Chronic psychic stress can cause metabolic syndrome through mild hypercapnia

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The author presents a new psychosomatic stress model. All the elements of the hypothesis are well known but, in this context, are published first. The following are the most critical aspects of the recommended chronic stress model. **1/** Stress contains both sympathetic and parasympathetic elements, but the latter predominate. **2/** The mediator of stress is carbon dioxide, the substance that can turn the psyche into soma. **3/** In humans, chronic stress is mainly social; people cause it to each other. Chronic social stress is created frequently due to deviations in civilisation, education and tolerance. **4/** The freeze response (or freezing behaviour) plays a subordinate role in the animal world; it lasts mainly for a maximum of minutes, while in humans, it dominates and can continue for decades. **5/** The decisive step of freeze is apnea, hypopnea, which occurs due to aversive psychological effects. After a more extended existence, mild chronic respiratory acidosis develops and most often appears in the clinical form of obstructive sleep apnea. **6/** Chronic hypercapnia can shape the metabolism into metabolic syndrome. **7/** After that, various cardiovascular and metabolic complications (hypertension, atherosclerosis, type 2 diabetes, depression) may develop - partly due to genetic and lifestyle reasons.

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INTRODUCTION

Despite extensive research, it remains unclear whether metabolic syndrome has a single cause or it is from multiple underlying risk factors (Wolk and Somers, 2007). The role of stress, environment, behaviour and genetics is also unclear in the pathophysiology of metabolic syndrome. Is there a connection between OSA and metabolic syndrome or not (Wolk and Somers, 2007)? The author of this review intends to shed light on these questions by arranging the literature data in a logical order.

Cannon's fight-or-flight response stress theory is based purely on sympathetic neuro-humoral reactions (Cannon, 1929). It may be because animal stress-related parasympathetic responses have remained hidden for a long time. Barlow suggested an adaptive fear-alarm model. This freeze reaction could develop in threatening situations when the momentary fright elicits a parasympathetic pathway (Barlow, 2002). The literature calls hypervigilance when the prey assesses the threat with a cool head (Bracha, 2004). This period mostly lasts for a few seconds to minutes in animals (Barlow, 2002).

The main threat to humans today is no longer animal predators but fellow human beings. The individual must adapt to the communities, and fit into the hierarchy of power, as there is nowhere to flee, so in most cases, the consequence will be compromised to live a relatively good life by following the rules. Cannon's fight-or-flight response theory deservedly conquered 20th-century stress researchers, but the result was that all stress damage was written at the expense of the sympathetic nervous system and adrenergic mechanisms (Borchard, 2001). Over time, it had to be seen that probably not adrenaline but "chronic stress" causes atherosclerosis, whatever it means (Vitaliano et al., 2002).

Stress, psychosocial distress, and pathophysiology of psychosomatic diseases are among the most researched areas of medicine. The Achilles' point of the question is what can be the mediator and pathophysiologic pathway of psychosomatic processes. There is a broad consensus that psychosocial stress correlates most with cortisol levels; however, the authors suggest that the mediator and mediating mechanism are unresolved (Ruesch, 1961; Lockhart et al., 2011). Few believe that a parasympathetic pathway could play a significant/determinant role in the pathophysiology of psychosomatic diseases. However, the human aspects of the parasympathetic freeze of the stress response have only been intensively researched recently (Roelofs, 2017).

The author et al. previously suggested carbon dioxide as a potential mediator of psychic and psychosomatic processes (Sikter et al., 2009). Alterations of emotion change the breathing pattern and the momentary pCO_2 level (Sikter et al., 2009). On the other hand, the changing level of pCO_2 affects mental and physical functioning and arousal - in a word, carbon dioxide is an essential link between psyché and soma.

CARBON DIOXIDE CAN MEDIATE BOTH EXTEROCEPTIVE AND INTEROCEPTIVE STRESS

Amygdala is an almond-shaped cluster of nuclei of the mammalian brain thought for processing fearful and threatening stimuli, including detecting threats and activating fear-related behaviours (Baxter and Croxson, 2012). The amygdala not only mediates fear and anxiety (Davis et al., 2010), but it also has a chemosensory role (Ziemann et al., 2009).

The intention to avoid imminent suffocation is an elemental stress response that has already appeared in animals such as Caenorhabditis elegans and Drosophila melanogaster (Bretcher et al., 2011; Suh et al., 2004). Organisms detect elevation in CO_2 levels with a high degree of accuracy at many points of their body. In mammals, the amygdala collects information from peripheral and central CO_2 chemoreceptors. Carbon dioxide level elevation is a much more sensitive indicator of imminent suffocation than the O_2 decrease (Feinstein et al., 2022). Feinstein distinguishes between interoceptive and exteroceptive threats (Feinstein et al., 2022). The interoceptive one is an interior CO_2 elevation, which immediately causes a suffocation alarm without touching the amygdala. It can be mimicked with concentrated (35%) CO_2 inhalation. In the case of exteroceptive notice, the information comes through various signalling systems and touches the amygdala, causing apnea in the brainstem. The consequent pCO_2 level elevation causes a feeling of threat through the amygdala.

The role of carbon dioxide is underestimated in stress and psychosomatic disorders. This review points out that CO_2 itself is the mediator of the stress reaction in both exteroceptive and interoceptive stress. CO_2 gas has excellent solubility in both body water and lipids, so it can penetrate through membranes without hindrance and act its effect in neurons and somatic cells. CO_2 is suitable for mediating negative emotions (fear, anxiety, suffocation alarm) as changes in pCO_2 levels occur rapidly. In this way, carbon

dioxide can link the psyche and soma, a device that mediates physiological functions but can also cause diseases; it is a mediator.

Not only the elevated pCO_2 can cause fear and anxiety, but the actual spiritual status also influences the respiratory process (we start breathing rarely, frequently, and irregularly), causing pCO_2 and pH alterations in the organism (Sikter et al., 2009). On the other hand, the actual cytosolic pH of neurons is one of the primary modifiers of Ca^{2+} conductance in the membranes, thereby fundamentally changing the working of the neurons and nervous system (Sikter et al., 2009).

AVOIDANCE COMES FROM THE FREEZE

Cannon did not notice that a fight-or-flight stress response is usually preceded by a short freeze response period, which Barlow first studied in detail (Barlow, 2002). However, the details of the freeze response are mostly unexplored in human cases (Roelofs, 2017). Freeze is an essential introductory part of the defence cascade that activates parasympathetic or sympathetic pathways according to need. In animals, usually, it continues with a fight-or-flight stress response (Kozlowska et al., 2015).

The emergency information travels to the amygdala and the brainstem, which can induce apnea; the developed hypercapnia triggers fear and other negative emotions (Feinstein et al., 2022). Meanwhile, motility decreases through a vagotonic reflex, it lasts for seconds or minutes (Barlow, 2002). During the freeze, the animal evaluates the size of the danger and things to do; this stress response promotes a cool-headed prey's decision: "stop, look, and watch" (Bracha, 2004).

The parasympathetic condition causes a slowdown in heart rate, although there are signs of a sympathetic tone. Freeze is a universal fear response, which varies from species to species and has a pronounced parasympathetic dominance in humans (Hermans et al., 2013).

The avoidance definition by the American Psychological Association (APA) is "any act or series of actions that enable an individual to avoid or anticipate unpleasant or painful situations, stimuli, or events, including conditioned aversive stimuli." In practice, freeze is first and foremost for avoiding the threat (Rösler and Garne, 2019). Immobility and hypervigilance increase the chances of avoiding and surviving an attack. Increasing carbon dioxide levels can be considered the ancient mediator of negative emotions and avoidance. Research has studied many natural, artificial, inescapable, and escapable forms of carbon dioxide expositions. Most species try to avoid it more or less successfully (Arméndola and Weary, 2020).

We must distinguish between the stresses threatening animals and humans and how to avoid them. While acute fight-or-flight stress response predominates in wild animals, freezing behaviour is more prevalent in humans. Terminologically and considering its metabolic effects, freeze is a parasympathetic phenomenon (Hermans et al., 2013). Both momentary current pCO_2 levels and intracellular pH fundamentally affect the functioning of the body's cells, which changes mimic the operation of the autonomic nervous system. The hypercapnia can mimic the parasympathetic tone and synergist with it. These facts are mostly overlooked (Sikter et al., 2017a, 2017b; Sikter, 2018). The body strives to achieve a balance in sympathetic-parasympathetic tone, so several sympathetic phenomena and humoral responses can occur during chronic human stress, and these often exacerbate the outcomes, leading to diseases of civilisation (Sikter et al., 2009, 2017a, 2017b; Sikter and Sonne, 2021a).

CHRONIC STRESS, SOCIAL STRESS, THE ROLE OF HUMAN BEHAVIOUR

If stress is not resolved in the short term, is prolonged or recurs, we are talking about chronic stress. Through violence against nature, humans have created a model with global warming - an increased concentration of CO_2 in living waters and air - in which researchers can study the consequences of chronic stress. Fish can be used for this stress model in a simple way, which is remarkable in several respects. Fish cannot avoid the rise in CO_2 in their body as it is ubiquitous.

Incorporating higher CO_2 mimics interoceptive stress, drawing attention to the danger of real environmental stress (Hermann, 2018). On the other hand, the rise in CO_2 levels seems not to be one of the threatening dangers but the mediator of chronic stress itself. Third, threat modelling has also been carried out at the cellular level in fish (Hermans et al., 2013). The exteroceptive and interoceptive stressors became the same: elevated CO_2 levels in the body's cells (Feinstein et al., 2022). According to the author's hypothesis of the present article, social stress in humans will also increase pCO_2 levels, which is the stress mediator through freeze response (see later).

In the wild animal kingdom, a freeze response is rarely followed by tonic immobility because it is usually not successful against the predator (Bracha, 2004). On the other hand, it becomes increasingly clear that freeze can be one of the primary weapons of humans in the defence against social threats. The individual often and effectively defends oneself in emergencies in a freeze-like way because a fight-or-flight response is mostly not allowed morally by humans (Noordewier et al., 2020).

Roelofs showed that a person could respond to a social threat with a freeze response (Roelofs et al., 2010). However, the neurobiological mechanism of freeze action is similar in animals and humans. Humans, as social beings, show significant differences in behaviour from animals (Roelofs, 2017). According to Roelofs, freezing in humans is not a passive state but a "parasympathetic brake on the motor system", which allows them to calmly consider the situation and thus successfully avoid the threatening position.

Wheaton distinguished seven problems that suggest chronic stress, but it can develop in many other ways (Wheaton, 1997). The severity of distress depends primarily on how deep a mark a psychic stressor leaves on the individual's soul. So we should distinguish between simple discomfort feeling and shame, as well as between all the psychic stressors that provoke helplessness and repressed anger. Several other psychological mechanisms can play a role, such as humiliation, helplessness, hopelessness, and feeling of insecurity (Bradley et al., 2001). Inhibited anger (together with fear) can indeed lead to somatic diseases (Scuteri et al., 2001).

It seems likely that salt-sensitive hypertension, which is well known to be much more common among Afro-Americans, does not develop primarily on genetic grounds but through a psychosomatic mechanism due to suffering from racism, as Anderson's publication suggests (Anderson et al., 2001). (If this statement is confirmed, it would be a considerable step ahead in the pathophysiology.)

In the short term, parasympathicotonia may be beneficial because it helps conserve and manage resources. Although, it is exceptionally detrimental to both psychiatric adaptation and its long-term metabolic consequences. Learned behaviours (tolerance) and education on civilised behaviour make chronic stress a universal phenomenon. Human education may generalise freezing behaviour; that is, it cools the manifestations of the fight-or-flight response, and a freezing-like behaviour becomes the sine qua non of civilian behaviour. No primate community would tolerate such high population levels of animals as humans. But it comes at a price: chronic social stress and distress. Many social and psychological factors hamper social coexistence. There are many degrees of difficulty, such as aversion, fear, anxiety and social defeat, which the individual wants to avoid naturally, but this is often unsolvable for subsistence and integration into a community. So most people give themselves up spiritually and put up with it. Age also plays a significant role; the question is whether mental factors (such as "wisdom" or opportunism) or the age-related slowing of metabolism play a more critical role. (In the latter, as a part of The Second Law of Thermodynamics, is also suspect (Sikter et al., 2017b).

Ethologists and behaviour researchers have long modelled the social defeat by caged rodents. It was shown in caged rats that persistent, repeated psychic or physical abuse can lead to freezing behaviour. The induced bradycardia and bradypnoea (hypercapnia) lasted for at least ten days (Brouillard et al., 2016). Although the stress had disappeared, half of the rats still had bradypnoea for weeks. Hypoventilation often becomes habitual and persists even after repeated or chronic stress is over.

The individual consciously (or subconsciously) accepts that he has no choice but to give up a part of the ego, which triggers a freeze response, one element of which is hypoventilation, which leads to the first materialised factor in the psychic stress - to the elevated pCO_2 level. If the stress lasts days to weeks, the hypercapnic acidosis becomes "compensated." And then, hypoventilation may become permanent or fragmented and repeated; it has more forms than OSA, OHS or COPD. OSA can be the most common manifestation of chronic hypercapnia in which psychosomatic mechanisms occur. After prolonged existence, it can develop somatic diseases (Sikter et al., 2017b). At the societal level, avoidance often does not work, which is why the mean pCO_2 levels and the intracellular HCO_3- /Cl- levels increase (Sikter and Sonne, 2021a, 2021b).

Chronic stress occurs because the body cannot avoid its oldest enemy, the pCO_2 level elevation. While the freeze response in animals - except for tonic immobility – lasts a maximum of minutes, in humans, a freeze-like state can continue for decades (Sikter et al., 2017b).

MILD CARBON DIOXIDE ELEVATION CAUSED BY CHRONIC STRESS COULD TRIGGER METABOLIC SYNDROME

It was repeatedly suggested that the metabolic syndrome would be of psychosomatic origin, but the pathway leading to it has not been found so far (Ghike, 2016). Others think the same about OSA (Vitaliano et al., 2002; Bergmann et al., 2014). Many have connected OSA with metabolic syndrome as there is a significant correlation between the two syndromes (Wolk and Somers, 2007; Lam et al., 2012; Gaines et al., 2018; Chan et al., 2019; Ryan et al., 2020). The carbon dioxide elevation could be their common denominator. However, the carbon dioxide level elevation is not included in a list of a recently published systematic review of physiological biomarkers of chronic stress (Noushad et al., 2021).

Well, recently, it has been suspected that intermittent hypercapnia may be a trigger for metabolic syndrome in OSA (Ryan et al., 2020)! The difference between the physiological and pathogenic levels of pCO_2 is relatively small, meaning that carbon dioxide would have a much stronger effect than previously thought and that the levels hitherto considered normal are questionable (Sikter and Sonne, 2021a). OSA correlates strongly with metabolic syndrome among the three major hypercapnic diseases (OSA, OHS, COPD). Because hypoxia and hypercapnia interact strongly, they have a synergistic effect (Berger et al., 2000; Ryan et al., 2020), and hypoxic periods enhance CO_2 retention in tissues (Berger et al., 2000). Although in OSA, the mean pCO_2 levels are usually slightly above normal (Eskandari et al., 2017).

Carbon dioxide has several strong effects, such as on intracellular pH and, through this, on the rate of metabolism, the immune system, and the endothelial cells of the lung alveoli (Relman, 1972; Zappulla, 2008; Curley and Laffey, 2014). It has been known for some time from experiments on primitive animal organisms that an increase in the level of carbon dioxide per se can alter the expression of specific genes and thus cause a metabolic change in, for example, carbohydrate or fat metabolism or immunity (Taylor and Cummins, 2011). Metabolism modification occurs by transcribing specific genes (Cormac and Taylor, 2011). A microarray technique study analyzed gene expression in human epithelial cells. They found that hypercapnia downregulated the expression of 183 genes and upregulated 126 (Casalino-Masuda et al., 2018). Among these, major gene clusters linked to lipid metabolism were predominantly upregulated. These new data show that CO_2 can trigger cholesterol and lipid biosynthesis. The elevated CO_2 levels can alter gene expression and activate signalling pathways, affecting cellular and tissue functions (Shigemura et al., 2020). Based on the above, we are talking about changes of phenotype, that is, increased or decreased function of specific genes, the genome remains unchanged. The question is, are these changes partially or entirely reversible or not?

In fish, it has been shown that elevated chronic CO_2 exposure alters lipid and triglyceride metabolism like humans; the similarity is hardly coincidental; these genes probably have already appeared at a lower level of phylogeny (Hermann, 2018).

CARBON DIOXIDE TOLERANCE – INDIVIDUAL DIFFERENCES IN STRESS RESPONSIVENESS

Exposure to elevated CO_2 can have marked effects on certain gene expressions controlling metabolism, fertility, and immunity (Cummins et al., 2020). CO_2 exposure has a strong and specific effect on lipid and triglyceride metabolism. It changes the body cells' functioning to such a degree and direction that mild chronic hypercapnia also could cause metabolic syndrome (Sikter 2020; Sikter and Sonne, 2021a). In this way, the metabolic syndrome and its complications would have a psychosomatic origin (Vitaliano et al., 2002). Based on the above, it is likely that carbon dioxide level elevation plays a significant role in chronic (social, psychic) stress and a determining role in the pathophysiology of psychosomatic diseases. Nevertheless, the details have yet to be revealed, as the degree of effective pCO_2 elevation shows a significant deviation in different individuals, so it should be assumed that individual sensitivity and responsiveness play a crucial role (Lovallo and Gerin, 2003).

The fine-tuning of CO_2 chemosensation is a crucial adaptive response to controlling acid-base balance in tissues (Cummins et al., 2020). In psychiatric diseases, it is known that CO_2 sensitivity ranges widely; the highest CO_2 sensitivity was observed in panic disorder, while the lowest was in depression (Freire et al., 2010; Sikter et al., 2017b).

There must also be a reduced CO_2 sensitivity, which is the opposite of CO_2 hypersensitivity. Both conditions have a prominent role in psychic, functional and psychosomatic disorders. While CO_2 hypersensitivity is relatively well explored in connection with anxiety and panic disorders, the

knowledge about the importance of reduced CO_2 sensitivity is severely lacking. In addition to psychic reactivity and emotional responsiveness, other factors can also influence the body's respiratory response to an increase in CO_2 levels. Due to its importance, the control of the pCO_2 level is "over-insured". For example, many hormones also regulate pCO_2 and pH levels - this crosstalking can result in dysregulation (Sikter et al., 2017a; 2017b; Cummins et al., 2020).

There is an unexpected pathophysiological effect among the harms of cigarette smoking; it can be explained by reduced CO_2 sensitivity (Dunn et al., 1982). The pathophysiology described above would largely explain why sudden infant death syndrome (SIDS) occurs due to mothers' smoking during pregnancy (Ali et al., 2016). Furthermore, it also explains why CO_2 hypersensitivity develops after smoking withdrawal, what is the psychic benefit of tobacco, and the mental hindrance of quitting (Abrams et al., 2011). Moreover, it is also explained that reduced respiratory CO_2 sensitivity may be the common root of the metabolic syndrome and the harms of smoke abuse, as smoking is associated with similarly serious cardiovascular risks as metabolic syndrome (Erhardt, 2009). Because of its importance, the impact of CO_2 on metabolism, gene expression and psychosomatic mechanisms has begun to be highly intensive research. Despite this, studies are still only at the beginning.

LIST OF ABBREVIATIONS

CO_2: carbon dioxide
COPD: chronic obstructive pulmonary disease
O_2: oxygen
OHS: obesity hypoventilation syndrome
OSA: obstructive sleep apnea
pCO_2: partial pressure of carbon dioxide

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A krónikus pszichés stressz kisfokú hiperkapnia révén metabolikus szindrómát okozhat

A szerző egy új pszichoszomatikus stresszmodellt mutat be. A hipotézis minden eleme jól ismert, de ebben az összefüggésben először publikálják. Az alábbiakban a javasolt krónikus stressz modell legkritikusabb szempontjait mutatjuk be. **1/** A stressz szimpatikus és paraszimpatikus elemeket egyaránt tartalmaz, de az utóbbiak vannak túlsúlyban. **2/** A stressz mediátora a széndioxid, az az anyag, amely képes „materializálni" a lelki változást. **3/** Emberben a krónikus stressz főként szociális jellegű; az emberek okozzák egymásnak. A krónikus szociális stressz gyakran a civilizáció, az oktatás és a tolerancia devianciái miatt jön létre. **4/** A fagyási reakció (freeze) az állatvilágban alárendelt szerepet játszik, és általában legfeljebb percekig tart, míg az embernél domináns és évtizedekig folytatódhat. **5/** A freeze döntő következménye az apnoé, hipopnoé, amely averzív pszichés hatások miatt következik be. Hosszabb fennállás után kisfokú krónikus légúti acidózis alakul ki, amely leggyakrabban obstruktív alvási apnoe klinikai formájában jelenik meg. **6/** A krónikus kisfokú hiperkapnia metabolikus szindróma irányában alakíthatja át az anyagcserét. **7/** Ezt követően különböző kardiovaszkuláris és anyagcsere-szövődmények (magas vérnyomás, érelmeszesedés, 2-es típusú cukorbetegség, depresszió stb.) alakulhatnak ki – részben genetikai és életmódbeli okok miatt.

Kulcsszavak: fagyasztási reakció (freeze), krónikus stressz, széndioxid, metabolikus szindróma, elkerülés, emberi viselkedés.