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# The Reaction of Various Functional Systems of the Body in the Dynamics of Oxygen Deficiency

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**Abstract:** The paper presents a comparative analysis of data on the effect of moderate and acute hypoxia on the functional state of systems at various levels of organization - molecular (amide groups of brain proteins), cellular (background electrical activity of neurons), systemic (electroencephalogram - EEG, electrocardiogram (ECG) and organismic (integrative signal of the body). Changes in electrographic parameters have an adaptive meaning for the body and are of a phase nature: in moderate hypoxia (4500-5000 m) the indicators are activated, and at acute hypoxia (7500 - 8000 m) - are depressed. 15-30 minutes after exposure to hypoxia at normal atmospheric pressure, the values of almost all indicators are back to normal. It is shown, that a prolonged aftereffect of acute hypoxia is observed at the organism molecular level. Under oxygen deficiency, the number of amide groups of brain proteins increases. After the hypoxic factor, this violation persists for a day. The data of the influence of hypoxia on animals, lead to the conclusion, that the functional systems of different levels of organization react ambiguously to the impact of increasing oxygen deficiency. However, in the dynamics of hypoxia in the values of the integrative signal recorded by a non-invasive method from the body surface, phase changes are not observed, on the contrary, the shifts are unidirectional. Certain deviations of the indicators of the integrative signal in the phase of moderate hypoxia increase during acute hypoxia and continue for several hours. We conclude that the remote "Bioscope" signal being integral in nature, is not the sum of individual electrographic indicators of various functional systems and has a high sensitivity and specificity to the change of physiological state of animal.

**Keywords:** Oxygen Deficiency, Neuronal Activity, Electroencephalogram (EEG), Electrocardiogram (ECG), Integrative Field, Brain Proteins

## 1. Introduction

Hypoxia occupies a special place among various unfavorable environmental factors. Hypoxia acts as a central link in the pathogenesis of many diseases. In the dynamics of hypoxic exposure, in accordance with the partial pressure of oxygen in the environment, the oxygen tension in the blood also changes, which also occurs during endogenous hypoxia in various diseases [1-4]. It is known that under extreme conditions, adaptive mechanisms are activated, indicators of various body systems change to maintain the functional activity of tissues and organs, both under conditions of endogenous oxygen deficiency and oxygen deficiency in the environment [5-7]. These changes are due to violations of the permeability of the cell membranes of these systems. As a result, the membrane potential difference changes, which is recorded as the electrical activity of the systems (electrical activity of neurons, electroencephalogram - EEG, electrocardiogram- ECG) [1, 6-8, 22, 23]. Naturally, hypoxia also has a certain effect on the general functional state of the body, which is a total reflection of all body systems and biochemical processes.

## 2. Material and Methods

The experiments were carried out on white male rats weighing 180-230 g. Recordings of EEG, ECG, neuronal activity was carried out first under normal conditions of atmospheric pressure ($pO_2$ = 160 mm Hg, 21%), then in the dynamics of oxygen deficiency (at various "heights"): with moderate hypoxia - at an "altitude" of 4500-5000 m ($pO_2$ =

98-85 mm Hg, 12,7-11.0%), with acute hypoxia - at an "altitude" of 7500-8000 m (pO2 = 64-58 mm Hg, 8,4-7,8%). Various degrees (moderate and acute) of oxygen deficiency were created in a laboratory pressure chamber by pumping out air. The “rise” and “descent” of the animals were performed at a speed of 15–20 m/s.

Extracellular recording of neuronal activity was carried out with microelectrodes. The coordinates of various brain structures were determined on a stereotaxic device. EEG and ECG were recorded on the multichannel electroencephalograph “Nihon Kohden”. The ECG took into account only the heart rate (HR).

In the next series of experiments, to assess the general physiological state of the body, the integrative signal of the body was recorded using the “Bioscope” hardware complex [9, 10].

Bioscope allows contactless registration of a specific signal (oscillation of a certain frequency) from the surface of the body, which is very sensitive to various exposures [11-13]. Experiments on the influence of stress effects, as well as a number of pharmacological preparations on the animal organism, revealed the high sensitivity and specificity of the bioscope signals to changes in the physiological state of the animal [14].

The principle of operation of the device is based on the estimation of the intensity of light (Figure 1), scattered in an opaque chamber from a sensor - a glass plate covered with a thin opaque material. To analyze the recorded signals in the Lab View environment, a complex program was developed. A typical example of rat’s bioscope signals is shown in Figure 2.

Bioscope experiments were carried out in two stages. At the beginning of each experiment, a 30-minute control recording of the integrative state of an animal placed in a laboratory chamber under normal atmospheric pressure was carried out.

In the first stage of the experiments, the signal was recorded at an “altitude” of 4500–5000 m for 30 minutes.

At the second stage, the signal was recorded at an altitude of 7500–8000 m. Both, at the first and second stages of the experiments, after the “descent” of the animal, a 30-minute signal was recorded under conditions of normal atmospheric pressure.

A biochemical study of the effect of acute hypoxia on the amidation of animal brain proteins was carried out. These studies were conducted in 3 groups of 10 rats each: 1 - intact; 2 - subjected to hypoxia; 3 - 24 hours after exposure to hypoxia. After decapitation, a brain homogenate was prepared. The amide groups of proteins were determined in the precipitate of the homogenate by the method of tough acid hydrolysis. The ammonia content in the hydrolysate was determined by the Zelingson microdiffusion method [15].

The significance of the mean values was determined by Student's t-test ($p<0.05$).

All animal manipulation was carried out in accordance with the rules of the European Convention for the Protection of Animals Used in Experiments (Directive 2010/63/EC) [16].

After all experiments, a qualitative comparison was made of the nature of changes in the integrative state of the body and indicators of impulse activity of neurons, the total electrical activity of the brain (EEG), heart rate (HR) and biochemical parameters in the dynamics of oxygen deficiency.

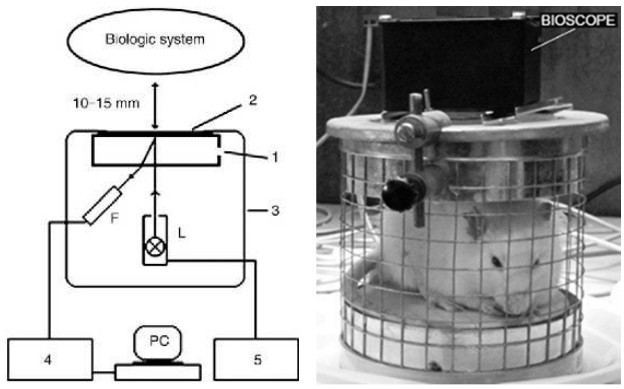


***Figure 1.*** *The general setup of the hardware for carrying the experiments.*

A – illustrates the diagram of measuring operation: 1 – glass plate, 2 cm width; 2 - covering material (thick black cardboard); 3 – partition; 4 – metallic case; 5 - rack for the investigated object; L – ordinary incandescent lamp (radiation spectrum 400-3000 nm, intensity maximum at 1000 nm); F – photodetector, vacuum photodiode, spectral sensitivity 200 – 600 nm, sensitivity maximum at 350 – 450 nm.

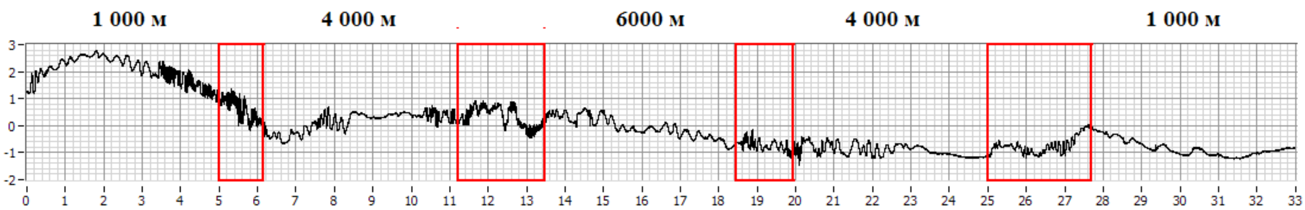


***Figure 2.*** *An example of Bioscope signals in the dynamics of pressure changes in a pressure chamber.*

The abscissa shows the time in minutes. The squares mark the time intervals of pressure changes in the pressure chamber.

## 3. Results

The central nervous system plays the main role in the adaptive activity of physiological systems of the body to various environmental conditions. An objective criterion for the functional state of the CNS, in particular the cortex and other structures of the brain, where processing and integration of afferent impulses occurs, is the electrical activity of these structures. The obtained data on the study of the total electrical activity of the brain (EEG) show that in the dynamics of hypoxia, changes are phasic in nature, namely, activation during moderate hypoxia (4500-5000m) and inhibition during the acute stage (7500-8000 m). Changes in the electrical activity of the brain are accompanied by characteristic shifts in behavioral reactions: intensification of respiration and cardiac activity, an increase in the animal's motor activity, etc. Full correspondence between the activity of the central nervous system, its electrophysiological correlates and behavioral reactions is also found at 7500-8000 m. (Table 1, Table 2, Table 3). The basis of all these changes is the restructuring of the CNS activity under severe conditions of hypoxia, which is reflected in the electrical activity of the brain [17-22], especially in the slower spectrum of fluctuations within the EEG delta rhythm.

***Table 1.*** *The ratio of waves of different EEG frequencies (%) of the cortex and hypothalamus in the norm and at different "heights"; * - (p<0.05).*

| | EEG waves | Before “rise” | At the height 4000-5000m | At the height 7500-8000m | After the “descent” |
|---|---|---|---|---|---|
| | Δ, delta (0,5-3 hz) | 38,7±2,2 | 32,8±2,1* | 42,7±2,7 * | 36,7±2,7 |
| | Θ, theta (4-8 hz) | 20,8±1,8 | 29,2±1,7* | 20,4±1,5 | 21,7±1,9 |
| CORTEX | A, alpha (8-13 hz) | 19,2±1,6 | 16,9±1,2* | 17,8±1,1* | 20,1±1,5 |
| | B, beta (14-30 hz) | 21,3±1,9 | 21,1±1,6 | 19,1±1,2 * | 21,5±1,8 |
| | Δ, delta (0,5-3 hz) | 38,3±2,2 | 34,4±2,3* | 46,2±3,1* | 36,5±2,2 |
| | Θ, theta (4-8 hz) | 21,4±1,7 | 32,1±2,4* | 22,5±1,8* | 20,6±1,5 |
| HYP OTHAL | A, alpha (8-13 hz) | 19,6±1,2 | 7,4±1,1* | 17,5±1.2* | 22,4±1,8* |
| | B, beta (14-30 hz) | 20,7±1,6 | 16,2±1,2* | 13,8±1,1* | 20,5±1,6 |

The development of these phases and their duration depend both on the level of pO2 and on the duration of hypoxia. With the deepening of oxygen deficiency (more than 11000 m), complete inhibition of the electrical activity of the brain, a respiratory and cardiac arrest will occur. Phase changes in activity in the dynamics of hypoxia were also observed in the study of the electrical activity of individual brain cells. At the "altitude" of 4500-5000 m, as the pO2 in the environment decreased, in all the studied brain structures, along with the activation of the EEG, an increase in the frequency of neuron discharge occurred, which can be interpreted as an exacerbation of the body's adaptive mechanisms. (Table 2).

***Table 2.*** *Changes in the frequency (imp/sec) of cortical and hypothalamic neuron firing in the course of oxygen deficiency; * - (p<0.05).*

| Height (m) | Cortex | Hypothalamus |
|---|---|---|
| Before “rise” | 14,5 ±1,1 | 19,6±1,4 |
| At the height 4,5-5000 | 24,5±1,9* | 22,5±1,9* |
| At the height 7,5-8000 | 5,9±0,3* | 16,3±1,2* |
| After the “descent” | 13,4±0,9 | 25,5±2,1* |

***Table 3.*** *Changes in heart rate (beat/m) in the dynamics of oxygen deficiency; * - (p<0.05).*

| Experiment conditions | Heart rate *(beat/m)* |
|---|---|
| Before “rise” | 460±28 |
| At the height 4,5-5000 m | 490±32 * |
| At the height 7,5-8000 m | 360±22 * |
| After the “descent” | 470±26 |

The direct effect of oxygen deficiency causes depolarization of the cell membrane and an increase in the impulse discharge of neurons [17, 18, 20, 22, 23]. Under conditions of acute hypoxia - at an "altitude" of 7500-8000 m, against the background of slow, delta EEG activity, inhibition of the impulse activity of neurons of brain structures was observed. The influence of severe acute hypoxia on the brain tissue presumably is exacerbated by the reason of widespread cell membrane prolonged depolarization, which leads to an extensive depression of synaptic transmission and the electrophysiological isolation of neurons, as well as the release of many inflammatory agents from glia and neuronal cells.

Research showed that in the body, along with physical and chemical processes, as a result of the interaction of molecules, cells, tissues, organs and systems, certain signals arise, which are largely determined by the oscillatory processes inherent in molecules and living cells. Such signals include an integrative signal contactless recorded on the surface of the body by a specially designed device - "Bioscope" [10-14] (Figure 1).

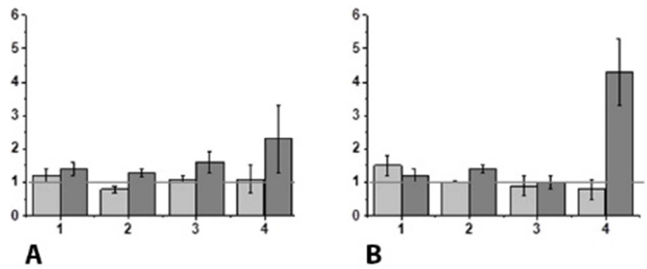


***Figure 3.*** *Relative to control values of the statistical indicators of the "Bioscope" signals at height - and after the "descent".*

A - "height" 4500-5000 m, B - "height" 7500-8000 m. 1 - Relative values for the frequency of oscillations - F_BB, 2 - coefficients of variation of BB intervals - CV%, 3 - power of the signal spectrum - FFT and 4 - power of the spectrum of successive BB intervals - FFT_BB.

When analyzing the obtained data, we took into account the indicators of the Bioscope that are somewhat more sensitive to hypoxia - the average frequency of oscillations, the coefficient of variation of inter-peak intervals, the total power of the spectrum of the original signals, and the power of the spectrum of successive intervals.

Under moderate hypoxia (4500-5000 m) of the tested indicators, only the coefficient of variation of the intervals decreases by 1.25 times. However, after the "descent", in comparison with the control, there is an increase in the values of all statistical indicators by 1.5-2 times (Figure 3). Under conditions of acute hypoxia (7500-8000 m), a significant increase (by 1.5 times) in the frequency of signal oscillations was observed. And after the “descent”, the values of the coefficients of variation of intervals increased by 1.5 times and the power of the spectrum of consecutive intervals increased by

4 times. The analysis also showed that the changes observed after oxygen deficiency in the nature of the spectral distributions and the values of the statistical indicators of the Bioscope signals persist for a long time - several hours or more.

Our biochemical studies have shown that a 30-minute exposure of acute hypoxia (at an "altitude" of 7500-8000 m) causes an increase in the total amide groups (TAGs) of brain proteins (Table 4). It can be seen that during hypoxia in the brain as a result of the development of inhibitory processes, the number of total amide groups compared to that in intact animals (20.0 μM/g) increases by 40% (28.02 μM/g). It should be noted that hypoxia has a prolonged aftereffect. 24 hours after the "descent" of the animal into normal conditions of atmospheric pressure, the content of amide groups of brain proteins decreases by only 25% (26.05 μM/g).

***Table 4.*** *The content of total amide groups (TAG) of rat brain proteins in normal conditions, under hypoxic conditions, and 24 hours after hypoxia ($p < 0.05$).*

| Experiment conditions | TAG content (μM/g) |
|---|---|
| Intact animals | 20,0±1,12 |
| Hypoxia | 28,02±1,38 * |
| 24 hours after hypoxia | 26,0,57±1,4 * |

# 4. Discussion

So, a comparative analysis of the results performed presented that the functional systems of different levels of organization show an ambiguous reaction to the effect of increasing oxygen deficiency. Phase changes were observed at the cellular and systemic levels - activation during moderate and inhibition during acute hypoxia in the EEG, indicators of the electrical activity of individual neurons, as well as the frequency of cardiac activity (Tables 1, 2, 3). This was reflected in the frequency and amplitude of these oscillations, their spatial distribution. Mentioned changes are explained by a violation of the mechanisms of membrane permeability and cell metabolism due to insufficient oxygen content in the cell [6-8, 24].

However, the observed shifts did not correlate with the data of the bioscope indicators - both in moderate and acute hypoxia, the vector of deviations hasn't been changed. These changes were even aggravated after the removal of the hypoxic factor.

In earlier studies, it was shown that the physical and chemical processes of the body are not of decisive importance in the nature of the formation of a bioscope remote signals. Our data confirm the opinion of the authors, that intersystem connections in the body are most sensitive to stress loads and are disturbed without visible changes in intracellular molecular bonds. So, a comparative analysis of the results performed presented that the functional systems of different levels of organization show an ambiguous reaction to the effect of increasing oxygen deficiency. The observed picture of the aftereffect of hypoxia on the integrative signal of the body can be compared with the long-term aftereffect of hypoxic stress on the number of amide groups of brain proteins.

Numerous studies have shown a change in the level of amidation of brain proteins depending on the functional state of the body and its response to the action of extreme environmental factors. It has been established that with the predominance of excitation processes in the brain of animals, protein deamidation occurs [6-8, 24]. In particular, during short-term electrical excitation, during hyperoxia, in parallel with the intensive consumption of energy substrates, the amide groups of brain proteins are also split. And in contrary, with the development of inhibitory processes in the brain, in particular, during drug-induced sleep caused by the administration of medinal, under the action of stress factors, especially during hypoxia, amidation of brain proteins occurs (Table 4).

# 5. Conclusion

It is concluded that functional systems of different levels of organization react ambiguously to the effects of increasing oxygen deficiency. Activation of electrographic indicators under conditions of moderate hypoxia (4500-5000 m) is the result of strengthening the adaptive mechanisms of the body. The impact of severe acute hypoxia (7500-8000 m) on neuronal tissue is presumably exacerbated by widespread long-term depolarization of the cell membrane, leading to extensive inhibition of synaptic transmission and electrophysiological isolation of neurons, as well as the release of many inflammatory agents from cells.

A biochemical study of the amidation of animal brain proteins, revealing a long aftereffect of acute hypoxia, suggests that the molecular level of organization plays a certain role in the mechanism of the genesis of the body's integrative signal.

When comparing the shifts of electrographic indicators with the results of a remote signal recorded from the surface of the body during hypoxia, it was suggested that the integrative signals of the remote hardware complex "Bioscope", having an integral character, are not the sum of individual electrographic indicators of various functional systems and have high sensitivity and specificity to changes physiological state of the animal.

Thus, the conducted experiments allow us to conclude that biological systems are capable of specifically affecting the surrounding objects. The data obtained can create prerequisites for the practical use of the Bioscope instrument complex for early prediction of the formation of pathological processes in the body.

However, this does not exclude other interpretations that may complement or exclude our working hypothesis.

# Conflict of Interest

All the authors do not have possible conflicts of interest.

# Acknowledgements

The "Bioscope" hardware complex had been developed by employees of the Laboratory of Integrative Biology of the

Institute of Physiology after L. Orbeli, of Academy of Sciences of the Republic of Armenia by Sargsyan R. S. and co-authors.

US Patent Application /0149866 A1: Draayer J. P., Grigoryan H. R., Sargsyan R. Sh., Ter-Grigoryan S. A. (2007) Systems and Methods for Investigation of Living Systems, Bioscope: a novel apparatus for the investigation.

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