, and πQ1983. Thus, πQ2721 again emerged as the leading compound. Despite the positive effects detected in πQ1983 and πQ2116, these metal complexes did not demonstrate dose-dependent effects at the final experimental stage. As for πQ2721, it provided a statistically significant increase in the preconditioning with dose escalation. The absence of dose-dependent action in πQ1983 and πQ2116 diminishes their prospects in terms of their potential use as pharmacological preconditioning agents.

Pharmacological preconditioning occurs only when a chemical compound initiates a distinct hypothermic effect. The hypobaric model is rightfully considered the most sensitive for detecting protective effects during acute hypoxia in animals, as it represents a "purer" form of oxygen deprivation compared to the hypercapnia, where carbon dioxide significantly influences the final outcome [22].

According to studies by Gavrilina [9] conducted on the AH+Hb model, cobalt and nickel chlorides provided the greatest preconditioning effect in mice among the tested compounds, demonstrating neuroprotective action and inducing pronounced hypothermia. However, these experiments did not investigate the dose-dependence of the effects of these compounds. The conclusion was drawn that hypothermia (direct or chemically mediated) is an essential component for successful initiation of pharmacological preconditioning.

Thus, based on our own data and literature analysis, we propose a hypothesis that the mechanisms of pharmacological preconditioning induced by the metal complex πQ2721 may involve two key factors. First, its ability to limit the rate of bioenergetic processes in body tissues, primarily in skeletal muscles and cerebral neurons. This effect likely enhances hypothermia by reducing the activity of neurons in the hypothalamic chemical thermoregulation center responsible for heat production. Second, according to chemistry experts, transition metal ions such as cobalt, nickel, and others can replace iron ions in heme oxygen sensors and mitochondrial complex III of the electron transport chain [10, 23]. Considering that the most active compound in our study, πQ2721, contains divalent zinc as the complexing metal, which does not change valence during biological reactions, its potential influence on oxygen sensors can be ruled out. However, it has been known since the 1960-s that zinc ions *in vitro*, even at trace concentrations (10^{-6}–10^{-5} M), effectively inhibit the mitochondrial respiratory chain by blocking the site between cytochromes b and c_1. Furthermore, the electron transport inhibition effect in the mitochondrial compartment may be enhanced through direct competitive interactions between Zn^{2+} and Fe^{2+} [20].

CONCLUSION

Among the three metal complexes—πQ1983, πQ2116, and πQ2721—studied in two models of acute exogenous hypoxia in mice, all demonstrated the preconditioning effect, which was most pronounced under AH+Hb conditions.

Unlike the metal complexes πQ1983 (zinc II) and πQ2116 (nickel II), the compound πQ2721 (zinc II) exhibited a distinct dose-dependent preconditioning effect in the AH+Hc and AH+Hb models, thereby significantly enhancing the animals' tolerance to oxygen deficiency.

The preconditioning effect of metal complexes is most pronounced in conjunction with hypothermia, which can serve as a valuable marker in the targeted search for novel pharmacological agents for preconditioning.

ADDITIONAL INFORMATION

Authors contribution. *O.A. Mosin, A.E. Belenky, D.V. Stepanov, A.V. Evseev*: writing—original draft, data analysis; *A.V. Evseev:* writing—review & editing, conceptualization. All authors made substantial contributions to the conceptualization, investigation, and manuscript preparation, and reviewed and approved the final version prior to publication.

Competing interests. The authors declare that they have no competing interests.

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Ethical review. The study was approved by the Local Ethics Committee of Northern State Medical University (Minutes No. 76 dated March 23, 2024).

Statement of originality. The authors did not use previously published information (text, illustrations, data) to create this paper.

Data availability statement. Data generated in this study are available in the article.

Generative AI. Generative AI technologies were not used for this article creation.

Provenance and peer-review. This work was submitted to the journal on its own initiative and reviewed according to the standard procedure. Two external reviewers, and a member of the editorial board participated in the review.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. О.А. Мосин, А.Э. Беленький, Д.В. Степанов, А.В. Евсеев — написание статьи, анализ данных; А.В. Евсеев — редактирование статьи, разработка общей концепции. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Этическая экспертиза. Рассмотрено и одобрено локальным этическим комитетом ФГБОУ ВО «СГМУ», протокол №76 от 23.03.2024 г.

Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).

Доступ к данным. Все данные, полученные в настоящем исследовании, доступны в статье.

Генеративный искусственный интеллект. При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.

Рассмотрение и рецензирование. Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали два внешних рецензента и член редакционной коллегии.

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