A 21st-century update of Claude Bernard's Theory about the Constancy of the Internal Environment

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The discovery of the functioning of intra- and extracellular ion compartments and cell membranes' operation opened the possibility of extending Claude Bernard's theory to intracellular ions. In contrast, by underestimating the role of ions, many misconceptions have prevailed. The author points out that maintaining the constancy of carbon dioxide is especially important. CO_2 is one of the most decisive signalling molecules, a mediator connecting the body and the soul. It interacts with intracellular pH, Ca^{2+}, $H_2PO_4^-$ and HPO_4^{2-} ions, but the intracellular ion pattern, as a whole, also has a primary signalling function. Chronic stress changes the intracellular ion patterns, increasing or decreasing the pCO_2 level, an increase in the HCO_3^-/Cl^- ratio leads to Metabolic Syndrome. The HCO_3^-/Cl^- ratio decrease due to chronic hypocapnia results in hyperarousal mental disorders, which seem reversible for decades. The organism starts to get exhausted around 50, and it is not excluded that respiratory alkalosis could turn into metabolic acidosis, making the kidneys reactor organs. (The hypothesis still needs to be verified.) The background of stress-caused age-related diseases is the threat of intracellular acidosis and the organism's fighting against it. With chronic hypo- vs hypercapnia, the humoral counter-regulation cannot fulfil its function and can result in (e.g.) salt-sensitive vs salt-resistant hypertension, respectively. Preserving the original ion pattern is essential but impossible without euventilation. We could control ventilation and stress by administering $H_2PO_4^-$ and HPO_4^{2-} ion salts. The life span correlates with the Body Cell Mass (BCM); we should preserve it as long as possible.

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Introduction

Claude Bernard was ahead of his time founding modern physiology with the theory of the interior milieu constancy (Habert, 2022). An organism's living cells' original structures and composition are entities created during their phylogeny. A permanent change in any part of the cell compartments of any species' tissue causes disease, and an alteration in the identity can signify various illnesses. Science has underestimated the function of intracellular ions, which may be because their concentrations' in vivo measurements still need to be solved. On the other hand, it has yet to reproduce experimental conditions similar to the cytosol in which they could measure the metabolic changes occurring due to the ions' quantitative changes.

In 1984, Busa & Nuccitelli proved that the intracellular pH (pHi) varies in a broad physiological range, controlling the metabolism (Busa & Nuccitelli, 1984). They rejected the century-old misconception that intracellular H^+ concentrations are fixed at certain levels. However, how many misbeliefs still need to be solved? The author believes that the lack of data on intracellular ion functions gives free rein to the fantasy and that if he puts a realistic picture together, it is, per se, proof which candisprove further misconceptions.

Extending Claude Bernard's milieu interérieur theory to the intracellular compartments and ions is a logical step. After the birth of his theory, formulating the concrete concept of the intracellular ion compartment had to wait a century. The discovery of Na^+- K^+-ATP-ase can be a cornerstone for reinterpreting the extra- and intracellular ionic compartments in 1957 (Skou, 1965). It has been continuously proven that the body restores the original ionic conditions with ion pumps built into membranes, and on the other hand, regulates metabolism by changing the intracellular ion compartments, for all there is used a significant amount of ATP energy and structural readiness, which indicates extreme importance of the ions. Ions, as small molecular particles with a specific size having an electric charge, have a wide range of functions, including regulating the metabolism of cells. Some ions accumulate in the cells using ATP energy directly or indirectly, indicating that the cell needs them very much. According to defined metabolism and construction material transit protocols, all this can happen in a very orderly.

The need to expand the milieu intérieur theory is proven by many such attempts (Robin & Bromberg, 1959; Robin, 1977; Sullivan, 1990; Billman, 2010, 2020; Rheinberger, 2023). Perhaps Noble went the farthest in concluding, and the current article's author agrees that we should place biology on a mathematical foundation (Noble, 2008). Therefore, the author uses easily identifiable and (in principle) measurable biological variables, such as ATP, body cell mass (BCM) or lean body mass (LBM).

Biological variables of cell and organism identity

The author created a cytoplasm model in which the intracellular ion pattern controls cell metabolism, having an equal role with ***ATP*** and ***cytosolic enzymes*** (Sikter, 2007). Life (living cell) is on a higher energy level than its inanimate environments. ***ATP*** is a universally used unique molecule as the principal energy currency in cells. It also can represent vitality or vitalism (Pinna et al., 2022), but it can only be stored to a limited extent (e.g. in the form of creatine-phosphate). Therefore, the organism/cell would be vulnerable without reserve cytoplasm; a larger ***BCM*** solves that as an energy and building materials' "warehouses". (Fat is only a ballast without burning, and it cannot replace the "nutrients' store" of BCM.) The sick cell obtains building blocks from the extracellular compartment to recover the cytoplasm. It partly liberates nutrients from the breakdown of BCM (muscle cells), which function as a nutrient stock (see below). At the same time, ATP production and consumption are fixed to the cells, meaning each cell must satisfy a possible raised energy demand and fight against its possible lack.

Hence, the long-observed conception of ***Locus Minoris Resistentiae*** (Latin=Path of least resistance) has been resolved. Those cells with poorer metabolism, poorer blood supply, and struggling with ion deficiency will die or be severely damaged. The cells' ATP-energy production is primarily adjusted to the consumption (Das, 2003). Those cells will die if ATP production cannot keep up with consumption (Farber, 1973; Sikter, 2018). The ability to produce ATP decreases in older age, an indirect reason for age-related diseases. Logically, energy consumption should also fall in its tendency. A shift towards intracellular acidosis is one of the most important mechanisms for reducing energy demand (Sikter, 2007).

The ***Body Cell Mass*** (***BCM***) is the most characteristic and embodiment of vitality and lifespan. (NB.: - ***Lean Body Mass LBM***- is a very similar description.) Tissues not containing enzyme proteins (such as

fats, fibres, and extracellular compartments) do not represent biological energy or biological identity, but BCM does. There is a close relationship between life expectancy and BCM (Anker et al., 1997; Hoffer, 2001; Newman et al., 2005). The LBM is inversely correlated with mortality in older people (P<0,001) (Toss et al., 2012).

An ancient desire of humanity to embody the life force, what the Chinese called "chi", the Indians "prana", ancient Greeks "pneuma", and the 19th-century scientists ***"vis vitalis"***. The 20th-century researchers did find the measurable life force because the momentary ATP concentration closely correlates with the biological performance capacity of cells/tissues (e.g. with the strength of muscles) and the body's current BCM (or LBM) with the expected lifespan (Sikter, 2007). We can also base variables numerically on them and plan cell, organism or disease models (Sikter, 2007). However, these theses should proven with further evidence.

We can understand metabolism if the anabolic pathways are separated from the catabolic ones (Sikter, 2007; 2020a; Sobotka et al., 2008). The two processes co-occur during life; sometimes, one, and other times, the other is dominant, or they are in balance. In childhood, there is a continuous predominance of anabolism because of growth, a cytoplasm-increasing process. A healthy body increases vitality by growing the BCM until it reaches full maturity. Around the age of 25, the speed of the building and breaking down metabolism equalises, after which, slowly, the catabolic mechanisms come to the fore (Newman et al., 2005; Sikter, 2007). Over 25, BCM gradually decreases, and life will be impossible if it reaches below <50% of its maximal level (Sikter, 2007, 2020a). The two mechanisms are the opposite, but in terms of metabolic pathways, they do not mirror images of each other. Because the cytoplasmic building materials can only be built in and broken down proportionally, from this point of view, catabolism and anabolism are opposites of each other and mirror images (Sikter, 2007; 2020a).

In humans, the body incorporates more than twenty essential cytoplasm-building nutrients into the cytoplasm in a strictly defined structure, ratio, and order, which it can only obtain during nutrition or from the breakdown of other cells ˙(Sikter, 2007; 2020a). Golden calls these ***Type II nutrients*** because, in the absence of only any one of them, cytoplasm construction stops; ***it is the all-or- nothing law of cytoplasm building*** (Golden, 1991; Sikter, 2007; 2020a). Golden mentions about twenty Type II nutrients, of which nine are essential amino acids, and the rest are mainly minerals (ions). The number of Type II nutrients should be greater than this, including some vitamins (such as vitamin B1), trace elements and unsaturated fatty acids. In the case of a highly protected organ disease, the muscles and bones provide quickly mobilised cytoplasm-building materials (Type II nutrients) for the cells of the primarily damaged, highly protected organs. They can do this due to their more significant mass without causing a direct threat to life. On the contrary, the large BCM provides a protective umbrella for the primarily protected viscera, brain and heart (Hoffer, 2001).

The signalling function of nearly all ions is proven, even though many details are unclear, and their signalling function is generally considered second or third-order in the case of most intracellularly accumulating ions (***Mg^{2+}***, ***K^{+}***, ***Zn^{2+}***, ***HPO_4^{2-}*** and ***$H_2PO_4^{-}$***) (Sikter, 2007; 2020a). An exception is ***Ca^{2+}***, whose second messenger and signalling function has been considered prime importance from the beginning (Bootman & Bultynck, 2020). Changes belong to the essence of life, but simultaneously, the organism and its cells must preserve their identity. We must state that restoring the original concentration of each intracellular and extracellular ion is inevitably crucial from the point of view of maintaining health (Gross, 1998).

The intracellular ion pattern (as a whole) has a primary signalling function

In living cells, ions cumulating by energy directly or indirectly (e.g. Mg^{2+}, K^{+}, Zn^{2+} and inorganic phosphates) form a unity with the ATP and the cell enzymes; their quantity increases or decrease together proportionally; that is, they form the cytoplasm together (Sikter, 2007; 2020a). The intracellular ion concentrations can play a central role in cell metabolism; small changes in ion concentrations can result in significant metabolic changes, as many enzymes have similar metal ion (e.g. Mg^{2+} or Zn^{2+}) coenzymes. The different metabolic processes are connected, thus amplifying or inhibiting each other effects while creating various metabolic pathways. The clinical measurement of ion concentrations in tissues (cells) has not been solved, nor can the cytoplasmic functions be modelled so far, thus leaving a wide field for speculations.

In some of his earlier works, the author assumed that the momentary intracellular ion pattern (as a

whole) has a regulatory, i.e. signalling, function. The intracellular ion pattern does not represent a static state, as some variables can rapidly change, such as the Ca^{2+} concentration or the H^+ ion concentration, also influencing each other (Busa & Nuccitelli, 1984). The metabolism regulation (signalling) function of intracellular ions is further complicated by the numerous cell organelles surrounded by membranes containing ion transporters and exchangers with additional regulatory possibilities. The physiological intracellular ion compositions of various tissues (cells) of each species differ and are specific to the species and tissue.

The pHi concentrations and their changes have even more robust effects on cell metabolism than other cytoplasmic ions. It may be because a pHi change also affects the H^+ bridges of the enzyme proteins; a slight shift in pHi can create significant reversible changes in their spatial structure (Relman, 1972). It can be attributed to the fact that the organs (primarily the lungs and kidneys) try to preserve the original intracellular H^+ concentrations with special care, even at the expense of other ions.

At the same time, pHi has a mutual relationship with the transmembrane processes of Ca^{2+}, changing the current intracellular concentration of Ca^{2+} and the dynamics of those changes, whose effects are still barely known in detail ˙(Busa & Nuccitelli, 1984; Phelan et al., 2021; Molinari & Nervo, 2021). Some effects are realised through H^+ concentrations, others through changes in the pCO_2 level itself. The cytosolic Ca^{2+} concentration increases due to both acidosis and alkalosis, but the volatility of Ca^{2+} decreases in acidosis and increases in alkalosis. The mild-moderate alkalosis will enhance the performance of the muscles' strength, nervous system activity, metabolism, and cardiac output. On the other hand, in acidosis, the motility of Ca^{2+} decreases, and the rigidity of the muscles increases - while the ability to relax and the heart's performance decreases. At the same time, the energy demand also decreases. In neurons, alkalosis increases excitability, i.e. arousal (Khambatta & Sullivan, 1974; Orchard & Kentish, 1990; John et al., 2018; Silva et al., 2021). There is a general rule that a rise in pH increases neuronal activity, whereas it is dampened by a fall in pH (Sinning & Hübner, 2013). It is partly due to the acidity relations of the cytoplasm of neurons, partially a transsynaptic regulation. It is clear from the above that pHi has a signalling function similar to Ca^{2+}; strong and fast signalling molecules also influence each other's role. On the other hand, H^+ can fully perform its signalling function only in the form of CO_2 gas because the H^+ ion penetrates through the membranes very slowly in just hours.

Since CO_2 and pHi are the primary cytosolic signalling molecules, they are also the best-controlled ones; even minimal changes in their cytosolic concentrations result in very significant changes in metabolism and nervous system functioning (Sikter et al., 2009; 2017b). In contrast, the official blood gas variables allow unacceptable differences (the normal pCO_2 average would be 35-45 mmHg) (Sikter et al., 2017b). This can be explained by the fact that pCO_2 levels show substantial differences in both directions during human sympathetic and parasympathetic chronic stress. Medicine did not recognize the pathogenetic role of CO_2 in stress and accepted these changes as normal (Sikter et al., 2017a; 2017b; Sikter, 2020b, 2022). The minority of physicians is still considered physiological at 38-42 mmHg CO_2 level (Bruton & Holgate, 2005).

The anabolism can only occur in a slightly alkaline cytosol (Busa & Nuccitelli, 1984; Phelan et al., 2021); the cytoplasm growth process may have its strict metabolic pathway protocol (see below). It requires a higher energy level, accelerated metabolism, increased ATP formation, and complete availability of every cytoplasm-building material (Sikter, 2007; 2020a). There are several ways to influence and control pHi. It can develop most quickly through changes in pCO_2 level, so carbon dioxide is one of the primary signalling systems recently discovered (Phelan et al., 2021). Carbon dioxide also affects the nervous system, mediating between the corpus and the psyche (Sikter et al., 2009). The kidneys and the humoral-hormonal systems can also be pHi regulators; they often develop these actions through membrane transport processes (Sikter et al., 2017a; 2017b).

The Mg^{2+}, Zn^{2+}, and K^+ ions would have subordinated signalling functions; they cannot reach their cell destination except at simultaneous correct pHi and pCO_2 values. It is supported by the organization's assessment, too, that their role is subordinate, although they are indispensable. The organism subordinates other ions with the guidance of pHi and pCO_2. The signalling function of $\boldsymbol{Cl^-}$ and $\boldsymbol{HCO_3^-}$ ions is only now being recognized (Shcheynikov et al., 2015; Valdivieso & Santa-Coloma, 2019).

"The phosphates" (Pi) is scientifically an incorrect term; it gives a general verdict about several different ions, yet this term is used in medical sciences. Phosphates (both inorganic and organic) are one of the most significant ingredients of the intracellular ionic compartment, and phosphates play primary roles

everywhere in cells (in DNA, RNA, membranes, ATP, and similar); by contrast, phosphates are considered one of the biggest enemies for human health; the two statements are incompatible. The background is a series of prejudices, scientifically unfounded studies, and misconceptions. The positive statement is primarily related to its biological and biochemical role, while the negative one is related mainly to its physical properties (the solubility of phosphate salts). The Pi occur in the cytosol in two forms (HPO_4^{2-} and $H_2PO_4^-$); their chemistry, biochemistry and signalling functions are entirely different and opposite in many ways. A multiple interaction exists between pHi and pCO_2 and the transmembrane transport of the two phosphate ions (Phelan et al., 2021; Knochel, 1977).

Physiology makes a capital error when it specifies the nutrient requirement (Recommended dietary allowance = RDA) in a static amount linked to age (Institute of Medicine, 1997). According to this, a 4-year-old child needs 500 mg of phosphorus (as inorganic phosphate) and an adult 700 mg; RDA is about 30mg/bwkg (body weight in kg), vs 10mg/bwkg of phosphorus is required. Phosphorus' RDA in little children is at least three times of adults. The explanation is that the children are in the stage of anabolism (a rapid cytoplasmic growth). The adult can be healthy (in this case, the 10mg/bwkg can be accurate). However, if they have an acute organic disease, the phosphorus requirement is close to zero, and if they are in a recovery stage, the phosphorus requirement can be about 20mg/bwkg! That is, the body's amount of cytoplasm-building (Type II) nutrients cannot be a fixed number; in disease, when ions flow out of the cells and flood the extracellular compartment, the demand is close to zero, while in recovery, when the body rebuilds the missing BCM, the official RDA amount could be several times higher, i.e. similar to childhood.

It can be explained by the signalling function of phosphates that they can play a central role in growth and anabolism; the GH, IGF1 and insulin also result in a positive phosphate balance in the body, and vitamin D3 increases Pi reabsorption by the kidneys (Tenenhouse, 2005). The anabolic effect of insulin would be explained by discovering that insulin promotes the Na/H_2PO_4 cotransport by PiT-1 into cells (Forand et al., 2016; Andres-Hernando et al., 2023). Insulin is a well-known and widely used anabolic (or anti-catabolic) hormone (Chow et al., 2006).

Logically, an anabolic, cell-building process should start with cytosolic phosphate uptake (e.g. by PiT-1 phosphate transporter), followed by an alkalinising activity (by Na^+/H^+ exchanger or H^+-ATPase) (Yang et al., 2002; Tenenhouse, 2005; Forand et al., 2016). The alkalotic intracellular compartment helps the mitochondrial ATP formation (see ADP+P= ATP), and glucose trafficking processes by GLUT4 (Yang et al., 2002), and then the cytoplasm-building cascade could follow these (Sikter, 2007; 2020a). Based on the above, we can, therefore, say that in addition to the Ca^{2+} ion, CO_2 gas, and H^+ (pHi), the HPO_4^{2-} and $H_2PO_4^-$ ions are also primary signalling molecules. Consequently, the entire intracellular ion pattern is of primary importance due to its cross-talking interactions (Phelan et al., 2021; Holliday, 2017).

Functional vs organic diseases

Arousal and anxiety are likely caused by the shift of the neurons' cytoplasm in an ***alkalotic*** direction, supported by the experiences (Sikter & Ricci, 2011). There is a mutual relationship between the soul and the body, which is mediated by ***changes*** in the ***pCO_2 level*** (Sikter et al., 2009). Young humans easily fall into a ***hypocapnic*** state, which tends to persist permanently due to human behavioural reasons; according to the author, chronic hypocapnia would be a mediator of sympathetic (hyperarousal) stress, the missing link (Sikter & Ricci, 2011; Sikter et al., 2017a; 2017b).

The organism's counter-regulation tries to compensate for the alkalosis and the increased arousal with various mechanisms, and the pendulum often swings in the opposite direction, causing dysthymia (Sikter et al., 2009). (NB: Dysthymia should not be confused with major depression, which is an entity!) The various ***hyper/hypo-arousal*** symptoms that emerge from the effect-counteraction result in different clinical pictures (Sikter et al., 2009). In alkalotic conditions, the metabolism in bodily cells also increases. Still, all this remains at the level of functionality as long as every cell in the body can satisfy the increased ATP energy demand (Sikter, 2018). In these cases, we are talking about ***functional disorders***, as there is no irreversible tissue damage or loss of cytoplasm (BCM) (Sikter, 2007; 2020a; Bell et al., 2020). If there are already places with reduced resistance (e.g. Coronary Heart Disease), a hypocapnic hyperarousal can even cause sudden death (Sikter, 2018). The author had assumed hypocapnia is an unavoidable pathogenetic and mortality factor in acute cardiorespiratory and other pathologies (Sikter, 2018). The thesis that hypocapnia is an independent

predictor of mortality for acute heart failure was proved recently (Tang et al., 2023).

There are ***age-related*** and not age-related ***diseases. Non-age-related organic diseases*** often have external causes, and they do not have a continuous or repetitional nature, e.g., infections and traumas. Non-age-related organic diseases are characterized by the fact that the BCM decreases. However, the original intracellular ion pattern and the ratio of these ions to each other do not change, so – if the cytoplasm-building nutrients are available – there is an excellent chance of BCM's recovery (Sikter, 2007; 2020a). These types of acute and chronic organic diseases entail a decrease in the cytoplasmic mass (BCM) because these conditions always result in a lower energy level and reduced ATP production; they also automatically mean catabolic processes until the condition stabilises. Catabolic phenomena are present in the tissues of the primarily diseased organ; simultaneously, the breakdown processes also increase in the striated muscles and bones as the body draws the "building blocks" (Type II nutrients) necessary for reconstruction from these organs (Sikter, 2007; 2020a).

Age-related chronic diseases are often regulatory diseases at the same time, as Metabolic Syndrome (MetS) and Exhausting Buffer Syndrome (EBS) both mean changes in metabolic pathways (dysregulation). Still, at the same time, they can maintain a stable state for many years, and in the short term, they do not involve a loss of cytoplasm (BCM) stock. (see below).

It is characteristic that psychic diseases usually do not involve structural changes in the body and do not cause BCM loss (Sikter, 2008; Bell et al., 2020). By contrast, major depression is often accompanied by a decrease in the grey matter of the amygdala, i.e. atrophy of cells and loss of cytoplasm, which suggests that major depression could be an age-related organic disorder that is closely related to the acidic pHi of the diseased neuronal cells. There is a correlation between depression and intracellular acidosis (Al-Khatib et al., 2022; Shirazian et al., 2016). Without medication, atrophy of the amygdala occurs, while effective drugs can stop the amygdala's volume decrease (Hamilton et al., 2008). The occurrence of depression is more common in old age; however, in many respects, the age-associated progression of major depression does not occur, which can also be attributed to effective drug treatment (Schaakxs et al., 2017). There are mutual relationships between depression and cachexia; they worsen each other, which can result in vicious circles and death (Al-Rasheed et al., 2018). Depression can also predict cardiac cachexia (Moughrabi et al., 2023).

In chronic organic diseases or malnutrition, the reduced energy state and the amount of BCM can remain unchanged for a long time or worsen (Sikter, 2007; 2020a). After a long chronic existence, the disease can become decompensated, which means that it is not only a disease of the primary target organ and the defensive striated muscle and bones, but the lack of cytoplasm spreads over also to other "protected organs" such as heart, brain or viscera (Hoffer, 2001). The logic of "decompensation" is the same in all cases: With various mechanisms, more and more organs are involved in the disease; the disease "progresses". Some metabolic disorder occurs in the newly affected organs, which leads to a lack of ATP. According to the author's cytoplasm model, this also means a cytoplasm loss from the diseased tissues to the same extent as the ATP deficiency (Sikter, 2007; 2020a).

The decompensation process is best known in the case of heart failure, but it can also occur in other organ diseases (Sikter, 2007; 2020a). Various chronic liver diseases' progression leads to cirrhosis; then, the progression could continue further (Moughrabi et al., 2023; Schuppan & Afdhal, 2008). Type 2 diabetes (T2D) can also be considered a decompensated form of MetS (Sikter, 2020c). After a long existence, T2D complications can occur when the disease spreads to other tissues (e.g., diabetic polyneuropathy, diabetic hepatopathy, diabetic myopathy), which causes a lack of cytoplasm mass in the complicatedly diseased organs' cells. Both cardiac and diabetes-caused cachexia are multiorgan phenomena, the main characteristic of which is an enormous decrease in BCM; a significant difference is that the latter is often affected by obesity (Sikter, 2020c). NB1: If obesity and cachexia occur together, it is also called "sarcopenic obesity" (Prado et al., 2018). NB2: Diabetes-caused cachexia is not the same as "Diabetic neuropathic cachexia"; the latter is only one of its manifestations (Jackson & Barohn. 1998).

All the Type II nutrients must be proportionately built in to get identical cytoplasm regulated by the organism's genome. Still, the rebuilding does not co-occur in one step, and regulation makes a spiral, an anabolic virtuous cycle. So, the organism reaches higher energy levels with the increased BCM. The author hypothesised that the spiral could start with Na^+ and $H_2PO_4^-$ ions transportation into the cytosol by the Na-Pi transporter (PiT1), followed by an alkalinisation process that increases the ATP production capacity (see above). After a ***time gap***,

the circle is completed by synthesising proteins (enzymes); the spiral moves to a higher level again (Jeejeebhoy,1994; Sikter, 2007; 2020).

A predisposition to MetS can also be an inherited disease; its characteristics are impairment of Pi transport and ATP formation, which can be diagnosed in insulin-resistant T2D parents' offspring already in a very early stage - although the exact mechanism has not been revealed (Petersen et al., 2005). Already mild chronic hypercapnic acidosis can be sufficient to trigger MetS (Sikter, 2020b; Sikter & Sonne, 2021). As a result, Pi transport may be damaged in MetS (Håglin, 2001). Acidosis has many aversive effects, which are adversely amplified in the case of MetS. The focus is on the difficulty of ATP production. During decompensation of the MetS, it becomes more and more difficult to burn the lipids and glucose, which is why lipids deposit in the tissues. An increasingly significant amount of ATP energy comes from burning the body's cytoplasm (Sikter, 2020c). Increased abdominal fat stores further worsen breathing, while lack of ATP increases appetite. Many vicious cycles start and worsen the clinical picture (Sikter, 2020c). The body needs enough ATP, an increasing part obtained from the burning of the cytoplasm. New and new organs' cytoplasm is involved in this catabolic progression, which is inconspicuous because obesity masks malnutrition (Sikter, 2020c). In other words, the T2D patients are starving despite enormous fat stores - for regulatory reasons.

Life is full of vicious circles associated with severely damaging the organism's condition. Regardless of the cause, organic diseases are usually associated with catabolism, decreased ATP levels, and BCM. The BCM amount could mathematically characterise the vitality. BCM recovery requires the same conditions as childhood: lots of Pi and Type II nutrients. Refeeding syndrome can occur during the rebuild of cytoplasm; we should remember its relation to inorganic phosphate because the main symptoms are severe hypophosphatemia and lack of phosphates. Moreover, the refeeding syndrome has almost been forgotten (Mehanna, 2008; Golden, 1991; Sikter, 2007; 2020a). Recognising and stopping vicious circles are complex physician tasks; they mainly need to support the body's defence systems. After stabilising metabolism, the rebuild of BCM could start, which is a virtuous circle, a reversed vicious cycle. However, to rebuild the cytoplasm stock, it is necessary to ensure the sufficient availability of Type II nutrients, above all phosphates (Sikter, 2007; 2020a). The author is convinced that a significant proportion of patients with chronic diseases could be cured by recognising and adequately treating aborted or atypical (forme fruste) cases of the refeeding syndrome (Mehanna, 2008; Sikter, 2007; 2020a).

The fighting against threatening intracellular acidosis can lead to changes in the intracellular ion pattern and age-related diseases in humans

An increase in the intracellular H^+ concentration is one of the main signs of stress; it also promotes age-related diseases (Osanai et al., 2018; Jin et al., 2022). On the other hand, ageing drives the metabolism more and more towards acidosis, as a minimal decrease in pHi saves a significant amount of ATP energy and is a more stable state [Sikter et al., 2017a; 2017b). The body wants to avoid intracellular acidosis at all costs, a typical danger above 50. In contrast, at a young age, the prevalence of chronic hyperventilation may exceed 10% of the population, while above 50, mild hypercapnia becomes increasingly widespread (Sikter et al., 2017a; 2017b; Sikter, 2020b; 2022a). Intracellular metabolic acidosis also starts to manifest above 50, which could even be a symptom of EBS (Sikter, 2020b; Sikter & Sonne, 2021a). According to some, age-related intracellular metabolic acidosis could only be offset by reducing 1-3 mmHg of the standard pCO_2 value (Frassetto & Sebastian, 1996). That is why a mild increase in the average pCO_2 level can be significant [Sikter et al., 2017a; 2017b). Both chronic respiratory and chronic metabolic acidosis slow down the metabolism and mitigate the demand for ATP and, at the same time, serve as the basis of age-related diseases; the former causes MetS, and the latter is EBS (Sikter, 2020b; Sikter & Sonne, 2021a).

Cannon also noticed that stress is accompanied by hyperventilation (hypocapnia), but he did not attach importance to it. 20th-century medicine was accompanied by a sharp ideological war regarding whether or not hypocapnia is a pathogenetic factor in the development of functional anxiety disorders (Sikter and Ricci, 2011; Sikter et al., 2017a; 2017b). The war ended with the "hyperventilation believers" laying down their arms (Sikter & Ricci, 2011; Sikter et al., 2017b). The author believes chronic hypocapnia is decisive in chronic sympathetic stress (Sikter et al., 2007; 2009; 2017a; 2017b). Due to their behaviour, people often remain in stressful situations even when the threat has passed. In contrast to Cannon's classical stress model, the stress reaction in humans becomes chronic because human behaviour (self-control)

prohibits both fighting among their population and running away; the individual remains in hypocapnic-hyperarousal psychic stress, which is made fixed in the cells by renal counter-regulation after a few days on a reduced intracellular HCO_3^-/Cl^- ratio and at a higher pHi, changing the identity of the interior milieu (Sikter & Ricci, 2011; Sikter et al., 2017a; 2017b). It is an open question: what will this population's fate be above 50? (see below)

Epel accurately described the effect of chronic psychological stress on metabolism, ageing, and endocrine dysregulation (cortisol overproduction, insulin resistance). However, she overlooked the pathophysiological role of increased carbon dioxide levels and MetS in stress (Epel, 2009). The author of the present article first described mildly elevated carbon dioxide as a mediator of chronic parasympathetic stress in humans (Sikter, 2022a). Similar stress situations were excellently modelled previously with captured animals (Brouillard et al., 2016). They call it social defeat, but we discuss the same phenomenon and mechanism (Brouillard et al., 2016; Sikter et al., 2017a; 2017b; 2022a). At the same time, the pathological pathways are well known, as obstructive sleep apnea (OSA) and MetS have been well-defined known issues for some time. Contrary to wild animals, humans often do not resolve even hypercapnic stress, mainly because of behavioural reasons from their upbringing, so it becomes chronic through renal counter-regulation (Sikter et al., 2017a; 2017b). The body is susceptible to mild hypercapnia, to which age-related intracellular metabolic acidosis, mostly of kidney origin, also contributes (Frassetto & Sebastian, 1996). Chronic psychological (psychic) parasympathetic stress causes persistent moderate hypercapnia, which can then become permanent in the form of OSA, OHS or COPD and result in MetS [Sikter, 2020b; 2022a; Sikter & Sonne, 2021a). Due to persistent hypercapnia, the intracellular HCO_3^- concentration increases, the Cl^- concentration decreases similarly, the HCO_3^-/Cl^- ratio increases, and so the organism's ion identity changes. It can cause, among others, ***salt-sensitive hypertension***, too (Sikter & Sonne, 2021a; 2021b; Sikter, 2022b). Based on the literature data, we can easily follow the individual stages of the consequences of chronic parasympathetic stress. We can also partially apply the lessons to chronic sympathetic (hypocapnic) stress.

In contrast, ***salt-resistant hypertension*** results from metabolic acidosis. Chronic kidney disease (CKD) or age-associated kidney function deterioration causes intracellular metabolic acidosis. Nephrologists believe that there can be a close causal relationship between nephrosclerosis and hypertension (Freedman et al., 1995). Putting the data together, we must say that metabolic acidosis is partly a consequence of kidney disease, and, on the other hand, it can cause hypertension via the upregulation of intrarenal ANG II (Aryal et al., 2020). Metabolic acidosis results in a reduced intracellular HCO_3^-/Cl^- ratio, which can maintain salt-resistant hypertension and could induce arteriosclerosis, nephrosclerosis and coronary sclerosis, too (Sikter & Sonne, 2021a). Several factors play a role in renal deterioration, but acidosis is present in all. It is generally accepted that CKD is a series of vicious cycles (Fogo, 2007; Melamed et al., 2021; Maranduca et al., 2023). It can also be called renal origin salt-resistant (primary) hypertension because the ***kidney becomes a reactor organ***. Salt-resistant hypertension responds well to ACE inhibitor drugs, and administering ACE inhibitors also has high benefits for preventing kidney events, cardiovascular outcomes, and death (Zhang et al., 2020). ***The issue is that neither organic nor functional kidney disease was found during the development of primary hypertension.***

Young human beings often respond to stress with hypocapnic hyperarousal, which is then fixed and becomes chronic, simultaneously changing the intracellular ion pattern in the direction of a decrease in the HCO_3^-/Cl^- ratio, the pHi slightly increased, but at the same time, it was strongly fluctuating (Sikter et al., 2007; 2009; Sikter & Ricci, 2011). It will result in hyper- and hypoarousal (with the dominance of the former), all creating a wide range of functional disorders (Sikter et al., 2007; 2009; 2017a; 2017b; Sikter & Ricci, 2011; Bell et al., 2020). An unsolved question is what the future of this population will be: Is chronic hypocapnia a harmless thing? Does the time heal it? Would chronic (sympathetic) stress somehow cause permanent organ damage? If so, by what mechanism? There are only beliefs here which must be clarified. Many researchers do not even accept that there is such an issue. However, if we take Claude Bernard's theory seriously, we must say that a permanent change in the intracellular ion pattern cannot pass without a trace. The issue: there is a chronic (sympathetic) stress population developed (mainly below 50), and we cannot see their future. On the other hand, there is a chronic metabolic acidosis population group, mainly above 50, whose previous life we do not know anything about (Sikter & Sonne, 2021a). The intracellular ion pattern is similar in both

(reduced IC HCO_3^-/Cl^- rate), with the difference that the pHi is alkalotic in the former and acidotic in the latter (Sikter & Ricci, 2011; Sikter et al., 2017a; 2017b). Could the two populations be the same, and the first would change into the second?

Could the respiratory alkalosis, the sympathetic stress of youth, change itself into the form of intracellular metabolic acidosis over 50? Many facts can support the hypothesis: the slowly exhausting cells' H^+ pump could not return H^+ ions to the extracellular compartment. On the other hand, dietary incorporated fixed acids could accumulate in the cytosol (Frassotto et al., 1996), and intracellular alkalosis gradually turns into acidosis while the low HCO_3^-/Cl^- ratio remains or worsens (Sikter & Sonne, 2021a). Dog experiments proved that persistent (or repeated) hypocapnic alkalosis could change to renal metabolic acidosis (Madias et al., 1977), and similar test results were also obtained in humans (Krapf et al., 1991). Respiratory alkalosis is unstable, and this mechanism could be a defence against instability. It is a surprising discovery that there is an inverse correlation between psychological well-being and CKD plus cardiovascular diseases, which would support the theory that anxiety disorders may trigger CKD (Park et al., 2021). However, even if the above mechanism works, only a maladaptive kidney function disturbance would develop (without structural kidney changes) for a long time (Madias et al., 1977; Krapf et al., 1991); CKD can only develop years later. This hypothetical theory would fundamentally change our opinion about the innocence of hyperventilation and anxiety disorders if confirmed.

EBS is not a well-defined syndrome, and we should better differentiate it from MetS in the future. In contrast to the elevated HCO_3^-/Cl^- intracellular ion pattern caused by intracellular respiratory acidosis, this syndrome has a decreased HCO_3^-/Cl^- ion ratio. The relationship between metabolic acidosis and insulin resistance is controversial (Mandel et al., 2012). Unlike metabolic syndrome, EBS does not cause obesity and salt sensitivity but predisposes patients to salt-resistant hypertension and cardiovascular diseases (Sikter & Sonne, 2021a; 2021b; Sikter, 2022b). The author's MetS hypothesis is strongly supported by the fact that the serum bicarbonate level was significantly higher in diabetic patients' renal failure than in nondiabetic renal failure (p=0.0001) (Caravaca et al., 1999). However, the accuracy of this hypothesis and the precise pathomechanism still need to be verified (Sikter & Sonne, 2021a; Sikter et al., 2017a; 2017b; Sikter, 2018).

The organism gives reflexive responses to changes in the internal environment, which were already tried during the evolution of the species; if it encounters a new challenge (e.g. chronic stress), the response is non-adaptive

A living organism does not have any metabolic goals. Their automatic (reflexive) responses are based on the fact that they have already occurred during the evolution of the species and that the reactions have proven helpful for the species' survival; on the other hand, it has been inherited into the individual's genome. Since many genome variations within a species exist, individuals can respond differently to a definite change. However, there is a hierarchy among responses.

1st. The body always restores everything, including the intra- and extracellular ion patterns. It assumes constant monitoring of ion concentrations, special ion transporters are built into the membranes, and uses more than 30% of the ATP energy of the basal metabolism. All this indicates that the integrity of the ion pattern is of primary importance.

2nd. If something harmful occurs suddenly, the deterioration must be stopped as soon as possible; the condition must be stabilised to prevent further progression. In connection with the disease, the body (certain tissues) loses a significant part of its cytoplasmic pool (BCM).

3rd. The stabilisation can be followed by recovery. The first step of this is to increase the production of ATP, which starts likely with Na-Pi transport into the damaged cells, followed by alkalinisation and returning the ions (K^+, Mg^{2+}, Zn^{2+}, $H_2PO_4^-$) into the cytosol. All cytoplasm-building Type II nutrients must be available (Sikter, 2007; 2020a). There is a distinct time gap between ATP production and the BCM recovery (Jeejeebhoy, 1994).

4th. Recovery of physiological pHi takes priority over other ions. During chronic stress, the CO_2 level will permanently deviate from the physiological level, which is followed by a change in the HCO_3^- concentration and the intracellular HCO_3^-/Cl^- ratio (Sikter et al., 2017b; 2020b; Sikter & Sonne 2021a). It is the most critical moment in developing diseases of civilization (i.e. human diseases); the background is the severe damage to the cellular identity and the severe injury of Claude Bernard's thesis.

5th. Mild chronic respiratory acidosis (MetS; elevated HCO_3^-/Cl^- ratio) or mild chronic metabolic acidosis (EBS; decreased HCO_3^-/Cl^- ratio) can occur at any age, but it becomes common over 50 in human

society. It can be explained by the fact that at this age, the energy reserves are starting to run out, and the body strives more and more for stability. Still, at the same time, it cannot eliminate the pathological changes in the intracellular ion pattern, so the body's metabolism will move in the direction of decompensation rather than restoration.

6th. After a more extended existence, the body's attempt to restore the original ion pattern begins in some tissues, in the case of MetS or EBS syndromes. The body needs to preserve/restore both the pHi status and the other ions. So, the restoration of HCO_3^- and Cl^- ions is also encoded genetically. However, due to the fixation - on too high or too low levels - of the pathological pCO_2 levels, it can only do this locally, with cell membrane transporters under hormonal-humoral control, which will result in regulatory chaos in the body. Recently, it has been confirmed that the regulation of intracellular Cl^- and HCO_3^- concentrations are closely related (Shcheynikov et al., 2015). The cells have Cl^- concentration sensing receptors, which control the cell-membranes' Na^+ -HCO_3^- cotransporters.

In the case of chronic mild hypercapnia, the intra- and extracellular ion pattern stabilises on a higher HCO_3^-/Cl^- ratio characteristic of MetS. However, the body also has a second line of defence, based on ion transporters built into cell membranes under humoral-hormonal control (Sikter et al., 2017a; 2017b). RAAS wants to restore not only the pHi but also the genetically encoded original Cl^- and HCO_3^- in the precapillary arteries of vascular smooth muscle cells (VSMCs) and the left ventricular myocardium. An increase in the HCO_3^-/Cl^- ratio primarily activates ALDOSTERONE (ALD) and, to a lesser extent, ANGIOTENSIN II (ANG-II). ALD enhances the Na^+/H^+ exchange mechanism in the membranes of vascular smooth muscle cells (VSMCs) and myocardial cells through NHE-1. It also promotes the Cl^- influx to the cytosol, according to the increased EC/IC gradient. – ***Salt sensitivity is a consequence of intracellular Cl^- deficiency and the increased EC/IC chloride gradient;*** Na^+ only follows the changes of the Cl^- ion concentrations (Chipperfield & Harper, 2000). A copious table salt intake promotes the entry of Cl^- and Na^+ into cells (Chipperfield & Harper, 2000). The regulation exerts to restore physiological ion conditions. The ALD effects (Na^+/H^+ exchange plus cells' Cl^- + Na^+ uptake) continue even after pHi normalisation because renal regulation and RAAS regulation add up, while the HCO_3^-/Cl^- ratio does not normalise. High IC Na^+ level triggers the Na^+/Ca^{2+} exchanger: the pHi alkalosis plus high IC Ca^{2+} causes hypertrophy in VSMCs and myocardium (Cingolani & Ennis, 2007; Sikter & Sonne, 2021b; Sikter, 2022b). ***Salt-sensitive hypertension could, therefore, also be called respiratory or psychosomatic hypertension (Sikter, 2022b).***

In contrast, ***salt-resistant hypertension results from metabolic acidosis*** and CKD. The decreased HCO_3^-/Cl^- ratio with intracellular acidosis can upregulate the ANG II level via RAAS. ANG II activates the Na^+-HCO_3^- cotransporter (NBCn1) in the membranes of vascular smooth muscle cells (VSMCs) and the heart cells. As a result, it reduces the intracellular H^+ and Cl^- concentration towards the physiological ion conditions (Sikter & Sonne, 2021a; 2021b; Sikter, 2022b). However, the alkalinisation of VSMCs mediated by the NBCn1 and controlled by ANG II does not stop even after reaching physiological pHi. On the contrary, it switches the intracellular compartment to alkalotic, increasing Na^+/Ca^{2+} exchange and inducing VSMCs hypertrophy (Cingolani & Ennis, 2007).

The present hypothesis is based partly on the fact that humoral regulations of both types of acidosis exert to restore the original intra- and extracellular ionic conditions, in our example in VSMCs. At the same time, either ALD or ANG II restoration actions fail because the ion transport processions continue even after pH normalising, the pH becomes overcompensated, and VSMC and heart hypertrophy develop due to an increased Na^+/Ca^{2+} exchange. However, it would not have happened if respiratory or metabolic acidosis had not occurred previously. The regulation of acidity by respiration (via pCO_2 level) is incompatible with the humoral one, and they cannot replace each other. The body uses the membrane H^+ transporters, which are under humoral-hormonal control and regulate a particular tissue's ionic milieu (in this case, VSMCs), confronting the central respiratory regulation. All this results in dysregulation and metabolic disorders (Cingolani & Ennis, 2007; Sikter et al., 2017a; 2017b; Sikter & Sonne, 2021a; 2021b; Sikter, 2022b).

Differentiating between the two opposing mechanisms (salt-sensitive and salt-resistant) is a matter of life and death from the point of view of treatment, as they require a completely different treatment strategy. NaCl withdrawal can be even harmful (Garg et al., 2014)! It is accepted that the low salt diet could decrease the systolic pressure in salt-sensitive hypertension but, at the same time, increase insulin resistance. It is a fact that salt-

sensitive hypertension and insulin resistance mainly occur together (Yatabe et al., 2010). The background is that the pathophysiology of both diseases is based on MetS: on a higher HCO_3^-/Cl^- ratio and higher pCO_2 values (Sikter 2020b; 2022b; Sikter & Sonne, 2021a; 2021b). Mathematically provable, and also according to literary data, that there are Cl^-, Mg^{2+}, (Barbagallo & Dominguez, 2015) and phosphate deficiency (Håglin, 2001; Håglin et al., 2011) beside Na^+, HCO_3^- and CO_2 predominance. The solution is simple: by administering KH_2PO_4, we stimulate breathing and increase pHi, and by supplementing $MgCl_2$ and KCl, we restore all known ion deficiencies and reduce the increased HCO_3^-/Cl^- ratio meanwhile reducing both salt-sensitive hypertension and insulin resistance (Sikter, 2020d). Because the high HCO_3^-/Cl^- ion constellation upregulates ALD levels (Sikter & Sonne, 2021a; 2021b; Sikter, 2022b), the ALD antagonist drugs can specifically reduce salt-sensitive hypertension (Ayuzawa & Fujita, 2021).

Depression is more frequent in acidic constellations such as MetS and CKD, supporting a cause-and- effect relationship with both intracellular ion constellations, suggesting that it would be an age-related disorder (Al-Khatib et al., 2022; Shirazian et al., 2016). However, this statement is controversial (Schaakxs et al., 2017).

Extensive studies are being conducted with $NaHCO_3$ therapy to restore the serum HCO_3^- level in CKD to reduce progression (Melamed et al., 2021; Cheng et al., 2021) when a low HCO_3^-/Cl^- ion gradient is present. In this case, the ion constellation upregulates the ANG II levels (Sikter & Sonne 2021a; 2021b; Sikter, 2022b), and ACE inhibitor drugs specifically reduce salt-resistant hypertension (Zhang et al., 2020). The first results of $NaHCO_3$ therapy are encouraging, although contradictory in several respects (likely, the treatment still needs to be refined and specified). In some studies, even the antihypertensive medication could be reduced in the group treated with $NaHCO_3$ (Beynon-Cobb et al., 2023). According to one of the studies, $NaHCO_3$ supplementation significantly improved the outcome of cardiovascular events and reduced mortality (Cheng et al., 2023).

It is a new realisation that breathing can be accelerated by a careful administration of small doses of monobasic phosphate salts ($H_2PO_4^-$), while we could slow down and control it with $H_2PO_4^-/HPO_4^{2-}$ buffers and, thereby, also the pCO_2 level. The unexplored possibilities open new horizons in treating and eliminating stress and the diseases of civilisations, such as MetS (Sikter, 2020d; 2022b; Sikter & Sonne 2021a; 2021b).

Constancy of the Milieu Intérieur vs Homeostasis vs Allostasis

Homeostasis – allostasis – allostatic load – allostatic overload concepts are the stations of the history of stress and Claude Bernard's Milieu Intérieur theory. All three theories carry a great deal of truth, but at the same time, stress and the "continuation of a healthy, free life" can only happen in their dynamics and dialectics (Sterling & Eyer, 1988; Goldstein & Kopin, 2007; Billman, 2020; Habert 2022). If we examine it stripped down, the constancy of the milieu intérieur is a goal that can only be approached but not reached. Indeed, eternal life would only be possible if we did not change at all - time would stop. Homeostasis reflects the reality that life is a continuous change; therefore, within certain limits, the changes occur necessarily, i.e. over time and after recovery from stress, the body is no longer "the same" only "similar" (Billman, 2020; Habert 2022). Allostasis emphasizes that significant or chronic stresses can cause instability that can only be stabilised by significant internal changes (Goldstein & Kopin, 2007). Longer, prolonged stress leads to allostatic load and allostatic overload; the latter means an already manifested disease (McEwen, 2000). The creators of the allostasis theory pointed out that if the organism has to choose between long-term instability and changed identity, it remains at the latter: "to maintain stability through change" (Goldstein & Kopin, 2007). Allostatic load, disease, and chronic stress are closely related concepts (McEwen & Stellar, 1993; Goldstein & Kopin, 2007). The author of the current article hypothesized that chronic stress has two primary directions, which lead to two well-distinct changes in the intracellular ion compartment. The body's humoral-hormonal counter-regulation strives to restore the original intracellular ion status, which is impossible in every detail due to irregular breathing and PCO_2 level deviation and results in regulatory diseases such as hypertension, diabetes, and atherosclerosis.

Changes during life are natural; the organism's development, growing up during a unique life and reaching the maximum BCM also means changes, but these are in a positive direction. The individual achieves this through implementing a genetically coded program, such that there is a constant anabolic predominance in childhood, and the body's cytoplasm stock increases continuously (Sikter, 2007; Newman et al., 2005). It is followed by slow and slightly faster degradation when catabolism exceeds anabolic events. Trends in the opposite direction are initiated

by the cessation of encoded growth potential and the manifestation of irreversible changes (ageing). Life expectancy depends on how much the BCM decreasing trend can be slowed down.

In cells, vitality is best expressed by the cell's ability to produce ATP and the actual ATP concentration. In the case of organisms, vitality is mainly defined by the mass of the organism's cytoplasm (BCM or LBM). A higher mass of BCM provides higher protection against potential diseases. Therefore, the development of the maximum possible level of BCM corresponding to age and gender, its preservation, and the restoration of the original state after illnesses are of primary importance (Sikter, 2007; 2020a).

One of the essential parts of Claude Bernardi's "extended interieur milieu" is the whole of the genetically encoded intracellular ion pattern, specific to species, gender, and tissue, which in the past was considered by few as content to be protected (Robin & Bromberg, 1959; Robin, 1977; Sikter, 2020a; 2020b). Every part of the intracellular ion pattern must be protected from permanent changes as far as possible. After it has changed, efforts must be made to restore its original state. The importance of this can be explained, among other things, by the fact that a permanent change in the ion pattern results in severe metabolic changes. The author's opinion is that ions have a much more significant role in the second messenger-signalling system than previously believed because not only the previously recognised Ca^{2+} ion (Bootman & Bultynck, 2020) but CO_2 gas and through it pHi, and $H_2PO_4^-$ and HPO_4^{2-} ions also have primary signalling functions (Phelan et al., 2021).

As has been guessed for thousands of years, euventilation (breathing that keeps a regular, normal CO_2 level) is a signalling method of primary importance, and it precedes all other ions' signalling functions because it helps to maintain the ion pattern in all tissues. Changes in the level of carbon dioxide are closely related to mental functioning, as the current mental state is also manifested in changes in breathing, almost without loss of time. On the other hand, the current level of pCO_2 fundamentally influences pHi and, through this, the degree of excitability of nerve cells. The average pCO_2 level also affects the intracellular ion pattern through HCO_3^- concentration changes. Stress affects respiration, thus also the current pCO_2 level, and in the case of long-term or chronic stress, it changes the HCO_3^- concentration and the intracellular HCO_3^-/Cl^- ratio, which changes can be an essential pathomechanism of psychosomatic diseases (Sikter et al., 2009; Sikter et al., 2017a; 2017b, Sikter & Sonne, 2021a, 2022b). Intracellular acidosis, which occurs more and more often with age, changes the function of many ion transporters through hormonal and humoral control and also affects changes in HCO_3^- and Cl^- levels. These reflexes intend to restore original ion patterns but are incompatible with the abnormally functioning pCO_2 level changes (Sikter et al., 2017a; 2017b; 2022b; Sikter & Sonne, 2021a; 2021b).

The changes in the intracellular ion pattern reflect the stresses that have occurred during life and serve as the basis for pathophysiological metabolic changes. Considering all known factors, the continuation of the thought process described by Claude Bernard's heritage is justified: Preserving the original concentration level of intra- and extracellular ions is essential in every detail for the "continuation of a healthy free life" (Habert, 2022), which is impossible without the restoration of steady breathing in narrow average pCO_2 values (preserving the euventilation).

ABBREVIATIONS

ACE: angiotensin-converting enzyme; ALD: aldosterone; ANG II: angiotensin II; ATP: adenosine triphosphate; BCM: body cell mass; bwkg: body weight in kg; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; DNA: deoxyribonucleic acid; EBS: exhausting buffer syndrome (~chronic intracellular metabolic acidosis); EC: extracellular; GH: growth hormone; IC: intracellular; IGF1: insulin- like growth factor 1; LBM: lean body mass; MetS: metabolic syndrome; NBCn1: Na^+-HCO_3^- cotransporter n1; NHE-1: Na^+/H^+ exchanger-1; OHS: obesity hypoventilation syndrome; OSA: obstructive sleep apnea; pCO_2: partial pressure of carbon dioxide (gas) in blood; pHi: intracellular pH; Pi: inorganic phosphate; PiT-1: Na/H_2PO_4 cotransporter; RAAS: renin-angiotensin-aldosterone system; RDA: recommended dietary allowance; RNA: ribonucleic acid; T2D: type 2 diabetes; VSMCs: vascular smooth muscle cells.

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Claude Bernard „A belső környezet állandósága” elméletének egy XXI. századi frissítése

Az intra- és extracelluláris ionterek működésének, valamint a sejtmembránok működésének felfedezése lehetővé tette Claude Bernard elméletének intracelluláris ionokra való kiterjesztését. Ezzel szemben az ionok szerepének alábecsülésével sok tévhit kerekedett felül. A szerző kiemeli, hogy a széndioxid állandó szintjének megőrzése különösen fontos. A CO_2 az egyik legmeghatározóbb jelzőmolekula, a testet és a lelket összekötő közvetítő. Kölcsönhatásba lép az intracelluláris pH-val, Ca^{2+}, $H_2PO_4^-$ és HPO_4^{2-} ionokkal, de az intracelluláris ionmintázat összességében elsődleges jelátviteli funkciót tölt be. A krónikus stressz megváltoztatja az intracelluláris ionmintázatot, növelve vagy csökkentve a pCO_2 szintet, a HCO_3^-/Cl^-arány növekedése metabolikus szindrómához vezet. A krónikus hipokapnia miatti HCO_3^-/Cl^- arány csökkenése hiperarouzális mentális zavarokhoz vezet, amelyek évtizedekig visszafordíthatónak tűnnek. A szervezet 50 körül kezd kimerülni, és nem kizárt, hogy a légúti alkalózis metabolikus acidózisba fordulhat át, s így a vesék reaktorszervekké válnának. (A hipotézist még igazolni kell.) A stressz okozta életkorral összefüggő betegségek hátterében az intracelluláris acidózis veszélye és a szervezet ezzel szembeni küzdelme áll. Krónikus hipo- vs hiperkapnia esetén a humorális ellenszabályozás nem tudja betölteni funkcióját, és (többek között) sóérzékeny, illetve sórezisztens hipertoniát eredményezhet. Az eredeti ionmintázat megőrzése elengedhetetlen, de euventiláció nélkül lehetetlen. A légzést és a stresszt H_2PO_4- és HPO_4^{2-} tartalmú sók adagolásával szabályozni lehet. Az élettartam korrelál a testsejt tömeggel (BCM), meg kell őriznünk, ameddig csak lehetséges.

Kulcsszavak: életkorral összefüggő zavarok, széndioxid jelátvitel, krónikus stressz, ionmintázat jelátvitel, metabolikus szindróma