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ARTICLE

The Optimal Coexistence of Cells: How Could Human Cells Create The Integrative Physiology

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ABSTRACT

A general view of human physiology is proposed. Each of 220 cell types must provide its intimate functions despite occasional or chronic obstacles created by other cells. The physiological mechanisms are independently emerged and evolutionarily saved due to their ability to provide optimal-like coexistence of cells on a background of destructive challenges of external/internal environments. In certain limits, both cells and organs are adaptive. The cell has accumulated both passive adaptation mechanisms mainly parallel working in the biochemistry, and active physiological mechanisms fighting for the optimal cell metabolism. Its rate depends on the cell type and current phase into the cell cycle. The adaptive properties of organs and their functional systems have resulted from the cells' adaptivity. The impaired cells (under energy lack and/or contaminated cytoplasm) produce adaptation factors acting both in the cell and at multiple organism-scales. Multicellular mechanisms, enhancing the cell fight for energy balance, creating the due cytoplasm for optimizing metabolism, force the most physiological characteristics, including the mean arterial pressure to fluctuate or shift. The view is a basis for re-thinking the concept of the so-called physiological norm and fundamental mechanisms of age-associated pathologies, in particular, hypertension.

1. Introduction

The article is an essay providing a non-standard systems analysis thus, requiring an extraordinary introduction. The term "adaptation", pivotal in the essay, is used in the sense, concerning the phenomena that throughout life cover an organism's reversible re-tunings in response to internal/external physicochemical and information alterations. The phenomena exceed events usually being under terms of acclimation and acclimatization [1–4].

Currently, the physiology in general and the human physiology in part are almost exclusively empirical sciences. But the empiricism, well provided researchers during studying of isolated organs or their limited systems, meet serious problems when it is necessary to understand how the entire organism is functioning in unstable environments. The data basis accumulated by means of empirical study of human adaptation to the altered environmental conditions (atmosphere fronts' passing, high altitude, low or increased temperatures, weightlessness, physical exer-

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cises, others) is rather a set of fragmentary observations than internally connected causal-consequential regularities.

Figures 1-3 below represent two typical examples of a healthy human person's adaptive physiological responses to alterations of the external environment. In figure1 depicted temporal changes occurring during acclimatization to the higher altitude [1].

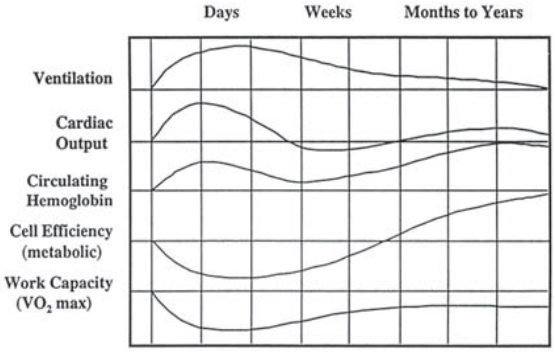

Figure 1. Typical temporal changes occurring during acclimatization to the higher altitude [1]

Principally, the character of adaptive responses is confirmed in many investigations (in particular [3,4]).

Certainly, the high altitude affects not exclusively the respiratory system, but also others. According to [5], average cardiovascular and autonomic changes in healthy subjects during the first 10 days of acute high altitude exposure look like shown in figure 2.

As figure 2 shows, the hypoxia stimulation of the cardiovascular system (CVS) reaches its maximum effect during the first few days of high-altitude exposure. Then, on a background of the elevated sympathetic activity, heart rate, cerebral blood flow, and cardiac output are slowly returning to their approximately initial values. Stroke volume, decreasing in parallel with increasing of heart rate, is still significantly lesser than its initial value was. Mean arterial pressure (MAP), and pulmonary arterial pressure are still elevated.

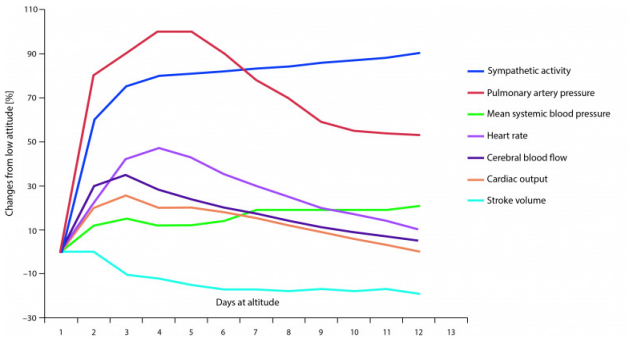

Figure 2. Average cardiovascular and autonomic changes in healthy subjects during the first 10 days of acute high altitude exposure between 3800 m and 4559 m. [4]

Generally, physiological responses to the elevated altitude, illustrated in figure 1 and figure 2, are in accordance with the current presentations that the hypoxia is the main disturber here. However, other factors accompanying mountains' climbing (namely, temperature and atmospheric pressure decreasing, radiation increasing) are also disturbing the stable physiological mechanisms. Stylized rapid responses of two virtual physiological variables to linear changes of atmospheric pressure are depicted in figure3.

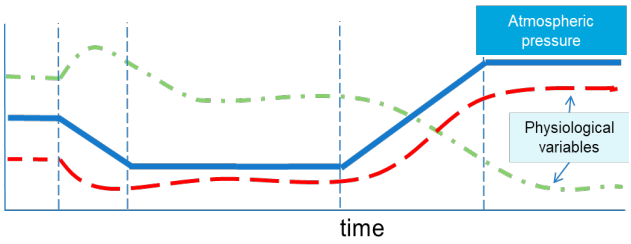

Figure 3. Typical phases (divided by vertical dotted lines) of human two virtual physiological variables' responses to gradual changes of atmospheric pressure

Under initial stable pressure, physiological parameters (green and red lines) are also stable. The second phase begins just after the atmospheric pressure is linearly decreasing: both variables, starting to alter (though in this situation in opposite directions) display a complex dynamics.

Already these examples demonstrate that the human organism is entirely adapting to the new environmental conditions. To imagine how deep may be external environmental influences, useful is to look at figure 4.

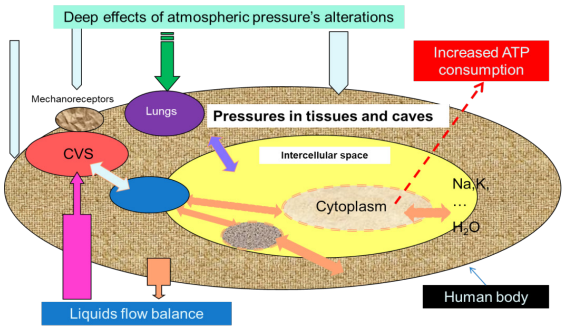

Figure 4. A scheme illustrating deep physical effects of atmospheric pressure (AP) alterations on human body

Initially, under stable AP, stable pressures in different body structures and cavities determine balances of water and ions in liquid environments including cytoplasm. Mechanoreceptors of CVS are reacting only to violations of blood pressures. Under alterations of AP, they affect both CVS' mechanoreceptors and gas concentrations in lungs and their ventilation. In addition, due to pressure transfer through tissues, initial balances become violated

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in liquids of intercellular and intracellular environments. This causes ions imbalance too. To create a new balance on all structural levels, the cell must expend energy. This is a basis for assuming that under general energy lack, the organism's vulnerability to the passing of atmospheric fronts may increase.

Relationships between AP and human body are much complex than it is commonly assumed. The external pressure passes through our tissues almost without attenuation. AP takes part in formation of both transmural blood pressures and driving forces for trans-membrane passing of water and ions. Finally, internal balances at every organization level determine the activity of a lot of physiological mechanisms. Thus, every alteration of AP physically affects these structures and creates imbalances. To counteract them and create new biological balances into organism's structures (cells, intercellular liquid environment, cavities), cells are forced to activate their pumps working with ATP expenditures. So, during passing of atmospheric fronts, the organism has to activate energy production. Perhaps, this is why the aged persons (likely, having mitochondrial problems) are vulnerable to rapid and essential alterations of AP. None empirical investigation is capable to cover all aspects of this, seeming to be simple, problem. Only mathematical models and computer simulations allow assess the possible investments of each mechanism in providing of our tolerance to AP's alterations [5].

One more picture, shown in figure5, is to demonstrate that our organism, at cells-scale, at tissues and organs scale well-adapted to the earth living environment, is forced to response to alterations of practically every physical-chemical parameters of the environment.

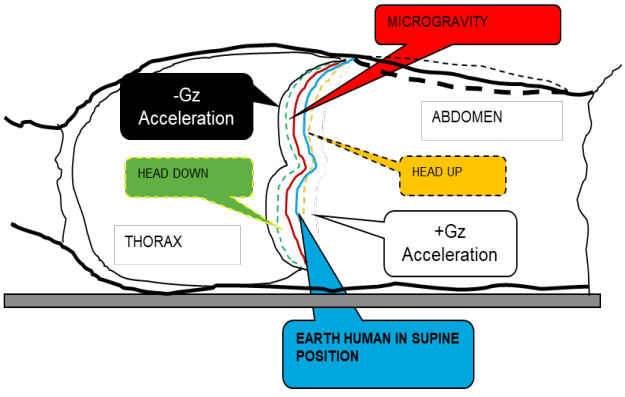

Figure 5. Gravity-associated biomechanical shifts of abdominal organs' location in the body and their likely role in astronaut's acute adaptation to microgravity conditions

The pleural pressure is one of modulators of the venous return to heart. The descending aorta, the lower vena cava, as well as the esophagus are breaking through the diaphragm. As the abdominal organs have certain weight, normally, they influence on diaphragm position. It is shifting both under postural changes and under positive (+Gz), negative (-Gz) accelerations, as well us just after the spaceship's engine stops to work and the astronaut is appearing into the microgravity environment. Computer simulations on the model of a three-dimensional cardiovascular system has shown that the slight elevation of the pleular pressure is the most likely mechanism impeding venous return from the cranial basin [6].

For a long time, the space physiology and medicine used a paradigm stating that under weightlessness, in CVS some additional forces are appearing: they cause cranial shift of blood volumes thus initiating headache and other negative effects [7,8]. Although the earth-based physical models of circulatory effects of the weightlessness (mainly, the anti-orthostatic position of 6-12°) have provided this hypothesis, later direct measures during real space flight have not confirmed the assumption that the central venous pressure is elevated relatively to its preflight level [7]. Special computer simulations provided by means of a three-dimensional CVS's model have clarified this contradiction [6]. Indeed, additional driving forces in hemodynamics have not been found. It was shown that the weightlessness creates new balance of the mechanical forces, acting on the diaphragm from the abdominal and thoracic cavities. Namely, the diaphragm is shifting into the thorax thus slightly increasing the pleular pressure. As the latter is a modulator of the venous return, the flow from the cranial basin is complicated. The asymmetry is because the vasculature of lower body normally has a more musculature and is better provided by sympathetic nerves. This is a result of human organism long adaptation to the upright position against earth gravity.

Although there is a big amount of publications, concerning different aspects of human adaptation to the altered environments, let me limit the citings, and do several interim conclusions, that will clarify my approach to problems concerned.

(1) Evolution has accumulated multiple mechanisms adapting the human organism to environmental challenges. None empirical approach is able to measure the entire spectrum of biological adaptive re-buildings: behind every empirical result many uncontrolled and unknown responses are still. Adaptive mechanisms, genetically predetermined but continuously being re-tuned throughout ontogenesis, are reversible. Principles of the retuning are described in [9].

(2) As the reversible adaptation is individual, its regularities hardly can be revealed on a basis of the existing empirical data: in fact, they are representing a statistically processed description of the mean results. This is why

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physicians working in traditional or sports medicine are not capable to create optimal cure or training trajectories.

(3) Individual physiological adaptation to the altered external/internal conditions is a transitory process from the initial quasi-stable situation (at cells-level, assimilation-dissimilation rates are almost equal) to a new one. In a parametric dimension, this transition suggests that there have to be adaptation driving forces (ADF), that appear and act until the new quasi-stable physiology is achieved. The empirical adaptation biology is focused on the description of observable life variables and nothing knows about ADF. One of the main purposes of the theoretical analysis provided in the article is to clarify the nature of ADF, causes for their appearing/disappearing. These uncertainties, complicating the control of adaptation trajectories, that namely, could allow optimizing the training algorithms in sports medicine and the cure of human certain pathologies that are slowly developing for many years.

(4) Certain facts and previous research [10-20] point that the necessity to balance the mean energy production rate in each cell, from the one side, with its mean energy consumption rate, from the other side, is one of the most critical criterions for both the cell's and an organism's well-being.

(5) The traditional physiology is aimed at analysis. There is a need to supplement traditional empiricism with a theoretical synthesis also based on reasonable initial heuristics (hypotheses), as it has long been done in physics. As a physiologist-theorist, for many years I am using mathematical modeling and computer simulations illustrated that behind the things, physiologists have had seen in their experiments and published, often exist deeper and simply working mechanisms that can be comprehended only due to the synthesis.

Taking into account these considerations, the purpose of the article is to propose an internally consistent synthetic theory to explain the most general laws of human physiology that is a way for ensuring the optimal coexistence of our specialized cells.

2. Facts and Heuristics to be Used in the Synthesis

The traditional physiology was developed in the opposite direction to organisms' natural evolution. Since Harvey used experiments on ships' hearts and calculations for proving the concept of bloods' circulation, researchers use animals as a model to understand the human organism. Due to reductions, the main roles of every organ in the functioning of the entire organism are established. But somewhat strange situation came to be spread: even nowadays, most physiologists think that the human integrative physiology (HIP) entirely concerns the interactions of organs for providing behaviors. This simplified view does not take into account that physiological mechanisms of life support are operating continuously. As even under rest conditions the organism provides its functional integrity, HIP mandatorily includes all intercellular interactions. Unfortunately, this aspect of HIP is studied very superficially. Even the molecular-biological approaches, since the 80-s of XX Century penetrated into the physiological researches, did not change their character: in fact, both the genetic and the molecular data mainly serve the current physiology as useful appendages.

The matter is that the unicellular organisms (UO) were the elements that have had been aggregated into the one multicellular organism (MO). At this historical moment, the hypothetic ancestor UO has long been evolved in unstable environments. It is highly likely to assume this UO should have been armed with specific mechanisms adequately coping with the environmentally caused intracellular destructions. Also likely is the next assumption: cells, successfully being aggregated into the first MO, had not lost most of these adaptive properties of their ancestors. The question is whether these mechanisms themselves were capable to cope with the novel challenges that occurred in MO?

Let me skip the problems arisen in plant and fungi organisms and focus the question: what new threats for the existence of cells in the animal organism have arisen? Currently, all we know in this aspect is provided by comparative and evolutionary biologists. In fact, they are carefully fixing differences observed in the general anatomy and anatomy of organs of species. Unfortunately, the smallest structures-cells have been compared very roughly. As to the roles of genetic and molecular differences in the organization of physiological nuances at organism-scales, there is practically none investigation. This fact, though complicating our comprehending the cells' coexistence, requires additional logic efforts.

Useful is to underline that the circadian and season rhythmic environmental challenges were the main external violators of UO, thus, the most part of its adaptive mechanisms likely have the same rhythms. What additional violations of the cell life the animal organism origins?

First of all, the animal organism cells are taking nutrients in the same internal source – arterial blood. If the amount of nutrients there is less than the summary needs of all cells is then they cannot provide the required rate of their metabolism. So, the competition for the nutrients (or their several representatives) is a problem that first had to be solved during the evolution of animals. The second problem that has to be solved by animals during their evolution was the problem of how to support the biophysical and biochemical

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parameters of cytoplasm in a narrow corridor for ensuring the optimal-like rate of the cell metabolism?

Animals to solve these two but not the exclusive fundamental problems have been needed adequate physiological mechanisms. In fact, they have to create: (1) at least two canalization systems (one for providing incomes flow, another – for the in-time removing of metabolic trashes); (2) organs for filling the first canalization system by nutrients; (3) organs, for collecting and removing trashes produced by all cells. Let us call these mechanisms effector-mechanisms (EM).

Assuming EM appeared thanks to mutations and chromosomal aberrations throughout zigzags of evolution, one can conclude that EM could provide optimal-like cell metabolism only in case if certain additional mechanisms are coordinating the activities of these EM. So, we came to the most important for the current HIP question: what mechanisms coordinate the activities of organs and systems materially supporting the optimal-like metabolism of human cells?

The most spread answer to this question sounds like: the homeostatic mechanisms are the supporters. But this answer is correct only in part. In every real organism, homeostatic mechanisms are in non-trivial relationships with mechanisms of reversible adaptation [10-13].

Since Cannon has formulated the homeostasis concept [21], a huge number of researchers tried to establish specific mechanisms providing the homeostasis at organism's different organization levels. Body fluid homeostasis is directed at achieving stability of the two major functions of body fluids: maintenance of body osmolality within narrow limits, and maintenance of extracellular fluid and blood volume at adequate levels. Osmotic homeostasis prevents large osmotic shifts of water into and out of cells, which would interfere with normal cell function. However, on the background of real homeostatic mechanisms, many mechanisms that are not homeostatic at all also have been considered to them [22-25].

Here important is to stress that regulators balancing energy in a cell are principally different of those known as classical homeostatic regulator (see figure 6).

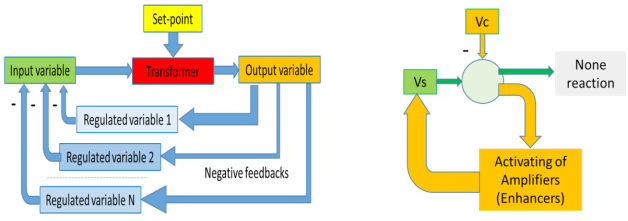

Figure 6. A simplified presentation of the homeostatic system (left) and regulators balancing energy in a cell (right)

The homeostatic regulator activates negative feedback mechanisms to minimize the difference of the constant (defined by the set-point organ) from the current value of the input variable. The cell energy balancer, active for every value of Vs and Vc, uses enhancer mechanisms for leveling the current value of Vs with the current value of Vc.

In fact, the homeostasis is a self-regulating process that returns critical systems of the body to activities determined by a set-point. In contrast, energy balancers try to level energy synthesis with energy consumption for its entire range of alterations. Note, the special energy state called energy deficiency (ED) does appear only in cases if within some time interval of τ the number of ATP molecules in a cell is less than a critical level of E_c is. E_c, characterizing the number of ATP molecules and allowing the cell to provide its immanent functions, is specific for each cell but depends on phases of the cell cycle. Formally, both the current energy status $E(t)$ and ED can be calculated using the following equation:

$$E(t) = E(t-\tau) + \int_{t-\tau}^{t} (V_s(t) - V_c(t)dt$$

Although the homeostasis concept explains why certain life characteristics stay practically stable despite their violating, the most problem is that the brain structures responsible for the set-point, in most cases are not found yet.

Spaceflights have had compelled physiologists and physicians to re-think the reversible adaptation phenomena. In the introduction, it was accentuated only one aspect of the human cardiovascular acute response to the microgravity conditions. The adaptive changes are much wider and deeper. Already in a few days of the flight, due to increased diuresis, the total blood volume is decreasing of about 10% [7,8]. This alteration is caused by the activation of both carotid sinus baroreceptors and volume receptors in the brain. But in parallel with the increase of space flight duration, the adaptivity displayed an involvement of additional mechanisms. Namely, the smooth muscles of the vasculature in body lower areas becoming thinner, the legs musculature loses in mas [7]. Moreover, space flights of several moths duration also led to Ca loses in bones of legs and in other parts of the skeleton [7,8]. All these changes are reversible: after several days, weeks, and months of the spacemen's returning to the earth, the organism is recovering. This prompted researchers to think that our skeleton, CVS, neural-hormonal systems, and the organism entirely are a product of human beings' long evolutionary adaptation to the earth's gravity. Using this

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conclusion based on a set of facts, one can do a more general conclusion: our body is an adaptive living object built of multiple adaptive mechanisms that likely are reversible and cover every cell, multicellular tissues, and organs, as well as functional systems.

Recent investigations in other sectors of biology – genetics, and epigenetics [26-28] –, formed additional information concerning the reversible adaptation mechanisms. The more and more publications are convincing that the food assortment, physical, emotional loads, and even the meditation are capable of changing the biochemistry by a way which does not change the genotype but through the switching-on or -of specific groups of genes cardinally varies the physiology. Even there are researches proving the inheritance of epigenetically acquired properties in two generations [29].

It was commonly assumed that there are two mechanisms for providing these adaptations – functional, and structural. However, already the early morphological data have shown that the adaptation to a physical load, high altitude conditions, and arid zones always has its structural indicators both at the cell-level and at tissue-levels [30]. Further deepening in this problem revealed that the so-called functional adaptation also is based on the reorganization of previously achieved structures of tissues and organs [10]. Namely, this fact is depicted in figure7.

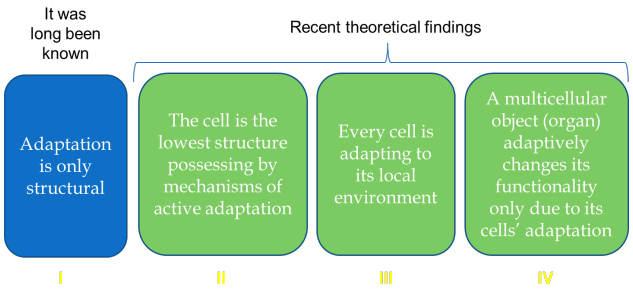

Figure 7. Basic statements of the individual adaptation that explain the so-called functional adaptation, as well as the self-tuning of organs and the entire organism to altered living conditions

The four statements, depicted in each box in figure 7, sound louder if one imagines specific mechanisms governing of multicellular structures' natural dynamics.

2.1 The Elementary Structural-functional Unit

Most biologists are sure that in MO, the cell is the elementary structural-functional unit. But it is not correct assumption capable of origin wrong interpretations of observations and experiments. Though cells are the smallest structural units of MO, none specialized cell exists in a single exemplar. Every specialized cell is a constructive element of the specialized cells population (SCP). Namely, SCP is the lowest functional unit. Most organs include certain types of SCP. The organs' functionality and dynamic characteristics depend on both spatial organizations of its SCP-s and specific internal statistical characteristics, representing the distribution of internal ultra-structural differences. The matter is that within the one and the same SCP, cells, being consequential generated by cells of previous generations, rarely are absolutely clones. Their certain parameters (for example, threshold level, saturation level, rest potential) are slightly different. Two main factors determine these internal heterogeneities. One follows from the temporal non-stability of blood inflows during cell division and further growing, another - from the cell's spatial localization: the vascular net usually is not an ideal three-dimensional symmetric structure thus several cells are better provided by nutrients than others.

Additional three rules, indicated in right boxes in figure7, had been formulated by taking into account these internal ultra-structural heterogeneities in SCP [10].

Namely, due to such kind of internal heterogeneities, the heart demonstrates its characteristic dynamics during both systole and diastole. Would all cells of the myocardium of the heart chamber absolutely identical, the heart is to react to impulses of the sinus node step-wise! We have used this knowledge for creating a mathematical model, providing natural-like pulsatile human hemodynamics [5]. By the way, internal heterogeneities are the cause of organs displaying non-linear input-output relationships.

These facts and logical considerations above are the necessary but not yet the sufficient conditions to do the first step toward constructing of a virtual MO, providing cells optimal coexistence. As every biological mechanism is working against the second law of the thermodynamics, the pivotal question is: how the energy supply is organized? Although this problem has long been in a focus of biological investigations, currently, the most data concerns specific aspects that are covering only the homeostatic regulation of food intakes (energy inflow) and energy expenditures (energy outflow). However, the energy problem in human organism has an additional aspect till recently even not posed.

2.2 Specific Role of Energy

Life is a way for decreasing the entropy in a local space using the energy of the outer space. Therefore, life is possible until energy is present. Already our ancestor aerobic UO-s, being a modification of anaerobic UO-s that created energy macroerges (ATP molecules) by using cytoplasm glycolysis, have had been armed with an additional mechanism synthesizing ATP by means of pyruvate oxygen-

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ation in mitochondria. The second mechanism is almost 17-times more powerful than the first one. However, this achievement created an additional problem: oxygen concentrations in the cytoplasm (consequently, in mitochondria) must be proportional to pyruvate's concentration. As the pyruvate is one of the products of anaerobic glycolysis, the cell is empowered enough only for those situations when oxygen and carbohydrates' incomes are duly associated. This is why most aerobic UOs in nature is displaying unstable metabolism depending on the incomes.

2.3 Cell Energy Balance Versus Cell Energy Homeostasis

Most researchers use the term cell energy homeostasis to distinguish physiological events at organism scale [22,24]. But the term homeostasis was coined to characterize the approximate stability of certain physiological variables [21]. Above was marked that every cell can produce ATP on different stabile rates. It also can consume ATP on different stabile rates if the cell is capable to synthesize ATP at these rates. So, it is much correct to use the term cell energy balance instead of the term cell energy homeostasis. This clarification does indicate that there should be special mechanisms that realize the floating of the ATP production rate.

figure8 illustrates problems concerned with a cell energy balance (CEB).

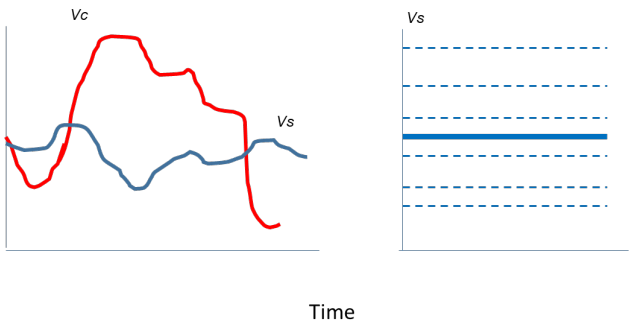

Figure 8. In a cell, stochastic variations of ATP production (V_S) and consumption (V_C) rates, each depending on multiple variables, lead to energy deficiency if $V_C > V_S$

The right-side picture schematically illustrates the fact that every cell may have many stable levels of V_S. Each such level is to serve current but stabile cellular needs in ATP. The bold line is to stress that under rest conditions, the cell provides such some level of V_S that supports all biological works. But under suppressed modes V_S may be lower, as well as under cell's activation, proportionally to the activity $V_S$may be elevated up to a maximal level, determined by current value of S_m. the left-side picture illustrates that both V_S and the energy consumption rate V_C are variables.

In figure8, the left-side picture illustrates that both V_S and the energy consumption rate V_C are variables: $V_S(x_1(t)\ x_2(t),...,x_m(t))$; $V_C(y_1(t)y_2(t),...,y_n(t))$. Situations of $V_C \leq V_S$ or $V_C > V_S$ are possible. Special energy mode appearing when $V_C > V_S$ is termed as hypoergia. Pay attention - both V_S and V_C can have a lot of values. However, only the long lasting situation of $V_S(x_1(t)x_2(t),...,x_m(t)) \geq V_C(y_1(t)\ y_2(t),...,y_n(t))$ provides the cell by due number of ATP molecules. The big question is how this exclusive energy mode can be provided for trillions of human cells each having almost stochastic dynamics of energy consumption rate $V_C(y_1(t)y_2(t),...,y_n(t))$. The most likely answer is that the cell possesses by autonomous mechanisms coping at least low or moderate energy shortages. Indeed, such mechanisms (at least, three) are described [6].

Figure 9 below illustrates the fact that the aerobic cell possesses by a battery of at least three mechanisms specially activating under cell energy problems

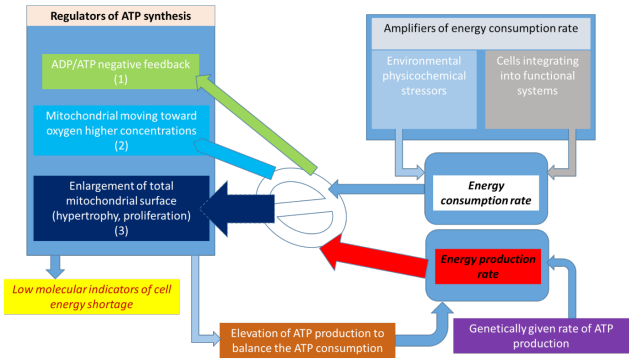

Figure 9. Determiners of the mean energy production and consumption rates in a cell and its mechanisms resisting to critical situations of energy imbalance

The variable rate of energy production in a cell is given genetically and associated with phases of the cell cycle. Extracellular events, including those involving cells into organism's integrative functioning, may elevate the rate of energy consumption thus cause ATP's lack (the state ED). Under ED, three intracellular mechanisms (shown in left side) each possessing by specific speed and power try to level ATP's synthesis and consumption rates. Due to low molecular indicators of cell energy shortage, the most powerful but inertial mechanism (3) enlarges the cell's total mitochondrial surface via their hypertrophy (including the fusion) and/or proliferation.

According to figure 9, the battery of intracellular regulators of the rate of ATP synthesis is built of three mechanisms. The first and most rapid intracellular mechanism, based on mitochondrial ratio of $[ADP]/[ATP]$, is chemical negative feedback automatically increasing the value of V_S under decreasing of $[ATP]$. The second mechanism, most

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effective in big neurons and especially in their long axons that have essential differences of oxygen concentrations in different regions, uses the mitochondrial motility towards higher oxygen concentrations in cytoplasm. The mechanism acts slower than the first one. The third mechanism using the hypertrophy and/or proliferation of mitochondria is the most inertial but the most effective fighter against chronic energy lack.

As the organism uses both glucose and other energy-rich nutrients, additional problems arose. The pyruvate is a common net product of both glucose consumption and consumption of carbohydrates, fatty acids, lipids, and even proteins (in extreme cases). Each of these source products has its transformation chains and efficiency [31-33]. Under changes in arterial blood carbohydrates' concentrations, the net effect of both pyruvate and ATP production also is changing. In fact, these changes reflect a phenomenon further in the article called a passive adaptation: the adjective stresses the fact that this form of the cell adaptation to current local environmental conditions does not use ATP. In contrast, a special mechanism (called a cellular mechanism of reactive adaptation (CMRA) [10]) that uses ATP to fight the environmentally induced intracellular destructions is also in human every cell.

Our cells, as well as cells of virtually every animal, are under influences of essentially more dynamic factors, capable of creating energy problems than our far ancestor cells were. To clarify this very important for the human physiology statement, let us analyze the metabolism of a virtual specialized cell (VSC) in the human organism. Remember that the ancestor UO has two physicochemical environments – cytoplasm and space out of the cell membrane. In the frame of the human organism, the outer space, in turn, is divided into two environments – intercellular, and the environment around the body. Assume the latter environment has its independent dynamics. If our exteroceptors react to these alterations, then the cells, functionally integrated with these receptors, also will alter their current activity. Most exteroceptors represent the first link of the long functional chains that include certain groups of organs.

Here important is to highlight that animals provide distinguish, specific functions (movement, rapid responses to environmental challenges, effective heterotrophy, reproduction) not least thanks to a group of so-called excitable cells. The group includes neurons, muscle cells, and secretory cells. They have two distinguish signs: (1) a creation and providing a stable level of a resting potential (RP); (2) recovering the RP after its external violations. The matter is that passive mechanisms, based on the initially created high trans-membrane gradients (concentration and electrical), are not capable of a strong recovery of the value of RP. Thus, the excitable cells (at least neurons and myocytes) use a certain number of ATP to exact recovery the value of RP. Although the absolute amount of these energy expenditures is the very little part of the cell's general energy expenditures, in [11] for the first was argued that under the high frequency of external violations of cell's RP, this internal problem may lead to a deficiency of ATP. So, the providing of the basic functions of the cell is associated and critically depended on how often the excitable cell is involving in systems (outer) functions.

Every specialized cell (excluding adult erythrocytes) must provide its metabolism and regularly divide. Namely, these functions are the immanent functions of each cell. Despite namely the outer functions of specialized cells were used by biologists to denote cell's type, none cell is "interested" in the supporting of its outer functions. They are indirect effects using which the multicellularity arose [9]. It sounds like a paradox, but the excitable cells that are the constructive elements of our functional systems, are the best illustration of this statement. Namely, the indirect effects of excitable cells (neurons' impulse generation, muscular cells' contraction, secretory cells' secret) have had made animals in general. Moreover, animals had been successfully passed through the sieve of evolution precisely thanks to these indirect functions that allow them to carry out their nutrition, survival, and reproduction in a competitive environment.

Figure 10 below illustrates principal events appearing in a cell in case of chronic energy deficiency.

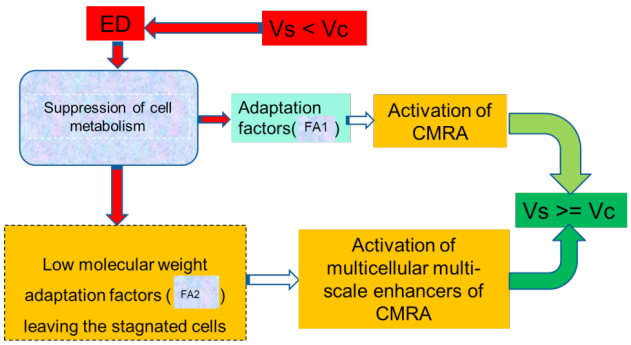

Figure 10. Principal events in a cell in case of chronic energy deficiency (ED)

Adaptation factors FA1 and FA2, appearing in the cell under energy deficiency, activate intracellular mechanisms (CMRA) and their external enhancers to produce some more ATP and normalize cell energy supply and metabolism.

It is assumed that under energy lack (happening because of long-lasting situation formally looking as Vs<Vc), the cell metabolism is suppressed. Among inter-

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im metabolic products, there may be two specific factors (FA1 and FA2). FA1, activating CMRA, is acting exclusively into the cell. The activated mechanisms of CMRA try to increase Vs until it becomes equal to the current level of Vc or higher than it is. If the energy deficiency in the cell is not liquidated, low molecular chemicals FA2, leaving the cell and penetrating into the lymph and venous blood, further do circulate until their decaying or meeting with the receptors of organs regulating activities of multicellular enhancers of CMRA. So, the cellular factors are activators of both intracellular and extracellular negative feedbacks capable to elevate the rate of ATP synthesis until it is balanced with the current (genetically given or environmentally induced) rate of ATP consumption.

The next figure represents a version of the so-called binary model of the human organism conventionally divided into two virtual cells (VC).

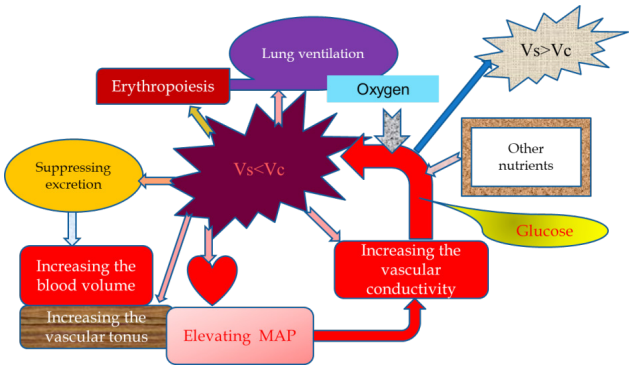

Figure 11. A simplified (binary model) presentation of the fight of the energy-lack virtual cell (Vs<Vc) for energy

The organism is maximally reduced to reflect cells' role in involving organs and systems for cell supply by source chemicals necessary for ATP synthesis. All cells are reduced to two virtual cells (VC): one with Vs>Vc does not have an energy problem while the second VC in a central part needs to increase its Vs to level it with the current value of Vc. It is assumed that the second VC is releasing into the circulation adaptation factors that are capable of increasing blood flows and nutrients incomes predominantly toward the stagnated cell. Due to elevated rates of erythropoiesis, and lung ventilations arterial blood becomes better saturated by oxygen. Another adaptation factor, suppressing fluids excretion, increases the total blood volume – the main factor for MAP's elevation. The latter is also provided by increased vascular tonus and heart function. The vasodilatation increases arterial blood flow (enriched by glucose and other substrates) mainly to the stagnated VC while the normal VC (depicted in the right upper part) is supplying by lesser blood inflow.

The cell (depicted with a Vs>Vc) does not have energy problems while the second one (depicted with a Vs<Vc) represents all cells feeling energy lack. It is assumed namely, the second group of cells creating efforts for mobilizing organs that are supporters of source chemicals for providing ATP synthesis.

The energy mega-system (EMS) does include some more organs and functional systems than they are shown in figure 10. As it was argued in [16], EMS is one of the complex physiological super-systems that emerged and evolved as providers of cells' well-being in wide ranges of disturbances. In the light of this concept, a complex of adaptation factors released by the ED-cells could both modulate the activities of these organs and redirect their increased products toward the suffered cells. Namely, the negative feedbacks and a more detailed illustration of such an energy super-system are shown in the next figure12 [12].

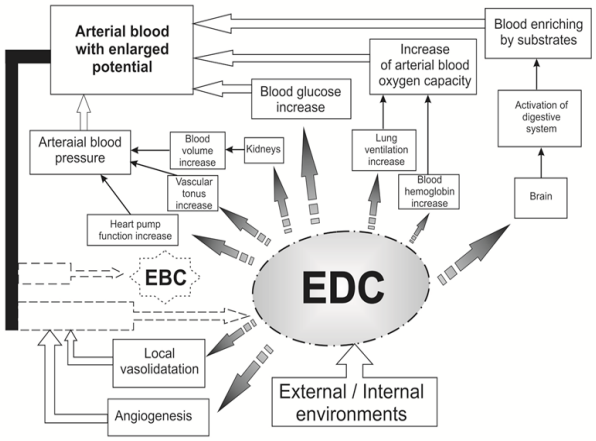

Figure 12. A version of the energy mega-system: it is assumed that the organism struggles with sustained severe hypoxia caused by circulatory disorders in a big body region

Conventionally, EBC represents the organism's energy balanced cells while EDC represents energy-deficit cells with the activated CMRA. Under the functional insufficiency of CMRA, EDC causes local and distant effects enhancing the CMRA. Local effects include rapid vasodilatation and inertial angiogenesis. Distant effects are aimed at creating a more potent arterial blood: its pressure and oxygenation become higher. To reach this effect, as well as to direct the major part of the potent blood towards EDC, distant influences of EDC are targeted to the mechanisms controlling the rates of erythropoiesis, pulmonary ventilation, and reabsorption in kidney tubular channels. Due to the increase of blood volume, heart rate and vascular tone the MAP becomes elevated. If the elimination of energy deficit is not possible because of the general short-

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age of source materials, EDC also activates the digestive system.

In figure12, it also is assumed that under total energy deficit specific adaptation factors do activate brain structures organizing and controlling behaviors aimed at search for foods and their assimilation.

3. General Vision of Mechanisms Optimizing Cells Coexistence

To correctly analyze mechanisms optimizing human cell's coexistence, a clarification of the notion "optimal" is necessary. The optimality is relatively notion requiring its criterion or even multiple criteria. In some cases, the optimality used to technical objects (engines) silently supposes that the engine is maximally effective. However, this interpretation is not applicable to biological objects. The natural evolution does not create ideal structures. All living objects, providing the species by the ability to pass their genes to the next generations, have had been passed through the sieve of evolution. As mutations and chromosomal aberrations are the main material basis of evolution, there is no reason for assuming the mechanisms that appeared on this basis are maximally effective. In fact, zigzags of evolution are continuously changing the genome either by heaping with new pieces which at the organism level result in a heap of many biological mechanisms or losing some pieces. They may not obligatorily act synergistically: often parallel mechanisms may act in an antagonistic manner. Therefore, their optimal coexistence means a compromise. Namely, our trillions of cells, competing for common nutrients and influencing one-another by their metabolites or output functions (in particular, in pairs containing at least one type of excitable cells), can come to situational stabile coexistence (SSC). As far as both external and internal environments are not strongly stable, SSCs, reflecting the non-stationary processes, normally are fluctuating in time. Under environmental trends, certain SSCs may display more or less regular shifts. So, we should define two types of cells optimal SSC: (1) a short-time, and (2) a long-time. Both fluctuations and shifts have their projections in certain life variables.

The short-time optimal SSC of cells may be provided by involving either intracellular resources or local regional potentials. In contrast, to maintain the long-time optimal SSC of cells, multicellular enhancers are required. One scenario suggests that their activation and coordination is provided by CNS. Indeed, many brain structures are involved in the modulation of organ' activities. However, it hardly is possible that every cell is being under continued control of neurons of CNS. From one side, such a hypothetical organism could have essentially more neurons. From the other side, neurons do not create the due density of their terminal branches. The third reason concerns the internal heterogeneity of every cell population. These reasons forced to conclude that the brain may solve certain acute problems of cells material supply while the chronic problems, that always are local, have to be solved by local mechanisms.

So, local mechanisms have to create and control locally optimal nets of both macroscopic and microscopic vasculature. It does effectively provide both substrates and oxygen incomes and metabolites outcomes. The efficiency mostly will be in those physiological modes that last longer. The brain does not participate in these basic events. Its role will be minimal also under acute but low or moderate energy or metabolic problems. The assimilation/dissimilation relationships have to be under metabolites in the local intercellular environment. Only in extreme situations when the local mechanisms are not capable of solving cells' problems, distant mechanisms must be involved. The traditional view suggests that receptors located in each organ increasing their afferent impulses to activate neural-reflector negative feedbacks. However, neuronal activation is energetically too expensive to be continuously provided. Therefore, the new view adds that specific chemicals, that left the suffered cells, to play a role of also specific adaptation factors. Their main role is to re-tune cells and tissue architecture in such a manner that the modified cells become capable to provide their both intimate and output functions via minimal energy expenditures. Theoretically required mechanisms for the restructuring are mainly described in [15,17,20]. The question is whether they really exist?

In general, the concept of cells' optimal coexistence (CCOC) briefly is described below.

3.1 Compromises

Throughout ontogenesis, an individual organism uses its tuning-mechanisms to be structured in a manner that is best adapted to local environmental almost stable conditions. This physiological mode is a compromise achieved due to the competitive efforts of cells for foods. Because it is looking like an ideal Greek's democracy, in [20], this mode is specially termed a "cellcracy". Every local problem, for example, appearing because of local circulatory impairment is adequately eliminated by local vasodilatation. As the stability may be violated from time to time, including informational alterations, the brain, reacting to them, activates its efferent activities to correct the activities of certain organs for providing the acute behaviors. If these brain efforts are long-drawn-out, the ideal (comfort)

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existence of those effector-cells that have been essentially stimulated from out and thus increased their energy expenditures, step-by-step will drop into the energy lack mode. This is why in [10] the brain was figuratively called a "despot". Such an organism could not exist for a long time. Thus, organisms, again passed through the sieve of evolution, likely had been armed with mechanisms effectively counteracting wit this "despot".

The most likely way the stagnated cells to not be died is to release adaptation factors that will re-organize blood flows and enrich the arterial blood by currently most needed nutrients. These efforts combined with the effects of local vasodilatation will return the impaired cells to the balanced state. In fact, this is a new compromise between the body's effector-cells, from the one hands, and the brain, from the other hands. This compromise determined relative temporal characteristics of both participants: neither the brain domination nor the domination of mechanisms supporting the intracellular comfort state can be endless.

As the organism's surviving is critically depended on functionalities of the brain and heart, evolution created preferences for their material supply. The brain and heart are practically minimal sympathetic vasoconstriction but the best vasodilating, self-regulatory mechanisms. So, the "cellcracy" later has been transformed substituted to more complex compromise mechanisms providing the coexistence of cells in unstable environments. Namely, the compromise involving multiple organs, directly or indirectly participating in creation of comfort intracellular environment, led to appearance of so-called physiological relativity [34]. It states that in the human organism, both the biochemical and the physiological characteristics that according to the homeostasis concept were assumed to be constants, in fact, are reciprocally variables.

Nevertheless, under relatively long-term environmental stability, the cellular humoral mechanisms, continuing to act, may again dominate and minimize the CNS's invasion in providing cells metabolism and other immanent functions. Namely, the blood chemical composition determines the long-time mean activities of organs that form specific super-systems materially supplying cells.

3.2 The Nature of ADF

At organism-scale, the stability suggests that there is an approximate balance between assimilation and dissimilation rates. At the cell-scale, stability has also resulted in a balance between anabolism and catabolism. Both these balances can be provided on different rates that normally, are provided by mean balances of arterial and venous flows. When a cell is forced to increase its catabolic rate (in particular, the rate of ATP consumption) within a certain time interval, CMRA increases Vs. This causes a decrease in cytoplasmic concentrations of source chemicals necessary for ATP-synthesis. Consequently, under increased concentrations' difference (gradient) between local capillaries and cytoplasm, these chemical compounds are penetrating into the cell. But this does increase their gradients between local arterioles and capillaries. These events promote the cells that currently have higher assimilation rates to take from the common local intercellular space the greater part of nutrients. So, additional mechanical forces appearing as concentrations' gradients are the main local ADF-s that will disappear, just after the active phase of the adaptation of the cell to the elevated catabolism is finished. Additional ADF-s appear because of local vasodilatation: by a decreasing of local vascular resistance, the vasodilatation re-directs arteriolar flows predominantly towards actively adapting cells.

In real organisms, this theoretical scenario never will bring to stabile conditions thus both biochemical and physiological characteristics permanently fluctuate. If the adaptive up-building is covering a huge number of cells and thus changing their rest energy consumption rates, the physiological integral characteristics like MAP, lung ventilation, the blood concentration of erythrocytes, the density of arterioles, as well as the number and sizes of cells' mitochondria become stabile shifted too. In other words, the entire organism becomes to be adapted to the new conditions.

The internal heterogeneities in SCP suggest that for every time moment, one part of cells of the population request much ATP than others. So, the energy shortage does not simultaneously cover the entire population but only those cells that have the greatest rates of ATP consumption. Whether mechanisms balancing V_s falsewith V_c false are so perfect to take into account such nuances are not known. I think the human organism does not possess of mechanisms capable of such precise controlling energy supplying of cells. A virtual scenario, supposing that the activities of organs-providers of oxygen, carbohydrates, and other substrates depend on concentrations of venous blood chemical factors while the local cell problems can be solved due to passive diffusion of nutrients from the intercellular environment, seems to be a most likely one. Certainly, in the frame of this concept, the optimality of cell life is not synonymous with maximally comfort cell metabolism. In the population scale, the metabolism is optimal when a compromise of forces worsening the cytoplasm composition, from the one side, and purifying it, from the opposite side, is achieved.

As to the inverse adaptation of a cell from the initially high levels of anabolic transformations to lower levels, it

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goes passively. The matter is that most cellular macromolecules are tertiary and quaternary structures vulnerable to destructive forces including thermodynamic fluctuations of protons. So, molecular destructions are background events. The only way to compensate for their negative effects is to adequately re-synthesize them. When the cell is not more forced to provide the high levels of assimilation (in particular, ATP-synthesis) the background destructions will slowly bring the cell to a newer balance provided on lower rates of anabolism.

4. Discussion: Endogenous Mechanisms Providing of Organism's Adequate Flexibility

The human organism is a flexible construction. The main flexibility is known to be concerned with the velocities of cell division and death. However, the deeper we understand the organism-environment relations the newer aspects of the flexibility become clear. Arguments above are to convince that the necessity to maintain the cell-scale energy balance despite its disturbances was one of the fundamental requirements for minimizing initially UO's, later MO's vulnerability to critical energy imbalance (CEI).

In the article, the energy aspect in general, and CEI, in particular, are in the focus not because of they are the exclusive initiators of the reversible adaptation. The matter is that other factors (like the cytoplasm contaminators) are already taken into account in traditional physiological concepts [10,36-40].

As the energy consumption rate in our cells depends on multiple stochastic variables, there cannot be an effective strategy for excluding CEI. Possible ways for coping with this dangerous and destructive state were and are still in specific mechanisms effectively reacting to consequences of CEI. Empirical data shows that under CEI, at least three intracellular mechanisms, being also found in UO's and indicated in the left upper side in figure9, represent a battery working against CEI. As elements of the battery have different dynamic characteristics and power, under specific forms of CEI (acute or chronic) they are activating specifically. Only under severe CEI of long duration, all the three mechanisms do working synergistically.

Normally, mitochondria produce about 94% of the total amount of ATP molecules. figure13 below illustrates that this synthesis is critically dependent on activities of complex physiological mechanisms of three different branches. Mitochondria, providing pyruvate oxygenation, represent the Branch 1. Mitochondrial characteristics determining the rate of ATP synthesis (V_S) are analyzed some later.

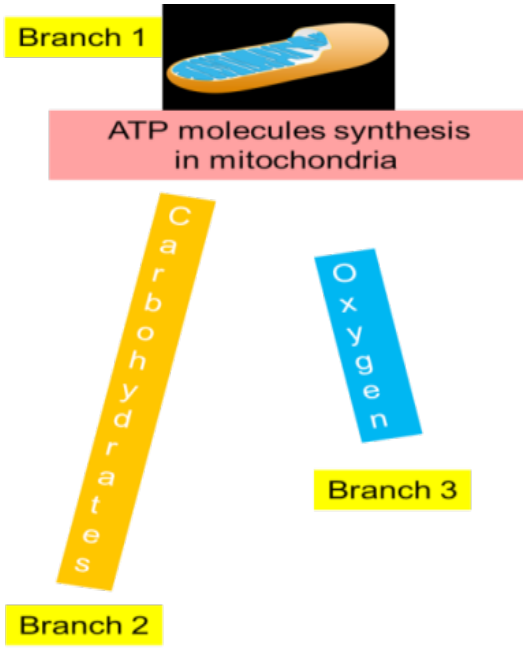

Figure 13. Physiological mechanisms providing the synthesis of ATP molecules in mitochondria cover events taking place in three different branches: (1) mitochondria, (2) carbohydrates, and (3) oxygen incomes. Besides, concentrations of certain mitochondrial enzymes also play their roles in determining the value of current V_S. This is a reason to think that these mechanisms are likely associated.

To comprehend energy-conditioned local or integrative physiological events and causalities, one must analyze roles playing by each of the branches illustrated in figure13. All the biochemistry revealed mainly concerns the chains yielding ATP molecules. But the cellular physiology is not reduced to chemical transformations. Moreover, in the human organism, the efficiency of the chemical machinery of a cell is both under cellular and multicellular physiology. The latter is not duly understood yet.

It was long known that under hypoxia conditions, the chemoreceptor reflexes work to remove the excess CO_2 from blood. The reflex possesses by three independent acting blocks. One block increases lung ventilation. The second block increases MAP and blood flows. The third block activates the erythropoietin release and enriches the blood of oxygen and carbon dioxide carriers – erythrocytes. Thanks to multiple researchers, the interim mechanisms mediating the hypoxia and the erythropoietin release have been revealed: specific proteins called hypoxia-inducible factors (HIFs) have been found out [41]. Since that time, hypoxia-inducible factors, being in the mainstream of molecular-biological and genetic researches (for example, [42-47]), were acknowledged by the Nobel Prize-2019.

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It is necessary to stress that the pyruvate is a common product of anaerobe glycolysis provided in the cytoplasm. Concentrations of pyruvate $[P_y]$ entering the mitochondria critically depend on the inflow of carbohydrates. Thus the machinery regulating this inflow is denoted as Branch 2. By analogy, mechanisms concerned oxygen support denoted to be Branch 3. Note that under the given total size of the cell's mitochondria (if more correctly – the total surface of their inner membranes S_m), V_s is maximal only for certain proportions of carbohydrates and oxygen. Already this fact hints that the physiological mechanisms controlling oxygen and carbohydrates' incomes to cells are highly likely associated.

According to Chance, et al [32], current mitochondrial V_s can be calculated if its maximal value $V_s^{\max}$, and mitochondrial concentrations of $[NADH]$, inorganic phosphor $[P_i]$, $[ADP]$, $[O_2]$ are known.

$$V_s \approx \frac{V_s^{\max}}{1+\frac{K_1}{[ADP]}+\frac{K_2}{[P_i]}+\frac{K_3}{[O_2]}+\frac{K_4}{[NADH]}} \qquad (1)$$

where K_1, K_2, K_3, K_4, and ϕ are approximation constants individual for the mitochondrion. Under certain circumstances, these constants can be increased or decreased via concentrations of regulatory enzymes.

But it is known that both the number of cell mitochondria and the size of each mitochondrion are variables. Factors initiating and controlling these alterations will be analyzed later. Here important is to note that these alterations, changing the total area of inner membranes of the cell mitochondria, also alter S_m relatively to its initial value of S_{m0}. Thus, the formulae (1) is modified as:

$$V_s \approx \frac{(1+\phi(S_m-S_{m0})\,V_s^{\max}}{1+\frac{K_1}{[ADP]}+\frac{K_2}{[P_i]}+\frac{K_3}{[O_2]}+\frac{K_4}{[NADH]}} \qquad (1a)$$

$[ADP]$ does depend on $[AMP]$ which is a product of pyruvate's oxygenation. In the linear interval, as it was shown recently [19], mitochondrial variables $[O_2]$, $[P_y]$ false(or glucose in cytoplasm), and S_m can be quantitatively related to $[AMP]$ by means of an approximate equation:

$$[AMP] \approx [O_2]\cdot[P_y]\cdot S_m \cdot \frac{\overline{P_A}}{R} \qquad (2)$$

where $\overline{P}_A$ – the mean arterial pressure (MAP), and *R*– the total peripheral resistance.

As $\frac{\overline{P_A}}{R} \approx Q$, where Q is the cardiac output, by analogy, for every regional tissue with a regional vascular resistance r, the regional blood flow can be calculated as $\frac{\overline{P_A}}{r} \approx q$.

Before to analyze the physiological consequences of formalisms $(1a)$, and (2), it is useful to pay attention to an additional aspect of cell energy machinery not taken into account in theoretical concepts concerning so-called energy homeostasis [24,31,33].

Mitochondrial impairment is considered to be the commonplace and possible initiator of many diseases that have the specific sign – are slowly developing and definitely manifesting mainly in old-age peoples [46-48]. Mutations in mitochondrial genes are the likely cause of arterial hypertension [12-15]. Mitochondrial dysfunction is associated with the development of numerous cardiac diseases such as atherosclerosis, ischemia-reperfusion injury, hypertension, diabetes, cardiac hypertrophy, and heart failure [49,50]. In cancer research, mitochondria are also in a focus of interests [51-53]. Even the Parkinsonism has its mitochondrial projections [54,55]. I have cited the very little part of publications concerned with mitochondrial investments in normal and pathological situations.

4.1 Mechanisms Regulating AMP Concentration

It is known that in response to low glucose, hypoxia, ischemia, and heat shock, AMP-activated protein kinase (AMPK) plays a role of a master regulator of cellular energy homeostasis. Most researchers focus their efforts on revealing mechanisms and regularities concerned with the excess concentrations of AMP. AMPK regulates diverse metabolic and physiological processes and is dysregulated in major chronic diseases, such as obesity, inflammation, diabetes, and cancer. [55-58]. The most well-defined mechanisms of AMPK activation are phosphorylation at T172 of the α-subunit and by AMP and/or ADP binding to γ-subunit. ATP competitively inhibits the binding of both AMP and ADP to the γ-subunit, which suggests that AMPK is a sensor of AMP/ATP or ADP/ATP ratios [57]. In the frame of the article, specific interest does relate to hypoglycemia causing low mitochondrial concentrations of AMP. Recently [31,59] it has been argued that AMPK activates the glycogen-glucose transformation in both muscles and liver. So, in this way, AMPK could increase the rate of ATP production. I think this aspect of APMK has to be deeper studied. Novel regulators of the rate of AMP synthesis are not excluded too.

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4.2 Computer Modeling of Complex Physiological Systems

Another aspect worth to be discussed here is concerned with the research methodology. Since1960-s, mathematical modeling of physiological systems is an additional and effective method for revealing their quantitative properties. Every mathematical model is an equation (or equations system) containing variables and constants. Variables identification never was a serious problem: they directly present in the empirical data. In contrast, constants identification is still problematic: most of them are either not a subject for physiological research or have been measured for conditions far from those used in model experiments. When the model describes complex systems, as it was in the most known model created by Guyton et al [35,38] and describing interactions of 17 physiological organs, heuristics are the mandatory method for constants choosing. But the biggest problem is that their values, assessed for the physiological norm, under simulating of other conditions, must be changed. Nobody knew how to provide these changes. This problem still is also for recent models [60-63]. Physiologists not like the modelers' voluntarism. They know that every organism itself is doing these changes. But they could not capable of providing by rules to be used for adapting each so-called physiological constant (included in the model) for new physiological conditions that have to be modeled. In fact, the general approach, provided in the article and for the first time described in detail in [17], is the lonely way to rationally re-tune constants of models.

4.3 Problems Concerned with the New Understanding of Cardiovascular Endogenous Control

Above marked new interpretation of the optimality forces us to re-asses the role that the cardiovascular system and the circulation are playing in HIP.

CVS, being both the supplier of cells and the collector of their metabolites plays an exclusive role in the organism. The functional activity of CVS is tightly associated with the functional activities of those organs and systems that are responsible for the chemistry of arterial blood. As the chemistry is permanently varying, both MAP and the cardiac output (CO) are important variables that cannot be exclusively subjects for regulators thought to be specific controllers of hemodynamics. In this regard, traditional concepts of CVS's control should be also revised.

The problem of MAP-s long-term control is still actually in the cardiovascular physiology. The most common current general vision of physiological mechanisms controlling the long-term level of MAP and simultaneously providing cells by adequate blood flows has been developed in Guyton's research team [35,37,38]. The concept, later in detail developed by Cowley's research team [39,40], is also known as the concept of "pressure-diuresis-natriuresis" [37,40].

The concept integrates the regulation of CO with the baroreceptor control of MAP. An essential role is given to Na intake and its contribution to total blood volume as one of the main investors of the MAP.

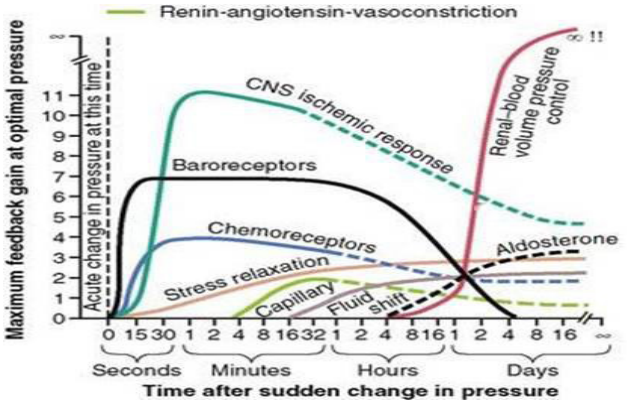

Figure 14. Approximate potency of various arterial pressure control mechanisms at different time intervals after onset of a disturbance to the arterial pressure [7]

In fact, figure14 demonstrates an interesting idea: most of the mechanisms, capable of shifting the level of MAP, might be initiated by events having no direct relation to hemodynamics' self-regulation. Different hypotheses were proposed concerning the goals of the known mechanisms and their influences on CVS. However, even in this general vision of physiological mechanisms controlling the long-term level of MAP, the cell energy aspect is absent at all. In a personal communication with Prof. Allen Cowley we have discussed this problem and he, assessing it to be a very serious gap, promised to think about how this problem could be experimentally investigated. The same evaluation was also by other physiologists. But nobody is armed with proper technologies to provide the required empirical research. The only way for testing the energy hypothesis of MAP-level and its floating I saw in the creation of a special software-modeling tool for providing computer simulations. The main results, published in [64,65], demonstrated that the energy view on arterial pressure is both rather realistic and capable to explain MAP's individual variations depending on also individual ontogenetic scenarios of organism's formation.

Theoretically, under stable structural characteristics of body vasculature and heart chambers, CO and MAP (also above denoted as $\overline{P}_A$) are functions of seven variables: total blood volume (V_Σ), contractility of right (C_r) and

left (C_l) ventricles' myocardium, heart rate (F), total peripheral resistance (R), rigidity (D), and unstressed volume (U). They all may be under nervous-humoral influences that are variables too.

Assume the function $\overline{P}_A(t)=f(V_\Sigma(t),C_r(t),C_l(t),F(t),R(t),D(t),U(t))$ is known. Changes at least one of these variables do alter MAP and CO. The question is whether each mechanism, capable to alter current values of variables, is a regulator of MAP and CO? The physiologist using the term regulator is sure that it has both a goal and mechanisms for its providing. However, among eight mechanisms (see figure 14) usually called MAP' regulators, the baroreceptor reflex is the single mechanism, satisfying the requirements to be a regulator. However, normally, even this mechanism does not set or control the level of MAP: arterial baroreflexes only damp regular (in each cardiac cycle) or stochastic elevation of systolic arterial pressure. Receptors stop to be active in the most part of diastole. Besides, because of the receptors' threshold, they are silent in the initial stage of systolic pressure's elevation. So, the mechanism which does not receive information about the end-diastolic level of arterial pressure and the duration of the diastole is not capable to calculate and control the level of MAP. Despite this conclusion [10], physiologists continue to seek data to confirm that the baroreflex is a long-term controller of arterial pressure [66]. In this research, the authors state that baroreceptors are active even under elevated values of MAP. Yes, it is so. Moreover, according to CCOC, baroreceptors, being neurons, mandatorily have to adapt their energetics to every relatively stable mean rate of ATP consumption. As far as the elevated MAP compels the receptor cell to spend ATP on the higher rates, the CMRA is re-tuning the cell mitochondria for maintaining a new energy balance on the elevated level of ATP consumption. So, the receptor, being forced to transitorily decrease the number of its afferent impulses, again adequately reacts to alterations of systolic pressure. In my opinion, this particular case evidently shows the impact of CCOC as a general biological theory.

4.4 Other Mechanisms Changing MAP

Figures 11 and 12 above contain boxes indicating that the angiogenesis is one of the mechanisms potentially being under adaptation factors produced by energetically suffering cells. Indeed, the angiogenesis continues the growth of the vasculature by processes of sprouting and splitting. Numerous inducers of angiogenesis have been identified, including the members of the vascular endothelial growth factor family, angiopoietins, transforming growth factors, platelet-derived growth factor, tumor necrosis factor-alpha, interleukins and members of the fibroblast growth factor family. Vascular endothelial growth factor [67,68].

Endogenous vasodilators can promote vascular smooth muscle relaxation at three major sites, the noradrenergic nerve terminal, the smooth muscle cell, and the vascular endothelium. Many vasodilator agonists may use the endothelium to produce their effect (for example, acetylcholine, serotonin, thrombin, others).NO is a powerful vasodilator with a half-life of a few seconds in the blood.

The renin-angiotensin system has powerful effects on the control of MAP and sodium homeostasis. These actions are coordinated through integrated actions in the kidney, CVS and the central nervous system. Along with its impact on the MAP, the renin-angiotensin system also influences a range of processes from inflammation and immune responses to longevity.

Reactive oxygen species influence vascular, renal, and cardiac function and structure by modulating cell growth, contraction/dilatation, and inflammatory responses via redox-dependent signaling pathways. However, the clinical evidence is still controversial [50].

Generally, the MAP is not one of the strong homeostatic constants. Although physicians know that hypertension is a common end-point for multiple disorders [27,40,50], the instabilities of MAP-level rarely have been understood as a consequence of its adaptation to actual energetic needs of the organism. These causalities, first formulated in the paradigm of "floating" arterial pressure [11,19], schematically are depicted in figure 2.

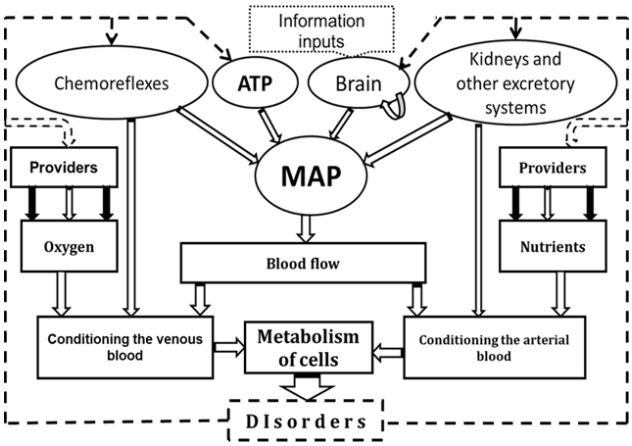

Figure 15. Diagram of the relationship of the main determinants of MAP-level to maintain the proper metabolism of cells

The blood flow, mainly determined by the mean arterial pressure, is a source factor for providing cells' metabolism. However, alterations in both arterial and venous blood are capable of aggravating the metabolism. Metabolic disorders stagnate cell life. In this state, cells release low molecular weight agents that can modulate cardio-

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vascular mechanisms determining MAP. There are four potential target mechanisms for such modulations: chemoreceptor reflexes; kidneys and other excretory systems that alter the total blood volume; mitochondria providing the aerobe synthesis of ATP; and brain structures entering the sympathetic and parasympathetic neurons that control the heart function and vessels' tonus. Both external and internal stimuli are the information background that independently affects the level of MAP. Under certain conditions, several low molecular weight agents can modulate current activities of mechanisms that provide cell metabolism by oxygen and nutrients. In general, this closed physiological system is capable of coping main challenges and to provide an optimal metabolism in most of the cells despite casual alterations of local extracellular physiochemical conditions.

The blood flow, mainly determined by MAP, is a source factor for providing cells' metabolism. However, alterations in both arterial and venous blood are capable of aggravating the metabolism. Metabolic disorders are suppressing cell life. In this state, cells release low molecular weight agents (for example, see [69-77]) that can modulate cardiovascular mechanisms determining MAP.

There are four potential target mechanisms for such modulations: chemoreceptor reflexes [78]; kidneys and other excretory systems that alter total blood volume [79,80]; mitochondria providing the aerobe synthesis of ATP [81-84]; and brain upper structures forming synapses on the sympathetic and parasympathetic neurons that control the heart function and vessels' tonus [85]. Both external and internal stimuli are the information background that independently affects the level of MAP. Under certain conditions, several low molecular weight agents can modulate current activities of mechanisms that provide cell metabolism by oxygen and nutrients. In general, this closed physiological system is capable of coping main challenges and providing optimal metabolism in most of the cells despite casual alterations of local extracellular physiochemical conditions.

4.5 Concerning Theories

There are two interpretations of what the theory is for. One group of researchers-empiricists suggests that the theory is a short description of all observable data. But the only value of such a theory is limited to its didactic capabilities. Much valuable are theories that use limited data for doing general conclusions. Neither Newton nor Einstein have had been armed with data covering events in every point of the universe. But they logically argued why the local regularity should be spread to the universe scale.

The human organism is like a universe. We never can control thousands of biological variables in each of the trillions of human cells. Here heuristics are the necessary method for proposing general concepts but using very limited data. As CCOC is an example of such theory, it should point out both the most likely events not observed yet and possible ways for their registering and evaluating.

CCOC suggests that mitochondrial disorders are the most likely fundamental cause of age-associated disorders.

CCOC prompts that the chemistry of local or central venous blood contains much more information about biochemical and physiological statuses (health indicators) of cells that form the chemistry than it can be registered by current measurement technologies. So, it is necessary to develop technologies capable of precisely fixing concentration changes of such health indicators. In this way, physicians could much earlier diagnose complex disorders. As the physiology is the theory of the medicine, the identification of molecular mechanisms potentially providing cells' optimal coexistence is also a priority direction. At last, the much thorough and accurate analysis of the chemical composition of arterial blood could make it possible to understand the trends of endogenous normalization of disorders to develop effective methods for their exogenous support.

Certainly, CCOC only dashed outlined the general rules for the optimal integration of specialized cells in a single organism. These rules apply not only to the human body, but also to the organisms of all animals. Perhaps it is appropriate to mention here that renin was initially found only in the kidneys, when their cells were not supplied with a sufficient blood flow. For a long time, experts discussed only the role of the renin-angiotensin system in the body. However, it soon became clear that renin-like agents are produced in almost all organs in which blood flow is impaired [36,49,72]. The situation was similar with HIFs: at first they were found in the kidneys, and only then in other specialized cells [87-89].

I saw that the metabolic products of some cells can be used by other types of cells. Since I am a theoretician, I saw in this a possible general pattern. Empiricism alone is capable of filling individual gaps, but it is unlikely to close them all. SCP-s of different specialization can form the simplest pair in which cells of the next SCP consume at least one of the chemicals produced by cells of the previous SCP. By linking such producer-consumer pairs into a long chain, organisms have created functionally associated structures. Normally, their activities display almost synchronized changes.

There exist also types of SCP-pairs in which the prod-

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uct of a first SCP inhibits or stimulates the activity of cells of the next SCP. Namely, the second type SCP-pairs are the structural-functional units of our three-dimensional organs. Virtually, one can decompose the human organism to these structural-functional units and assemble (re-assemble) them and theoretically study properties of the virtual organism. However, the vague knowledge of human SCP-s makes this task not yet actual.

There is a sufficient basis to state that HIF-s, which occurred in certain cells of the given tissues, have not mandatorily modifying the current activity of genes in every cell of the tissue. Moreover, only one type of hypoxic state (namely, the long-term hypoxia caused by circulatory insufficiency) does create problems for the entire cell population. In fact, the lack of carbohydrates is the mandatory accompanier of this kind of hypoxia. So, the tissue is suffering rather of hypoergia than of hypoxia. This indicates that organisms suffering from chronic heart insufficiency could serve physiologists as the best objects for studying individual adaptation dynamics much deeper than it is possible in cultures of cells.

5. Conclusion

Each of our cells is a flexible (soft) object possessing by mechanisms that in certain boundaries can cope with local internally or externally induced destructions. The energy is the necessary resource for supporting both cell intimate functions and resisting to its functional impairment or structural degradation. The sufficient condition for cell well-being is the optimal physiochemical cytoplasm. Our organs and their functional systems have passed through the sieve of evolution because they are capable to provide an optimal-like coexistence of cells.

Both the energy demands and parameters of the optimal cytoplasm are altering regularly with phases of the cell cycle and stochastically because of extracellular influences. Their power and frequency may depend on the information and physiochemical dynamics of the outer environment, as well as on alterations induced by other cells. Cells' responses to these influences are making the entire organism, its physiology, and biochemistry flexible too. Cells through these influences adaptively re-build and re-tune both their internal structures and by activating cellular proliferation in organs that currently have accumulated certain concentrations of specific adaptation factors. In fact, cells continuously alter material inflows until a situational or a long-lasting compromise is achieved. The compromise, individual in each organism and displaying temporal variations, we can feel as health's alterations. Physiologists and physicians, assessing the health by values of its indicators, do not require a strong falling of the measured values of the so-called homeostatic constants into their normative intervals. Homeostasis is not only an individual concept, but also a relative one, therefore health should not be evaluated by the absolute value of the measured vital activity indicator, but only on the basis of how much assimilation-dissimilation processes are balanced.

The CCOC, as a hypothetic yet concept presented and argued in the article, is a call to empiricists for searching for adequate methods allowing both concept's examination and further identifying the missing adaptation factors.

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