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STUDY OF THE ANTIHYPOXIC ACTIVITY OF A COMPOSITION OF L-CARNITINE AND SUCCINIC ACID IN EXPERIMENTAL MODELS OF HYPOXIA.

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Abstract: The antihypoxic properties of a composition based on l-carnitine and succinic acid were studied in comparison with the drug Mildronate, manufactured by JSC Grindex, Latvia, in normobaric and hemic hypoxia models in 48 male white outbred mice.

Key words: hypoxia condition, sodium nitrite, dry extract, L-carnitine, amber acid, normobaric and hemic hypoxia, protection coefficient.

Аннотация: l-карнитин ва қахрабо кислотаси асосида олинган композициясини гипоксияга қарши хусусиятлари АО ГРИНДЕКС, Латвия ишлаб чиқарилган Милдронат препарати билан солиштирма тартибда нормобарик ва гемик гипоксия моделларида 48 та, оқ зотсиз эркак сичқонларда ўрганилди.

Таянч сўзлар: гипоксия холати, натрий нитрит, қуруқ экстракт, Л-карнитин, қахрабо кислотаси, нормобарик ва гемик гипоксия, химоя коэффициенти.

Hypoxia is a physiological state resulting from decreased oxygen delivery to organs or impaired oxygen utilization by body tissues. Consequently, hypoxia represents a universal pathological process and a primary cause of functional disorders in various diseases. It plays a decisive role in both the onset and progression of numerous conditions, as any pathological state is directly or indirectly associated with oxygen deficiency [2,3,5]. Hypoxia can occur both at rest and during functional strain of organs and systems, triggering compensatory reactions to mitigate the oxygen deficit. Therefore, the development of antihypoxic agents remains a critical and relevant challenge in modern medicine.

In this context, we investigated the effect of a composition containing L-carnitine and succinic acid on the development of normobaric hypoxia with hypercapnia and hemic hypoxia. The combination of L-carnitine and succinic acid exhibits a synergistic effect, aimed at intensive energy metabolism support and cellular protection against oxygen deprivation. This composition facilitates more efficient oxygen utilization by tissues, which is vital during vascular disorders and tissue acidosis.

Succinic acid participates in the Krebs cycle, accelerating the oxidation of nutrients and allowing cells to replenish energy reserves rapidly, even under hypoxic conditions. Furthermore, it improves tolerance to physical and psycho-emotional stress and accelerates post-stress recovery. Previous studies have demonstrated the pronounced actoprotective activity of the L-carnitine and succinic acid composition. In this report, we present the findings regarding the impact of this composition on normobaric hypoxia with hypercapnia and hemic hypoxia.

MATERIALS AND METHODS

The experiments were conducted on 48 male white mice weighing 19–21 g. Animals of the same body weight (with a variation of no more than 2 g per group) were subjected to normobaric hypoxia with hypercapnia (jar hypoxia) and placed individually in hermetically sealed jars with a volume of 200 cm^3. The time from placement in the container to respiratory arrest and death of the animal was recorded [1,4]. The results obtained were expressed as a percentage of the control.

The criteria for efficacy were the survival time (ST) of the experimental animals and the protection coefficient (PC), which is determined by the formula: PC = ST (experimental) / ST (control) [6]. Hemic hypoxia was induced by a single subcutaneous administration of sodium nitrite at a dose of 200 mg/kg to white mice [7]. The white mice were divided into 4 groups of 6 animals each: a control group and 3 experimental groups. The test compound of L-carnitine with succinic acid was administered 1 hour before induction of the hypoxia model at doses of 350 mg/kg and 500 mg/kg intragastrically. To compare the antihypoxic activity of the preparation, the experimental animals received the drug mildronate manufactured by (JSC GRINDEX, Latvia) at a dose of 200 mg/kg. The control group of experimental animals was administered saline in a volume equivalent to that of the administered drug. The obtained data were statistically analyzed using the Statistica program for Windows 95.

RESULTS

The experimental results show that, after being placed in a jar, animals in the control group develop hypoxia—that is, a decrease in the partial pressure of oxygen in the inhaled air. Against the backdrop of acute oxygen deprivation, all animals in the experiment died. The average survival time of white mice was 25.2 minutes. As shown in Table 1, when a mixture of L-carnitine and succinic acid was administered at a dose of 350 mg/kg one hour before the experiment, the average survival time of the test animals increased by 22% compared to the control group. Under similar conditions, the drug mildronate (manufactured by GRINDEX JSC, Latvia) at a dose of 500 mg/kg prevented the death of test animals by 29%, respectively. When the dose was increased to 500 mg/kg, the survival time of white mice was 35.44 minutes. It should be noted that the half-life was 1.50 minutes (Table 1).

Table 1

Effect of a mixture of L-carnitine and succinic acid on the lifespan of white mice under norm baric hypoxia with hypercapnia (M ± m, n=6)

Dose, mg/kg	Volume of solution, mL	Survival time under hypoxic conditions, min	Protection coefficient
Control group			
		25,2±1,1	
l-carnitine and succinic acid formulation			
350	0,35	**35,4±1,2***	1,40
500	0,5	37,8±1,3*	1,50
Mildronate manufactured by GIRNDEKS, Latvia			
500	0,5	39,2±1,1*	1,55

Note: * indicates a statistically significant difference at $p < 0.05$ compared to the control group.

In another series of experiments, the ant hypoxic activity of the formulation was studied in cases of hemic hypoxia. Chemical hypoxia arises due to disturbances in the blood system,

specifically a decrease in its oxygen-carrying capacity. This led to the development of metabolic acidosis. Under the influence of sodium nitrite, methemoglobin forms in the body, which is unable to reversibly bind oxygen. As a result, oxygen transport by the blood is disrupted, and chemical hypoxia occurs. In the control group of experimental animals, shortness of breath and clonic-tonic seizures appeared after the administration of sodium nitrite. All animals died. The average lifespan of the white mice was 21.5 minutes. In the experiment, the average lifespan of animals receiving the L-carnitine and succinic acid formulation increased the resistance of white mice to hypoxia at doses of 350 mg/kg and 500 mg/kg; an increase in the time to onset of the first convulsions and an increase in the animal's lifespan were observed compared to the control group, and, compared to the control group, significantly extended the animals' lifespan by 35% and 50%, respectively. Consequently, under similar conditions, the study of the drug mildronate (manufactured by GRINDEX JSC, Latvia) at a dose of 500 mg/kg showed a survival rate of 1.53, and it prevented the death of test animals in 52% of cases (Table 2).

Table 2

Effect of a mixture of L-carnitine and succinic acid on the lifespan of mice under hemic hypoxia

(Mean ± SD, n=6)

Dose, mg/kg	Volume of solution, mL	Survival time under hypoxic conditions, min	Protection coefficient
Control group			
		21,5± 1,2	
l-carnitine and succinic acid formulation			
350	0,35	**29,3±1,3***	1,36
500	0,5	32,6±1,2*	1,51
Mildronate manufactured by GIRNDEKS, Latvia			
500	0,5	33,1 ± 1,1*	1,53

Note: * indicates a statistically significant difference at $p < 0.05$ compared to the control group.

Thus, the results of the study, as well as data from the literature, suggest that the protective effect of the L-carnitine and succinic acid formulation and the reference drug mildronate (GRINDEX JSC, Latvia) in hypoxia is associated with a reduction in the body's oxygen demand.

Conclusion. Studies of the L-carnitine and succinic acid composition under conditions of norm baric hypoxia with hypercapnia and hemic hypoxia have demonstrated ant hypoxic activity. In terms of its ant hypoxic effect, it is comparable to the reference drug mildronate (GRINDEX JSC, Latvia). These studies provide an opportunity to expand the range of ant hypoxic medications.

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