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IMPACT OF INDOLINE DERIVATIVES ON CARBOHYDRATE METABOLISM OF RATS WITHIN A COLD STRESS MODEL

This study investigated the protective effect of 2-oxoindoline-3-glyoxylic acid derivatives and its mechanisms upon cold injury in rats. The protective activity of 13 newly synthesized 2-oxoindoline-3-glyoxylic acid derivatives was evaluated at a dose of 12 mg/kg body weight administered intraperitoneally. One hour after administration, the physical endurance of male rats was assessed under cold stress conditions (water temperature +10 °C) with an additional load (10% of body weight) by measuring the duration of swimming (in seconds) until the appearance of complete fatigue (immersion). The results were compared to those of the reference substance ethylthiobenzimidazole at a dose of 50 mg/kg. The most effective results were observed after the administration of 2-hydroxy-2-(5-methyl-2-oxy-1,2-dihydroindol-3-ylidene)-N-phenylacetamide. In animals, serum glucose levels and carbohydrate metabolism indicators in hepatocytes (glycogen, glucose, pyruvate, lactate content and their ratio) were determined. It was established that administering 2-hydroxy-2-(5-methyl-2-oxy-1,2-dihydroindol-3-ylidene)-N-phenylacetamide significantly prolonged the duration of swimming in cold water, compared to both the control group and the group administered ethylthiobenzimidazole. Under hypothermic conditions, this compound prevented hypoglycaemia and positively affected carbohydrate metabolism in the liver, as evidenced by preserved glycogen, glucose and pyruvate content, and increased lactate levels.

Key words: *2-oxoindoline derivatives, glyoxylic acid, cold resistance, cold exposure, carbohydrate metabolism, glycogen, glucose, pyruvate, lactate, male rats.*

The adverse effects of cold can have a negative impact on the body, causing various pathologies to develop. [18]. Excessive exposure to low temperatures can result in considerable harm, with the potential to cause disability and even fatality.

Cold exposure is one of the unfavorable environmental factors affecting the population of Ukraine, especially under current conditions of ongoing warfare [3]. Cold injuries most frequently occur among mountaineers, homeless individuals, workers in refrigeration units, and military personnel [5]. Contributing factors include high humidity, disorders affecting thermoregulation (cachexia, hypothyroidism, alcohol intoxication), and excessive physical exertion [4].

In winter time in Ukraine, military personnel often sustain cold-related injuries, particularly in challenging combat conditions. [8]. It should be noted that cold weather has a negative effect on the cardiovascular system and increases mortality from this pathology [9].

This highlights the urgent need for new, safe, and effective means of preventing and treating cold injuries, particularly under extreme conditions in

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which most hypothermia cases result in poor outcomes. To maintain physical performance, especially under excessive cold stress, actoprotectors can be used, although their range is currently very limited.

Glyoxylic acid and its derivatives are actively being studied. Derivatives of 2-oxoindoline-3-glyoxylic acid have demonstrated antihypoxic, antioxidant, nootropic, antidepressant, analgesic, and antistress activities [10, 11]. These compounds exhibit low toxicity and are capable of modulating the activity of neurotransmitter systems and/or endogenous ligands [12]. The presence of a glyoxylic acid fragment in the molecule may contribute to improved water solubility as well as favorable membrane-tropic and metabolic effects.

A review of the literature revealed that sufficient information has been accumulated on the neurotropic activity of 2-oxoindoline-3-glyoxylic acid derivatives for the treatment of cold injury. This information is a prerequisite for searching for and studying new compounds with similar pharmacological properties [10].

Since glucose and its metabolites play an important role in compensating for energy metabolic processes that develop in response to cold factors [6, 7], the effect of these limited processes became the basis for predicting the effect of the compounds under study.

The aim of this study was to investigate the effect of 2-oxoindoline-3-glyoxylic acid derivatives on carbohydrate metabolism during cold exposure.

MATERIALS AND METHODS

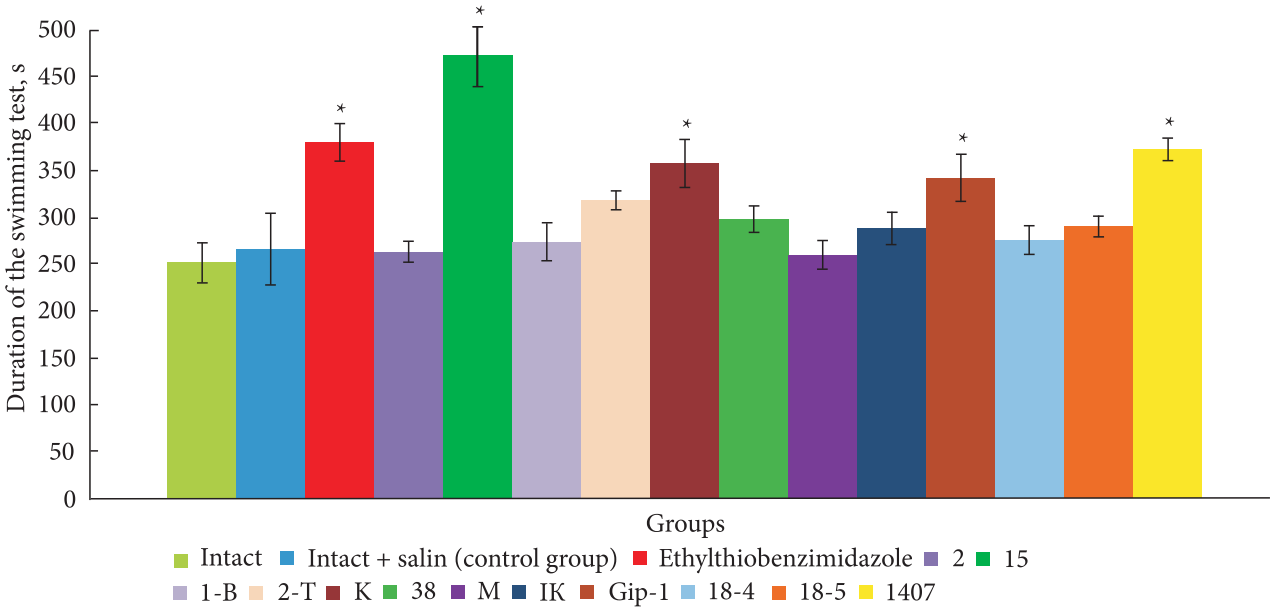
The study was conducted at the vivarium of Poltava State Medical University and was approved by the Ethics Committee of Poltava State Medical University (Protocol No. 225 of March 21, 2024). Experimental studies were conducted in accordance with the main requirements of the Law of Ukraine "On the Protection of Animals from Cruel Treatment" (No. 3446-IV of February 21, 2006), the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (18 March 1986), Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes (22 September 2010).

Experiments were performed in 150 sexually mature (6—7-month-old) male Wistar rats weighing 180—200 g. The animals were housed under a 12-hour light/dark cycle (8:00—20:00 light; 20:00—8:00 dark) in cages of 4–5 rats each, received a diet in the form of feed mixture, and given free access to water. Experiments were conducted in the spring, during the first half of the day. Each group consisted of 10 animals.

Simple amides of 2-oxoindoline-3-glyoxylic acid with laboratory codes were used for the study: 2 (2-hydroxy-2-(2-oxy-1,2-dihydro-indole-3-ylidene)-N-phenethyl-1-acetamide); 15 (2-hydroxy-2-(5-methyl-2-oxy-1,2-dihydroindol-3-ylidene)-N-phenylacetamide); 1-B (N-biphenyl-2-yl-2-hydroxy-2-(2-oxy-1,2-dihydroindol-3-ylidene)-acetamide); 2-T (2-hydroxy-2-(2-oxy-1,2-dihydroindol-3-ylidene)-N-[1,2,4]triazol-4-ylacetamide); K (2-hydroxy-N-(4-methyl-2-oxy-2H-chromen-7-yl)-2-(2-oxy-1,2-dihydroindol-3-ylidene)-acetamide); 38 (2-hydroxy-2-(2-oxy-1,2-dihydroindol-3-ylidene)-N-phenylacetamide); M (2-hydroxy-N-[2-(naphthalen-1-ylamino)-ethyl]-2-(2-oxy-1,2-dihydroindol-3-ylidene)-acetamide); IK (hydroxy-(2-oxy-1,2-dihydroindol-3-ylidene)-acetamide); Hip-1 (N-[(2-oxy-1,2-dihydroindol-3-ylidene)-phenethylcarbamoyl-methyl]-benzamide); 18-4(E)-2-hydroxy-N-(4-hydroxy-naphthalen-1-yl)-2-(2-hydroxyindolin-3-ylidene)-acetamide), 18-5 ((E)-2-hydroxy-N-(5-hydroxy-naphthalen-1-yl)-2-(2-hydroxyindolin-3-ylidene)-acetamide); 1407 (ethyl ester of [2-hydroxy-2-(2-oxo-1,2-dihydro-indol-3-ylidene)-acetamido]acetic acid), whose molecules differed in amino acid residues. These compounds were synthesized at the Department of Analytical Chemistry, National University of Pharmacy (Kharkiv), under the supervision of Prof. S.V. Kolisnyk.

The compounds *ex tempore* were suspended in water for injection using the emulsifier «Tween-80» (Sigma-Aldrich, USA) (1 drop per 25 mg of test substance) and administered intraperitoneally at a dose of 12 mg/kg body weight one hour before testing. The doses were selected based on previous studies in which 2-oxoindoline-3-glyoxylic acid derivatives exhibited antioxidant, neurotropic, and stress-protective effects [11, 12]. Ethylthiobenzimidazole at a dose of 50 mg/kg body weight, synthesized at the experimental plant of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine (Kyiv), was used as a reference compound.

The control group consisted of animals that were given the same volume of solvent (0.9% sodium



The effect of 2-oxoindoline-3-glyoxylic acid derivatives on the duration of the swimming test in rats under cold conditions (10 °C) with additional load (10% of body weight). * — differences are significant compared to the corresponding value of the control group, $p < 0.05$

chloride solution) containing one drop of Twin-80 emulsifier. These animals were subjected to the same exposure as the experimental cohort.

The effects of 2-oxoindoline derivatives were studied under cold exposure, which involved forced swimming in water at +10 °C with an additional load equal to 10% of the rat's body weight. The time to exhaustion (submersion) was recorded, as well as the total swimming time (in seconds). This model simulates cold injury, specifically immersion hypothermia under extreme conditions [1].

The mechanisms underlying the protective action of the most active 2-oxoindoline derivative were examined one hour after the experiment. The glycogen content in rat livers was studied using the anthrone method [17], serum glucose using standard kits from NVP "Philisit-Diagnostika" (Ukraine), as well as lactate and pyruvate (Spine-Lab, Ukraine), and calculated the lactate/pyruvate ratio in rat liver homogenate.

Statistical analysis of the experimental data was performed using "Statistika 6.0" (StatSoft, USA) software and the Kruskal–Wallis criteria. Differences were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

The study showed that the average swimming duration in intact rats in water at +10 °C was 251 ± ± 30.4 seconds. Administration of the solvent with emulsifier to control group animals did not significantly affect swimming duration, which under stressful conditions was 265 ± 25.4 seconds.

A 1.4-fold increase in swimming duration was observed in relation to the use of the substance ethylthiobenzimidazole, compared to the control group ($p < 0.01$).

Preventive administration of 2-oxoindoline-3-glyoxylic acid derivatives promoted increased physical endurance in rats under hypothermic conditions, as evidenced by prolonged swimming time with added weight compared to controls (see Figure).

The introduction of compound 15 prolonged the swimming time of rats by 1.8 times ($p < 0.01$) compared to the control group and by 1.3 times in comparison with the substance ethylthiobenzimidazole ($p < 0.05$). K and Gyp-1 labeled compounds increased swimming time by an average of 1.3 times compared to the control group ($p < 0.05$). Compound 1407 prolonged swimming time by 1.4 times compared to the control group ($p < 0.05$) (see Figure). Conversely, compounds 2, 1-B, 2-T, 38, M, IK, 18-4, and 18-5 had no significant effect on swimming time under hypothermia with an addi-tional load, indicating a lack of protective action.

Thus, some derivatives of 2-oxoindoline-3-glyoxylic acid (specifically compounds 15, K, Gyp-1, and 1407) demonstrated protective effects under cold exposure. These effects were comparable to those of ethylthiobenzimidazole. Notably, com-

Effect of 2-hydroxy-2-(5-methyl-2-oxy-1,2-dihydroindol-3-ylidene)-N-phenylacetamide (compound 15) on carbohydrate metabolism indices in liver of rats under cold exposure (M ± m, *n* = 10)

Animal group	Serum	Liver				
	Glucose mmol/L	Glucose mmol/kg	Glycogen mg/g	Pyruvate mg/kg	Lactate mmol/kg	Pyruvate/ Lactate
Intact	6.13 ± 0.29	6,10 ± 0,43	61,2 ± 2,73	36,2 ± 2,13	1,12 ± 0,09	32,3 ± 2,11
Intact + solvent (control group)	5.93 ± 0.31	6,13 ± 0,45	59,8 ± 2,86	37,4 ± 1,74	1,09 ± 0,08	34,3 ± 2,34
Cold exposure + solvent (pathological control)	3.42 ± 0.27 *	3,56 ± 0,21 *	38,7 ± 2,11 *	25,9 ± 1,72 *	1,92 ± 0,14 *	13,5 ± 1,12*
Cold exposure + ethylthiobenzimidazole 50 mg/kg	4.21 ± 0.33 *	4,34 ± 0,35 *	50,7 ± 4,32 *, #	32,4 ± 2,40 #	1,43 ± 0,12 *, #	22,7 ± 1,76 *, #
Cold exposure + compound 15, 12 mg/kg	4,36 ± 0,29 *, #	4,58 ± 0,41 *, #	54,2 ± 3,83 *, #	34,3 ± 2,12 *, #	1,32 ± 0,09 *, #	26,0 ± 2,04 *, #

Notes: * — differences are significant compared to the corresponding control group value; $p < 0.05$; # — differences are significant compared to the corresponding value in the pathological control group; $p < 0.05$.

pound 15 (2-hydroxy-2-(5-methyl-2-oxy-1,2-dihydroindol-3-ylidene)-N-phenylacetamide) exhibited significantly greater activity than ethylhiobenzimidazole.

Based on these findings, further investigation was conducted to identify the mechanisms underlying the protective effects of the most active compound (2-hydroxy-2-(5-methyl-2-oxy-1, 2-dihydroindol-3-ylidene)-N-phenylacetamide), focusing on changes in carbohydrate metabolism under these experimental conditions.

Administration of physiological saline did not cause significant changes in carbohydrate metabolism parameters in rat liver (see Table). Cold exposure led to marked alterations in energy substrate levels, as indicated by a 1.7-fold decrease in glucose levels in blood serum and liver ($p < 0.001$) compared to the control group. Liver glycogen content decreased 1.6-fold ($p < 0.001$), while pyruvic acid levels fell by 1.4 times ($p < 0.001$). These changes were accompanied by a 1.8-fold increase in lactic acid levels ($p < 0.001$) and a 2.5-fold shift in the pyruvate/lactate ratio ($p < 0.001$) compared to controls.

Preventive administration of ethylthiobenzimidazole (50 mg/kg) significantly mitigated the decrease in glycogen, pyruvate, and lactate levels in hepatocytes, increasing them by 1.3 times on average compared to animals exposed to cold without correction ($p < 0.05$). Under these conditions, the pyruvate/lactate ratio increased by 1.7 times ($p < 0.001$) (see Table).

Preventive administration of compound 15 helped prevent cold-induced hypoglycemia. Glucose levels in blood serum and liver increased 1.3 times ($p < 0.05$) compared to the pathological control group. Following the administration of this compound, glycogen content in the studied organ increased significantly by 1.4 times ($p < 0.05$), as did the level of pyruvic acid, compared with the corresponding values in the control pathology group. Under these conditions, the level of lactic acid decreased by 1.5-fold ($p < 0.05$), contributing to a 1.9-fold increase in the pyruvate/lactate ratio ($p < 0.001$) compared to values after cold exposure without correction.

Thus, compound 15 (2-hydroxy-2-(5-methyl-2-oxo-1,2-dihydroindol-3-ylidene)-N-phenylacetamide) effectively prevented changes in key carbohydrate metabolism products in hepatocytes under cold exposure.

Cold exposure under extreme conditions led to significant metabolic disturbances in the organism, particularly changes in key carbohydrate metabolism products, such as activation of glycogenolysis and glycolysis. The cold-induced reduction in liver glycogen was due to its intensive breakdown into glucose, which was rapidly metabolized. Decreased blood glucose levels can be explained by accelerated glycolysis under extreme stress conditions [19], resulting in the accumulation of under-oxidized carbohydrate metabolites such as pyruvate and lactate, and the onset of fatigue. One possible mechanism of exhaustion is tissue hypoxia and the predominance of anaerobic metabolism, particularly glycolysis activation, which disrupts the synthesis of high-energy phosphate compounds (macroergs) under cold exposure [14]. Another potential mechanism for fatigue and reduced skeletal muscle contractility may be reduced neuromuscular transmission due to decreased reticular formation activity and increased serotonin levels in the frontal cortex and hippocampus [13].

It was established that compound 15 showed the strongest protective effect under cold exposure among the tested 2-oxoindoline-3-glyoxylic acid derivatives. This effect is likely associated with its positive influence on carbohydrate metabolism products in rat liver. Additionally, its involvement in myogenesis cannot be ruled out, as glyoxylic acid has recently been shown to promote myogenesis and prevent dexamethasone-induced muscle atrophy [15]. This was evidenced by the prevention of glycogenolysis and the increase in liver and serum glucose levels, potentially due to the compound's hormonal regulatory influence on these processes.

The 2-oxoindoline derivative also reduced levels of under-oxidized products and shifted the glycolysis product ratio in favor of pyruvate. Pyruvate, as a precursor of tricarboxylic acid cycle substrates, may enhance the energy potential of hepatocytes [2]. The increase in pyruvate may result from improved oxygenation of liver cells or from a direct effect of compound 15 on glycolytic processes, particularly by regulating lactate dehydrogenase activity. Previous studies have shown that 2-oxoindoline-3-glyoxylic acid derivatives exhibit high activity in models of oxygen deprivation, attributed to reduced tissue sensitivity to hypoxia and optimization of cellular respiration [16].

CONCLUSIONS

1. Derivatives of 2-oxoindoline-3-glyoxylic acid have a positive effect on the resistance of rats to cold exposure.

2. The protective effect of compound 15 (2-hydroxy-2-(5-methyl-2-hydroxy-1,2-dihydroindol-3-ylidene)-N-phenylacetamide) (12 mg/kg) under cold exposure is determined by its regulatory effect on carbohydrate metabolism in the rat liver; apparently, the functional group in this compound is the methyl group in the 5 position in the benzol radical, which was not present in any of the compound studied.

3. The protective effect of 2-oxoindoline-3-glyoxylic acid derivatives is not very dependent on the chemical composition or structure of the molecule, but introducing a methyl group enhances it.

This work is a part of the research project conducted by the Department of Pharmacology of Poltava State Medical University (Poltava) titled "Pharmacological study of biologically active substances and medicinal products for the development and optimization of indications for their use in medical practice" (State registration number 0125U002468) (2025—2029).

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ЗМІНИ ВУГЛЕВОДНОГО ОБМІНУ В ПЕЧІНЦІ ЩУРІВ ПІД ДІЄЮ ПОХІДНИХ ІНДОЛІНІВ У МОДЕЛІ ХОЛОДОВОГО СТРЕСУ

У роботі досліджували наявність захисної дії похідних 2-оксоіндолін-3-гліоксилової кислоти та її механізми за холодової травми щурів-самців. Вивчали захисну дію нових похідних 2-оксоіндолін-3-гліоксилової кислоти (13 сполук) у дозі 12 мг/кг маси тіла тварин в умовах холодового впливу, які вводили внутрішньоочеревинно. Через 1 годину досліджували фізичну витривалість щурів-самців при температурі 10 °С із додатковим навантаженням (10 % від маси тіла тварини) шляхом визначення тривалості плавання до появи ознак повної втоми (занурювання) і порівнювали з тривалістю плавання після ведення 50 мг/кг етилтіобензімідазолу. Найкращий ефект спостерігався після введення 2-гідрокси-2-(5-метил-2-окси-1,2-дигідроіндол-3-іліден)-N-фенілацетаміду. У тварин визначали рівень глюкози у сироватці крові показники вуглеводного обміну в гепатоцитах (вміст глікогену, глюкози, пірувату, лактату та їх співвідношення). Встановлено, що введення речовини 2-гідрокси-2-(5-метил-2-окси-1,2-дигідроіндол-3-іліден)-N-фенілацетаміду значуще сприяло подовженню тривалості плавання у холодній воді порівняно з показниками контрольної групи і групи з введенням етилтіобензімідазолу. За умов гіпотермії дана сполука запобігала розвитку гіпоглікемії та позитивно впливала на обмін вуглеводів у печінці, що підтверджувалось збереженням вмісту глікогену, глюкози, пірувату та підвищенням рівня лактату.

***Ключові слова*:** похідні 2-оксоіндоліну, гліоксилова кислота, холодова стійкість організму, холодовий вплив, обмін вуглеводів, глікоген, глюкоза, пірувати, лактат, щури-самці.