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Psychosomatic Molecular Mechanisms of Metabolic Syndrome and Type 2 Diabetes. Part 2. Psychosomatic Mechanism of Metabolic Syndrome (a Theory)

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Abstract

The author had hypothesized that the prevailing Momentary Intracellular Ion-Pattern as a whole has an essential, perhaps the primary signaling function. (See Part 1.) The concentration of intracellular H^+ (pHi) is the most critical of all ions to maintain homeostasis; that is why regulation wants to preserve the permanence of pHi. Recent researches have shown that caged rodents can be well-modelizing for human hypoarousal diseases of civilization, which may correspond to Metabolic Syndrome or Depression. Repeated Social Defeat results in such psychic mechanisms that induce persistent hypoventilation among most of the observed rodent populations. Hypoventilation continued for weeks, even after stress, and presumably associated with hypercapnia. It may correspond to a larval version of the freeze response well known in the animal world, but it becomes chronic at people. The author., *et al*. previously presented in their papers how social or mental stress can be converted into an increased or decreased arousal by the body's closed-loop systems. Human 'low-grade hypercapnia' usually lasts for decades - to the end of life. One of the results is the Metabolic Syndrome, which often tends to the classic Type 2 Diabetes or other Related Disorders. Persistent elevation of the pCO_2 level launches a compensational cascade through chemical and hormonal-humoral alterations that can lead to various forms of readjustment. The Metabolic Syndrome is a latent, stealth catabolic state of the body that develops due to slight but chronic hypercapnic acidosis. Although chronic hypercapnia is usually compensated, a moderate intracellular acidotic state persists in continuing. Metabolic Syndrome is often the result of a learned 'civilized behavior'; the Social Defeat can also develop in captive animals due to chronic or repeated stress. The point is that this type of load does not increase but decreases arousal through hypercapnic acidosis, which can also cause Depression. Slight cytosolic acidosis also results in reduced metabolism, which is associated with moderately reduced anabolic and increased catabolic activity in the body with insulin resistance and reduced ATP producing capacity. As a consequence, the whole metabolism has become remodeled and dysregulated because of the disturbed Intracellular Ion Pattern.

Keywords: Diseases of Civilization; Low-Grade Chronic Hypercapnia; Metabolic Remodeling; Pathogenesis of Metabolic Syndrome (a Hypothesis); Social Defeat Theory

Abbreviations

ATP: Adenosine Triphosphate; CBIs: Cytoplasm Builder Ions (K^+, Mg^{2+}, Zn^{2+}, HPO_4^{2-} and $H_2PO_4^-$ Together) – these also called 'Intracellular Ions'; COPD: Chronic Obstructive Pulmonary Disease; MetS: Metabolic Syndrome; OHS: Obesity Hypoventilation Syndrome; OSA: Obstructive Sleep Apnea; OSAS: Obstructive Sleep Apnea Syndrome; $paCO_2$: partial arterial pressure of carbon dioxide; pCO_2: partial pressure of carbon dioxide; pHi: intracellular pH; SRH: Sleep Related Hypoventilation; T2D: Type 2 Diabetes

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Introduction

Pathophysiology of Metabolic Syndrome (MetS) cannot be considered to be solved, although many hypotheses were proposed. MetS and its Related Disorders are primarily diseases of civilized humans and captive or tamed animals. After Cannon's and then Selye's stress-theories, new ideas started to emerge in the 21st century. We should mention allostasis/allostatic load theory [1] as an original ruling thesis. Zimmet suggested renaming of MetS to 'Circadian Syndrome' as the solvation of the problem [2]. The author of this book able to identify with the Social Defeat theory because Brouillard's animal experiments [3] show such a behavioral/physiological happening (hypoventilation), which can be adapted to humans. Persistent hypoventilation was seen in the trial, which could be a link that may lead from a psychic event to a bodily change. The observed hypoventilation can also explain the hard-to-understand mystery of why MetS Related Disorders have robust comorbidity with Depression [4], for which no commonly accepted explanation has been found so far. To understand, we needed to go back to Claude Bernard's Milieu Intérieur theory in the 19th century.

The author of the book has not encountered a detailed, puzzle-assembled theoretical description of the psychosomatic pathomechanism; that is, how does psychic become somatic? How does the soul materialize during Social Defeat or other psychological stress? And how can these processes lead to organic diseases and Depression at the same time? And how and why does this process realize and also continue today? How do we differ from wild animals in our behavior and mental functioning? And why do captive animals get 'diseases of civilization'? Is it hereditary or learned behavior? Some also question the common root of diseases of civilization - namely the MetS. And if it exists such a common source, why and how does it diversify, e.g., into Hypertension, T2D, Cardiovascular Disorders? Is it possible to modelize MetS?

The author of this book had begun for four decades then continued to develop his cytoplasmic model (see Part 1.) - initially in a deductive and then inductive way - to help understand the essence, course, complications of illnesses, recovery from a disorder, and death. Also, one of the primary goals was to understand the difference between functional and somatic diseases and how they could cause each other. The model seems to have been useful help as the author has come to such conclusions that others have not thought them.

The author., *et al.* previously hypothesized a new stress model derived from human behavior based on teaching and education [5,6]. It would have two primary forms, the overheated 'hyperarousal' and 'hypoarousal'. Pathophysiologically of the latter one is equivalent to 'human freeze response.' Still, it is entirely different from that of wild animals due to its persistence since it can continue for years-decades. This behavior is characteristic of humans and domesticated or captive animals. The chronic stress-response is characterized by low-grade hypercapnia with a reduced physical and psychic activity; when the Depression is common. It usually occurs in the following clinical pictures: Obstructive Sleep Apnea (OSA), Chronic Obstructive Pulmonary Diseases (COPD), and Significant Obesity (its severe form is the OHS). The co-existence of low-grade hypercapnia with hypoarousal - according to the author of this book - can lead to Metabolic Syndrome and its Related Disorders, e.g., to Type 2 Diabetes, over the years and decades.

How can psychic stress affect cells and cause Metabolic Syndrome?

Not too long ago, in the era before the discovery of membrane receptors, most psychiatrists believed that mental and psychosomatic diseases develop solely through a psychic mechanism. However, it is clear that psychic and social stress have to materialize, but how can the psyche become soma? The author of this book pointed out in their previous work [5] that human behavior reshapes the stress defense cascade by placing the stressed individual in a waiting position, who should be 'pulling himself together.' Pathophysiologically, this course is equivalent to the animal freeze response [7]. It means a reduced mode, decreases physical activity, movements, and mental functions – hypoarousal develops. From a physiological point of view, perhaps the most important are slower breathing, elevated CO_2 levels, and reduced metabolism. From a sociological point of view, it can be essential that this behavior allows many people on Earth to live together. Carbon dioxide, as well as the intra- and extracellular pH, are one of the best-regulated parameters since maintaining intracellular H^+ concentration is vital for health and life. There are regulators at nearly all levels of the central nervous system, from the medulla oblongata to the cortex - which regulates, influences breathing. Ventilation can also be influenced by voluntarily or emotions. The following shows that 1) The opposite of the above mentioned, the $PaCO_2$ levels can permanently differ from normal because of various stimuli. 2) If pCO_2 alters from

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physiological, this will trigger counter regulations ranging from metabolic renal and tissular compensations to membrane transports. 3) In the case of the altered high (or low) pCO_2 levels, the recovery of the Intracellular Ion-Pattern can not be complete, and even the pHi restitution can not be perfect. 4) Permanently altered CO_2 level changes the responsiveness to CO_2 stimuli (hypocapnia enhances CO_2 sensitivity, while hypercapnia decreases it) [8]. 5) Garay has observed a diminished ventilatory response to hypoxia and hypercapnia [9]. Therefore, periodic hypercapnia and apnea can trigger vicious circles [10]. Others have confirmed the possibility of vicious cycles generated by hypercapnia [11]. 6) In this case, not only the elevated carbon dioxide level but also the pathological state associated with it could be reversed by mechanical ventilation [12]. Higher pCO_2 levels are associated with a different intracellular ion-milieu-pattern; according to a case study, the patient was only removable from the machine when the electrolyte deficiency was eliminated (See Part 1. [34]). Hopeful CPAP treatments of OSAS also show that not only CO_2 but also the clinical picture (Depression, T2D) can improve after mechanical ventilation [13]. If getting used to high levels of CO_2 caused a decreased CO_2 sensitivity of breathing centers, then prolonged CPAP treatment can restore CO_2 sensitivity, though some dispute it [11]. CPAP treatment appears to be somewhat useful not only on pCO_2 restoration but also on the MetS Related Disorders' complications [14,15,16]. However, respiratory machines are neither physiological nor perfect restorers. In summary, the conditions of the formation and fixation of low-grade hypercapnia exist at most of the people if it persists for a while or repeat. A rise in pCO_2 reprograms a significant portion of cellular metabolism [17], if it is not irreversible, there is also a chance to restore it to its original state.

About Milieu Intérieur and maintenance of homeostasis

The need to preserve the permanent status of the Milieu Intérieur (see Part 1.) applies not only to the extracellular but also to the intracellular space. Walter Cannon discovered stress and also homeostasis, the 'wisdom of the body,' which after stress, tries to restore the original ionic milieu in the body. Here comes the first essential difference between wildlife and humans. While wild animals are characterized by the 'Fight or Flight' stress-response, humans most often resolve social stress with inactivity (freezing behavior or freeze response) [5,6]. Stress is often not resolved, or very slowly, and becomes chronic [5]. The most important consequence of a Freeze Response, according to the author of this book, is that chronic hypoventilation, hypercapnia, albeit in a moderate form, but persists. The organism tries to restore the original Milieu Intérieur, but this cannot succeed without restoring the pCO_2 [5,6]. Since it is mathematically impossible to restore the original ionic and pH milieu, the regulation tries to preserve at least the pH of intracellular and extracellular spaces as a priority. Although this homeostatic function ("the compensated hypercapnic acidosis") stabilizes the metabolism for a long time, the problem stems from the stability itself.

According to the author of this book, medical thinking has made two severe mistakes in this regard: 1) It tacitly accepted that the compensated respiratory acidosis or alkalosis is tolerable. (This is probably due to the extremely difficult, often impossible undertaking to recover them, or could only be via a significant intervention: using respirators). 2) It was conceived and accepted by the majority that pCO_2 is considered normal over a wide range (from 35 to 45 mmHg), instead of the conventional 38 - 42 mmHg range. It is also unacceptable because intracellular pH changes immediately follow changes in pCO_2 [2], and as we have seen, the body wants to preserve pHi (intracellular pH) to be unchanged. If we accept the hypothesis that Momentary Intracellular Ion-Pattern directs the cellular metabolism primarily, the need to maintain its original state becomes even more apparent. On the other hand, keeping the immutability of the interior milieu can only be approachable. Still, the not achievable goal as the changes in the body (e.g., aging, illnesses, death) unavoidably occur - the Second Law of Thermodynamics is in the background. The whole life of the cells takes place in the battle against the equalization of the ionic concentration gradients through membranes, which also maintain the electrochemical potential through the membranes [18].

Recently a new concept started; instead of homeostasis, allostasis is increasingly being used. Sterling and Eyer (1988) introduced the concept of allostasis, recognizing that the organism is not able to restore the original conditions, only to stabilize them. Allostasis means "to maintain stability through change" [1]. As a result, the need for restoring the Milieu Intérieur is sacrificed on the altar of stability. Allostatic loads refer to long-lasting or prolonged stress [19]. The accumulated allostatic load, however, leads to allostatic overload, i.e., diseases. The concept of allostasis has a tremendous amount of literature, while the idea of restitution of the Milieu Intérieur (i. e. restitutio ad integrum) has come to a complete standstill.

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The starting point for the hypothesis of the author of this book may be that the stress response of wild animals and civilized people in most cases are significantly different. While wildlife struggles against stress more with a homeostatic defense, in humans, allostasis dominates in most cases. Wildlife balances stress with physical exercise (fighting or escaping), so it does not become chronic. By contrast, civilized people are not allowed to follow their instincts. People live in society. They have to rule over themselves, tolerate their companions, and existing relationships, even if they don't accept them in the depths of their souls.

Chronic hypoventilation caused by repeated psychosocial stresses

There is a close correlation between OSA and Metabolic Syndrome (MetS) [20]. Some believe that OSA is a manifestation of MetS. According to the author of this book, however, MetS can be a consequence (expression) of either OSA, COPD, or OHS. It is explained by the fact that the onset of MetS is primarily linked to low or moderate grade hypercapnia. In the US, both OSA and MetS - according to the estimation of Drager., *et al.* - can be over 50% of the population [21]. Both conditions are primarily civilization diseases, and psychosocial stress plays a significant role in their pathophysiology.

Stress concept connects so much to the name of Cannon that people almost always consider an adrenergic, sympathetic process on the stress reaction. Textbooks also mention freeze response as an exception, as an unusual reaction of some animals [7]. The essence of this reaction is a parasympathomimetic, acetylcholinergic mechanism, which is just the opposite of the former. Some experts have previously already clarified that before the sympathetic stress response phase, mostly, there is a parasympathetic stress phase [22]. The parasympathetic period - which usually lasts only a few seconds (1 - 10 sec) - precedes the sympathetic response: the prey (or predator) is watching without breathing. The benefit of this initial hypoarousal is that [7], in this case, and the animal can estimate the danger (or the prey) with a cold head (stop, look, and listen). Meanwhile, a vital physiochemical process is taking place in the body [7]. Breath retention increases pCO_2 levels, and the acidotic feedback also increases the levels of stress hormones, primarily catecholamines. When the creature starts to hyperventilate, its energy will be multiplied by hypocapnia. Hypocapnia alkalosis increases the sensitivity for catecholamines and the cumulated catecholamines 'detonate' the 'energy bomb' in this way, it can perform maximal muscle work [5].

However, in humans, the parasympathetic response given to psychosocial and other stressors is robust and long-lasting; it even increases and worsens over time. It lasts most often for decades, triggered by repeated or durable psychosocial stressors. If they survive more and more mental stress, this 'freeze response analog' will cumulate; that's why more than half of people over 40 exist in this 'low-grade hypercapnic sate.' This stress mechanism was hardly studied, it is also challenging to model in animals, although there are some papers.

Researches show that the psychosocial status of the disadvantaged people is a risk factor for psychosomatic disorders. Handicaps have been studied, among other things, concerning occupational stresses regarding job insecurity, job quality, job strain, wages, overstrain [23]. Several psychological mechanisms can play a role, e.g., humiliation, helplessness, hopelessness, feeling of insecurity. Inhibited anger (together with fear) indeed leads to somatic diseases [24]. Social stress can trigger a freeze response [25], which can cause somatic disorders through chronic hypercapnia, according to the above-discussed hypothesis. It is troublesome to draw definitive conclusions about this important area [26], although the comorbidity between MetS Related Disorders and Depression is frequently described in the literature [4].

Psychosocial stress and human social behavior have been observed primarily in caged rodents. The behavior of the rodents relatively well modeled the social defeat/subordination, social isolation, or social instability of humans. Although the authors remained debtors with the exact paths, which could lead to an onset of MetS (and T2D) in humans. The traditional stress mechanisms can be poorly adapted to the 'human freeze response.' According to the author of the book, this is precisely the opposite of Cannon's fight-or-flight response. The human individual does not fight, has no place to flee, so he/she defeats himself, and this tolerating behavior has become the basic rule of social coexistence, civilization behavior; this is where the whole educational strategy has built on it.

They were closest to the truth [3], who observed sustained hypoventilation and depression-like states of the rats undergoing repeated defeated reactions. Important that stress is was not alone but repeated. Brouillard., *et al.* [3] tested an animal model that

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mimicked human enduring psychosocial stress. They investigated the effects of repeated social defeat on breathing. Due to persistent psychic stress, bradypnoea developed and lasted for at least ten days, but half of the defeated animals' bradypnoea lasted even a few weeks after the stress was over; that is, it became fixed. It can be assumed that bradypnoea means hypercapnia as well; on the other hand, hypoventilation often became habitual after the stress was over. This stress response may correspond to human hypoventilation syndromes (e.g., OSA)! A similar case has been described for adult rats after maternal separation from their cubs. It was observed a decreased respiratory rate, mainly during non-REM periods [27].

How can mental stresses cause organic 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. In the higher pCO_2 intracellular pH becomes acidic. High (rising) pCO_2 level is associated with hypoarousal [28], and despite the higher catecholamine levels, arousal and irritability decrease. (Elevated H^+ concentration 'cools' working of body cells, nervous system, slows down metabolism.) Alterations of the carbon dioxide levels thus may be a link between the soul and body [28]. Various metabolic mechanisms immediately counterbalance the respiratory acidosis: renal response, bone, and other tissues buffering and membrane transport mechanisms. (Important note: it is a fundamental observation that renal and tissular compensation is usually incomplete and overcompensation does not occur: in hypercapnic acidosis, a reserve intracellular acidosis persists.) While pCO_2 level changes very rapidly also intracellularly, 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 before. Changes in CO_2 levels are followed slowly by metabolic alterations. In the case of humans, the restoration of the standard CO_2 level often fails because muscular activity (fight or flight) lags. 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. Homeostasis can be more or less successful in wild animals as the third phase of the defensive cascade, and the muscle work is almost always present. However, civilized humans are different from animals; 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.

Chronic hypercapnia triggers activities of ion-transporters and -exchangers

It is a rule that simple acid-base disorders (at present case hypercapnic acidosis) are never overcompensated [29]. In this way, renal and tissular compensation cannot eliminate the cytosolic acidosis utterly. On the other hand, the immutability of pHi is extremely important for the organism. As a result, it has been developed several dozens of defense mechanisms against acidosis that operate with membrane transporters [30]. In part, they act as independent membrane transporters in other cases, hormones, growth factors, cytokines, interleukins influence their work [5]. It is an evident mathematical impossibility to restore all intracellular ions to their original state - since primarily HCO_3^- levels connected to CO_2 should be normalized, and this cannot be done without the restoration of pCO_2.

According to the instantaneous Intracellular Ion-Pattern Theory (see Part 1), it is determinative, that which one of the available ion exchangers is used by the cell predominantly [4] (e.g., the Na^+ -H^+ Exchanger or Na^+ Driven Cl^- HCO_3^- Exchanger). It can be coded genetically. Even the same chemical process can be carried out by different enzymes, and these isoenzymes have different kinetic parameters that have metabolic consequences too, though it is a separate science. On the other hand, orders of magnitude more regulators (hormones, growth factors, interleukins, etc.) are attached to H^+ -ion-exchanger/transporter systems than other ions [5], indicating the extreme importance of this topic for the body. It is also likely that the internal receptors of the H^+ sensors in the tissues are highly sensitive to changes [31]- as it is also known from respiratory physiology -, but these sensors can also be hurt or disturbed. As an illustration of metabolic remodeling, we present Packer's article [32]. Intracellular acidosis due to low-grade hypercapnia, among other things, activates the different isoforms of the Na^+/H^+ exchanger, which can adversely affect both the course of diabetes and cardiac failure.

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On the other hand, the concentration of ions at any given time depends on many physical, chemical, and biological, energetical factors: from osmolality, cell electricity, anion/cation equality, membrane ion transporters, synergism/antagonism of ions, etc. As a result, the plethora of receptors that want to restore intracellular pH (and other ion levels) make the intracellular ionic conditions and the functions of cells dysregulated and cloudy. Considering that all tissues have different receptors, which expression varies: consequently, the synchronized function of central neurohumoral control is abolished; after that, a particular stimulus will be few for one cell type and the same stimulus will be much for another. That is, a change in a single ion concentration - mainly if it also affects pHi - produces an enormous amount of change, ripple effects, not least because we do not know the genome of the individuum and his/her previously survived, but not wholly healed diseases [5].

If the Momentary Intracellular Ion-Pattern as a second messenger theory is accepted, we have to say that the most important statement is: hormones and other regulators affect intracellular ion composition and, that is why they also have metabolic effects. In psychic stress, we are talking about alterations 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 summary, the Momentary Intracellular Ion-pattern acts as a whole, in a manner of a second messenger, significantly modifying/directing cellular metabolism. Returning to Claude Bernard's thesis on Milieu Intérieur, to the cell "to be able to work according to its duty," the ions have to be everywhere in their "original" place.

The number of modulators that influence the intracellular H^+ concentration is surprisingly large. That is because intracellular pH has a high priority; a small amount of change of intracellular H^+ can induce a significant degree of changing of biochemical reactions (Part 1. [9]). Restoration of the intracellular H^+ ion concentration can be achieved by various mechanisms [30]. The different pumps that may be similarly capable of restoring the H^+ concentration alone are not enough to preserve and/or restore the healthy identity, because the recovery of all ions on own places; would be a part of the identity. The constancy of the Milieu Intérieur and the Intracellular Ion-Pattern is essential because the ions inhibit certain enzymes and activate others. Cell enzymes form a network. In the enzyme lines, metabolic pathways processes can be multiplied or reduced if the activity of several enzymes increase or decrease simultaneously. For example, a slight change in the concentration of H^+ can significantly amplify (or inhibit) specific metabolic pathways.

Genome (the 'hardware') and Momentary Intracellular Ion-Pattern (the'software') determine the metabolism of the cell together. During intracellular ionic remodeling, hidden genetic defects might arise, which would not be defects at all if the Intracellular Ion-Pattern had not changed. In different individuals, the metabolic changes can be manifested by the above mechanism, and consequently, the diseases, show various forms of manifestations; they diverge because the Intracellular Ion-Pattern has changed the phenotype of metabolism. A consequence: 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 remodeling, which points out the diseases of civilization, which cannot be avoided if their circumstances persist for years or decades. These diseases of civilization do not occur or are limited in wild animals. Still, they are pandemic in humans and show a wide range, also possibly including a significant part of mental illnesses (e.g., depression) and psychosomatic diseases.

Is the chronic low-grade hypercapnia the base of Metabolic Syndrome and T2D?

Chronic compensated low-grade hypercapnia cannot be considered as harmless accompanying phenomena, although it can be latent for years. Psychosomatic disorders develop over the years and decades, causing irreversible changes. The author of this book., *et al.* discussed in their previous publications [4,5] that low-grade chronic hypercapnia developed due to civilized behavior, induced by chronic mental stress. It is often manifested in OSA (Obstructive Sleep Apnea), COPD (Chronic Obstructive Pulmonary Disease), and OHS (Obesity Hypoventilation Syndrome), and their less pronounced formes frustes. After many years or a decade of existence, these are often complicated with T2D, Hypertension, Cardiovascular Disorders, Immunological Diseases, Depression, etc.

The hypothesis could be assumed because the measurement of intracellular pH (pHi) is currently under development; i.e., pathophysiological data are still incomplete in this topic [33]. On the other hand, very few researchers have a deal with the potentially

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harmful effects of chronic low-grade hypercapnia. This state resembles Metabolic Syndrome, but it probably the relationship has not been investigated. Low-grade chronic hypoventilation ($PaCO_2$ average is from 42 - 46 mmHg or above) affects a vast population that has not yet been precisely identified, most often, over 40 years of age, but under 40 y-o, also occurs in 1 - 2%. Sleep-Related Hypoventilation (SRH) is the milder form and initial stage of OSA (formerly 'habitual snoring'), it can reach 20% [15,34,35], while OSA occurs in 2 - 7% of the US population [36]. As claimed by Verbraecken and McNicholas, more than 10% of the population over 40 years of age suffers from COPD, and 10% from OSA [11]. 1.5% of the US population is severely obese; 10 - 20% of them suffer from OHS (pCO_2 is above 45 mmHg even during daytime) [37]. All sleep-related hypoventilation (SRH) and all obese patients are prone to nightly and intermittent daytime hypercapnia. The prevalence of Metabolic Syndrome in the US was 34% in 2006 and showed a steady upward trend [38]. A similar incidence was found among Indian urban populations in 2003 (31.6%) [39].

The prevalence of low- and moderate-grade hypercapnic population together (OSA + COPD + Significant Obesity) and of the Metabolic Syndrome are similar. The two populations overlap robustly with each other or are identical. There are plenty of studies about syndromes concerned with MetS; What are their definitions? How do they relate to each other? What causes what? Statistical data, their prevalence, co-morbidity are very diverged; this is because the pathomechanisms of the diseases are unclear, and no one has been able to model these metabolic disorders. There are many theories concerning them. There is a strong correlation (above 60%) between OSA and MetS [40], and similarly high between COPD and Mets (about 50%) [41]. It seems that co-morbidity alone between obesity and MetS is small, but some state that "obesity may precede the development of other metabolic syndrome components" [42]?

Conclusion

According to hypothesize, all forms of chronic hypercapnia are pathogenic; there are mainly quantitative differences. Intermittent hypercapnic overshooting and hypoxia are aggravating circumstances. Phenomena of OSA are also consequences of the existence of hypercapnia, some genetically coded predisposition is necessary [43]. The CO_2 hyposensitivity also promotes the occurrence of OSA. The hypothetical logical chain is Psychosocial Stress - Hypercapnia –Intracellular Electrolyte Disturbances –Metabolic Dysregulation –Diseases (MetS and Related Disorders).

On the one hand, intracellular alkalosis accelerates metabolism, enhances ATP turnovers, increases psychomotor excitability - anxiety is common [5,6], on the other hand, it can be a severe complication if the severely ill body would unable to produce enough ATP [44]. In contrast, already, the low-grade intracellular acidosis lowers metabolism and affects ATP turnover. It can be life-saver in an acute emergency [45]. In the longer term, however, low-grade hypercapnic acidosis due to counter-regulation and dysregulation could cause metabolic disorders, which are most likely to appear in the clinical picture of Metabolic Syndrome. The low-grade chronic hypercapnia is the primary cause of intracellular acidosis. The theory of the author of this book can be valid because acidosis tends to increase serum lipid levels and can cause insulin resistance (see Part 3).

We should take into account the consequence of the Second Law of Thermodynamics (see Part 1.), or as commonly referred to as the wear and tear phenomenon. It can be associated with irreversible damage (e.g., oxidative stress), acidogenic diet, and aging mechanism [46]. One of the constant companions of these damaging agents is intracellular acidosis. Age-related, partially irreversible metabolic acidosis associated with impairment of renal function [47] and could aggravate acidosis, which could only be offset by a decreased pCO_2 [48]. According to this, at age 80, the physiological pCO_2 range would be 35 - 38 mmHg? If it were valid, the average 40mmHg pCO_2 levels in high age would be abnormally high. Metabolic acidosis of various origins usually comes along insulin resistance, which can lead to a vicious cycle [49]. Another vicious circle that Diabetes and OSA can mutually worsen each other [50].

We can only be guessing how the latent stealth intracellular acidosis and the body's counter-regulation will go on during riffle effects, resulting in a reduced amount of the cytoplasm (that is CBIs, proteins, and ATP parallelly) in the "sick cells" (see Part 1). The clinical picture is divergent because the genomes of individuals differ from each other. Both the cells themselves and the body as a whole are defending themselves, that is why dysregulation and disturbed metabolism would develop. MetS, which is a disease that is pandemic in humans, is a hotbed of many diseases of civilization, such as Type 2 Diabetes, although barely known in wildlife. According to the author of this book, the human freeze response can lead to

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low-grade hypoventilation, hypercapnia. It is clinically manifested as OSA, COPD, and Significant Obesity, which can overlap each other. The human hypercapnic population may be similar or same to the Metabolic Syndrome, or at least to their more significant parts.

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