REVIEW

Isolation from Nervous Effects: a Mechanism of Adaptation of Biological Systems to Disease

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A concept of functional isolation of the heart from nervous effects as a mechanism of heart adaptation to extreme states has been formulated. In moderate hypoxia, isolation of the cardiovasomotor center from nonhypoxic afferention provides the compliance of myocardial hyperfunction to the intensity of hypoxia and limits heart participation in different forms of activity of the organism. In thermal hypoxia, myocardial isolation from sympathetic and parasympathetic effects ensures its minimal function and economy of energy due to transfer to the autorhythmical mode of function and rules out heart participation in circulatory reactions. Functional isolation of the heart in hypoxia is caused by energy deficiency and depends on the training of an organism and coordination of the sympathetic and parasympathetic effects. High prevalence of isolation of cells, organs, and systems from regulating effects in health and disease is demonstrated and its mechanisms, levels, and impact are disclosed. Both the "extension" of nervous bonds and hyperfunction and the "narrowing" of nervous bonds and hypofunction of biological systems are aimed at adaptation of an organism.

Key Words: *range of nerve bonds; isolation from nervous effects; heart; hypoxia; adaptation*

When it is difficult for an organism to obtain a useful result, more and more nerve bonds are "extended" (switched on), the executive structures in functional systems are rearranged, and the adaptive effect is thus attained. Such a situation is common both in health and disease, when homeostatic or behavioral systems even strained, cannot normalize the internal parameters or meet the requirements of the organism by the means of behavioral reactions.

It is doubtful whether these are the only means of adaptation of an organism and that the organism always attains positive result by extending the bonds and triggering more and more structures at various levels of vital activity and activating them more and more, in fact resorting to hyperfunction of cells, organs, and systems. At all stages of natural history and in all live organisms there are states based on adaptive minimization of functions: sporulation in bacteria, "sham death" in insects, anabiosis in amphibians and reptiles, hibernation in rodents and other animals, and sleep in man. "Change" of functional principle [4] is widely utilized during individual adaptation in humans and animals for economy of plastic material and energy and for creating a functional reserve of structures. During exposure to stress factors (exercise, hypoxia, psychoemotional stress) activation of systems most significant for adaptation (gas transporting, muscular, nervous, etc. activities) is paralleled by inhibition of nonpredominating systems (digestion, reproductive and sometimes immune activities). Isolation of the uterus from maternal neuroendocrine effects in normal gestation determines normal development of a fetus and pre-

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vents preterm labor [5,19]. Paired organs are functionally heterogeneous, for instance, kidneys, suborganic units such as nephrons and alveoli, cells (cardiomyocytes), and organelles, which is clearly seen in mitochondria. Passive inhibition of neurons during the torpid stage of shock and in coma, probably during syncopes in man, is an adaptive and sparing phenomenon.

Circulation and respiration occupy a special place among physiological systems. They cannot excessively increase or decrease their function in hypoxia, because it is fraught with injury to the myocardium and respiratory neurons and death. Increased sympathoadrenal effects observed in moderate hypoxia could lead, if excessive, to noncoronarogenic myocardial necrosis, while in severe hypoxia drastic increase in parasympathetic effects can cause an asystole. It is not clear how the hemodynamic system works under extreme and terminal conditions when life depends on hypoxia.

We investigated afferent stimulatory and inhibitory effects on circulation and its sympathetic and parasympathetic regulation in rabbits and rats exposed to hypoxia caused by oxygen deficit in a normobaric and hypobaric ("lifting" in a pressure chamber) gaseous environment [27,30,31]. In moderate hypoxia stimulating cardiac and circulatory functions, various nonhypoxic afferent signals directed to the cardiovasomotor center are generally ineffective. With aggravation of hypoxia (10 and 7-8% O_2 in N_2), stimulatory and later inhibitory afferent effects caused by fluctuations of systemic arterical pressure or by electrical stimulation of the central portions of the sinus and sciatic nerves are attenuated (pressure reflex in the formar case). Such a deafferentation is apparently regulatory, because the hypoxic signal (oxygen driver) to circulation is realized, vascular reactivity to the neurohormones adrenaline, noradrenaline (NA), and acetylcholine (AC) is retained, and their reserve in cardiac tissue is not decreased. This indicates that the sympathetic and parasympathetic systems affect the heart in such a hypoxia. The reserve potential of the myocardium is not decreased in moderate hypoxia, if this potential is assessed from the maximum intraventricular pressure under conditions of isometry induced by occlusion of the aorta.

In a very severe hypoxia (5 and 3-4% O_2 in N_2) with suppressed circulation all afferent effects fail, but in parallel with this, cardiovascular reactivity to adrenaline and AC decreases, particularly to adrenaline. Both in gaseous and hypobaric (at the height of 10,000-11,000 m) hypoxia, the NA and AC reserves in cardiac tissue are depleted, although the latter to a lesser extent. Similar shifts have been observed in isolated perfused rat heart under hypoxic (30% O_2+65% N_2+5% CO_2) and anoxic (95% N_2+5% CO_2) conditions (normally 95% O_2+5% CO_2). In this case, the inotropic reaction to increasing NA doses is attenuated, and less so the reaction to AC, as their reserves in cardiac tissue decrease. These changes result in a drop of efficacy of electrostimulation (particularly low-frequency) of stellate ganglion and peripheral portion of the vagus nerve isolated together with the heart [27]. The decrease in neurotransmitter reserve in isolated heart tissue is smaller than the drop in myocardial reactivity, although still playing an important role in the development of isolation, because a previous decrease in NA reserve in cardiac tissue of heparin-treated rats also attenuates the effect of electrostimulation of stellate ganglion on myocardial function.

Therefore, two ranges of hypoxia, differing by the status and regulation of circulation, can be distinguished in oxygen deficiency. In moderate oxygen deficiency and heart hyperfunction caused by realization of hypoxic signal (from chemoreceptors of sinocarotide glomeruli), extra afferent effects are attenuated when reaching the cardiovasomotor center. The initial failure of stimulating and late inhibitory afferent effects do not depend on suppression of neurohumoral processes in cardiac tissue and limitation of myocardial functions, because such an isolation forms at the level of cardiovasomotor neurons. Isolation of the cardiovasomotor center from stimulatory effects ensures adequacy of myocardial hyperfunction with severity of hypoxia, saves energy, and limits the contribution of circulation to numerous total systemic activities of the organism. Sympathetic and late parasympathetic effects on the myocardium are attenuated in extremely severe hypoxia suppressing cardiac function. The myocardium is isolated from nervous effects primarily as a result of its decreased reactivity to neurotransmitters, first to NA and then to AC. The content of neurotransmitters in the heart exposed to hypoxia decreases less markedly and is not completely exhausted even in heart arrest. Due to isolation of the myocardium from nervous effects, the heart starts functioning in the autorhythmic mode. Isolation at the level of the myocardium rules out the participation of the heart in any hemodynamic reaction and preserves the minimal possible function of the myocardium and the ultrastructure of cardiomyocytes [27].

In augmenting hypoxia caused by oxygen deficiency in the environment, the stimulatory and inhibitory effects on circulation and the mechanisms of various levels of their realization fail heterochronously. The heterochronic pattern is manifested by a decrease in the reactivity of contractile myocardium

and of cardiac pacemaker cells. As oxygen deficiency increases, stimulating effects are the first to be attenuated and then the inhibitory. This is explained as follows: cardiovasomotor reactivity to stimulating afferentation decreases sooner than to inhibitory afferentation; the reaction of circulation and isolated heart to catecholamines decreases to greater extent than the reaction to AC; their reserve in cardiac tissue decreases in the same order. Hypoxic changes in afferent regulation of the circulation anticipate a decrease in cardiovascular reactivity to neuro-hormones, and the drop in myocardial reactivity to NA and AC anticipates a decrease in their reserve in the heart. Hypoxic changes in afferent regulation of circulation anticipate a decrease in cardiovascular reactivity to neurohormones, and a drop in myocardial reactivity to NA and AC anticipates a decrease in the reserve in cardiac tissue. Hypoxic suppression of isolated heart during attenuation of inotropic responses of the myocardium to neurotransmitters can enhance for some time chronotropic response [11] maintaining the integral reaction of the heart (the Opie index).

There is a transitory type between two types of hypoxia: stimulating and suppressing the circulation. This type is based on heterochronous switching off the nervous effects of different modality and various levels of circulation regulation. The inhibitory afferent and efferent (parasympathetic) effects can persist in hypoxia progressing during the fading of stimulating afferent and efferent (sympathetic) effects. It means that the stimulating (signal) and suppressive (direct) effects of hypoxia on the regulatory and executive systems are manifested simultaneously and overlap each other in the transitory type.

Changes in myocardial regulation systems during progressive hypoxia develop earlier than cardiac contractile and rhythmic functions are suppressed. The capacity of neurons to maintain the mediator reserve in cardiac tissue in severe hypoxia is retained even when the contractile myocardium no longer reacts to neurotransmitters. Under conditions of hypoxic disturbance in deposition and irregular release of NA and AC, heterochronous pattern prevents their damaging effect on the myocardium (cardionecrosis and asystole), although supports the metabolic effect.

The above-discussed regularities in changes of circulation regulation pose new questions: what causes heart isolation from nervous effects in hypoxia, is this regularity universal for different types of hypoxia, why nervous effects on cardiac contractile and rhythmic functions drop out heterochronously, and what is the impact of this heterochronous drop-out for the organism? In order to answer these questions, we examined exogenous and circulatory (acute post-hemorrhagic status), hemic (intoxication with the methemoglobin inducing agent sodium nitrite), and tissue (cyanide poisoning) hypoxias and studied the regulation of circulation and isolated perfused heart during dissociated biological oxidation by 2,4-dinitrophenol (2,4-DNP). It did not reduce, but enhanced oxidation in the mitochondria and caused a negative shift in energy balance of the organism [6,18].

The heart is isolated from nervous effects at the level of the cardiovasomotor center and myocardium in the order characteristic of oxygen deficiency in hypoxias of different types, i. e., it does not depend on the agent which caused oxygen starvation and is reproduced by means of 2,4-DNP in ascending doses [24-26,28]. Therefore, isolation of the heart from nervous effects in hypoxia is caused by energy deficiency, and the stimulatory and inhibitory nervous effects at different levels of regulation fall out heterochronously because of different stability of neurons of different components and levels of regulation and of cardiomyocytes and heart pacemaker cells to ATP deficiency.

In terminal hypoxia, isolation of the myocardium from sympathetic and parasympathetic effects depends on energy deficiency and on combined effect of hyperkaliemia and lactate acidosis. Perfusion of isolated oxygenated (95% O_2 and 5% CO_2) heart with Krebs-Hanzeleit solution with high potassium concentration (9.4 mM *vs.* 4.7 mM in the control) or lactic acid (pH 7.28-7.29 *vs.* 7.40 in the control) induced no changes in its reactivity to NA and AC, typical of myocardial isolation. Combined perfusion with these solutions at ascending levels of K^+ and H^+ approximating those in terminal states results in hyperkaliemia and acidosis which lead to drop-out of inotropic responses to neurotransmitters and to a temporary increase of chronotropic reaction. We can conclude that alteration of metabolism in the myocardium damaged by hypoxia, which manifests by ATP deficiency and increased extracellular content of K^+ and H^+, releases the heart from the regulating sympathetic and parasympathetic effects [27].

Preliminary 10-min hypoxic or anoxic perfusion of isolated heart with Krebs-Hanzeleit solution containing NA (200 ng/ml) increased the level of K^+ and normalized the K^+/Na^+ ratio in cardiac tissue and simultaneously increased the reactivity of pacemaker cells to testing doses of both mediators, i. e., at the expense of chronotropic reaction [27]. Unlike cardiomyocytes, the conduction system cells receive energy mainly due to glycolysis [8], and NA stimulates glycolytic production of ATP and normalizes polarization of damaged heart cells [9]. It was demonstrated that vagal effects and AC improve oxygen utilization in the myocardium during hypoxia and

ischemia [3,7,34]. Therefore, in terminal hypoxia the heart is isolated from the mediator effects on myocardial function, although the effects on energy and ion balance are retained. This agrees with the hypothesis [12] that regulation can be limited by the sphere of metabolism in hypoxia.

Along with general changes in nervous regulation and cardiac function in hypoxia, we should like to note some specific features depending on the type of hypoxia and manifesting themselves primarily in the range transitory from moderate hypoxia, which stimulates the circulation, to extremely severe hypoxia, which suppresses cardiovascular function [27]. In acute exogenous and tissue hypoxia, bradycardia progressed as intraventricular and systemic arterial pressure were retained for some time (the bradyarrhythmic variant) during transition from moderate to terminal hypoxia. By contrast, during the transitory period of hypoxia in acute posthemorrhagic state and poisoning with sodium nitrite, tachycardia persisted for some time with intraventricular and systemic arterial pressure progressively decreasing (the tachyrhythmic variant). Adrenaline accumulating in the myocardium in circulatory and hemic hypoxia might be responsible for tachyrhythmic heart work.

Heart isolation from nervous effects in hypoxia depends on individual experience of an organism acquired during hypoxic training. Rabbits and rats were trained in oxygen-deficient gaseous environment for one week under conditions of oxygen deficiency growing in severity from 21 to 9-10% O_2 in N_2 5 h daily at the same daytime and then under the same conditions (9-10% O_2 in N_2 for 5 h) for two additional weeks. Adaptation was assessed by the time of rat survival in gaseous environment with 3-4% O_2 in N_2 18-24 h after the final session every week during training and for 2 weeks after it (disadaptation).

Oxygen deficiency training and adaptation prevented the development of isolation of cardiovasomotor center from nonhypoxic stimulatory and inhibitory afferentation during test hypoxia. During exposure to severe test hypoxia, the adreno- and cholinoreactivity of the myocardium was decreased in adapted animals, and the drop in NA and AC reserve in the heart was lesser than in intact animals. Isolated hearts of adapted animals responded by clear-cut inotropic but not chronotropic reactions to neurotransmitters and electrical stimulation of peripheral portions of autonomic nerves even in hypoxic perfusion [20,21,27]. This regulation of the heart is lost after training is over (during disadaptation). Therefore, adaptation preserves the intra- and intersystemic nerve bonds and ensures active participation of the circulation in various forms of the organism's activity, despite a strong hypoxic factor.

Study of the time course of acquisition and loss of new properties by the mechanisms regulating the myocardium and heart in adaptation and disadaptation has revealed the following regularities. Judging from the stability of myocardial adreno- and cholinoreactivity and neurotransmitter reserve under conditions of severe hypoxia, changes in the regulation during adaptation and its loss anticipate changes in the myocardium, which are manifested by fluctuations in its contractility. This suggests that extension of circulation potentialities during adaptation is at first due to increasing resistance of regulating mechanisms to severe hypoxia, while during early disadaptation (first week) the myocardium with its high functional potential, when exposed to severe hypoxia is sooner than normally isolated from nervous effects due to anticipating loss of new properties by regulating mechanisms acquired during training [27].

Increased resistance to hypoxia and changes in the mechanisms regulating the heart and myocardial parameters, typical of long-term adaptation, can be achieved by training under conditions of oxygen deficiency in gaseous environment and by regular injections of 2,4-DNP. Such a training leads to cross adaptation of animals to oxygen deficiency and to 2,4-DNP; moreover, one training factor can be replaced by the other and lead to the development of resistance to these factors, varying in degree [22,23]. These data indicate that energy deficiency is the active factor in hypoxia, which stimulates, suppresses, or trains the circulatory system, depending on the degree, frequency, and regularity of exposure.

Although stimulatory effect of hypoxia on cardiac function is realized by the sympathoadrenal effects, urgent and long-term adaptive changes are observed in the parasympathetic domain of circulation regulation. The sympathetic and parasympathetic systems exert opposite effects on cardiac function, and this is an important mechanism of adaptive potential of an organism. However, there is evidence on close cooperation of these two components of regulation at the neurohormonal and receptor levels in the heart. Their interactions and impact on the heart in disease, including hypoxia, are unknown.

Isolated intervention in the sympathetic or vagus innervation alters neurohormonal processes in both compartments of heart regulation. Seven-ten days after removal of stellate ganglia the levels of NA and AC in rabbit heard decrease, as well as AC and NA levels after vagotomy. Therefore, changes in the balance between sympathetic and parasympathetic effects caused by attenuation of one of them leads to transfer of neurohormonal supply of the heart to

a new lower level [23,27,31]. In different types of moderate hypoxia stimulating sympathetic effects and cardiac function, myocardial AC content increases; preliminary stellectomy in rabbits prevents cardiac hyperfunction and AC rise in it [27]. There are good grounds to suggest that in signal cardiac hyperfunction, AC decreases NA release from the sympathetic fibers [39,41], stimulates its production [40], and decreases myocardial adrenoreactivity [37,39]. Therefore, when sympathetic influence is increased, AC has no specific functional significance but limits sympathetic effects by preventing the depletion of NA reserve and myocardial exertion. On the other hand, in severe hypoxia NA loses specific functional significance for the heart and maintains the cholinoreactivity of cardiac pacemaker and AC reserve. Decline of NA level in the heart in severe hypoxia becomes a factor leading to isolation of the myocardium from parasympathetic effects [27].

The obvious relationship between sympathetic and parasympathetic effects and the role of this relationship in organization of these effects at the level of neurohormonal and receptor processes in the heart clarify mutual transformation of these effects in adaptation and disadaptation to hypoxia. In adapted animals the relationship between the sympathetic and parasympathetic mechanisms realizing opposite effects on the heart increases [36].

Presumably, neurohormonal mechanisms of both components of cardiac regulation (sympathetic and parasympathetic) contribute to nervous effects both stimulating and inhibiting myocardial functions. The impact of each of these components of heart regulation in two ranges of hypoxia, stimulating and attenuating cardiac function, is ambiguous. In moderate hypoxia, which stimulates sympathetic effects and cardiac function, AC corrects them. By contrast, in severe hypoxia, which enhances parasympathetic effects and leades to cardiac hypofunction, NA corrects them, and a drop in its reserve can promote complete isolation of cardiac pacemaker from parasympathetic effects. Regulation of the heart by sympathetic and parasympathetic effects depends, among other factors, on their relationship based on alteration of functional and metabolic effects of NA and AC neurotransmitters in the heart.

Based on these facts, we can conclude that the range of nerve bonds in the circulatory system and the range of these bonds with other physiological systems can be extended or limited, up to isolation of the circulation pacemaker, the heart. This range depends on energy reserve, on the experience gained by the organism in energy deficiency control, and on the interactions between various neuron populations, depending on energy supply to a different degree and with different significance for regulation of the hemodynamic system.

Isolation of the heart from nervous effects is observed in general classical hypoxia; moreover, ischemic zone of the heart can be isolated in acute coronary failure [14,15,29], in toxinemic shock; when hypoxic factor plays the crucial role in changing the regulation of circulation. Isolation from nervous effects has been described for the external respiration system in different extreme states, including hypoxia; it develops under terminal conditions at the level of the bulbar respiratory center, a pacemaker of this center. Here isolation also manifests itself as areactivity of respiratory neurons to afferent effects of different modality and leads to autorhythmic activity of the respiratory center, requiring minimal energy [7].

Functional isolation occurs at the level of the heart and bulbar cardiovasomotor center, the sensory systems, and their receptor [28] and central [16] formations. The relationship between the analyzer systems ensures selection of the signal most significant for the organism among numerous stimuli in each specific moment. Under conditions of oxygen deficiency, the reactivity of central neurons of the somatosensory system to specific afferentation is retained in rabbits, while the reactivity of central neurons of visual analyzer to the corresponding signals drops. In contrast to visual, somatosensory afferentation is important for organization of behavior aimed at the search for the optimal gaseous environment (gaseous prefendum), and therefore elimination of disturbances coursing from visual to somatosensory analyzer provides optimal function of the latter analyzer under conditions of hypoxia.

Isolation of cells and organs from various regulatory effects (nervous, endocrine, hormonal, etc.) occurs in hypoxia, ischemia, and other pathological processes. In a focus of inflammation, the initial alteration zone is isolated from effects of the organism due to degeneration of nerve fibers, minimized efficacy of mediator and hormonal effects under conditions of acidosis and an increasing level of extracellular potassium, formation of a limiting border, etc. [20]. Many scientists regard "autonomization" of a tumor as a mechanism and a manifestation of its malignant growth [10,33]. Isolation from conditioned signals and from many unconditioned effects, even the nociceptive, aimed at preventing exhaustion of higher cerebral neurons is observed in shock and in some neuroses, specifically, in acquired helplessness developing under conditions of information indefiniteness of the environment, an experimental model of hypasthenic neurasthenia [17]. Isolation from external signals is observed in humans

in extreme psychoemotional stress and is manifested in depression and stupor [32].

In any specialized cell the bulk of ATP energy is spent for functioning and realization of regulating signals; much less energy is spent for plastic processes and structure maintenance. Decrease in intracellular regeneration of ATP leads first to a drop in energy resources for realization of regulatory effects, which leads to isolation (autonomization) of the cell or a population of cells, because the production of the second messengers cAMP and cGMP involves utilization of ATP.

Later the function of cardiac pacemakers and respiratory neurons ceases or is minimized to the threshold incompatible with life. Functional isolation and minimization of the function permits maintaining for some time at a normal level the plastic processes and cellular structure. Cellular ultra-structure is damaged starting from the moment when a drop in energy supply surpasses the level required for functioning. This does not mean that in severe energy deficiency changes in cellular function do not involve ultrastructural modification; on the contrary, ultrastructural and functional changes correlate, and structural modifications of cell membranes are adaptive [27].

Isolation from the regulatory effects and minimization of functions are natural mechanisms of adaptation of live organisms. In disease, functional isolation develops in various processes, is supported by a variety of mechanisms, and can have different impacts on a cell, organ, system, and organism. In some cases functional isolation is a common adaptation mechanism yielding an adaptation effect, in others it can be regarded as a mechanism and a manifestation of damage (for instance, tumor autonomization). In the majority of cases functional isolation is dubious: it limits the participation of biological system in complex activities of the organism and preserves it as an integral structure. Under extreme conditions artificial isolation of the heart and vessels from nervous effects by drugs or other means improves their resistance to oxygen and energy deficiency, while attempts at modifying myocardial function by excessive neurogenic stimulation or inhibition can lead to untoward consequences [3,13,27].

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