OXIDATIVE STRESS EFFECT ON MEMORY AND LEARNING PROCESSES AND BLOOD RHEOLOGICAL PROPERTIES CAUSED BY HYPERTHERMIA OF THE WHOLE BODY IN WHITE RATS

Rtveladze T.Z.[1], Mitagvaria N.P.[2], Iosebidze T.I.[3]
Email: Rtveladze6118@scientifictext.ru

[1]Rtveladze Tekla Zakharevna – Prosthodontist, PhD Student;
[2]Mitagvaria Nodar Prokofievich - Academician of Georgian National Academy of Sciences, Dr., Professor,
DEPARTMENT OF PHYSIOLOGY; FACULTY: MEDICAL SCHOO,
NEW VISION UNIVERSITY,
TBILISI;
[3]Iosebidze Tinatin Iosifovna – Associate Professor,
DEPARTMENT OF BIOLOGY, FACULTY OF EDUCATION, EXACT AND NATURAL SCIENCES,
GORI STATE TEACHING UNIVERSITY, GORI,
GEORGIA

Abstract: *the medical capabilities of the thermal factor have been used since ancient times. This is reported by the famous Maximus of Hippocrates (460-356 BC) "Those diseases which medicines do not cure, iron cures; those which iron cannot cure, fire cures; and those which fire cannot cure, are to be reckoned wholly incurable." [6, p. 35-42].*
It is probably difficult to find any pathological condition that does not accompany or is not involved in the development of this phenomenon - neurodegenerative disorders, cancer, ischemic cascade, Parkinson's and Alzheimer's diseases, etc. [1, p. 891-910; 2, p. 44-52; 3. p. 187-193].
A study of hyperthermia in white rats revealed the effects of oxidative stress on animal behavior and the possibility of the occurrence of the hormesis phenomenon and its role in changes in animal behavior in particular, learning and memory [4]. Research on (WBH) learning and memory processes and blood rheological properties has revealed new therapeutic potential for whole-body hyperthermia.
Keywords: *whole body hyperthermia, white rats, hormesis; oxidative stress, experiments.*

ВЛИЯНИЕ ОКИСЛИТЕЛЬНОГО СТРЕССА НА ПАМЯТЬ, ПРОЦЕССЫ ОБУЧЕНИЯ И РЕОЛОГИЧЕСКИЕ СВОЙСТВА КРОВИ, ВЫЗВАННОЕ ГИПЕРТЕРМИЕЙ ВСЕГО ТЕЛА У БЕЛЫХ КРЫС

Ртвеладзе Т.З.[1], Митагвария Н.П.[2], Иосебидзе Т.И.[3]

[1]Ртвеладзе Текла Захаревна – врач-ортопед, аспирант;
[2]Митагвария Нодар Прокофьевич – академик Национальной академии наук Грузии, доктор, профессор,
кафедра физиологии, факультет: школа медицины,
Университет New Vision,
г. Тбилиси;
[3]Иосебидзе Тинатин Иосифовна – доцент,
кафедра биологии, факультет образования, точных и естественных наук,
Горийский государственный педагогический университет, г. Гори,
Грузия

Аннотация: *лечебные возможности теплового фактора использовались с давних времен. Об этом сообщает знаменитый Максим Гиппократа (460-356 гг. До н.э.): «Те болезни, которые не лечат лекарства, лечит железо; те, которые не лечит железо, лечит огонь; и те, которые не лечит огонь, следует считать полностью неизлечимыми." [6, с. 35-42].*
Наверное, сложно найти какое-либо патологическое состояние, которое не сопровождает или не участвует в развитии этого явления - нейродегенеративные расстройства, рак, ишемический каскад, болезни Паркинсона и Альцгеймера и др. [1, с. 891-910; 2, с. 44-52; 3, с. 187-193].
Изучение гипертермии у белых крыс выявило влияние окислительного стресса на поведение животных и возможность возникновения феномена гормезиса и его роль в изменениях в поведении животных, в частности, в обучении и памяти [4]. Исследования процессов обучения и памяти, а также реологических свойств крови выявили новый терапевтический потенциал гипертермии всего тела.
Ключевые слова: *гипертермия всего тела, белые крысы, гормезис, окислительный стресс, эксперименты.*

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Intensive study of the mechanisms of oxidative stress began in the mid-1960s, and, in our time, the urgency of this problem has not diminished, on the contrary, it has increased. There are several pathological conditions at this time

where no association with oxidative stress has been shown. One of the important aspects of the multifaceted problem of oxidative stress is the study of tissue-specific mechanisms [5, p. 97-112].

The aim of our study was to investigate the effects of oxidative stress induced by hyperthermia in white rats on animal behavior and changes in blood rheological properties, the possibility of the occurrence of the phenomenon of hormesis, and the role of this phenomenon in changes in animal behavior.

What is most convenient and simple to use in experiments on rats in terms of learning and memory processes turned out to be a multi-layered labyrinth consisting of 30 cm high supports fixed to platforms (Fig. 1). The use of various labyrinth constructions in animals began in the early twentieth century and is still used today to study their behavioral reactions, learning and memory processes.

This construction of the labyrinth is easy and simple to change - it creates more complex or simple tasks and allows observations of animal behavior in different experimental conditions. Its construction is shown in Figure 1.

By the trial and error method, the rat learns to move in the optimal (shortest) trajectory, depending on the experimental conditions, and as a result of learning, the animal reaches the full passage of the labyrinth in a range of a few minutes to a few seconds.

This particular method of learning proved to be the most acceptable and suitable for performing the experimental tasks that were planned in our experiments. That is, to assess the animal's level of learning and memory retention.

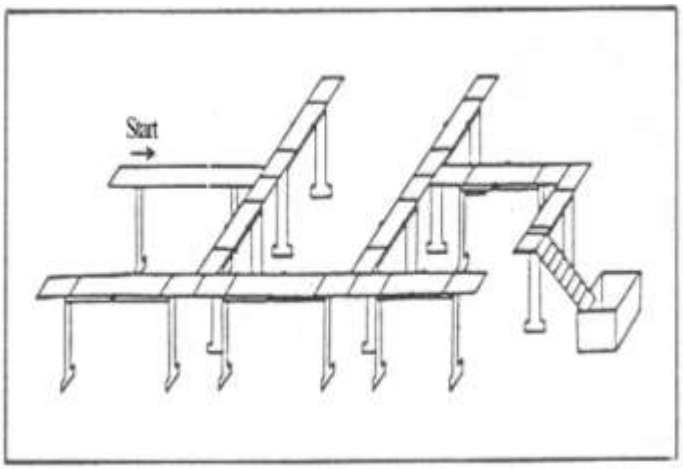

Fig. 1. Construction of a multi-layered elevated labyrinth

The following parameters are usually used: the number of errors allowed (the number of deviations from the optimal route) and the time required to exit the maze. We believe that this approach is the most adequate for the tasks set in our study.

Completion of the first phase of this study allowed us to obtain reliable information about what influences the WBH learning process in a multistory labyrinth after exposure to three different temperatures in a special hyperthermia cabin.

Before analyzing the results of a further experiment, it is advisable to mention a few important facts about changes in brain temperature in relation to temperature changes inside the hyperthermic cabin (HC), in particular the brain temperature. The fact is that if we increase the temperature in the hyperthermic cabin (HC) to 44-45C^0, the temperature in the brain tissue does not change and is maintained in the range of about 36-36.5 C^0. Although further increase in temperature in HC causes the brain temperature to rise and when it reaches about 41 C^0 the animal usually dies. Thus, with exposure to 38, 39, and 40^{0}C in HC, the animals' brain temperature does not change dramatically even if the WBH exposure lasts for several hours.

In a series of experiments, we studied the learning ability of animals in a maze for 2 and 4 hours after exposure to hyperthermia at temperatures of 38, 39, and 40^{0}C, respectively. The most pronounced results were obtained after exposure to 40C^0 for 4 hours: the total passage time through the labyrinth (compared to control animals (Figure 2) and at temperatures of 38 and 39^{0}C) was significantly reduced.

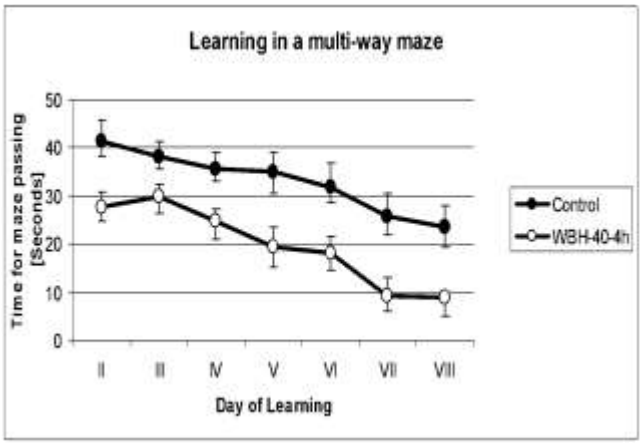

Fig. 2. Labyrinth passage time of control and WBH Exposure Group for animals (4 hours, 40^0C)

Interesting results were obtained after determining the rheological properties of blood in the above experimental conditions. We found that the erythrocyte aggregation index is a parameter significantly dependent on temperature. Its changes occur within 4 hours of WBH exposure at different temperatures (e.g., 38^0C shown in Figure 3).

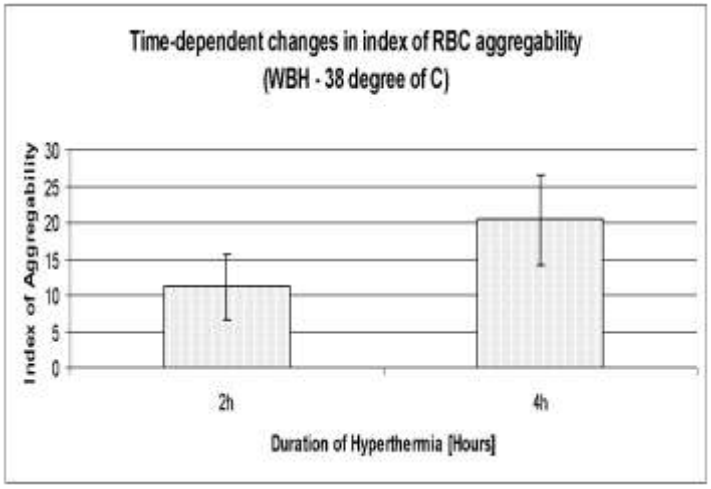

Fig. 3. Changes in temporal dependence in the erythrocyte aggregation index

It should be noted that despite the duration of exposure, we did not observe any statistically significant change in erythrocyte aggregation index level induced by WBH exposure (38, 39, and 40^0C). The same can be said about changes in WBH memory processes. Animals that reached the level of "automatic" behavior in the maze did not change such behavior after exposure to WBH (38, 39, or 40^0C). As mentioned above, we got the clearest results after 4 hours of exposure to 40^0C.

The passage time through the labyrinth (compared to control animals and animals at 38 and 39^0C) was significantly reduced. We admit this fact as a well-defined behavioral manifestation of the effect of WBH hormesis.

A very significant increase in behavioral activity aimed at escaping from non-etiological conditions in response to oxidative stress (caused by hyperthermic exposure), in our view, indicates that the dose of stress induced in this case was to stimulate the mechanisms of hormonalization.

Within the required range, given that the most noticeable changes in animal behavior were observed after exposure to 40^0C, we focus on this temperature, but according to the obtained results,

the use of 45^0C temperature (Fig. 4) shows the effect of elevated temperature (up to 45^0C) in the hyperthermia chamber on the behavior of groups of tested animals.

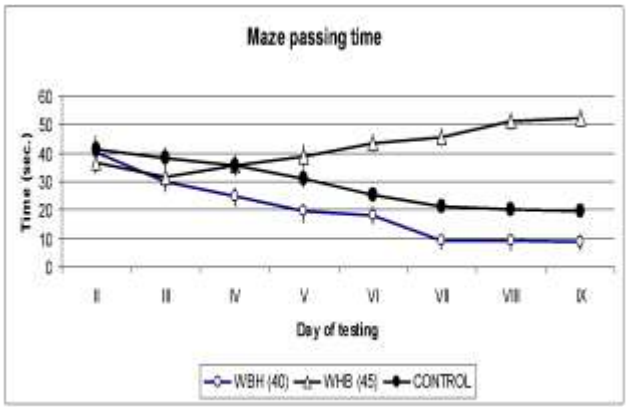

Fig. 4. Labyrinth passage time for groups of control and tested animals at WBH (40 and 45^0C)

As we can observe, the behavior of this group of animals differed dramatically from the third day of testing. Animals exposed to 45^0C hyperthermia took more than 50 seconds (5 times higher than 40^0C, and 2.6 times higher than the control group) to cross the maze. All differences were statistically significant ($p < 0.01$).

Thus, from the third day of testing, the effect of hyperthermia on 45^0C was disrupted. We note that the main idea of hormesis (the dose-dependent effect of induced stress) has become very clear.

In the following series of experiments, we attempted to demonstrate the rheological properties of artificially altered (aggravated) blood induced by injection of a 10% solution of high molecular weight dextran T-500, labyrinthine experiments without combined and WBH exposure (40^0C) behavior of animals in four groups tested (4 × 12 animals).

As shown in Figure 5, the behavior of the control and dextran-initiated groups did not differ significantly. The group of animals subjected to hyperthermia (40^0C) had a pronounced hormesis effect, while the same temperature exposure of animals with aggravated blood viscosity induced by dextran T-500 injection significantly altered (and statistically confirmed) that hormesis was eliminated. Experiments have also shown that all the investigated effects have a fairly strong monotonous dependence on the dose of fluid exposure measured in a wide range of parameters, and their dimensional combinations are far from lethal and quaternary levels even at sufficiently low exposure doses. They can therefore be not only an effective means of stimulating hormesis and immune defense mechanisms, but also a practically harmless method for testing toxicity using experimental animals.

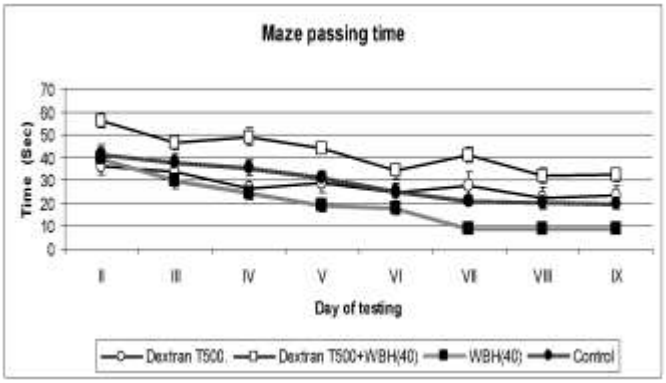

Fig. 5. Time of passage of control, dextran T500-derived and WHB (40^0C) affected animals into the labyrinth

Thus, the research on the possible effects of whole-body hyperthermia (WBH) on learning and memory processes and blood rheological properties has revealed a new, previously unknown healing potential for hyperthermia of the whole body. Experiments using laboratory observations of behavioral parameters and measurement of blood rheological characteristics in laboratory rats in a hyperthermic chamber showed that:

In all cases where we use WBH as a hormesis phenomenon it is fundamentally important in oncological or other studies to keep the temperature range of hyperthermia within the "hormsis range". This is extremely important not only for the effectiveness of the hormesis mechanism, but also for keeping the rheological parameters of the blood within the appropriate norm.

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