New aspects in the pathomechanism of diseases of civilization, particularly psychosomatic disorders. Part 1. Theoretical background of a hypothesis

Andras Sikter[1], Zoltan Rihmer[2,3] and Roberto de Guevara[4]

[1] *Municipal Clinic of Szentendre, Internal Medicine, Szentendre, Hungary*
[2] *Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary*
[3] *National Institute of Psychiatry and Addictions, Laboratory for Suicide Research and Prevention, Budapest, Hungary*
[4] *Respiras-performance breathing, Colorado Springs, United States of America*

The stress defence-cascade is mostly not biphasic as Cannon thought, the sympathicotonic stress response is preceded by a vagotonic phase called freeze response. Alteration of the carbon dioxide level plays an important role during defence-cascade as its changes interfere with stress hormones, e.g. with catecholamines, thus affecting the degree of arousal. In case of humans, learned behaviour dominates instead of instinctive, so the fight-or-flight often lags; the consequence can be persistent hypocapnia or hypercapnia. The hypoventilation or hyperventilation may continue even after a stressful situation, as tissular and renal compensation stabilizes and makes the pathological breathing patterns chronic. The organism tries to restore the original milieu intérieur (sec. Claude Bernard), but this cannot succeed without restoring pCO_2. The regulation operates the preservation of intracellular and extracellular pH as a priority, while neurohumoral compensations change the ionic milieu in the body's cells. Present hypothesis specifies the permanent lack or excess of carbon dioxide which can cause allostatic load by psychosomatic pathomechanism. Carbon dioxide is equivalent to stress hormones; its alterations become a means of somatization, resulting in ion-pattern changes in intracellular and extracellular spaces, consequently causing disintegration of the body's function. (See also: network theory, ripple effect, metabolic remodeling.) Intracellular ion-pattern alterations emerge new genetic phenotypes to the surface. The variety of phenotypes explains the diversity of induced diseases. The theory appreciates the role of ions by considering the instantaneous ion pattern of the cytoplasm (all the ions together) as a decisive second messenger.

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INTRODUCTION

Inasmuch as there are a huge number of articles published on the topic of stress, the authors want to clarify their interpretations. Every factor is stress (a stressor) for the living entity that has any impact on it (or in other words which forces it to change). There are many types of stresses, two extremes are the psychic stress and its opposite: stress which acts directly injuring the body, one of the most known stresses is the oxidative stress.

The concepts of stress and homeostasis have been closely related since Cannon's work. According to Cannon, "stress occurs when the organism perceives a disruption or a threat of disruption of homeostasis" (Goldstein 2003). According to Walter Cannon, the acute stress reaction is aimed not only at addressing the stress but also on the restoration of the original physiological parameters. The homeostasis is "the wisdom of the body", according to him (Cannon 1939).

The whole life of cells takes place in the battle against the equalization of the ions (through the

membranes), according to the electrochemical gradient (Barbagallo et al. 1997, Sikter 2007). In nature, wild animals usually undergo acute stress. The prey either survives the attack or it will die. Chronic stress is a human "invention" (Maestripieri et al. 2011). It primarily occurs among civilized people and domesticated or captive animals (Talegon et al. 2011). Reduction of living spaces of wildlife also causes chronic stress, which can lead to diseases.

CANNON'S FIGHT/FLIGHT RESPONSE VERSUS FREEZE RESPONSE (OR FREEZING BEHAVIOUR)

The acute stress response (fight or flight) theory discovered by Cannon reigned in the 20th century. It is evident now that it needs a revision in many respects (Goldstein 2003, Goldstein et al., Bracha et al. 2004). According to Cannon, the acute stress response is always associated with an increased hyperarousal, caused by adrenaline (and other catecholamines) and by activation of the sympathetic nervous system. Cannon mentioned the hyperventilation as a part of the stress response, even though the hypocapnia as a potential etiopathogenetic factor had not occurred to him. By contrast to previous statements, Van Diest et al. (2001) found that hyperventilation is not related to negative affectivity but hyperarousal.

Gray (1971) described the freeze response to stress as a particular behaviour of certain animals. Freeze response (or freezing behaviour) is the reverse of Cannon's fight/flight stress response because it is parasympathetic and associated with hypoarousal. It was discovered first by the playing dead of opossum as a freezing behaviour (freeze response) because it takes enough time and easy to observe. The observation of Norwegian researchers on the behaviour of incubating willow ptarmigan is a milestone (Steen et al. 1998). In this case, the freezing behaviour is long enough (up to 20 minutes) to allow basic observations. Steen et al. (1998) described a defence cascade introduced by freezing behaviour (Figure 1.). In rest, a standard mode exists. The bird sits in the nest and there are resting (average) vegetative functions, pulse, and breathing rate and normal arousal. When she notices danger, the respiration and pulse rate of the bird drops below the standard. Freezing behaviour develops with parasympathicotonia and hypoarousal. When the risk becomes very high the bird begins to hyperventilate, its pulse is multiplied, and sympathicotonia (hyperarousal) begins. Hardly inseparable from this time point, the bird flies away (suddenly enormous energies are released for muscular work) (Figure 1.). As a result of subsequent research (Kozlowska et al.), we can conclude that with the end of phase three the reactivity falls. The bird is reset to normal mode with normal arousal.

Until recently, it was thought that this defence cascade (hypoarousal – hyperarousal – muscular activity) is an unusual defensive reaction. However, it is increasingly apparent that this is very common among wild animals (and healthy people) (Bradley et al. 2001, Schmidt et al. 2008). The classic Cannon's fight/flight reaction would develop, according to some, "when animals are confronted with imminent danger, such as being actively pursued or attacked by a predator" (Kozlowska et al. 2015). Knowing Bradley et al.'s work, however, it is likely that all stress cascades of animals start with a few seconds of freeze response. Examining a large number of experimental animals, it was found that this cascade is typical for both defensive and hunting cascade. In the typical case, the standard mode is followed by a few seconds of parasympathetic hypoarousal (indicated by hypoventilation, bradycardia, decreased skin sweating, and lengthened reflex time) followed by sympathicotonic hyperarousal and the cascade ends with motoric activity.

In the light of new observations, Cannon's fight/flight theory would be modified that the hyperarousal response is preceded by a hypoarousal period (some time to evaluate the situation and decide). This is what we call freeze response, and we experience it when we face a stressful or frightening situation. The body becomes motionless, the breath is extremely slow, or it stops for a while. The duration of freeze response is usually 1-10 seconds, however, it may be multiplied. 20 to 60 minutes of freeze responses were also observed in animals. In the case of wild animals, the freeze response is instinctive. It is decided at the level of the amygdala, using the previous experience that will be the answer. People often choose not to choose either the fight or the escape, in this way the freeze response can last for a long time and even deepen. Often, really, this is the proper response. According to Bracha (2004b), the benefit of the initial hypoarousal is that, in this case, the prey can estimate the danger with a cold head (stop, look and listen). The prey can remain unnoticeable by its immobility in front of the predator. If it does not come in, there is continue the escape or the fight and, in final desperation, playing dead.

The defence cascade prevails through the nuclei of the central nervous system (amygdala, hypothalamus, periaqueductal gray, etc.) (Kozlowska et al. 2015).

Figure 1. Freezing behaviour at willow ptarmigan
(Steen JB et al., Acta. Physiol. Scand. 1988; 134:299-304.) with permission of author (Geir Gabrielsen)

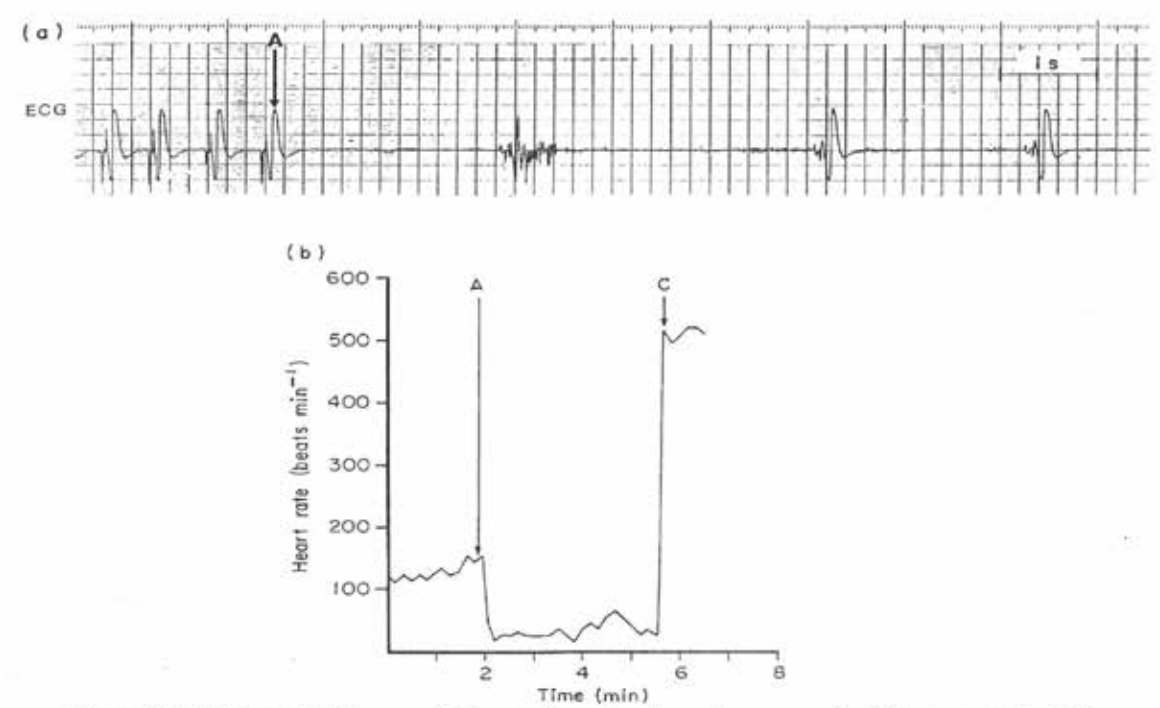


Fig. 1. (a) ECG records from a wild incubating ptarmigan hen approached by one person. (b) Heart rate response in a wild incubating ptarmigan hen when approached by one person. (A) Start of provocation. (C) Hen flew away from the nest.

According to this hypothesis, the alteration of the carbon dioxide level, connecting to breathing patterns is also substantial. It is in addition to the autonomic nervous and hormonal system which plays a leading role during stress responses. CO_2 continuously modifies the level of arousal (since the arousal is positively correlated to the momentary cytoplasmic pH of neurons) (Sikter et al. 2007, 2009, 2011). The amygdala also has a chemosensor role – the rising pCO_2 generates the feeling of fear (Ziemann et al. 2009). There is an inverse correlation between the intracellular H^+ concentration and the catecholamine sensitivity while there is a linear correlation between intracellular H^+ concentration and catecholamine production (Tenney 1960, Sikter et al. 2009). As a consequence, a feedback mechanism develops. On the other hand, variable tissular carbon dioxide levels and variable catecholamine levels often interfere so that intracellular pH changes rapidly. According to the authors, this phenomenon would constitute, among other things, the pathophysiological and neurohumoral background of panic disorder (Sikter et al. 2007). Adjusting to the hypothesis, the arousal alterations of Lang's defensive cascade would look something like this (Kozlowska et al. 2015):

- In standard mode, both pCO_2 and catecholamine levels are in normal range.
- In the event of an emergency, the respiration becomes very slow; the pCO_2 level suddenly rises, the catecholamine production increases, but the catecholamine sensitivity simultaneously decreases to a greater extent – a hypoarousal state (freeze response) will exist. It takes a time, then
- Hypoarousal suddenly converts to hyperarousal, which is due in large part to hypocapnia, because the catecholamine sensitivity abruptly raises, while the previously elevated catecholamine level is decomposed slowly, only a few minutes, in a synergistic mechanism.
- In case of wild animals, hyperarousal is followed by muscle work. The acute stress response ends when the body's carbon dioxide tension is normalized again after the muscle work, and after the stress, the creature has returned to the standard mode. The stress goes down.

It is well-known that muscular work has a normalizing effect on arousal. It is also used therapeutically (Kozlowska et al. 2015). Physical work modulates

reactivity of the amygdala as well (Greenwood et al. 2011, Sciolino et al. 2012). Several mechanisms have emerged in the background (e.g., serotoninergic, noradrenergic) (Kozlowska et al. 2015). The chemosensors of the amygdala detect the changes in pCO_2 and intercellular H^+ concentration (Ziemann et al. 2009, Paul et al. 2014), which certainly have a significant role in the formation of arousal.

The most important difference between wild animal and human stress response is that people are able to withhold, postpone, or block the fight-or-flight response. One possibility is that blocking develops in the hypercapnic period before the hyperarousal is formed. In this case, hypercapnia persists, which is consistent with the human freeze response. Physiologically it means that the body is maintained at the level of hypoarousal (hypoventilation, hypercapnia, bradycardia, parasympathicotonia). In the other case, acute stress response is blocked at the hyperarousal level (long-lasting hyperventilation, hypocapnia, tachycardia, sympathicotonia) – muscular activity in both cases is absent. "Unlike animals, which generally are able to restore their standard mode of functioning once the danger in past, humans often are not…" (Kozlowska et al. 2015). According to the hypothesis, this may be the leading cause of psychosomatic diseases.

A CONNECTION BETWEEN THE HUMAN BEHAVIOUR AND BREATHING PATTERN

Freeze response is very frequent in case of homo sapiens (Barlow 2002), although it mostly differs from that was described at wild animals. In humans, both freeze response (hypoarousal) and hyperarousal are common occurrences after repeated or prolonged stresses, that is, the organism does not return to the standard mode (Kozlowska et al. 2015). (These states are equivalent to chronic or psychic stress). As mentioned above, human psychic stress can be attributed to the persistence of hypoarousal or hyperarousal. In the background of psychic stress, civilized behaviour may play a role; consequentially leading to diseases of civilization many of which can also be considered psychosomatic.

The moral and statutory rules of human coexistence had fundamentally changed the behaviour of homo sapiens in case of emergency. The stress response is often cortical instead of instinctive (amygdala) (Schmidt et al. 2008). People have the ability to reign over their instincts and also adapt to extreme environmental stress at cognitive levels (Leach 2016); they can stop the cascade of the stress response at the level of hyperarousal or hypoarousal. In this way, the stress cascade does progress to muscular activity (fight-or-flight), and the arousal does not return to the standard mode. That is to say, in the case of the human stress, homeostasis often does not work. However, the breathing pattern also changes in this relation.

The defence cascades in the case of wild animals:

A. Standard mode of arousal – danger – freeze (hypoarousal) – hyperarousal – muscular activity (fight-or-flight) – standard mode of arousal.
B. Standard mode of arousal – danger – freeze (hypoarousal) – playing dead (hypoarousal deepens)

The defence cascades in the case of humans:

A. Standard mode of arousal – danger – freeze (hypoarousal) – switches to hyperarousal (hypocapnia)
B. Standard mode of arousal – danger – freeze (hypoarousal with hypercapnia)
C. and D. Similar to wild animals' A. and B. defence cascade (Bracha, 2004b)

Humans are able and mostly forced to stop the defence cascade either in hypercapnia or hypocapnia, in this way the muscular activity fails, so the arousal level does not restore to the standard mode or only very slowly. Human action after stress is only partially instinctive, it is mostly voluntary (Leach 2016). Its physiological consequences are seemingly innocuous: the milieu intérieur slightly changes; chronic hypercapnia or chronic hypocapnia develops, which is chemically compensated by the body.

The psychological result: at the end of the defence cascade, arousal does not return to standard mode (Kozlowska et al. 2015), it will remain on a lower or higher level. The organism will react to the following stress usually similarly but more responsively. Due to civilized behaviour, the stress situation often remains unresolved – a state of mental stress emerges. A mechanism is developed which appears to be a good solution, and in a short-term it indeed is, but in the longer term, the allostatic load results in a destructive effect (see later).

Both human (chronic) hypoarousal and hyperarousal constitute a parking track which makes the human defence cascade easier to launch, which is different from the wild animals' defensive cascade, and is thus pathological. The tens of thousands of years since the beginning of civilization were not

enough for the people to adapt biologically to these unfinished defence cascades.

However, neither hyperarousal nor hypoarousal is a constant state since the level of arousal can vary from time to time (we might say to breath-to-breath). It is partly due to the constant contra-regulation, partly due to the irregularity of the respiration and other factors affecting the level of pCO_2 (Sikter et al. 2009). We can only say that hypercapnia tends to regulate the nervous system to the direction of hypoarousal, while hypocapnia to the direction of hyperarousal.

THE CONSEQUENCES OF ALLOSTATIC DEFENCE. MATERIALIZATION OF THE HUMAN MENTAL STRESS

Claude Bernard wrote (1878): "The constancy of the internal environment is the condition of a free and independent existence." An interpretation of this quotation can also be that preserving the unchanged milieu intérieur is indispensable to preserve the identity of an organism that is, its health. Péter Bálint, a Hungarian professor of physiology interpreted Bernard's thesis as that the rule should not only be applied to the extracellular but also to the intracellular milieu (verbal communication). On the other hand, preserving of the immutability of the interior milieu can be only an approachable, but not achievable goal as the changes in the body (e.g., aging, illnesses, death) unavoidably occur. Ions (electrolytes, trace elements, ionized forms of vitamins) are the most important constituents of the internal milieu, which, among others, function as coenzymes.

Cannon reviewed Bernard's thesis and created the concept of homeostasis. According to Cannon, the ability of mammals to maintain the relative stability of their internal environment through the self-regulation of autonomic nervous system and hormones developed during the evolution. Today, instead of homeostasis (the new stress concept) allostasis is increasingly being used. Sterling and Eyer (1988) introduced the concept of allostasis recognizing that people are not able to restore the original conditions, only to stabilize them. While the homeostatic defence restores physiological parameters, including also interior milieu, the allostatic defence achieves a stability with an alteration of the milieu intérieur. Accordingly, defensive systems start up compensatory mechanisms. Allostasis means "to maintain stability through change" (Goldstein and Kopin 2007). As a result, restoring of the milieu intérieur (even the pursuit) is sacrificed on the altar of stability. (Compensating mechanisms, without doubt, change the composition of interior milieu). Allostatic load refers to long-lasting or prolonged stress (McEwen et al. 1993). The accumulated allostatic load, however, leads to allostatic overload, i.e. diseases. The allostasis concept has a huge literature, while the idea of restoration of the milieu intérieur (restitutio ad integrum) has come to a complete standstill. (For a summary of allostatic load concept, see McEwen's review, 2003.) McEwen (2000) itself pointed out also the soft spot of the allostatic load theory when it was indicated that he cannot pinpoint an exact mechanism. "Allostasis and allostatic load are concepts that are mechanistically based and only as good as the information about mechanisms that lead to disease" (McEwen 2000).

The starting point for this hypothesis may be that stress response of wild animals and civilized people in most cases are significantly different. While wildlife struggles against stress more with a homeostatic defence, in case of humans allostasis dominates in most cases. While wildlife balances stress ("relieves") with any movement (fighting or escaping), so it does not become chronic, the same thing for civilized people is not created and often impossible. People live in society. They have to tolerate their companions and the existing relationships even if they do not accept them in the depths of their soul. (They prevail in their instincts). The consequence is that action (motion) lags behind, while arousal persists at a higher or lower level than the standard mode. Often, even the stress situation is persistent, so all conditions are given for stress to become chronic. Researches show that disadvantaged psychosocial status is a risk factor for psychosomatic disorders and diseases of civilization. Handicaps have been studied, among other things, in the relation to occupational stresses regarding job insecurity, job quality, job strain, wages, overstrain (Cuffee et al. 2014). Several psychic mechanisms can play a role, e.g., humiliation, helplessness, hopelessness, feeling of insecurity. Inhibited anger together with fear certainly can lead to somatic diseases (Scuteri et al. 2001). Social stress can trigger a freeze response (Roelofs et al. 2010), which can cause somatic disorders through chronic hypercapnia, according to the hypothesis.

HOW CAN PSYCHIC STRESSES CAUSE PHYSICAL ILLNESSES? HOW DOES PSYCHIC BECOME SOMATIC?

In the human stress response, the first material change in metabolism which differs from that in wild animals and leads to intracellular and extracellular ion

changes (see the idea of constant milieu intérieur) occurs in pCO_2: hypocapnia hyperarousal or hypercapnia hypoarousal. Chronic, recurrent or unresolved human stress can trigger a tendency to chronic hypocapnia or hypercapnia.

There are no credible data about the distribution of the pCO_2 in the population, because momentary CO_2 level almost does not say anything, it can be even the result of a measurement stress. Verifiable measurements could be performed with an $ETCO_2$ capnography, in continuous mode, which can be done in a laboratory environment, in small series (Meuret et al. 2010). Also, utilizing a blood gas test, the fact and the extent of chronic hypocapnia can be calculated from pCO_2 and serum bicarbonate levels (Meuret et al. 2010), but this is not a routine test either. The best estimation of the prevalence of chronic hypocapnia and hypercapnia may be by looking at the prevalence of those diseases where pathomechanisms of pCO_2-level differences certainly play a role, such as panic disorder and asthma bronchiale (Meuret et al. 2010), anxiety disorders (Bandelow et al. 2015, Meuret et al. 2010, Sikter et al. 2009), certain organic diseases, etc. The sum of the prevalence of these diseases will be certainly two-digit. Both chronic hypocapnia and chronic hypercapnia are very common in humans (while in wild animals it is certainly not the case). Earlier, the standard range of arterial pCO_2 was from 38 to 42 (even 39-41) mmHg (Bruton et al. 2005). The minority still insists on this range, many others see it as the ideal, although presently 35 to 45 mmHg is the official range. It is assumed that the average band was broadened because otherwise the proportion of abnormal populations would be too high. The authors think that much of the civilized population has moderate hypocapnia (pCO_2 35-37 mmHg) while the other part may be a moderately hypercapnic (pCO_2: 43-45 mmHg) subpopulation. In this way, only about one-third of the population would have eucapnia. It is also surprising because intracellular pH and the body's pCO_2 level are among the strictest controlled parameters.

Most psychological processes also change breathing: accelerate it, slow it down, and/or make it irregular; certain emotions, mental illnesses can lead to specific breathing patterns (Van Diest et al. 2001). Fluctuating CO_2 level can affect mental functioning, and it also influences arousal (Van Diest et al. 2001, Meuret et al. 2010). Alterations in pCO_2 level appear almost instantly in the cells. CO_2 can easily pass through cell membranes, both its excess and its absence usually relate to the entire organism (Tenney 1960, Laffey et al 2002) if there are no areas closed from the circulation. Reduced H^+ concentration stimulates the activity of most enzymes, increases passive Ca^{2+} permeability of the membranes. It is related to the increased reactivity of the neurons and the muscle cells in alkalosis, and increased arousal. At the rise of pCO_2, an opposite phenomenon occurs with hypoarousal (Sikter et al. 2007, 2009, 2011). Intracellular acidosis, high (and rising) CO_2 tension is associated with hypoarousal, and despite the higher catecholamine levels irritability decreases. Carbon dioxide thus may be a link between the soul and the body (Sikter et al. 2009).

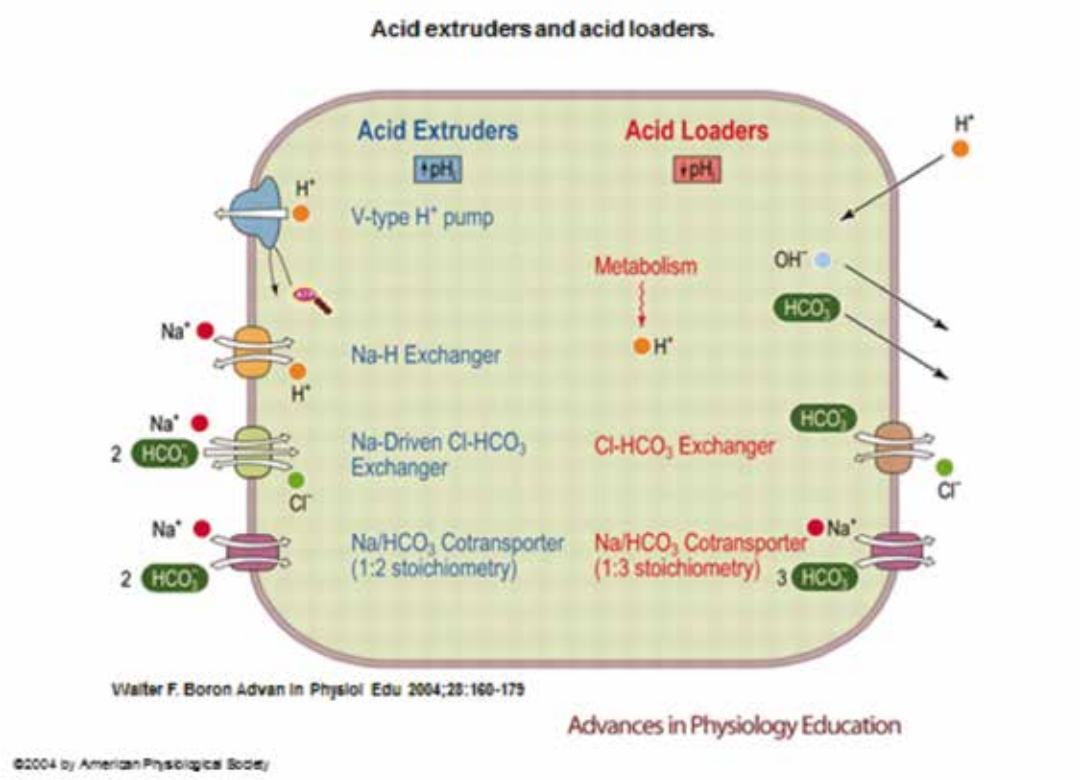
The pH changes caused by decreased or increased ventilation are immediately counterbalanced by various metabolic mechanisms (kidney, bone, tissue buffers, membrane exchange mechanisms). While CO_2 level changes very rapidly, metabolic compensations in the tissues last for hours, the renal compensatory effect for days. However, if the compensation has already occurred, it is equally stable (or even more stable) than in case of the physiological parameters (this is an allostatic phenomenon). Changes in CO_2 levels are followed slowly by metabolic compensation – and also vice versa.

In case of humans, the restoration of the standard CO_2 level often fails because muscular activity (fight or flight) lags behind. However, other pH level repair controls work smoothly. The kidney function needs about 5-7 days to restore H^+ ion deviation to the standard level, metabolically increasing or decreasing HCO_3^- secretion. If this happens, it stabilizes not only the metabolism but also the pathological breathing pattern.

Cannon's "wisdom of the body" (which is the development of Bernard's thesis) works with phylogenetically tested mechanisms to restore, as far as possible, the quickest and best possible repair of the milieu intérieur, such as the genetically encoded intracellular ion pattern. Homeostasis can be more or less successful in wild animals as the third phase of the defensive cascade, the muscle work is almost always present. However, civilized humans are different, that is why it was necessary to introduce new concepts (allostasis, allostatic load, allostatic overload). The allostasis theory does not make a sharp distinction between wildlife and humans, although a large part of the observations has been performed in humans.

The role of second messenger function of Ca^{2+} is already a textbook data. It is also evident, though neglected, that the H^+ ion is also one of the second messengers (Sikter et al., 2009, Molinari 2015). After

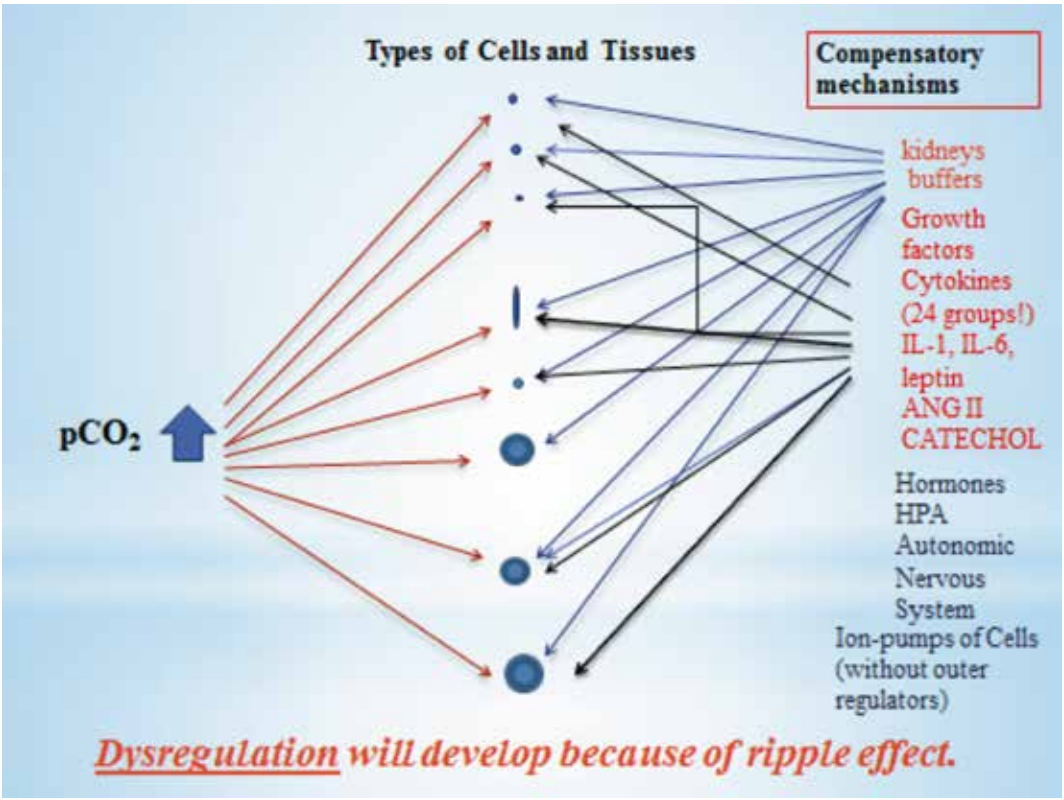
Figure 2. Cytoplasmic pH regulation (Boron, 2004) (with permission of the author)



little bibliographic research, it is obvious that various cytoplasmic ions can function as second messenger (Molinari 2015, Li, Yamasaki et al. 2007, Valdivieso et al. 2016, Chaigne-Delalande et al. 2014). A long-lasting alteration in the concentration of a single ion can lead to a change of the entire intracellular ion-pattern, as ionic concentrations influence the concentration of one another in many ways: through osmolality, cell electricity, cell energetic state (Sikter, 2007), anion/cation equality, membrane ion transporters, neurohormonal effects, ionic synergism or antagonism, etc. So far, we have said, most hormones have metabolic effects and, incidentally, affect the ion composition of the organism. If the intracellular ion-pattern as a second messenger theory is proven, we have to say that the most important hormones and regulators affect intracellular ion composition and therefore also have a metabolic effect. In psychic stress, we are talking about changes in the body's carbon dioxide level, which lead to H^+ change in the first step, and to alteration of HCO_3^- level as the second step; further phases cannot be predicted due to a ripple effect. In conclusion, the intracellular ion-pattern acts as a whole, in a manner of a second messenger, significantly modifying/directing cellular metabolism.

Returning to Claude Bernard, in order to the cell "to be able to work according to its duty," the ions have to be everywhere in their "original" place. A huge number of regulators are involved in the restoration (repairing or stabilizing) of the milieu intérieur. According to the terminology, regulators are such mediators (hormones, growth factors, cytokines, interleukins, etc.) which interfere with the intracellular ion-pattern by connecting to one of the membrane ion-exchangers. Most of the regulators are specialized in the restoration/alteration of intracellular H^+ concentration, but naturally, other ion concentrations are also controlled by other regulators. Some of the regulators attempt to restore the status quo of ions as a part of the feedback mechanism, while the others, in contrast, want to change it to achieve a metabolic effect. The number of modulators that influence the intracellular H^+ concentration is surprisingly large. It implies the high priority of the role of intracellular pH that a small amount of change of intracellular H^+ is able to induce a significant degree of changing of biochemical reactions. Restoration of the intracellular H^+ ion concentration can be achieved by various mechanisms (Boron 2004, Figure 2.). The different pumps that may be similarly capable of restoring the H^+ concentration

Figure 3. Raising pCO_2 versus tissular and metabolic counter-regulation



of such cells at the same time will certainly lead to different ionic patterns in these cells. An example of this is Angiotensin II (ANG II), which is linked to the Na-driven Cl-HCO_3 exchanger of vascular smooth muscle cells (VSMC) which – while alkalizing the cytoplasm of these cells – brings twice as much Na^+ ions to these cells as the Na/HCO_3 cotransporter (see Figure 2.). As a result, pH and Ca^{2+} concentration increase in the smooth muscle cells of arterioles, leading to increased muscle tone in the VSMCs, and with time to smooth muscle hypertrophy and ultimately hypertension.

The most common acid extruder mechanism is the Na^+/H^+ ion-exchanger (Boron 2014), which is also referred to as NHE1 (Casey et al. 2010). In the schematic Figure 3., mediators that transport H^+ outward from the cells, ie alkalize the cytoplasm in the cells are labelled red. At first glance, it seems that the more mechanisms taking care of the maintenance of the ion-integrity the better, but the opposite is true. The effect will be entirely different in the ionic composition of the cell of observation when one pump is activated instead of another. Somewhere there is need for ion sensors to control the ion concentrations (Casey et al. 2010). Ion concentration can vary by cells even in the same tissue, so the amount of the produced hormone (or intracellular ion-regulator) can be much for one cell and a little for the other one. The number of hormone receptors varies by type of tissue; not all tissues have all hormone receptors. Diffusion of carbon dioxide is extremely fast, and the regulation by ion-exchangers can follow it often only hours or days later. Consequently, there are many arguments for the fact that the highly fragmented counter-regulation can hardly restore correctly the original intracellular ion-pattern after the lasting pCO_2 change. On the other hand, the mediator (endocrine) status may also be significantly changed. There will be over-regulated tissues, and others will be under-regulated, leading to the development of dysregulation, which will result in metabolic remodeling, that is, diseases.

Both living cells and the body form a complicated and extensive network that is self-regulating through positive and negative feedbacks. In self-regulation, it is important to be able to find stable, balanced states at different energy levels and also different metabolic conditions (see allostasis theory). However, stability

alone is not enough to preserve and/or restore health (identity). (Compare Bernard's milieu intérieur and McEwen-Stellar's allostatic load theories.)

The constancy of the milieu intérieur and the intracellular ion-pattern is important because the ions actively inhibit certain enzymes and promote others. Cell enzymes form a network. In the enzyme lines, some degree of multiplication/degradation of processes can occur when the activity of several enzymes increases or decreases simultaneously. For example, a slight change in concentration of H^+ can significantly amplify (or inhibit) certain metabolic pathways. Thus, it is understandable that the restoration of physiological intracellular pH is a primary goal. However, due to a large number of regulators, the result will be mixed: a chronic respiratory or metabolic acidosis may be over-compensated in some cases by a counterbalancing humoral effect (e.g., ANG II already mentioned result could cause alkalosis and hypertrophy in the VSMCs, leading to hypertension). However, many other tissues are under-regulated: for example, the insulin decreased alkalizing effect (Yang et al. 2002) might stand in the background of insulin resistance and diabetes. Similarly, a reduction in leptin alkalizing ability would contribute to obesity. Acidosis of the cytoplasm may lead to increased Na^+/H^+ exchange and consequently to intracellular Na^+ and Ca^{2+} overload (Casey et al. 2010). As a result of the change in the intracellular ion-pattern, the formation of certain metabolites may be significantly accelerated, and others may be slowed down. The genetic background and intracellular ion-pattern determine metabolism together. Hidden genetic defects might arise, which would not be defects at all if the intracellular ion-pattern (the software) had not changed. In different individuals, the metabolic changes caused by the above mechanism, and consequently the diseases, take different directions; they diverge because the intracellular ion-pattern has changed the phenotype of metabolism.

CONCLUSION

Human stress causes a long-lasting alteration in pCO_2 and hence leads to a persistent change of bicarbonate levels, which also change intracellular ion-patterns. Because of a ripple effect, this leads to humoral and metabolic dysregulation and metabolic remodelling, which is the antecedent of diseases of civilization which cannot be avoided after the persistence of such changes for years or decades. These diseases of civilization do not occur or are limited in wild animals, but they are epidemic in humans and show a wide range also possibly including a significant part of mental illnesses and psychosomatic diseases. (See also diseases triggered by psychosocial handicaps.) On these grounds, our hypothesis is intended to give rise to thoughts and to start a fruitful debate.

Corresponding Author: Andras Sikter
Kanonok utca 1., Szentendre, Hungary 2000
E-mail: andrassikter3@gmail.com

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A civilizációs betegségek patomechanizmusának egy újabb szemlélete, különös tekintettel a pszichoszomatikus betegségekre.
1. rész. A hipotézis elméleti háttere

Mostanra kiderült, hogy a stressz defence-kaszkád legtöbbször nem kétfázisú, minthogy a Cannon által leírt szimpatikotóniás stressz választ (fight-or-flight) megelőzi egy vagotoniás jellegű fázis, amit freeze response-nak neveztek el. A defence-kaszkádban fontos szerepet tölt be a széndioxid szint, minthogy változásai interferálnak a stressz-hormonokkal, pl. a katekolaminokkal, így befolyásolva az arousal mértékét. Az embernél az ösztönös helyett a tanult viselkedés kerül előtérbe, ezért a motoros válasz (fight-or-flight) legtöbbször elmarad, aminek tartós hipoarousal (hiperkapniával) vagy hiperarousal (hipokapniával) lesz a következménye. A stresszhelyzet elmúltával is fennmaradhat a hipo- vagy hiperventiláció, minthogy a szöveti és renális kompenzáció stabilizálja és krónikussá teszi a patológiás légzési patternt. A szervezet igyekszik helyreállítani az eredeti milieu intérieurt (sec. Claude Bernard), ez azonban nem sikerülhet a pCO_2 normalizálása nélkül. A reguláció prioritásként kezeli az intra- és extracelluláris pH normalizálását, a neurohumorális kompenzáció során viszont megváltozik a szervezet sejtjeiben az ionmiliő. Sterling és Eyer (1988) bevezették az allosztázis fogalmát, mint a homeosztázis alternatíváját, felismervén, hogy az ember nem képes az eredeti állapotok teljes helyreállítására, csupán annak stabilizálására. Jelen hipotézis a széndioxid tartós hiányában és/vagy túlsúlyában nevesíti a pszichoszomatikus patomechanizmussal kialakuló allostatic loadot. A széndioxid a stressz-hormonokkal egyenértékű szereplő; változásai a szomatizáció eszközévé válnak, maga után vonva az intra- és extracelluláris ionpattern változásait, aminek következtében a szervezet működése dezintegrálódik. (V. ö. hálózatelmélet, tovagyűrűző hatás, anyagcsere remodeling.) Az intracelluláris ion-pattern változások új genetikai fenotípusokat hoznak felszínre, melyek divergenciája megmagyarázza az indukált betegségek sokszínűségét. Az elmélet felértékeli az ionok szerepét, amennyiben a citoplazma pillanatnyi ion-patternjét (mint egészet) tekinti second messengernek.

Kulcsszavak: széndioxid mint kapocs a lélek és test között, milieu intérieur helyreállításának eszméje, intracelluláris ion-készlet mint második hírvivő, emberi stressz-válasz aktualizálása