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Secrets of Preconditioning

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Abstract

The aim of the work is to account for the mechanism of a well-known today phenomenon of preconditioning the heart and brain, i.e. the survival of these organs during abrupt weakening or a short time arrest of their circulation and the following arrest of respiration. Oxygen in the blood is supplied by the lungs and is the oxidizer of foodstuffs in the cells and the only full-value source of energy for humans and highest organisms. Assumed nowadays various substances and biochemical processes cannot replace oxygen. This is the basis of modern bioenergetics. According to published data and our experiments we believe that the restoration of the functions of these organs during preconditioning can occur only due to an increase in the oxygen supply via direct and indirect circulation and lung respiration.

Keywords: *Hypoxia; Blood Flow Rate; Preserving the Life; Respiration*

Introduction

Circulation and respiration are the most important functions in maintaining and development of life. It is well known that after the arrest of circulation in the human brain the respiration stops in 4 - 5 minutes and a man dies. The disruption of circulation in the brain is the most threatening and the most frequent reason for human death. Hence the physiology and pathology of the brain circulation always were a major focus of interest in medicine. In 1986 Murry and coworkers found the so called phenomenon of preconditioning [1]. It implies that if circulation in the heart is cut, after a lapse of time the majority of cells in the heart die. However if the heart was preliminary subjected to several short time cessations with the subsequent short time reperfusion with the blood, 60 - 70% of the cells survive. A weak respiration is preserved in this case. This effect resulted in a great interest in the specialists. It was found in various animals in the heart and brain. During the period from 1986 to 2016 several hundreds of papers were published on this topic. However, the main problem – the physiological mechanism of preconditioning remained unknown.

Reviews on preconditioning

The first reviews (Chicherin, 2003 [2]; Giddey, 2006 [3]) presented various assumptions and guess works about the essence of this problem. They ranged from urgent adaptation to oxygen deficit or to its absence on the tissue level and to the formation of antihypoxic substances and compounds in the tissues. However the authors in no cases were able to find and validate these mechanisms with any reliability. The following large review of Obrenovich [4] is distinguished by greater details. It contained more than 400 references. However no unambiguous and multifactor mechanisms of preconditioning are contained in this review. The author speculates about 20 biochemical reactions in the hypothalamus, which he takes as the mechanisms of preconditioning. But any particular explanations of biochemical mechanisms of their action are absent in the review. Thus this review is identical to the two first reviews in its significance.

In the review of Samoilov and Rybnikova [5] it is advocated that the adaptation to oxygen deficit during preconditioning is associated with complex action of “molecular-cell mechanisms”. However, these mechanisms are not deciphered. A particular significance is attached to endocrine factors in the increase in the tissue tolerance to oxygen deficit, but it is incomprehensible how these factors really provide for this tolerance. Mention is made of the adaptation to oxygen deficit developed during evolution, but they are not particularly designated. In the same year the review of the data on preconditioning was published by Shlyakhto and coworkers [6]. The review touched the problems of the influence of endogene antioxidant systems, inflammation, immune responses, changes in the functions of glial cells, changes in the metabolism of neurons, and of many other factors on the ishemic tolerance of the brain. All these reviews have no relevance to the energy supply of the cells and cannot affect their tolerance to oxygen deficit. It is interesting that for the first time for such reviews the question was raised as to the role of amplification of the regional circulation in preconditioning. But those very authors argued against these assumptions. Recently a short review was published by Lishmanov and coworkers [7]. It is devoted to the mechanisms of preconditioning. The problem of the "time lag" of this effect is put forward. A detailed consideration of this problem is believed to be able to help to reveal the origin of preconditioning. However no explanation of this fact is given in the review. We think that there is no necessity to give and consider all this large number of reviews. Their essence is in general the same: neither respiration nor circulation have attached any significance in the restoration of the cell functions during preconditioning. For some reason the specialists in preconditioning in their experiments do not measure either the rate of direct or indirect circulation or the volume of respiration, though it has long been known that after smallest decreases in respiration and disruptures in the blood flow in the heart or brain a more or less powerful compensation of respiration or blood flow follows. Instead of such measurements the authors of the reviews prefer to pay attention to various assumptions, which do not agree with fundamental science and cannot account for the mechanisms of compensation for the deficiency in energy.

About the mechanisms of preconditioning

Before passing to the new modern concept of preconditioning it is necessary to consider two axioms of energy transformation in the living tissues. They have a direct relationship to the phenomenon of preconditioning. The first axiom: in an organism of a man and highest animals at rest and during intensive physiological work a quantity of energy for maintaining life may by supplied only with the help of oxidation with oxygen of the foodstuffs, i.e. proteins, fats, and carbohydrates. The second axiom: oxygen cannot be replaced by any other substance in the process of oxidation reactions with the aim of obtaining energy.

These two axioms exclude the possibility to consider any substances, but oxygen as energy donors. Oxygen in essentially large quantities is contained in an organism only in the blood. Consequently, the physiological functions may be restored only at the expense of increasing the volume of the blood flow in the preconditioned tissues. What can be stimulated by the circulation deficit along the blood vessels supplying the brain or heart? The circulation deficit may reflectively stimulate collateral or indirect circulation, but it is developed comparatively slower. Sometimes the researchers put the emphasis on glycolysis. It is well known [8] that glycolysis is by a factor of 16 less by its power than aerobiosis and cannot serve as a constant source of energy. An increase in the blood flow rate both increases pO_2 in the vessels and is the most efficient tool for increasing oxygen content in the blood. Over many years we have recorded this with the help of oxygen microelectrodes in various blood vessels under various conditions. The blood flow rate was determined with the help of a special contact microscope by the velocity of a leukocyte movement along a vessel. We give several series of our experiments here as examples.

In table 1 the preconditioning was carried out as the result of introducing the blood with pO_2 40 mm Hg into the blood channel of an animal [9]. In this case the blood flow rate in the venulas 10 - 15 microns in diameter increased about twofold on the average. The oxygen consumption of the brain on the average almost did not change and remained at the starting level. This was a complete preconditioning of the brain.

In table 2 the preconditioning was carried out with the help of diluting the blood with albumin solution to the hematocrit 31.5% and further to 20.2% [10]. As follows from table 2, upon such a decrease in hematocrit the blood flow rate increased by about 100%.

Brain temperature (°C)	Content of O_2 in the inhaled air (vol%)	Number of experiments	Volume blood flow rate (ml/g·min)	Oxygen consumption by the brain, (ml/g·min)
37	21	9	0.68 ± 0.06	0.059 ± 0.007
	7.5	8	1.50 ± 0.01	0.062 ± 0.003

***Table 1:** Oxygen regime of the rat brain as a function of oxygen content in the inhaled air.*

Characteristic	Starting data	Replacing the blood with 6% solution of albumin	
		33% of albumin in the blood	55% of albumin in the blood
Hematocrit (Ht),%	48.2 ± 0.9	31.5 ± 0.6	20.2 ± 0.5
Oxygen consumption of the brain, ml/100g·min	1.46 ± 0.08	1.69 ± 0.11	1.70 ± 0.10
Minute volume of circulation, ml/100g·min	27.5 ± 1.8	53.5 ± 3.7	54.5 ± 5.0

***Table 2:** Minute volume of circulation in a rat as a function of hematocrit.*

Table 3 shows an increase in the capillary blood flow rate in the brain cortex of rats upon decreasing the content of oxygen in the inhaled air to 7.3% (pO_2 in the arterial blood 38 mm Hg). The blood flow rate in the capillaries increased on the average by 63%, i.e. from 0.96 to 1.59 mm/s [10]. However, in some capillaries the blood flow rate increased by 80 - 100%.

Characteristics	Number of experiments	Starting data	Hypoxemia	Restoration
Arterial blood pressure (mm Hg).	42	104 ± 3	82 ± 28*	95 ± 2
pCO_2 in the arterial blood	42	45.2 ± 1.9	26.3 ± 1.4*	35.8 ± 2.5
pO_2 in the arterial blood	42	85.3 ± 1.4	38.0 ± 1.8*	77.4 ± 1.8
Blood flow rate in the capillaries, mm/s	42	0.96 ± 0.08	1.59 ± 0.13*	1.61 ± 1.4*

***Table 3:** Increase in the blood flow rate in the capillaries of the rat brain upon a decrease in the oxygen content in the arterial blood to 7.3% (pO_2 38 mm Hg)*

*Note. * $p < 0.01$ - 0.005*

Table 4 shows the dilatation of brain venulas in rats during the animals inhaling the air with oxygen content 7.5% (pO_2 40 mm Hg) [10]. It can be seen from the table that in 99 experiments the venulas dilated on the average by 1/3 of the starting diameter. According to approximate calculations given such a dilatation of the vessels the rate of the volume blood flow might increase by about 1.5 times.

Number of vessels with the given diameter	Starting diameter, (microns)	Hypoxia	Restoration
51	16 ± 1	23 ± 1*	22 ± 1*
34	36 ± 1	47 ± 1*	45 ± 1*
14	56 ± 1	72 ± 2*	66 ± 2*

***Table 4:** Dilatation of the brain venulas upon a decrease in the oxygen content in the inhaled air to pO_2 38 mm Hg.*

*Note. * The average value reliably differs from the starting value ($p < 0.01$)*

The histogram of the distribution of average blood flow rates in the brain venulas with the minimal diameter of 8 - 12 microns in rats is shown in the figure. After hemodilution the hematocrit decreased from 44% to 32% and further to 22%. It is evident that a decrease in the hematocrit decreases the content of oxygen in the blood, which is accompanied, according to the Figure, by an increase in the average blood flow rate in venous vessels differing by their diameter [11].

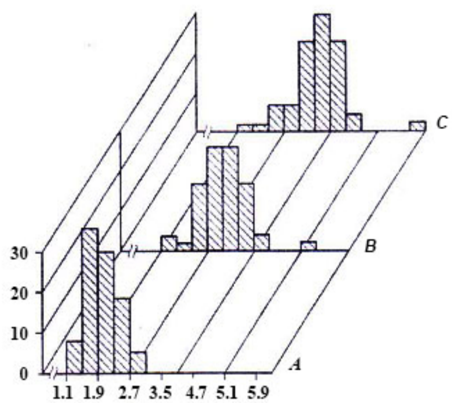

***Figure:** Histogram of the distribution of average blood flow rates in the smallest venulas (D = 8 -12 mcm) of the rat brain cortex after hemodilution. A – starting state, hematocrit 44 ± 1 %, 42 venulas. Prevailing rate 1.9 mm/s, sometimes to 1.0. B - hematocrit 32 ± 1 %, 42 venulas. Prevailing rate 3.0 mm/s. C – hematocrit 22 ± 1%, 42 venulas, prevailing rate 4.1 mm/s (sometimes up to 4.7-5.9 mm/s). The number of inhales at the starting hematocrit A - 81 ± 2; at hematocrit B - 95 ± 2; at hematocrit C - 115 ± 3.*

It must be noted that the blood flow rates in various brain vessels from 4 - 5 to 50 - 100 microns in diameter differ markedly. This follows from the figure. This is the law of microcirculation, which is still scarcely known, since the quantitative studies of microcirculation present difficulties up to now. We hope to tell about the reasons for this law in the next paper.

Now let us turn our attention to the data of Balykin and Karkobatov [12]. They showed that when the dogs were lifted to the height 3200m (520 mm Hg) pO_2 in their arterial blood decreased to 61 - 63 mm Hg. With the help of complicated and sophisticated methods described in detail in the work the authors demonstrated that the blood flow rate through the heart, brain, kidneys, pancreas, adrenal glands, and spleen in 5 - 7 days of staying at this height was kept at the level by 15 - 50% higher than the norm in all these organs.

Over a period of latest years we continued to study the blood flow in the brain and obtained a number of facts supporting our earlier observations of the brain blood flow in mammals [13-16].

Conclusions

The fact known to each physiologist is that upon a sudden or gradual decrease or a complete cessation of circulation or respiration a compensation reaction always develops. We give this fact as the freshest material with numerical results. Of course, if compensation fell behind or is disrupted, everything may end in a catastrophe. However, if the disruptions of circulation are periodically restored, this may end in a gradual restoration of the brain and heart functions.

It is evident that the main thing which we were able to register during preconditioning is an increase in the blood flow rate upon the brain hypoxia, which compensate for oxygen deficit. Just another case is associated with developing indirect circulation. We could fix also an increase in the frequency of respiration movements. The respiration in dogs increased from 160 to 210 ml/min·kg during their stay at the height 3200m for 5 - 7 days [12]. This is an additional source of oxygen.

All these cases of compensation are well understood and explicable and also easily reproducible. Hence the attempts of many authors studying preconditioning to account for the restoration of physiological functions by various assumptions, which have no relationship to any additional energy supply in a living organism, seem to us irrelevant. Such, for example are the assumptions about the emergence of "antihypoxants" in the preconditioned tissues, i.e. substances, which compensate for oxygen deficit in some fantastic manner. Another point of view assumes the existence of "molecular-cell" reactions, which in some other, no less fantastic manner make up for oxygen deficit [5]. Various biochemical reactions having no relevance to energy generation cannot supply deficient energy to the tissues. Therefore we can say that the secret of preconditioning consists of an increase in the direct or indirect supply of the tissues with the blood and also in an increase in the volume of respiration. There is not any fantastic mechanisms of oxygen supply to the cells on the "molecular cell" level.

A gradual transition from ancient methods of energy supply of the tissues to aerobiosis occurred in the process of evolution development of the living organisms during no less than a billion years. Over this great time interval the oxygen supply of the living tissues with oxygen in humans and highest animals had achieved a high sophistication and provided a man with greatest advantages in his vital activity. Aerobiosis is associated with the emergence of intellectual activity in man, which raises him above the whole animated world of the planet.

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