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Hypoxic Preconditioning Eliminates Differences in the Innate Resistance of Rats to Severe Hypoxia

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Abstract

Hypoxic preconditioning is able to increase the body's resistance to hypoxic/ischemic stress. Understanding how to apply the hypoxic response to initiate the protective mechanism of ischemic preconditioning is a high priority. However, the relationship between innate resistance to hypoxic stress and preconditioning efficiency of moderate hypoxia has been poorly studied. In our work, the efficiency of single moderate hypobaric hypoxia (HBH) for resistance to severe hypobaric hypoxia (SHBH) was studied on intact rats and those pre-tested under SHBH with low, intermediate and high resistance to hypoxia. HBH has a significant preconditioning action on the resistance to hypoxia over a wide range from 270 to 1464 s (4.5 to 24.5 min) and at the same time eliminates the differences in the endurance under SHBH between all rat groups. It is concluded that 1) HBH preconditioning efficiency does not depend on an innate resistance to SHBH and prior hypoxic experience of rats; and 2) the pre-testing to severe hypoxia has no value for predicting the hypoxic preconditioning efficiency and study of adaptive mechanisms.

Keywords

Resistance to Hypoxic Stress, Severe Hypoxia, Hypoxic Preconditioning

1. Introduction

Short episodes of non-damaging stress impacts of different aetiologies are capable of increasing the body's resistance to various pathological factors. Among them, the hypoxic/ischemic adaptive factors are of greatest interest, because it is likely that the hypoxic component (tissue hypoxia) forms the pathogenesis of many diseases. Murry *et al.* [1] were the first to describe the protective effect of the short ischemic exposure against ischemic stroke, suggested a preconditioning term for this phenomenon. Subsequently, the authors made it clear that the second most important component of the

adaptive effect is the subsequent re-oxygenation (reperfusion) [2].

The hypoxic and ischemic preconditionings are two closely related processes by nature and therapeutic potential. Hypoxic factor is the main in ischemic preconditioning effect. Hypoxic or ischaemic preconditioning *in vitro* and *in vivo* is a powerful protective mechanism against ischaemic injury and other acute injuries in many organ systems. Thus, the preconditioning effects were identified for the heart [1] [3] [4] [5], brain [6]-[13], liver [14] [15] [16] and kidneys [17] [18] *in vivo*.

Hypoxic/ischaemic preconditioning is a multifactorial process requiring the interaction of numerous signals, second messengers and effector mechanisms [8] [9] [12] [13] [19] [20] [21]. Understanding how to apply the hypoxic response to initiate the protective mechanism of ischemic preconditioning is a high priority [13]. Direct preconditioning action or the molecular effectors of the hypoxic protective response could reveal promising therapeutic targets.

Systemic hypoxic preconditioning is achieved by short-term adaptation to a single one-three-hour moderate hypoxic continuous or intermittent exposure, in which hypoxia alternates with normoxia or hyperoxia [11] [12] [21] [22] and may be maintained for one day [11] [20] [22] [23]. The advantage of the short-term adaptation, especially after continuous hypobaric hypoxia, is the most pronounced and rapid preconditioning effect in the first minutes of the re-oxygenation [20] [22] [23].

Animals of any species show very different resistances to hypoxia. This implies different mechanisms of resistance. Therefore, pre-testing has been developed for the study of mechanisms of severe hypoxia, which are incompatible with life (3% - 4.5% O_2 for rats). The idea belongs to Purushottam and Ghosh [24]. Experimental animals were pre-tested under the same severe hypoxic conditions and divided into groups of high, intermediate and low resistance to hypoxia [24] [25] [26] [27] [28]. Later, the pre-testing under severe hypoxia was applied to rats for the investigation of mechanisms of hypoxic preconditioning [22] [23].

Using this pre-test, we found that a single session of moderate hypobaric hypoxia (HBH, 11% O_2, 60 min) eliminated differences in the resistance to severe hypobaric hypoxia (SHBH, 4.5% O_2) between the high- and low-resistant rats [29]. However, it was unclear whether this is a consequence of SHBH pre-testing or HBH action only.

Since the resolution of this issue was directly related to the mechanisms of hypoxic preconditioning, a comparative study of the high-, intermediate- and low-resistant rats pre-tested under SHBH, and of the intact rats was carried out. In these rat groups, the HBH influence was evaluated in the resistance to SHBH.

2. Materials and Methods

2.1. Animals and Ethical Policy

Experiments were performed on laboratorial male outbred albino rats aged 2 - 2.5 months (weight 200 - 250 g) at the beginning of the study. The rats were supplied from the animal nursery "Light Mountains" (Russian Federation) and then kept in the vivarium of the Institute of General Pathology and Pathophysiology.

All animal care and experimental procedures were conducted in accordance with the official regulations of the European Communities Council Directive on the use of laboratory animals of 24 November 1986 (86/609/EEC). The study was approved by the Ethical Committee of the Institute of General Pathology and Pathophysiology created by the Institute Order "On the formation of the new Ethical Committee" number 01-01/147 of 12 October 2009. All efforts were made to minimize the number of animals used and their suffering.

The rats were housed in a temperature-controlled room (20˚C - 24˚C) with 5 - 7 animals per cage, with free access to food and water, and maintained with a 12 h light/dark cycle. The rats were handled for at least two consecutive days prior to being placed in the pressure chamber. At the end of the experiment, the animals were killed by inhalation of CO_2 euthanasia using apparatus for euthanasia AE0904 (Open Science, Russian Federation).

2.2. Hypoxic Models

We used the same hypoxic models as before [22] [29] [30]. Hypoxia of varying severity was created in the pressure chamber. The barometer of the chamber (altitude gauge) was calibrated to an altitude above sea level. The rats in the chamber "were raised" at a speed of 50 m/s to the adaptive altitude of 5000 m (HBH, 3.0 Pa, equivalent to 11% O_2, 60 min) or to the critical altitude of 11500 m (SHBH, 1.2 Pa, equivalent to 4.5% O_2). In the latter test, resistance to hypoxia was recorded with respect to endurance under SHBH conditions that was time (T) until agonal inspiration (apnea) in combination with a loss of voluntary control of body tone.

2.3. Experimental Protocol

Some of the rats were pre-tested under SHBH conditions and the values of innate primary T (T1) were estimated. The animals were divided into groups of low, intermediate and high resistance to hypoxia with T1 < 210 s, T1 between 210 - 420 s and T1 > 420 s, respectively. For the following 4 - 5 weeks, all rats were kept under standard vivarium conditions, after which the low-, intermediate-, high-resistant and not pre-tested intact rats were subdivided into the experimental and control groups.

The rats of experimental HBH groups were subjected to a single HBH session; four min after the end of the session, the rats from each HBH group were subjected to SHBH. Values of T1 for the intact rats and T2 for the high-, intermediate- and low-resistant rats were estimated.

Each experimental group had a control group. The control groups duplicated the experimental groups, but the HBH exposure was omitted from the protocol. All of the experiments with the influence of HBH were tested simultaneously to the corresponding control group. Thus, all rats from the pre-tested control and experimental (HBH) groups were subjected to SHBH exposure twice: the first time, when rats pre-tested (T1) and then during the experiment (T2) after HBH (the HBH groups) or without it (the control groups). Unlike the pre-tested rats, those intact of the control and HBH

groups were subjected to SHBH exposure only once during the experiment, and, accordingly, had values of T1.

All data (T1 and T2) were generated in a double blind manner which has been achieved thanks to the technical assistance of our colleague.

2.4. Statistics

The data were calculated using the non-parametric one-sided Fisher's Exact Test and the r-criterion of the Pearson's correlative test in Microsoft Excel with the formula being adjusted for a small number of observations (n = 4 - 15) [31]. Differences were considered to be statistically significant if $P < 0.05$. Data are shown as means and standard errors (SE) in **Figures 1-3** and as individual values in **Figure 2**, **Figure 4**, and **Figure 5**. The quantity of rats in each group is given in the figure legends.

3. Results and Discussion

3.1. Resistance to SHBH of the Intact, High and Low Resistance Rats in the Control Groups

Mean values of the resistance to hypoxia in the control pre-tested rat groups are shown in **Figure 1**. In our study, the rats with low, intermediate and high resistance to SHBH comprised 36%, 27% and 38%, respectively, of the tote pre-tested rats (n = 64), which corresponds to the usual composition of outbred rats in an experimental lot [28] [32].

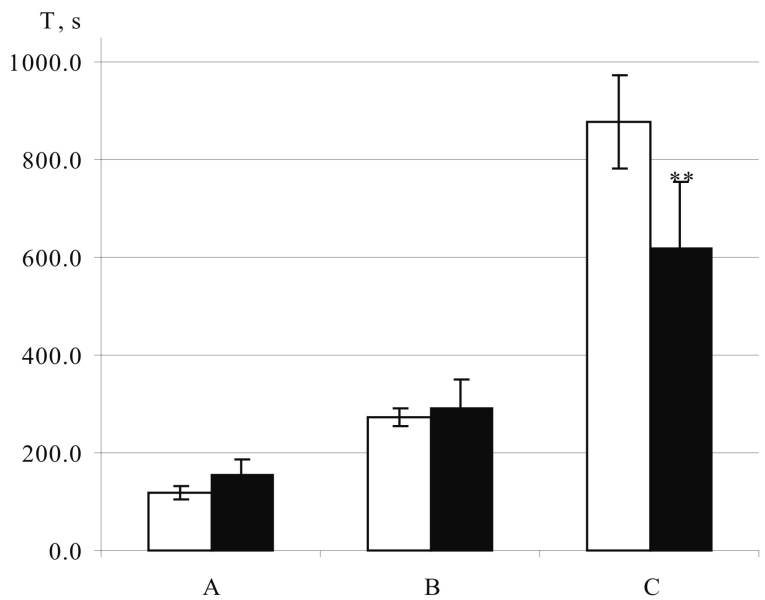

Figure 1. Resistance to SHBH in the control groups of low- (A), intermediate- (B) and high-resistant (C) rats. T(s), endurance under SHBH exposure. T values are means ± SE. For each group of bars: empty bars, T1 values of the resistance to SHBH under primary hypoxic exposure; black bars, T2 values of the resistance to SHBH under secondary hypoxic exposure. N = 12, 9, and 14 for A, B, and C, respectively. $^{**}P < 0.025$ between T2 and T1 within the high-resistant rat group (C), the Fisher's Exact test.

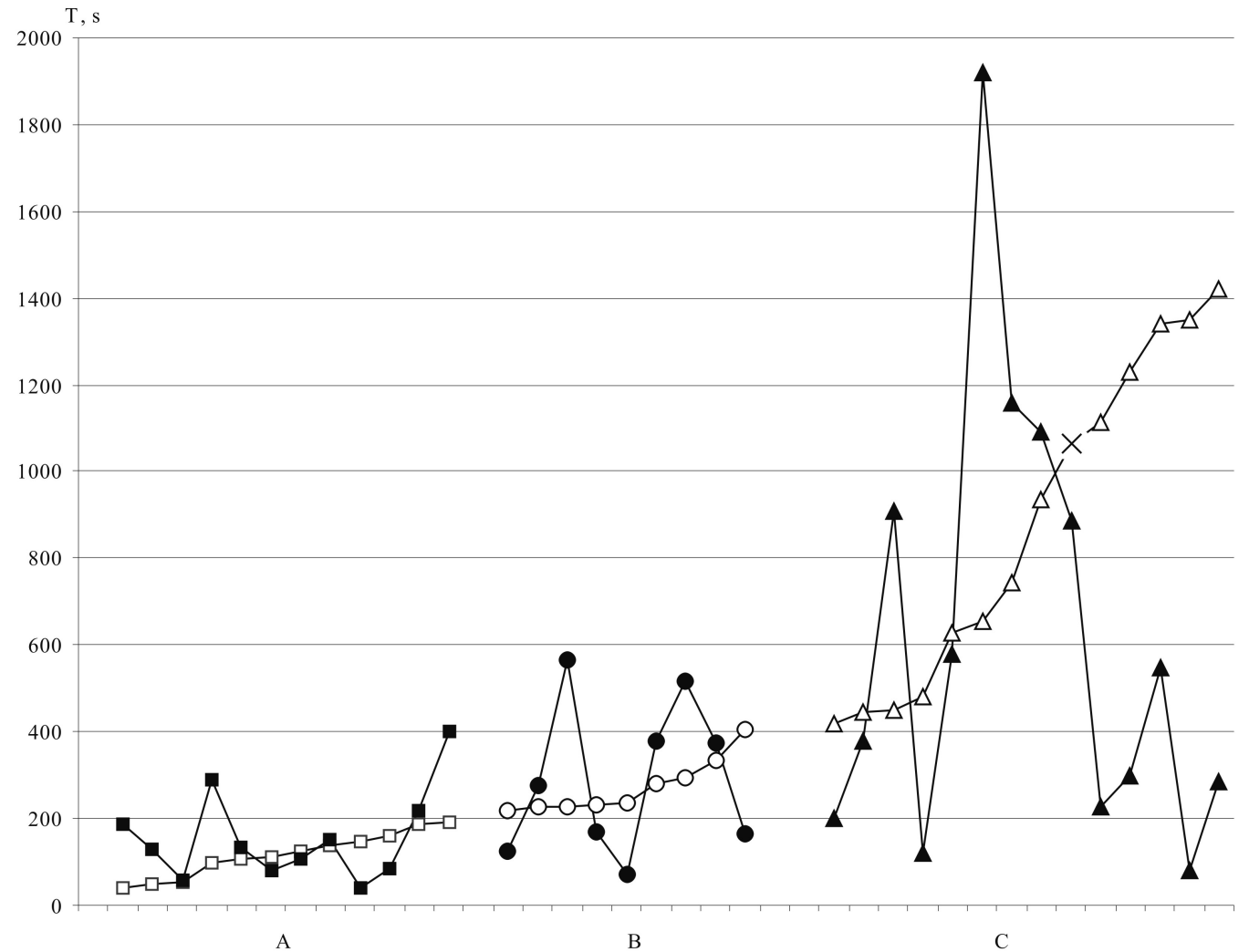

Figure 2. Individual values of the resistance to SHBH in the control groups of low- (A), intermediate- (B) and high-resistant (C) rats. Empty squares, circles or triangles, individual T1 values for A, B and C, respectively; black squares, circles or triangles, the corresponding individual T2 values. Cross mark in T1 sequences of the high-resistant rat group (C), the value of T1, from which all T2 < T1. In T1 sequences, individual values are located according to an increase. In T2 sequences, each T2 value corresponds to the T1 value to demonstrate uncertainty of T2 values. R = +0.323, +0.054, and −0.342 for T1-T2 in A, B, and C, respectively, n = 12, 9, and 14 as in **Figure 1**, P > 0.05, the Pearson's correlative test.

The control group of intact rats also included all categories of the rat resistance (38%, 13% and 50% for low-, intermediate- and high-resistant rats, respectively, n = 8).

With repeated testing, the mean values of T2 confirmed the T1 values in the groups of low- and intermediate-resistant rats (**Figure 1(a)** and **Figure 1(b)**). In the high-resistant rat group, half of the rats showed T2 < 420 s. In this rat group, the mean T2 value was significantly lower than T1 (**Figure 1(c)**) and the values were T2 < T1 for all rats with T1 > 930 - 1050 s (**Figure 2(c)**). In our previous study of HBH effects, the mean T2 value of high-resistant rats was not significantly reduced compared with T1 value [29]. At the same time, a significant decrease of T2 values in rats with T1 > 900 - 1020 s are confirmed in other studies (unpublished). The same decrease of T2 values

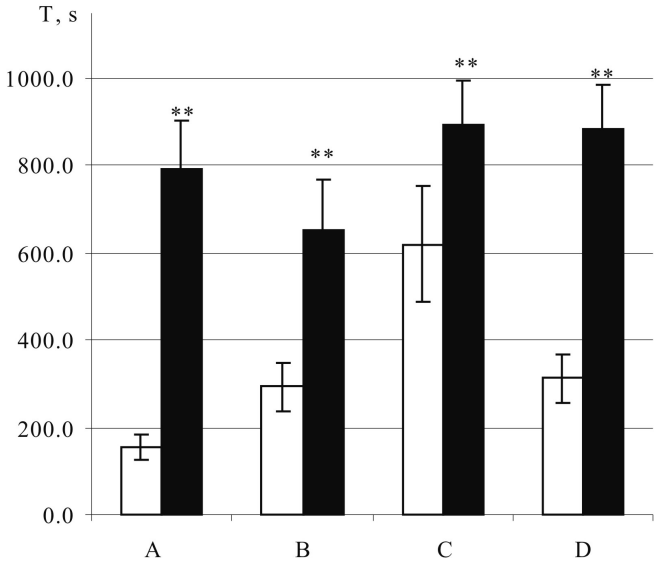

Figure 3. HBH effects on the resistance to SHBH of the low- (A), intermediate- (B), high-resistant (C) and intact (D) rats. T values are expressed as means ± SE. For each group of bars: empty bars, T2 values in the control pre-tested rat groups (A, B, C, SHBH only; n = 12, 9, 14, respectively) and T1 value in the control intact rat group (D, SHBH only, n = 8); black bars, T2 (A, B, C) or T1 values (D) in the corresponding HBH groups (HBH + SHBH; n = 11, 8, 10 and 9 in A, B, C and D, respectively). $^{**}P < 0.025$ compared to the respective control, the Fisher's Exact test.

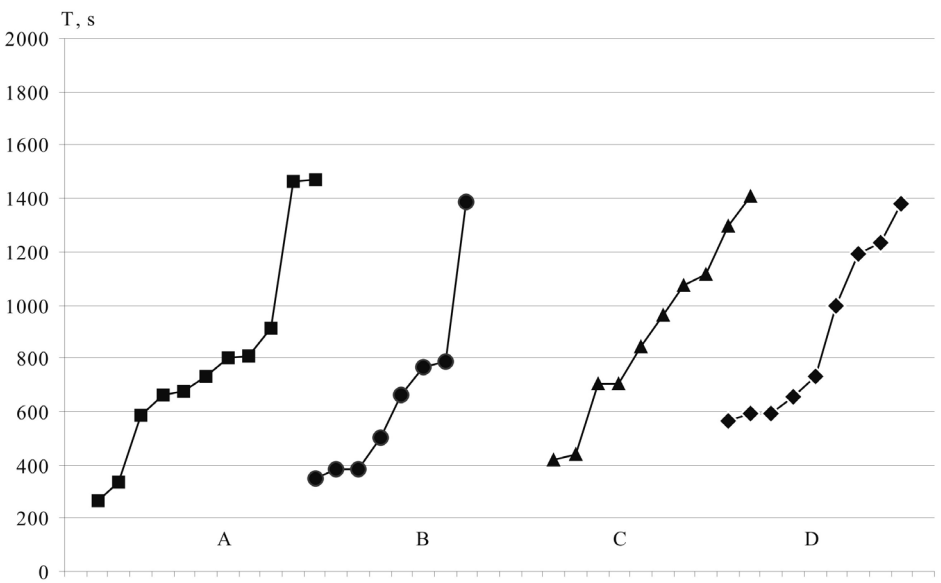

Figure 4. Individual values of the resistance to SHBH after HBH in the low- (A), intermediate- (B), high-resistant (C) and intact (D) rat groups. For each rat group, marks indicate the individual values of resistance to SHBH after HBH to demonstrate that T values of all HBH groups formed the same variational series. N = 11, 8, 10, and 9 in A, B, C, and D as in the corresponding HBH groups in **Figure 3**.

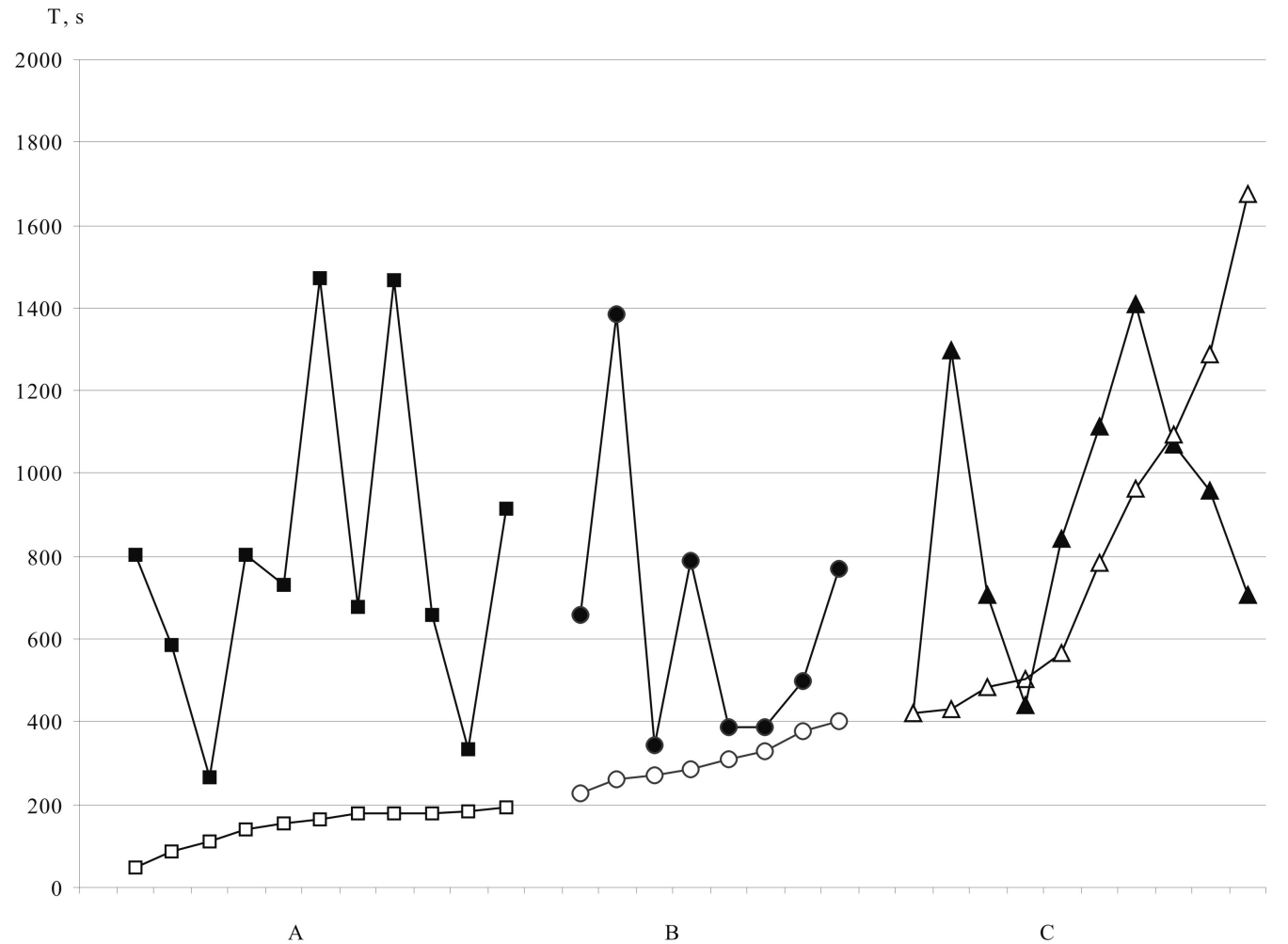

Figure 5. Individual values of the resistance to SHBH in the HBH groups of low- (A), intermediate- (B) and high-resistant (C) rats. Empty squares, circles or triangles, individual T1 values for A, B and C, respectively; black squares, circles or triangles, the corresponding individual T2 values after HBH exposure. T values are disposed as in **Figure 2**: T1 values are located according to increase; each T2 value corresponds to the T1 value to demonstrate absolute absence of T2 dependence on T1. $R = +0.244$, -0.218 and $+0.182$ for T1-T2 in A, B, and C, respectively, n = 12, 9, and 14 as in **Figure 3** and **Figure 4**, $P > 0.05$, the Pearson's correlative test.

was observed 30 - 40 min after pre-testing under more severe hypoxia (0.8 Pa, 3% O_2) in Nembutal-anesthetized rats with T1 > 900 s [28]. Thereby, the data of this study reflect typical relations between T1 and T2 in the high-resistant rat group.

As a rule, rats with T1 < 930 s had significant multidirectional deviations of T2 from T1 values (**Figure 2**).

Vector of the deviations showed virtually equal probability in any group of rats. As a result, significant T2 dependence on T1 was absent in all control pre-tested rat groups. Moreover, a sufficiently high probability to repeat their own category of resistance under the secondary SHBH exposure took place only among the low-resistant rats, while such probability was absent among intermediate- and high-resistant rats. Thus, there was a high level of uncertainty as to the last two groups, regarding in what category the HBH effects were studied.

Therefore, we assumed that the single pre-test under SHBH reserves a prolonged adaptive trace. Earlier, on the models of chronic brain hypoperfusion (2VO model), we had found a protective effect of pre-testing for high- and low-resistant rats (see below). According to the modern physiological concepts, the brain can generate long-term memory [33], and in a broader sense, any organ can form "biological memory" [34] in response to a single adequate extreme stimulus.

3.2. HBH Effects on the Resistance to SHBH of the Intact, High and Low Resistance Rats

HBH markedly increased the mean values of the resistance of rats to SHBH in all investigated groups (**Figure 3**). After HBH, the individual T values in the low- and intermediate-resistant rats and in the intact rats had no overlap with values for the control groups. In the high-resistant rats, HBH actually restored the original status of the group. The mean T2 value in the HBH high-resistant rat group was significantly higher than T2 value in the control group and did not differ from own mean T1 value (T2 = 896 s ± 101 s versus T1 = 821 s ± 128 s).

Accordingly, HBH has a marked preconditioning effect on rats, increasing or restoring (in the case of the high-resistant rats) resistance to SHBH. This is consistent with the data for the low-resistant rats [22] [23] and confirms our previous data for the low- and high-resistant rats [29].

After HBH sessions, all rat groups showed a similar range of values for resistance to SHBH with mean T values of 792 s ± 108 s, 654 s ± 114, 896 s ± 101 and 882 s ± 102 s in the low-, intermediate-, high-resistant and intact rat groups, respectively (**Figure 3**). In fact, the T values of these groups formed the same variational series (**Figure 4**). Accordingly, individual values initiated by HBH were completely random in nature with respect to their own T1 values in any pre-tested rat group (**Figure 5**).

These results also confirm our previous data for high- and low-resistant rats [29]. The same HBH effect for the intact- and intermediate-resistant rat groups was revealed for the first time, and was unexpected for us with regard to the intact rats. As revealed earlier, mortality was 3 - 5.5 times lower among both the high- and low-resistance rats compared with the intact animals under 2VO conditions (unpublished). Analysis of the results of this study also points to a trace which remains after the pre-testing under SHBH conditions and affects the resistance to hypoxia. Therefore, we assumed that HBH affects the resistance of the intact rats with another compared with those of the pre-tested rats.

The same preconditioning effects of HBH in the intact rats and those pre-tested under SHBH can be explained only by the fact that HBH preconditioning is, apparently, realized by its own mechanisms which do not depend on innate resistance to SHBH and prior hypoxic experiences.

Thus, a single severe hypoxia alters the resistance to secondary severe hypoxia and does not affect the preconditioning efficiency. Furthermore, the pre-testing under SHBH alters preconditioning synaptic mechanisms. In the intact rats, the opposite cholinergic reaction to HBH was revealed in the synaptic pool in the brain stem and cortex

those in the high and low resistant rats [30]. This implies that the preliminary estimate of resistance to severe hypoxia has no value for predicting the hypoxic preconditioning efficiency for pre-tested rats.

Therefore, we would like to emphasize a problem that awaits solution. Individual sensitivity to adaptive hypoxia and risk of no dangerous side effects (sickness, dizziness, tendency to hyperventilation, some others) are well known in clinical practice. Therefore, be sure to monitoring of physiological parameters of a patient is carried out at the beginning of hypoxic training to correct training regime [35] [36]. In our study, we used a very soft hypoxic model. Monitoring of physiological parameters did not reveal individual sensitivity and shows no side effects in rats under HBH conditions [37] [38]. Nevertheless, the limit of resistance to hypoxia which was initiated by HBH varies over a wide range. The extreme values of resistance to hypoxia after HBH could differ significantly, and by up to 5.5 times in our experiments. It is very likely that the reaction to HBH can be based on different mechanisms of hypoxic preconditioning. This is also indicated by the inhibitory effects of methyllycaconitine (MLA, a selective antagonist of the alpha 7 subtype of nicotinic receptors) in the group of low-resistant rats, which took place only in the range of rats with high efficiency of HBH [29].

Thus, for the hypoxic preconditioning efficiency predicting and study of innate adaptive mechanisms, it is necessary to look for other, non-stressor methods for the separation of animals in their sensitivity to adaptive hypoxia. This will help to better understand the mechanisms of hypoxic preconditioning and to identify additional novel therapeutic targets for diverse acute and, possibly, chronic pathologies [13] [39].

Standardization of the range of adaptive resistance to stress was observed in experiments with stressors of other types. August and Wistar are lines of rats with different genetic resistance to acute emotional stress [37]. Classical criterion of the resistance to emotional stress is gastric ulceration (number of ulcers and size of affected area). Both indicators were usually 7 - 10.5 times higher in Wistar rats than in August rats [40] [41] [42]. Preliminary intermittent action of the moderate stressor of the same etiology led to a decrease in the ulceration in Wistar rats (3 - 6 times) and, conversely, to an increase (to 1.2 - 2 times) of this in August rats in response to strong emotional stress [41] [42]. At the same time, illustrations in both articles demonstrate that the stress indicators in Wistar and August rats become equal after emotional stress adaptation.

Interestingly, the resistance to emotional stress increased both in Wistar and August rats and, thereby, preserved significant differences in the values of stress indicators after the hypoxic adaptation [40]. Thus, it is possible that the phenomenon of the standardization of the resistance to stressors occurs only after adaptation to factors of the same etiology.

We assume that HBH initiates the optimum homeostatic resistance to SHBH of rat as a species. It is possible that such resistance reflects the most balanced nervous organization of physiological functions in the given environmental conditions.

4. Conclusions

1) HBH has a marked hypoxic preconditioning effect on rats, increasing and restor-

ing the resistance to SHBH.

2) The preliminary estimate of resistance to severe hypoxia has no value for predicting the hypoxic preconditioning efficiency for pre-tested rats and the study of preconditioning mechanisms.

3) HBH preconditioning is realized by its own mechanisms which eliminate the differences in resistance to hypoxia between groups of rats with different innate resistance to severe hypoxia and with different prior hypoxic experiences.

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