# BRAIN MORPHOLOGY AND FUNCTION IN ANIMALS DIFFERING IN INDIVIDUAL TOLERANCE TO HYPOXIA

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KEY WORDS: tolerance; hypoxia; RNA; total protein.

The problem of adaptation of the individual to oxygen deficiency has recently become very important. The reason is that virtually any pathological state is accompanied by hypoxia, the depth of which in many cases determines the severity and outcome of the pathological process. Man may also develop a state of hypoxia during work: at high altitudes, at great depths, in aviation, and in space flight. We know that the brain responds most intensively to oxygen deficiency. Besides the general rules governing adaptive changes there exist also individual differences in response to the action of extremal factors and, in particular, to hypoxia. Their study, which was the aim of the investigation described below, is therefore an urgent task of great prospective values.

## EXPERIMENTAL METHODS

Experiments were carried out on 50 mature male rats weighing 180-200 g. The animals were first "raised to an altitude" of 11,000 m, and the length of time they remained in the pressure chamber until the first agonal inspiration was recorded. Animals which endured less than 2.5 min were classed in the "low tolerance" group, those enduring over 5 min were classed in the "high tolerance" group. Each group was then divided into two parts with equal numbers of animals in each part. One part of the animals served as the control, the other was adapted for 8 h daily in a pressure chamber of an "altitude" of 5000 m for 1 month. The brain for investigation was taken from the decapitated animals, fixed in Carnoy's fluid, and embedded in paraffin wax. The visual cortex (area 17) was studied as the structure most vulnerable to hypoxia, and the reticular formation (RF) in the medulla was studied as the structure most tolerant to hypoxia [2, 3]. The RNA concentration was studied by Einarson's and total protein by Geyer's histochemical methods. Quantitative analysis was carried out on a frame scanning microspectrophotometer [1]. To evaluate the morphological and functional response of the neurons to long-term adaptation to hypoxia, methods of morphometry and karyometry were used. The results were subjected to statistical analysis by the method in [4]. Changes in structural metabolism in the animals of each group before and after pressure chamber adaptation were compared by means of a standardized index [6]. Cross-correlation between the parameters studied was estimated by correlation analysis [5].

## RESULTS

Animals with high and low tolerance to hypoxia differed in their brain tissue metabolism and realized their adaptive powers differently (Table 1). Structural metabolism in RF was at a higher level than in the cerebral cortex in animals of both low and high tolerance groups. The area of the neurons studied in highly tolerant animals was significantly greater than in those with low tolerance. However, whereas the area of the cytoplasm in the pyramidal cells of cortical layer V was virtually identical in animals of both groups, at the RF level it was significantly greater in rats with high tolerance to hypoxia. The morphological and functional response to long-term adaptation to hypoxia also differed. For instance, in animals with low tolerance, the most marked changes, namely lowering of the RNA level and raising of the protein concentration per unit area of cytoplasm, were observed in the cerebral cortex. Changes in structural metabolism at RF level were less marked in these animals and were characterized by a synchronized but very small decrease in the RNA and protein concentrations,

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TABLE 1. Cytometric and Karyometric Data, and RNA and Total Protein Concentrations in Parts of Brain of Animals Differing in Individual Tolerance to Hypoxia, before and after Pressure Chamber Adaptation

| Brain structure | Parameter studied | Rats with low tolerance | | Rats with high tolerance | |
|---|---|---|---|---|---|
| | | control | experiment | control | experiment |
| Cerebral cortex | RNA/$\mu^2$ | 0,0129±0,0004 | 0,0121±0,0006 | 0,0119±0,0006 | 0,0143±0,0005 |
| | Protein/$\mu^2$ | 0,0254±0,0003 | 0,0309±0,0015 | 0,0259±0,0007 | 0,0300±0,0002 |
| | RNA/protein | 0,509±0,02 | 0,402±0,05 | 0,385±0,007 | 0,476±0,02 |
| | Cells | 210,6±1,6 | 159,0±4,0 | 228,5±1,2 | 211,0±5,2 |
| | Cytoplasm | 107,5±1,1 | 70,7±2,8 | 107,2±1,3 | 107,1±4,1 |
| | RNA | 1,388 | 0,860 | 1,200 | 1,529 |
| | Total protein | 2,727 | 2,292 | 2,800 | 3,213 |
| CO | RNA/$\mu^2$ | 0,0180±0,0003 | 0,0149±0,0013 | 0,0216±0,0003 | 0,0281±0,0001 |
| | Protein/$\mu^2$ | 0,0461±0,001 | 0,0426±0,0001 | 0,0368±0,0003 | 0,0481±0,0007 |
| | RNA/protein | 0,392±0,01 | 0,327±0,03 | 0,588±0,003 | 0,585±0,008 |
| | Cells | 367,0±12,4 | 366,7±7,0 | 454,1±9,2 | 368,6±7,0 |
| | Cytoplasm | 238,1±10,7 | 239,8±6,0 | 294,1±7,5 | 207,7±7,1 |
| | RNA | 4,291 | 3,421 | 6,3 | 5,875 |
| | Total protein | 10,980 | 10,220 | 10,8 | 9,999 |

TABLE 2. Values of RNA/Protein Ratio in Neurons of Various Brain Structures of Animals Differing in Tolerance to Hypoxia

| Brain structure | Group of animals | Rats with low tolerance | | Rats with high tolerance | |
|---|---|---|---|---|---|
| | | RNA/protein | normalized index (E/C) | RNA/protein | normalized index (E/C) |
| Cortex | Control (C) | 0,51 | 0,73 | 0,44 | 1,1 |
| | Experiment (E) | 0,37 | | 0,48 | |
| RF | Control (C) | 0,38 | 1,0 | 0,59 | 1,0 |
| | Experiment (E) | 0,39 | | 0,59 | |

while the dimensions and area of cytoplasm of the neurons remained as before. In highly tolerant animals the greatest changes after pressure chamber adaptation were observed in RF where, against the background of a marked decrease in the area of the cytoplasm, an increase in the density of distribution of RNA and total protein was observed, so that a high level of structural metabolism could be preserved in that structure. Considering that the performance by neurons of their specific functions depends on their protein concentration it can be tentatively suggested that in highly tolerant animals the process of adaptation to hypoxia is realized largely on account of subcortical structures, but in rats with low tolerance, on account of the cerebral cortex. The RNA/protein ratio in structures tested before and after adaptation remained unchanged and the standardized index was 1 (Table 2). This fact can evidently be regarded as the result of the stability of structural metabolism in the brain tissue of the animals of this group which, in turn, may perhaps provide for (determine) a high level of adaptation to an extremal factor such as hypoxia.

In animals with low tolerance to hypoxia the RNA/protein ratio in the structures fell after long-term hypxia; whereas in RF these changes were exceedingly slight, in the cortex they were significant (Table 2). This is further confirmation that RF is a structure more tolerant to hypoxia than the cortex. Analysis of the normalized index suggests that the RNA/protein ratio can be used as a test to determine tolerance and plasticity of structures to an extremal factor.

Comparative analysis of levels of correlation between the RNA andprotein concentrations in brain tissue, on the one hand, and tolerance of the animals to hypoxia, on the other hand, showed that negative correlation exists between these parameters in the cortex of highly tolerant rats of the control group (r = −0.4), but very high positive correlation (r = +1.0) was found in RF, i.e., metabolism in this structure is so organized that an increase in RNA synthesis is accompanied by an increase in protein synthesis. This synchronization between these two interconnected processes evidently leads to greater economy of energy-yielding material and maintains the balanced state of the system for structural metabolism; in turn, this may also determine the greater resistance of this structure to hypoxia. After pressure chamber adaptation of highly tolerant animals for 1 month, correlation between the RNA–protein values strengthened, while the sign of the correlation was preserved. This can evidently be interpreted as maintenance of homeostasis, for the trend of metabolism initially present in each structure was preserved ($r = -1.0$ in the cortex and $r = +0.2$ in RF). Analysis of this parameter in animals with low tolerance reveals very high negative correlation ($r = -0.97$) for the cortex of the control rats, and that in RF correlation was almost absent ($r = -0.03$). After pressure chamber adaptation, while correlation in the cortex remained at a very high level, its sign was reversed ($r = +1.0$), and in the writers' view this indicates greater economy of energy-yielding material if RNA and protein synthesis follow similar trends. In RF of the animals of this group, negative correlation ($r - -0.68$) was found between RNA and protein concentrations, and this can probably be regarded as evidence of the inadequate development of compensatory changes in RF during long-term exposure to hypoxia.

Animals differing in their individual tolerance to hypoxia thus have a strictly individual level of structural metabolism in their brain tissue and realize their reserve capacity during adaptation to hypoxia differently. In the group of animals with high tolerance to hypoxia the principal changes in structural metabolism take place in subcortical structures (RF), whereas in animals with low tolerance, adaptive changes take place mainly in the cerebral cortex. RNA and total protein concentrations and, in particular, the RNA/protein ratio in the cytoplasm of the neurons are parameters adequately reflecting the functional state of the neurons in animals differing in their individual tolerance to hypoxia.

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# CHARACTERISTICS OF THE CORONARY VASODILATOR RESERVE DURING PARTIAL RESTRICTION AND SUBSEQUENT RESTORATION OF THE CORONARY BLOOD FLOW

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The leading place among adaptive responses of the coronary vascular bed, activated during coronary insufficiency, is occupied by reactive hyperemia, which is manifested as the use of the coronary vasodilator reserve, and is aimed at restoring the disturbed dynamic equilibrium between the blood supply of the myocardium and its oxygen consumption [1, 5, 8]. It is this response which, even in the case of a subcritical narrowing of the coronary vessels, enables an adequate level of coronary blood flow to be maintained unchanged for a long time in a state of relative rest [10, 15], and during reperfusion it is a very important mechanism determining the effectiveness of reperfusion and reoxygenation measures as regards restoration of the contractile function of the heart [3, 6, 7].

The main aim of this investigation was to study the state of the coronary vasodilator reserve in experimental coronary insufficiency and in the early reperfusion period after its termination.

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